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Cyanide in Drinking-water

Background document for development of
WHO *Guidelines for Drinking-water Quality*

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Preface

One of the primary goals of the World Health Organization (WHO) and its Member States is that "all people, whatever their stage of development and their social and economic conditions, have the right to have access to an adequate supply of safe drinking water." A major WHO function to achieve such goals is the responsibility "to propose ... regulations, and to make recommendations with respect to international health matters ...."

The first WHO document dealing specifically with public drinking-water quality was published in 1958 as *International Standards for Drinking-water*. It was subsequently revised in 1963 and in 1971 under the same title. In 1984–1985, the first edition of the WHO *Guidelines for Drinking-water Quality* (GDWQ) was published in three volumes: Volume 1, Recommendations; Volume 2, Health criteria and other supporting information; and Volume 3, Surveillance and control of community supplies. Second editions of these volumes were published in 1993, 1996 and 1997, respectively. Addenda to Volumes 1 and 2 of the second edition were published in 1998, addressing selected chemicals. An addendum on microbiological aspects reviewing selected microorganisms was published in 2002. The third edition of the GDWQ was published in 2004, the first addendum to the third edition was published in 2006 and the second addendum to the third edition was published in 2008. The fourth edition will be published in 2011.

The GDWQ are subject to a rolling revision process. Through this process, microbial, chemical and radiological aspects of drinking-water are subject to periodic review, and documentation related to aspects of protection and control of public drinking-water quality is accordingly prepared and updated.

Since the first edition of the GDWQ, WHO has published information on health criteria and other supporting information to the GDWQ, describing the approaches used in deriving guideline values and presenting critical reviews and evaluations of the effects on human health of the substances or contaminants of potential health concern in drinking-water. In the first and second editions, these constituted Volume 2 of the GDWQ. Since publication of the third edition, they comprise a series of free-standing monographs, including this one.

For each chemical contaminant or substance considered, a lead institution prepared a background document evaluating the risks for human health from exposure to the particular chemical in drinking-water. Institutions from Canada, Japan, the United Kingdom and the United States of America (USA) prepared the documents for the fourth edition.

Under the oversight of a group of coordinators, each of whom was responsible for a group of chemicals considered in the GDWQ, the draft health criteria documents were submitted to a number of scientific institutions and selected experts for peer review. Comments were taken into consideration by the coordinators and authors. The draft documents were also released to the public domain for comment and submitted for final evaluation by expert meetings.

During the preparation of background documents and at expert meetings, careful consideration was given to information available in previous risk assessments carried out by the International Programme on Chemical Safety, in its Environmental Health Criteria monographs and Concise International Chemical Assessment Documents, the International Agency for Research on Cancer, the Joint FAO/WHO Meetings on Pesticide Residues and the Joint FAO/WHO Expert Committee on Food Additives (which evaluates contaminants such as lead, cadmium, nitrate and nitrite, in addition to food additives).

Further up-to-date information on the GDWQ and the process of their development is available on the WHO Internet site and in the current edition of the GDWQ.

Acknowledgements

The first draft of Cyanide in Drinking-water, Background document for development of WHO *Guidelines for Drinking-water Quality*, was prepared by Mr J.K. Fawell, United Kingdom, to whom special thanks are due. It is an update of the background document published in the second edition in 1996.

The work of the following working group coordinators was crucial in the development of this document and others contributing to the fourth edition:

Dr J. Cotruvo, J. Cotruvo & Associates, USA (*Materials and chemicals*)
Mr J.K. Fawell, United Kingdom (*Naturally occurring and industrial contaminants* and *Pesticides*)
Ms M. Giddings, Health Canada (*Disinfectants and disinfection by-products*)
Mr P. Jackson, WRc-NSF, United Kingdom (*Chemicals – practical aspects*)
Professor Y. Magara, Hokkaido University, Japan (*Analytical achievability*)
Dr Aiwerasia Vera Festo Ngowi, Muhimbili University of Health and Allied Sciences, United Republic of Tanzania (*Pesticides*)
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The draft text was discussed at the Expert Consultation for the fourth edition of the GDWQ, held on 19–23 June 2008. The final version of the document takes into consideration comments from both peer reviewers and the public. The input of those who provided comments and of participants at the meeting is gratefully acknowledged.

The WHO coordinators were Mr R. Bos and Mr B. Gordon, WHO Headquarters. Ms C. Vickers provided a liaison with the International Programme on Chemical Safety, WHO Headquarters. Mr M. Zaim, Public Health and the Environment Programme, WHO Headquarters, provided input on pesticides added to drinking-water for public health purposes.

Ms P. Ward provided invaluable administrative support at the Expert Consultation and throughout the review and publication process. Ms M. Sheffer of Ottawa, Canada, was responsible for the scientific editing of the document.

Many individuals from various countries contributed to the development of the GDWQ. The efforts of all who contributed to the preparation of this document and in particular those who provided peer or public domain review comments are greatly appreciated.

Acronyms and abbreviations used in the text

CAS	Chemical Abstracts Service
FAO	Food and Agriculture Organization of the United Nations
GAC	granular activated carbon
GDWQ	*Guidelines for Drinking-water Quality*
K_{ow}	octanol/water partition coefficient
LD_{50}	median lethal dose
LOAEL	lowest-observed-adverse-effect level
NOAEL	no-observed-adverse-effect level
pK_a	acid dissociation constant
T_3	triiodothyronine
T_4	thyroxine
TDI	tolerable daily intake
USA	United States of America
USEPA	United States Environmental Protection Agency
UV	ultraviolet
WHO	World Health Organization

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This document is largely taken from Concise International Chemical Assessment Document No. 61, published by the International Programme on Chemical Safety in 2004 (IPCS, 2004). A number of sections of text from that document have been reproduced here. Other recent reviews have been carried out by national and local authorities (e.g. California Environmental Protection Agency, 1997; ATSDR, 2006).

1. GENERAL DESCRIPTION

1.1 Identity

Cyanides comprise a wide range of compounds of varying degrees of chemical complexity, all of which contain a CN moiety, to which humans are exposed in gas, liquid and solid form from a broad range of natural and anthropogenic sources. Whereas many chemical forms of cyanide are used in industrial application or are present in the environment, the cyanide anion CN^- is the primary toxic agent, regardless of origin (IPCS, 2004).

Cyanides are usually found only at very low concentrations in drinking-water sources. According to the United States Environmental Protection Agency's (USEPA) STORET database, the mean cyanide concentration in most surface waters in the United States of America (USA) is less than 3.5 µg/l. Data from the late 1970s to early 1980s indicated that the levels are higher only in limited areas, where they may exceed 200 µg/l (ATSDR, 1997). However, there are occasions on which large spills of cyanide, associated with industry, occur, and these can give rise to very high concentrations in drinking-water source waters, particularly surface waters. Although low concentrations of cyanide in water sources can occur, these are easily removed by treatment, such as with chlorine (IPCS, 2004). The objective of this document is, therefore, to consider cyanide in the context of short-term exposure following a significant spill of cyanide to a drinking-water source water.

Cyanogen chloride (CNCl) can be formed as a by-product during the chlorination of drinking-water and in the in situ production of chloramines as a residual disinfectant to maintain the hygienic condition of distribution systems. However, it slowly hydrolyses to form cyanide, and the guideline value for cyanogen chloride is based on the chronic toxicity of the cyanide moiety.

1.2 Physicochemical properties

Hydrogen cyanide (HCN) is a colourless or pale blue liquid or gas with a faint bitter almond-like odour. Common synonyms are hydrocyanic acid and prussic acid. Hydrogen cyanide is a very weak acid, with an acid dissociation constant (pK_a value) of 9.22 at 25 °C. It is soluble in water and alcohol. Hydrogen cyanide is commercially available as a gas or as a technical-grade liquid in concentrations of 5%, 10% and 96–99.5%. Phosphoric acid is added to liquid hydrogen cyanide as a stabilizer to prevent decomposition and explosion (ATSDR, 1997). Some important physical and chemical properties of hydrogen cyanide are summarized in Table 1.

Table 1: Physical and chemical properties of hydrogen cyanide (CAS No. 74-90-8)[a]

Property	Value
Relative molecular mass	27.03
Boiling point (°C)	25.70
Solubility (at 30 °C)	Miscible with water; soluble in ethanol
Henry's law constant (dimensionless)	180–300[b]
Octanol/water partition coefficient (log K_{ow})	0.66
Vapour pressure (kPa)	35.2 at 0 °C 107.2 at 27.2 °C

CAS, Chemical Abstracts Service

[a] From ACGIH (2001); DECOS (2002).

[b] Hine & Weimar (1965); Edwards et al. (1978); Gaffney et al. (1987).

Sodium cyanide (NaCN) and potassium cyanide (KCN) (see Table 2) are both soluble in water, and aqueous solutions are strongly alkaline and decompose rapidly. Both produce hydrogen cyanide on contact with acids or acid salts.

Table 2: CAS numbers, molecular formulae and relative molecular mass of selected cyanide compounds[a]

Compound	CAS number	Molecular formula	Relative molecular mass
Sodium cyanide	143-33-9	NaCN	49.02
Potassium cyanide	151-50-8	KCN	65.11
Calcium cyanide	592-01-8	$Ca(CN)_2$	92.12
Copper cyanide	54-92-3	CuCN	89.56
Potassium silver cyanide	501-61-6	$KAg(CN)_2$	198.01
Cyanogen chloride	506-77-4	CNCl	61.47

CAS, Chemical Abstracts Service

[a] From Windholz (1983); ACGIH (2001); ECETOC (2004).

1.3 Organoleptic properties

The odour of cyanides is that of almonds or bitter almonds, and the reported threshold odour concentrations in air and water are 0.7 mg/m^3 and 0.17 mg/l, respectively (IPCS, 2004).

1.4 Major uses and sources in drinking-water

Hydrogen cyanide is ubiquitous in nature, including as cyanogenic glycosides in at least 2000 plants. It is widely used for industrial processes, and it has been estimated that the present total annual production of hydrogen cyanide worldwide is 1.4 million tonnes (Mudder & Botz, 2000). It is used in chemical manufacture and for the production of sodium cyanide, potassium silver cyanide and calcium cyanide. Cyanides are used in a large number of industrial processes, including electroplating and case-hardening of metals; the extraction (cyanidation) of gold and silver from ores; base metal flotation; coal gasification; and the fumigation of ships, railroad cars, buildings, grain silos, flour mills, seeds in vacuum chambers and soil.

Large quantities of sodium cyanide are used to introduce cyano groups into organic compounds, in particular through a reaction with organic halogen compounds to yield

nitriles. The nitriles can then be converted to a variety of carboxylic acids, amides, esters and amines. Potassium cyanide is used for electrolytic refining of platinum, for metal colouring and as an electrolyte for the separation of gold, silver and copper from platinum (Eisler et al., 1999; Patnaik, 1999; ACGIH, 2001; ECETOC, 2004). Cyanide salts are used as chelating agents, and the complex cyanides of copper, zinc and cadmium are used in electroplating processes, principally the plating of iron, steel and zinc (ECETOC, 2004). Calcium cyanide is used chiefly as a fumigant, because it readily releases hydrogen cyanide when exposed to air; as a fertilizer, defoliant, herbicide and rodenticide; as a stabilizer for cement; and in stainless steel manufacture (ACGIH, 2001). Potassium silver cyanide is used in silver plating and as a bactericide.

As indicated above, the primary concern is the release of large quantities of cyanide to drinking-water sources. More than 30 large-scale accidental releases of cyanide to water systems have been reported since 1975; these include transportation accidents, pipe failures and tailings dam–related releases (Korte, Spiteller & Coulston, 2000; Mudder & Botz, 2000). The extraction of gold from low-grade ores by cyanidation processes results in significant use of cyanide, and the major point sources of cyanide release to water are discharges from gold mining, iron and steel production and the organic chemical industries. An estimated 3 billion litres (i.e. 3×10^9 litres) of wastes containing cyanides were generated in the USA in 1983, principally from spent cyanide plating bath solutions from electroplating operations (except for precious metals) and from spent stripping and cleaning bath solutions from electroplating operations (Grosse, 1986). During cassava starch production, large amounts of cyanoglycosides are released and hydrolysed by plant-borne enzymes, leading to cyanide concentrations in wastewater as high as 200 mg/l (Siller & Winter, 1998).

1.5 Environmental fate

Cyanide ions are relatively stable in the environment unless they are oxidized. The fate and behaviour of cyanides in water will be controlled by various parameters of the water body—namely, pH, trace metal levels, dissolved oxygen and temperature.

2. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

2.1 Air

Trace concentrations of cyanide in air are not an issue for short-term exposure to high cyanide levels in drinking-water following a spill.

2.2 Water

Levels of cyanide in water sources are generally low but depend on the upstream sources and discharges. Data from the USA (USEPA STORET database) indicate that the mean cyanide concentration in most surface waters in the USA is less than 3.5 µg/l. Data from the late 1970s to early 1980s indicated that the levels are higher only in limited areas but may exceed 200 µg/l (ATSDR, 1997). Cyanide can be destroyed by drinking-water treatment, but cyanogen chloride can also be formed during treatment, and this breaks down to release cyanide. In 1978, a USEPA survey of drinking-water supplies showed that about 7% of the supplies had cyanide

concentrations greater than 10 µg/l (USEPA, 1993a). In a survey in 1987 of over 35 drinking-water supplies, the quarterly median cyanogen chloride concentrations in drinking-water ranged from 0.45 to 0.80 µg/l (from 0.19 to 0.34 µg cyanide/l) (Krasner et al., 1989; ATSDR, 1997). More current published data regarding the cyanide and cyanogen chloride levels in drinking-water are lacking. Cyanide levels of 1.58–7.89 mg/l have been found in natural water sources near large-scale cassava processing facilities in Nigeria (Okafor et al., 2001).

2.3 Food

Cyanide is naturally occurring in many foods. Many edible plants contain cyanogenic glycosides, whose concentrations can vary widely as a result of genetic and environmental factors, location, season and soil type (Ermans et al., 1980; FAO/WHO, 1993). Some of the foodstuffs and their cyanide contents are shown in Table 3. The concentrations can vary not only with the type of plant, but also with the variety. Hydrogen cyanide is released from the glycoside by hydrolysis catalysed by various enzymes. It is common practice to soak cassava tubers so that fermentation releases hydrogen cyanide, which is then washed free. If cyanogenic glycosides are not removed by pretreatment, hydrogen cyanide is usually liberated from cyanogenic glycosides after ingestion and hydrolysis by the glycosidases of the intestinal microflora and, to a lesser degree, by glucosidases of the liver and other tissues (Padmaja, 1995).

Table 3: Cyanide concentrations in food products.[a]

Type of product	Cyanide concentration (in mg/kg or mg/l)
Cereal grains and their products	0.001–0.45
Soy protein products	0.07–0.3
Soybean hulls	1.24
Apricot pits, wet weight	89–2170
Home-made cherry juice from pitted fruits	5.1
Home-made cherry juice containing 100% crushed pits	23
Commercial fruit juices	
Cherry	4.6
Apricot	2.2
Prune	1.9
Tropical foodstuffs	
Cassava (bitter) / dried root cortex	2360
Cassava (bitter) / leaves	300
Cassava (bitter) / whole tubers	380
Cassava (sweet) / leaves	451
Cassava (sweet) / whole tubers	445
Gari flour (Nigeria)	10.6–22.1
Sorghum / whole immature plant	2400
Bamboo / immature shoot tip	7700
Lima beans from Java (coloured)	3000
Lima beans from Puerto Rico (black)	2900
Lima beans from Burma (white)	2000

[a] From Nartey (1980); Honig et al. (1983); FAO/WHO (1993); ATSDR (1997).

2.4 Contribution from drinking-water

The contribution to total cyanide intake from drinking-water is uncertain, but will depend largely on the levels of cyanogen chloride generated in drinking-water treatment. However, concentrations are expected to be less than 10 µg/day (ATSDR, 1997). The major source of cyanide exposure for the general population not exposed through high levels of cyanogenic glycosides in food, particularly cassava, is cigarette smoke.

The exposure from drinking-water in an incident in which high concentrations of cyanide are present in source water can be much more significant than that from any other source. However, in assessing safe levels from drinking-water in such an incident, it would be important to consider populations exposed to high levels of cassava and other dietary components with high concentrations of cyanogenic glycosides.

3. KINETICS AND METABOLISM IN LABORATORY ANIMALS AND HUMANS

3.1 Absorption

Hydrogen cyanide is readily absorbed following inhalation, oral and dermal exposure (ATSDR, 1997). Gastrointestinal absorption of inorganic cyanide salts is slower than pulmonary absorption. The onset of symptoms is delayed and the severity of symptoms diminished compared with inhalation. When simple cyanide salts such as potassium and sodium cyanide are ingested, free cyanide ion can rapidly bind hydrogen ion to form hydrogen cyanide in the acidic medium of the stomach. Essentially all cyanide ingested as cyanide salts will form hydrogen cyanide and will be quickly absorbed. However, after oral intake, only part of the dose reaches the systemic circulation due to first-pass metabolism by the liver (ECETOC, 2004). In vitro studies with sodium cyanide and human skin have shown more rapid absorption of the undissociated hydrogen cyanide. In water following a spill, the cyanide will largely be in the undissociated form.

3.2 Distribution

Hydrogen cyanide has a pK_a of 9.22; thus, at physiological pH (about pH 7), it is distributed in the body primarily in its undissociated form, and very little is present as the free cyanide ion. Hence, the form of cyanide to which exposure occurs, the salt or the free acid, does not influence distribution, metabolism or excretion from the body (ECETOC, 2004). Inhaled or percutaneously absorbed hydrogen cyanide passes immediately into the systemic circulation. In contrast, high proportions of ingested sodium and potassium cyanide pass through the liver and are detoxified by the first-pass effect.

The major portion of hydrogen cyanide in blood is sequestered in the erythrocytes, and a relatively small proportion is transported via the plasma to target organs. Hydrogen cyanide is concentrated in red blood cells at a red blood cell to plasma ratio of 199:1; levels in plasma reflect tissue levels better than levels in whole blood or

erythrocytes. After cessation of exposure, plasma hydrogen cyanide levels tend to return to normal within 4–8 h (Feldstein & Klendshoj, 1954; Ansell & Lewis, 1970).

In rats dosed by gavage, highest concentrations of hydrogen cyanide were found in the liver, followed by the lungs and blood (Yamamoto et al., 1982). Hydrogen cyanide has not been shown to accumulate in the blood and tissues following oral exposure to inorganic cyanide (ATSDR, 1997), and no cumulative effect on the organism during repeated exposure has been demonstrated.

3.3 Metabolism

Although hydrogen cyanide can interact with substances such as methaemoglobin in the bloodstream, the majority of cyanide metabolism occurs within the tissues. Hydrogen cyanide is metabolized in mammalian systems by one major route and several minor routes. The major route of metabolism for hydrogen cyanide is detoxification in the liver by the mitochondrial enzyme rhodanese, which catalyses the transfer of the sulfane sulfur of thiosulfate to the cyanide ion to form thiocyanate (Williams, 1959; Ansell & Lewis, 1970). About 80% of hydrogen cyanide is detoxified by this route. The rate-limiting step is the amount of thiosulfate. Although rhodanese is present in the mitochondria of all tissues, the species and tissue distributions of rhodanese are highly variable. In general, the highest concentrations of rhodanese are found in the liver, kidney, brain and muscle. However, the supply of thiosulfate is limited (Aminlari, Vaseghi & Kargar, 1994).

A number of other sulfur transferases can also metabolize hydrogen cyanide, and albumin, which carries elemental sulfur in the body in the sulfane (hydrogen sulfide) form, can assist in the catalysis of cyanide to thiocyanate as well (Sylvester et al., 1982; Westley et al., 1983). Cyanide and thiocyanate can also be metabolized by several minor routes, including the combination of cyanide with hydroxycobalamin (vitamin B_{12a}) to yield cyanocobalamin (vitamin B_{12}) (Boxer & Rickards, 1952) and the non-enzymatic combination of cyanide with cysteine, forming 2-iminothiazoline-4-carboxylic acid, which appears to be excreted without further change (Rieders, 1971).

The limiting factor in cyanide metabolism is the concentration of the sulfur-containing substrates in the body—primarily thiosulfate, but also cystine and cysteine. The rate of spontaneous detoxification of cyanide in humans is about 1 µg/kg body weight per minute (Schultz et al., 1982), which is considerably slower than in small rodents (Schubert & Brill, 1968) or dogs (Lawrence, 1947).

3.4 Elimination

Absorbed cyanide is principally excreted as thiocyanate in the urine; traces of free hydrogen cyanide may also be excreted unchanged from the lungs and through saliva, sweat or urine (Hartung, 1982). It is lost as carbon dioxide in expired air or as β-thiocyanoalanine in saliva and sweat (Friedberg & Schwarzkopf, 1969; Hartung, 1982; FAO/WHO, 1993).

4. EFFECTS ON LABORATORY ANIMALS AND IN VITRO TEST SYSTEMS

4.1 Acute exposure

Symptoms of cyanide toxicity can occur within seconds of inhalation of hydrogen cyanide or within minutes of ingestion of cyanide salts. Acute oral doses of cyanide cause cardiovascular, respiratory and neuroelectric alterations. Many studies have shown that the brain is the organ most sensitive to cyanide toxicity. Death from cyanide poisoning is believed to result from central nervous system depression, subsequent to inhibition of brain cytochrome oxidase activity (Way, 1984). A marked dose rate dependence has also been noted for oral exposure. While the single-dose gavage median lethal dose (LD_{50}) of potassium cyanide was 10 mg/kg body weight in Sherman rats, no mortality was observed when a dose of 250 mg/kg body weight was given in the diet for 90 days. The author ascribed this remarkable difference to the difference in dose rate and vehicle (bolus versus dietary exposure): at the low dose rate, the liver is capable of detoxifying cyanide before it reaches the general circulation (Hayes, 1967).

4.2 Short-term exposure

Forty-six male adult inbred Wistar rats were divided into four experimental groups and one control group and treated with potassium cyanide at 0, 0.3, 0.9, 3.0 or 9.0 mg/kg body weight per day in the drinking-water for 15 days (equivalent to cyanide doses of 0, 0.12, 0.36, 1.2 and 3.6 mg/kg body weight per day). The high dose group exhibited a 70% lower body weight gain compared with the control animals. Histological changes were observed in the kidney, liver and thyroid. Cytoplasmic vacuolation, considered to reflect hydropic degeneration of proximal tubular epithelial cells, was noted in animals treated at potassium cyanide doses of 3.0–9.0 mg/kg body weight per day and in hepatocytes of those animals treated at a potassium cyanide dose of 9.0 mg/kg body weight per day. A dose-dependent increase in the number of reabsorption vacuoles on follicular colloid in the thyroid gland was noted in animals from all experimental groups. No changes were observed in serum triiodothyronine (T_3), thyroxine (T_4), creatinine or urea levels; a decrease was observed in serum alanine aminotransferase activity at the two lowest exposure levels. Serum aspartate aminotransferase activity was elevated by 30% at the two lowest dose levels and by 21% at the potassium cyanide dose of 3.0 mg/kg body weight per day; it was decreased by 29% at the highest dose level (Sousa et al., 2002). These findings were not replicated in other well-conducted studies at higher doses and for longer periods.

4.3 Long-term exposure

Few data exist on the effects of chronic cyanide exposure.

In a subchronic study (13 weeks), groups of F344/N rats and B6C3F1 mice (10 of each sex) were administered sodium cyanide at 0, 3, 10, 30, 100 or 300 mg/l in drinking-water (NTP, 1993). The equivalent cyanide ion doses were 0, 0.2, 0.5, 1.4, 4.5 and 12.5 (in males) and 0, 0.2, 0.5, 1.7, 4.9 and 12.5 (in females) mg/kg body weight per day for rats and 0, 0.3, 1, 3, 9 and 26 mg/kg body weight per day for both sexes of mice. No deaths, clinically significant effects on body or organ weights or

histopathological or clinical pathology changes were noted in either rats or mice. In particular, no lesions were found in the brain or thyroid gland.

Effects on the reproductive organs were analysed in animals in the three highest dose groups. A slight (7–13%) but statistically significant reduction in sperm motility and in the weight of cauda epididymis was observed in all studied groups of male rats. In the males of the 300 mg/l group (12.5 mg/kg body weight per day as cyanide), statistically significant decreases in the weight of the left epididymis, left cauda epididymis, left testis and the number of spermatid heads per testis were observed. Sodium cyanide at doses of 4.9 and 12.5 mg/kg body weight per day as cyanide caused a statistically significant increase in the time spent by female rats in proestrus and diestrus relative to estrus and metestrus. In male mice, a statistically significant decrease in the left cauda epididymis weights was noted at 26 mg/kg body weight per day as cyanide, but no changes in sperm motility or spermatid head density were observed. No changes in the estrous cycle length in female mice were noted. The authors noted that the changes in male rats are consistent with a small but measurable adverse effect on reproduction. Although these changes are insufficient to decrease fertility in rats, the relative sensitivity of humans to such changes is considered to be greater than that of rats; therefore, a potential for adverse reproductive effects in humans exists (NTP, 1993).

In their evaluation of this study, ATSDR (1997) identified 12.5 mg/kg body weight per day as cyanide as the lowest-observed-adverse-effect level (LOAEL), based on all the effects on reproductive organs observed in the male rats, and 4.5 mg/kg body weight per day as cyanide as the no-observed-adverse-effect level (NOAEL); the findings in female rats were not considered adverse.

In a 2-year dietary study, weanling albino rats (10 per sex per group) were administered food fumigated with hydrogen cyanide (special jars were used in order to limit volatilization of hydrogen cyanide from the feed) (Howard & Hanzal, 1955). The average concentrations of cyanide in the feed were 0, 73 and 183 mg/kg diet, as estimated by USEPA (1993b) based on the authors' data for concentrations at the beginning and end of each food preparation and by assuming a first-order rate of loss for the intervening period and on the corresponding daily cyanide doses of 4.3 and 10.8 mg/kg body weight per day. No treatment-related effects on survival or growth rate, signs of toxicity or haematological or histopathological changes in the organs examined (heart, lung, liver, spleen, gastrointestinal tract, kidneys, adrenals, thyroid, testes, uterus, ovaries, cerebrum, cerebellum and brain) were observed in the treated male or female animals. A NOAEL of 10.8 mg/kg body weight per day as cyanide was established.

The effects of cyanide on thyroid function were investigated in groups of 10 male weanling rats fed either a semipurified casein-based diet supplemented with methionine or the same diet supplemented with vitamin B_{12}, potassium iodide and 3 times the amount of methionine for 11.5 months. Both dietary groups were divided into three: one served as the control, the second received potassium cyanide at 1500 mg/kg diet and the third received potassium thiocyanate at 2240 mg/kg diet. The rats given the potassium cyanide would have received cyanide doses of 30 mg/kg body weight per day. Cyanide, but not thiocyanate, caused a consistent reduction in weight gain in the animals fed the complete and restricted diets. Both cyanide and

thiocyanate caused decreased thyroid gland activity in young rats, particularly in those fed the restricted diet. Depression of both plasma T_4 and the T_4 secretion rate, suggestive of depressed thyroid function, was found at 4 months and to a lesser degree after 1 year. At autopsy, the animals were found to have enlarged thyroids, which suggested a mechanism of adaptation (Philbrick et al., 1979).

4.4 Reproductive and developmental toxicity, genotoxicity and carcinogenicity

Relatively few data are available on the reproductive and developmental toxicity of cyanides. No reproductive and developmental toxicity studies are available for hydrogen cyanide (IPCS, 2004), although the NTP (1993) data are suggestive of possible effects on male reproductive organs and sperm. Although somewhat limited, the weight of evidence of available data indicates that cyanide is not genotoxic and that it induces developmental effects only at doses or concentrations that are overtly toxic to the mothers. No data on cyanide carcinogenicity have been identified.

4.5 Mode of action

As a respiratory poison, hydrogen cyanide or cyanide ion has high acute toxicity due to its primary toxic effect of inhibiting cytochrome oxidase (by binding with haem iron), the terminal enzyme of the mitochondrial electron transport chain (Isom & Way, 1974). Tissue utilization of oxygen is impaired, and, with time, a state of histotoxic anoxia occurs (i.e. aerobic metabolism ceases). Cyanide can also inhibit approximately 40 enzymes, including a number of other important metalloenzymes containing, for the most part, iron, copper or molybdenum (e.g. alkaline phosphatase, carbonic anhydrase, catalase, peroxidase, ascorbic acid oxidase, xanthine oxidase and succinic dehydrogenase); these reactions may also contribute to cyanide toxicity (Rieders, 1971; Ardelt, Borowitz & Isom, 1989; USEPA, 1990; ATSDR, 1997).

Owing to its high dependency on oxidative metabolism and limited anaerobic capacity, the central nervous system is particularly vulnerable to cyanide intoxication (Way, 1984). The central nervous system symptoms observed in cyanide toxicity parallel those observed following accumulation of calcium in the brain. Potassium cyanide also alters calcium homeostasis in a neuronal model, the PC-12 cell, and cytosolic calcium ion overload has been implicated as an intracellular mediator of cellular injury during and after anoxic hypoxia (Maduh et al., 1988; Pettersen & Cohen, 1993).

Hydroperoxide generation with subsequent peroxidation of lipids and subsequent changes in structure and function of certain membranes have been suggested as a possible further mechanism of cyanide toxicity (Ardelt, Borowitz & Isom, 1989).

A number of experimental animal and human toxicological studies of cyanide and cyanogenic glycosides provide suggestive evidence that poor diet, low dietary protein, vitamin B_{12} and folic acid confound or exacerbate cyanide toxicity. Although the role of vitamin B_{12} deficiency has not been fully elaborated, it may be a protective factor against cyanide's neurotoxic effects. Experimentally, vitamin B_{12} restriction is hypothesized to sensitize the animal to cyanide toxicity (Philbrick et al., 1979). One study has demonstrated depletion of stores of protein-bound cobalamin in cyanide-treated animals, and it is theoretically possible that the formation of cyanocobalamin

could deplete the amount of vitamin B_{12} in its hydroxocobalamin form, leading to secondary folate deficiency effects (Blanc et al., 1985).

5. EFFECTS ON HUMANS

The best-characterized data regarding cyanide toxicity in humans relate to inhalation exposure. The dose–effect curve of the acute effects in humans is steep. Whereas slight effects occur at exposure to hydrogen cyanide levels of 20–40 mg/m^3, 50–60 mg/m^3 can be tolerated without immediate or late effects for 20 min to 1 h, 120–150 mg/m^3 is dangerous to life and may lead to death after 0.5–1 h, 150 mg/m^3 is likely to be fatal within 30 min, 200 mg/m^3 is likely to be fatal after 10 min and 300 mg/m^3 is immediately fatal. It should be emphasized that this represents crude average exposure estimates, based on various studies (DECOS, 2002).

Acute exposure to cyanide has occurred most frequently by the oral route from attempted suicides and homicides by ingestion of sodium or potassium cyanide or by accidental poisonings due to ingestion of apricot kernels or almonds from wild (not domesticated) trees (Rieders, 1971; NIOSH, 1976; USEPA, 1990; ATSDR, 1991; Alarie, 2002). Based on analyses of cyanide contents in tissues and in gastrointestinal tract contents among fatal (oral) poisoning cases (and comparative kinetics with dogs), Gettler & Baine (1938) estimated that the lowest fatal absorbed dose in four suicide cases was 0.54 mg/kg body weight as hydrogen cyanide, whereas an average fatal dose was 1.4 mg/kg body weight as hydrogen cyanide. In most poisoning cases, a large part of the ingested cyanide remained in the gastrointestinal tract at the time of death (thus, using the dose ingested as an indicator of the lethality of cyanide is misleading). The doses were calculated by Gettler & Baine (1938) from the total amount of hydrocyanic acid in the body at the time of death and the amounts found in the digestive tract, although the period elapsing between death and the investigation is uncertain.

There is considerable uncertainty regarding the actual doses in most case-study reports, and some individuals ingesting 1–3 g of cyanide salts (about 9–27 mg/kg body weight as sodium cyanide for a 60 kg adult) have survived (ATSDR, 1991). Cleven & van Bruggen (2000), in investigating a cyanide spill, stated that low oral exposures to cyanide (2.9–4.7 mg/day) are not fatal to humans who have an efficient detoxification system whereby cyanide is converted to thiocyanate, which is non-toxic at low levels, through the rhodanese and thiosulfate enzyme systems. The half-life for the conversion of cyanide to thiocyanate from a non-lethal dose in humans is between 20 min and 1 h.

The effects of acute cyanide exposure are dominated by central nervous system and cardiovascular disturbances (ATSDR, 1991). Typical signs of acute cyanide poisoning include tachypnoea, headache, vertigo, lack of motor coordination, weak pulse, cardiac arrhythmias, vomiting, stupor, convulsions and coma (Ballantyne, 1983; Way, 1984; Johnson & Mellors, 1988). Pathological findings may include tracheal congestion with haemorrhage, cerebral and pulmonary oedema, gastric erosions and petechiae of the brain meninges and pericardium (Way, 1984). Sequelae of severe acute cyanide exposure may also include Parkinson-like syndromes and cardiovascular signs of delayed post-hypoxic myocardial lesions, as well as neuropsychiatric manifestations similar to those seen with post-hypoxic post-carbon

monoxide encephalopathy (Uitti et al., 1985; Carella et al., 1988; Kadushin et al., 1988; ATSDR, 1991).

6. PRACTICAL ASPECTS

6.1 Analytical methods and analytical achievability

Cyanide can be determined in water by both titrimetric and photometric techniques, with a detection limit of 2 µg/l (ISO, 1984).

6.2 Treatment and control methods and performance

Activated carbon can be used to adsorb cyanide. The amount adsorbed was reported to be 2–3 mg/g, as determined by adsorption isotherm tests. The addition of copper increased the capacity to 25 mg/g. Copper increases the efficiency of the catalytic oxidation of cyanide by the carbon, and the copper cyanides formed are more strongly adsorbed (Huff & Bigger, 1978).

Granular activated carbon (GAC) was found to adsorb potassium cyanide; cyanide at 1 mg/l was prepared in ultrapure water and added to varying amounts of GAC (0–800 mg/l). Equilibrium was obtained (90–95% uptake) after 35 h of contact. Initial rates varied according to GAC particle size (9 µg/h >1.4 mm, 22 µg/h <0.5 mm). The amount of cyanide sorbed was found to vary directly with the initial concentration of cyanide, providing there was an excess of GAC. A GAC dose of 200 mg/l mixed with potassium cyanide at 1 mg/l (pH 9) adsorbed approximately 32% of the initial concentration after 20 h, increasing to 45% after 33.5 h of contact. The presence of aluminium (10 mg/l), iron (10 mg/l), calcium (100 mg/l) and magnesium ions (100 mg/l) reduced adsorption by 33–50% over a 2 h contact period (Guo et al., 1993).

Approximately 10% removal from a cyanide solution at 20 mg/l was obtained by treatment with coconut-based activated carbon at 1 g/l. The adsorption capacity was greatly enhanced by pretreatment of the carbon with silver or copper salts, silver nitrate giving the best results (Williams & Petersen, 1997).

The adsorption capacity onto unmodified activated carbon from a 40 mg/l cyanide solution was reported to be 7 mg/g carbon. In column tests, rapid breakthrough of cyanide occurred (Adhoum & Monser, 2002). In a similar study, the capacity was reported to be 6.6 mg/g from a 40 mg/l solution (Monser & Adhoum, 2002). In small-scale column tests with an empty bed contact time of 8 min, breakthrough of cyanide started after treatment of approximately 50 bed volumes, and complete breakthrough occurred after approximately 100 bed volumes.

The removal of cyanide by activated carbon is pH dependent. At pH 10 after 8 h, 50% removal was obtained from a 265 mg/l cyanide solution treated with carbon at 1.5 g/l. At pH 7, approximately 90% removal was obtained under the same conditions. A wood-based carbon was found to be superior to peat-, coal- and coconut-based carbons (Adams, 1994).

Ozone reacts with the cyanide ion extremely rapidly in alkaline media; the resulting cyanate ion is much more slowly oxidized by ozone. The oxidation reaction is

affected by pH, temperature, ozone dose and cyanide concentration. Complex cyanides of copper and other metals are less amenable to ozone decomposition. Ultraviolet (UV) irradiation in conjunction with ozone did not improve removal rates. Overall, ozonation is more suited to treatment of large concentrations of cyanide (>20 mg/l), such as may be found in wastewaters (Versinina et al., 1990).

Cyanide is slowly degraded by hydrogen peroxide. A 100 mg/l solution treated with hydrogen peroxide at 3000 mg/l was 80% degraded after 4 h and 90% degraded after 24 h. In the presence of UV irradiation from a 25 W mercury lamp and hydrogen peroxide at 1200 mg/l, complete degradation of a 100 mg/l solution was obtained in 40 min (Sarla et al., 2004).

A comparison was made of the effectiveness of ozone/hydrogen peroxide, UV/hydrogen peroxide, UV/ozone and UV/ozone/hydrogen peroxide to treat plating waste containing cyanide at 157 mg/l with pH adjusted to 11 (Kim, Qureshi & Min, 2003). A 1500 W high-pressure mercury lamp, ozone at 6.4 mg/l per minute and hydrogen peroxide at 0.68–2.72 g/l were used. All of these systems were effective, with an initially high rate of cyanide destruction (half-life approximately 15 min). However, only UV/ozone/hydrogen peroxide reduced the cyanide concentration to below 1 mg/l.

Laboratory experiments were conducted on the oxidation of cyanide spiked at 100, 250 and 500 µg/l into river water (Montiel & Ouvrard, 1985). Chlorine, chlorine dioxide and ozone were compared. Chlorine was dosed at four levels: to form monochloramine (NH_2Cl), to reach breakpoint (BP) and at BP plus 1 and 2 mg/l. The results are summarized in Table 4.

Table 4: Comparison of cyanide removal from river water by chlorine, chlorine dioxide and ozone

			CN concentration after treatment (µg/l) at following initial CN concentrations (µg/l):		
Oxidant	Dose (mg/l)	Contact time (h)	100	250	500
Chlorine	NH_2Cl	2	95	240	475
	BP	2	65	165	364
	BP + 1	2	<5	<5	<5
	BP + 2	2	<5	<5	7
Chlorine dioxide	0.5	2	60	173	330
	1	2	60	150	330
	2	2	48	115	320
Ozone	1	0.5	25	18	<5
	2	0.5	12	15	16
	3	0.5	13	11	12

When chlorine is applied to solutions containing free cyanide, cyanogen chloride is formed practically instantaneously. To ensure that cyanogen chloride is converted to cyanate, the pH has to be adjusted to above 8 (White, 1998).

Chlorination is unlikely to be a practical process for completely oxidizing cyanide to form nitrogen, as a two-stage treatment is necessary. In the first stage, chlorination is

carried out above pH 11.5 to obtain rapid oxidation to cyanate (and avoid formation of cyanogen chloride). The pH then has to be reduced to 5–8 in order to allow oxidation of cyanate to nitrogen gas (Roques, 1996). Such a process has been suggested, although it is probably more applicable to wastewater treatment: in the first stage, cyanide is oxidized to cyanate in the presence of an excess of sodium hypochlorite at pH 11; in the second stage, cyanate is converted to nitrogen and other stable inert products by sodium hypochlorite, at a reduced pH of 9 (Teo & Tan, 1987). Chlorine dioxide will oxidize cyanide, but only to cyanate under practical conditions (Roques, 1996).

7. CONCLUSION

7.1 Risk assessment

Cyanide is highly acutely toxic. It is detoxified in the liver by first-pass metabolism following oral exposure. As a consequence, exposure to a dose spread over a longer period, for example through a day, will result in lower toxicity, or higher tolerance, than the same dose given in a single bolus dose. Exposure to high doses can give rise to thyroid toxicity as a secondary effect of exposure due to the inhibition of iodine uptake from the thiocyanate generated through the detoxifying action of rhodanese.

Gettler & Baine (1938) estimated that the lowest fatal absorbed dose from four suicide case-studies was 0.54 mg/kg body weight as hydrogen cyanide and the average absorbed fatal dose was 1.4 mg/kg body weight as hydrogen cyanide. Some individuals ingesting 1–3 g of cyanide salts (about 9–27 mg/kg body weight as sodium cyanide for a 60 kg adult) have survived (ATSDR, 1991). Daily oral doses of 2.9–4.7 mg cyanide are generally considered to be non-injurious to humans, owing to the efficient detoxification of cyanide to thiocyanate (Cleven & van Bruggen, 2000). However, the data are uncertain, in view of the difficulty in assessing the actual absorbed dose in humans following acute fatal intoxication and the lack of well-conducted studies on sublethal toxicity.

In its evaluation of 13-week studies conducted by NTP (1993) in which F344/N rats and B6C3F1 mice were administered sodium cyanide at 0, 3, 10, 30, 100 or 300 mg/l in drinking-water—equivalent to cyanide ion doses of 0, 0.2, 0.5, 1.4, 4.5 and 12.5 (in males) and 0, 0.2, 0.5, 1.7, 4.9 and 12.5 (in females) mg/kg body weight per day for rats and 0, 0.3, 1, 3, 9 and 26 mg/kg body weight per day for mice—ATSDR (1997) identified a cyanide dose of 12.5 mg/kg body weight per day as the LOAEL, based on all the effects on reproductive organs observed in the male rats, and a cyanide dose of 4.5 mg/kg body weight per day as the NOAEL; the findings in female rats were not considered adverse.

7.2 Selection of health-based value for short-term exposure

Cyanide sometimes reaches drinking-water sources, particularly surface waters, as a consequence of accidental releases that can be very large. Under these circumstances, there is a need to consider whether abstraction of the water should be stopped while the highest concentrations in a plume of pollution pass the intake to the drinking-water treatment works. Stopping abstraction may cause significant problems in supplying consumers with drinking-water under circumstances where stored water is

limited. A decision will be required about whether it is possible to cease abstraction without also stopping the supply of drinking-water. While there may be additional actions that will be required, such as advising consumers not to drink the water, the loss of water for maintaining hygiene is also potentially serious for public health. There is, therefore, a need for guidance regarding concentrations that would not be of concern for public health following short-term exposure to cyanide. However, because cyanide is unlikely to occur in drinking-water at concentrations of toxicological concern, it is considered unnecessary to derive a formal guideline value for short-term exposure to cyanide.

The data on acute exposure to cyanide are unsuitable for use in deriving a health-based value for short-term exposure because of the high uncertainty surrounding the data. The NTP (1993) 13-week study is considered the most appropriate well-conducted study available. The NOAEL in this study was 4.5 mg/kg body weight as cyanide, and the exposure was through drinking-water. An uncertainty factor of 100 (×10 for intraspecies variation and ×10 for interspecies extrapolation) was applied to derive a tolerable daily intake (TDI) of 0.045 mg/kg body weight as cyanide. Because this health-based value is intended for short-term use and exposure would not exceed 5 days, it is considered to be acceptable to allocate 40% of the TDI to drinking-water to allow for exposure to cyanogenic glycosides in food. Therefore, assuming a 60 kg adult drinking 2 litres of water with an allocation of 40% of the TDI to drinking-water, a health-based value of 0.5 mg/l (rounded value) for short-term exposure can be calculated. This value is well below the level that is normally considered to be injurious to health for humans. Cyanide is rapidly detoxified, and exposure spread throughout the day will further reduce the potential for effects. It would be suitable for use for a limited period of up to 5 days, which is the longest period likely to be required under the circumstances of such an emergency. However, it is probable that, in most circumstances, this value will be highly conservative for short-term exposure.

It should be noted that the lowest reported odour threshold for cyanide in drinking-water is 0.17 mg/l, which is below the short-term health-based value. It is, therefore, possible that a small number of individuals will detect cyanide by odour at concentrations below the health-based value.

The health-based value relates to total cyanide concentration at the tap, including cyanide from cyanogen chloride in drinking-water as a by-product of disinfection with chlorine. Cyanogen chloride rapidly breaks down to cyanide in the distribution system or when ingested. As the low levels of cyanide normally found in drinking-water are mostly a consequence of the presence of cyanogen chloride, it is not considered necessary to develop a guideline value for long-term exposure to cyanide (see background document on cyanogen chloride: WHO, 2009).

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