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Cyanide Hazards to Fish, Wildlife, and Invertebrates: A Synoptic Review

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Abstract. Cyanides are used widely and extensively in the manufacture of synthetic fabrics and plastics, in electroplating baths and metal mining operations, as pesticidal agents and intermediates in agricultural chemical production, and in predator control devices. Elevated cyanide levels are normally encountered in more than 1,000 species of food plants and forage crops, and this probably represents the greatest source of cyanide exposure and toxicosis to man and to range animals. Anthropogenic sources of cyanide in the environment include certain industrial processes, laboratories, fumigation operations, cyanogenic drugs, fires, cigarette smoking, and chemical warfare. Although cyanide is ubiquitous in the environment, levels tend to be elevated in the vicinity of metal processing operations, electroplaters, gold-mining facilities, oil refineries, power plants, and solid waste combustion.

Many chemical forms of cyanide are present in the environment, including free cyanide, metallocyanide complexes, and synthetic organocyanides, also known as nitriles. But only free cyanide (i.e., the sum of molecular hydrogen cyanide, HCN, and the cyanide anion, CN^-) is the primary toxic agent, regardless of origin.

Cyanides are readily absorbed through inhalation, ingestion, or skin contact and are readily distributed throughout the body via blood. Cyanide is a potent and rapid-acting asphyxiant; it induces tissue anoxia through inactivation of cytochrome oxidase, causing cytotoxic hypoxia in the presence of normal hemoglobin oxygenation. Diagnosis of acute lethal cyanide poisoning is difficult because signs and symptoms are nonspecific, and numerous factors modify its biocidal properties, such as dietary deficiencies in vitamin B_{12}, iodine, and sulfur amino acids. Among the more consistent changes measured in acute cyanide poisoning are inhibition of brain cytochrome oxidase activity, and changes in electrical activity in heart and brain. At sublethal doses, cyanide reacts with thiosulfate in the presence of rhodanese to produce the comparatively nontoxic thiocyanate, most of which is excreted in the urine. Rapid detoxification enables animals to ingest high sublethal doses of cyanide over extended periods without harm. Antidotes in current use to counteract cyanide poisoning include a combination of sodium nitrite and sodium thiosulphate (United States), cobalt edetate (United Kingdom, Scandinavia, France), or a mixture of 4-dimethylaminophenol and sodium thiosulphate (Germany).

All available evidence suggests that cyanides are neither mutagenic, teratogenic, nor carcinogenic. Moreover, there are no reports of cyanide biomagnification or cycling in living organisms, probably owing to its rapid detoxification. Cyanide seldom persists in surface waters and soils owing to complexation or sedimentation, microbial metabolism, and loss from volatilization. More data are needed on cyanide distribution and transformation in the atmosphere.

Analytical methods for the determination of free and bound cyanides and cyanogenic compounds in biological materials are under constant revision. Further, unless tissue samples are obtained promptly after cyanide exposure and analyzed immediately, erroneous analytical values will result.

Higher plants are adversely affected by cyanide through cytochrome oxidase inhibition; the rate of production and release of cyanide by plants to the environment through death and decomposition is unknown. Nonacclimatized soil bacteria are adversely affected at 0.3 mg HCN/kg; acclimatized populations, however, can degrade wastes containing up to 60 mg total cyanide per kilogram. In some cases, soil bacteria and fungi produce cyanides as secondary metabolites, with adverse effects on certain plants. Several species of arthropods normally contain elevated whole-body cyanide concentrations, and these confer protection against predators and allow consumption of cyanogenic plants.

Fish were the most sensitive aquatic organisms tested. Adverse effects on swimming and reproduction were observed between 5 and 7.2 µg free cyanide per liter; lethal effects usually occurred between 20 and 76 µg/L. Biocidal properties of cyanide in aquatic environments were significantly modified by water pH, temperature, and oxygen content; life stage, condition, and species assayed; previous exposure to cyanides; presence of other chemicals; and initial dose tested.

Birds that feed predominantly on flesh were more sensitive to cyanide than were herbivores. Free cyanide levels associated with high avian death rates include 0.12 mg/L in air, 2.1-4.6 mg/kg body weight (BW) via acute oral exposure, and 1.3 mg/kg BW administered intravenously. Dietary levels of 135 mg total cyanide per kilogram ration resulted in growth reduction of chicks, but 103 mg total cyanide per kilogram ration had no measurable effect on domestic chickens.

Cyanogenic plants represent a problem for various range animals and wildlife, primarily among species that eat rapidly. Intakes of 4 mg HCN/kg BW are lethal to these species if it is consumed quickly. Cassava (*Manihot esculenta*) is a cyanogenic plant that accounts for up to 70% of human caloric intake in some areas, and this is associated with serious, long-term toxic effects including ataxia, optic nerve lesions, altered thyroid function, demyelination, and increases in tissue thiocyanate levels. Acute oral LD50 values for representative species of mammals ranged between 2 and 3.6 mg HCN/kg BW. Despite the high lethality of large single exposures, repeated sublethal doses--especially in diets--can be tolerated by many species for extended periods, perhaps indefinitely. Mammalian deaths were also recorded at air concentrations of 140 mg HCN/m^3 (exposure for 60 min) and 4,400 mg HCN/m^3 (exposure for 1 min), and at dermal applications between 2.3 mg HCN/kg BW for abraded skin and 100 mg HCN/kg BW for intact skin. Adverse nonlethal effects were noted at drinking water concentrations >150 mg HCN/L and at dietary concentrations >720 mg HCN/kg ration.

Free cyanide criteria currently proposed for natural resource protection include <3 µg/L medium for aquatic life, and <100 mg/kg diet for birds and livestock. For human health protection, free cyanide values are <10 µg/L drinking water, <50 mg/kg diet, and <5 mg/m^3 air.

Key words: Cyanide, toxic effects, wildlife, cyanogenic plants, aquatic organisms, criteria.

The origin of terrestrial life probably depended on the presence and reactivity of hydrogen cyanide and its derivatives; paradoxically, hydrogen cyanide is toxic to the majority of living matter (Marrs and Ballantyne 1987). Cyanide is a general respiratory poison--although uptake can also occur through ingestion or dermal absorption--producing reactions within seconds, and death within minutes (Towill et al. 1978; Environmental Protection Agency [EPA] 1980). The toxic mechanism of cyanide primarily involves the inhibition of cytochrome oxidase, the terminal oxidative enzyme of the mitochondrial electron transport chain, producing blockage of aerobic ATP synthesis (Egekeze and Oehme 1979; Younes and Strubelt 1988). Because of their highly effective lethal potency, cyanides were used for genocidal programs in Germany in World War II, in mass suicides by members of the People's Temple religious sect in Guyana, and in the substitution of medication in Tylenol capsules in drugstores in various cities in the United States. In fact, cyanides are responsible for more human deaths than any other chemicals known, owing to their deliberate use in suicide, murder, chemical warfare, genocide, and judicial execution (Way 1981, 1984; Ballantyne and Marrs 1987a; Gee 1987; Marrs and Ballantyne 1987; Yamamoto 1989). High sublethal doses of cyanide are rapidly detoxified, and accidental acute cyanide poisonings in humans are uncommon (Towill et al. 1978).

Cyanide compounds are useful to society in terms of their key role in synthetic and industrial processes, for certain fumigation and agricultural uses, and for some therapeutic applications (Ballantyne and Marrs 1987a). Cyanides are present in effluents from iron and steel processing plants, petroleum refineries, and metal-plating plants, and constitute a hazard to aquatic ecosystems in certain waste-receiving waters (Smith et al. 1979), and to livestock (EPA 1980;Towill et al. 1978). Cyanide serves no useful purpose in the human body, yet it is present in our food, air, and water (Becker 1985).

Natural sources of cyanide include various species of bacteria, algae, fungi, and higher plants that form and excrete cyanide (Way 1984). The most widely distributed major food crop with a high content of cyanogenic glycosides is cassava (*Manihot esculenta*), also known as manioc. Cassava is a staple food in human diets in over 80 countries, and it is sometimes added to animal feeds as a substitute for more expensive cereal grains (Gomez et al. 1988). In humans, chronic cyanide intoxication caused by consumption of cassava is the main etiological factor in the debilitating tropical ataxic neuropathy (Egekeze and Oehme 1980). Other plants having comparatively elevated cyanide content include fruit pits, sweet potatoes (*Ipomoea batatas*), corn (*Zea mays*), bamboo shoots (*Bambusa* spp.), linseed, (*Linum* sp.), lima beans (*Phaseolus lunatus*), and millet (*Panicum miliaceum*; Way 1984). In higher plants that contain cyanogenic glycosides, at least 20 of these compounds have been identified (EPA 1980). Amygdalin--one of the more intensively studied cyanogenic glycosides--is found in seeds of the cherry (*Prunus* spp.), plum (*Prunus* spp.), peach (*Prunus persica*), apricot (*Prunus armenaica*), apple (*Malus domestica*), pear (*Pyrus communis*), and many parts of the cherry laurel (*Prunus laurocerasus;* EPA 1980). Apricot seeds and peach kernels are food delicacies in Turkey, and have caused at least nine poisonings (two fatal) in children from that country (Gee 1987). Acute cyanide poisoning has occurred in the United States from the ingestion of almond-flavored milkshakes prepared from apricot kernels (Way 1984). Amygdalin is also the chief ingredient in laetrile, a medication prescribed by some physicians to control tumors. Both laetrile and amygdalin-containing fruit pits have been implicated as the causes of acute cyanide poisoning in humans (EPA 1980). Another naturally occurring group of organic cyanides (nitriles) is the highly toxic pseudocyanogenic glycosides, especially cycasin, and these have been implicated in a variety of tropical diseases of the nervous system, and partial or total blindness (EPA 1980). Other nitriles found in plants include the lathyrogenic compounds, glucosinolates, and the cyanopyridine alkaloids (EPA 1980).

That certain plants, such as bitter almonds *(Prunus dulcis),* cherry laurel leaves, and cassava, are poisonous if consumed in sufficient quantities has been known for at least 2,000 years. But it was not until the 1700's that cyanide was recognized as the basis for their lethal toxicity. The first account of an experimental administration of extract of bitter almonds and other poisons to dogs (*Canis familiaris*) dates from 1679, as reviewed by Sykes (1981) and Ballantyne (1987a). In 1731, two fatal cases of human poisoning in Ireland were caused by drinking cherry laurel water, in this instance used as a flavoring agent in cooking and to dilute brandy. In that same year it was shown that cherry laurel water administered to dogs by various routes proved rapidly fatal. By 1781, it was well established that mammals, birds, reptiles, amphibians, fish, and insects could all be killed with small doses of laurel water, and that death was more rapid than that produced by other poisons tested. It was also at this time that cyanide was first implicated as a homicidal agent in England. In 1782, hydrocyanic acid was isolated from Prussian blue (a dye) by the Swedish chemist Scheele. In 1786, Scheele accidentally broke a vial of the material and died from vapor poisoning. In 1787, it was determined that hydrocyanic acid contained hydrogen, carbon, and nitrogen, but did not contain oxygen, formerly believed to be an essential component of all acids. Between 1802 and 1815, hydrocyanic acid was found to be lethal in small quantities to birds and dogs, and to act rapidly when given orally, intravenously, or applied to the eye surface. By 1803, it was known that cyanide occurred naturally and could be extracted from apricots or almonds. In 1815, hydrocyanic acid was prepared in a semipure form. Between 1817 and 1948, cyanide, in appropriate doses, was used therapeutically in England for the treatment of pulmonary diseases and tuberculosis, and as a sedative. By 1830, cyanogenic glycosides containing HCN were isolated from cassava; today, more than 800 species of cyanogenic plants have been identified. In 1876, it was first demonstrated that cyanide inhibited tissue oxidation. In 1894, cobalt compounds were suggested as antidotes due to their marked cyanide-binding capacity. Studies on cyanide detoxification conducted between 1877 and 1894 showed that thiosulphate administration caused the formation of thiocyanate--a relatively harmless metabolite. By the late 1800's, cyanide was regarded as a common plant metabolite rather than as an unusual poison. In 1929, it was conclusively demonstrated that cyanide combines with the trivalent iron atom in cytochrome oxidase, a respiratory enzyme that links the tricarboxylic acid cycle and formation of metabolic water. Many reviews have been published on cyanide in the environment; particularly useful are those by Doudoroff (1976), Towill et al. (1978), Smith et al. (1979), Egekeze and Oehme (1980), EPA (1980, 1989), Vennesland et al. (1981a), Leduc et al. (1982), Leduc (1984), Way (1984), Ballantyne and Marrs (1987a), and Evered and Harnett (1988).

Cyanide hazards to fish, wildlife, and livestock are well documented. Massive kills of freshwater fish by accidental discharges of cyanide wastes are fairly common (Holden and Marsden 1964; Leduc 1978; Towill et al. 1978; EPA 1980). In one case, cyanide-containing mine effluents from a Canadian tailings pond released into a nearby creek killed more than 20,000 steelhead (Oncor*hynchus mykis;* Leduc et al. 1982). Many species

of birds were found dead near burrows of the blacktailed prairie dog (*Cynomys ludovicianus*) after the burrows had been treated with calcium cyanide to control prairie dog populations; dead birds included the burrowing owl (*Athene cunicularia*), the bald eagle (*Haliaeetus leucocephalus*), and the golden eagle (*Aquila chrysaetos;* Wiemeyer et al. 1986). An endangered California condor (*Gymnogyps californianus*) found dead in Kern County, California, in November 1983 had particles of a yellow fluorescent tracer in its mouth; these particles were similar to those mixed with sodium cyanide in M-44 spring-loaded ejector mechanism devices used in a U.S. Fish and Wildlife Service Animal Damage Control Program in that vicinity, suggesting that cyanide was a possible cause of death (Krynitsky et al. 1986). M-44 devices are known to have caused the death of magpies (*Pica* sp.), ravens and crows *(Corvus* spp.), wild turkeys *(Meleagris gallopavo),* and various unidentified species of hawks and vultures (Wiemeyer et al. 1986). Between 1980 and 1989, 519 mammals--mostly rodents (35%) and bats (34%)--were found dead at cyanide-extraction, gold-mine leach ponds in California, Nevada, and Arizona; the list included coyote *(Canis latrans),* foxes, skunks, badger *(Taxidea taxus),* weasels, rabbits, deer, and beavers (Clark and Hothem 1991). Also found dead at these same leach ponds were 38 reptiles, 55 amphibians, and 6,997 birds (Clark and Hothem 1991), including many species of waterfowl and songbirds (Allen 1990). The influence of cyanide-extraction gold-mining operations on wildlife is currently under investigation by scientists at the Patuxent Wildlife Research Center.

The major threat of cyanide poisoning to livestock and terrestrial mammalian wildlife is through ingestion of plants containing high levels of cyanogenic glycosides (Towill et al. 1978; Marrs and Ballantyne 1987). Plants implicated in cyanide poisoning of animals include the sorghums (Johnson grass, *Sorghum halepense;* Sudan grass, *Sorghum sudanense*), arrowgrass (*Triglochin* spp.), elderberry (*Sambucus* spp.), wild cherry (*Prunus* spp.), and the pits of several common fruits, such as apple, peach, and apricot; these plants and fruit pits have the potential of releasing cyanide upon ingestion (Egekeze and Oehme 1980). Domestic goats (*Capra* spp.) died of cyanide poisoning after eating leaves and fruit of the crab apple *(Malus sylvestris);* the crab apple contains cyanogenic glycosides in its leaves and fruit (Shaw 1986). Cyanide poisoning of cattle (*Bos* spp.) by forage sorghums and various hybrid cultivars has been reported in India (Bapat and Abhyankar 1984) and elsewhere (Cade and Rubira 1982; Biehl 1984). Cattle appear to be more vulnerable to cyanide poisoning than are sheep (*Ovis aries*), horses (*Equus caballus*), and pigs (*Sus* spp.; Cade and Rubira 1982). *Equine sorghum cystitis ataxia* is a condition observed in horses grazing on Sorghum or hybrid Sudan grass pastures; it is characterized by urinary incontinence, posterior incoordination, and degenerative central nervous system lesions (Egekeze and Oehme 1980). Grazing cyanogenic plants can induce sulfur deficiency in sheep, presumably because sulfur detoxifies the released cyanide (Towill et al. 1978). The increasing use of cassava and other cyanogenic plants in animal feeding portends a greater exposure to dietary cyanides (Davis 1981).

This report briefly reviews the technical literature on ecological and toxicological aspects of cyanide, with emphasis on fishery and wildlife resources, and provides recommendations for the protection of sensitive species of concern to the U.S. Fish and Wildlife Service. This account is part of a continuing series of synoptic reviews prepared in response to informational requests from Service environmental specialists.

Chemical Properties

The chemical speciation of cyanides varies according to their source. Specific terms used to describe cyanide include free cyanide, cyanide ion, simple cyanides, complex cyanides, nitriles, cyanogens, and total cyanide. The most common forms of cyanide in the environment are free cyanide, metallocyanide complexes, and synthetic nitriles. A brief description of each cyanide species follows (Smith et al. 1978, 1979; Towill et al. 1978; Egekeze and Oehme 1980; EPA 1980, 1989; Davis 1981; Leduc 1981, 1984; Leduc et al. 1982; Simovic and Snodgrass 1985; Ballantyne 1987a; Homan 1987; Marrs and Ballantyne 1987).

Free cyanide is the primary toxic agent in the aquatic environment. Free cyanide refers to the sum of molecular HCN and the cyanide anion (CN^-), regardless of origin. In aqueous solution with pH 9.2 and lower, the majority of the free cyanide is in the form of molecular HCN. The chemical names for HCN include hydrogen cyanide, hydrocyanic acid, cyanohydric acid, and prussic acid. Hydrogen cyanide (Table 1) is a colorless, flammable liquid or gas that boils at 25.7° C and freezes at -13.2° C. The gas rarely occurs in nature, is lighter than air, and diffuses rapidly; it is usually prepared commercially from ammonia and methane at elevated temperatures with a platinum catalyst. It is miscible with water and alcohol, but is only slightly soluble in ether. In water, HCN is a weak acid with the ratio of HCN to CN^- about 100 at pH 7.2, 10 at pH 8.2, and 1 at

pH 9.2. HCN can dissociate into H and CN^-. Cyanide ion, or free cyanide ion, refers to the anion CN^- derived from hydrocyanic acid in solution, in equilibrium with simple or complexed cyanide molecules. Cyanide ions resemble halide ions in several ways and are sometimes referred to as "pseudohaline" ions. For example, silver cyanide is almost insoluble in water, as are silver halides. Cyanide ions also form stable complexes with many metals.

Simple cyanides typically refer to alkali water-soluble salts, such as NaCN, KCN, $Ca(CN)_2$, and $Hg(CN)_2$, but also include several cyanide salts of alkali, alkaline earth, or heavy metals, that is, $Zn(CN)_2$, $Cd(CN)_2$, $Ni(CN)_2$, and AgCN, of varying degrees of solubility. In water, NaCN and KCN will completely dissociate to give free cyanide. All simple cyanides ionize in water to release cyanide ion which, depending on pH, will form hydrocyanic acid. For sodium cyanide, the reaction proceeds as follows:

(1) $NaCN \quad Na^+ + CN^-$

(2) $CN^- + HOH \quad HCN + OH^-$

Increased pH will maintain a larger fraction of the cyanide as CN^-, and acidification will cause the reverse. At pH 7, about 99% of the free cyanide is in the form of HCN, whereas at pH 9.3 HCN composes 50%. Since HCN is extremely water soluble and is also one of the most toxic cyanide species, it is noteworthy that the toxicity of simple cyanides will not be affected measurably below pH 8.3. Acidification of dilute (milligrams per liter) cyanide solutions will not initiate any greater release of HCN, but acidification of concentrated (grams per liter) solutions promotes HCN formation and release.

Table 1. Some properties of potassium cyanide, hydrogen cyanide, and sodium cyanide (from EPA 1989).

Property	Potassium cyanide	Hydrogen cyanide	Sodium cyanide
CAS number	151-50-8	74-90-8	143-33-9
Chemical formula	KCN	HCN	NaCN
Molecular weight	65.12	27.03	49.01
Physical state	Solid	Gas or liquid	Solid
Boiling point (º C)	--	25.7	1,496
Melting point (º C)	634.5	–13.21	563.7
Specific gravity	1.5	0.7 (liquid)	1.6
Solubility in water (g/L)	716 at 20º C	Miscible	480 at 10º C

Complex cyanides are compounds in which the cyanide anion is incorporated into a complex or complexes; these compounds are different in chemical and toxicologic properties from simple cyanides. In solution, the stability of the cyanide complex varies with the type of cation and the complex that it forms. Some of these are dissociable in weak acids to give free cyanide and a cation, while other complexes require much stronger acidic conditions for dissociation. The least-stable complex metallocyanides include $Zn(CN)_4^{2-}$, $Cd(CN)_3^-$, and $Cd(CN)_4^{2-}$; moderately stable complexes include $Cu(CN)_2^-$, $Cu(CN)_3^{2-}$, $Ni(CN)_4^{2-}$, and $Ag(CN)^{2-}$; and the most stable complexes include $Fe(CN)_6^{4-}$and $Co(CN)_6^{4-}$**.** The toxicity of complex cyanides is usually related to their ability to release cyanide ions in solution, which then enter into an equilibrium with HCN; relatively small fluctuations in pH significantly affect their biocidal properties.

Cyanogen [$(CN)_2$] is the simplest compound containing the cyanide group. Cyanogen is an extremely toxic, flammable gas that reacts slowly with water to form HCN, cyanic acid, and other compounds; it is rapidly

degraded in the environment. Cyanogen and its halide derivations are comparable in toxicity to hydrogen cyanide.

Nitriles are defined as organic compounds (RCN) containing the cyanide group. Cyanide bound to carbon as nitriles (other than as cyanogenic glycosides) are comparatively innocuous in the environment, and are low in chemical reactivity and are biodegradable. For simple mononitriles there is a clear progression, with more cyanide being released as chain length increases. A similar pattern exists in dinitriles, but corresponding compounds require a longer carbon chain than mononitriles before free cyanide is produced. Based on studies with chicken liver homogenates (Davis 1981), mononitriles were more toxic than dinitriles, and within each group the order of toxicity was $CH_3 > C_2H_5 > C_3H_7 > C_4H_9 > C_5H_{11} > C_7H_{15}$. Cyanohydrins [$R_2C(OH)CN$] and cyanogenic glycosides [$R_1R_2C(OR_3)CN$] are special classes of nitriles, in that under appropriate conditions they will decompose to HCN and cyanide ions. Cyanogens (not to be confused with cyanogen), such as acrylonitrile, propionitrile, and succinonitrile, are nitrile-containing materials of varying complexity and lability, and can liberate free and toxicologically available amounts of cyanide. But the nonnitrile portion of the cyanogen molecule may exert an independent or interactive toxicity, causing a complex response.

Cyanates contain the OCN group. Inorganic cyanates that are formed industrially by the oxidation of cyanide salts hydrolyze in water to form ammonia and bicarbonate ion. Alkyl cyanates are insoluble in water and form cyanurates. Alkyl isocyanates contain the OCN radical, are formed from cyanates, and, like cyanates, are readily hydrolyzed. Thiocyanates (SCN group) are formed from cyanides and sulfur-containing materials and are relatively stable.

Total cyanides refers to all cyanide-containing compounds, including simple and complex cyanides, cyanoglycosides, and free cyanide. Total cyanides is a chemical measurement of free cyanide present in solution or released by acidification or digestion. Only free cyanide is considered to be a biologically meaningful expression of cyanide toxicity. Under most circumstances, the concentration of total cyanide will exceed that of HCN. In some waters, however, the total cyanide concentration may consist almost entirely of free cyanide, or it may contain cyanides that readily photodecompose or dissociate to yield HCN. The relation between total cyanide and free cyanide in natural waters varies with receiving-water conditions, type of cyanide compounds present, degree of exposure to daylight, and presence of other chemical compounds.

Hydrogen cyanide has frequently been associated with the odor of bitter almonds (Ballantyne 1983; Gee 1987). The threshold odor for olfactory detection of atmospheric HCN is 1 mg/L, but the odor may not be detected for various reasons, including the presence of other odors and the fact that only 20% to 40% of those tested could detect a cyanide odor.

Analytical methods for determining free and bound cyanide and cyanogenic compounds in biological materials are under revision. Current methods include chromatography; enzymic postcolumn cleavage; electrochemical detection; and ultraviolet, infrared, proton, and carbon-13 nuclear magnetic resonance spectroscopies (Brimer 1988). Proposed newer analytical methodologies include chemiluminescence (Wu et al. 1989); deproteinization techniques (Krynitsky et al. 1986); thin film dissociation coupled with preferential ultraviolet irradiation (Kelada 1989); differential pulse polarography (Westley 1988); and modified spectrophotometric (Blago 1989; Ohno 1989), colorometric (Lundquist and Sorbo 1989), and ion chromatographic determinations (Nonomura and Hobo 1989). Analysis of cyanide and cytochrome oxidase is usually conducted with samples of whole blood, serum, plasma, brain, or ventricular myocardium tissues. Samples should be obtained as soon as possible after cyanide exposure and analyzed immediately, otherwise erroneous analytical values will result (Towill et al. 1978; Ballantyne 1983). Brain and liver are recommended for cyanide analysis if removed and analyzed within a week (Ballantyne et al. 1974). Cyanide measurements are further confounded by the presence of various antidotal agents (Ballantyne 1983); by various tissue preservatives, such as formaldoxime (Knocke 1981) and sodium fluoride (Curry et al. 1967); and by the spontaneous postmortem production of cyanide in various tissues (e.g., sterile blood, brain, liver, kidney, uterus, intestines) over time in cases of noncyanide death (Curry et al. 1967; Ballantyne et al. 1974).

Mode of Action

Cyanide is a potent and rapid-acting asphyxiant. At lethal doses, inhalation or ingestion of cyanide produces reactions within seconds and death within minutes. Cyanide's toxic effect is due to its affinity for the ferric heme form of cytochrome a_3, also known as cytochrome c oxidase, the terminal oxidase of the mitochondrial respiratory chain (Towill et al. 1978; Egekeze and Oehme 1980; Solomonson 1981; Way 1981, 1984; Leduc et al. 1982; Biehl 1984; Ballantyne 1987a; Marrs and Ballantyne 1987; Yamamoto 1989). Inhibition of the enzyme cytochrome c oxidase is thought to involve a two-step reaction--initial penetration of cyanide into a protein crevice followed by binding to heme iron. Formation of a stable cytochrome c oxidase-CN complex in the mitochondria produces a blockage of electron transfer from cytochrome oxidase to molecular oxygen and cessation of cellular respiration, causing cytotoxic hypoxia in the presence of normal hemoglobin oxygenation. Tissue anoxia induced by the activation of cytochrome oxidase causes a shift from aerobic to anaerobic metabolism, resulting in the depletion of energy-rich compounds such as glycogen, phosphocreatine, and adenosine triphosphate, and the accumulation of lactate with decreased blood pH. The combination of cytotoxic hypoxia with lactate acidosis depresses the central nervous system--the most sensitive site of anoxia--resulting in respiratory arrest and death. If the absorption rate is significantly greater than the detoxification rate, there will be a rapid accumulation of free cyanide in tissues and body fluids, resulting in the prompt onset of signs of acute cyanide poisoning. Acute cyanide poisoning is frequently encountered as a relatively massive overdose, where the amount of cyanide greatly exceeds the minimal concentration necessary to inhibit cytochrome c oxidase. In such cases, many enzymes and biological systems are disrupted, including various metalloenzymes, nitrate reductase, nitrite reductase, myoglobin, various peroxidases, catalase, and ribulose diphosphate carboxylase, resulting in severe signs of toxicity and rapid death.

The great majority of the absorbed cyanide reacts with thiosulfate in the presence of enzymes to produce thiocyanate, which is excreted in the urine over a period of several days. Owing to this rapid detoxification, animals can ingest high sublethal doses of cyanide over extended periods without harm (Towill et al. 1978; Egekeze and Oehme 1980; EPA 1980; Davis 1981; Solomonson 1981; Leduc 1984; Ballantyne 1987a; Oh et al. 1987; Marrs and Ballantyne 1987; Westley 1988; Mengel et al. 1989). Authorities are also in general agreement on several points: thiosulfate is usually low in the body, and higher levels can significantly protect against cyanide toxicity; species vary considerably in both the extent to which thiocyanate is formed and the rate at which it is eliminated from the body; thiocyanate metabolites resulting from the transulfuration process are about 120 times less toxic than the parent cyanide compound; thiocyanate may accumulate in tissues and has been associated with developmental abnormalities and other adverse effects; the two enzyme systems responsible for the transulfuration process are thiosulfate-cyanide sulfurtransferase--also known as rhodanese--and beta-mercaptopyruvate cyanide sulfurtransferase. Rhodanese is widely distributed in the body, but activity levels in mammals are highest in the mitochondrial fraction of liver. Rhodanese activity levels in catalyzing the transformation of thiosulfate to thiocyanate are limited by the availability of sulfur.

Minor detoxification pathways for cyanide include exhalation in breath as HCN and as $C0_2$ from oxidative metabolism of formic acid; conjugation with cystine to form 2-iminothiazolidene- 4-carboxylic acid or 2-aminothiazoline-4-carboxylic acid; combining with hydroxocobalamin (B_{12}) to form cyanocobalamin, which is excreted in urine and bile; and binding by methemoglobin in the blood (Towill et al. 1978; EPA 1980; Ballantyne 1987a; Marrs and Ballantyne 1987).

Absorption of hydrogen cyanide liquid or gas readily occurs through inhalation, ingestion, or skin contact (Towill et al. 1978; Egekeze and Oehme 1980; EPA 1980; Homan 1987). Inhalation and skin absorption are the primary hazardous routes in cyanide toxicity in occupational exposure. Skin absorption is most rapid when the skin is cut, abraded, or moist. Inhalation of cyanide salts is also potentially hazardous because the cyanide dissolves on contact with moist mucous membranes. Regardless of route of exposure, cyanide is readily absorbed into the bloodstream and distributed throughout the body. Cyanide concentrates in erythrocytes through binding to methemoglobin (Towill et al. 1978; EPA 1980), and free cyanide concentrations in plasma are now considered one of the better indicators of cytotoxicity (Ballantyne 1987a). Because of the affinity of cyanide for the mammalian erythrocyte, the spleen may contain elevated cyanide concentrations when compared to blood; accordingly, spleen should always be taken for analysis in cases of suspected cyanide poisoning (Ballantyne 1975). Cyanide also accumulates in various body cells through binding to metalloproteins or enzymes such as catalase and cytochrome c oxidase (EPA 1980). The brain is probably the major target organ

of cytotoxic hypoxia, and brain cytochrome oxidase may be the most active site of lethal cyanide action, as judged by distribution of cyanide, thiosulfate, and rhodanese (Solomonson 1981; Ballantyne 1987a). Significant positive correlations exist between cyanide concentrations in plasma, cerebrospinal fluid, and brain (Ballantyne 1987a); these correlations need further exploration.

Hydrogen cyanide formation may contribute to the toxicity of snake venom, owing to the high levels of L-amino acid oxidase in some snake venoms (Vennesland et al. 1981b). This enzyme is harmless on injection, but the tissue destruction caused by other venom components probably provides the required substrate and cofactor for HCN production.

Cyanide inhibits ion transport mechanisms in amphibian skin, gall bladder, and proximal renal tubules (Bello-Reuss et al. 1981). Measurable changes in cell membrane potentials of isolated gall bladder epithelium cells, for example, were induced by NaCN in a salamander (Bello-Reuss et al. 1981). Cyanide-induced hyperpolarization was caused primarily by an increase in permeability of the cell membrane to potassium, which, in turn, was mediated by an elevation of intracellular calcium ion activity, attributable to release from mitochondrial sources.

The binding rate of CN to hemeproteins, specifically hemoglobin components Ill and IV, is 370 times to 2,300 times slower in a marine polychaete annelid (*Glycera dibranchiata*), when compared to guinea pig (*Cavia* spp.), soybean (*Glycine* max), and sperm whale (*Physeter macrocephalus*); the significance of this observation is unclear but warrants further exploration (Mintorovitch et al. 1989).

Clinical Features

Accidental exposure to cyanides or cyanogens through inhalation, skin exposure, and swallowing occurs in agricultural fumigation, laboratories, industrial operations, domestic abuse, and products of combustion (Ballantyne and Marrs 1987b). Intentional exposure is reported from homicides, suicides (usually uncommon), judicial executions, chemical warfare, and covert activities (Ballantyne and Marrs 1987b).

Diagnosis of lethal cyanide poisoning is difficult because of the absence of gross pathology or histology, nonspecific congestion of viscera, and cerebral or pulmonary edema. Sometimes the blood is bright red, and sometimes the odor of bitter almonds is detected, but neither is sufficiently consistent for diagnostic purposes (Ballantyne and Marrs 1987b).

At low lethal doses of cyanide, the effects are principally on cytochrome oxidase in the central nervous system. At higher doses, cardiovascular signs and changes in electrical activity of the brain are among the most consistent changes measured (Way 1981, 1984). Acute and subacute toxic effects of poisoning with cyanide can vary from convulsions, screaming, vomiting, and bloody frothing to less dramatic events, such as a slow, quiet onset to coma and subsequent death (Way 1981). In the first stage of cyanide poisoning, victims exhibit headache, vertigo, weak and rapid pulse, nausea, and vomiting. In the second stage, there are convulsions, falling, dilated pupils, clammy skin, and a weaker and more rapid pulse. In the final stage, heartbeat becomes irregular and slow; body temperature falls; there is cyanosis of lips, face, and extremities, coma, frothy bloody saliva flow from mouth, and death (Way 1981). If acute exposure is to a sublethal dose of cyanide, this may lead to signs of toxicity, but as detoxification proceeds these signs will become less obvious and eventually vanish, and cyanide will be excreted as thiocyanate without accumulating (Ballantyne 1987a).

Chronic cyanide poisoning may develop in individuals who ingest significant quantities of cyanide or cyanide precursors in their diets; effects are exacerbated by dietary deficiencies in vitamin B_{12}, iodine, and sulfur amino acids, as well as by low levels and insufficient distribution of detoxifying enzymes such as rhodanese (Solomonson 1981). Cyanide toxicity of dietary origin has been implicated in acute animal deaths and as a major etiologic factor in toxic ataxic neuropathy in humans, and as a cause of blindness in humans suffering from tobacco amblyopia and Leber's hereditary optic atrophy (Egekeze and Oehme 1980). An increase in blood plasma cyanide is observed in healthy individuals who smoke cigarettes (Cailleux et al. 1988). An increase in blood plasma thiocyanate is also seen in smokers and in hemodialysis patients just before dialysis (Cailleux et al. 1988). Continuous intake of cyanide causes high levels of plasma thiocyanate and goiters in mammals; the antithyroid action (goiters) results from cyanide interference with iodine transport and thyroxine synthesis (Solomonson 1981; Leduc 1981, 1984). Signs of chronic cyanide poisoning include demyelination, lesions of the optic nerve, decrease in sulfur-containing amino acids, increase in thiocyanate, goiter, ataxia, hypertonia,

and depressed thyroid function (Solomonson 1981). These effects are common in areas that depend on cyanogenic plants--such as cassava--as a major dietary component (Solomonson 1981).

Biochemically, cyanide affects the citric acid cycle; strongly inhibits catalases and proteinases; induces glycolysis in protozoans, fish, and mammals; produces vitamin B_{12} deficiency; and modifies the phosphorylation mechanism of respiratory mitochondrial enzymes, causing arrested respiration due to inability to use oxygen (Leduc 1984).

Cyanide biomagnification or cycling has not been reported, probably because of cyanide's high chemical reactivity and rapid biotransformation (Towill et al. 1978; Marrs and Ballantyne 1987).

There is no evidence that chronic exposure to cyanide results in teratogenic, mutagenic, or carcinogenic effects (EPA 1980). Cyanide possibly has antineoplastic activity, as judged by a low therapeutic success against rat sarcomas (EPA 1980), but this requires additional documentation.

Confirmatory evidence of cyanide poisoning includes elevated blood thiocyanate levels--except, perhaps, when death was rapid--and reduced cytochrome oxidase activity in brain and myocardium, provided that all tissues were taken within a day or so of death, frozen quickly, and analyzed shortly thereafter (Biehl 1984; Marrs and Ballantyne 1987). Evaluation of cyanide poisoning and metabolism includes signs of toxicity, LD50 values, measurement of cyanide and thiocyanate concentrations, cytochrome c oxidase activity, metabolic modification of in vivo cyanogenesis, rate of cyanide liberation in vitro, and influence of modifying factors such as the animal species, dose, rate and frequency of administration, route of exposure, differential distribution of cyanide, detoxification rates, circadian rhythm interactions, age of the organism, and presence of antidotes (Ballantyne 1987a). For example, the concentration of cyanide measured in body fluids and tissues in humans and other animals following lethal administration of cyanide depends on several factors: route of exposure, with oral route yielding highest residues and inhalation route the lowest; amount and duration of exposure; nature of the material, with HCN and CN^- being most toxic; time to death; antidotes used; time to autopsy, with marked loss documented from simple evaporation, thiocyanate formation, hydrolysis, and polymerization; and time from autopsy to sample analysis, wherein cyanide concentrations may increase due to microbial action (Ballantyne and Marrs 1987b).

Antidotes

The antagonism of cyanide intoxication has been under investigation for at least 150 years. In 1840, cyanide lethality was reported to be antagonized by artificial respiration. In 1888, amyl nitrite was reported effective in antagonizing lethal effects of cyanide in dogs. In 1894, cobalt was shown to form a stable metal complex with cyanide and was used to antagonize cyanide. In 1933, the use of sodium thiosulfate as the sulfur donor was described (Way 1984). Many compounds are used today as cyanide antidotes including cobalt salts, rhodanese, sulfur donors, methemoglobin producers, carbohydrates, drugs used to treat acidosis, oxygen, methylene blue, 4-dimethylaminophenol, various aromatic amino- and nitro-compounds (such as aniline, p-aminopropiophenone, nitrobenzene), carbonyl compounds, and sodium pyruvate (Egekeze and Oehme 1980; EPA 1980; Solomonson 1981; Way 1981, 1984; Biehl 1984; Becker 1985; Ballantyne 1987b; Marrs 1987; Marrs and Ballantyne 1987; Way et al. 1988). Different antidotes are preferred in different countries: in the United States, a mixture of sodium nitrite and sodium thiosulfate; in France and the United Kingdom, cobalt edetate, also known as Kelocyanor; and in Germany, a mixture of 4-dimethylaminophenol and sodium thiosulfate.

The classic nitrite-thiosulfate treatment of cyanide poisoning, developed almost 60 years ago, is one of the antidotal combinations still employed (Way 1981). Excess oxygen improves this antidotal combination by potentiating the effectiveness of the nitrite-thiosulfate combination, as confirmed by studies in sheep and rats (Way 1984), even though, theoretically, oxygen should serve no useful purpose (Way et al. 1988). This therapeutic regimen protected rats against 20 LD50 doses of cyanide (Towill et al. 1978). Nitrite converts hemoglobin to methemoglobin, which has a high affinity for cyanide. The methemoglobin-HCN complex then slowly releases cyanide, which is converted to thiocyanate by way of rhodanese (Solomonson 1981). Sodium nitrite, administered intravenously, is now considered one of the more rapid therapeutic methods (Way 1984). The injection of sodium thiosulfate provides sulfur for the enzyme rhodanese to mediate the biotransformation of cyanide to the much less toxic thiocyanate (Egekeze and Oehme 1980). Multiple injections of sodium thiosulfate protected mice against death by organic cyanides and were more effective than sodium nitrite

(Willhite and Smith 1981). The nitrite-thiosulfate antidotal combination is one of the most effective treatments of cyanide poisoning, even though the specific mechanism of action of these two compounds is now being questioned, and concerns have been raised because of the toxicity of nitrite (Way 1981, 1984). One accepted therapy is an intravenous combination of sodium nitrite (1 mL of 20% solution) and sodium thiosulfate (3 mL of 20% solution), giving 4 mL of this mixture per 45 kg of body weight (Egekeze and Oehme 1980). For maximal effectiveness in treating cyanide intoxication in sheep, large doses of sodium thiosulfate (660 mg/kg BW) are given in combination with conventional doses of sodium nitrite (6.6 mg/kg BW; Egekeze and Oehme 1980). Livestock treatment in cases of suspected cyanide intoxication consists of intravenous administration of sodium nitrite at 10-20 mg/kg BW followed by sodium thiosulfate at 30-40 mg/kg BW; however, a sodium thiosulfate dose of 500 mg/kg BW, or more, may be more efficacious (Biehl 1984). Once clinical signs have abated, 1 g of activated charcoal per kilogram BW may be administered as a drench by way of a stomach tube (Biehl 1984). A 30-kg female goat *(Capra* sp.) was successfully treated after eating the leaves and fruit of the crab apple *(Malus sylvestris),* a plant that contains high levels of cyanogenic glycosides in leaves and fruits (Shaw 1986). Treatment consisted of four hourly treatments of 100 g of animal charcoal and bismuth subnitrate in water as a drench, followed by 300 mg sodium nitrite as a 1% aqueous solution, then 25 g of sodium thiosulfate. Another goat died despite identical treatment (Shaw 1986).

Cobalt compounds, such as hydroxocobalamin and its derivatives (i.e., cobalt histidine, cobalt chloride, dicobalt ethylenediamine tetracetic acid) have been used to treat cyanide poisoning for more than 100 years. Their efficacy was confirmed in pigeons (*Columba* sp.) and rabbits (*Oryctolagus sp*.), but cobalt compounds did not receive wide support as cyanide antagonists because of the inherent toxicity of cobalt ion (Way 1981, 1984). Nevertheless, proponents of the use of cobalt compounds (i.e., the United Kingdom, Scandinavia, much of Europe) stress the rapidity of action in forming a stable metal complex with cyanide, thereby preventing its toxic effect (Towill et al. 1978; Way 1984). One of the more frequently used cobalt compounds in cyanide treatment is hydroxocobalamin, which reverses cyanide toxicity by combining with cyanide to form cyanocobalamin (EPA 1980; Solomonson 1981). Hydroxocobalamin has been used in guinea pigs and baboons *(Papio anubis)* to lower blood cyanide levels, and in humans after inhalation or ingestion of cyanide compounds (Egekeze and Oehme 1980).

Dimethylaminophenol (DMAP) forms methemoglobin by setting up a catalytic cycle inside the erythrocyte, in which oxygen oxidizes the DMAP to N-N-dimethylquinoneimine, the latter oxidizing the hemoglobin to methemoglobin (Marrs 1987). Dogs poisoned with KCN and given DMAP intravenously had restored respiration and decreased plasma cyanide levels. The 4-dimethylamino-phenol induced ferrihemoglobin production, which combined with the cyanide in the red cells to form ferrihemoglobin cyanide (Christel et al. 1977).

No usable cyanide prophylactic therapy now exists for humans, although sodium thiosulfate, hydroxocobalamin, and other compounds have been used to protect against cyanide toxicity in laboratory animals (Mengel et al. 1989). For example, pyridoxal 5-phosphate, the active form of vitamin B_6, readily forms complexes with cyanides, and was effective in providing significant protection to rats (Keniston et al. 1987). Fructose fed prior to insult lessens cyanide-induced hepatotoxicity in rats (Younes and Strubelt 1988). L-ascorbic acid and dehydroascorbic acid probably act as protectants against cyanide toxicity by way of nontoxic cyanohydrin formation (Sprince et al. 1982). Carbon tetrachloride pretreatment was effective in protecting mice against death from most nitriles (Willhite and Smith 1981), and pretreatment with p-aminopropiophenone serves to protect against cyanide toxicity (D'Mello 1987).

Sources and Uses

Production of cyanides in the United States increased from about 136 million kg in 1963 to 318 million kg in 1976 (Towill et al. 1978; Way 1981; Marrs and Ballantyne 1987). Cyanide consumption in North America was 64 million kg in 1988 and 98 million kg in 1989; about 80% of these amounts was used in gold mining (Knudson 1990).

About 84% of domestic HCN production is used to produce organic cyanides, also known as nitriles, including acrylonitriles, methyl methacrylate, and adiponitrile (Towill et al. 1978). Nitriles tend to polymerize, which is the basis for their use in the manufacture of synthetic fibers, resins, plastics, dyestuffs, vitamins, solvents, elastomers, agricultural insecticides, and high pressure lubricants (Willhite and Smith 1981). The widespread usefulness of HCN is related to its strong tendency and that of its inorganic salts to form complexes

with metals. For example, sodium cyanide is used in metallurgy for the extraction of gold and silver from ores and in electroplating baths because it forms stable soluble complexes. Similar behavior makes alkali cyanide solutions excellent for cleaning silverware and other precious metals and is responsible for their general use in industry as metal cleaners (Towill et al. 1978). In Canada, more than 90% of the gold mined is extracted from ores with the cyanidation process. This process consists of leaching gold from the ore as a gold-cyanide complex, and gold being precipitated with the addition of zinc dust. A variety of cyanide compounds are produced during gold cyanidation (Simovic and Snodgrass 1985). In addition to their primary use in the metals and electroplating industries, and in the manufacture of synthetic fibers and plastics, various cyanide compounds have been used directly or as an intermediate to produce synthetic rubber, fumigants, rodenticides, insecticides, predator control agents, rocket fuels, paints and paint finishes, paper, nylon, pharmaceuticals, photographic chemicals, mirrors, cement, perfume, bleaches, soaps and detergents, riot control agents, fertilizers, and herbicides (Towill et al. 1978; Way 1981; Willhite and Smith 1981; Leduc 1984; Homan 1987).

Hydrogen cyanide vapor, because of its high and rapid acute lethal toxicity and ready diffusion, has been used widely to fumigate buildings, ships, and warehouses; to exterminate rabbits, rodents, and large predators; and in horticultural practice, to control insect pests that have developed resistance to other pesticides (Homan 1987; Ballantyne 1988). Typically, fumigation powders containing either calcium cyanide, $Ca(CN)_2$, or sodium cyanide, NaCN, are blown into burrows or scattered over the floor in greenhouses. On coming into contact with water, such powders liberate HCN vapor (Ballantyne 1988). Hydrogen cyanide released from $Ca(CN)_2$ is registered for use on almonds, dried beans, citrus, cocoa beans, grains, nuts, and spices (Towill et al. 1978). Cyanide-containing compounds are used for a variety of agricultural and pesticidal agents. These compounds include cyanogen (NCCN), as an intermediate in the production of some commercial fertilizers; cyanogen chloride (CNCl), in the manufacture of triazine herbicides; cyanogen bromide (CNBr), as a pesticidal fumigant; hydrogen cyanide, in the synthesis of methionine for animal feeds; ammonium thiocyanate (NH_4SCN), as a cotton defoliant; sodium thiocyanate (NaSCN), as a weedkiller; and calcium cyanamide (CaNCN), as a plant fertilizer, herbicide, pesticide, and defoliant of cotton and tomatoes (Homan 1987). Cyanide compounds have also been used as preservatives for raw vegetables (Towill et al. 1978).

Sodium cyanide has been used for about 50 years by the U.S. Fish and Wildlife Service against coyote in attempts to protect livestock, especially sheep. The Service has made extensive use of two NaCN ejector devices: "the coyote getter," from the late 1930's to 1970; and the M-44, from about 1968 to the present, except for the period 1972-74, when all uses of NaCN for predator control were canceled (EPA 1976a; Connolly and Simmons 1984). Although both ejectors dispense toxicant when pulled, they differ in the way ejection is achieved. In the coyote getter, the toxicant is in a 0.38-caliber cartridge case and is expelled by the explosive force of the primer plus a small powder charge. The M-44 uses a spring-driven plunger to push out its toxic contents. M-44 capsules weigh about 0.94 g, and consist of about 89% NaCN, 6% Celatom MP-78 (mostly diatomaceous silica), 5% potassium chloride, and 0.25% FP Tracerite yellow--used as a fluorescent marker (Connolly and Simmons 1984). Coyote getters and M-44's are set into the ground with only their tops protruding. Fetid scent or lure stimulates a coyote to bite and pull, whereupon a lethal dose of NaCN is ejected into its mouth; coma and death follow in 30 to 60 s. Although coyote getters were about 99% effective against coyotes, compared with 73% for M-44's, the Service decided that spring-driven plungers were less hazardous to operators than were explosive-driven plungers (Connolly and Simmons 1984). The coyote getter was generally much more selective than the trap for the capture of coyotes. It was less destructive than traps to small mammals, birds of prey, ground-nesting birds, deer, antelope, and domestic sheep, but more destructive to dogs, bears, and cattle (Robinson 1943). In a 1-year test period (1940-41) in Colorado, Wyoming, and New Mexico, the following numbers of animals were killed by the coyote getter: 1,107 coyotes, 2 bobcats (*Lynx rufus*), 24 dogs, 14 black-billed magpies (*Pica pica*), 7 foxes (*Vulpes* sp.), 8 unidentified skunks, 2 badgers, 2 unidentified eagles, 2 bears (*Ursus* sp.), and 1 each of hawk (unidentified), pika (*Ochotona* sp.), and cow (Robinson 1943).

Cyanide compounds have been used to collect various species of freshwater fish. In England and Scotland, cyanides are used legally to control rabbits, and illegally to obtain Atlantic salmon (*Salmo salar*) and brown trout (*Salmo trutta*) from rivers, leaving no visible evidence of damage to the fish (Holden and Marsden 1964). Sodium cyanide has been applied to streams in Wyoming and Utah to collect fish through anesthesia; mountain whitefish (*Prosopium williamsoni*) were sensitive to cyanide and died at concentrations that were tolerable to salmon and trout (Wiley 1984). Sodium cyanide was also used as a fish control agent in Illinois, Nebraska,

South Dakota, Missouri, and in the lower Mississippi River valley, but was never registered for this use because of human safety concerns (Lennon et al. 1970).

Cyanide compounds have been prescribed by physicians for treatment of hypertension and cancer (Sprince et al. 1982). Sodium nitroprusside ($Na_2Fe(CN)_5NO\text{-}2H_2O$) was widely used for more than 30 years to treat severe hypertension and to minimize bleeding during surgery (Solomonson 1981; Vesey 1987). Laetrile, an extract of ground apricot kernels, has been used for cancer chemotherapy and, in deliberate high intakes, as an attempted suicide vehicle (Gee 1987).

Road salt in some areas may contribute to elevated cyanide levels in adjacent surface waters (Ohno 1989). In climates with significant snowfall, road salt is applied as a deicing agent. Road salts are commonly treated with anticaking agents to ensure uniform spreading. One anticaking agent, sodium hexacyanoferrate, decomposes in sunlight to yield the highly toxic free cyanide that contaminates surface waters by runoff (Ohno 1989). Another anticaking agent, yellow prussiate of soda (sodium ferrocyanide), has been implicated in fish kills when inadvertently used by fish culturists (Barney 1989).

The military uses of HCN were first realized by Napoleon III, but it was not until World War I (WW I) that this application received widespread consideration. About 3.6 million kg of hydrogen cyanide were manufactured by France as a chemical weapon and used in WWI in various mixtures called Manganite and Bincennite, although its use was not highly successful because of limitations in projectile size and other factors. During WW II, the Japanese were armed with 50-kg HCN bombs, and the United States had 500-kg bombs. More than 500,000 kg of HCN chemical weapons were produced during WWII by Japan, the United States, and the Soviet Union, but it is not known to what extent these weapons were used in that conflict (Way 1981).

Cyanides are widely distributed among common plants in the form of cyanogenic glycosides (Egekeze and Oehme 1980; Solomonson 1981; Way 1981; Biehl 1984; Homan 1987; Marrs and Ballantyne 1987). Their toxicity following ingestion is primarily related to the hydrolytic release of HCN. Ingestion of cyanogenic plants probably has accounted for most instances of cyanide exposure and toxicosis in man and range animals. Of chief agricultural importance among plants that accumulate large quantities of cyanogenic glycosides are the sorghums, Johnson grass, Sudan grass, corn, lima beans, flax, pits of stone fruits (cherry, apricot, peach), vetch, linseed, sweet potatoes, bamboo shoots, southern mock orange, millet, almonds, and cassava. Factors favoring cyanide build-up in cyanogenic plants include high nitrogen and low phosphorus in soils (Biehl 1984); the potential for high glycoside levels is greatest in immature and rapidly growing plants (Egekeze and Oehme 1980). At present, more than 28 different cyanoglycosides have been measured in about 1,000 species of higher plants (Leduc 1984). In cassava, for example, more than 90% of the cyanide is present as linamurin, a cyanogenic glycoside, and the remainder occurs as free (nonglycoside) cyanide (Gomez et al. 1983). Laetrile, a preparation made from apricot kernels, contains high levels of amygdalin, a cyanogenic glycoside that can be degraded in the gut to cyanide and benzaldehyde. Several cases of cyanide poisoning in humans have been reported from intake of laetrile, either orally or anally (Solomonson 1981; Homan 1987). Cyanide formation in higher plants and microorganisms can also occur with compounds other than cyanogenic glycosides, such as glycine, glyoxylate plus hydroxylamine, or histidine (Solomonson 1981; Vennesland et al. 1981b). In some cases, plants may contain cyanide residues resulting from fumigation with HCN (Way 1981).

Many species of plants, including some fungi, bacteria, algae, and higher plants, produce cyanide as a metabolic product (Leduc et al. 1982; Leduc 1984). Some species of soil bacteria suppress plant diseases caused by soilborne pathogens by producing metabolites with antibiotic activity. Certain strains of *Pseudomonas fluorescens,* a soil bacterium, suppress black root rot of tobacco caused by the fungus *Thielaviopsis basicola* by excreting several metabolites, including HCN (Voisard et al. 1989). A wide variety of bacteria and fungi can degrade cyanide compounds, and may be useful in the treatment of cyanide wastes (Towill et al. 1978). For example, several species of fungi known to be pathogens of cyanogenic plants can degrade cyanide by hydration to formamide; dried mycelia of these species are now sold commercially to detoxify cyanide in industrial wastes (Knowles 1988).

Anthropogenic sources of cyanide in the environment include industrial processes, laboratories, fumigation operations, cyanogenic drugs, fires, cigarette smoking, and chemical warfare operations (Marrs and Ballantyne 1987). Cyanides are present in many industrial wastewaters, especially those of electroplaters; manufacturers of paint, aluminum, and plastics; metal finishers; metallurgists; coal gasification processes; certain mine

operations; and petroleum refiners (Towill et al. 1978; Egekeze and Oehme 1980; Way 1981, 1984). Electroplaters are a major source. In the United States alone, electroplaters discharge about 9.7 million kg of cyanide wastes annually into the environment from 2,600 electroplating plants (Marrs and Ballantyne 1987). Paint residues annually contribute an additional 141,300 kg of cyanide wastes into the environment, and paint sludges 20,400 kg (Way 1981; Marrs and Ballantyne 1987). Cyanide can also originate from natural processes, such as cyanide production by bacteria, algae, and fungi, and from many terrestrial plants that release free HCN when their cellular structure is disrupted (Leduc 1981). Hospital wastewaters usually contain no detectable cyanide, but concentrations up to 64 µg CN^-/L have been measured after alkali chlorination treatment (Tatsumoto and Hattori 1988). It seems that various compounds common in hospital wastewaters will produce 15-25 µg CN^-/L after alkali chlorination; these compounds include hydantoin (an antiepilepsy agent) and related nitrogenous compounds, such as hydantonic acid, 5,5-diphenyl hydantoin, imidazole, and 2-imidazolidinone (Tatsumoto and Hattori 1988).

Free hydrogen cyanide occurs only rarely in nature because of its high reactivity. The gas is sometimes found in the atmosphere, however, as a result of emissions from the petrochemical industry, malfunctioning catalytic converters on automobiles, fumigation of ships and warehouses, incomplete combustion of nitrogen-containing materials, and from tobacco smoke (Towill et al. 1978; Way 1981, 1984). Hydrogen cyanide is known to be produced in fires involving nitrogen-containing polymers and is probably the most important narcotic fire product other than carbon monoxide (Purser et al. 1984). Cyanide-related fire deaths and injuries, as judged by elevated blood cyanide and thiocyanate concentrations, have been documented in airplanes, jails, and high-rises (Becker 1985; Ballantyne 1987b; Lundquist and Sorbo 1989). In a study of fire victims in Scotland, elevated blood cyanide levels were found in 78% of fatalities, and 31% had blood levels considered to be toxic (Purser et al. 1984). Major factors that influence HCN release include the chemical nature of the material, temperature, oxygen availability, and burning time (Ballantyne 1987b). Substantial quantities of free HCN and organic cyanides are known to be produced in fire settings involving horsehair, tobacco, wool, silk, and many synthetic polymers, such as polyurethane and polyacrylonitriles (Egekeze and Oehme 1980; Purser et al. 1984; Becker 1985; Ballantyne 1987b). Polyacrylonitrile, for example, is used in fabrics, upholstery covers, paddings, and clothing; about 50% of the mass of the polymer is theoretically available as HCN under thermal decomposition (Purser et al. 1984; Homan 1987).

Background Concentrations

The reactivity of HCN, and its ability to condense with itself and other compounds, was probably responsible for the prebiotic formation of the majority of biochemical compounds required for life (Marrs and Ballantyne 1987). Cyanide is now known to be present in a number of foodstuff and forage plants, as a metabolite of certain drugs, and in various industrial pollutants; it also may be formed by the combustion of cyanide-releasing substances, such as plastics in airplane fires and tobacco in smoking (Robinson et al. 1985). Hydrogen cyanide production may occur in hepatopancreas of mussels, *Mytilus edulis* (Vennesland et al. 1981b), in rat liver (Solomonson 1981), and in green and blue-green algae during nitrate metabolism (Leduc et al. 1982). Except for certain naturally occurring organic cyanide compounds in plants, it is uncommon to find cyanide in foods consumed in the United States (EPA 1980).

The cyanide anion is found in a variety of naturally occurring plant compounds as cyanogenic glycosides, glycosides, lathyrogenic compounds, indoleacetonitrile, and cyanopyridine alkaloids. Plants that contain cyanogenic glycosides are potentially poisonous because bruising or incomplete cooking can result in glycoside hydrolysis and release of HCN (Towill et al. 1978). Cyanide concentrations in cyanogenic plants are usually highest in leaves of young plants; levels drop rapidly after pollination (Biehl 1984). There are about 20 major cyanogenic glycosides, of which usually only one or two occur in any plant. They are synthesized from amino acids and sugars and are found in many economically important plants, such as sorghum, flax, lima bean, cassava, and many of the stone fruits (Table 2; Towill et al. 1978; Shaw 1986). Cassava contains linamurin and lotaustralin, whereas the main cyanogenic glycoside in cereals is dhurrin; consumption of foods containing toxic cyanogens (primarily cassava) has been associated with death or morbidity--on an acute basis--or goiter and tropical ataxic neuropathy on a chronic consumption basis (Okolie and Ugochukwu 1989). Cassava is a perennial shrub, native to the neotropics, grown for its tuberous starchy roots, and a traditional dietary staple of many indigenous populations in Amazonia, especially the Tukanoan Indians in northwestern Amazonia (Dufour 1988). Cassava is one of the few food plants in which the cyanide content may create toxic problems. All

varieties of cassava contain cyanogenic glycosides capable of liberating HCN, but amounts vary greatly depending on variety and environmental conditions. Bitter cultivars of cassava provide over 70% of the Tukanoan's food energy, appearing in the diet as bread, meal, a starch drink, and boiled cassava juice. The greatly elevated total cyanide content in bitter varieties (Table 2) may contain 5.1-13.4% of the total as the toxic free cyanide (Dufour 1988).

The production of HCN by animals is almost exclusively restricted to various arthropods: 7 of about 3,000 species of centipedes; 46 of 2,500 species of polydesmid millipedes; and 10 of 750,000 species of insects, including 3 species of beetles, 4 moths, and 3 butterflies (Duffey 1981). Millipedes--which are eaten frequently by toads and starlings--secrete cyanide for defensive purposes in repelling predators; in zygaenid moths, cyanide seems to be localized in eggs (Table 2; Duffey 1981).

Cyanide concentrations in fish from streams that were deliberately poisoned with cyanide ranged between 10 and 100 µg total cyanide per kilogram whole body fresh weight (FW; Wiley 1984). Total cyanide concentrations in gill tissues of salmonids under widely varying conditions of temperature, nominal water concentrations, and duration of exposure ranged from about 30 µg/kg FW to >7,000 µg/kg (Holden and Marsden 1964). Unpoisoned fish usually contained < 1 µg/kg FW in gills, although values up to 50 µg/kg occurred occasionally. Lowest cyanide concentrations in gills occurred at elevated (summer) water temperatures; at lower temperatures, survival was greater and residues were higher (Holden and Marsden 1964). Fish retrieved from cyanide-poisoned environments, dead or alive, can probably be consumed by humans because muscle cyanide residues were considered to be low (i.e., <1,000 mg/kg FW; Leduc 1984).

Cyanide pollution is likely to occur in many places, ranging from industrialized urban areas to gold mines in the western United States and Northwest Territories of Canada (Table 2). Cyanides are ubiquitous in industrial effluents, and their increasing generation from power plants and from the combustion of solid wastes is expected to result in elevated cyanide levels in air and water (Leduc 1984). However, data are scarce on background concentrations of cyanides in various nonbiological materials. In soils, for example, high concentrations are unusual and are nearly always the result of improper waste disposal (Towill et al. 1978). Cyanides in soils are not absorbed or retained; under aerobic conditions, microbial metabolism rapidly degrades cyanides to carbon dioxide and ammonia; under anaerobic conditions, cyanides are converted by bacteria to gaseous nitrogen compounds that escape to the atmosphere (Towill et al. 1978). Heat treatment wastes from metal processing operations may contain up to 200 g CN/kg, mostly as NaCN, and are frequently hauled to landfills for disposal (Lagas et al. 1982). The presence of cyanide in landfill waste is potentially hazardous because of the possibility that cyanide may leach to soil and groundwater, release HCN, and disturb natural microbiological degradation of organic materials. Measurements at landfills in England and the Netherlands showed total cyanide levels up to 560 g/kg in soil and 12 µg/L in groundwater (Lagas et al. 1982). However, 7-month-long experimental studies of cyanide in heat treatment wastes in landfills showed that between 72 and 82% of the cyanide was converted, mostly to ammonium and organic nitrogen compounds; between 4 and 22% of the cyanide leached as free or complex cyanide; and up to 11% remained in the landfill (Lagas et al. 1982).

Table 2. Background concentrations of cyanide in selected living resources and nonbiological materials. Values are in milligrams total cyanide per kilogram fresh weight or milligrams per liter.

Environmental compartment	Concentration[a] (mg/kg or mg/L)	Reference[b]
Biological		
Cyanogenic plants		
Bamboo (*Bambusa, Arundinaria, Dendrocalamus*)		
Tip	Max. 8,000	1
Stem	Max. 3,000	1
Stargrass, *Cynodon plectostachyus*, whole	180	1
Rose family, *Malus* spp., *Pyrus* spp.	Max. 200	2
Cassava, *Manihot esculenta*		
Bitter varieties		
Leaves	347–1,000	3, 4

Roots	327–550	1, 4
Dried roots	95–2,450	1, 3, 4
Stem	1,130	1
Mash	162	5
Bark		
Total cyanide	1,351	6
Free cyanide	102	6
Peel		
Total cyanide	1,390	6
Free cyanide	255	6
Pulp		
Total cyanide	810	6
Free cyanide	53	6
Sweet varieties		
Leaves	377–500	3, 4
Roots	138	4
Dried roots	46–<100	3, 4
Mash	81	5
Lima beans, *Phaseolus lunatus*		
United States	100–170	1
Burma	2,100	1
Puerto Rico	3,000	1
Java	3,120	1
Almond, *Prunus amygdalus*, nut		
Bitter	(280–2,500)	1
Spicy	(86–98)	1
Sweet	(22–54)	1
Seeds, 4 species, Nigeria, whole, frequently consumed by humans		
Phaseolus sp.	(381–1,093)	7
Vigna sp.	(285–1,223)	7
Cajanus sp.	(208–953)	7
Canavalia sp.	(285–953)	7
Sorghum, *Sorghum spp.*, young plant, whole	Max. 2,500	1
Cyanogenic arthropods		
Millipede, *Apheloria corrugata*, whole	428	8
Millipede, *Apheloria kleinpeteri*, whole	18	8
Zygaenid moth, *Zygaena filipendulae*, whole	668	8
Mammals		
Humans, *Homo sapiens*		
Blood		
Normal	<0.2	9
Afflicted with Leber's optic atrophy	1.4	9
Plasma		
Nonsmokers	0.05; Max. 0.11	10
Smokers	0.075; Max. 0.3	10
Nonbiological		
Air		
Automobile exhaust		
Adverse conditions	Max. 10.0	1
Equipped with catalytic convertor	1.1	1
Sewage sludge		

From publicly owned treatment works, United States	749[c]	18
Water, uncontaminated		
Rural watersheds	0.003	11,12
Industrial areas	0.02	11, 12
Small watersheds, covered with grasslands and forest, uninhabited by humans	0.0007–0.002; Max. 0.005	12
Western and central Canada, 11 rivers, 1974–77	Max. 0.006	12
U.S. water supplies, 2,595 samples nationwide	0.0009; Max. 0.008	1, 13
U.K. water supplies	<0.05; Max. 0.1	1
Wastewaters/runoff		
Electroplaters		
Total cyanide	0.2; Max. 3.0	14, 15
Dissociable cyanide	0.07	15
Complex cyanide	0.2	15
Thiocyanate	0.02	15
Plating wastewater		
Before treatment with alkaline chlorination	0.18	16
After treatment	0.005	16
Road salt dock		
Total cyanide	25.6	15
Dissociable cyanide	2.9	15
Complex cyanide	23.1	15
Thiocyanate	0.0	15
Steel industry		
Plating baths	72 (9–115)	1, 14
Coke oven liquor	6 (0–8)	1
Oil refineries		
Total cyanide	0.01; Max. 4.0	14, 15
Dissociable cyanide	0.0	15
Complex cyanide	0.01	15
Thiocyanate	2.2	15
Coking operations		
Total cyanide	2.1	15
Dissociable cyanide	0.3	15
Complex cyanide	0.8	15
Thiocyanate	23.6	15
Hospital wastewaters		
Before alkaline chlorination	ND	17
After treatment	0.06	17
Gold mills, Canada	0.3–26.5	14
Gold mine cyanide extraction leach ponds, California, Nevada, and Arizona	Usually 200–300, frequently 700, occasionally 9,000	19
Wastewater treatment plants,		
Chicago		
Treated effluent		
Total cyanide	0.005–0.03	15
Dissociable cyanide	0.003–0.007	15
Complex cyanid	0.002–0.02	15
Thiocyanate	0.006–0.03	15
Untreated wastewater		
Total cyanide	0.02–0.06	15

Dissociable cyanide	0.004–0.05	15
Complex cyanide	0.02–0.08	15
Thiocyanate	0.03–0.27	15
Sludge		
Total cyanide	0.49–3.79	15
Dissociable cyanide	0.06–0.44	15
Complex cyanide	0.43–5.4	15
Thiocyanate	0.2–0.9	15

[a]Concentrations are shown as means, range (in parentheses), and maximum (Max.).

[b]1, Towill et al. 1978; 2, Shaw 1986; 3, Gomez et al. 1983; 4, Casadei et al. 1984; 5, Ukhun and Dibie 1989; 6, Dufour 1988; 7, Okolie and Ugochukwu 1989; 8, Duffey 1981; 9, Berninger et al. 1989; 10, Egekeze and Oehme 1980; 11, Leduc 1981; 12, Leduc 1984; 13, EPA 190; 14, Leduc et al. 1982; 15, Kelada 1989; 16, Nonomura and Hobo 1989; 17, Vennesland et al. 1981a; 18, Beyer 1990; 19, Clark and Hothem 1991.

[c]Concentration is in milligrams per kilogram dry weight.

Hydrogen cyanide (HCN) is a common industrial pollutant and frequently occurs in water at concentrations between 0.1 and several milligrams per liter of free HCN (Leduc 1978; Leduc et al. 1982). Total cyanides is the most often cited measurement in aqueous solutions, owing to limitations in analytical methodologies (Leduc et al. 1982). Cyanides have been identified in fresh waters of rural and wilderness areas in Canada and Germany. Concentrations ranging between 30 and 60 µg total cyanides per liter seem related to runoff, with cyanide peaks more frequent in fall and winter during periods of minimal runoff (Leduc et al. 1982). In larger rivers, cyanide was low in winter owing to dilution by high runoff, but peaked in summer because of cyanide production by plants (Leduc 1984). Cyanides do not seem to persist in aquatic environments. In small, cold oligotrophic lakes treated with 1 mg NaCN/L, acute toxicity was negligible within 40 days. In warm shallow ponds, toxicity disappeared within 4 days after application of 1 mg NaCN/L. In rivers and streams, toxicity rapidly disappeared on dilution (Leduc 1984). Cyanide was not detectable in water and sediments of Yellowknife Bay, Canada, between 1974 and 1976, although the bay receives liquid effluents containing cyanides from an operating gold mine. Nondetection was attributed to rapid oxidation (Moore 1981). Several factors contribute to the rapid disappearance of cyanide from water. Bacteria and protozoans may degrade cyanide by converting it to carbon dioxide and ammonia. Chlorination of water supplies can result in conversion to cyanate (EPA 1980). An alkaline pH favors oxidation by chlorine, and an acidic pH favors volatilization of HCN into the atmosphere (EPA 1980).

Persistence in Water, Soil, and Air

In water, cyanides occur as free hydrocyanic acid, simple cyanides, easily degradable complex cyanides such as $Zn(CN)_2$, and sparingly decomposable complex cyanides of iron and cobalt; complex nickel and copper cyanides are intermediate between the easily decomposable and sparingly degradable compounds (Towill et al. 1978). Cyanide has relatively low persistence in surface waters under normal conditions but may persist for extended periods in groundwater (Way 1981). Volatilization is the dominant mechanism for removal of free cyanide from concentrated solutions and is most effective under conditions of high temperatures, high dissolved oxygen levels, and at increased concentrations of atmospheric carbon dioxide (Leduc et al. 1982; Simovic and Snodgrass 1985). Loss of simple cyanides from the water column is primarily through sedimentation, microbial degradation, and volatilization (Leduc et al. 1982; Marrs and Ballantyne 1987). Water-soluble strong complexes, such as ferricyanides and ferrocyanides, do not release free cyanide unless exposed to ultraviolet light. Thus, sunlight may lead to cyanide formation in wastes containing iron-cyanide complexes (Towill et al. 1978; Leduc et al. 1982; Simovic and Snodgrass 1985; Marrs and Ballantyne 1987).

Alkaline chlorination of wastewaters is one of the most widely used methods of treating cyanide wastes. In this process, cyanogen chloride, (CNCl) is formed, which at alkaline pH is hydrolyzed to the cyanate ion (CNO^-). If free chlorine is present, CNO^- can be further oxidized (Way 1981; Leduc et al. 1982; Simovic and Snodgrass 1985; Marrs and Ballantyne 1987). Other methods used in cyanide waste management include lagooning for natural degradation, evaporation, exposure to ultraviolet radiation, aldehyde treatment, ozonization, acidification-volatilization-reneutralization, ion exchange, activated carbon absorption, electrolytic

decomposition, catalytic oxidation, and biological treatment with cyanide-metabolizing bacteria (Towill et al. 1978; EPA 1980; Way 1981; Marrs and Ballantyne 1987). In the case of Canadian gold-mining operations, the primary treatment for cyanide removal is to retain gold mill wastewaters in impoundments for several days to months; removal occurs through volatilization, photodegradation, chemical oxidation, and, to a lesser extent, microbial oxidation. Microbial oxidation of cyanide is not significant in mine tailing ponds, which typically have pH >10, a low number of microorganisms, low nutrient levels, large quiescent zones, and cyanide concentrations >10 mg/L (Simovic and Snodgrass 1985).

Cyanide seldom remains biologically available in soils because it is either complexed by trace metals, metabolized by various microorganisms, or lost through volatilization (Towill et al. 1978; Marrs and Ballantyne 1987). Cyanide ions are not strongly adsorbed or retained on soils, and leaching into the surrounding ground water will probably occur. Under aerobic conditions, cyanide salts in the soil are microbially degraded to nitrites or form complexes with trace metals. Under anaerobic conditions, cyanides denitrify to gaseous nitrogen compounds that enter the atmosphere.

Volatile cyanides occur only occasionally in the atmosphere, due largely to emissions from plating plants, fumigation, and other special operations (Towill et al. 1978). Under normal conditions cyanide has relatively low persistence in air, usually between 30 days and 1 year (Way 1981), although some atmospheric HCN may persist for up to 11 years (Marrs and Ballantyne 1987). Data are lacking on the distribution and transformation of cyanide in the atmosphere (Towill et al. 1978) and should be acquired.

Lethal and Sublethal Effects

Terrestrial Flora and Invertebrates

Bacteria exposed to cyanide may exhibit decreased growth, altered cell morphology, decreased motility, mutagenicity, and altered respiration (Towill et al. 1978). Mixed microbial populations capable of metabolizing cyanide and not previously exposed to cyanide were adversely affected at 0.3 mg HCN/kg; however, these populations can become acclimatized to cyanide and can then degrade wastes with higher cyanide concentrations (Towill et al. 1978). Acclimatized populations in activated sewage sludge can often completely convert nitriles to ammonia, sometimes at concentrations as high as 60 mg total cyanides per kilogram (Towill et al. 1978). Cyanide can be degraded by various pathways to yield a variety of products, including carbon dioxide, ammonia, beta-cyanoalanine, and formamide (Knowles 1988). Several species of fungi can accumulate and metabolize cyanide, but the products of cyanide metabolism vary. For example, carbon dioxide and ammonia are formed as end products by *Fusarium solani*, whereas alpha-amino butyronitrile is a major cyanide metabolite of *Rhizoctonia solani*(Towill et al. 1978). Significant amounts of cyanide are formed as secondary metabolites by many species of fungi and some bacteria by decarboxylation of glycine (Knowles 1988). Rhizobacteria may suppress plant growth in soil through cyanide production. In one case volatile metabolites--including cyanide--from fluorescent pseudomonad soil bacteria prevented root growth in seedlings of lettuce, *Lactuca sativa* (Alstrom and Burns 1989). Not all cyanogenic isolates inhibited plant growth. Some strains promoted growth in lettuce and beans by 41-64% in 4 weeks versus 49-53% growth reduction by inhibitory strains (Alstrom and Burns 1989).

In higher plants, elevated cyanide concentrations inhibited respiration (through iron complexation in cytochrome oxidase) and ATP production and other processes dependent on ATP, such as ion uptake and phloem translocation, eventually leading to death (Towill et al. 1978). Cyanide produces chromosomal aberrations in some plants, but the mode of action is unknown (Towill et al. 1978). At lower concentrations, effects include inhibition of germination and growth, but cyanide sometimes enhances seed germination by stimulating the pentose phosphate pathway and inhibiting catalase (Towill et al. 1978; Solomonson 1981). The detoxification mechanism of cyanide is mediated by rhodanese. This enzyme is widely distributed in plants (Solomonson 1981; Leduc 1984). The rate of production and release of cyanide by plants to the environment through death and decomposition is unknown (Towill et al. 1978).

Free cyanide is not found in intact plant cells. Many species of plants, such as cassava, sorghum, flax, cherries, almonds, and beans, contain cyanogenic glycosides that release HCN when hydrolyzed (Towill et al. 1978). Cyanide poisoning of livestock by forage sorghums, such as Sudan grass and various hybrid cultivars, is well known (Cade and Rubira 1982) and has led to the development of several variations of sorghums that have a reduced capability of producing cyanide poisoning (Egekeze and Oehme 1980). Cyanogenesis has an

important role in plant defense against predatory herbivores. This herbivore-plant interaction is not simple; the degree of selectivity by herbivores varies among individuals and by differences in hunger and previous diet (Jones 1988).

Cyanide metabolism in higher plants involves amino acids, N-hydroxyamino acids, aldoximes, nitriles, and cyanohydrins (Halkier et al. 1988). Cyanide is a coproduct of ethylene synthesis in higher plants. The increase in ethylene production that occurs during the senescence of certain flowers and the ripening of fruits is accompanied by a rise in beta-cyanoalanine activity; activity of this enzyme correlates closely with that of ACC (1-aminocyclopropane-l-carboxylic acid) oxidase, the last enzyme in the ethylene pathway. Manning (1988) suggested that ACC oxidase reacts with various amino acids to liberate cyanide. Cyanide added to isolated castorbean (*Ricinus communis*) mitochondria significantly enhanced the rate and amount of protein synthesis. Cyanide stimulated mitochondrial protein synthesis in a dose-dependent manner, with an optimal stimulation of over 2 times at 26 µg/L, but at this concentration mitochondrial respiration was inhibited by 90% (Kaderbhai et al. 1989). Cyanide is a weak competitive inhibitor of green bean *(Phaseolus vul*garis) lipoxygenase, an enzyme that catalyzes the formation of hydroperoxides from polyunsaturated fatty acids (Adams 1989). Because degradation of hydroperoxides causes unacceptable changes in bean flavor and color, compounds that inhibit lipoxygenase may enjoy wide application in the frozen vegetable industry (Adams 1989). Corn seedlings from cold-resistant cultivars were more resistant to 65 mg KCN/L at low temperatures (13°C) than were seedlings from cold-susceptible cultivars (25°C), as judged by respiratory activity of mitochondria (Van De Venter 1985). Results suggest that cyanide-resistant respiration may play a role in cold resistance in maize seedlings, although more evidence is needed to demonstrate that cold-resistant plants actually use their greater potential for alternative respiration at low temperatures (Van De Venter 1985).

The cyanogenic system comprising cyanogenic glycosides, cyanohydrins, betaglucosidases, and nitrile lyases is widespread in plants, but also occurs in several species of arthropods, including the tiger beetle (*Megacephala virginica*), leaf beetle (*Paropsis atomaria*), zygaenid moths, and certain butterflies (Nahrstedt 1988). In *Zygaena trifolii*, cyanide compounds seem to function as protection against predators (Nahrstedt 1988). Defensive secretions of cyanide have also been reported in polydesmid millipedes, and these organisms seem to be more tolerant than other species when placed in killing jars containing HCN (Towill et al. 1978). In a millipede (*Apheloria* sp.), cyanide is generated in a two-compartment organ by hydrolysis of mandelonitrile; cyanide generation occurs outside the gland when the components of the two compartments are mixed during ejection (Towill et al. 1978).

Highly toxic substances, such as cyanides, are sometimes feeding cues and stimulants for specialized insects. For example, instar larvae of the southern armyworm (*Spodoptera eridania*) strongly prefer cyanogenic foods, such as foliage of the lima bean, a plant with comparatively elevated cyanide content--up to 31 mg/kg in some varieties--in the form of linamurin (Brattsten et al. 1983). Feeding was stimulated in southern armyworms at dietary levels up to 508 mg KCN/kg (208 mg HCN/kg) for first to fourth instar larval stages, and between 1,000 and 10,000 mg KCN/kg diet for fifth and sixth instar larvae (Brattsten et al. 1983). Sixth instar larvae preexposed to diets containing 5,000 mg KCN/kg showed no adverse affects at dietary levels of 10,000 mg KCN/kg; however, previously unexposed larvae showed reversible signs of poisoning at 10,000 mg/kg diet, including complete inhibition of oviposition and 83% reduction in adult emergence (Brattsten et al. 1983). Experimental studies with southern armyworm larvae and thiocyanate--one of the in vivo cyanide metabolites--showed that 5,000 mg thiocyanate per kilogram diet reduced pupation by 77%, completely inhibited oviposition, and reduced adult emergence by 80% (Brattsten et al. 1983), strongly suggesting that thiocyanate poisoning is the primary effect of high dietary cyanide levels in southern armyworms.

Resistant species, such as southern armyworms, require injected doses up to 800 mg KCN/kg BW (332 mg HCN/kg BW) or diets of 3,600 mg KCN/kg for 50% mortality (Brattsten et al. 1983), but data are scarce for other terrestrial invertebrates. Exposure to 8 mg HCN/L air inhibits respiration in the granary weevil (*Sitophilus granarius*) within 15 min and kills 50% in 4 h; some weevils recover after cessation of 4-h exposure (Towill et al. 1978).

Aquatic Organisms

Numerous accidental spills of sodium cyanide or potassium cyanide into rivers and streams have resulted in massive kills of fishes, amphibians, aquatic insects, and aquatic vegetation; sources of poisonings were storage reservoirs of concentrated solutions, overturned rail tank cars, or discharge of substances generating free HCN

in the water from hydrolysis or decomposition (Leduc 1984). Data on the recovery of poisoned ecosystems are scarce. In one case, a large amount of cyanide-containing slag entered a stream from the reservoir of a Japanese gold mine as a result of an earthquake (Yasuno et al. 1981). The slag covered the streambed for about 10 km from the point of rupture, killing all stream biota; cyanide was detected in the water column for only 3 days after the spill. Within 1 month flora was established on the silt covering the above-water stones, but there was little underwater growth. After 6-7 months, populations of fish, algae, and invertebrates had recovered, although species composition of algae was altered (Yasuno et al. 1981).

Fish were the most sensitive aquatic organisms tested under controlled conditions. Significant adverse nonlethal effects, including reduced swimming performance and inhibited reproduction, were observed in the range of 5.0-7.2 µg free cyanide per liter; deaths were recorded for most species between 20 and 76 µg/L (Table 3). Among invertebrates, adverse nonlethal effects were documented between 18 and 43 µg/L, and lethal effects between 30 and 100 µg/L--although some deaths were recorded in the range 3-7 µg/L for the amphipod *Gammarus pulex* (Table 3). Algae and macrophytes were comparatively tolerant; adverse effects were reported at >160 µg free cyanide per liter (Table 3).

Table 3. Cyanide effects on selected species of aquatic organisms. All concentrations are shown as micrograms of hydrogen cyanide per liter (ppb) of medium at start unless indicated otherwise.

Species, concentration, and other variables	Effects	Reference[a]
Algae and macrophytes		
Alga, *Chlorella* sp.		
7,300	Inhibition of photosynthesis	3
30,000	Enzyme inhibition	2
Water hyacinth, *Eichhornia crassipes*		
300,000	Nonphytotoxic in 72 h; plants contained total cyanide of 6.7 g/kg dry weight (DW), equivalent to bioconcentration factor (BCF) of x22	5
Freshwater aquatic plants, nine species, 65,000, 30-min exposure	No effect on respiratory oxygen uptake in six species of angiosperms (*Myriophyllum* sp., *Potamogeton* spp., *Elodea* sp., *Ruppia* sp., *Cabomba* sp.); some effect on two species of bryophytes (*Rhynchostegium riparioides*, *Fontinalis antipyretica*) and one species of alga (*Cladophora glomerata*)	4
Alga, *Microcystis aeruginosa*		
7,990	90% kill	2
Alga, *Prototheca zopfi*		
3,000	Inhibition of respiration	2
Alga, *Scenedesmus quadricauda*		
160, as CN^-	Toxic	1
Invertebrates		
Copepod, *Acartia clausi*		
30	LC50 (96 h)	2
Isopod, *Asellus communis*		
29–40	MATC[b]	2, 8
1,834	LC50 (11 days)	
Oyster, *Crassostrea* sp.		
150	Motor activity suppressed after 10 min	2

Daphnid, *Daphnia magna*		
160	LC50 (96 h)	10
Daphnid, *Daphnia pulex*		
83	LC50 (96 h)	2
Amphipod, *Gammarus pseudolimnaeus*		
16–21	MATC[b]	8
58	LC50 (96 h) at 20º C	8
184	LC50 (96 h) at 5.2º C	8
Amphipod, *Gammarus pulex*		
3	LC50 (15 h); 50% dead in 14 days after exposure for 5 h	6
7.5	LC50 (9h); exposure for 66 min results in 50% mortality 14 days after exposure	6
15	LC50 (6 h); exposure for 45 min causes 50% mortality 14 days after exposure	6
75	LC50 (3 h); exposure for 18 min results in 50% kill 14 days after exposure	6
Mussel, *Mytilus edulis*		
18	After exposure for 14 days growth was reduced and uptake of glycine was inhibited	9
100	LC20 (14 days)	9
Mysid shrimp, *Mysidopsis bahia*		
11, 20, 43, or 70	Life-cycle (29 days) exposure produced adverse effects on survival at 70 µg/L, and on reproduction at 43 µg/L; no measurable effects at lower doses of 11 and 20 µg/L	7
93–113	LC50 (96 h)	2, 7
Snail, *Physa heterostropha*		
432	LC50 (96 h)	3, 10
Fiddler crab, *Uca tangeri*		
Isolated perfused gills subjected to 26,000 CN^-/L, as KCN	Inhibited sodium chloride absorption across gill epithelium; effect reversible if exposure <5 min and nonreversible if >30 min. Salt absorption effect regulated by $(Na^+ + K^+)$ ATPase	11
Fish		
Brown bullhead, *Ictalurus nebulosus*		
Subjected to steadily increasing concentration of waterborne cyanide over a 9-h period: 200 at 1 h, 600 at 3 h, 1,000 at 5 h, and 1,800 at 9 h	Increased heart beat rate at lower concentrations and decreased rate at higher concentrations; hyperventilation in first 3 h followed by decrease in ventilation rate; oxygen consumption paralleled changes in heart and ventilatory rates. Death in 9 h	21
Longnose gar, *Lepisosteus osseus*		
12 µg CN^-/kg BW, as sodium cyanide, equivalent to 10.7 µg CN or 20 µg NaCN, single injection	Hypoxic response and bradycardia; effects appear earlier when administered into the ventral aorta or conus than into the dorsal aorta	27
Bluegill, *Lepomis macrochirus*		
5.0	Inhibited spawning following chronic exposure	22
5.2	Complete inhibition of spawning after exposure for 57–289 days	2, 8
9.3–19.8	MATC[b]	2

19.4	Reduced survival of fry in 57-day exposure which began with eggs	8
50	Tolerated concentration at higher temperatures, but no reproduction	8
56–227	LC50 (96 h) for juveniles	8, 22
109–218	LC50 (96 h) for fry	8
232–365	LC50 (96 h) for eggs	22
535–690	LC50 (96 h) for eggs at hatching	8
Largemouth bass, *Micropterus salmoides*		
101	LC50 (96 h) for juveniles	8
Cutthroat trout, *Oncorhynchus clarki*		
1,000 for 20 min	All fish recovered within 12 min and fed and grew normally during the next 6 months	31
Coho salmon, *Oncorhynchus kisutch*		
7.0	Reduction of 50% in swimming performance during 8-day exposure	13
10	Swimming speed reduced after exposure for 2 h	2
Rainbow trout, *Oncorhynchus mykiss*		
0.1 or 1.0	No effect on sperm motility or on fertilization rate at lower dose; some effect on sperm motility at higher dose	12
5.0	Reduction of 50% in swimming performance in 20-day exposure	13
10	No effect on growth during 20-day exposure at 6º C	13
10	Increased respiration rate in 4 days, growth reduction and liver damage in 9 days, abnormal oocyte development and reduced spermatogonia production in 18–20 days	2
10, 20, or 30 for 7 days, sexually mature females	Exposure to 10 or 20 µg/L caused a reduction in serum calcium to levels insufficient for the production of exogenous yolk; this was not observed in the 30 µg/L group	14
10, 20, or 30 for 18 days, juveniles	Degenerative necrosis of liver hepatocytes at all concentrations in a dose-dependent pattern. Severe initial growth repression at all concentrations followed by a significant increase, but growth remained depressed 40% and 95% in the 20 and 30 µg/L groups, respectively, at 18 days	15
10 or 20, exposure for 20 days during midsummer, sexually maturing females	Both concentrations resulted in abnormal oocytes, delayed development, and significantly reduced the number of eggs for spawning	16
15	No effect on growth during 20-day exposure at 12º C	13
18	No deaths in 96 h at 6º C	13
20	65% reduction in weight gain after 21 days	2
28	LC50 (96 h) at 6º C	10, 13, 17
30	No effect on growth during 20-day exposure at 18º C	13
32	No deaths in 96 h at 12º C	13
42	LC50 (96 h) at 12º C	13
43	LC50 (96 h) for nonexercised juveniles	18

	during winter	
46–75	LC50 (96 h) for juveniles	8, 19
52	LC50 (96 h) for exercised juveniles during winter	18
60	No deaths in 96 h at 18º C	13
68	LC50 (96 h) at 18º C	10, 13, 17
96	LC50 (144 h)	20
Subjected to steadily increasing concentrations of waterborne cyanide: 0 at start, 200 at 1 h, 600 at 3 h, 1,000 at 5 h, and 1,800 at 9 h	Reduction in heart rate, hyperventilation, increased oxygen consumption, death in 9 h	21
Chinook salmon, *Oncorhynchus tshawytscha*		
10	After 64 days, increased growth rate and production when compared to controls	13
20	Growth reduced 27% after exposure for 64 days	2
Yellow perch, *Perca flavescens*		
76–108	LC50 (96 h) for juveniles	8, 22
288–>389	LC50 (96 h) for eggs and fry	8, 22
Fathead minnow, *Pimephales promelas*		
12.9–19.6	MATC[b]	8, 22
18–58	Reduction in RNA content in larva in 96 h at 18–36 µg HCN/L, and in DNA and protein at 18–58 µg/L	28
19	Egg reduction of 59% after exposure for 265 days at 25º C	13
35	Reduction in growth rate during chronic exposure	5
44	Hatching reduced 83% after chronic exposure	13
47	Growth reduction in 30 days	28
58	Toxicosis occurred in yolk-sac larvae within 24 h as judged by significant reductions in content of RNA and protein; however, effects were not measurable in 96 h suggesting development of partial tolerance	29
>61	Adverse effects on growth and survival during lifetime exposure	13
82–113	LC50 (96 h) for fry at 25º C	8
83–137	LC50 (96 h) for juveniles	8, 22
99	LC50 (96 h) for fry at 20º C	8
107	Reduced survival in 96 h	28
121–202	LC50 (96 h) for eggs at 25º C	8
121–352	LC50 (96 h) for eggs; more toxic at low dissolved oxygen	22
122	LC50 (96 h) for fry at 15º C	8
Mixture of NaCN plus $CdSO_4$, equivalent to 170 µg CN/L	LC50 (96 h) for adults	30
Mixture of NaCN plus $ZnSO_4$, equivalent to 180 µg CN/L	LC50 (96 h) for adults	30
230, as NaCN	LC50 (96 h) for adults	30
273	LC50 (96 h) for eggs at 20º C	8
352	LC50 (96 h) for eggs at 15º C	8
Mixture of NaCN plus $NiSO_4$, equivalent to 650 µg CN/L	LC50 (96 h) for adults	8
Black crappie, *Pomoxis nigromaculatus*		
60	Some deaths in <24 h	3

101	LC50 (96 h) for juveniles	8
Plainfin midshipman, *Porichthys notatus*		
Isolated photophores exposed to 2,600, as KCN	Maximal luminescence induced by KCN; effect inhibited by d-glucose, d-glyceraldehyde 3-phosphate, and 3-phosphoglycerate	32
Atlantic salmon, *Salmo salar*		
5.0 for 12 days, adult females	Decline in plasma and gonad vitellogenin levels	23
10	Abnormal embryonic development after 58-day exposure	2
10, 80, or 100; newly fertilized eggs continually exposed for 5 months to end of sac-fry stage	Hatching delayed 6–9 days at 80 and 100 µg/L. Hatching success reduced 15% to 40% at all test concentrations, but no measurable effects on growth or survival after hatching. Abnormalities (mostly defects of eye, mouth, vertebral column) were 6% at 10 µg/L, and 19% at 100 µg/L	24
24	LC50 (24 h) at dissolved oxygen of 3.5 mg/L	25
73	LC50 (24 h) at dissolved oxygen of 10 mg/L	25
5,000, 10,000, 25,000, 50,000, or 125,000 for 30 min	Total cyanide residues in gills ranged from 1.0 to 6.6 mg/kg fresh weight (FW) in a dose dependent manner	26
50,000 for 10, 15, 20, 25, or 30 min	Residues in gills, in mg total CN/kg FW, ranged from 1.3 (10 and 15 min) to 1.9 (15 and 20 min) to 4.5 (30 min)	26
Brown trout, *Salmo trutta*		
90	LC50 (96 h)	10
5,000, 10,000, 25,000, 50,000, 75,000, or 100,000, as CN- for 30 min	Residues in gills ranged in a dose-dependent manner from 0.6 mg CN/kg FW in the 5 mg/L group to 3.4 mg/kg FW in the 100 mg/L group	26
50,000 for 10, 15, 20, or 25 min	Residues in tissues, in mg/kg FW, ranged from 0.7 to 1.8 in gill, 0.6 to 2.3 in brain, and 1.3 to 2.5 in liver; concentrations were directly related to length of exposure	26
Brook trout, *Salvelinus fontinalis*		
5.0	Reduction of 50% in swimming performance in 29-day exposure	13
5.7–11.2	MATC[b]	8, 22
10	75% reduction in swimming endurance after exposure for 26 min	2
10–50	Swimming ability reduced 98% after exposure for 29 days	20
11	Continuous exposure of mature females for 144 days before spawning resulted in 50% reduction in number of eggs produced and 15% reduction in egg viability; however, 90 days after hatch trout were 18% heavier and 10% longer than controls	13
25	Inhibited oxygen intake after 5 h	2
33	Adverse effects on juvenile growth rate during exposure for 90 days	2, 8
56–112	LC50 (96 h) range for swimup fry and juveniles	8, 22
108–518	LC50 (96 h) for sac-fry	8, 22
>212	LC50 (96 h) for eggs	8, 22

[a]1, Towill et al. 1978; 2, EPA 1980; 3, EPA 1973; 4, Azcon-Bieto et al. 1987; 5, Low and Lee 1981; 6, Abel and Garner 1986; 7, Lussier et al. 1985; 8, Smith et al. 1979; 9, Thompson 1984; 10, Leduc et al. 1982; 11, Drews and Graszynski 1987; 12, Billard and Roubaud 1985; 13, Leduc 1984; 14, Da Costa and Ruby 1984; 15, Dixon and Leduc 1981; 16, Lesniak and Ruby 1982; 17, Kovacs and Leduc 1982b; 18, McGeachy and Leduc 1988; 19, Marking et al. 1984; 20, Ballantyne 1987a; 21, Sawyer and Heath 1988; 22, Smith et al. 1978; 23, Ruby et al. 1987; 24, Leduc 1978; 25, Alabaster et al. 1983; 26, Holden and Marsden 1964; 27, Smatresk et al. 1986; 28, Barron and Adelman 1984; 29, Barron and Adelman 1985; 30, Doudoroff 1956; 31, Wiley 1984; 32, Rees and Baguet 1989.

[b]Maximum acceptable toxicant concentration. Lower value in each pair indicates highest concentration tested producing no measurable effect on growth, survival, reproduction, or metabolism during chronic exposure; higher value indicates lowest concentration tested producing a measurable effect.

Adverse effects of cyanide on aquatic plants are unlikely at concentrations that cause acute effects to most species of freshwater and marine fishes and invertebrates (EPA 1980). Water hyacinth *(Eichhornia crassipes)* can survive for at least 72 h in nutrient solution containing up to 300 mg CN/L and can accumulate up to 6.7 g/kg dry weight (DW) plant material. On this basis, 1 ha of water hyacinths has the potential to absorb 56.8 kg of cyanide in 72 h, and this property may be useful in reducing the level of CN in untreated wastewater from various electroplating factories, where concentrations generally exceed 200 mg CN/L (Low and Lee 1981). Cyanide may also affect plant community structure. Some algae, for example, metabolized CN at water concentrations <1 mg/L, but at concentrations of 1-10 mg/L, algal activity was inhibited, leaving a biota dominated by *Actinomycetes*--a filamentous bacterium (Knocke 1981).

Cyanide adversely affects fish reproduction by reducing the number of eggs spawned, and the viability of the eggs by delaying the process of secondary yolk deposition in the ovary (Lesniak and Ruby 1982; Ruby et al. 1986). Vitellogenin, a glycolipophosphoprotein present in plasma of fish during the process of yolk formation, is synthesized in liver under stimulation of estrogen and subsequently sequestered in the ovary; it is essential for normal egg development. Exposure of naturally reproducing female rainbow trout to as little as 10 µg HCN/L for 12 days during the onset of the reproductive cycle caused a reduction in plasma vitellogenin levels and a reduction in ovary weight. The loss of vitellogenin in the plasma would remove a major source of yolk (Ruby et al. 1986). Reproductive impairment in adult bluegills (*Lepomis macrochirus*) has been reported following exposure to 5.2 µg CN/L for 289 days (EPA 1980). Fertilized fish eggs are usually resistant to cyanide prior to blastula formation, but delayed effects occur at 60 to 100 µg HCN/L, including birth defects and reduced survival of embryos and newly hatched larvae (Leduc et al. 1982). Concentrations as low as 10 µg HCN/L caused developmental abnormalities in embryos of Atlantic salmon after extended exposure (Leduc 1978). These abnormalities, which were absent in controls, included yolk sac dropsy and malformations of eyes, mouth, and vertebral column (Leduc 1984).

Other adverse effects of cyanide on fish include delayed mortality, pathology, impaired swimming ability and relative performance, susceptibility to predation, disrupted respiration, osmoregulatory disturbances, and altered growth patterns. Free cyanide concentrations between 50 and 200 µg/L were fatal to the more-sensitive fish species over time, and concentrations >200 µg/L were rapidly lethal to most species of fish (EPA 1980). Cyanide- induced pathology in fish includes subcutaneous hemorrhaging, liver necrosis, and hepatic damage. Exposure of fish for 9 days to 10 µg HCN/L was sufficient to induce extensive necrosis in the liver, although gill tissue showed no damage. Intensification of liver histopathology was evident at dosages of 20 and 30 µg HCN/L and exposure periods up to 18 days (Leduc 1984). Cyanide has a strong, immediate, and long-lasting inhibitory effect on the swimming ability of fish (Leduc 1984). Free cyanide concentrations as low as 10 µg/L can rapidly and irreversibly impair the swimming ability of salmoneds in well-aerated water (Doudoroff 1976). Osmoregulatory disturbances recorded at 10 µg HCN/L may affect migratory patterns, feeding, and predator avoidance (Leduc et al. 1982; Leduc 1984). In general, fish experience a significant reduction in relative performance (based on osmoregulation, growth, swimming, and spermatogenesis) at 10 µg HCN/L, and although fish can survive indefinitely at 30 µg HCN/L in the laboratory, the different physiological requirements necessary to survive in nature could not be met (Leduc 1978, 1981; Leduc et al. 1982; Figure). Increased predation by green sunfish (*Lepomis cyanellus*) on fathead minnows *(Pimephales promelas)* was noted at sublethal concentrations of HCN, but it was uncertain if fatheads became easier prey or if green sunfish had greater appetites (Smith et al. 1979).

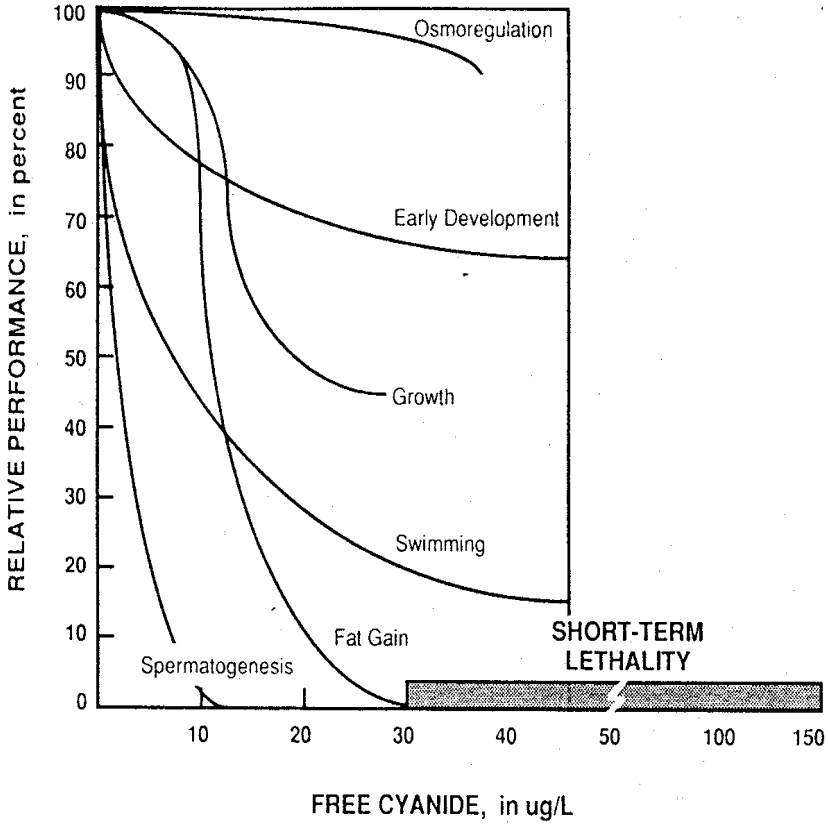

Figure. Summary of lethal and sublethal effects of free cyanide on freshwater fish. Modified from Leduc et al. (1982).

Sodium cyanide has stimulatory effects on oxygen-sensitive receptors in lungfish, amphibians, reptiles, birds, and mammals (Smatresk 1986). Facultative and aquatic air breathers appear to rely on air breathing when external chemoreceptors are stimulated, whereas obligate air-breathing fish are more responsive to internal stimuli (Smatresk 1986). Gill ventilation frequency of longnose gar (*Lepisosteus osseus*), for example, was little affected by external cyanide application, but responded strongly when cyanide was administered internally by injection (Smatresk 1986). Cyanide, like many other chemicals, can stimulate growth of fish during exposure to low sublethal levels. This phenomenon, referred to as hormesis, is little understood and warrants additional research (Leduc 1984).

The observed toxicity to aquatic life of simple and complex cyanides was attributed almost entirely to molecular (undissociated) HCN derived from ionization, dissociation, and photodecomposition of cyanide-containing compounds. The toxicity of the cyanide ion, CN^-, which is a minor component of free cyanide (HCN + CN^-) in waters that are not exceptionally alkaline is of little importance (Doudoroff 1976; Towill et al. 1978; Smith et al. 1979; EPA 1980). The acute toxicity of stable silver cyanide and cuprocyanide complex anions is much less than that of molecular HCN, but is nevertheless important; these ions can be the principal toxicants, even in some very dilute solutions. The much lower toxicities of the ferrocyanide and ferricyanide complexions--which are of high stability but subject to extensive and rapid photolysis, yielding free cyanide on direct exposure to sunlight--and the nickelocyanide ion complex are not likely to be of practical importance (Doudoroff 1976). Toxicity to aquatic organisms of organic cyanide compounds, such as lactonitrile, is similar to that of inorganic cyanides because they usually undergo rapid hydrolysis in water to free cyanide (Towill et al. 1978). There is general agreement that total cyanide concentrations in water in most cases will overestimate the actual cyanide toxicity to aquatic organisms, and that the analytically determined HCN concentration in cyanide-polluted waters

is considered to be the most reliable index of toxicity (Doudoroff 1976; Smith et al. 1979; EPA 1980; Abel and Garner 1986).

Cyanide acts rapidly in aquatic environments, does not persist for extended periods, and is highly species selective; organisms usually recover quickly on removal to clean water. The critical sites for cyanide toxicity in freshwater organisms include the gills, egg capsules, and other sites where gaseous exchange and osmoregulatory processes occur. On passing through a semipermeable membrane, the HCN molecules are usually distributed by way of the circulatory system to various receptor sites where toxic action or detoxification occurs (Leduc 1984). Once in the general circulation, cyanide rapidly inhibits the electron transport chain of vital organs. Signs of distress include increased ventilation, gulping for air at the surface, erratic swimming movements, muscular incoordination, convulsions, tremors, sinking to the bottom, and death with widely extended gill covers (Leduc 1981, 1984). The acute mode of action of HCN is limited to binding those porphyrins that contain Fe^{+3}, such as cytochrome oxidase, hydroperoxidases, and methemoglobin. At lethal levels, cyanide is primarily a respiratory poison and one of the most rapidly effective toxicants known (Leduc et al. 1982). The detoxification mechanism of cyanide is mediated by thiosulfate sulfur transferase, also known as rhodanese. This enzyme is widely distributed in animals, including fish liver, gills, and kidney. Rhodanese plays a key role in sulfur metabolism, and catalyzes the transfer of a sulfane-sulfur group to a thiophilic group (Leduc 1984). Thiosulfate administered in the water with cyanide reduced the toxicity of cyanide to fish, presumably by increasing the detoxification rate of cyanide to thiocyanate (Towill et al. 1978).

Additive or more-than-additive toxicity of free cyanide to aquatic fauna has been reported in combination with ammonia (Smith et al. 1979; Leduc et al. 1982; Alabaster et al. 1983; Leduc 1984) or arsenic (Leduc 1984). However, conflicting reports on the toxicity of mixtures of HCN with zinc or chromium (Towill et al. 1978; Smith et al. 1979; Leduc et al. 1982; Leduc 1984) require clarification. Formation of the nickelocyanide complex markedly reduces the toxicity of both cyanide and nickel at high concentrations in alkaline pH. At lower concentrations and acidic pH, solutions increase in toxicity by more than 1,000 times, owing to dissociation of the metallocyanide complex to form hydrogen cyanide (Towill et al. 1978). Mixtures of cyanide and ammonia may interfere with seaward migration of Atlantic salmon smolts under conditions of low dissolved oxygen (Alabaster et al. 1983). The 96-h toxicity of mixtures of sodium cyanide and nickel sulfate to fathead minnows is influenced by water alkalinity and pH. Toxicity decreased with increasing alkalinity and pH from 0.42 mg CN/L at 5 mg $CaCO_3$/L and pH 6.5; to 1.4 mg CN/L at 70 mg $CaCO_3$/L and pH 7.5; to 730 mg CN/L at 192 mg $CaCO_3$/L and pH 8.0 (Doudoroff 1956).

Numerous biological and abiotic factors are known to modify the biocidal properties of free cyanide, including water pH, temperature, and oxygen content; life stage, condition, and species assayed; previous exposure to cyanide compounds; presence of other chemicals; and initial dose tested. There is general agreement that cyanide is more toxic to freshwater fish under conditions of low dissolved oxygen (Doudoroff 1976; Towill et al. 1978; Smith et al. 1979; EPA 1980; Leduc 1984); that pH levels within the range 6.8-8.3 had little effect on cyanide toxicity but enhanced toxicity at acidic pH (Smith et al. 1979; EPA 1980; Leduc et al. 1982; Leduc 1984); that juveniles and adults were the most sensitive life stages tested and embryos and sac fry the most resistant (Smith et al. 1978, 1979; EPA 1980; Leduc 1984); and that substantial interspecies variability exists in sensitivity to free cyanide (Smith et al. 1979; EPA 1980). Initial dose and water temperature both modify the biocidal properties of HCN to freshwater teleosts. At slowly lethal concentrations (i.e., < 10 µg HCN/L), cyanide was more toxic at lower temperatures; at high, rapidly lethal HCN concentrations, cyanide was more toxic at elevated temperatures (Kovacs and Leduc 1982a, 1982b; Leduc et al. 1982; Leduc 1984). By contrast, aquatic invertebrates were most sensitive to HCN at elevated water temperatures, regardless of dose (Smith et al. 1979). Season and exercise modify the lethality of HCN to juvenile rainbow trout (McGeachy and Leduc 1988); higher resistance to cyanide correlated with higher activity induced by exercise and higher temperatures, suggesting a faster detoxification rate or higher oxidative and anaerobic metabolisms. Low levels of cyanide that were harmful when applied constantly may be harmless under seasonal or other variations that allow the organism to recover and detoxify (Leduc 1981). Acclimatization by fish to low sublethal levels of cyanide through continuous exposure might enhance their resistance to potentially lethal concentrations (Leduc 1981, 1984), but studies with Atlantic salmon and rainbow trout indicate otherwise. Prior acclimatization of Atlantic salmon smolts to cyanide increased their resistance only slightly to lethal concentrations (Alabaster et al. 1983). Juvenile rainbow trout previously exposed to low sublethal concentrations showed a marked reduction in fat synthesis and swimming performance when challenged with higher cyanide doses; effects were

most pronounced at low water temperatures (Kovacs and Leduc 1982a). Experimental evidence is lacking on exposure to lethal concentrations after prior exposure to high sublethal concentrations; some investigators predict decreased resistance (Leduc 1984), and others increased survival (Towill et al. 1978).

Birds

First signs of cyanide toxicosis in sensitive birds appeared between 0.5 and 5 min after exposure, and included panting, eye blinking, salivation, and lethargy (Wiemeyer et al. 1986). In more-resistant species, such as domestic chickens, signs of toxicosis began 10 min after exposure. At higher doses, breathing in all species tested became increasingly deep and labored, followed by gasping and shallow intermittent breathing. Death usually followed in 15-30 min, although birds alive at 60 min frequently recovered (Wiemeyer et al. 1986). The rapid recovery of some birds exposed to cyanide may be due to the rapid metabolism of cyanide to thiocyanate and its subsequent excretion. Species sensitivity to cyanide was not related to body size but seemed to be associated with diet (Wiemeyer et al. 1986). Birds that feed predominantly on flesh, such as vultures, kestrels, and owls, were more sensitive to cyanide than were species that feed mainly on plant material--with the possible exception of mallard (Anas *platyrhynchos*)--as judged by acute oral LD50 values (Table 4).

Table 4. Cyanide effects on selected species of birds.

Species, dose, and other variables	Effects	Reference[a]
Mallard, *Anas platyrhynchos*		
Single oral dose of NaCN		
0.53 mg CN/kg body weight (BW), equivalent to 1 mg NaCN/kg BW	No deaths	7
1.1 mg CN/kg BW (2.0 mg NaCN/kg BW)	About 6% dead	7
1.27 mg CN/kg BW (2.4 mg NaCN/kg BW)	About 33% dead	7
1.43 mg mg CN/kg BW (2.7 mg NaCN/kg BW)	LD50; 95% confidence interval (C.I.) of 2.2 and 3.2 mg NaCN/kg bW	7
Turkey vulture, *Cathartes aura*		
Single oral dose of 19.1 mg CN/kg BW, equivalent to 36 mg NaCN/kg BW	Up to 80% of the cyanide in blood was present as free cyanide and the remainder as bound cyanide	1
Single oral dose of 19.1 mg CN/kg BW, equivalent to 36 mg NaCN/kg BW	Average time to death was about 19 min and ranged between 8 and 41 min; cyanide residues postmortem, in mg CN/kg fresh weight (FW), were 6.7 in blood (Max. 21) and 0.6 in liver (Max. 2.8)	2
Rock dove, *Columba livia*		
0.12 mg CN/L air, as HCN	All dead in 10 min	2
1.6 mg CN/kg BW, equivalent to 4.0 mg KCN/kg BW	Minimum lethal dose when administered intravenously or intramuscularly	2
Black vulture, *Coragyps atratus*		
Single oral dose, as NaCN		
1.6 mg CN/kg BW	No deaths in 60 min. Mean and maximum blood CN concentrations, in mg/kg FW, were 0.7 and 0.9, respectively	2
2.4 lmg CN/kg BW	Some deaths within 30 min. Mean blood CN residues in	2

	mg/kg FW, were 0.7 in dead birds vs. 1.2 in those surviving 60 min	
2.54 mg CN/kg BW	Acute oral LD50; 95% C.I. of 2.3 and 2.8 mg CN/kg BW (4.4–5.3 mg NaCN/kg BW)	2
3.7 and 19.1 mg CN/kg BW	All dead within 16 min; maximum blood CN levels postmortem were 2.1 mg/kg FW in the low dose group and 4.2 in the high dose group	2
Japanese quail, *Coturnix japonica*		
Single oral dose, as NaCN		
4.5 mg CN/kg BW	Acute oral LD50 for adult females; 95% C.I. of 3.1 and 6.5 mg CN/kg BW	2
5.5 mg CN/kg BW	Acute oral LD50 for adult males; 95% C.I. of 4.0 and 7.5 mg CN/kg BW	2
American kestrel, *Falco sparverius*		
2.12 mg CN/kg BW, as NaCN	Acute oral LD50; 95% C.I. of 1.6 and 2.8 mg CN/kg BW	2
Domestic chicken, *Gallus domesticus*		
Intravenous route		
0.01 µg/kg BW	Most of dose recovered in urine as thiocyanate in 6 h; excretion limited by availability of transferable sulfur	3
0.6 mg CN/kg BW, equivalent to 1.5 mg KCN/kg BW	Lethal	2
0.78 mg CN/kg BW, as KCN	Sublethal; thiocyanate excretion increased 10 times after 10 min and returned to normal levels after 3.5 h; the total thiocyanate collected was equivalent to 85% of the administered dose	4
1.3 mg CN/kg BW, as KCN	Lethal	4
Inhalation route		
0.12 mg HCN/L air	All survived for at least 60 min	2
Single oral dose, as NaCN		
3.2 mg CN/kg BW, equivalent to 6.0 mg NaCN/kg BW	No deaths in 30 min; maximum CN levels, in mg/kg FW, were 1.1 in blood and 0.06 in liver	2
6.4 mg CN/kg BW	Some deaths in 30 min; maximum CN levels, in mg/kg FW were 1.6 in blood and 0.12 in liver	2
11.1 mg CN/kg BW	Acute oral LD50; 95% C.I. of 6.4 and 19.1 mg CN/kg BW	2
25.4 mg CN/kg BW	Advanced signs of acute poisoning; death probable within 30 min; maximum CN levels, in mg/kg FW, were 1.5 in blood and 0.6 in liver	2
Dietary route		
Fed cassava diets containing 4, 37, 70,	At all dietary levels, there	5

or 103 mg total cyanide per kilogram ration to day-old chicks for 8 weeks	was no significant effect on survival, growth, histology, hemoglobin, hematocrit, or lymphocyte number; however, serum thiocyanate levels increased in a dose-dependent manner	
Fed diets containing 135 mg HCN/kg Chicks, 20-day exposure	Growth and food intake significantly depressed; plasma thiocyanate concentration increased	6
Adults, 14-day exposure	Urinary excretion of thiocyanate increased 5 times in laying hens	6
California condor, *Gymnogyps californianus*		
Juvenile (8.4 kg), found dead, presumably of cyanide poisoning	No evidence of injuries or disease; yellow fluorescent particles found in mouth appeared like those placed in NaCN ejector mechanisms used in predator control. However, blood cyanide concentration was similar to that found in nonexposed vultures, including two captive California condors	2
Eastern screech-owl, *Otus asio*		
4.6 mg CN/kg BW, equivalent to 8.6 mg NaCN/kg BW	Acute oral LD50; 95% C.I. of 3.8 and 5.4 mg CN/kg BW	2
Canary, *Serinus canarius*		
0.12 mg HCN/L air	All dead in 3 min	2
European starling, *Sturnus vulgaris*		
9.0 mg CN/kg BW, as NaCN	Acute oral LD50; 95% C.I. of 4.8 and 17 mg CN/kg BW	2
Andean condor, *Vultur gryphus*		
Single oral dose of 19.1 mg CN/kg BW (36 mg NaCN/kg BW)	Blood sampled immediately after death contained 1.2 mg free CN per liter and 0.5 mg bound CN per liter	1

[a]1, Krynitsky et al. 1986; 2, Wiemeyer et al. 1986; 3, Oh et al. 1987; 4, Davis 1981; 5, Gomez et al. 1988; 6, Elzubeir and Davis 1988b; 7, Personal communication, E. F. Hill, Patuxent Wildlife Research Center.

Many species of migratory birds were found dead in the immediate vicinity of gold-mine heap-leach extraction facilities and tailings ponds, presumably as a result of drinking the cyanide-contaminated (>200 mg total cyanide per liter) waters (Clark and Hothem 1991). Migratory bird mortality from cyanide toxicosis may be eliminated at these facilities by screening birds from toxic solutions (Hallock 1990) or lowering the cyanide concentrations with hydrogen peroxide to <50 mg total cyanide per liter (Allen 1990), although the latter procedure requires verification (Clark and Hothem 1991).

Some birds may not die immediately after drinking lethal cyanide solutions. In Arizona, a red-breasted merganser *(Mergus serrator)* was found dead 20 km from the nearest known source of cyanide, and its pectoral muscle tissue tested positive for cyanide (Clark and Hothem 1991). A proposed mechanism to account for this phenomenon involves weak-acid dissociable (WAD) cyanide compounds. Cyanide bound to certain metals, usually copper, is dissociable in weak acids such as stomach acids. Clark and Hothem (1991) suggested that drinking of lethal cyanide solutions by animals may not result in immediate death if the cyanide level is

sufficiently low; these animals may die later when additional cyanide is liberated by stomach acid. More research is needed on WAD cyanide compounds.

Elevated cyanide concentrations were found in blood of chickens that died of cyanide poisoning; however, these concentrations overlapped those in survivors. Despite this variability, blood is considered more reliable than liver as an indicator of cyanide residues in exposed birds (Wiemeyer et al. 1986). No gross pathological changes in birds related to cyanide dosing were observed at necropsy (Wiemeyer et al. 1986), similar to other taxonomic groups tested.

Cyanide-nutrient interactions are reported for alanine, which appears to exacerbate cyanide toxicity, and for cystine, which seems to alleviate toxicity (Davis et al. 1988). Dietary cyanide--at levels that do not cause growth depression--alleviates selenium toxicity in chickens, but not the reverse (Davis et al. 1988; Elzubeir and Davis 1988a). For example, dietary selenium, as selenite, at 10 mg/kg for 24 days, reduced growth, food intake, and food utilization efficiency, and produced increased liver size and elevated selenium residues; the addition of 45 mg CN/kg diet (100 mg sodium nitroprusside per kilogram) eliminated all effects except elevated selenium residues in liver. The mechanism of alleviation is unknown and may involve a reduction of tissue selenium through selenocyanate formation, or increased elimination of excess selenium by increasing the amount of dimethyl selenide exhaled (Elzubeir and Davis 1988a). At dietary levels of 135 mg CN/kg plus 10 mg selenium per kilogram, chick growth was significantly decreased (Elzubeir and Davis 1988a). This interaction can be lost if there is a deficiency of certain micronutrients or an excess of vitamin K (Davis et al. 1988).

Mammals

Much of the toxicological interest in cyanide relating to mammals has focused on its rapid lethal action; however, its most widely distributed toxicologic problems are due to its toxicity from dietary, industrial, and environmental factors (Way 1981, 1984; Gee 1987; Marrs and Ballantyne 1987). Chronic exposure to cyanide is correlated with specific human diseases: Nigerian nutritional neuropathy, Leber's optical atrophy, retrobulbar neuritis, pernicious anemia, tobacco amblyopia, cretinism, and ataxic tropical neuropathy (Towill et al. 1978; Way 1981; Sprince et al. 1982; Berninger et al. 1989; Ukhun and Dibie 1989). The effects of chronic cyanide intoxication are confounded by various nutritional factors, such as dietary deficiencies of sulfur-containing amino acids, proteins, and water-soluble vitamins (Way 1981).

Most authorities now agree on five points: (1) cyanide has low persistence in the environment and is not accumulated or stored in any mammal studied; (2) cyanide biomagnification in food webs has not been reported, possibly due to rapid detoxification of sublethal doses by most species, and death at higher doses; (3) cyanide has an unusually low chronic toxicity, but chronic intoxication exists and, in some cases, can be incapacitating; (4) despite the high lethality of large single doses or acute respiratory exposures to high vapor concentrations of cyanide, repeated sublethal doses seldom result in cumulative adverse effects; and (5) cyanide, in substantial but sublethal intermittent doses can be tolerated by many species for long periods, perhaps indefinitely (Towill et al. 1978; EPA 1980; Way 1984; Ballantyne and Marrs 1987a; Table 5).

The toxicity of cyanogenic plants is a problem for both domestic and wild ungulates. Poisoning of herbivorous ungulates is more prevalent under drought conditions, when these mammals become less selective in their choice of forage; dry growing conditions also enhance cyanogenic glycoside accumulations in certain plants (Towill et al. 1978). Animals that eat rapidly are at greatest risk, and intakes of 4 mg HCN/kg BW can be lethal if consumed quickly (Egekeze and Oehme 1980). In general, cattle are most vulnerable to cyanogenic plants; sheep, horses, and pigs--in that order--are more resistant than cattle (Cade and Rubira 1982). Deer *(Odocoileus* sp.) and elk *(Cervus* sp.) have been observed to graze on forages that contain a high content of cyanogenic glycosides; however, cyanide poisoning has not been reported in these species (Towill et al. 1978).

Ruminant and nonruminant ungulate mammals that consume forage with high cyanogenic glycoside content, such as sorghums, Sudan grasses, and corn, may experience toxic signs due to microbes in the gut that hydrolyze the glycosides, releasing free hydrogen cyanide (Towill et al. 1978). Signs of acute cyanide poisoning in livestock usually occur within 10 min and include initial excitability with muscle tremors, salivation, lacrimation, defecation, urination, and labored breathing, followed by muscular incoordination, gasping, and convulsions; death can occur quickly, depending on the dose administered (Towill et al. 1978; Cade and Rubira 1982). Thyroid dysfunction has been reported in sheep grazing on stargrass *(Cynodon plectostachyus),* a plant with high cyanogenic glycoside and low iodine content. Sheep developed enlarged thyroids and gave birth to

lambs that were stillborn or died shortly after birth (Towill et al. 1978). Cyanogenic foods can exacerbate selenium deficiency, as judged by the increased incidence of nutritional myopathy in lambs on low-selenium diets (Elzubeir and Davis 1988a). A secondary effect from ingesting cyanogenic glycosides from forage is sulfur deficiency as a result of sulfur mobilization to detoxify the cyanide to thiocyanate (Towill et al. 1978).

Cyanide poisonings of livestock by forage sorghums and other cyanogenic plants are well documented (Cade and Rubira 1982). Horses in the southwestern United States grazing on Sudan grass and sorghums developed posterior muscle incoordination, urinary incontinence, and spinal cord histopathology; offspring of mares that had eaten Sudan grass during early pregnancy developed musculoskeletal deformities (Towill et al. 1978). Salt licks containing sulfur (8.5%) have been used to treat sheep after they failed to gain weight when grazing on sorghum with high HCN content (Towill et al. 1978). Sugar gum (*Eucalyptus cladocalyx*) and manna gum (*Eucalyptus viminalis*) contain high levels of cyanogenic glycosides, and both have been implicated as the source of fatal HCN poisoning in domestic sheep and goats that had eaten leaves from branches felled for drought feeding, or after grazing sucker shoots on lopped stumps (Webber et al. 1984). In one case, 10 goats died and 10 others were in distress within 2 h after eating leaves from a felled sugar gum. Dead goats had bright red blood that failed to clot and subepicardial petechial hemorrhages. Rumens of dead goats contained leaves of *Eucalyptus* spp. and smelled of bitter almonds. The 10 survivors were treated intravenously with 3 mL of a 1-L solution made to contain 20 g of sodium nitrite and 50 g of sodium thiosulphate; four recovered and six died. Of 50 afflicted goats, 24 died within 24 h and the remainder recovered (Webber et al. 1984). In rare instances HCN poisoning occurs when animals are exposed to chemicals used for fumigation or as a fertilizer (Webber et al. 1984), but there is general agreement that ingestion of plants containing high levels of cyanogenic glycosides is the most frequent cause of cyanide poisoning in livestock.

Cassava, also known as maniac, tapioca, yuca, or guacamate, is one of the very few--and, by far, the most important--food crops in which the cyanide content creates toxic problems (Cooke and Coursey 1981). Cassava is a major energy source for people and livestock in many parts of the world; it accounts for an average of 40% of the human caloric intake in Africa (Casadei et al. 1984), to more than 70% in some African diets (Way 1984). In comparison to other tropical crops it produces the highest yield per hectare (Okeke et al. 1985). Cassava is native to tropical America from southern Mexico to northern Argentina and probably has been under cultivation there for 4,000-5,000 years. It has been introduced to east Africa, Indian Ocean islands, southern India, and the Far East (Cooke and Coursey 1981). The global production of cassava roots was estimated at 50 million tons in 1950, and 100 million tons in 1980; about 44.2 million tons are grown annually in Africa, 32.7 million tons in tropical America, and 32.9 million tons in Asia (Cooke and Coursey 1981). Linamurin is the principal cyanogenic glycoside in cassava; its toxicity is due to hydrolysis by intestinal microflora releasing free cyanide (Padmaja and Panikkar 1989). Rabbits *(Oryctolagus cuniculus)* fed 1.43 mg linamurin per kilogram BW daily (10 mg/kg BW weekly) for 24 weeks showed effects similar to those of rabbits fed 0.3 mg KCN/kg BW weekly. Specific effects produced by linamurin and KCN included elevated lactic acid in heart, brain, and liver; reduced glycogen in liver and brain; and marked depletion in brain phospholipids (Padmaja and Panikkar 1989).

The use of cassava in animal feed presents two major problems: the presence of cyanogenic glycosides in the tuber, and the remarkably low protein levels in fresh and dried cassava. Pigs fed low-protein cassava diets for 8 weeks had reduced food consumption and lowered liver weight; addition of protein supplement to the diet reversed these trends (Tewe 1982b). Removal of cyanogenic glycosides from cassava tubers, mash, peels, and root meal is accomplished with several techniques. Usually, the cassava root is dried in the sun for several weeks, and this process removes most of the cyanogenic glycosides; however, under conditions of famine or food shortage, this process cannot be carried out properly (Cliff et al. 1984). Long fermentation periods, especially under conditions of high moisture content, may be effective in substantial detoxification of cassava mash (Ukhun and Dibie 1989). Cassava peels containing as much as 1,061 mg HCN/kg FW can be rendered suitable for feeding to livestock (4-625 mg/kg) by boiling for 7 min, roasting for 30 min, soaking for 15 h, or drying in the sun for 7.6 days (Okeke et al. 1985). Cassava root meal (up to 40% of cassava meal) is satisfactory as a diet supplement for domestic pigs, provided cyanide content is <100 mg/kg ration (Gomez et al. 1983).

Neuropathies associated with cassava ingestion (i.e., cyanide intoxication) can develop into a syndrome in humans and domestic animals, characterized by nerve deafness, optic atrophy, and an involvement of the sensory spinal nerve that produces ataxia. Other symptoms include stomatitis, glossitis, and scrotal dermatitis (Way 1981). Potentially more serious are long-term effects such as ataxic neuropathy, goiter, and cretinism,

which have been attributed to high cassava content in diets. Thiocyanate--one of the detoxification products--inhibits iodine absorption and promotes goiter, a common ailment in tropical countries (Cooke and Coursey 1981). At high dietary cyanide intakes there is an association with diabetes and cancer (Cliff et al. 1984), but this requires verification. The first case of cassava toxicity occurred almost 400 years ago (Cooke and Coursey 1981). The toxic principle was later identified as a cyanogenic glycoside, shown to be identical with flax linamurin (2-(beta-D-glucopyranosyloxy)-isobutyronitrile). All parts of the plant, except possibly the seeds, contain the glycoside together with the enzyme linamarase. This enzyme effects hydrolysis of the nitrile to free HCN when the tissue cellular structure is damaged (Cooke and Coursey 1981). Mantakassa disease is related to chronic cyanide intoxication associated with a diet consisting almost exclusively of cassava; in times of famine and sulfur-poor diets, Mantakassa effects were more pronounced (Casadei et al. 1984). Symptoms of Mantakassa disease include the sudden onset of difficulty in walking, increased knee and ankle reflexes, elevated serum thiocyanate levels, fever, pain, headache, slurred speech, dizziness, and vomiting. Women of reproductive age and children were the most seriously affected. Symptoms persisted for up to 4 months after treatment with hydroxycobalamin, vitamin supplements, and a high protein, energy-rich diet (Cliff et al. 1984). Mantakassa was reported in 1,102 victims in Mozambique in 1981 from a drought-stricken cassava staple area; from Zaire in 1928, 1932, 1937, and again in 1978-81; in Nigeria; and in the United Republic of Tanzania. The mean serum thiocyanate level in patients with Mantakassa is 2.6 times higher than in non-Mantakassa patients in Nigeria, and 3.5 times higher than in Tanzanian patients. Pesticides, infection, viruses, and consumption of food other than cassava were eliminated as possible causative agents in Mantakassa disease. Still unresolved is whether the disease is triggered when a threshold level of thiocyanate is reached, or when a critical combination of cyanide intoxication plus nutritional deficiency occurs (Cliff et al. 1984).

Routes of administration other than dietary ingestion should not be discounted. Livestock found dead near a cyanide disposal site had been drinking surface water runoff from the area that contained up to 365 mg HCN/L (EPA 1980). The use of cyanide fumigant powder formulations may be hazardous by contact of the powder with moist or abraded skin, contact with the eye, swallowing, and inhalation of evolved HCN (Ballantyne 1988). In rabbits, lethal systemic toxicity was produced by contamination of the eye, moist skin, or abraded skin (but not dry skin) with cyanide powder formulations (40% NaCN plus 60% kaolin) administered at 1-5 g powder per cubic meter (Ballantyne 1988). Hydrogen cyanide in the liquid state can readily penetrate the skin, and skin ulceration has been reported from splash contact with cyanides among workers in the electroplating and gold extraction industries--although effects in those instances were more likely due to the alkalinity of the aqueous solutions (Homan 1987). In one case, liquid HCN ran over the bare hand of a worker wearing a fresh air respirator; he collapsed into unconsciousness in 5 min, but ultimately recovered (EPA 1980).

Use of poisons in livestock collars is both specific and selective for animals causing depredations, as is the case for cyanide collars to protect sheep against coyotes (Sterner 1979; Table 5). These collars contain a 33% NaCN solution and are usually effective against coyotes. However, field results indicate that some coyotes kill by means other than neck attack, and some exhibit great wariness in attacking collared sheep (Savarie and Sterner 1979).

Calcium cyanide in flake form was used in the 1920's to kill black-tailed prairie dogs and pocket gophers *(Geomys bursarius)* in Kansas, and various other species of rodents in Nova Scotia (Wade 1924). For prairie dog control, the usual practice was to place 43-56 g of calcium cyanide 0.3-0.7 m below the rim of the burrow and to close the entrances. The moisture in the air liberated HCN gas, which remained in the burrow for several hours, producing 100% kill. A lower dose of 28 g per burrow was about 90% effective (Wade 1924). Control of prairie dogs with cyanide sometimes resulted in the death of burrowing owls that lived in the prairie dog burrows (Wade 1924).

Clinical signs of acute cyanide poisoning in mammals last only a few minutes after ingestion and include rapid and labored breathing, ataxia, cardiac irregularities, dilated pupils, convulsions, coma, respiratory failure, and rapid death (Egekeze and Oehme 1980; Ballantyne 1983). Cyanide poisoning causes cardiovascular changes as well as its better known effects on cellular respiration. Cyanide increases cerebral blood flow in rabbits and cats, and disrupts systemic arterial pressure in dogs (Robinson et al. 1985). Cyanide affects mammalian behavior, mostly motor functions, although these effects have not been quantified. Cyanide-induced motor alterations observed in rats and guinea pigs include muscular incoordination, increased whole-body locomotion, disrupted swimming performance, and altered conditioned avoidance responses (D'Mello 1987). As a consequence of the cytotoxic hypoxia in acute cyanide poisoning, there is a shift from aerobic to

anaerobic metabolism, and the development of lactate acidosis. A combination of rapid breathing, convulsions, and lactate acidosis is strongly suggestive of acute cyanide poisoning (Ballantyne 1983). As with other chemical asphyxiants, the critical organs that are most sensitive to oxygen depletion are the brain and heart (Egekeze and Oehme 1980). The only consistent postmortem changes found in animals poisoned by cyanide are those relating to oxygenation of the blood. Because oxygen cannot be utilized, venous blood has a bright-red color and is slow to clot (Egekeze and Oehme 1980). Bright-red venous blood is not a reliable indicator of cause of death, however, because it is also associated with chemicals other than cyanide (Ballantyne 1983).

Cyanide poisoning is associated with changes in various physiological and biochemical parameters. The earliest effect of cyanide intoxication in mice seems to be inhibition of hepatic rhodanese activity, due to either blockage by excess binding to the active site or to depletion of the sulfane-sulfur pool. These changes do not seem to occur in blood, where rhodanese functions at its maximal rate, thus preventing cyanide from reaching the target tissues and causing death (Buzaleh et al. 1989). Cyanide causes dose- and species-dependent responses on vascular smooth muscle; studies with isolated aortic strips indicate that rabbits are 80 times more sensitive than dogs or ferrets (*Mustela putorius*; Robinson et al. 1985). Rabbits killed with HCN had higher concentrations of cyanide in blood and other tissues and lower tissue cytochrome oxidase activities than did those killed with KCN (Ballantyne et al. 1972). Cyanide promotes dose- and calcium-dependent release of dopamine tissues in the domestic cat, and reductions in adenosine triphosphate (ATP) content of the carotid body (Obeso et al. 1989). Cyanide-induced hypoxia is believed to decrease ATP content of Type I glomus cells. The decrease in the phosphate transfer potential is a crucial step in the overall transduction process, that is, the activation of the transmitter release from Type I cells, with resultant release and activation of sensory nerve endings (Obeso et al. 1989). Studies with isolated heart of the domestic ferret demonstrate that cyanide affects intracellular ionic exchange of H^+, Na^+, and calcium (Fry et al. 1987); inhibits cardiac action potential (Elliott et al. 1989); and inhibits oxidative phosphorylation accompanied by an intracellular acidosis, a decrease in phosphocreatinine, and a rise in inorganic phosphate (Eisner et al. 1987). When oxidative phosphorylation is inhibited in cardiac muscle, there is a rapid decrease of developed force or pressure; most of the decrease of developed pressure produced by cyanide in ferret heart is not produced by intracellular acidosis, and may result from increased inorganic phosphate (Eisner et al. 1987). Observed changes in rat cerebral oxidative responses to cyanide may be due to redistribution of intracellular oxygen supply to mitochondria respiring in an oxygen-dependent manner or by branching effects within brain mitochondria (Lee et al. 1988). Hyperammonemia and the increase of neutral and aromatic amino acids may also be important in loss of consciousness induced by cyanide (Yamamoto 1989).

Table 5. Cyanide effects on selected species of mammals.

Species, dose, and other variables	Effects	Reference[a]
Cattle, *Bos* sp.		
Fed hybrid sorghum Sudan grass cross 988 at 15–20 kg per animal daily for 3–8 days	Of 180 cows, 21 were affected and 13 died; toxic cyanide levels were measured in fodder and in liver and ruminal contents of dead cows	44
Dog, *Canis familiaris*		
Administered doses up to 2 mg NaCN/kg body weight (BW), once or twice daily for 15 months	Acute toxic signs evident after each administration, but complete recovery within 30 min; no measurable adverse effects after 15 months	1
5.4 mg NaCN/kg BW, single subcutaneous injection	LD50	2
24 mg CN/kg BW, single oral or slow intravenous injection	Lethal; at time of respiratory arrest, blood plasma	3

route	concentration was 1 mg total CN per liter or about 0.4 mg free cyanide per liter	
Fed diets containing 150 mg NaCN/kg for 30 days	No measurable effect on food consumption, blood chemistry, behavior, or organ histology	1
Coyote, *Canis latrans*		
Single forced oral dose of NaCN, in mg/kg BW		
4	Immobilized in 13 min, but all survived for at least 30 days; some sacrificed after 30 min: NaCN residues in mg/kg fresh weight (FW) were 0.03 in blood and 0.9 in stomach	2
4.1 (2.1–8.3)	LD50	2
8	Immobilization in 9 min, death within 41 min	2
16, 32, or 64	All immobilized in less than 1 min and all died in less than 8 min. Maximum NaCN residues were 0.14 mg/L in blood and 13.0 mg/L FW in stomach	2
"Toxic" collars attached to neck of sheep and camouflaged with wool; each collar contained 50 mL of a 33% NaCN solution; toxic action commences when coyote attacks sheep and punctures collar; all coyotes tested were known to attack sheep in laboratory pens	Of three coyotes tested, one was immobilized in 1 min and died within 18 min; the other two coyotes recovered; the dead coyote had mouthed the collar for about 2 s; residues in mg NaCN/kg, were 0.26 in blood and <0.1 in stomach; the other two coyotes had mouthed the collar for 3–15 s and had NaCN levels, in mg/kg FW, of 0.014 and 0.029 in blood, and 0.6 and <0.1 in stomach	2
Toxic collar, as above; each coyote tested was known to have fatally attacked at least three domestic sheep within a 30-day period	Of the 12 coyotes that attacked the neck region of the sheep and punctured the collar, nine received lethal doses and became immobilized in 1–3 min and died 3–25 min later; the mean time to death was 11.6 min; one of the three sublethally dosed coyotes survived at last three successful attacks in which the collar was punctured, and two survived two attacks; in all cases, contact with NaCN	4

	produced shaking of the head, pawing at the mouth, rubbing the snout on the ground, and ataxia	
African giant rat, *Cricetomys gambianus*		
Weanlings fed diets for 16 weeks containing 0 mg HCN/kg (maize), 110 mg HCN/kg (cassava pulp), 150 mg HCN/kg (cassava tuber), or 597 mg HCN/kg (cassava peel)	Food consumption was similar in all diets; no pathology was observed in any organ of animals on all treatments; rats on maize and cassava pulp diets had significantly increased growth rate, feed efficiency, and protein efficiency; rats on cassava peel and tuber diets had significantly increased thiocyanate levels in serum, organs, and urine	5
Juveniles, age 10–14 weeks, fed cassava peel diets for 2 weeks containing 720 mg HCN/kg	Adverse effects on growth when cassava peel exceeds 7.8% of the ration	6
Weanlings fed 1,000 mg CN/kg diet, as KCN, for 12 weeks	Reduction in feed intake, reduced body weight, elevated thiocyante concentrations in serum (37.4 mg/L vs. 12.6), urine (341 mg/L vs. 25), liver (1.7 g/kg FW vs. 0.4), kidney (2.4 g/kg FW vs. 0.4), and spleen (2.1 g/kg FW vs. 0.3)	7
Humans, *Homo sapiens*		
Intentional oral ingestion of unknown amount of NaCN or KCN, three cases	Death between 5 and 30 min; stomach cyanide concentrations ranged between 100 and 164 mg; tissue residues postmortem in mg/kg FW, were 0.3–1.1 in blood, 0.3–1.0 in liver, and 0.2–0.3 in brain	8
Found dead, four cases, time to death unknown	Maximum cyanide concentration in stomach was 230 mg; maximum tissue residues, in mg/kg FW were 3.5 in blood, 6.3 in liver, and 0.5 in brain	8
Attempted suicide by 39-year-old-male, unknown amount of NaCN	Severe tremors and progressive loss of muscle tone--representing the first case of cyanide intoxication with delayed onset of symptoms	9
Inhalation of HCN gas, in mg/m^3, for various time intervals		

140 for 60 min	Calculated LC50	10
220 for 30 min	Calculated LC50	10
504 for 10 min	Calculated LC50	10
680 for 5 min	Calculated LC50	10
1,500 for 3 min	Calculated LC50	10
4,400 for 1 min	Calculated LC50	10
Inhalation of 2,000 mg HCN/L	First breath results in deep, rapid breathing, with collapse, convulsions, and death within 1 min	11
Inhalation of cyanogen chloride, in mg/L, for various time intervals		
1, 10 min	Irritant	1
48, 30 min	Fatal	1
159, 10 min	Fatal	1
Inhalation of cyanogen bromide, in mg/L, for various time intervals		
1.4, no time given	Irritant to eyes and nose	1
92, 10 min	Fatal	1
Single oral dose		
0.5–3.5 mg HCN/kg BW	Lethal	12, 41
0.7–3.5 mg KCN/kg BW, equivalent to 50 to 250 mg KCN/adult	Fatal	10
2 mg HCN/kg BW, or total of about 150 mg HCN	Acute LD50 for adults	13
1–5 g of NaCN or KCN, equivalent to 0.2 g/adult or 3 mg/kg BW	Minimum lethal dose	14
Tissue residues		
Whole blood, 1–2 mg free cyanide per liter	Usually lethal	42
Whole blood, 2.6–3.1 mg total CN per liter	Minimum cyanide concentration associated with death in an otherwise healthy individual	13
Whole blood, 2.6–3.1 mg total CN per liter	Minimum cyanide concentration associated with death in an otherwise healthy individual	13
Whole blood, 4–45 mg total CN per liter	Levels measured in known suicides	13
Whole body, 7 mg HCN/kg BW	Residue associated with minimum lethal dose	11
Daily dietary intake of 15–31.5 mg hydrogen cyanide from cassava	Mantakassa disease--see text for discussion	15
100 mg HCN/kg BW applied to skin surface	LD50	11
Clothing inundated with 10% NaCN solution, pH 11.4	Clinical signs of toxicity within 25 min and death in about 60 min	13
Livestock		
>200 mg HCN/kg plant materials in diet	Potentially dangerous	13

Cynomolgus monkeys, *Macaca* spp.		
Given multiple sublethal doses of KCN (5–18 mg) for 23 days	Brain histoapathology	3
Exposed to HCN gas produced from combustion of polyacrylonitrile materials at various temperatures		
300º C, 87–170 mg HCN/L air	Incapacitated in 16–30 min; blood cyanide of 4.3 mg/L	16
600º C, 120–174 mg HCN/L air	Incapacitated between 6 and 24 min, blood cyanide of 2.96 mg/L	16
900º C, 166–196 mg HCN/L air	Incapacitated between 2 and 13 min; blood cyanide concentration of 3.1 mg/L	16
Exposed to HCN gas at air concentrations of 60, 80, or 150 mg HCN/L for 30 min	At 60 mg/L, HCN had only a slight depressive effect on the central nervous system; at 80 and 150 mg/L, severe CNS depression and incapacitation occurred	17
Exposed to HCN gas at air concentrations of 100, 1092, 123, 147, or 156 mg HCN/L air	Incapacitated in 8 min at higher doses to 19 min at lowest dose tested; blood cyanide after 30 min exposure ranged between 1.7 mg/L at 100 mg HCN/L and 3.2 mg/L at 156 mg HCN/L; after recovery for 60 min, blood CN ranged between 2.0 and 2.9 mg/L	16
Domestic mouse, *Mus* spp.		
Single intraperitoneal injection		
HCN, 2.8 mg/kg BW	LD50	10
NaCN, 4.6–5.9 mg/kg BW	LD50	10
KCN, 5.3–6.7 mg/kg BW	LD50	10
Acetone cyanohydrin, $(CH_3)_2C(OH)CN$, 8.7 mg/kg BW	LD50 (7 days); first death in 5 min	18
Malonitrile, $NCCH_2CN$, 18 mg/kg BW	LD50 (7 days); first death in 4.8 h	18
Propionitrile, CH_3CH_2CN, 28 mg/kg BW	LD50 (7 days); first death in 21 h	18
N-butyronitrile, 38 mg/kg BW	LD50 (7 days); first death in 2.2 h	18
Acrylonitrile, CH_2CHCN, 46 mg/kg BW	LD50 (7 days); first death in 2.3 h	18
Succinonitrile, $NCCH_2CH_2CN$, 62 mg/kg BW	LD50 (7 days); first death in 5.1 h	18
Acetonitrile, CH_3CN, 175 mg/kg BW	LD50 (7 days); first death in 7.1 h	18
Single subcutaneous injection		
HCN, 7.8–12.0 mg/kg BW	LD50	10
KCN, 10 mg/kg BW	Loss of consciousness in 100%; blood ammonia levels increased 2.5 times; brain amino acid levels (i.e., leucine,	19

	isoleucine, tyrosine, phenylalanine) increased by 1.5–3.0 times; alpha ketoglutarate, at 500 mg/kg BW by intraperitoneal injection, completely blocked the development of cyanide-induced loss of consciousness and hyperammonemia	
Single oral dose		
8.5 mg KCN/kg BW, equivalent to 3.4 mg CN^-/kg BW	LD50	10, 20
Drinking water, 1,000 mg KCN/L, exposure for 40 days	Marked inhibition of cytochrome oxidase activity in liver, brain, and blood; increased cyanide concentrations in all tissues; inhibition of rhodanese activity; diminished labile sulfur tissue levels	43
Rabbit, *Oryctolagus* spp.		
Isolated aorta strips, 0.00014 µg NaCN/L–140 µg/L	Small contractions measured at lowest dose tested, ED50 at 70 µg/L, and maximum response at 140 µg/L; higher doses up to 14 mg/L produced relaxation	21
Single intramuscular injection, in mg/kg BW		
0.5–1.5	LD50 for HCN	10
1.6	LD50 for NaCN	10
3.1–3.3	LD50 for KCN	10
8.0		
Killed with KCN	Cyanide concentrations, in mg/kg FW, were 1.6 in serum, 5.3 in blood, and <0.4 in other tissues sampled	22
Killed with HCN	Cyanide concentrations, in mg/kg FW, were 9.3 in blood, 2.1 in brain, 2.0 in serum, 0.5 in myocardium, and <0.4 in other tissues	22
Single intravenous injection, in mg/kg BW		
0.6	LD50 for HCN	10
1.2	LD50 for NaCN	10
1.9	LD50 for KCN	10
Single dose administered to eye surface, in mg/kg BW		
1.0	LD50 for HCN	10
4.5–5.1	LD50 for NaCN	10
7.9	LD50 for KCN	10
11.2	Signs of NaCN poisoning in 3 min, death in 7 min	23
Single intraperitoneal injection, in mg/kg BW		
1.7–2.0	LD50 for HCN	10
2.8–2.9	LD50 for NaCN	10

3.6–4.0	LD50 for KCN	10
Administered as solution to skin, in mg/kg BW		
2.3	LD50 for HCN and abraded skin	10
6.9	LD50 for HCN and intact skin	10
14.3	LD50 for KCN and abraded skin	10
19.3	Abraded skin; signs of NaCN poisoning evident in 25 min, death in 41 min	23
22.3	LD50 for KCN and intact skin	10
29.5	Moist skin; signs of NaCN poisoning evident in 79 min, death in 117 min	23
>110	Dry skin; no signs of NaCN poisoning, no deaths	23
Single oral dose, in mg/kg BW		
2.5	LD50 for HCN	10
5.1	LD50 for NaCN	10
5.8	LD50 for KCN	10
12.8	Signs of NaCN poisoning in 4 min, death in 22 min	23
Single oral dose, NaCN, 10–15 mg/kg BW	All dead in 14–30 min; blood cyanide ranged between 3.7 and 5.4 mg/L	24
Inhalation of HCN from combustion of 20 g of polyacrylonitrile	All dead in 12–16 min; blood cyanide ranged between 1.6 and 3.1 mg/L	24
Interval between death and removal of tissues for analysis in rabbits killed by KCN		
Brain	Concentrations dropped from 1.6 mg/kg FW immediately after death to 1.2 in 1 day, 0.92 in 3 days, and 0.04 in 7 days	25
Blood	Residues, in mg/kg FW were 5.7 immediately after death and 2.3 after 21 days	25
Lung	Cyanide concentrations dropped from 2 mg/kg FW just after death, to 0.8 in 7 days	25
Domestic sheep, *Ovis aries*		
Intravenous or intraarterial injection, fetal lambs 80% through gestation (120 days), NaCN, 50–400 µg	Slowing of fetal heart rate, disruption of respiratory movements, significant but inconsistent changes in arterial blood pressure	26
Single intramuscular injection of 10 mg KCN/kg BW	All dead within 17 min; cyanide concentrations postmortem, in mg/kg FW, were 3.3 in blood, 1.5 in plasma, 1.6 in serum, 1.4 in cerebrospinal fluid, 0.9 in brain grey matter, and 1.0 in brain white matter	3, 10, 27
Laboratory white rat, *Rattus* spp.		
Single intraperitoneal injection		

0.1–10 mg CN/kg BW	LD50	28
5 mg NaCN or KCN/kg BW	50% decrease in brain cytochrome oxidase activity within 5–10 min	14
5 mg KCN/kg BW	Reversible intracellular metabolic changes including acidosis and increased lactate levels--typical of cellular anoxia	29
Intravenous injection, constant infusion of 0.15–0.20 mg CN/kg BW per min	LD50 in about 20 min. Rapid progressive reduction in cerebrocortical cytochrome oxidase (cytochrome aa_3) concomitant with increases up to 200% in cerebral blood flow	30
Single intracartoid artery injection of KCN		
1–2 mg/kg BW	Modest acute clinical dysfunction and incomplete suppression of brain electroencephalographic (EEG) activity	31
2.5 mg/kg BW	Some deaths; survivors showed rapid abolition of brain EEG activity, 52% reduction in brain cytochrome oxidase activity, 600% increase in lactate, 85% decrease in glycogen, 32% reduction in ATP, and 73% increase in ADP; all values returned to normal in 6–24 h, and remained normal for balance of 7-day observation period	31
3.5–5 mg/kg BW	High incidence of cardiovascular collapse and death within minutes	31
Tissue residues 2.6–2.9 mg HCN/L	Minimum lethal concentrations in rats poisoned orally with KCN	13
Inhalation exposure route, HCN vapor, in mg/m^3, for various periods		
3,778 for 10 s	LC50	10
1,128 for 1 min	LC50	10
493 for 5 min	LC50	10
151–173 for 30–60 min	LC50	10
Single oral dose		
3.4 mg KCN/kg BW	LD25	32
3.6–4.2 mg HCN/kg BW	LD50	10
5.1–5.7 mg NaCN/kg BW	LD50	10
5.7 mg KCN/kg BW	LD50	32
6, 10, or 14 mg KCN/kg BW	Some deaths in all groups; all dead at higher doses within 60 min; those killed 10 min postadministration had	13

	higer blood CN concentrations than those killed near death or at survival at 60 min	
6.4 mg NaCN/kg BW	LD50	13
7.5–10 mg KCN/kg BW	LD50	10, 13
8.6 mg KCN/kg BW	LD98	32
10 mg KCN/kg BW, equivalent to 4 mg HCN/kg BW	LD50	20
13.2 mg NaCN/kg BW or 7 mg HCN/kg BW	Dead in 10.3 min; tissue cyanide levels, in mg/kg FW, were 8.9 in liver, 5.9 in lung, 4.9 in blood, 2.1 in spleen, and 1.5 in brain	33
40 mg NaCN/kg BW, equivalent to 21 mg HCN/kg BW	Dead in 3.3 min	33
Drinking water exposure		
Equivalent to 8 mg CN/kg BW daily for 21 days	Liver normal	20
Equivalent to 21 mg CN/kg BW daily for 21 days	Significantly increased liver weight	20
200 mg CN/L for 4 weeks	Reduced growth	34
Drinking water of adults contained 150 mg CN/L, as KCN, for 2 weeks, followed by injection with radioselenium-75 and observed for 15 days	Cyanide-treated rats excreted significantly more radioselenium in urine than did controls; half-time persistence of radioselenium in treated group was 28 days vs. 38 days in controls	35
Drinking water of weanling males contained 150 mg CN/L for 9 weeks	Significant reduction in glutathion activity, and in selenium concentrations in blood kidney, liver, and muscle	35
Dietary exposure		
Fed 12 mg CN/kg BW daily for 2 years, equivalent to 300 mg HCN/kg ration	No measurable adverse effects on blood chemistry, growth, survival, or histology; elevated thiocyanate levels in liver and kidneys	1
Fed 500 mg HCN/kg ration to pregnant rats through gestation and lactation	No effect on reproduction	20
Weanlings fed diets of raw lima beans containing 727 mg CN/kg for 3 weeks, or 727 mg CN/kg diet as KCN for 3 weeks	Lima bean diet alone increased hepatic glutamate dehydrogenase (GLDH) and decreased isocitrate dehydrogenase (ICDH) activities; KCN diet had no effect on GLDH and increased ICDH activity, emphasizing the importance of dietary components when evaluating CN-containing diets	36
750 mg CN/kg diet (1,875 mg KCN/kg diet) for 8 weeks,	No measurable effect on food consumption or growth rate;	37

adequate protein	significantly increased serum and urinary thiocyanate concentrations	
As above, protein deficient diet	Reduction in body weight gain, reduction in serum thiocyanate concentration	37
Weanling males fed diets containing 1,500 mg KCN/kg, or 2,240 mg potassium thiocyanate (KSCN)/kg for 50 weeks	No deaths or clinical signs of toxicity; both groups had decreased thyroid gland activity; cyanide, but not thiocyanate, caused reduction in growth rate	38
Isolated liver segments from starved rats exposed to 100 mg KCN/L	Oxygen consumption reduced 80%, and evidence of hepatotoxicity as judged by enzyme release, glutathione depletion, and calcium accumulation in liver; hepatotoxicity prevented by feeding rats fructose	39
Domestic pig, *Sus* spp.		
Fed diet containing 96 mg CN/kg ration, as cassava peel for 72 days	No effect on food consumption or protein metabolism	40

[a]1, EPA 1980; 2, Sterner 1979; 3, Christel et al. 1977; 4, Savarie and Sterner 1979; 5, Tewe 1984; 6, Tewe 1988; 7, Tewe 1982a; 8, Curry 1963; 9, Grandas et al. 1989; 10, Ballantyne 198a; 11, Towill et al. 1978; 12, Ukhun and Dibie 1989; 13, Egekeze and Oehme 1980; 14, Way 1981; 15, Casadei et al. 1984; 16, Purser et al. 1984; 17, Purser 1984; 18, Willhite and Smith 1981; 19, Yamamoto 1989; 20, EPA 1989; 21, Robinson et al. 1985; 22, Ballantyne et al. 1972; 23, Ballantyne 1988; 24, Yamamoto et al. 1979; 25, Ballantyne et al. 1974; 26, Itskovitz and Rudolph 198; 27, Ballantyne 1975; 28, Brattsten et al. 1983; 29, Lotito et al. 1989; 30, Lee et al. 1988; 31, MacMillan 1989; 32, Keniston et al. 1987; 33, Yamamoto et al. 1982; 34, Palmer and Olson 1981; 35, Beilstein and Whanger 1984; 36, Aletor and Fetuga 1988; 37, Tewe and Maner 1985; 38, Philbrick et al. 1979; 39, Younes and Strubelt 1988; 40, Tewe and Pessu 1982; 41, Way 1984; 42, Marrs and Ballantyne 1987; 43, Buzaleh et al. 1989; 44, Bapat and Abhyankar 1984.

Organic cyanide compounds, or nitriles, have been implicated in numerous human fatalities and signs of poisoning—specially acetonitrile, acrylonitrile, acetone cyanohydrin, malonitrile, and succinonitrile. Nitriles hydrolyze to carboxylic acid and ammonia in either basic or acidic solutions. Mice *(Mus* sp.) given lethal doses of various nitriles had elevated cyanide concentrations in liver and brain; the major acute toxicity of nitriles is CN release by liver processes (Willhite and Smith 1981). In general, alkylnitriles release CN much less readily than aryl alkylnitriles, and this may account for their comparatively low toxicity (Davis 1981).

No human cases of illness or death due to cyanide in water supplies are known (EPA 1980). Accidental acute cyanide poisonings in humans are uncommon (Towill et al. 1978); however, a man accidentally splashed with molten sodium cyanide died about 10 h later (Curry 1963). Human cyanide deaths usually involve suicides, where relatively large amounts of sodium cyanide or potassium cyanide are ingested and the victims die rapidly in obvious circumstances. Recovery after oral ingestion is rare. In one case, a spouse emptied capsules containing medicine and repacked them with 40% solid NaCN. The victim took one capsule and ingested about 0.05 g, but vomited and recovered completely (Curry 1963). Human deaths are increasing from gas or smoke inhalation from urban fires, possibly owing to the increased toxicity of fire atmospheres caused by the use of organocyanide plastics in modern construction and furnishings (Egekeze and Oehme 1980). Hydrogen cyanide may be important in some fires in producing rapid incapacitation, causing the victims to remain in the fire and die from carbon monoxide or other factors, although HCN concentrations of 60 mg/L air and lower had minimal effects (Purser 1984). Exposure to the mixture of HCN and carbon monoxide, with accompanying changes in cerebral blood flow during attempts to escape from fires, may be a cause of collapse and subsequent death

(Purser 1984). For example, cynomolgus monkeys (*Macaca* spp.) exposed to pyrolysis products of polyacrylonitrile (PAN) and to low-level HCN gas had similar physiological effects in both atmospheres, specifically: hyperventilation, followed by loss of consciousness after 1-5 min; and brachycardia, with arrhythmias and T-wave abnormalities. Recovery was rapid following cessation of exposure (Purser et al. 1984). Because HCN is the major toxic product formed by the pyrolysis of PAN, Purser et al. (1984) suggested that HCN may produce rapid incapacitation at low blood levels of cyanide in fires, while death may occur later due to carbon monoxide poisoning or other factors.

Finally, cyanide does not appear to be mutagenic, teratogenic, or carcinogenic in mammals (EPA 1980; Ballantyne 1987a). In fact, there has been a long-standing hypothesis for an anticancer effect of the cyanogenic glycoside amygdalin (also called laetrile). The hypothesis is based on amygdalin's selective hydrolysis by a beta glucosidase, liberating cyanide and benzaldehyde at the neoplastic site. The cyanide then selectively attacks the cancer cell, which is presumed to be low in rhodanese, whereas normal cells are assumed to possess sufficient rhodanese and sulfur to detoxify the cyanide (Way 1981). However, many tumors are neither selectively enriched in beta glucosidase nor low in rhodanese (Way 1981).

Recommendations

Proposed free cyanide criteria suggest that sensitive species of aquatic organisms are protected at <3 µg/L, birds and livestock at <100 mg/ kg diet, and human health at concentrations of <10 µg/L drinking water, <50 mg/kg diet, and <5 mg/m^3 air (Table 6).

Analytical methodologies need to be developed that differentiate between free cyanide (HCN and CN^-) and other forms of cyanide, and that are simple, sensitive (i.e., in the µg/L range), and accurate (Smith et al. 1979; Leduc et al. 1982). Procedures need to be standardized that ensure prompt refrigeration and analysis of all samples for cyanide determination because some stored samples generate cyanide while others show decreases (Gee 1987).

Periodic monitoring of cyanide in waterways is unsatisfactory for assessing potential hazards because of cyanide's rapid action, high toxicity, and low environmental persistence. A similar case is made for cyanide in the atmosphere. Development of a continuous monitoring system of cyanides in waterways and air is recommended, with emphasis on point source dischargers, such as industrial and municipal facilities (Towill et al. 1978; Egekeze and Oehme 1980; Leduc et al. 1982). Information is needed on the fate of cyanide compounds in natural waters, relative contributions of natural and anthropogenic sources, and critical exposure routes for aquatic organisms (Leduc et al. 1982). Additional research is needed on the origin of cyanide in wilderness and rural watershed areas, specifically the roles of organic wastes and their associated bacterial flora, aquatic vegetation induced by nutrient enrichment, and terrestrial plant cover in the watershed (Leduc 1984).

Table 6. Proposed free cyanide criteria for the protection of living resources and human health.

Resource criterion, and other variables	Concentration	Reference[a]
Freshwater organisms		
Effect levels, in µg/L medium		
Minimal impairment, most species of fish	3–5	1, 2, 3, 4, 5, 6
Reduced survival, amphipods	>3–34	1, 7
Safe, most fish species	3.5 (24-h average, not to exceed 52 at any time)	7
Significant impairment, most species of fish	8–16, exposure for at least 20 days	6, 7
Hazardous		
Most fish species	>11	1, 4
Microorganisms	>300	8

Reduced survival, chronic exposure		
Bivalve molluscs, larvae	>14	1
Fish, many species	30–150	1, 5
Impaired reproduction, sensitive species of fish	>25	2
Impaired swimming ability, growth, development, and behavior	>100	3, 6
Lethal to rapidly lethal, acute exposure	300–1,000	5
Marine organisms		
Effect levels, in µg/L seawater		
Adverse effects, chronic exposure	>2	7
Minimal risk	<5	1
Hazardous	>10	1
Lethal	>30	7
Sediments, Great Lakes		
Effect level, in mg total cyanide/kg dry weight (DW)		
Nonpolluted	<0.10	20
Moderately polluted	0.1–0.25	20
Heavily polluted	>0.25	20
Birds		
Domestic chickens		
Diet, safe level, in mg total cyanide/kg ration fresh weight (FW)	90–<100	9, 10
Waterfowl		
Drinking water, safe	<50	21, 22
Livestock		
level in mg/L total cyanide		
Diet, safe level, in mg/kg FW		
Free cyanide	<100	9
Total cyanide	<625	11
Forage, hazardous level, in mg/kg FW	>200	8
Laboratory white rat		
Diet, safe level, in mg/kg ration FW	<1,000	19
Blood, in mg/L		
Normal	0.25–0.45	12
Minimum lethal concentration	2.6–2.9	12
Liver		
Minimum lethal concentration, in mg/kg FW	0.5–6.1	12
Human health		
Drinking water, in µg/L		
Recommended	<5–<10	1, 6, 8, 13
United States nationwide survey	Max. 8	7
Safe	<10	1
Goal, United States	<10	7, 14
Maximum allowable limit, United States	10	13
Goal, Canada	<20	7
Lifetime health advisory, United States and Canada	<154	14

Acceptable	<200	7
Mandatory limit	200	13
Rejected	>200	1, 8
10-day health advisory		
Child	<220	14
Adult	<770	14
Diet		
Acceptable daily intake		
Water	1.5 mg, equivalent to 0.02 mg/kg body weight (BW) daily for 70-kg adult	15
Food, in mg/kg BW	8.4	7
Food, in mg/kg FW	<50	15
Food, in mg total cyanide/kg FW	<415	11
Cassava, *Manihot esculenta*, roots, total cyanide, in mg/kg FW		
Safe	<50	16
Moderately toxic	50–100	16
Very poisonous	>100	16
Food items, in mg/kg		
Cocoa	<20 DW	13
Beans, nuts	<25 DW	1
Cereals, grains	<25 DW	13
Citrus fruits	<50 FW	1
Uncooked pork	<50 FW	13
Grains	<75 FW	1
Cereals flours	<125 DW	13
Spices	<250 FW	1, 13
Frozen meat	<950 FW	1, 13
Bakery products, yeast	<1,500 DW	13
Egg white solids	<1,000 DW	13
Tissue residues		
Blood and spleen, in µg/L or µg/kg FW		
Normal	77	17
Suspected poisoning	>1,000	17
Whole blood, in µg/L		
Usually fatal	1,000–2,000	15
Whole body, in mg/kg BW		
Fatal	4, if taken rapidly	18
Air, in mg/m^3		
Recommended safe levels		
Soviet Union, Romania, Hungary, Bulgaria, Czechoslovakia	<0.3	1
United States	<5	14
Most countries	<11	1, 15
Occupational exposure		
Proposed safe level, United States	<3	15
Safe ceiling concentration	<5	1
Hazardous levels	4.2–12.4	1
Soils in mg/kg DW		
Free cyanide		
Background	1	20
Moderate contamination	10	20
Requires cleanup	100	20
Complex cyanide		
Background	5	20

Moderate contamination	50	20
Requires cleanup	100	20

[a]1, Towill et al. 1978; 2, Smith et al. 1979; 3, Doudoroff 1976; 4, Leduc 1981; 5, Leduc 1984; 6, Leduc et al. 1982; 7, EPA 1980; 8, Egekeze and Oehme 1980; 9, Gomez et al. 1983; 10, Gomez et al. 1988; 11, Okeke et al. 1985; 12, Egekeze and Oehme 1979; 13, EPA 1973; 14, EPA 1989; 15, Marrs and Ballantyne 1987; 16, Dufour 1988; 17, Gee 1987; 18, Shaw 1986; 19, Tewe 1982; 20, Beyer 1990; 21, Allen 1990; 22, Clark and Hothem 1991.

In aquatic systems research is needed in several areas: (1) long-term effects of cyanide on life cycles, growth, survival, metabolism, and behavior of a variety of aquatic organisms and microorganisms in addition to fish (Towill et al. 1978; Leduc et al. 1982); (2) effects of seasonal pulses of cyanide on aquatic organisms in rural and wilderness areas (Leduc 1984); (3) influence of various environmental parameters (e.g., oxygen, pH, temperature), if any, on adaptive resistance to cyanide (Leduc 1981, 1984); and (4) usefulness of various biochemical indicators of cyanide poisoning, such as cytochrome oxidase inhibition (Gee 1987) and vitellogenin levels in fish plasma (*gairdneri*) (Ruby et al. 1986).

The use of M-44 sodium cyanide capsules for predator control was suspended and cancelled by the U.S. Environmental Protection Agency on 9 March 1972. M-44 use was again permitted by the U.S. Environmental Protection Agency beginning on 4 February 1976, provided that "each authorized or licensed applicator shall carry an antidote kit on his person when placing or inspecting M-44 devices. The kit shall contain at least 6 pearls of amylnitrite and instructions on their use. Each authorized or licensed applicator shall also carry on his person instructions for obtaining medical assistance in the event of accidental exposure to sodium cyanide" (EPA 1976a, 1976b).

Farmers need to be aware of factors that influence the cyanogenic potential of forage crops and to conduct regular inspections of grazing fields for cyanogenic plants. Moreover, hay and silage should be properly cured in order to minimize cyanide content before feeding to livestock (Egekeze and Oehme 1980). Selective breeding of plants with low cyanide content will help reduce livestock poisoning, but the most advisable prevention method at present is to prohibit grazing on fields where cyanogenic plants are present (Egekeze and Oehme 1980). More research seems needed on (1) effects of drought and other factors that may increase the concentration of cyanogenic glycosides in livestock forage plants, (2) mechanisms of cyanide liberation by plants, and (3) effects of cyanide on wildlife and range animals that graze on foliage with high cyanogenic glycoside content (Towill et al. 1978).

Research is needed on low-level, long-term cyanide intoxication in mammals by oral and inhalation routes in the vicinities of high cyanide concentrations, especially on the incidence of skin dermatitis, nasal lesions, and thyroid dysfunction, and on urinary thiocyanate concentrations. These types of studies may provide a more valid rationale in establishing standards and threshold limit values for HCN and inorganic cyanide (Towill et al. 1978; Egekeze and Oehme 1980).

Data are scarce on the carcinogenic, teratogenic, and mutagenic properties of cyanide, and on the distribution and transformation of cyanides in air, land, or water. Additional analysis of available information and more research in these areas is recommended. Finally, more research is needed on cyanide toxicokinetics because cyanide is a very reactive nucleophile that distributes widely through the body, is permeable to cell membranes, and may accumulate in the fetus (Towill et al. 1978).

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