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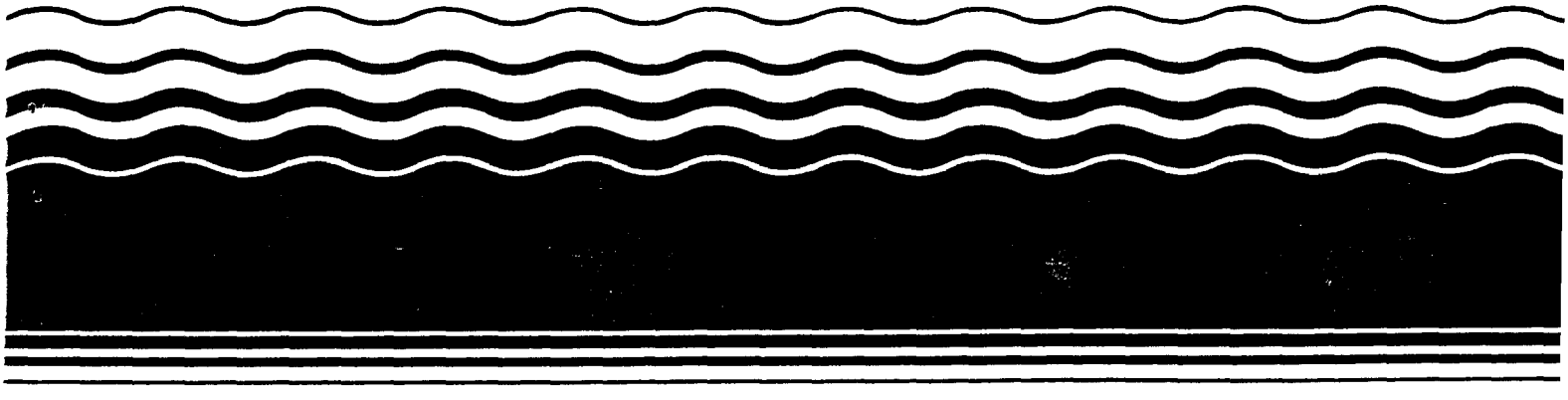
HEALTH EFFECTS ASSESSMENT FOR SODIUM CYANIDE



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U.S. Environmental Protection Agency
Office of Research and Development
Office of Health and Environmental Assessment
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Cincinnati, OH 45268

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Office of Emergency and Remedial Response
Office of Solid Waste and Emergency Response
Washington, DC 20460

DISCLAIMER

This report has been funded wholly or in part by the United States Environmental Protection Agency under Contract No. 68-03-3112 to Syracuse Research Corporation. It has been subject to the Agency's peer and administrative review, and it has been approved for publication as an EPA document. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

PREFACE

This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with sodium cyanide. All estimates of acceptable intakes and carcinogenic potency presented in this document should be considered as preliminary and reflect limited resources allocated to this project. Pertinent toxicologic and environmental data were located through on-line literature searches of the Chemical Abstracts, TOXLINE, CANCERLINE and the CHEMFATE/DATALOG data bases. The basic literature searched supporting this document is current up to September, 1984. Secondary sources of information have also been relied upon in the preparation of this report and represent large-scale health assessment efforts that entail extensive peer and Agency review. The following Office of Health and Environmental Assessment (OHEA) sources have been extensively utilized:

U.S. EPA. 1980a. Ambient Water Quality Criteria for Cyanides, with Errata for Ambient Water Quality Criteria Documents dated June 9, 1981 (updated February 23, 1982). Prepared by the Environmental Criteria and Assessment Office, Cincinnati, OH, OHEA for the Office of Water Regulations and Standards, Criteria and Standards Division, Washington, DC. EPA 440/5-80-035. NTIS PB 81-117483.

U.S. EPA. 1985. Drinking Water Criteria Document for Cyanide. Prepared by the Environmental Criteria and Assessment Office, Cincinnati, OH, OHEA for the Office of Drinking Water, Washington, DC. Final draft.

The intent in these assessments is to suggest acceptable exposure levels whenever sufficient data were available. Values were not derived or larger uncertainty factors were employed when the variable data were limited in scope tending to generate conservative (i.e., protective) estimates. Nevertheless, the interim values presented reflect the relative degree of hazard associated with exposure or risk to the chemical(s) addressed.

Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, the AIS or acceptable intake subchronic, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval (i.e., for an interval that does not constitute a significant portion of the lifespan). This type of exposure estimate has not been extensively used or rigorously defined, as previous risk assessment efforts have been primarily directed towards exposures from toxicants in ambient air or water where lifetime exposure is assumed. Animal data used for AIS estimates generally include exposures with durations of 30-90 days. Subchronic human data are rarely available. Reported exposures are usually from chronic occupational exposure situations or from reports of acute accidental exposure.

The AIC, acceptable intake chronic, is similar in concept to the ADI (acceptable daily intake). It is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan [see U.S. EPA (1980b) for a discussion of this concept]. The AIC is route specific and estimates acceptable exposure for a given route with the implicit assumption that exposure by other routes is insignificant.

Composite scores (CSs) for noncarcinogens have also been calculated where data permitted. These values are used for ranking reportable quantities; the methodology for their development is explained in U.S. EPA (1983).

For compounds for which there is sufficient evidence of carcinogenicity, AIS and AIC values are not derived. For a discussion of risk assessment methodology for carcinogens refer to U.S. EPA (1980b). Since cancer is a process that is not characterized by a threshold, any exposure contributes an increment of risk. Consequently, derivation of AIS and AIC values would be inappropriate. For carcinogens, q_1^*s have been computed based on oral and inhalation data if available.

ABSTRACT

In order to place the risk assessment evaluation in proper context, refer to the preface of this document. The preface outlines limitations applicable to all documents of this series as well as the appropriate interpretation and use of the quantitative estimates presented.

Adequate data are available for experimental animals orally exposed to cyanide. The various studies agree well in terms of suggesting a NOEL. U.S. EPA (1985) has calculated a NOEL of 10.8 mg CN^-/kg for female rats exposed to cyanide in their food as a basis for estimating acceptable exposure levels (Howard and Hanzal, 1955). By analogy, an AIC for NaCN of 2.8 mg/day for a 70 kg human is calculated. A CS of 11.4, based on CNS lesions in dogs treated by capsule with NaCN was calculated.

Data for effects following inhalation exposure to CN^- are extremely limited. An AIC has been estimated based on the TLV of 5 mg/m^3 but should not be adopted because of presumed greater toxicity due to exposure by the inhalation route.

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LIST OF ABBREVIATIONS

ADI	Acceptable daily intake
AIC	Acceptable intake chronic
AIS	Acceptable intake subchronic
BCF	Bioconcentration factor
bw	Body weight
CAS	Chemical Abstract Service
CNS	Central nervous system
CS	Composite score
GI	Gastrointestinal
K_{ow}	Octanol/water partition coefficient
LD_{50}	Dose lethal to 50% of recipients
LOAEL	Lowest-observed-adverse-effect level
MED	Minimum effective dose
RNA	Ribonucleic acid
RV_d	Dose-rating value
RV_e	Effect-rating value
TLV	Threshold limit value
TWA	Time-weighted average
UF	Uncertainty factor

1. ENVIRONMENTAL CHEMISTRY AND FATE

The relevant physical and chemical properties for sodium cyanide are given below.

Chemical class:	inorganic cyanide
Molecular weight:	49.01
Vapor pressure:	0.76 mm Hg at 800°C (Towill et al., 1978)
Water solubility:	48 g/100 mℓ at 10°C (Weast, 1980)
Log octanol/water partition coefficient:	0.44 (estimated)
BCF:	0.27 (estimated)

The value for the K_{ow} has been estimated by the method of Leo et al. (1971) from the value given by Hansch and Leo (1979). The value of 0.27 for the BCF has been estimated from the log K_{ow} value given above and the equation of Veith et al. (1979).

The atmospheric fate of sodium cyanide has not been comprehensively studied. The most likely chemical reaction for sodium cyanide in the atmosphere is heterogenous reaction with OH• radicals. Considering the half-life of the homogenous hydrogen cyanide reaction with OH• radicals (Graedel, 1978), it appears unlikely that sodium cyanide will have any significant chemical loss mechanism in the troposphere. The primary removal process for atmospheric sodium cyanide appears to be physical. Both dry deposition and wet deposition may dominate the fate of sodium cyanide in the atmosphere, although, considering the aqueous solubility of sodium cyanide, the latter process appears to be more important than the former process.

Sodium cyanide may be lost from aquatic media primarily through the volatilization process (Callahan et al., 1979). Sodium cyanide at low concentrations may undergo some biodegradation, but biodegradation is likely to be far less significant in determining the fate of sodium cyanide in aquatic media (Callahan et al., 1979). Similarly, because of its low tendency to adsorb onto sediments, sorption may not be an important process for sodium cyanide in aquatic media (Callahan et al., 1979).

The fate of sodium cyanide in soil is inadequately studied. To draw an analogy from its expected fate in water, it is likely that the fate of sodium cyanide in soil may be pH dependent. In acidic soils, the loss of hydrogen cyanide through volatilization may be the predominant mechanism from soil surfaces. In subsurface soil, sodium cyanide present in small concentrations (below the toxic levels for microorganisms) may undergo some microbial degradation (Callahan et al., 1979), and a part may leach through the soil because of its high water solubility and low soil sorption characteristics. In basic soils, the mobility of sodium is expected to be greatly restricted.

The simple metal cyanides, such as sodium cyanide, are not expected to bioaccumulate in aquatic organisms (U.S. EPA, 1980a). As can be seen from the selected physical and chemical properties for sodium cyanide, the estimated value of 0.27 for the BCF for sodium cyanide is in conformity with the U.S. EPA (1980a) prediction.

2. ABSORPTION FACTORS IN HUMANS AND EXPERIMENTAL ANIMALS

2.1. ORAL

Cyanide is readily absorbed by the GI tract. Yamamoto et al. (1982) exposed rats orally by gavage to either 7 or 21 mg NaCN/kg bw. Following treatment and subsequent death (minutes later), levels of cyanide in the blood were 5.01±1.61 and 4.79±2.04 µg/mℓ for the low-dose and high-dose, respectively. This indicates that sodium cyanide is readily absorbed by the GI tract. Gettler and Baine (1938) exposed dogs to potassium cyanide equivalent to 1.57, 4.42 or 8.42 mg HCN/kg bw by gavage. Upon death (155, 21 and 8 minutes post-treatment), the amount of hydrogen cyanide remaining in the GI tract was measured and subtracted from the amount administered; this was considered to be equivalent to the amount absorbed, and was 72, 24 and 16.6% for dogs receiving 1.57, 4.42 and 8.42 mg/kg, respectively.

2.2. INHALATION

Pertinent data regarding the absorption of sodium cyanide by inhalation could not be located in the available literature.

3. TOXICITY IN HUMANS AND EXPERIMENTAL ANIMALS

3.1. SUBCHRONIC

3.1.1. Oral. In evaluating studies regarding the oral toxicity of cyanide, factors affecting the rate of absorption may be as important as the dose administered (U.S. EPA, 1985). Cyanide is metabolized rapidly by the liver to thiocyanate, an enzymatic rate-saturable reaction. Factors that enhance absorption may result in severe toxic manifestations from a dose that ordinarily would not cause toxicity, because the ability of the liver to metabolize cyanide as a first pass phenomenon had been exceeded. The volume of the intestinal contents and rate of peristalsis are factors that affect the rate of GI absorption. It may also be expected that toxicity would be more likely if cyanides are given as a bolus rather than in smaller aliquots throughout the day.

Another important consideration regarding dietary studies is the propensity for cyanide to volatilize from treated foodstuffs, resulting in a lack of toxic manifestations at potentially dangerous levels (U.S. EPA, 1985). Also, animals (and presumeably humans) can successfully withstand higher doses of cyanide when administered in the diet rather than by inhalation, because of the first pass conversion of orally administered cyanide to thiocyanate (detoxification) in the liver when it is orally administered.

Because of the expected similarities in the toxicity of sodium cyanide and other cyanides, studies with other cyanides are included in the toxicity sections.

Data regarding the subchronic toxicity of orally administered cyanide are summarized in Table 3-1. Palmer and Olson (1979) reported significantly higher liver weights in adult rats exposed to 200 mg KCN/ℓ drinking water, but no effect on liver weight when potassium cyanide was administered as 200

TABLE 3-1

Subchronic Toxicity of Orally Administered Cyanide

Species/ Weight or Age	Number/Sex	Dose of Compound	Dose[a] as CN^-	Period of Exposure	Effects	Reference
Rat/70 g	7M/group	0 and 200 mg KCN/ℓ drinking water	0 and 80 mg/ℓ (8 mg/kg bw/day)	21 days	Treated animals: significantly increased ($p<0.05$) liver weights (15.8 g), compared with controls (13.5 g). No effect on body weight.	Palmer and Olson, 1979
	7M/group	0 and 200 mg KCN/kg diet	0 and 80 mg/kg diet (4 mg/kg bw/day)	21 days	Treated animals: no increase in liver weights (13.7 g), compared with controls (13.5 g). No effect on body weight.	
Rat/adult	NR	0, 10 mg KCN/kg bw/day in diet	0, 4 mg/kg bw/day	25 days	No mortality.	Hayes, 1967
	NR	0-250 mg KCN/kg bw/day in diet	0-100 mg/kg bw/day	90 days	No mortality; this dose was 25 times the acute oral LD_{50} for rats. Animals tolerated CN^- better when it was mixed in feed.	
Rat/weanling	8M&F/group	0, 1875 mg KCN/kg diet	0, 750 mg/kg diet (37.5 mg/kg bw/day)	56 days	No effect on body weight, ratio of liver and kidney weight to body weight, food consumption, or protein efficiency ratio.	Tewe and Maner, 1982
African giant rat/ weanling/~90 g	6M and 2F/ group	0, 2500 mg KCN/kg diet	0, 1000 mg/kg diet (36 mg/kg bw/day)[b]	84 days	Treated animals: slight reduction in food consumption and weight gain, compared with controls. No histopathological changes in spleen, liver, kidney or thymus.	Tewe, 1982
Pig/weanling	1M and 1F	0, 1875 mg KCN/kg diet	0, 750 mg/kg diet(~30 mg/kg bw/day)[b]	56 days	Treated animals: small but significant reduction in food consumption ($p<0.05$), compared with controls. No effect on body weight, food efficiency ratio, protein efficiency ratio, or ratio of various organ weights (spleen, liver, kidney, heart, thyroid) to body weight. No histopathological changes.	Tewe and Maner, 1980

TABLE 3-1 (cont.)

Species/ Weight or Age	Number/Sex	Dose of Compound	Dose[a] as CN^-	Period of Exposure	Effects	Reference
Dog/7.6 kg	1 control, 3 treated (sex NR)	0, 500 ppm NaCN in diet	3 mg/kg bw/day	30-32 days	No effects on food consumption, body weight gain, hematology, gross or microscopic pathology	American Cyanamid Co., 1959
Dog/NR	1 control, 3 treated (sex NR)	NaCN at 0, 0.5, 1.0 up to 2x2.0 mg/kg bw/day by capsule	0, 0.27, 0.53 up to 2x1.1 mg/kg bw/day (average 3 mg/kg bw/day in high group)	15 months	Toxicity observed in high group: acute toxicity immediately after dosing, full recovery in <0.5 hours. All treated dogs: degeneration of ganglion and Purkinje cells of CNS	Hertting et al., 1960

[a]Values in parentheses were calculated as follows:

1) For CN^- in the diet, the dose in mg/kg/diet is multiplied by the fraction of body weight consumed by a rat/day (0.05).

2) For CN^- in the water, the dose in mg/ℓ is multiplied by the average amount of H_2O consumed by a rat/day (0.035 ℓ/day), and divided by the weight of the rat (if unknown, it is assumed to be 0.35 kg), e.g., rats assumed to drink water equivalent to 10% of their body weight/day.

[b]Calculated by U.S. EPA (1985) from body weight and food consumption data provided by investigators.

mg/kg diet. Tewe (1982) and Tewe and Maner (1980, 1982) treated weanling pigs and rats with potassium cyanide, and observed only a slight reduction in food consumption with no other effects. Hayes (1967) reported that adult rats could tolerate 25 times the LD_{50} dose of potassium cyanide when it was administered in the diet. When given in the diet, NaCN at 3 mg CN^-/kg bw/day had no effect in dogs (American Cyanamid Co., 1959). The same dosage given by capsule led to signs of acute toxicity in dogs from which recovery was complete within 0.5 hours (Hertting et al., 1960). When given by capsule to dogs for 15 months, 6 mg NaCN/kg bw/day was sufficient to cause cellular degeneration in the CNS. Although animals in this study were exposed to a range of potassium cyanide concentrations, these investigators only reported mortality.

3.1.2. Inhalation. Only one animal study regarding the subchronic toxicity of cyanide was located in the available literature. Hugod (1981) exposed rabbits (22/group) to either 0 or 0.55 mg/m³ hydrogen cyanide in air. After 28 days, the treated animals were not different from controls in myocardial ultrastructure.

In humans, exposure to cyanide by inhalation and dermal routes has been reported in the metal industry. Sandberg (1967) reported on a goldsmith apprentice who polished gold 5-10 times/day for 4 years. The polishing solution he used was prepared by adding 15 g of potassium cyanide to water, bringing it to a boil, then adding hydrogen peroxide; this process liberated hydrogen cyanide gas and splattered the skin. Symptoms of toxicity in this man included headache, listlessness, numbness and partial paralysis of his left arm and leg, and partial loss of vision in his left eye. Other cases in which similar symptoms have been reported are summarized by NIOSH (1976).

There have also been reports of goiter associated with occupational exposure to cyanide (Hardy et al., 1950). In addition, many case-control studies regarding exposure to cyanide have been reported. Several of these are summarized in Table 3-2.

3.2 CHRONIC

3.2.1. Oral. Data pertaining to the chronic toxicity of orally administered cyanides are summarized in Table 3-3. Howard and Hanzal (1955) exposed rats to 0, 76, or 190 mg HCN/kg diet (equivalent to 0, 73, 183 mg CN^{-1}/kg) for 104 weeks. Animals treated at any level had no signs of toxicity; no histopathological changes in the heart, lungs, liver, spleen, stomach, intestines, kidney, adrenals, thyroid, reproductive organs, cerebellum or cerebrum; and no differences in growth rate compared with controls. The only effects of treatment were elevated levels of CN^{-1} in the erythrocytes and elevated thiocyanate in the blood, liver and kidneys.

Philbrick et al. (1979) treated groups of 10 male weanling rats with 0 or 1500 mg KCN/kg diet and reported signs of primary myelin degeneration in the spinal cord after 11.5 months treatment. Rats maintained on methionine and vitamin B_{12} deficient diet appeared to be affected more severely.

With respect to humans, the high incidence of amblyopias, thyroid disorders and neuropathies seen in tropical regions of Africa has been associated with chronic ingestion of cassava, a dietary staple containing a cyanogenic glycoside that releases hydrogen cyanide when metabolized in vivo (Monekosso and Wilson, 1966; Osuntokun, 1968, 1972; Osuntokun et al., 1969, 1970; MacKenzie and Phillips, 1968; Makene and Wilson, 1972; Ermans et al., 1972; Delange and Ermans, 1971). Sufficient data to quantify dose and effects were not available in these studies.

TABLE 3-2

Representative Control Studies of Occupational Exposure to Cyanide by Inhalation or Dermal Routes

Study Population	Control Population	Period of Exposure	Level of Exposure	Effects	Reference
36 male electroplaters from 3 factories, >30 years of age, all nonsmokers	20 males of comparable age and socioeconomic status: nonsmokers not exposed to cyanide	5-15 years	mean concentration in the breathing zone: 7.1, 8.9 and 11.5 mg/m^3 for the three factories	Exposed men: headache (29); weakness (28); changes in smell and taste (28); giddiness (20); throat irritation (16); vomiting (16); difficulty breathing (16); precordial pain (7); difficulty focusing eyes (3); psychosis (2). Nonexposed workers had much lower incidences of these symptoms. Exposed workers also had significantly higher ($p<0.001$) hemoglobin to lymphocyte counts, and significantly higher (<0.001) uptake of ^{131}I by the thyroid.	El Ghawabi et al., 1975
13 HCN fumigators who had suffered acute symptoms of HCN poisoning with loss of consciousness	4 HCN fumigators who had not reported symptoms of acute HCN poisoning	1-27 years	NR	13 symptomatic men: high incidence of nervous disorders; precordial pain (9); EKG abnormalities (11); hypertropic gastritis (11). 4 controls: no stomach or intestinal disorders.	Carmelo, 1955
31 men, 12 women in Romanian metal galvanizing operation	NR	0.25-16 years (mean: 5.4 years)	average exposure over 5 years: 0.26 mg/m^3	Significantly reduced activity of cytochrome oxidase and other redox enzymes.	Dinca et al., 1972

NR = Not reported

TABLE 3-3

Chronic Toxicity of Orally Administered Cyanide

Species/ Starting Weight	Number	Dose of Compound	Dose as CN^-	Period of Exposure	Effects	Reference
Rat/57 g	10F and 10M/group	0, 76, 190 mg HCN/kg diet	0, 73, 183 mg/kg diet	104 weeks	No effects with regard to body weights or histopathological changes of many organs.	Howard and Hanzal, 1955
Weanling rat/43 g	10M/group	0, 1500 mg diet	0, 600 mg/kg diet (0.30 mg/kg bw/day)*	11.5 months	Treated rats: primary myelin degeneraton and vacuoles in spinal cord. Decreased plasma thyroxin levels at 4 months with recovery by 11 months.	Philbrick et al., 1979

*Assuming rats eat food equivalent to 5% of their body weight/day.

3.2.2. Inhalation. Animal studies pertaining to the chronic toxicity of inhaled cyanide could not be located in the available literature. Exposure to cyanide in tobacco smoke, however, has been associated with tobacco amblyopia, Leber's hereditary optic atrophy, retrobulbar neuritis and optic atrophy (Wokes, 1958; Pettigrew and Fell, 1972, 1973; Wilson and Matthews, 1966; Foulds et al., 1968; Wilson, 1983). These disorders involve defective cyanide metabolism (the conversion of cyanide to thiocyanate by rhodanase is defective) and vitamin B_{12} deficiency.

3.3. TERATOGENICITY AND OTHER REPRODUCTIVE EFFECTS

3.3.1. Oral. The reproductive performance of rats fed 500 mg CN^-/kg diet throughout gestation and lactation was unaffected (Tewe and Maner, 1981a). Furthermore, litter size, weight of the pups at birth, and food consumption and growth rate of pups after birth were not significantly different from controls.

In contrast, the fetuses of pigs (9/level) fed 276.6 or 520.7 mg CN^-/kg diet throughout gestation to lactation had reduced organ to body weight ratios for thyroid, heart and spleen when compared with those born to pigs fed 30.6 mg CN^-/kg diet. Sows treated at all levels had hyperplasia of the glomeruli (Tewe and Maner, 1981b). Teratogenic affects per se were not reported in either of these studies.

3.3.2. Inhalation. Pertinent data regarding the teratogenicity of inhaled cyanide could not be located in the available literature.

3.4. TOXICANT INTERACTIONS

Since cyanide is a known inhibitor of cytochrome oxidase, compounds such as sulfide or azide, which also inhibit cytochrome oxidase, may synergize with cyanide (Nicholls, 1975; Smith et al., 1977). Vitamin C may also enhance the toxicity of cyanide. Basu (1983) treated a group of guinea pigs

first with vitamin C, then with potassium cyanide, and another group only with potassium cyanide. Vitamin C-treated animals had a 100% incidence of severe tremors, ataxia, muscle twitches, paralysis and convulsion. Animals exposed only to potassium cyanide had a 38% incidence of these symptoms. It was hypothesized that vitamin C may tie up cysteine, a sulfur donor potentially involved in the conversion of cyanide to thiocyanate, its less harmful metabolite.

Compounds that generate methemoglobin (sodium nitrate, amyl nitrate, hydroxylamine or methylene blue) antagonize the toxic effects caused by cyanide, since methemoglobin competes with cytochrome oxidase for cyanide (Smith and Olson, 1973; Way, 1981). Cobalt-containing compounds also antagonize the toxicity of cyanide, since cobalt has an affinity for cyanide (Mushett et al., 1952; Friedberg and Schwarzkopf, 1969; Davison, 1969).

4. CARCINOGENICITY

4.1. HUMAN DATA

4.1.1. Oral. Pertinent data regarding the carcinogenicity of orally ingested cyanide (hydrogen cyanide, potassium cyanide or sodium cyanide) could not be located in the available literature.

4.1.2. Inhalation. Pertinent data regarding the carcinogenicity of inhaled cyanide could not be located in the available literature.

4.2. BIOASSAYS

4.2.1. Oral. Pertinent data regarding the carcinogenicity of orally administered cyanide could not be located in the available literature.

4.2.2. Inhalation. Pertinent data regarding the carcinogenicity of inhaled cyanide could not be located in the available literature.

4.3. OTHER RELEVANT DATA

Of the three mutagenicity studies located in the available literature, two were negative and one was marginally positive. De Flora (1981) reported that potassium cyanide was not mutagenic to five strains of Salmonella typhimurium, regardless of the presence or absence of S-9 (mammalian activation system). Karube et al. (1981) also reported negative results from a rec-assay in Bacillus subtilis. Kushi et al. (1983) reported that hydrogen cyanide gas was marginally mutagenic to S. typhimurium strain TA100 in the absence of S-9, but not mutagenic to strain TA98 in the presence or absence of S-9.

Tewe and Maner (1981a) reported that no teratogenic effects were observed when Wistar rats were exposed to 500 ppm of cyanide in the diet throughout pregnancy; however, Tewe and Maner (1981b) reported that fetuses of pigs fed 276.6 or 520.7 mg CN (as KCN)/kg diet throughout pregnancy had reduced ratios of organ weight to body weight. At these levels, sows had kidney hyperplasia and morphological changes in thyroid cells.

4.4. WEIGHT OF EVIDENCE

IARC has not evaluated the risk to humans associated with oral or inhalation exposure to cyanide. Since data are lacking regarding the carcinogenicity of cyanides to animals or humans, applying the criteria proposed by the Carcinogen Assessment Group of the U.S. EPA (Federal Register, 1984) for evaluating the overall weight of evidence of carcinogenicity to humans, cyanide is most appropriately designated a Group D-Not Classified chemical.

5. REGULATORY STANDARDS AND CRITERIA

FAO and WHO have established an interim ADI for cyanide in food of 3.5 mg/man/day, assuming a 70 kg man (U.S. EPA, 1980a). In the June 9, 1981 Errata for Ambient Water Quality Criteria (U.S. EPA, 1980a), an interim ADI of 7.56 mg CN^-/day water was established, based on a NOAEL of 10.8 mg/kg/day derived from the chronic study of Howard and Hanzal (1955) (see Section 3.2.1.). In the calculation of this value, an uncertainty factor of 100 was used. In addition, an average body weight of 70 kg and consumption of 2 ℓ water/day and 6.5 g fish/day were assumed.

The U.S. Public Health Service (1962) has recommended that levels of cyanide in water not exceed 0.2 mg/ℓ.

ACGIH (1983) has recommended a TWA-TLV of 5 mg/m³ for cyanides, with the indication that dermal absorption may also be involved. This value is based on irritation to the respiratory system and is intended to protect from the effects of chronic exposure to hydrogen cyanide (derived primarily from the report by El Ghawabi et al., 1975). NIOSH (1976) and OSHA (1981) have also adopted this value as a recommended standard

Tolerances have been set for residues of hydrogen cyanide when used as a post-harvest insecticide fumigant. Those tolerances have been presented in Table 5-1 (Code of Federal Regulations, 1982).

TABLE 5-1

Tolerances for Hydrogen Cyanide in Foodstuffs
When Used as a Post-Harvest Fumigant*

Foodstuff	Tolerance (ppm)
Cereal flours	125
Cereals cooked before eaten	90
Uncooked ham, bacon, sausage	50
Cocoa	200
Several spices	250
Several grains	75
Dried beans, peas, nuts	25

*Source: Code of Federal Regulations, 1982

6. RISK ASSESSMENT

6.1. ACCEPTABLE INTAKE SUBCHRONIC (AIS)

6.1.1. Oral. Data from animal studies are insufficient for the calculation of an AIS for subchronic oral exposure to sodium cyanide. In the studies by Palmer and Olson (1979), Tewe and Maner (1980, 1982) and Tewe (1982), animals were exposed to only one level of treatment in addition to the control level of exposure (0 mg KCN/kg diet). Furthermore, Palmer and Olson (1979) reported an increase in liver weight in animals exposed to 4 mg/kg bw/day in the diet, but no effect on animals exposed to the same dose in drinking water. While Hayes (1967) exposed rats to a range of doses (0-250), he reported only mortality. Effect levels cannot be established from these studies.

6.1.2. Inhalation. Only one subchronic animal study pertaining to cyanide exposure (Hugod, 1981) was located in the available literature. In this study, rabbits were exposed to a single level of hydrogen cyanide gas for only 28 days. Furthermore, the human occupational exposure studies are lacking in quantitative detail. Therefore, these studies cannot be used in quantitative risk assessment.

6.2. ACCEPTABLE INTAKE CHRONIC (AIC)

6.2.1. Oral. The U.S. EPA (1985) has recently reevaluated the data from the Howard and Hanzal (1955) 2-year experiment with HCN in rats and used these data to calculate an ADI for CN^-. The Drinking Water Criteria Document for Cyanide (U.S. EPA, 1985) contains an in-depth discussion of the assumptions and calculations used in derivation of the ADI. This discussion is presented here in abbreviated form.

The U.S. EPA (1985) chose to derive an ADI for CN^- rather than HCN because CN^- is presumed to be the toxic moiety in cyanide compounds.

In determining the doses of CN^- to which the rats in this study were exposed on a mg/kg bw/day basis, the average body weights were estimated using the mean body weights at the beginning and end of the experiment and the growth charts provided by the investigators. Average body weights arrived at by the U.S. EPA (1985) were 390 g and 394 g in low- and high-dose males and 232 g and 255 g in low- and high-dose females, respectively. Food consumption was measured by the investigators and averaged 19.46 g and 18.50 g/rat/day in the low- and high-dose males and 14.69 g and 17.24 g/rat/day in the low- and high-dose females, respectively. The diets were prepared by fumigation and HCN was measured in the food offered to the rats. From these data, averaged over the entire treatment period, the U.S. EPA (1985) calculated that the low-dose diet contained 73 ppm CN^- and the high-dose diet, 160 ppm CN^-.

From the above data, the U.S. EPA (1985) calculated the animal doses of CN^-, expressed as mg/kg/day, for the male and female rats in the low- and high-dose groups as follows:

low-dose male:

73 mg CN^-/kg diet x 0.01946 kg diet/0.39 kg bw=3.6 mg CN^-/kg bw/day

high-dose male:

160 mg CN^-/kg diet x 0.01850 kg diet/0.394 kg bw=7.5 mg CN^-/kg bw/day

low-dose female:

73 mg CN^-/kg diet x 0.01469 kg diet/0.232 kg bw=4.6 mg CN^-/kg bw/day

high-dose female:

160 mg CN^-/kg diet x 0.01724 kg diet/0.255 kg bw=10.8 mg CN^-/kg bw/day

Since effects were not observed in treated rats, the animal dose of 10.8 mg CN^-/kg bw/day calculated for high dose females represents the highest NOEL. The U.S. EPA caluclated an ADI of 1.5 mg CN^-/day for a 70 kg human by multiplying the animal dose, 10.8 CN^-/kg bw/day by 70 kg and dividing by a UF of 500. This corresponds to an ADI for NaCN of 2.8 by multiplying the ADI for CN^- by the ratio of the formula weight of NaCN (49.01) to CN^- (26.02). A UF of 500 was chosen as follows: a factor of 10 to account for animal to human extrapolation, a factor of 10 to afford greater protection for unusually sensitive individuals and a final factor of 5 because a criterion for drinking water was derived from a dietary study. Measurements by the investigators demonstrated that HCN volatilized from the diet prepared by fumigation. It was believed that the final UF of 5 may adjust for the uncertainty associated with volatilization of HCN from the diet. The U.S. EPA (1985) also suggested that absorption of CN^- from drinking water might be facilitated but that absorption from the diet may be retarded by adsorption to food particles. The additional UF of 5 was also intended to account for some of the uncertainty associated with this phenomenon. Since this ADI (2.8 mg NaCN/day for a 70 kg human) was derived by analogy from data processed by the U.S. EPA (1985) based on the most complete chronic data available and by a rationale that logically addressed the issues involved in risk assessment, this ADI is adopted as the AIC for NaCN in this document.

A CS was calculated for the effects observed (degeneration of ganglion cells in the CNS) in the study by Hertting et al. (1960) using dogs treated by capsule for 15 months with NaCN at 6 mg NaCN/kg bw/day. A human MED was calculated by multiplying the animal dose by the cube root of the ratio of the body weight of dogs (assumed: 14 kg) to that of humans (assumed:

70 kg) and multiplying the result by 70 kg to express the MED in mg/day for a 70 kg man. A human MED of 245.6 mg/day, corresponding to an RV_d of 1.9, was calculated. The effects observed were assigned an RV_e of 6, because lesions were observed that were not reported to cause a decrement in organ function. A CS of 11.4 was calculated as the product of RV_d and RV_e.

Although limited data using dogs (Hertting et al., 1960) suggest a lower effect level, the dog has been questioned as an appropriate model (U.S. EPA, 1985). The dog is especially susceptible to CN^- poisoning, presumably due to low levels of hepatic rhodaneese, an enzyme involved in the primary detoxification pathway for cyanide.

6.2.2. Inhalation. Only one subchronic study pertaining to exposure to cyanide by inhalation (Hugod, 1981) was located in the available literature. Since this study involved exposure of rabbits for only 28 days, derivation of an AIC for chronic exposure from these data would be imprudent. The TLV of 5 mg/m³ established by ACGIH (1983), however, can be used to derive an interim ADI in the following manner. Assuming that a 70 kg man breathes a volume of 10 m³ air/8-hour workday and works 5 days/week, the TLV of 5 mg/m³ is multiplied by the product of 10 m³/day and 5/7 days/week to arrive at an inhaled dose of 35.7 mg CN^-/man/day. Dividing this value by an uncertainty factor of 10 to account for the range of sensitivities in the human population results in an interim ADI of 3.57 mg CN^-/man/day.

This ADI (3.57 mg CN^-/man/day) is larger than the ADI derived for oral exposure to CN^- by the U.S EPA (1985). Since cyanide is readily absorbed by the pulmonary system and since the first pass effect of the liver (very important in CN^- detoxification) is bypassed by this route, it is strongly recommended that the ADI derived from the TLV not be adopted as an inhalation ADI for CN^-.

6.3. CARCINOGENIC POTENCY (q_1*)

6.3.1. Oral. The lack of data regarding the carcinogenicity of ingested cyanide precludes assessment of carcinogenic risk.

6.3.2. Inhalation. The lack of data regarding the carcinogenicity of inhaled cyanide precludes assessment of carcinogenic risk.

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APPENDIX

Summary Table for Sodium Cyanide

	Species	Experimental Dose/Exposure	Effect	Acceptable Intake (AIS or AIC)	Reference
Inhalation					
AIS	NA	NA	NA	NA	NA
AIC				ND	
Oral					
AIS	NA	NA	NA	ND	NA
AIC	rat	NOEL = 10.8 mg CN-/kg/day	NA	2.8 NaCN mg/day	Howard and Hanzal, 1955; U.S. EPA, 1985
Maximum composite score	dog	6 mg/kg bw/day for 15 months (RV_d=1.9)	degeneration of ganglion cells in CNS (RV_e=6)	11.4	Hertting et al., 1960

NA = Not applicable; ND = not derived