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TOXICOLOGICAL PROFILE FOR CYANIDE

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FOREWORD

The Superfund Amendments and Reauthorization Act of 1986 (Public Law 99-499) extended and amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund). This public law (also known as SARA) directed the Agency for Toxic Substances and Disease Registry (ATSDR) to prepare toxicological profiles for hazardous substances which are most commonly found at facilities on the CERCLA National Priorities List and which pose the most significant potential threat to human health, as determined by ATSDR and the Environmental Protection Agency (EPA). The list of the 100 most significant hazardous substances was published in the *Federal Register* on April 17, 1987.

Section 110 (3) of SARA directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list. Each profile must include the following content:

> "(A) An examination, summary, and interpretation of available toxicological information and epidemiologic evaluations on a hazardous substance in order to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects.
>
> (B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine levels of exposure which present a significant risk to human health of acute, subacute, and chronic health effects.
>
> (C) Where appropriate, an identification of toxicological testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans."

This toxicological profile is prepared in accordance with guidelines developed by ATSDR and EPA. The guidelines were published in the *Federal Register* on April 17, 1987. Each profile will be revised and republished as necessary, but no less often than every three years, as required by SARA.

The ATSDR toxicological profile is intended to characterize succinctly the toxicological and health effects information for the hazardous substance being described. Each profile identifies and reviews the key literature that describes a hazardous substance's toxicological properties. Other literature is presented but described in less detail than the key studies. The profile is not intended to be an exhaustive document; however, more comprehensive sources of specialty information are referenced.

Each toxicological profile begins with a public health statement, which describes in nontechnical language a substance's relevant toxicological properties. Following the statement is material that presents levels of significant human exposure and, where known, significant health effects. The adequacy of information to determine a substance's health effects is described in a health effects summary. Research gaps in toxicologic and health effects information are described in the profile. Research gaps that are of significance to protection of public health will be identified by ATSDR, the National Toxicology Program of the Public Health Service, and EPA. The focus of the profiles is on health and toxicological information; therefore, we have included this information in the front of the document.

The principal audiences for the toxicological profiles are health professionals at the federal, state, and local levels, interested private sector organizations and groups, and members of the public. We plan to revise these documents in response to public comments and as additional data become available; therefore, we encourage comment that will make the toxicological profile series of the greatest use.

This profile reflects our assessment of all relevant toxicological testing and information that has been peer reviewed. It has been reviewed by scientists from ATSDR, EPA, the Centers for Disease Control, and the National Toxicology Program. It has also been reviewed by a panel of nongovernment peer reviewers and was made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.

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1. PUBLIC HEALTH STATEMENT

1.1 WHAT IS CYANIDE?

Cyanide is a substance that is found in combination with other chemicals in the environment. Of these combinations (compounds), the ones people are most likely to come in contact with are hydrogen cyanide, sodium cyanide, and potassium cyanide. Hydrogen cyanide is a colorless gas or liquid with a faint, bitter almond odor. Sodium cyanide and potassium cyanide are both colorless solids that have a slight odor of bitter almonds in damp air.

Cyanides are both man-made and naturally occurring substances. They are found in a number of foods and plants and are produced by certain bacteria, fungi, and algae. Very small amounts of cyanide, in the form of vitamin B_{12} (cyanocobalamin), are a necessary part of the human diet. Most of the cyanide found in the environment comes from industrial processes. Hydrogen cyanide is used mainly in the production of organic chemicals. Cyanide salts are used primarily in electroplating and metal treatment. Cyanide gained public attention when it was found to have caused the deaths of seven people who swallowed capsules contaminated with it.

1.2 HOW MIGHT I BE EXPOSED TO CYANIDE?

Humans can be exposed to cyanide from environmental, occupational, and consumer product sources. The single largest source of cyanide in air is from vehicle exhaust. Other sources of release to the air may include emissions from chemical processing industries, steel and iron industries, metallurgical industries, metal plating and finishing industries, and petroleum refineries. Cyanides may also be released from public waste incinerators, from waste disposed of in landfills, and during the use of cyanide-containing pesticides. When certain types of plastics, silk, wool, and paper are burned, cyanides are released. People who smoke tobacco take in larger amounts of cyanide than nonsmokers.

The major sources of cyanide release to water are discharges from publicly owned wastewater treatment works, iron and steel production plants, and organic chemical industries. Much smaller amounts of cyanide may enter water through storm-water runoff in locations where cyanide-containing road salts are used. Groundwater can be contaminated by the movement of cyanide through soil from landfills. The largest sources of cyanide releases to soil are probably from the disposal of cyanide wastes in landfills and the use of cyanide-containing road salts.

Cyanide has been found in at least 134 of the 1,177 sites on the National Priorities List (NPL) of hazardous waste sites in the United States.

Workers may be exposed to cyanides in a wide variety of occupations including electroplating; metallurgy; metal cleaning; pesticide application; firefighting; steel manufacturing; gas works operations; manufacture of cyanides and some dyes, some pharmaceuticals, and some chelating agents; tannery work; blacksmithing; photoengraving; and photography.

Cyanide also occurs naturally in a variety of fruits, vegetables, and grains. In the United States, only low levels of cyanide are taken in from eating food because foods with high cyanide levels are not a major part of the American diet.

1.3 HOW DOES CYANIDE GET INTO MY BODY?

Cyanide can enter the body when a person breathes air containing hydrogen cyanide vapor or dust containing cyanide compounds. This may be a common pathway of exposure for individuals who work with the chemical, and for those who smoke. It is probably also a common exposure pathway for those who live near industrial and commercial areas where large amounts of the compound are used or disposed of in waste sites. Cyanide can also enter the body when a person eats food or drinks water containing it. If cyanide is present at a waste site, it may get into underground water as it passes downward through the soil. It is not common for persons to be exposed to cyanide through skin contact, although it can enter the body this way. Skin exposure usually happens only in the workplace.

1.4 HOW CAN CYANIDE AFFECT MY HEALTH?

Cyanide in the form of vitamin B_{12} (cyanocobalamin) is needed as part of a healthy diet to prevent iron poor blood, or anemia.

The effects of cyanide may vary from person to person depending upon things such as health, family traits, age, and sex. Exposure to high levels of cyanide for a short period harms the central nervous system, respiratory system, and cardiovascular system. Short-term exposure to high levels of cyanide can cause coma and/or death. Brief exposures to lower levels result in rapid, deep breathing; shortness of breath; convulsions; and loss of consciousness. These short-term effects go away with time because cyanide does not stay in the body. In some cases, quick medical treatment can revive a person who has been poisoned by cyanide.

Skin contact with dust from certain cyanide compounds can cause skin irritation and ulcerations.

People have developed damage to the nervous system and thyroid gland after eating food containing low levels of cyanide for a long time (months to years).

Effects on the nervous system believed to be from long-term exposure to cyanide include deafness, vision problems, and loss of muscle coordination. Effects on the thyroid gland can cause cretinism (retarded physical and mental growth in children), or enlargement and overactivity of the gland.

These effects have been seen in people who eat large amounts of cassava, a cyanide-containing vegetable, and who don't have enough iodine and other necessary nutrients in their diet. These effects have not been seen at levels of cyanide exposure usually found in foods in the United States.

Some animal data show that cyanide may cause harm to the unborn offspring, but the studies are not complete enough to measure this effect. No evidence exists to tell if cyanide causes cancer.

1.5 IS THERE A MEDICAL TEST TO DETERMINE IF I HAVE BEEN EXPOSED TO CYANIDE?

Blood and urine levels of cyanide and thiocyanate, a compound produced from cyanide, can be measured. Because these compounds are always found in the body, these measurements are only useful when exposure to large amounts of cyanide has occurred.

1.6 WHAT LEVELS OF EXPOSURE HAVE RESULTED IN HARMFUL HEALTH EFFECTS?

The graphs on the following pages show the relationship between exposure to cyanide and known health effects. In the first set of graphs, labeled "Health effects from breathing cyanide," exposure is measured in parts of hydrogen cyanide per million parts of air (ppm). In all graphs, effects in animals are shown on the left side and effects in humans on the right side.

In the second set of graphs, the same relationship is shown for known health effects from eating products containing cyanide. Exposures are measured in milligrams of cyanide per kilogram of body weight per day (mg/kg/day). The health effects resulting from skin exposure to cyanides were not complete enough to put on a graph.

The effects shown in the first column of Fig. 1.1, labeled "Short-Term Exposure," represent health effects from exposure lasting for 14 days or less. Inhalation exposure to cyanide causes rapid effects. Exposure of humans at a level of 110 ppm can cause death within 30 minutes to 1 hour. At a level of about 18 ppm, persons may have headaches, weakness, and nausea (after several hours of exposure). Hydrogen cyanide vapor has a smell of bitter almonds that some individuals can first smell at about 0.6 ppm. This smell will not alert everyone to the fact that hydrogen cyanide is in the air, because not all persons can smell hydrogen cyanide. Deaths in animals have been reported at exposure levels ranging from 20 ppm for 4.5 hours to 503 ppm for 5 minutes. Heart effects in rats have been reported following exposure at 200 ppm for 12.5 minutes.

The effects shown in the second column of Fig. 1.1, labeled "Long-Term Exposure," are those resulting from exposures of more than 14 days. Little long-term exposure information is available. In humans exposed to cyanides in the workplace, effects on the thyroid gland and other health problems (breathing difficulty, headache, throat irritation, weakness, changes in taste and smell, abdominal pain, vomiting, and nervous instability) have been reported at levels of 6.4 to 10.3 ppm. Nervous system effects have been seen in dogs exposed to hydrogen cyanide at 45 ppm for 30 minutes a day for up to 22 weeks.

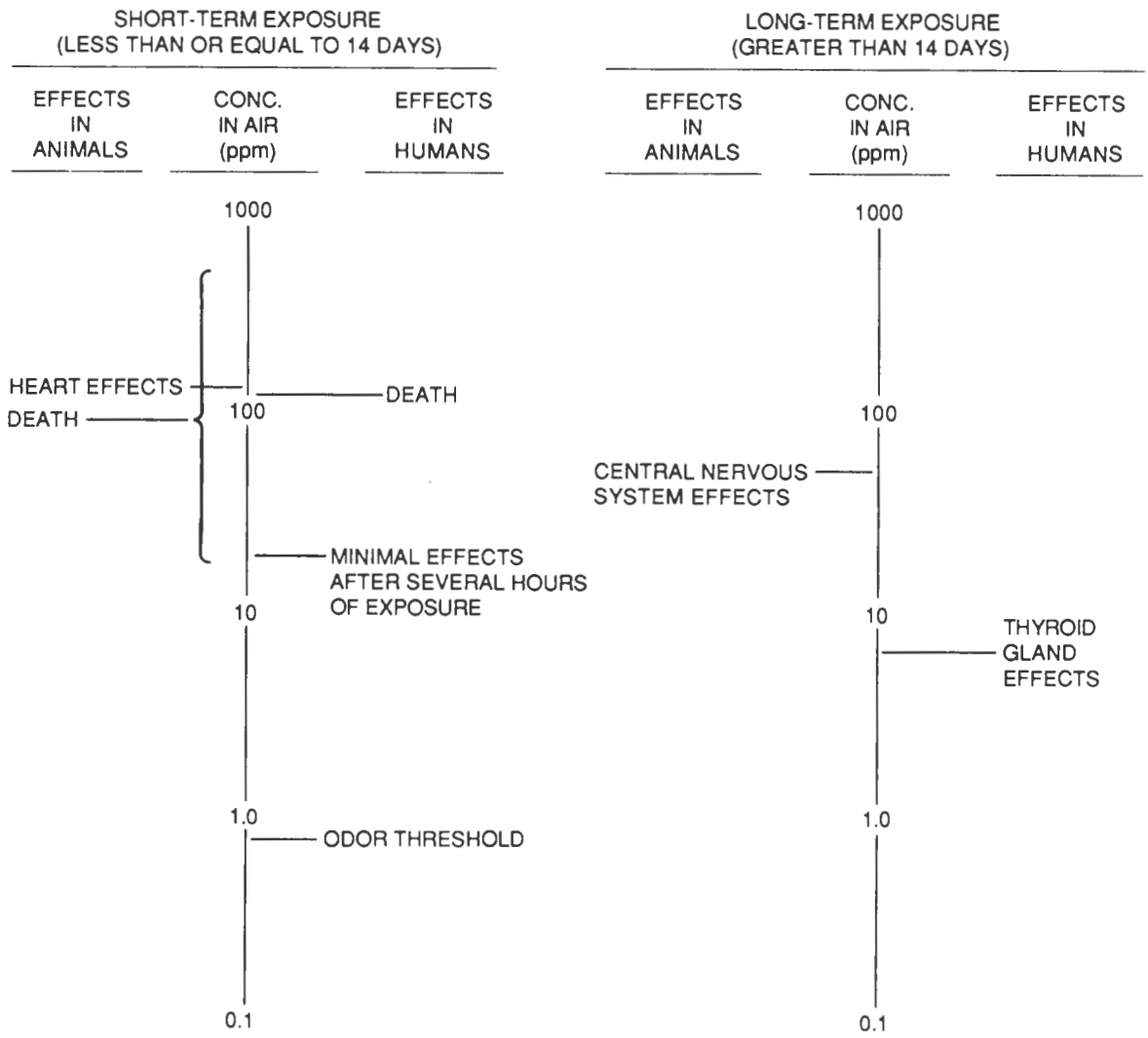


Fig. 1.1. Health effects from breathing cyanide.

Figure 1.2 shows the known health effects from eating cyanide. Little information is available. Short-term exposures resulting from suicides and suicide attempts have been reported. The lowest amount eaten causing death was 0.56 mg/kg/day. There is no information showing that long-term exposure to cyanides in food or water causes health effects in humans. Harm to the nervous system and developing offspring has been seen in animals fed cyanides. A single dose of 3.4 mg/kg has caused death in animals. Rats died when a cyanide compound was placed directly into their stomachs daily for 90 days. A comparison of short-term and long-term animal studies shows that a single dose given all at one time can cause death, while higher levels of cyanides given in food over a longer time do not cause death. The reason for this may be that cyanides enter the body more slowly when given in food.

1.7 WHAT RECOMMENDATIONS HAS THE FEDERAL GOVERNMENT MADE TO PROTECT HUMAN HEALTH?

The government has made recommendations to limit the exposure of the general public to cyanide in food and the exposure of workers to cyanide in the workplace. Hydrogen cyanide is sometimes used to treat food after it is harvested to prevent pest damage. The Environmental Protection Agency (EPA) allows levels of cyanide in food ranging from 25 ppm in dried beans, peas, and nuts to 250 ppm in spices.

Cyanide levels in the workplace are regulated by the Occupational Safety and Health Administration (OSHA). OSHA has a legally enforceable exposure limit of 5 milligrams of cyanide per cubic centimeter of air (mg/cm^3) for cyanide and 11 mg/cm^3 (or 10 ppm) hydrogen cyanide in air for an 8-hour workday, 40-hour workweek. The National Institute for Occupational Safety and Health (NIOSH) recommends that employee exposure to hydrogen cyanide and cyanide salts should not be more than 5 mg/m^3 in air for a 10-minute sampling period.

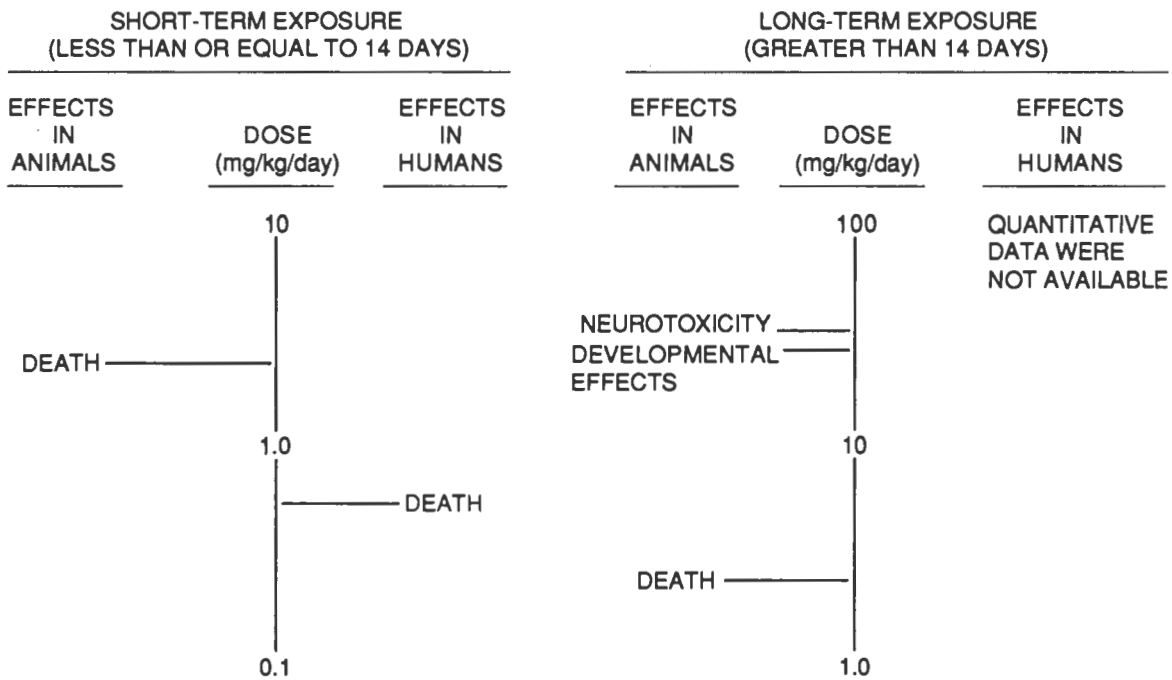


Fig. 1.2. Health effects from ingesting cyanide.

2. HEALTH EFFECTS SUMMARY

2.1 INTRODUCTION

This section summarizes and graphs data on the health effects concerning exposure to cyanide. The purpose of this section is to present levels of significant exposure for cyanide based on key toxicological studies, epidemiological investigations, and environmental exposure data. The information presented in this section is critically evaluated and discussed in Sect. 4, Toxicological Data, and Sect. 7, Potential for Human Exposure.

This Health Effects Summary section comprises two major parts. Levels of Significant Exposure (Sect. 2.2) presents brief narratives and graphics for key studies in a manner that provides public health officials, physicians, and other interested individuals and groups with (1) an overall perspective of the toxicology of cyanide and (2) a summarized depiction of significant exposure levels associated with various adverse health effects. This section also includes information on the levels of cyanide that have been monitored in human fluids and tissues and information about levels of cyanide found in environmental media and their association with human exposures.

The significance of the exposure levels shown on the graphs may differ depending on the user's perspective. For example, physicians concerned with the interpretation of overt clinical findings in exposed persons or with the identification of persons with the potential to develop such disease may be interested in levels of exposure associated with frank effects (Frank Effect Level, FEL). Public health officials and project managers concerned with response actions at Superfund sites may want information on levels of exposure associated with more subtle effects in humans or animals (Lowest-Observed-Adverse-Effect Level, LOAEL) or exposure levels below which no adverse effects (No-Observed-Adverse-Effect Level, NOAEL) have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Level, MRL) are of interest to health professionals and citizens alike.

Adequacy of Database (Sect. 2.3) highlights the availability of key studies on exposure to cyanide in the scientific literature and displays these data in three-dimensional graphs consistent with the format in Sect. 2.2. The purpose of this section is to suggest where there might be insufficient information to establish levels of significant human exposure. These areas will be considered by the Agency for Toxic Substances and Disease Registry (ATSDR), EPA, and the National Toxicology Program (NTP) of the U.S. Public Health Service in order to develop a research agenda for cyanide.

2.2 LEVELS OF SIGNIFICANT EXPOSURE

To help public health professionals address the needs of persons living or working near hazardous waste sites, the toxicology data summarized in this section are organized first by route of exposure--inhalation, ingestion, and dermal--and then by toxicological end points that are categorized into six general areas--lethality, systemic/target organ toxicity, developmental toxicity, reproductive toxicity, genetic toxicity, and carcinogenicity. The data are discussed in terms of three exposure periods--acute, intermediate, and chronic.

Two kinds of graphs are used to depict the data. The first type is a "thermometer" graph. It provides a graphical summary of the human and animal toxicological end points (and levels of exposure) for each exposure route for which data are available. The ordering of effects does not reflect the exposure duration or species of animal tested. The second kind of graph shows Levels of Significant Exposure (LSE) for each route and exposure duration. The points on the graph showing NOAELs and LOAELs reflect the actual doses (levels of exposure) used in the key studies. No adjustments for exposure duration or intermittent exposure protocol were made.

Adjustments reflecting the uncertainty of extrapolating animal data to man, intraspecies variations, and differences between experimental vs actual human exposure conditions were considered when estimates of levels posing minimal risk to human health were made for noncancer end points. These Minimal Risk Levels were derived for the most sensitive noncancer end point for each exposure duration by applying uncertainty factors. These levels are shown on the graphs as a broken line starting from the actual dose (level of exposure) and ending with a concave-curved line at its terminus. Although methods have been established to derive these Minimal Risk Levels (Barnes et al. 1987), shortcomings exist in the techniques that reduce the confidence in the projected estimates.

2.2.1 Key Studies

Dose-response duration data for the toxicity of cyanide are displayed in two types of graphs. These data are derived from key studies on cyanide compounds described in the following sections. Inhalation and oral NOAELs and LOAELs are presented on "thermometer" graphs in Figs. 2.1 and 2.2, respectively. NOAELS and LOAELs for lethality and the most sensitive target organ end points for acute, intermediate, and chronic durations for inhalation and oral exposures are presented graphically in Figs. 2.3 and 2.4, respectively. Data were insufficient to graphically display dermal data.

2.2.1.1 Inhalation

Lethality and decreased longevity. It is well known that inhalation exposure to hydrogen cyanide (HCN) gas at high concentrations can result in lethality after short periods of time. A 5-min LC_{50} in rats of 503 ppm has been reported (Higgins et al. 1972). Thirty-minute LC_{50}s of 410 and 182 ppm have been reported in goats and cats, respectively (ten Berge et al. 1986). Three of five dogs exposed to HCN at 537 to 637 ppm for 1.75 or 2 min died 16 to 20 h following the

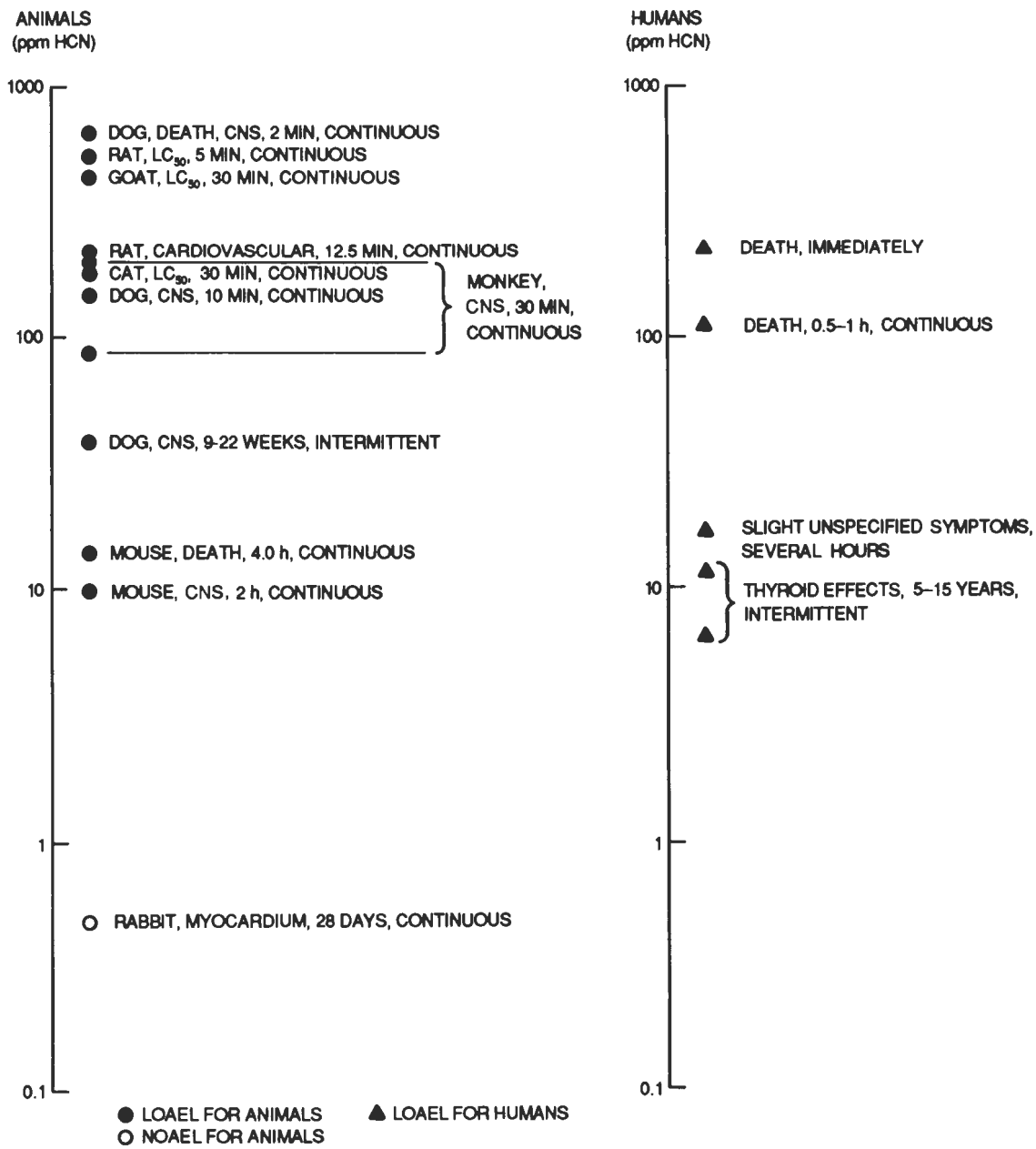


Fig. 2.1. Effects of cyanide—inhalation exposure.

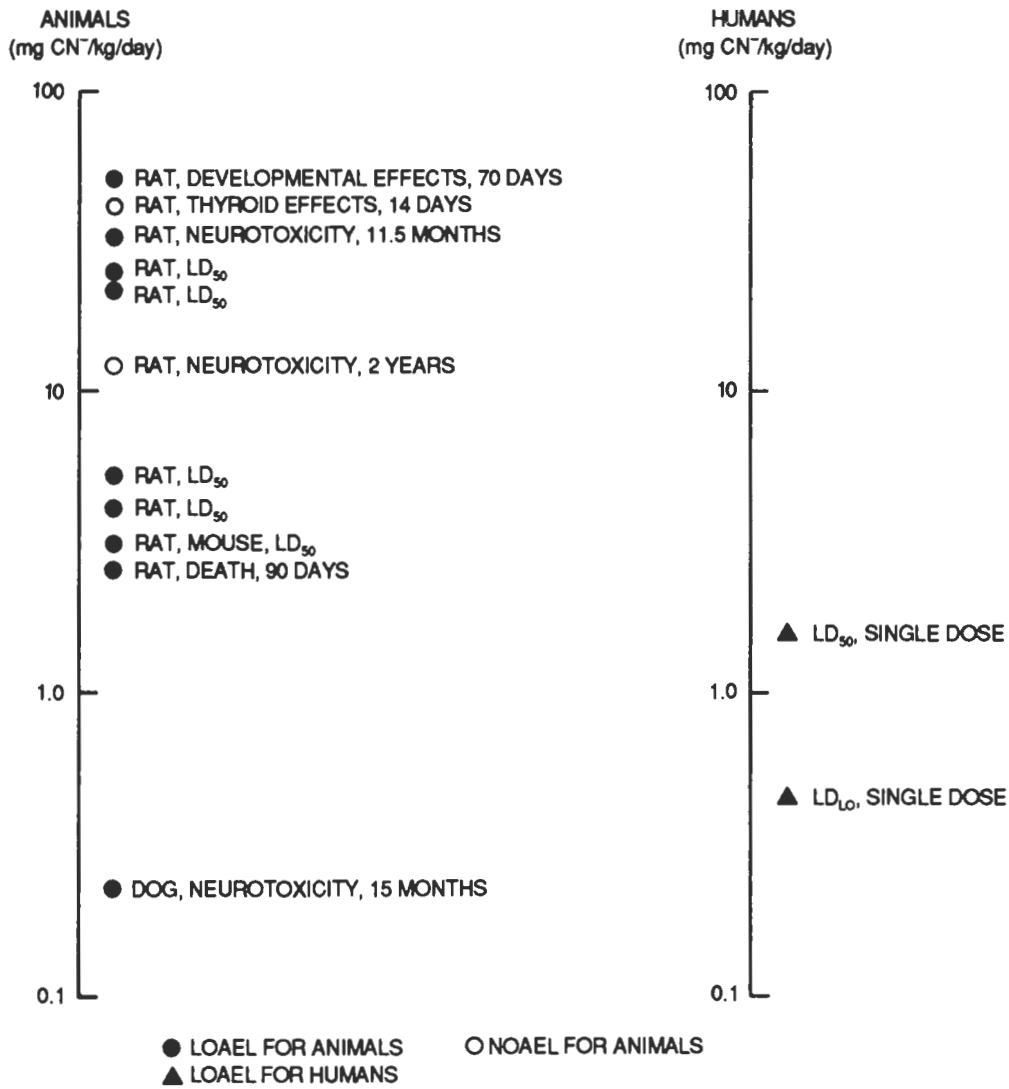


Fig. 2.2. Effects of cyanide—oral exposure.

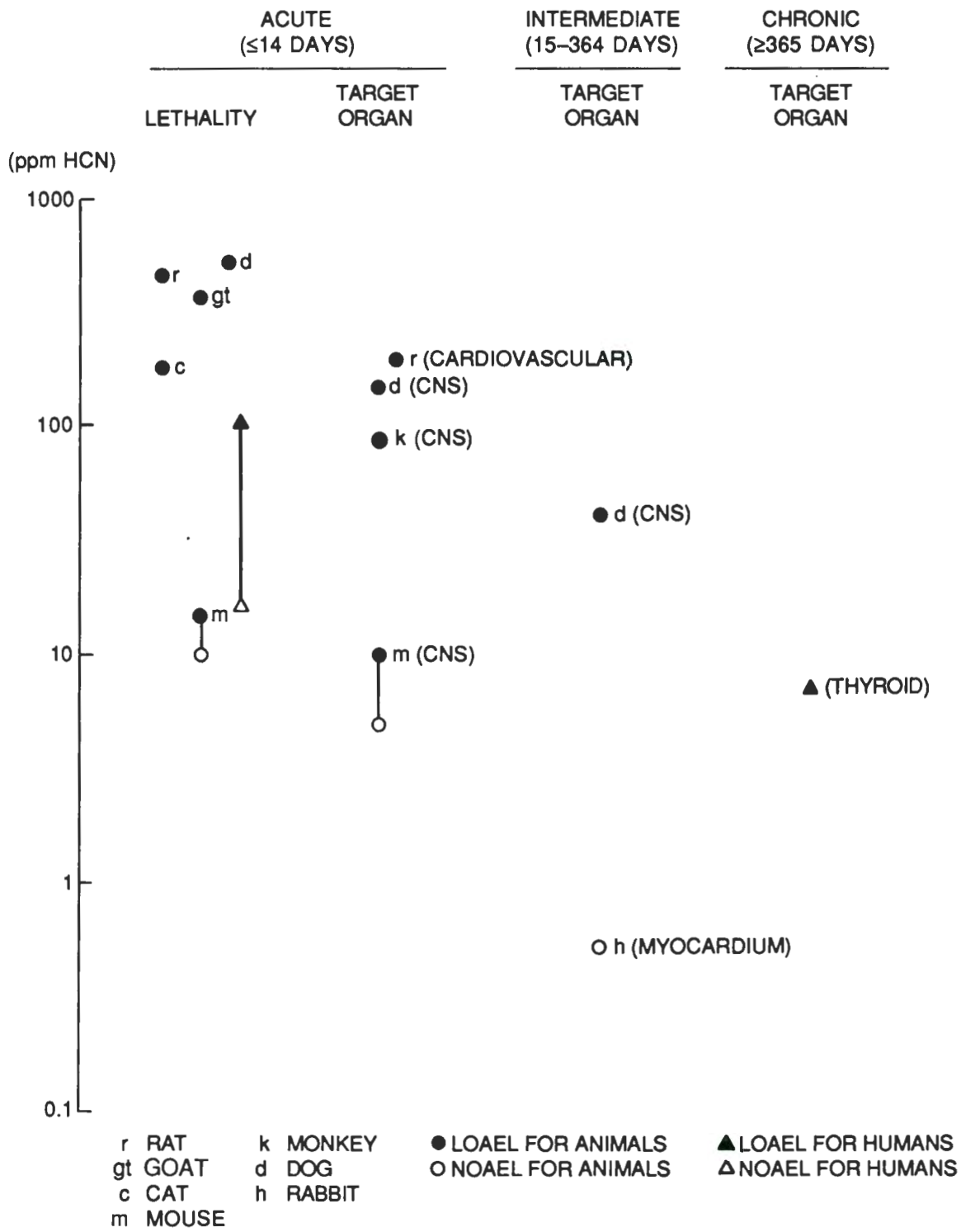


Fig. 2.3. Levels of significant exposure for cyanide—inhalation.

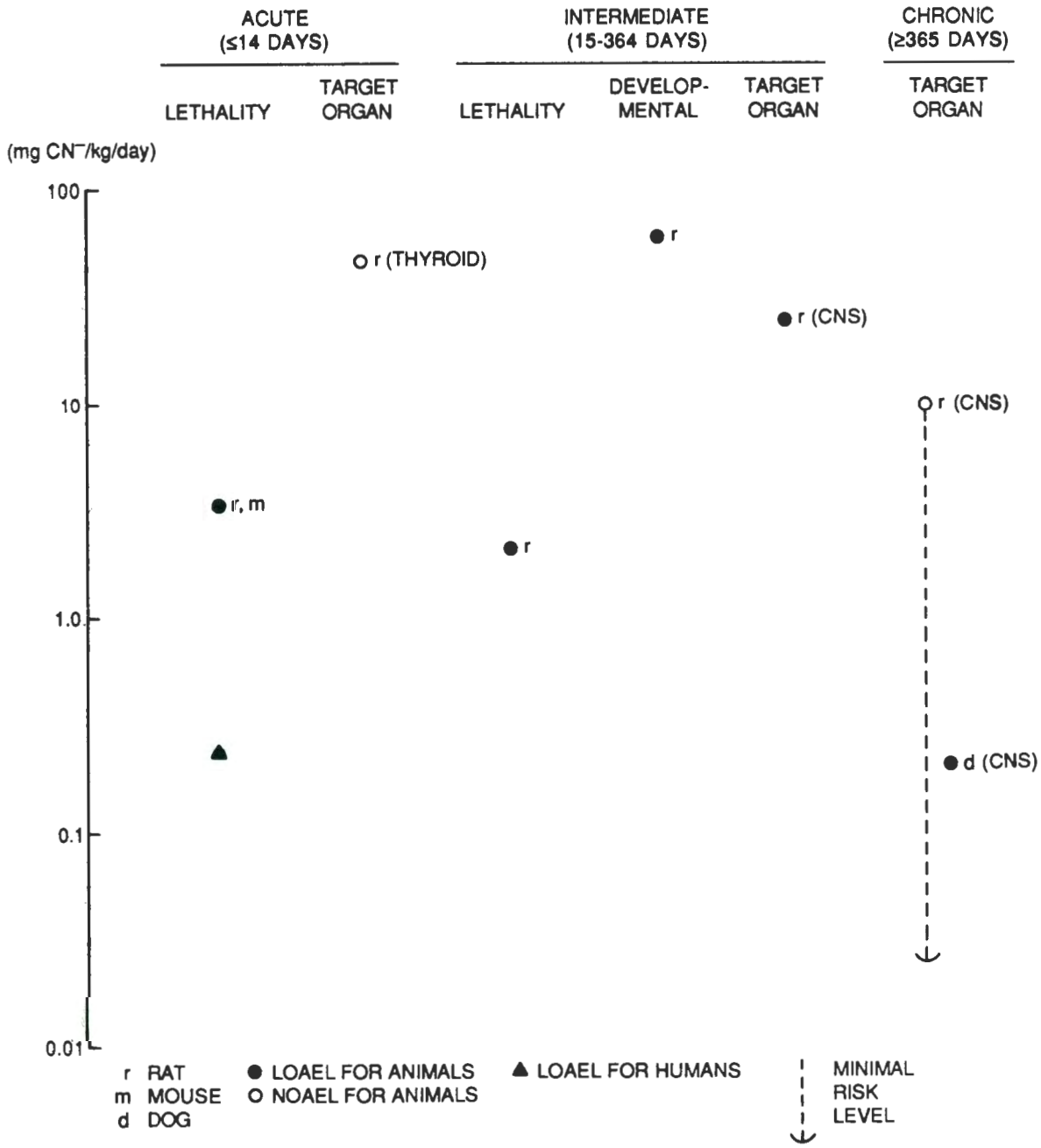


Fig. 2.4. Levels of significant exposure for cyanide—oral.

exposure (Haymaker et al. 1952). Sato et al. (1955) observed deaths in mice exposed to HCN at 15 ppm for 4 h. No deaths were reported when mice were exposed at 10 ppm for 2 h. In humans, Hartung (1981) reported that exposure to HCN at 270 ppm is immediately fatal, whereas exposure at 110 ppm can be fatal after 0.5 to 1 h. Exposure of humans at 18 ppm for several hours is reported to result in slight, unspecified symptoms. The concentrations of cyanide that resulted in death and the levels that did not result in death are plotted in Figs. 2.1 and 2.3 as LOAELs and NOAELs, respectively, for acute lethality. There are no longer-term inhalation studies for which death was the predominant effect.

Systemic/target organ toxicity, nervous system. The central nervous system (CNS) is a target of cyanide toxicity in humans, but specific dose-response data for nervous system effects are not available. Effects observed after acute inhalation exposure to HCN include headaches, numbness and paresis, and necrosis of brain tissue in fatal cases. Cardiac and respiratory effects, which may be attributed to cyanide-induced effects on the central nervous system, have also been reported (Carmelo 1955, El Ghawabi et al. 1975). The cardiac and respiratory effects are discussed in Sect. 2.2.1.1.

Studies in animals also indicate that the nervous system is a target of cyanide toxicity. Haymaker et al. (1952) exposed six dogs to HCN at 150 to 637 ppm for 1.75 to 10 min. Three dogs died 16 to 20 h after exposure, with the survivors sacrificed 24 to 48 h after exposure. When the brains of these dogs were examined microscopically, necrosis, primarily in regions of gray matter, was observed. The concentrations of 149 ppm for 10 min, a regimen which dogs survived, is plotted in Figs. 2.1 and 2.3.

To examine brain lesions produced by cyanide, Levine and co-workers (Levine and Stypulkowski 1959a,b; Levine 1967; Hirano et al. 1967) exposed rats to HCN at unspecified concentrations that produced intoxication for up to 60 min. These studies indicated that a deeper, longer intoxication was required to damage gray matter, with damage occurring to white matter after less severe exposures.

Purser et al. (1984) observed loss of consciousness, hyperventilation, bradycardia, arrhythmias, and T-wave abnormalities in monkeys exposed to HCN at 87 to 196 ppm for 30 min. This concentration range is presented in Fig. 2.1 as the range resulting in CNS effects in monkeys. The low end of the range (87 ppm) is presented in Fig. 2.3 as an acute LOAEL for CNS effects in monkeys.

Sato et al. (1955) found that exposure of mice to HCN at 10 ppm for 2 h resulted in motor dysfunction and labored respiration. A decrease in food intake, with no effect on motor function or respiration, was observed in mice exposed to HCN at 5 ppm for 4 h. The 10- and 5-ppm concentrations are presented in Figs. 2.1 and 2.3 as a LOAEL and a NOAEL, respectively, for CNS effects in mice following acute exposure. This early Japanese study lacks details concerning the methodology and the parameters of toxicity studied.

The only study of intermediate duration concerning CNS effects is a repeated acute exposure study in which 17 dogs were exposed to HCN at 45 ppm for 30-min periods at 2- to 8-day intervals for up to nineteen

30-min periods (Valade 1952). The effects observed during exposure included tremors, loss of equilibrium, and convulsions. Microscopic examinations revealed brain lesions. The 45-ppm concentration is plotted in Figs. 2.1 and 2.3 for CNS effects in dogs following intermediate exposure.

The studies available concerning CNS effects following inhalation exposure to cyanide are inadequate for the development of Minimal Risk Levels. Deficiencies in the available studies include the use of an inadequate number of animals, the lack of complete descriptions, the use of concentrations considered to be lethal to humans, and the observation of frank effects at the exposure concentrations studied.

Systemic/target organ toxicity, cardiovascular and/or respiratory effects. Cardiovascular and respiratory effects have been reported in humans and animals exposed to cyanide. Because there is little evidence showing direct myocardial damage, it is likely that many of the cardiovascular effects are secondary to effects on the central nervous system.

Carmelo (1955) reported EKG abnormalities in 11 of 13 fumigation workers who had all experienced episodes of acute HCN intoxication. Exposure concentrations were not reported. El Ghawabi et al. (1975) reported breathing difficulty in 16 of 36 electroplaters exposed to cyanide at 6.4 to 10.3 ppm. This concentration range is presented in Fig. 2.1 as the range resulting in thyroid effects. The low end of the range (6.4 ppm) is presented in Fig. 2.3 as a LOAEL for effects on the thyroid (see this section under Systemic/target organ toxicity, thyroid effects).

Cardiovascular and respiratory effects have been observed in acute animal studies. O'Flaherty and Thomas (1982) found increased levels of cardiac-specific creatine phosphokinase in blood samples from four rats 2 h after they were exposed to HCN at 200 ppm for 12.5 min at 2-day intervals. Histopathological examinations of the heart did not reveal any treatment-related changes. The 200-ppm concentration is presented in Figs. 2.1 and 2.3 as an acute LOAEL for target organ toxicity in rats. This study is inadequate for the development of a Minimal Risk Level because only four rats were studied at a single exposure level that was greater than concentrations considered to be lethal to humans.

Purser et al. (1984) observed bradycardia, arrhythmias, T-wave abnormalities, hyperventilation, and loss of consciousness in monkeys exposed to HCN at 87 to 196 ppm for 30 min. Sato et al. (1955) reported rough respiration and hindered mobility in mice exposed to HCN at 10 ppm for 2 h, with a decrease in food intake the only effect noted in mice exposed to HCN at 5 ppm for 4 h. The results of the Purser et al. (1984) and Sato et al. (1955) studies on CNS effects are presented in Figs. 2.1 and 2.3 (see this section under Lethality and decreased longevity).

In a study of intermediate duration (intermediate NOAEL in Figs. 2.1 and 2.2), Hugod (1981) observed no histopathological changes in the myocardium of rabbits exposed to HCN at 0.5 ppm continuously for 28 days. No other parameters were examined. Histopathological changes in the heart have not been reported in animals exposed to cyanide at levels that resulted in other signs of heart damage (O'Flaherty and Thomas

1982). Therefore, the lack of histopathological changes in the heart in the Hugod (1981) study may not be sufficient evidence to indicate that the exposure concentration level studied was truly a NOAEL for heart effects, which seem to be secondary to effects on the CNS. The Hugod (1981) study is the only inhalation study available with continuous exposures to cyanide at durations longer than several hours. Because the only concentration examined did not show any effects, and because it is not clear if histopathological examinations of the heart were sufficient to rule out CNS-induced heart effects, this study was not used as the basis for an intermediate Minimal Risk Level.

Systemic/target organ toxicity, thyroid effects. An epidemiology study by Blanc et al. (1985) indicated that occupational exposure to high levels (time-weighted average of 15 ppm) of cyanide for about 1 year may result in thyroid effects, as evidenced by increased levels of thyroid-stimulating hormones in exposed workers. The epidemiology study by El Ghawabi et al. (1975) reported enlargement of the thyroid in 56% of workers (all nonsmokers) occupationally exposed to cyanide at 6.4 to 10.4 ppm for 5 to 15 years. The range is presented in Fig. 2.1, whereas the low end of the range (6.4 ppm) is presented in Fig. 2.3 as a chronic human LOAEL for target organ toxicity. This study cannot be used for the basis of a Minimal Risk Level since only 36 exposed workers were examined, quantification of the extent of thyroid enlargement was not made, and it is likely that the workers were exposed to other volatiles. Additional signs and symptoms reported in the El Ghawabi et al. (1975) study at 6.4 to 10.4 ppm include breathing difficulty, headache, throat irritation, weakness, changes in taste and smell, abdominal pain, vomiting, and nervous instability.

Developmental and reproductive toxicity. There are no human or animal studies concerning developmental and reproductive effects following inhalation exposure to cyanide. Teratogenic effects in hamsters exposed to acetonitrile vapor, which can be metabolized to cyanide (Willhite 1981), indicate that inhalation exposure to cyanide may have the potential to cause developmental effects.

Genotoxicity. In vitro studies of genotoxicity have been negative except for a marginally mutagenic response for HCN in *Salmonella typhimurium* strain TA100 (Kushi et al. 1983). No in vivo genotoxicity studies were found.

Carcinogenicity. Cyanides have not been associated with carcinogenic effects in animals or humans.

2.2.1.2 Oral

Lethality and decreased longevity. An LD_{50} of 1.52 mg/kg CN^- for humans has been reported (EPA 1987a). The lowest fatal oral dose reported in humans is 0.56 mg/kg CN^- (Gettler and Baine 1938). These fatal doses are plotted in Figs. 2.2 and 2.4 for acute oral lethality in humans.

Oral LD_{50}s in rats for various cyanide compounds are 6.4 mg/kg for sodium cyanide (3.4 mg/kg CN^-) (EPA 1987a), 10 mg/kg for potassium cyanide (4.0 mg/kg CN^-) (Hayes 1967), 39 mg/kg for calcium cyanide (22 mg/kg CN^-) (Smyth et al. 1969), 123 mg/kg for silver cyanide

(26 mg/kg CN^-), and 21 mg/kg for potassium silver cyanide (5.5 mg/kg CN^-) (Sax 1984). In terms of cyanide, the lowest LD_{50} is 3.4 mg/kg. An oral LD_{50} of 3.4 mg/kg CN^- has also been reported for potassium cyanide (KCN) in mice (Sheey and Way 1968).

The only longer term oral study reporting lethality is the 90-day study of potassium silver cyanide in rats that was conducted by ITT Research Institute (1987). In this study, groups of 20 Sprague-Dawley rats per sex were treated by gavage with potassium silver cyanide in a 1.5% carboxymethylcellulose solution at 0.8, 2.62, 7.85, or 15.7 mg/kg CN^- per day for 90 days. The most significant finding was increased mortality, with 3 (1 male, 2 female), 9 (6 male, 3 female), 28 (14 male, 14 female), and 20 (10 male, 10 female) rats dying in the 0.8-, 2.62-, 7.85-, and 15.7-mg/kg/day groups, respectively. The rats in the group given 15.7-mg/kg CN^- per day died during the first 4 days of treatment; therefore, treatment of the surviving 20 rats was ended. Because four vehicle-control rats also died, 2.62 mg/kg CN^- per day is considered the lowest dose resulting in treatment-related lethality (see Figs. 2.2 and 2.4).

Target organ toxicity, nervous system. Quantitative data describing adverse neurological effects in humans following oral exposure to cyanides were not found. Money (1958), Makene and Wilson (1972), Conn (1973), Grant (1980), Osuntokun (1972, 1980), Osuntokun et al. (1969), and Monekosso and Wilson (1966) all describe cases of chronic degenerative neuropathy associated with cassava consumption. The diets of individuals in these cases tended to be nutritionally deficient, with a notable deficiency in vitamin B_{12}. Individuals experienced peripheral neurological abnormalities such as demyelination of peripheral nerves and decreased conduction velocity in these nerves, optic neuropathy, and deafness. Vitamin B_{12} deficiency itself, however, can result in progressive swelling of the myelinated neurons, demyelination, and cell death in the spinal column and cerebral cortex (Gilman et al. 1985). A Mozambique Ministry of Health (1984) report linked cassava consumption with spastic paresis and also identified a possible link with dietary deficiencies. No data were provided on the amount of cassava ingested or the method of preparation.

In a study by Philbrick et al. (1979), male weanling rats were fed two different diets with or without cyanide for 11.5 months. Three groups of rats received a diet containing 10% casein supplemented with 0.3% DL-methionine, potassium iodide (KI), and vitamin B_{12}; one group received no added cyanide, one group was fed KCN at 1,500 ppm, and the third group was fed potassium thiocyanate (KSCN) at 2,240 ppm. Other rats received a 10% casein diet with no added KI or vitamin B_{12}; one group received this diet plus 1,500 ppm KCN, whereas a second group was fed KSCN at 2,240 ppm. All rats fed cyanide compounds were treated at a dose level of ~30 mg/kg CN^- per day. Thus, of those groups receiving CN^-, one received a complete diet and the other was restricted in iodine and vitamin B_{12}. No deaths occurred, nor were there any signs of gross toxicity. Vacuolization and myelin degeneration were observed in spinal cord sections of rats fed cyanide, with effects more pronounced in rats fed the restricted diets. Depressed thyroid function was also observed in rats fed both diets. The 30-mg/kg/day dose level is plotted on Figs. 2.2 and 2.4 as an intermediate LOAEL for target organ toxicity in rats.

Hertting et al. (1960) dosed three dogs with NaCN for up to 14.5 months. One dog was treated at 0.27 mg/kg CN^- per day; the second dog received 0.53 mg/kg/day for 16 weeks, followed by 10.5 months of treatment with two daily doses at 1.1 mg/kg CN^- per day; and the third dog was treated with 1.1 mg/kg CN^- per day. One untreated dog served as a control. After each 1.1-mg/kg CN^- dose, acute signs of toxicity were observed immediately, with recovery in <0.5 h. These signs of acute toxicity remained similar throughout the study. All dogs treated with NaCN exhibited degenerative changes in CNS ganglion cells, especially in the Purkinje cells of the cerebellum. However, since only one dog was treated per dose and there is limited information available about the control dog, no Minimal Risk Level was calculated using this study. The lowest dose, 0.27 mg/kg CN^- per day, is plotted in Figs. 2.2 and 2.4 as the chronic LOAEL in dogs for target organ toxicity.

In a study by Howard and Hanzal (1955), groups of 10 rats per sex were maintained for 104 weeks on diets that had been fumigated with HCN. A similar group of rats fed the basal diet were maintained as controls. The diets provided CN^- doses of 0, 3.2, and 7.8 mg/kg/day for males and 0, 4.3, and 10.8 mg/kg/day for females. During the 2 years of the study, the growth curves for all groups did not vary as a result of treatment. Food consumption, hematologic values, and survival were also similar in all groups during the 2 years. Except for changes associated with aging, pathological changes in the CNS or other organ systems were not observed. The highest NOAEL (10.8 mg/kg CN^- per day for female rats) is plotted in Figs. 2.2 and 2.4 as the chronic oral rat NOAEL for target organ toxicity. The rat NOAEL of 10.8 mg/kg CN^- per day serves as the basis of the Minimal Risk Level for chronic oral exposure, as derived by EPA (1987a, 1987b). The rat NOAEL, which is higher than the dog LOAEL, is a more appropriate basis for a Minimal Risk Level because the method of dosing in the rat study was more consistent with chronic low-level exposures. The dogs were given bolus doses of cyanide, which may have resulted in short periods of anoxia, thus affecting the nervous system. Effects are observed in dogs at lower doses of cyanide (rather than in rats) because dogs are the most sensitive of the usual laboratory animals (Dudley et al. 1942, Hartung 1982).

Target organ toxicity, thyroid effects. In a 14-day study by Kreutler et al. (1978), male rats were fed a basal low-iodine diet that varied in the amount of protein. Three groups were fed a low-protein diet (2% casein); one group served as a control, with a 0.2% KCN (2,000 ppm) group and a 0.2% KCN and KI (added to drinking water) group. Two additional groups were fed diets containing 20% casein, one group with 0.2% KCN and the other without. The level of KCN added to the diet corresponded to a dose of 40 mg/kg CN^- per day. Increased plasma thyroid-stimulating hormone levels and significantly increased absolute and relative thyroid weights were only observed in the KCN low-protein group. Because the effect was only observed at low-protein levels, without added iodine, the 40-mg/kg/day dose is presented in Figs. 2.2 and 2.4 as an acute NOAEL for target organ toxicity.

Developmental and reproductive toxicity. Singh (1981) found a high incidence of embryo lethality and observed abnormalities including limb defects, open eyes, microcephaly, and retarded growth in rats from dams fed cassava as 80% of their diet. Low fetal body weight was the only

effect noted in offspring from dams fed cassava as 50% of their diet. This study cannot be presented graphically because cyanide dose information was not provided.

In a study by Tewe and Maner (1981a), female rats were fed a cassava diet containing 12 mg/kg HCN or the same diet with 500 ppm cyanide added. The rats were fed this diet from 20 days before mating through lactation. During gestation, the feed intake of controls was limited to the level consumed by rats fed the diet containing additional cyanide. Fetuses were not examined for abnormalities. At weaning, two female pups from each litter were randomly allotted to the experimental diets for 28 days, and the remaining pups were examined for serum thiocyanate levels. Compared with offspring fed the cassava diet, weanlings fed KCN-enhanced diets during the 28-day postweaning period experienced significant decreases in food consumption and growth rate, regardless of previous cyanide exposure. Those weanlings exposed to higher levels of cyanide in utero and during the 28-day postweaning period had significantly reduced protein efficiency ratios. If it is estimated that a young rat consumes food equivalent to 10% of its body weight per day (Lehman 1959), the control rats ate ~1.2 mg/kg CN^- per day and rats fed diets with added KCN ate ~51.2 mg/kg CN^- per day. The dose of cyanide from the KCN-added diet may be considered a LOAEL for developmental effects in rats, but because there were no untreated controls, it is not clear if the low dose was truly a NOAEL. The LOAEL for developmental effects is presented in Figs. 2.2 and 2.4.

Tewe and Maner (1981b) fed groups of six pregnant pigs either a low-cyanide (30.3 mg/kg CN^-) cassava diet or the cassava diet with added cyanide for total cyanide levels of either 276 or 520.7 mg/kg CN^- per diet, respectively. The sows were fed these diets beginning the day after breeding. At gestation day 110, two sows per group were sacrificed. The treatment had no significant effect on either the number or the weight of 110-day-old fetuses. Serum thiocyanate levels were slightly increased in the sows and fetuses of the 520.7-mg/kg added-cyanide group, with serum-bound iodine decreased during gestation in all groups. Histopathological examination of tissues of the sows showed proliferation of glomerular cells of the kidney in all groups and reduced activity of the thyroid gland in dams fed at 520.7 mg/kg. The remaining sows were fed their respective diets through parturition, at which time diets were changed to consist of corn and soybeans. After 21 days of lactation, a determination of blood thiocyanate showed significantly ($P < 0.05$) higher levels of serum thiocyanate in sows but not in piglets from sows fed diets containing 500 ppm added cyanide compared with other groups. Although effects on the sows were observed, this study did not identify any developmental effects. Because untreated controls were not included, the doses used in the study may not be NOAELs for developmental effects; therefore, this study is not presented graphically.

Teratogenic effects were observed in hamsters treated by gavage with amygdalin, a substance from which cyanide is released by bacterial beta-glucosidase in the gastrointestinal lumen (Willhite 1982). Cyanide dose levels could not be determined in this study.

Genotoxicity. See Sect. 2.2.1.1. of this profile on genotoxicity after inhalation exposure.

Carcinogenicity. Cyanides have not been associated with carcinogenic effects in humans or animals.

2.2.1.3 Dermal

Lethality and decreased longevity. Reiders (1971) reports a dermal LD_{50} of 100 mg/kg HCN for humans. Details were not provided.

In studies by Walton and Witherspoon (1926) and Fairley et al. (1934), guinea pigs died following exposure of small areas of shaved or clipped skin to HCN gas. Doses could not be quantified. Walton and Witherspoon (1926) also reported the deaths of shaved and unshaved dogs exposed to HCN (excluding their head and neck) at 10,800 to 15,400 ppm in chambers. Again, doses could not be quantified.

Systemic/target organ toxicity. Few reports of target organ toxicity in humans following dermal exposure to cyanides are available. Pontal et al. (1982) reported loss of consciousness and respiratory failure and Trapp (1970) reported loss of consciousness in persons who fell or jumped into vats containing silver cyanide and potassium cyanide. Doses were not determined, and concomitant oral and inhalation exposures were likely. Treatment was immediate and recovery was complete. In animal studies, convulsions and coma preceded death in guinea pigs treated dermally with unspecified doses of HCN (Walton and Witherspoon 1926, Fairley et al. 1934).

Developmental and reproductive toxicity. No studies were available.

Genotoxicity. See Sect. 2.2.1.1 of this profile on genotoxicity after inhalation exposure.

Carcinogenicity. No studies were available.

2.2.2 Biological Monitoring as a Measure of Exposure and Effects

The determination of thiocyanate and cyanide levels in the urine and blood have been used as a method of biological monitoring in persons occupationally exposed to cyanides. El Ghawabi et al. (1975) determined thiocyanate levels in urine collected over 24-h periods from 36 persons occupationally exposed to cyanides at 6.4 to 10.3 ppm at three different electroplating factories. All workers were nonsmokers. They found that urinary thiocyanate increased toward the middle of the week and became almost stable at the end of the week. Figure 2.5 shows the relationship between urinary thiocyanate levels during the second half of the workweek for 2 consecutive months; the concentration of cyanide in air is also shown. This relationship is represented by the equation $M = 0.65c$, where M is the thiocyanate in 24-h urine (in mg), and c is the concentration of cyanide in air (ppm). This equation cannot be used to correlate urine thiocyanate levels to low air concentrations of cyanide because thiocyanate is normally found in the urine at levels of ~0.17 mg/L in nonsmokers and 4.4 mg/L in smokers (Radojicic 1973).

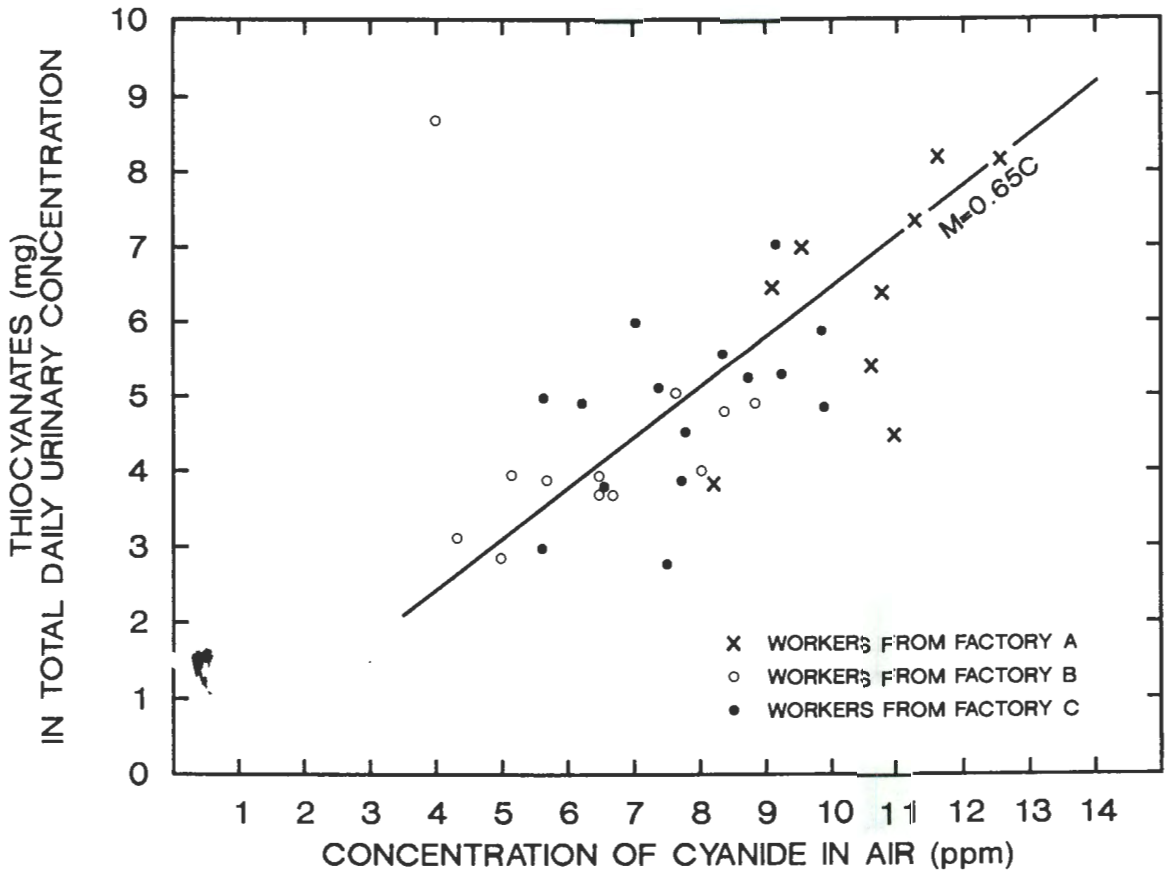


Fig. 2.5. Mean values of thiocyanate in urine of exposed workers during 2 successive months plotted against concentration of cyanide in air. *Source*: El Ghawabi et al. 1975.

In a study completed in India, Chandra et al. (1980) determined cyanide and thiocyanate levels in the urine and blood of 23 workers occupationally exposed to cyanide at 0.2 to 0.8 mg/m^3. Twenty unexposed control subjects were also examined. Both controls and exposed individuals were classified as smokers or nonsmokers, and all persons studied were asked to avoid cyanogenic foods (e.g., cabbage, almond, mustard) for at least 48 h prior to the collection of blood and urine samples. Urine was collected for 24 h, with collections at 2-h intervals during the workshift. The results of the analysis of urine collected at 2-h intervals did not show a pattern, leading the authors to conclude that 24-h urine samples should be analyzed for thiocyanate to give a reliable measure of exposure. Twenty-four-hour urinary cyanide and thiocyanate levels are presented in Table 2.1. Blood cyanide and thiocyanate levels are presented in Table 2.2. One worker who smoked had an unusually high blood cyanide level of 220 μg per 100 mL. When this high value is eliminated, the mean value for seven smokers occupationally exposed to cyanides is reduced from 56.0 to 23.3 μg per 100 mL. Fatal blood levels of cyanide have been reported to be 250 to 300 μg per 100 mL (Vogel et al. 1981).

According to Way (1984), the measurement of cyanide in whole blood may be more useful than the measurement of cyanide in serum. Cyanide binds to both serum albumin and hemoglobin, and the concept that cyanide in red blood cells is not biologically active may be erroneous. In addition, cyanide rapidly leaves serum and plasma, especially in the first 20 min. Way (1984) suggests, however, that when the thiocyanate concentration is high, measuring cyanide in both whole blood and plasma may be useful.

In cyanide poisoning cases, Berlin (1977) cautioned that blood levels should not be relied on to influence the therapy of intoxicated individuals. Blood levels may be misleading because the toxicity of cyanides is due to intracellular concentrations. Berlin (1977) suggests that a blood level >0.2 μg/L suggests a toxic reaction, but poisoning can occur at lower levels; therefore, the clinical condition of the patient should be used to determine therapy.

2.2.3 Environmental Levels as Indicators of Exposure and Effects

2.2.3.1 Levels found in the environment

The paucity of data on levels of cyanide detected in air or soil limits the ability to draw conclusions regarding the association of adverse health effects with environmental levels of cyanide. The relationship between the concentration of cyanide in occupational air samples and adverse health effects, however, has been documented and is presented in Blanc et al. (1985) and NIOSH (1976).

2.2.3.2 Human exposure potential

The physical properties of cyanides may affect the probable route and the extent of exposure to humans, as well as the subsequent absorption, distribution, and possible adverse health effects of these compounds. For example, the water-soluble cyanide salts and complexes, because of their higher mobility in water and soils, may pose a greater

Table 2.1. Urinary cyanide and thiocyanate excretion over 24 h

	Workers (23)[a]		Control (20)	
	Smokers (8)	Nonsmokers (15)	Smokers (10)	Nonsmokers (10)
Cyanide, μg/100 mL				
Range	0.0–18.0	0.0–14.67	0.0–8.45	0.0–4.36
Mean	6.23	5.4	3.2	2.15
Thiocyanate, mg/100 mL				
Range	0.15–1.65	0.15–1.29	0.24–1.20	0.0–0.32
Mean	0.62	0.57	0.41	0.08

[a]Figures in parentheses show the number of subjects.
Source: Chandra et al. 1980.

Table 2.2. Cyanide and thiocyanate in blood

	Workers (23)[a]		Control (20)	
	Smokers (8)	Nonsmokers (15)	Smokers (10)	Nonsmokers (10)
Cyanide, μg/100 mL				
Range	10.0–220.0	2.0–36.0	0.0–9.4	0.0–8.6
Mean	56.0	18.3	4.8	3.2
Thiocyanate, mg/100 mL				
Range	0.16–0.92	0.26–0.83	0.07–0.18	0.02–0.06
Mean	0.48	0.42	0.10	0.04

[a]Figures in parentheses show the number of subjects.
Source: Chandra et al. 1980.

ingestion exposure possibility through the contamination of groundwater. Cyanide salts and complexes that release HCN under acidic conditions may pose significant potential for inhalation exposure if these salts, disposed in waste sites, come into contact with acidic leachates of a pH at or below the pK_a of the compound. Cyanides are not known to bioaccumulate.

In addition to occupational exposure, exposure to cyanides may result from a number of sources such as cyanide-containing food, metabolism of certain drugs, and combustion of nitrogenous polymers.

Monitoring data on the detection of cyanide in the ambient environment are relatively limited; therefore, speculation on the relationship between sources and the level of exposure is not possible.

Cyanide is a constituent of foods such as sweet potatoes, almonds, lima beans, and many others. It appears that the occurrence of cyanide in these foods is the result of natural production within plants rather than the result of uptake from soil.

2.3 ADEQUACY OF DATABASE

2.3.1 Introduction

Section 110 (3) of SARA directs the Administrator of ATSDR to prepare a toxicological profile for each of the 100 most significant hazardous substances found at facilities on the CERCLA National Priorities List. Each profile must include the following content:

"(A) An examination, summary, and interpretation of available toxicological information and epidemiologic evaluations on a hazardous substance in order to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects.

(B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine levels of exposure which present a significant risk to human health of acute, subacute, and chronic health effects.

(C) Where appropriate, an identification of toxicological testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans."

This section identifies gaps in current knowledge relevant to developing levels of significant exposure for cyanides. Such gaps are identified for certain health effect end points (lethality, systemic/target organ toxicity, developmental toxicity, reproductive toxicity, and carcinogenicity) reviewed in Sect. 2.2 of this profile in developing levels of significant exposure for cyanides and for other areas such as human biological monitoring and mechanisms of toxicity. The present section briefly summarizes the availability of existing human and animal data, identifies data gaps, and summarizes research in progress that may fill such gaps.

Specific research programs for obtaining data needed to develop levels of significant exposure for cyanides will be developed by ATSDR, NTP, and EPA in the future.

2.3.2 Health Effect End Points

2.3.2.1 Introduction and graphic summary

The availability of data for health effects in humans and animals is depicted on bar graphs in Figs. 2.6. and 2.7.

The bars of full height indicate that there are data to meet at least one of the following criteria:

1. For noncancer health end points, one or more studies are available that meet current scientific standards and are sufficient to define a range of toxicity from no effect levels (NOAELs) to levels that cause effects (LOAELs or FELs).

2. For human carcinogenicity, a substance is classified as either a "known human carcinogen" or "probable human carcinogen" by both EPA and the International Agency for Research on Cancer (IARC) (qualitative), and the data are sufficient to derive a cancer potency factor (quantitative).

3. For animal carcinogenicity, a substance causes a statistically significant number of tumors in at least one species, and the data are sufficient to derive a cancer potency factor.

4. There are studies which show that the chemical does not cause this health effect via this exposure route.

Bars of half height indicate that "some" information for the end point exists, but does not meet any of these criteria.

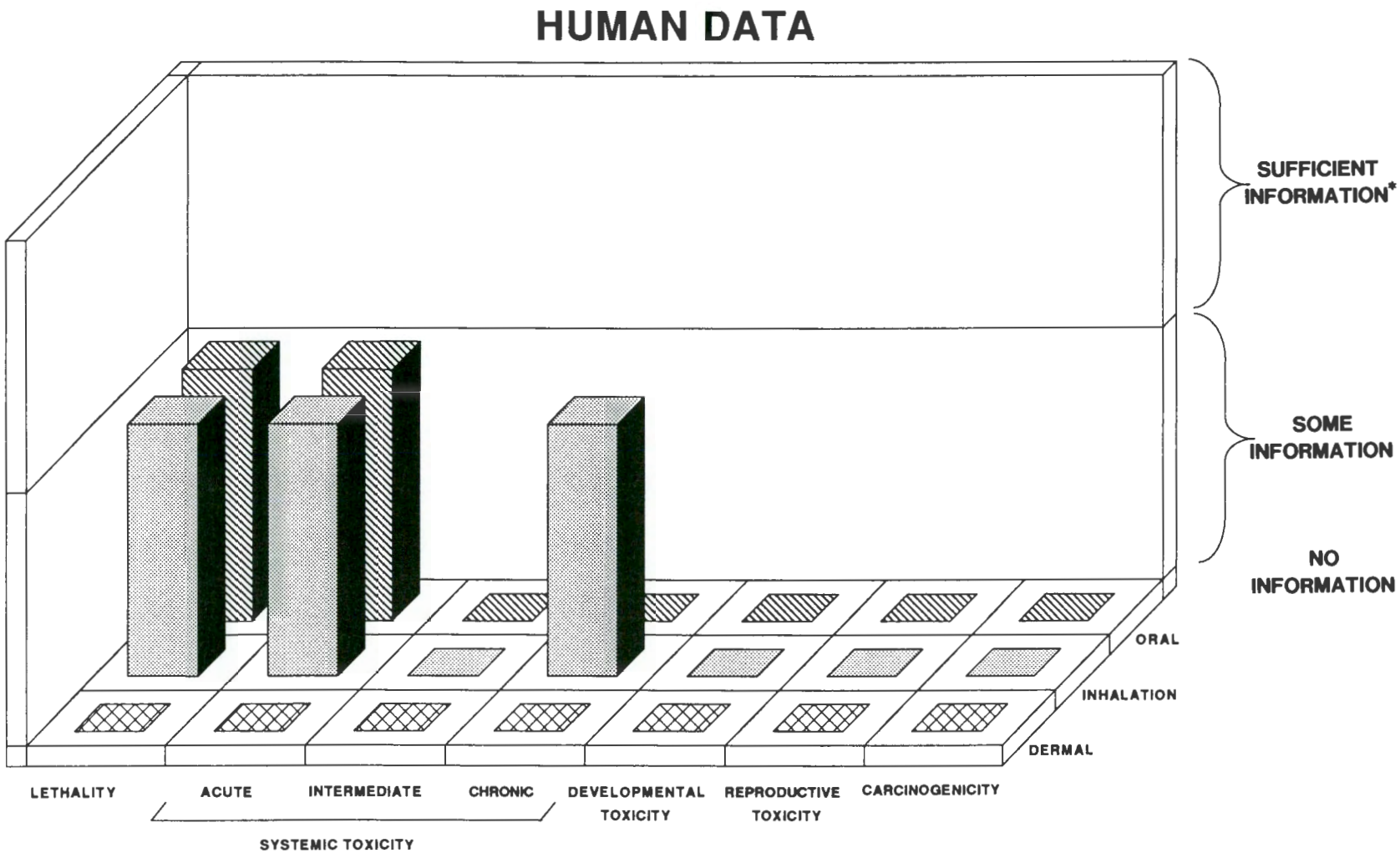
The absence of a column indicates that no information exists for that end point and route.

2.3.2.2 Description of highlights of graphs

Figures 2.6 and 2.7 summarize the adequacy of the database on health effects due to exposure to cyanides.

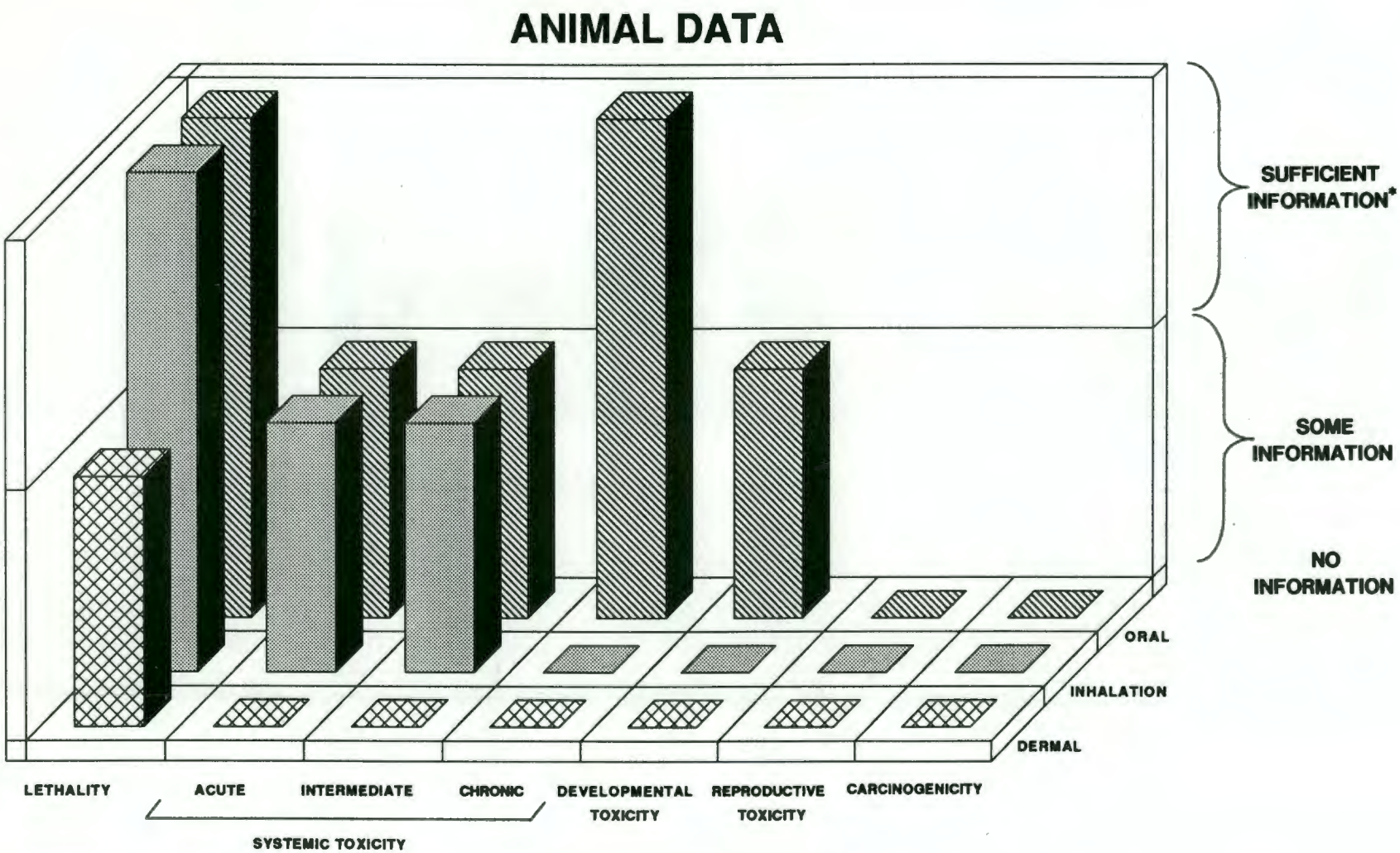
Figure 2.6 summarizes human data. Some data were available for lethality resulting from oral or inhalation exposure. Some data, primarily in the form of descriptive case studies or worker studies, were also available for systemic acute inhalation and oral exposure and chronic inhalation exposure. Very limited data were available for dermal exposure. There were no appropriate developmental studies, and no data were found for reproductive toxicity or carcinogenicity by any route of exposure.

Figure 2.7 summarizes animal data. Far more data exist for animals than for humans. As with human studies, only very limited data exist for dermal exposure. The dermal studies that are available were completed in 1926 and 1934. They indicate that cyanide can be fatal following dermal exposure but do not provide any additional information. Adequate data were available for lethal effects from inhalation and oral exposure and for chronic systemic effects following oral exposure. Some data were found for acute, intermediate, and chronic systemic effects for both inhalation and oral routes. Some data were also available that indicate



*Sufficient information exists to meet at least one of the criteria for cancer or noncancer end points.

Fig. 2.6. Availability of information on health effects of cyanide (human data).



*Sufficient information exists to meet at least one of the criteria for cancer or noncancer end points.

Fig. 2.7. Availability of information on health effects of cyanide (animal data).

that oral exposure to cyanide and/or cyanide-containing compounds can result in developmental effects. No inhalation developmental studies were available. No data on reproduction or carcinogenicity were identified.

2.3.2.3 Summary of relevant ongoing research

Prechronic drinking water studies of sodium cyanide in F344 rats and $B6C3F_1$ mice, sponsored by the NTP, are in progress (NTP 1987). The biochemical, cellular, and tissue effects of a range of neurotoxic agents, including cyanide, are being studied at Yeshiva University (Israel); at Vanderbilt University (Nashville, Tennessee), a clinical toxicology/epidemiology study of cyanide is under way.

At the National Institute for Standards and Technology (formerly the National Bureau of Standards), Dr. Barbara Levin and colleagues are investigating the physiological response of rats to acute inhalation exposure to HCN.

A possible link between exposure to components of tobacco smoke and a susceptibility to neoplastic transformation is being studied by Douglas Heimburger at the University of Alabama, Birmingham. In this research, cyanides and other components of tobacco smoke will be tested in vitro for their effects on vitamin B_{12} and folate coenzymes. In addition, B_{12} and folate coenzyme levels will be measured in smokers and nonsmokers. Following these measurements, the progression of dysplastic lesions of the bronchial epithelium of smokers will be monitored. The study may provide new information about the link between exposure to cyanide and bronchial neoplastic lesions.

2.3.3 Other Information Needed for Human Health Assessment

2.3.3.1 Pharmacokinetics and mechanisms of action

Mechanisms of action in humans and animals. The mechanism by which cyanide exerts its acute toxic effects at the molecular level through the inhibition of cytochrome oxidase is well understood and described extensively in the literature. The antithyroid effects of the cyanide metabolite, thiocyanate, have also been defined. The mechanisms of neurotoxicity are less well understood. The correlations between human neuropathies and cyanide exposure have not been established definitively, nor is the selective nature of cyanide-induced encephalopathy in animals completely understood. In addition, while cyanide-induced alterations to CNS neurotransmitter levels have been observed, the mechanism of action that causes these alterations is not clear. Similarly, many studies indicate an intraneural mediator role for calcium in cyanide toxicity, but the mechanism leading to disruption of calcium homeostasis has not been defined.

The effects of cyanide on the cardiovascular system are not well understood, although cyanide appears to affect vascular smooth muscle directly. It has been suggested that large doses of cyanide may produce pulmonary arteriolar and/or coronary arteriolar vasoconstriction, thus inducing cardiovascular-respiratory failure. The mode of action and importance of these changes in overall cyanide toxicity, however, are not understood and require further investigation.

Some preliminary evidence has been found that points to adverse developmental effects resulting from cyanide ingestion. More studies must be conducted to substantiate this evidence and to define effects for different dose levels and routes of exposure. Reproductive effects have not been studied.

Pharmacokinetics. Most of the data collected on the pharmacokinetics of cyanide were published between 1835 and 1965. As a result, much of the information is descriptive rather than quantitative. Where provided, the quantitative data in these reports are subject to question, since the analytical equipment and methodologies used to obtain the data were not accurate. Studies often used only one or a few test animals, and concurrent controls were not routinely run. Adequate data on the distribution of cyanide to various organs, indicating similarities or differences between humans and animal species, were not available. Also, data describing pharmacokinetic variations resulting from different routes of exposure are inadequate.

Ongoing research. A study of the mechanisms of cyanide-induced neurotoxicity is being conducted by Gary Isom at Purdue University (NTIS 1987). The research, sponsored by the National Institute of Environmental Health Sciences, is designed to investigate the disruption of calcium homeostasis by cyanide and to determine the role of these calcium fluctuations in the release of neurotransmitters and in lipid peroxidation. The data may help to fill an important gap in the role of calcium in cyanide-induced neurotoxicity.

William Barry at the University of Utah has designed a project to define the mechanisms of myocardial cell injury during ischemia. The study will try to determine the mechanisms by which cyanide and other metabolic inhibitors contribute to calcium overload during ATP depletion. Another goal of this research is to determine if increases in intracellular calcium concentrations contribute to cyanide-induced myocardial cell injury.

Current research in the area of cyanide pharmacokinetics does not address the data gaps previously described. One study is under way to investigate the role of the sulfur-sulfane pool in cyanide detoxification. Researchers are attempting to develop nutritional and/or pharmacological strategies to combat chronic exposure to cyanide resulting from cyanide-containing foods in the diet. Specific aims of this research include developing methods to alter the reactive sulfur and sulfane pools, establishing interrelationships among the enzymes that catalyze reactions with sulfane-sulfur, and examining the flux of sulfane-sulfur as a means of determining normal cyanide detoxification.

2.3.3.2 Monitoring of human biological samples

Methods for determining cyanide levels in human tissues and fluids are discussed in Sect. 8. Two studies (Finck 1969, Ansell and Lewis 1970) quantified the level of cyanide in human tissues and fluids following human ingestion or inhalation of fatal amounts of cyanide. Postmortem levels, however, are highly dependent on HCN losses from the tissues by volatilization, on the time between exposure and death, and on the metabolism of CN^- to SCN^- (EPA 1987a). Methods of measuring human

cyanide levels are currently being examined by Dr. Joseph Balkon of St. Johns University (Levin 1987).

2.3.3.3 Environmental considerations

A considerable data gap exists regarding the bioavailability of cyanide from air, water, soil, and food. Limited monitoring data indicate that the general population may be exposed to cyanide from each of these media; however, the average daily intake and the relative importance of intake from inhalation, ingestion of drinking water, and ingestion of foods are not known.

Limited data are available regarding the fate of cyanide in the environment, particularly in surface waters, soil, and groundwater.

Limited data are available on the interaction of cyanide with other chemicals in the environment. It has been reported that cyanide ions can complex with a variety of metals to form easily decomposed complex cyanides such as zinc cyanide or relatively stable complex cyanides such as ferrocyanide (Callahan et al. 1979).

In an ongoing research project, the fate of cyanide in soil and groundwater is being studied. The results of the first phase of this work have been reported by Chatwin and Trepanowski (1987), who reported that both volatilization and reaction/adsorption may be important mechanisms for attenuation of cyanide concentrations in soil. These authors have shown that both the increase in temperature and the decrease in soil pH will enhance volatilization and that the increase in alumina and organic matter content of the soil will increase soil sorption/reaction.

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3. CHEMICAL AND PHYSICAL INFORMATION

3.1 CHEMICAL IDENTITY

Data pertaining to the chemical identity of hydrogen cyanide, sodium cyanide, and potassium cyanide are listed in Table 3.1.

3.2 PHYSICAL AND CHEMICAL PROPERTIES

The physical and chemical properties of hydrogen cyanide and other selected cyanide compounds are presented in Table 3.2.

Table 3.1. Chemical identity of selected cyanide compounds

Chemical name	Hydrogen cyanide	Sodium cyanide	Potassium cyanide
Synonyms	Formonitrile, hydrocyanic acid, prussic acid	Cyanide of sodium, hydrocyanic acid, sodium salt	Cyanide of potassium, hydrocyanic acid, potassium salt
Trade name	Cyclone B	Cyanogran	
Chemical formula	HCN	NaCN	KCN
Wiswesser line notation	H CN	NA CN	KA CN
Chemical structure	H−C≡N	Na−C≡N	K−C≡N
Identification numbers			
CAS Registry No.	74-90-8	143-33-9	151-50-8
NIOSH RTECS No.	MW6825000	VZT530000	TS8750000
EPA Hazardous Waste No.	P063	P106	P098
OHM-TADS No.	7216749	7216892	7216862
DOT/UN/NA/IMCO Shipping No.	UN1051; IMCO2	NA[a]	UN1680; IMCO6.1
STCC No.	4921417	NA	4923225
Hazardous Substances Data Bank No.	165	734	1245
National Cancer Institute No.	NA	NA	NA

[a]NA = Not available.
Source: HSDB 1987.

Table 3.2. Physical properties of selected cyanide compounds

Property	Hydrogen cyanide	Sodium cyanide	Potassium cyanide	Calcium cyanide
Molecular weight	27.03	49.02	65.11	92.12
Color	Colorless	White	White	Colorless or white
Physical state	Gas	Solid	Solid	Solid
Odor threshold	0.58 ppm (v/v) in air 0.17 ppm (w/v) in water	NA[a]	NA	NA
Odor	Faint bitter almond odor	Odorless when dry, emits slight odor of HCN in damp air	Faint bitter almond odor	Faint bitter almond odor
Melting point	−13.24°C	563.7°C	634.5°C	Decomposes at >350°C
Boiling point	25.70°C	1,500°C	NA	NA
Autoignition temperature	538°C	NA	NA	NA
Solubility				
Water	Miscible	48 g/100 mL at 10°C[b]	71.6 g/100 mL at 25°C[b]	Soluble in water with gradual liberation of HCN
Organic solvents	Soluble in ethanol	Slightly soluble in ethanol and formamide	Slightly soluble in ethanol	NA
Density, g/cm^3	0.6884 (liquid at 20°C)	1.60 (for cubic)	1.553 (for cubic)	1.8–1.9 (commercial product)
Log octanol/water partition coefficient	0.66[b]	−0.44[b]	NA	NA
Vapor pressure, mm Hg	264.3 (at 0°C)	0.76 at 800°C	NA	NA
Henry's law constant	NA	NA	NA	NA
Refractive index	1.2675 at 10°C	NA	NA	NA
Flashpoint	−17.8 °C (closed cup)	NA	NA	NA
Flammability limits	6-41 vol % in air at 20°C	NA	NA	NA
Conversion factors				
ppm to mg/m^3 in air at 20°C	1 ppm = 1.123 mg/m^3	*d*	*d*	*d*
ppm to mg/L in water	ppm (w/v) = mg/L = μg/mL	ppm (w/v) = mg/L = μg/mL	ppm (w/v) = mg/L = μg/mL	ppm (w/v) = mg/L = μg/mL
ppm to mg/kg in soluble samples	ppm (w/w) = mg/kg = μg/g	ppm (w/w) = mg/kg = μg/g	ppm (w/w) = mg/kg = μg/g	ppm (w/w) = mg/kg = μg/g

Table 3.2 (continued)

Property	Barium cyanide	Cyanogen	Chlorine cyanide (cyanogen chloride)	Copper (1) cyanide
Molecular weight	189.40	52.04	61.48	89.56
Color	White	Colorless	Colorless	White
Physical state	Solid	Gas	Gas	Solid
Odor threshold	NA	NA	NA	NA
Odor	NA	Almond-like odor	Highly irritating	NA
Melting point	NA	−27.9°C	−6°C	473°C (in N_2)
Boiling point	NA	−21.17°C	13.8°C	Decomposes
Autoignition temperature	NA	NA	NA	NA
Solubility				
Water	Soluble	Soluble	Soluble	Insoluble
Organic solvents	Soluble in ethanol	Soluble in ethanol and ethyl ether	Soluble in ethanol and ethyl ether	Insoluble in ethanol
Density, g/cm^3	NA	0.9537 at −21.17°C	1.186	2.92
Log octanol/water partition coefficient	NA	NA	NA	NA
Vapor pressure, mm Hg	NA	3,800 at 20°C[c]	760 at 13.8°C	NA
Henry's law constant	NA	NA	NA	NA
Refractive index	NA	NA	NA	NA
Flashpoint	NA	NA	NA	NA
Flammability limits	NA	NA	NA	NA
Conversion factors				
ppm to mg/m^3 in air at 20°C	*d*	1 ppm = 2.164 mg/m^3	2.556	*d*
ppm to mg/L in water	ppm (w/v) = mg/L = μg/mL	ppm (w/v) = mg/L = μg/mL	ppm (w/v) = mg/L = μg/mL	ppm (w/v) = mg/L = μg/mL
ppm to mg/kg in solid samples	ppm (w/w) = mg/kg = μg/g	ppm (w/w) = mg/kg = μg/g	ppm (w/w) = mg/kg = μg/g	ppm (w/w) = mg/kg = μg/g

Table 3.2 (continued)

Property	Zinc cyanide	Silver cyanide	Potassium silver cyanide (potassium argento cyanide)
Molecular weight	117.42	133.89	199.01
Color	White	White	White
Physical state	Solid	Solid	Solid
Odor threshold	NA	NA	NA
Odor	NA	NA	NA
Melting point	Decomposes at 800°C	Decomposes at 320°C	NA
Boiling point	NR[e]	NR	NA
Autoignition temperature	NA	NA	NA
Solubility			
Water	Sparingly soluble	Insoluble	Soluble
Organic solvents	Insoluble in ethanol	Insoluble in ethanol	Slightly soluble in ethanol
Density, g/cm^3	1.852	3.95	2.36
Log octanol/water partition coefficient	NA	NA	NA
Vapor pressure, mm Hg	NA	NA	NA
Henry's law constant	NA	NA	NA
Refractive index	NA	NA	1.625
Flashpoint	NA	NA	NA
Flammability limits	NA	NA	NA
Conversion factors			
ppm to mg/m^3 in air at 20°C	*d*	*d*	*d*
ppm to mg/L in water	ppm (w/v) = mg/L = μg/mL	ppm (w/v) = mg/L = μg/mL	ppm (w/v) = mg/L = μg/mL
ppm to mg/kg in solid samples	ppm (w/w) = mg/kg = μg/g	ppm (w/w) = mg/kg = μg/g	ppm (w/w) = mg/kg = μg/g

[a]NA = Not applicable.
[b]These values obtained from EPA 1985a.
[c]This value obtained from Towill et al. 1978.
[d]Since these compounds do not exist in the atmosphere in the vapor phase, their concentrations are always expressed in weight by volume unit (e.g., mg/m^3).
[e]NR = Not reported.
Source: Jenks 1979, Hawley 1981, Windholz 1983, Weast 1985, Amoore and Hautula 1983.

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4. TOXICOLOGICAL DATA

4.1 OVERVIEW

This section discusses the toxicokinetics and toxicity of cyanides in humans and animals with the primary focus on hydrogen cyanide (HCN) and the soluble potassium and sodium salts (KCN, NaCN). The lethality of other compounds, including calcium cyanide, silver cyanide, and potassium silver cyanide, is described briefly.

Cyanides are readily absorbed following inhalation, oral, and dermal routes of exposure. Inhalation exposure to HCN provides the most rapid route of entry, resulting in the most rapid onset of toxic effects. Following absorption, cyanide is distributed throughout the body. Cyanide is detoxified by a mitochondrial enzyme, rhodanese, which catalyzes the transfer of sulfur from a donor to cyanide to form the less toxic thiocyanate, which is excreted in the urine. Other detoxification pathways include spontaneous reaction with cystine to form 2-imino-4-thiazolidinecarboxylic acid, and the reaction with hydroxycobalamin (vitamin B_{12}) to form cyanocobalamin. Some cyanide enters the metabolism of 1-carbon compounds, and CO_2 is eliminated in expired air. A small amount of unchanged HCN is eliminated in expired air.

Cyanide exerts toxic effects by reacting with iron in cytochrome oxidase, the enzyme that catalyzes the terminal step in the electron transport chain, thereby preventing utilization of oxygen by cell • Cyanide also has inhibitory effects on Schiff base intermediates and can bind to other biomolecules. These reactions may contribute to cyanide toxicity.

Signs of acute poisoning from cyanide include rapid breathing, gasping, tremors, convulsions, and death. The severity and rapidity of the onset of effects depend on route, dose, duration of exposure, and compound administered. Oral exposure to cyanide salts results in slower gastrointestinal absorption, passage to the liver, and faster detoxification.

Neurotoxicity may be the most sensitive target organ end point for cyanide, with cardiac/respiratory and thyrotoxic effects reported as well. Neurotoxicity has been observed in humans and animals following inhalation and ingestion of cyanide. Cardiac/respiratory effects have been found in animals following inhalation of HCN. Thyrotoxicity has been reported in humans and animals following inhalation and oral exposure to cyanides.

Exposure of pregnant rats to cyanide-containing diets has resulted in fetotoxicity. Little information was found that would indicate any significant reproductive, mutagenic, or carcinogenic effect of cyanide.

Synergistic and antagonistic interactions between cyanide and other compounds have been demonstrated. Cyanide and tributyltin act synergistically to produce hemolysis in vitro. Carbon monoxide and HCN, often found in fire environments, act in an additive manner in terms of lethality. Cyanide antagonists include nitrites, thiosulfate, and oxygen.

4.2 TOXICOKINETICS

4.2.1 Absorption

4.2.1.1 Inhalation

Human. Cyanides are rapidly absorbed following inhalation exposure. Rieders (1971) reported that HCN, at concentrations ≥2,000 ppm, is fatal in <1 min. Landahl and Herrmann (1950) found that humans retained 58 to 77% of HCN in the lungs following inhalation of the gas through normal mouth breathing.

Animal. Quantitative data on the absorption of HCN by inhalation in dogs was reported by Gettler and Baine (1938). The HCN gas was generated into an inhalation apparatus from a tube containing a solution of hydrocyanic acid. Exhaled cyanide was bubbled through a solution of sodium hydroxide. The amount of absorbed HCN was estimated by subtracting the amount of cyanide remaining in the apparatus from the initial amount in the tube (data not provided). By this method, one dog was calculated to have absorbed 16.0 mg (1.55 mg/kg); the other dog absorbed 10.1 mg (1.11 mg/kg). These doses were fatal to the dogs in 15 and 10 min, respectively. Quantitative data using more recent methods were not available.

4.2.1.2 Oral

Human. Absorption of cyanide across the gastrointestinal mucosa is dependent on the pH of the gut and the pK_a and lipid solubility of the cyanide compound. HCN is a weak acid with a pK_a of 9.2. The acidic environment in the stomach favors the nonionized form of HCN and facilitates absorption (EPA 1980). Information regarding the rapid lethal effects following oral intake of cyanides in humans (Gosselin et al. 1976) indicates that cyanides are absorbed from the gastrointestinal tract. Liebowitz and Schwartz (1948) reported a case in which an 80-kg male ingested an estimated 3 to 5 g of KCN in a suicide attempt. Based on a concentration of 220 mg/L HCN in the blood 2 h after ingestion, it was estimated that the patient had 1.2 g HCN in the blood, with ~2.3 g CN^- in the body.

Animal. Gettler and Baine (1938) conducted a study in which three dogs were given a KCN solution by stomach tube. The amount of cyanide absorbed was determined by the difference between the amount of cyanide given and the amount of cyanide left in the stomach and intestines. Dogs treated with KCN at 20, 50, and 100 mg/kg KCN absorbed 14.4, 12.0, and 16.6 mg KCN (72, 24, and 17%), respectively. All three dogs died, with death occurring 8, 21, and 155 min after dosing at the high, medium, and low doses, respectively.

4.2.1.3 Dermal

Human. Cyanides are moderately lipid-soluble, which allows them to rapidly penetrate the epidermis. In addition, some cyanide compounds, such as KCN, have a corrosive effect on the skin that increases the rate of absorption (NIOSH 1976). Potter (1950) described a case study in which an industrial worker, wearing a respirator, suffered severe cyanide poisoning within 5 min after spilling liquid HCN on his hand. Antidotes were administered, and after 55 min the worker regained consciousness. Drinker (1932) reported that three men working in an atmosphere of 20,000 ppm (22,000 mg/m^3) HCN gas for 8 to 10 min developed symptoms of dizziness, weakness, and throbbing pulse. Although these men were wearing gas masks, the possibility that some exposure occurred via inhalation cannot be dismissed.

Animal. Walton and Witherspoon (1926) exposed a small area of the shaved abdomens of eight guinea pigs to HCN vapor. The signs of cyanide toxicity observed included rapid respiration followed by general twitching of muscles, convulsions, and death. In a similar experiment, Walton and Witherspoon (1926) placed shaved and unshaved dogs in a chamber in which their bodies, with the exception of the head and neck, were exposed to HCN vapor. No symptoms of toxicity were reported after exposure to 5,500 mg/m^3 HCN (5,000 ppm) for 180 min. Deaths resulted after exposure to 14,700 mg/m^3 HCN (13,400 ppm) for 47 min, strongly suggesting dermal absorption.

4.2.2 Distribution

4.2.2.1 Inhalation

Human. Once cyanide is absorbed it is rapidly distributed by the blood throughout the body. Gettler and Baine (1938) reported a case study in which a human was found dead after the inhalation of HCN gas. Tissue levels of HCN were 0.75, 0.42, 0.41, 0.33, and 0.32 mg HCN per 100 g of tissue in the lung, heart, blood, kidney, and brain, respectively. Tissue cyanide levels from a man who died from the inhalation of HCN were reported as 0.5 mg per 100 mL of blood and 0.11, 0.7, and 0.3 mg per 100 g in the kidney, brain, and liver, respectively (Finck 1969). Urine levels were reported as 0.2 mg per 100 mL, and cyanide at 0.03 mg per 100 g was found in the gastric contents.

Animal. In two dogs exposed to unspecified fatal concentrations of HCN, the highest HCN levels were found in the lungs, blood, and heart (Gettler and Baine 1938). Yamamoto et al. (1982) exposed rats to HCN gas at 356 or 1,180 ppm (396 or 1,310 mg/m^3) and measured the distribution to various tissues. The time to death for each group was ≤10 and 5 min, respectively. Samples taken immediately after respiration stopped showed that the tissue distribution of cyanide did not vary with the concentration used. In averaging data for both dose groups, tissue concentrations, reported as micrograms per gram wet weight, were 4.4 in the lungs, 3.0 in the blood, 2.2 in the liver, 1.45 in the brain, and 0.68 in the spleen.

4.2.2.2 Oral

Human. Small but significant levels of cyanide are present in normal, healthy human organs at concentrations of ≤0.5 mg/kg CN^- (Feldstein and Klendshaj 1954). This cyanide includes vitamin B_{12}, with the source of cyanide attributed to the breakdown of cyanogenic foods and tobacco smoke by bacteriological action.

Ansell and Lewis (1970) reported a case in which a woman had ingested 2.5 g NaCN and died 30 min later. Cyanide levels (mg%) were reported as follows: stomach contents, 3.2; brain, 0.7; urine, 0.5; blood, 0.4; kidney, 0.2; stomach wall, 0.2; and liver, 0.1. Ansell and Lewis (1970) also reported mean organ levels of the cyanide ion in cases of fatal poisoning. These values in mg% were: stomach contents, 160 (49 cases); spleen, 3.77 (22 cases); blood, 2.39 (58 cases); liver, 1.62 (48 cases); brain, 1.2 (34 cases); kidney, 0.61 (34 cases); and urine, 0.08 (17 cases).

Getler and Baine (1938) reported brain cyanide levels ranging from 0.06 to 1.37 mg HCN per 100 g of tissue in four humans who ingested fatal doses of cyanide. Cyanide levels in the livers of these humans ranged from 0.22 to 0.91 mg HCN per 100 g of tissue. Finck (1969) described two cases in which men died from the ingestion of unknown quantities of unspecified cyanide salts. Cyanide levels were highest in the lungs and blood.

Animal. Using either 7 or 21 mg/kg CN^-, Yamamoto et al. (1982) dosed rats by gavage. Survival times following administration were 10.3 and 3.3 min for the low- and high-dose groups, respectively. Using combined data from the two groups, tissue concentrations of cyanide in micrograms per gram wet weight were: liver, 8.8; lung, 5.85; blood, 4.9; spleen, 2.1; and brain, 1.5.

Cyanide has not been shown to accumulate in the blood and tissues following chronic oral exposure. Howard and Hanzal (1955) treated rats with dietary concentrations of HCN at 100 and 300 ppm (mg/kg diet) for 2 years. At the end of the 2-year period, virtually no cyanide was found in plasma or kidneys. Low levels were found in erythrocytes (mean of 1.9 μg per 100 g). Increased levels of thiocyanate, the less toxic primary metabolite of cyanide, were found in plasma (1,123 μg per 100 g), erythrocytes (246 μg per 100 g), liver (665 μg per 100 g), and kidney (1,188 μg per 100 g).

4.2.2.3 Dermal

No human or animal studies were available.

4.2.2.4 Other routes

The pattern of distribution of cyanide may depend on the compound administered. Ballantyne et al. (1972) compared the tissue distribution of cyanide from KCN and HCN in rabbits following intramuscular injection. For both compounds, the administered dose of cyanide was 8 mg/kg. Levels of cyanide were measured in tissues of two groups of rabbits (6 per group) at 0.5 h after death. In another two groups of rabbits, the organs were perfused with saline to measure the actual tissue levels without interference from blood cyanide levels. The

results are presented in Table 4.1. The higher levels of cyanide in blood and tissues following the administration of HCN rather than KCN were presumably due to the more rapid absorption and distribution of HCN. High levels of cyanide were found in perfused brain and liver.

4.2.3 Metabolism

The pathways of cyanide metabolism illustrated in Fig. 4.1 are (1) the major pathway, conversion to thiocyanate by either rhodanese or 3-mercaptopyruvate; (2) conversion to 2-aminothiazoline-4-carboxylic acid, (3) incorporation into a 1-carbon metabolic pool, or (4) combining with hydroxycobalamin to form cyanocobalamin (B_{12}). Conversion of cyanide to thiocyanate is the pathway activated when cyanide poisoning is treated by the intravenous administration of a sulfur donor. The donor must have a sulfane sulfur, a sulfur bonded to another sulfur (e.g., sodium thiosulfate). During conversion by rhodanese, a sulfur atom is transferred from the donor to the enzyme, forming a persulfide intermediate. The persulfide sulfur is then transferred from the enzyme to cyanide, yielding thiocyanate. Thiocyanate is then readily excreted in the urine. Once the reaction-forming thiocyanate occurs, it is essentially irreversible (Way 1984).

Radioisotopic studies have provided some data that indicate that albumin may function as a sulfane carrier (Schneider and Westley 1969, Westley 1981). These studies showed that albumin interacts with elemental sulfur and that the serum albumin-sulfane sulfur carrier complex can react with cyanide. In a more recent paper, Rutkowski et al. (1985) found higher hepatic rhodanese and lower serum albumin levels in mice fed a protein-free diet for 14 days compared with mice fed a control diet. Despite the higher rhodanese levels, mortality following an intraperitoneal injection of NaCN was higher in mice fed the protein-free diet both with and without thiosulfate pretreatment. In mice fed the control diet in reduced amounts, serum albumin levels were higher than controls. Mortality in food-deprived mice was higher compared with controls, but only at high cyanide doses when thiosulfate was also administered. From these results, Rutkowski et al. (1985) suggested that neither hepatic rhodanese nor serum albumin may be important in the detoxification of cyanide. They also suggested that there is a need for new research into the biotransformation of cyanide.

The species and tissue distribution of rhodanese is highly variable (Himwich and Saunder 1948). In the dog, the highest activity of rhodanese was found in the adrenal gland, ~2.5 times greater than the activity in the liver. Monkeys, rabbits, and rats had the highest rhodanese activity in the liver and kidney, with relatively low levels in the adrenals. It should be noted that total rhodanese activity in other species was higher than that in dogs, which is consistent with the greater susceptibility of dogs to the acute effects of cyanide. Similar activities of the enzyme among the species were found for the brain, testes, lungs, spleen, and muscle.

The minor pathway for the metabolism of cyanide in mammalian systems, in which cyanide combines with the amino acid cystine to form 2-aminothiazoline-4-carboxylic acid and its tautomer, 2-iminothiazolidiene-4-carboxylic acid, is illustrated in Fig. 4.2.

Table 4.1. Concentrations of cyanide in blood, serum, and various normal (blood-containing) or saline-perfused tissues from female rabbits killed by an intramuscular injection of 8 mg/kg CN^- [a]

Compound	Tissue	Cyanide concentration[b] (mean ± standard error)		p[c]
		Normal	Perfused	
Intramuscular HCN	Skeletal muscle	35.0 ± 5.2	9.3 ± 2.7	0.001
	Kidney	74.7 ± 10.3	11.0 ± 4.3	0.001
	Liver	148.7 ± 32.3	43.7 ± 13.5	0.02
	Spinal cord	48.5 ± 4.9	49.8 ± 14.7	0.09
	Brain	145.3 ± 37.2	289.0 ± 67.7	0.1
	Whole blood	685.0 ± 83.0	761.0 ± 129.0	0.7
	Serum	275.0 ± 18.0	261.0 ± 48.0	0.8
Intramuscular KCN	Skeletal muscle	29.6 ± 2.4	7.8 ± 2.4	0.001
	Kidney	52.0 ± 11.0	2.3 ± 1.1	0.005
	Liver	82.0 ± 7.9	6.5 ± 0.8	0.001
	Spinal cord	36.8 ± 3.5	2.5 ± 3.8	0.05
	Brain	106.5 ± 12.4	98.0 ± 5.0	0.6
	Whole blood	450.0 ± 34.0	438.0 ± 8.0	0.7
	Serum	161.0 ± 21.0	134.0 ± 8.0	0.3

[a]Six rabbits per group.

[b]Concentrations expressed as μg of CN^- per 100 g wet tissue and μg of CN^- per 100 mL blood or serum. Blood removed from the left ventricle of perfused animals before saline injected.

[c]Significance of difference between normal and perfused tissues.

Source: Ballantyne et al. 1972.

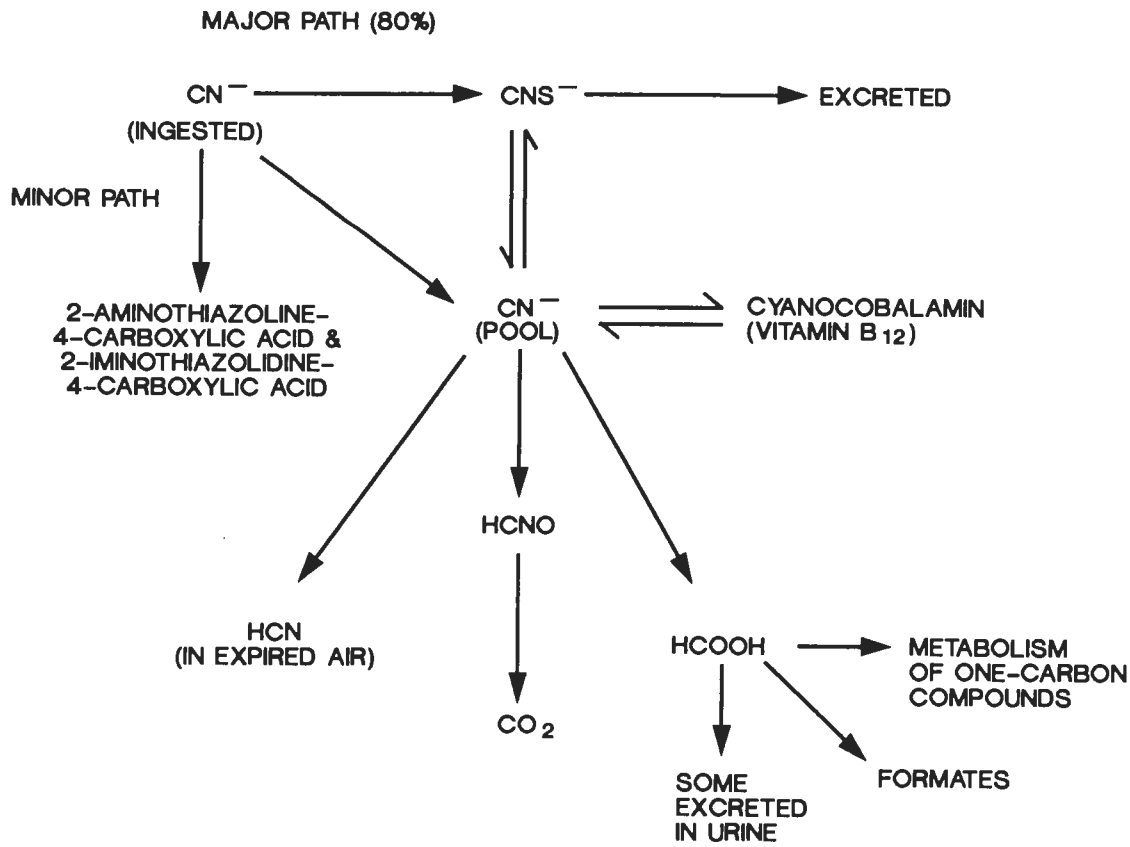

Fig. 4.1. Basic processes involved in the metabolism of cyanide. *Source*: Ansell and Lewis (1970).

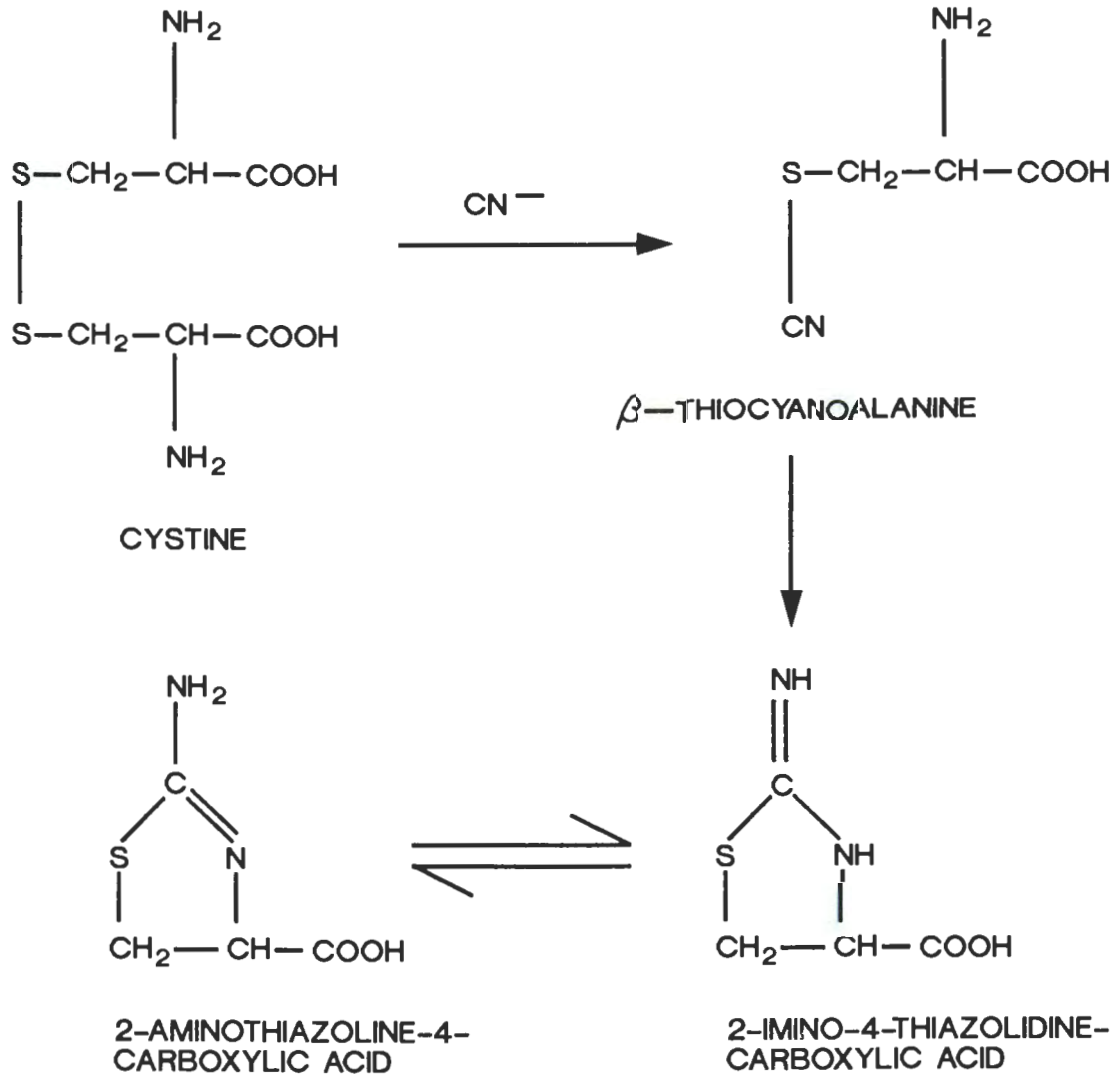

Fig. 4.2 Minor path for the removal of cyanide from the body. *Source*: Ansell and Lewis (1970).

4.2.4 Excretion

Once cyanides have been absorbed, excretion is similar in humans and animals. Cyanide metabolites are excreted primarily in the urine, with small amounts eliminated through the lungs.

Liebowitz and Schwartz (1948) monitored the urinary excretion of thiocyanate after a human ingested 3 to 5 g of KCN. The results indicated that the patient excreted 237 mg of thiocyanate over a 72-h period. This quantity was substantially more than the normal average amount of thiocyanate in urine, which varies between 0.85 and 14 mg per 24 h.

Wood and Cooley (1956) found that in rats pretreated with ^{35}S-cystine, 16% of a subcutaneous dose of NaCN was excreted in the urine as ^{35}S-labeled 2-imino-4-thiazolidine-carboxylic acid, whereas thiocyanate in the urine accounted for 80% of the cyanide dose. In a more recent study, Doherty et al. (1982) found that hamsters administered NaCN continuously by slow infusion over several days excreted only 10 to 15% of the total dose as urinary thiocyanate. Trace amounts of cyanide were also found in the urine; analysis for other metabolites was not conducted.

Friedberg and Schwarzkopf (1969) injected guinea pigs intravenously with 0.2 mg/kg NaCN and measured the exhalation of hydrocyanic acid. The results showed that the amount of hydrocyanic acid eliminated by the lung before respiratory standstill was ~1 to 2% of the dose in guinea pigs breathing spontaneously. Application of artificial respiration increased the exhalation of hydrocyanic acid three- to fourfold. In addition, the administration of thiosulfate decreased the levels of exhaled hydrocyanic acid, with the lowest levels reached 30 min after thiosulfate administration.

4.3 TOXICITY

4.3.1 Mechanisms of Toxicity

The mechanisms of cyanide toxicity are associated with the binding abilities of cyanide. HCN and cyanide salts dissociate in vivo, thereby releasing cyanide ions that disrupt enzyme systems by complexing with heavy metal ions contained in metalloenzymes (Way 1984). Cyanide ions also exert inhibitory effects on Schiff base intermediates, such as ribulose diphosphate carboxylase and 2-keto-4-hydroxy glutarate aldose, by forming a cyanohydrin intermediate (Marsho and Kung 1976, Hasen and Dekker 1976). Oxidative enzymes and coenzymes, in which ferric (Fe^{3+}) ions are present, are particularly sensitive.

The acute toxicity of cyanide may result from the production of cytotoxic anoxia through the inhibition of cytochrome oxidase (NIOSH 1976, Way 1984), which functions as the terminal oxidase of the mitochondrial respiratory chain. A two-step process has been proposed: cyanide first penetrates a protein crevice of cytochrome oxidase and binds to the protein. It then binds to the trivalent metal ion of the enzyme, forming a relatively stable coordination complex. As a result, the enzyme becomes unable to catalyze the reactions in which electrons would be transferred from reduced cytochrome to oxygen. Cellular oxygen

utilization is thus impaired, with a resultant reduction in or cessation of aerobic metabolism (Rieders 1971, Way 1984). Glucose catabolism then shifts from the glycolytic pathway to the pentose phosphate pathway, resulting in increased blood glucose, pyruvic acid, lactic acid, and NADPH levels, and a decrease in the ATP/ADP ratio (Reiders 1971, Way 1984).

The inhibition of oxygen utilization by cells causes oxygen tensions to rise in peripheral tissues; this results in a decrease in the unloading gradient for oxyhemoglobin. Thus, oxyhemoglobin is carried in the venous blood, causing it to be nearly as red as the arterial blood (Reiders 1971). The inhibition of oxygen utilization is thought to occur rapidly following cyanide exposure. Schubert and Brill (1968) found that inhibition of cytochrome oxidase activity peaked 5 to 10 min following the intraperitoneal administration of KCN to mice, rats, and gerbils.

In addition to binding to cytochrome oxidase, cyanide binds to catalase, peroxide, methemoglobin, hydroxycobalamin, phosphatase, tyrosinase, ascorbic acid oxidase, xanthine oxidase, and succinic dehydrogenase. These reactions may also contribute to cyanide's toxicity (DiPalma 1971). Signs of cyanide intoxication include an initial hyperpnea followed by dyspnea and then convulsions (Reiders 1972, Way 1984). These effects are due to initial stimulation of carotid and aortic bodies and effects on the central nervous system. When death occurs, it is a result of respiratory collapse resulting from central nervous system toxicity.

4.3.2 Lethality and Decreased Longevity

4.3.2.1 Inhalation

Human. Inhalation exposure to HCN gas can be rapidly lethal. This property has resulted in the use of HCN in gas chamber executions. Concentrations and durations of exposure that result in death are presented in Table 4.2. Dudley et al. (1942) reported that inhalation of 270 ppm HCN (300 mg/m^3) results in nearly immediate death, whereas inhalation of 135 ppm (150 mg/m^3) is fatal after 30 min of exposure.

According to Reiders (1971), intoxication at 2,000 ppm HCN (2,220 mg/m^3) or greater is characterized by a brief sensation of dryness and burning in the throat due to local irritation, a suffusing warmth, and a hunger for air. Hyperpnea, and sometimes a brief outcry, will follow the first breath. In <1 min, apnea, a few gasps, collapse, and convulsions occur. Cardiovascular failure may also occur, although the heart may continue to beat for 3 to 4 min after the last breath. Reported signs include a rose-colored hue of the skin and a bitter, almond-like odor on the breath. The total absorbed dose of HCN in such rapid deaths can be as low as 0.7 mg/kg.

NIOSH (1976) lists a number of investigations in which animal studies and human case studies were used to estimate lethal cyanide doses for humans. Based on these studies, it appears that exposure to 90 ppm HCN (100 mg/m^3) or more will cause death in humans, whereas 5 to 44 ppm (6 to 49 mg/m^3) will cause a variety of nonlethal effects.

Table 4.2. Human physiological response to various concentrations of hydrogen cyanide in air

Response	Concentration (mg/L)	Concentration (ppm)
Immediately fatal	0.3	270
Estimated human LC_{50} after 10 min	0.61	546
Fatal after 10 min	0.2	181
Fatal after 30 min	0.15	135
Fatal after 1/2-1 h or longer, or dangerous to life	0.12–0.15	110–135

Source: Hartung 1982.

Responses to cyanide may vary depending on individual susceptibility (see Sect. 7.4 for a discussion of populations at high risk).

Animal. A number of studies have determined LC_{50}s for inhalation exposure to cyanides. Higgins et al. (1972) reported 5-min LC_{50}s of 323 ppm for mice and 503 ppm for rats. In a more recent review, ten Berge et al. (1986) estimated LC_{50}s for 30-min exposures to HCN at 200 mg/m^3 (182 ppm) for cats and 450 mg/m^3 (410 ppm) for goats. Matijak-Schaper and Alarie (1982) calculated an LC_{50} in mice of 166 ppm HCN (184 mg/m^3) for a 30-min exposure.

Levin et al. (1987) reported an LC_{50} in rats of 110 ppm (123.5 mg/m^3) for a 30-min exposure to HCN, followed by a 24-h postexposure period. When only deaths occurring during the 30-min exposure period were considered, an LC_{50} of 160 ppm was calculated.

Gettler and Baine (1938) exposed two dogs to HCN gas so that they received doses of 1.1 or 1.6 mg/kg HCN (doses determined by investigators). Both dogs died following a 10- to 15-min exposure. In a study by Haymaker et al. (1952), dogs were exposed to HCN or cyanogen chloride. The exposure concentrations, durations of exposure, and the times to death are presented in Table 4.3.

Sato et al. (1955) exposed groups of 10 mice to HCN at various concentrations. The approximate median lethal dose was 20 ppm for 4.5 h, with mice also dying after 4 h at 15 ppm. A 2-h exposure at 10 ppm resulted in motor dysfunction and labored respiration, whereas exposure at 5 ppm for 4 h resulted in a decrease in food intake.

Valade (1952) conducted experiments in which groups of 4 to 5 dogs were exposed to HCN at 50 mg/m^3 (45 ppm) for 7 to 19 30-min periods at intervals of 2 to 8 days. All exposure regimens resulted in the death of at least one dog. One death was reported to be a result of intercurrent disease, three deaths were reported to be a result of pulmonary inflammation, and the remaining four deaths presumably were the result of cyanide treatment.

4.3.2.2 Oral

Human. Numerous reports describe suicides or suicide attempts through the ingestion of cyanide compounds. These studies, reviewed in NIOSH (1976), do not generally report dose levels.

After measuring tissue HCN levels in a number of suicide cases, Gettler and Baine (1938) determined that the average absorbed lethal dose of cyanide at the time of death is 1.4 mg/kg HCN (1.3 mg/kg CN^-). One suicide case reviewed by Gettler and Baine (1938) revealed that smaller HCN doses can be fatal to some individuals. Using tissue HCN levels, they estimated that a 51-kg woman had ingested a dose of ~29.8 mg HCN, which resulted in a minimum human lethal absorbed dose of 0.56 mg/kg CN^-.

The EPA (1987a) summarized a variety of other reports in which single fatal oral doses of cyanide compounds were estimated. From these data, a human oral LD_{50} of 2.86 mg/kg NaCN (1.52 mg/kg CN^-) was estimated.

Table 4.3. Data on dogs exposed to either CNCl or HCN by inhalation

Compound	Dog No.	Dose (mg/L)	Exposure duration (min)	Length of survival
CNCl	1	2.9 (1155)[a]	2.0	5 min
	2	3.1 (1234)	2.25	8.5 min
	3	3.5 (1394)	2.25	9 min
	4	3.3 (1314)	2.0	11 min
HCN	1	0.62 (564)[a]	2.0	16 h
	2	0.59 (537)	2.0	16 h
	3	0.70 (637)	1.75	20 h

[a]Numbers in parentheses refer to dose in ppm.
Source: Haymaker et al. 1952.

Wolnik et al. (1984) reported an incident in which seven persons died after ingesting capsules of an over-the-counter pain remedy that had been criminally contaminated with cyanide. Capsules were found to contain 500 to 800 mg KCN. No exposure levels could be calculated from the information provided.

Animal. A number of rat oral LD_{50}s for various cyanide compounds are presented in Table 4.4. For comparison, the values are also presented in terms of milligrams CN^- per kilogram body weight. An oral LD_{50} for KCN in mice has been reported as 8.5 mg/kg (3.4 mg/kg CN^-) (Sheehy and Way 1968). Isom and Way (1973) determined a 24-h oral LD_{50} in mice for KCN of 12 mg/kg (4.8 mg/kg CN^-).

In determining LD_{50}s for cyanide compounds, the volume of the vehicle appears to be important. Ferguson (1962) demonstrated that a concentrated solution of KCN administered in a small volume was less toxic to Sprague-Dawley rats than a more dilute solution. The LD_{50}s determined in the study were 10.8 (10.0 to 11.7) mg/kg KCN (4.3 mg/kg CN^-) and 15.8 (14.6 to 17.1) mg/kg KCN (6.3 mg/kg CN^-) for KCN administered in a volume of water corresponding to 5% and 1% body weight, respectively. No body weight values or statistical analyses were reported.

In a study by IIT Research Institute (1987), groups of 20 Sprague-Dawley rats per sex were treated by gavage with potassium silver cyanide in a 1.5% carboxymethylcellulose solution at 3, 10, 30, and 60 mg/kg/day (0.8, 2.62, 7.85, and 15.7 mg/kg CN^- per day) for 90 days. The most significant finding was increased mortality, with 3 (1 male, 2 female), 9 (6 male, 3 female), 28 (14 male, 14 female), and 20 (10 male, 10 female) rats dying in the 3-, 10-, 30-, and 60-mg/kg/day groups, respectively. Four rats in the vehicle control group also died, with no deaths among the untreated controls. The rats in the 60-mg/kg/day group died during the first 4 days of treatment; therefore, treatment of the surviving 20 rats was ended.

IIT Research Institute (1986) conducted a similar study in which rats were treated with copper cyanide at 0.5, 5, 15, or 50 mg/kg/day. Treatment-related deaths were observed in all dose groups. Deaths at 15 and 50 mg/kg were attributed to hemolytic anemia, an effect that is associated with copper toxicity. Rats treated at ≥5 mg/kg appeared pale relative to controls. At 15 and 50 mg/kg, labored respiration, fixed and prolonged posture, and thin appearance were observed; lethargy, red urine, and diarrhea were also observed in the 50-mg/kg dose group. At an interim bleed, decreased red blood cell values were observed in rats at 50 mg/kg. Because signs of classical copper-induced toxicity were observed in this study and were not considered to be cyanide induced, it will not be discussed further in this profile.

4.3.2.3 Dermal

Human. Without providing any details, DiPalma (1971) stated that fatalities occurred by the skin absorption of 5% aqueous HCN and 10% aqueous KCN. Reiders (1971) stated that a dermal LD_{50} for HCN was estimated at 100 mg/kg. No details were provided.

Table 4.4. A comparison of rat oral LD_{50} values of selected cyanide compounds

Compound	LD_{50} (mg/kg)	LD_{50} (mg/kg CN)	Solubility in water	References
Sodium cyanide	6.4	3.4	Soluble	EPA 1985a
Potassium cyanide	10	4.0	Soluble	Hayes 1967
Calcium cyanide	39	22.0	Soluble	Smyth et al. 1969
Silver cyanide	123	26.0	Insoluble	Sax 1984
Potassium silver cyanide	21	5.5	Soluble	Sax 1984

Animal. In a study by Walton and Witherspoon (1926), guinea pigs dermally exposed to HCN vapor died. The abdomens of the guinea pigs were shaved, and a 1-in.-diam area was exposed through a hole in a board to prevent inhalation exposure. Within minutes, rapid respiration, muscle convulsions, and death occurred. In similar experiments, the authors exposed shaved or unshaved dogs to 5,500 to 16,900 mg/m^3 HCN (5,000 to 15,400 ppm) (except for the head and neck) for up to 180 min. No symptoms were reported at levels ≤6,500 mg/m^3 HCN (5,900 ppm); several dogs exposed in the 11,900 to 16,900-mg/m^3 (10,800 to 15,400-ppm) range died. Exposure times and experimental conditions were varied. Fairley et al. (1934) found that coma, convulsions, and/or death resulted within 45 to 65 min when 1.23 in.^{2} of the clipped bellies of guinea pigs were exposed to HCN vapor at 347,000 to 505,000 mg/m^3 (312,000 to 455,000 ppm). The possibility that some inhalation exposure had occurred in these earlier studies cannot be dismissed; therefore, death may not have been due solely to dermal exposure.

4.3.2.4 Other routes of exposure

Human. Studies describing human lethality following other routes of exposure were not found.

Animal. Data regarding the lethality of cyanide compounds following parenteral routes of exposure are presented in Table 4.5. Because parenteral routes are not emphasized in this profile, these studies will not be discussed further.

Topical application to the eye will be considered because it is often discussed along with dermal absorption and it is a potential route of human exposure. Ballantyne (1983) determined LD_{50} values in rabbits by instilling aqueous solutions of HCN, NaCN, or KCN into the inferior conjunctival sac of the eye. The LD_{50} values determined were 1.09 mg/kg HCN (1.01 mg/kg CN^-), 7.87 mg/kg KCN (3.15 mg/kg CN^-), and 5.05 mg/kg NaCN (2.68 mg/kg CN^-). For all compounds, signs of toxicity and death occurred 3 to 12 min after the eyes were treated.

4.3.3 Systemic/Target Organ Toxicity

4.3.3.1 Nervous system

Inhalation, human. Thomas and Brooks (1970) reported a case in which tingling and numbness in the hands occurred in a photographic lab employee exposed to KCN when a bag of KCN powder burst in his face. Other symptoms reported included abdominal pain, pallor, and subsequent collapse. The employee recovered in 48 h following treatment with amyl nitrite inhalation, gastric lavage, and injections of sodium nitrite and sodium thiosulfate. Inhalation, oral, and dermal routes of exposure probably contributed to the total absorbed dose in this case.

In a fatality involving probable inhalation exposure to calcium cyanide and HCN, microscopic changes were found in the brain of a fruit tree sprayer (Courville 1963). Effects noted included damage to cortical nerve cells, occasional neuronophagia, focal necrosis in the hippocampus, and changes in the cerebellar cortex.

Table 4.5. Lethality of cyanide compounds following exposure via parenteral routes

Route	Administered compound	Species/strain/sex	Dose (as CN^-)	Duration	Results	References
Subcutaneous	KCN	Mouse/ Swiss Webster/M	4.7 mg/kg	Single dose	LD_{50}	Way et al. 1972
	NaCN	Dog/NR[a]/NR	2.84 mg/kg	Single dose	LD_{50}	Chen and Rose 1952
Intramuscular	HCN	Rabbit/NR/M Rabbit/NR/F	1.44 mg/kg 0.91 mg/kg	Single dose Single dose	LD_{50} LD_{50}	Ballantyne et al. 1971, 1972
	KCN	Rabbit/NR/M	1.22 mg/kg	Single dose	LD_{50}—rabbits lived longer following KCN administration	Ballantyne et al. 1971, 1972
		Rabbit/NR/F	1.31 mg/kg	Single dose	LD_{50}	
Intraperitoneal	KCN	Mouse/ Swiss Webster/M	0, 0.4, 0.8, 1.2, 1.6, 2.0, or 2.4 mg/kg	Single dose	Signs of toxicity scarcely observed at 0.4 and 0.8 mg/kg; at 1.2, 1.6, and 2.0 mg/kg, gasping, irregular breathing; at 2.4 mg/kg, 20% of the mice died	Isom et al. 1982
Subcutaneous	NaCN	Rat/Wistar/M	0.02 mg/kg	3 injections at 0.02 mg/kg, 10 min apart	The rats survived 5 h	Owasoyo and Iramain 1980
	NaCN	Rat/ Charles River/M	TWA doses 0.61, 1.31, and 1.72 mg/kg/day	3 days/week for 3 months	High mortality in all treated groups	Lessell 1971
Intramuscular	KCN	Monkey/rhesus/NR	TWA 0.76–15.2 mg/kg/day[b]	17–103 days	All treatments were fatal <2 hours to 13 days after the last dose	Hurst 1940

[a]NR = Not reported.
[b]TWA doses were calculated. In this study, the doses were increased throughout the experiment, the investigator supplied cumulative doses, and these cumulative doses were divided by 90 days to give the TWA doses.
Source: EPA 1987a.

Sandberg (1967) reported a case of cyanide poisoning in a worker potentially exposed to HCN dermally and by inhalation. The worker had a dilated left pupil, gray skin, paresis of the left extremities, headache, general malaise, left-sided hemianopsia, and an altered EEG. The worker used a 1.5% aqueous KCN solution, heated to boiling, to which hydrogen peroxide was added. Splashing on the skin and the production of a visible aerosol occurred during a cleaning process. Ventilation was poor and no protective clothing was worn. The patient's blood was found to contain 10 to 12 μg CN^- per 100 mL. No level of exposure could be ascertained from this study.

Carmelo (1955) studied ~600 HCN fumigators and found tachycardia accompanied by palpitation, vertigo, buzzing in the ears, headache, epigastric burning, vomiting, general weakness, tremor, sensory obtusion, dyspnea, precordial pain, and loss of consciousness among workers who had received "small acute intoxications from HCN." A more detailed examination was conducted on 17 fumigators who used HCN; 13 had experienced acute episodes with loss of consciousness. The men examined had worked with HCN for 1 to 27 years. The author reported a high incidence of nervous disorders including vertigo, equilibrium disturbances, and nystagmus. No other details of exposure were provided.

Inhalation exposure to cyanide in tobacco smoke by heavy smokers has been associated with the condition of tobacco amblyopia, which is characterized by a loss of visual acuity; Leber's hereditary optic atrophy, a similarly manifested disorder; retrobulbar neuritis; complicating pernicious anemia; and optic atrophy (Wokes and Moore 1958; Pettigrew and Fell 1972, 1973; Wilson and Matthews 1966; Foulds et al. 1968; Wilson 1983). These disorders may involve the defective metabolism of cyanide to thiocyanate, as well as a deficiency in vitamin B_{12} or defective vitamin B_{12} metabolism.

Inhalation, animal. In a study by Haymaker et al. (1952), six adult dogs of unreported sex were exposed to HCN at 165 to 700 mg/m^3 (150 to 637 ppm) for 1.75 to 10 min. Three dogs died 16 to 20 h after exposure, and the survivors were sacrificed 24 to 28 h after exposure. When the brains of these dogs were examined microscopically, necrosis, primarily in regions of gray matter, was observed. The areas most affected were the cerebral cortex, caudate nucleus and putamen, substantia nigra, globus pallidus, pulvinar of the thalamus, and the cerebellar cortex.

Valade (1952) conducted four experiments in which groups of 4 to 5 dogs were exposed to HCN at 50 mg/m^3 (45 ppm) for 7 to 19 30-min periods at intervals of 2 to 8 days. The use of control dogs was not discussed. All exposure regimens resulted in the death of at least one dog. The signs of intoxication observed included dyspnea, nausea, exaggerated intestinal peristalsis, and diarrhea followed by tremors, loss of equilibrium, and convulsions. Microscopic examination of the brain tissue of dogs that died and were sacrificed revealed vasodilation and hemorrhages that were most pronounced in the central gray nuclei, brain stem, bulb, and medulla cervicalis. Cytologic changes were also observed in the Purkinje cells of the cerebellum and in the bulbar gray nuclei. From his observations, Valade (1952) concluded that the lesions were a

result of anoxia caused by the inhibition of cytochrome oxidase or from a selective effect of cyanide.

Levine and Stypulkowski (1959a,b), Levine (1967), and Hirano et al. (1967) conducted a number of studies in which cyanide encephalopathy in rats was examined. In these studies, rats were exposed intermittently to unspecified concentrations of gaseous HCN until a certain stage of intoxication was observed. Symptoms of stage 1 intoxication were restlessness and increased activity. In stage 2, voluntary muscle activity decreased and the rat sank to the floor, although it responded to tapping of the exposure chamber. In stage 3, the loss of motor power was complete; a tap on the chamber elicited only an ear twitch. In stage 4, the ear did not respond to tapping and respiration was slow. The state of intoxication desired was maintained for varying periods of ≤60 min by occasional removal from cyanide exposure. Levine and Stypulkowski (1959a) found that exposure in stage 1 or 2 was ineffective in producing brain lesions. Exposure in stage 3 for 15 min or more injured the callosum and basal ganglia. When stage 4 intoxication predominated, damage to the gray matter (cortex, thalamus, hippocampus, striatum, and cerebellum) was observed.

Levine and Stypulkowski (1959b) exposed carotid artery ligated and nonligated female Wistar rats to HCN (as described above) so that intoxication between stages 3 to 4 was maintained for 25 to 35 min. Microscopic examination of brain tissue revealed similar lesions in the white matter of both ligated and nonligated rats. Lesions in the gray matter were also observed in both ligated and nonligated rats, but ligation resulted in the localization of lesions to the side of carotid ligation. The authors stated that the study supported the idea that ischemic or anoxic anoxia from deep cyanide intoxication might be partly responsible for bilateral gray lesions, especially those of the cortex.

Following similar methods, Levine (1967) examined the brains of rats 5 h after they were kept intoxicated (stage 3) with cyanide for 20, 30, 45, or 60 min. This study revealed various gradients of lesions in the corpus callosum, depending on the duration of intoxication. Levine (1967) concluded that the distribution of brain lesions was dependent on the vascular anatomy, with the inhibition of cytochrome oxidase as the basic cause of the lesions.

Using electron microscopy, Hirano et al. (1967) examined the brain tissue of rats 1, 2, and 24 h, and 1 and 3 weeks after rats were intoxicated with cyanide (stage 3) for 30 min. Examinations of the lesions in the corpus callosum led the authors to conclude that the lesions were due to cyanide-induced anoxia and that the lesions were not caused by hematogenous, extracellular edema fluid or by damage to neuronal perikarya.

Using monkeys, Purser et al. (1984) studied the toxicity of HCN gas atmospheres and of atmospheres produced by the pyrolysis of polyacrylonitrile (PAN). It was determined that the dramatic and rapid incapacitating effects in monkeys exposed to pyrolyzed PAN were due to HCN. These effects consisted of the rapid induction of a state of semiconsciousness accompanied by severe disruptive changes in respiration, EKG, and EEG; these were always preceded by a hyperventilatory episode. The effects were seen at HCN concentrations

ranging from about 87 to 196 ppm. Over this range there was a "loose" linear relationship between the concentration of HCN and the time to incapacitation. One unexpected finding in the study was that for a given HCN level, the smoke atmospheres generated from pyrolyzed PAN, which also contained other nitriles as well as carbon monoxide (CO), were less toxic than HCN gas alone both in time to incapacitation and the severity of clinical signs, which is discussed further in Sect. 4.4.

Oral, human. Uitti et al. (1985) described a suicide attempt in which an 18-year-old man ingested between 975 and 1,300 mg of KCN (390 to 519 mg CN^-) with amobarbital sodium-secobarbital sodium (Tuinal). Although rapid treatment was obtained, degeneration, behavioral changes, and central nervous system depression were noted during the months following exposure. Parkinsonian syndrome was diagnosed, and anticholinergic therapy was prescribed without apparent effect. The man died from an imipramine/alcohol overdose 19 months later. Examination of the brain revealed changes in the globus pallidus and putamen. Because there were no known exposures to other agents that selectively involve those sites, the authors attributed the changes to cyanide toxicity and concluded that cyanide may cause parkinsonian syndrome.

Quantitative data describing adverse neurological effects following longer-term exposure to cyanide were not found in the available literature. Several studies do describe an association between ingestion of cassava, a tuberous root vegetable containing cyanogens, and neurotoxic effects. Money (1958), Makene and Wilson (1972), Conn (1973), Grant (1980), Osuntokun et al. (1969), Osuntokun (1972, 1980), and Monekosso and Wilson (1966) describe cases of chronic degenerative neuropathy associated with cassava consumption and nutritionally deficient diets, including those deficient in vitamin B_{12}. Individuals experienced peripheral neurological abnormalities such as demyelination of peripheral nerves with decreased conduction velocity, optic neuropathy, and deafness. Vitamin B_{12} deficiency itself, however, can result in progressive swelling of the myelinated neurons, demyelination, and cell death in the spinal column and cerebral cortex (Gilman et al. 1985).

The Ministry of Health, Mozambique (1984) published a report for the World Health Organization in which cassava consumption was linked with spastic paraparesis. No data were available on the amount of cassava ingested or the method of preparation, which, according to Ermans et al. (1972), could have affected the amount of cyanide available. The report concluded that there is a likely association between the epidemic spastic paraparesis and cassava consumption, with a possible link to dietary deficiencies. Chronic exposure to dietary levels of cyanides usually encountered in the United States has not been associated with adverse effects.

Oral, animal. Philbrick et al. (1979) fed groups of 10 male weanling rats two different diets with or without cyanide for 11.5 months. One group of rats (the positive control) received a diet containing 10% casein supplemented with 0.3% DL-methionine, potassium iodide, and vitamin B_{12}. Two groups received this diet along with either 1,500 ppm KCN or 2,240 KSCN. Another group (the negative control) received a 10% casein diet with no added potassium iodide or vitamin

B_{12}. Two additional groups received the negative control diet along with either 1,500 ppm KCN or 2,240 KSCN (30 mg/kg/day CN^- for both compounds). Thus, of those groups receiving CN^-, one received a complete diet while the other was restricted in iodine and vitamin B_{12}. No deaths occurred nor were there any signs of gross toxicity. Vacuolization and myelin degeneration were observed in spinal cord sections of rats fed cyanide, with effects more pronounced in rats that were fed the restricted diets. According to the authors, the modest myelin degeneration of the spinal cord tracts may be either a direct result of histotoxic anoxia or an indirect effect of altered oligodendoglial myelin metabolism. The lesions reportedly did not resemble those from vitamin B_{12} deficiency, and the authors concluded that the dietary vitamin B_{12} restriction in the control diet was not severe enough to produce evidence of frank vitamin B_{12} deficiency.

In a study by Howard and Hanzal (1955), groups of 10 male and 10 female Carworth Farm rats were maintained for 104 weeks on diets that had been fumigated with HCN. The average measured HCN concentrations in the diet were 76 mg/kg of food for the low-dose level and 190 mg/kg of food for the high-dose level. A similar group of rats fed the basal diet were maintained as controls. The diets provided CN^- doses of 0, 3.2, and 7.8 mg/kg/day for males and 0, 4.3, and 10.8 mg/kg/day for females. These doses were calculated from food consumption and body weight data provided by the authors. During the 2 years of the study, the growth curves for all groups did not vary as a result of treatment. Food consumption, hematological values, and survival were also similar in all groups during the study. Except for changes associated with aging, pathological changes in the CNS or other organ systems were not observed.

Hertting et al. (1960) dosed three dogs (sex not stated) with NaCN in capsules. One dog was treated at 0.5 mg/kg/day NaCN (0.27 mg/kg/day CN^-) for 13.5 months. A second dog was dosed at 1 mg/kg/day NaCN (0.53 mg/kg/day CN^-) for 16 weeks followed by 10.5 months of treatment with two daily doses at 2 mg/kg/day NaCN (1.1 mg/kg/day CN^-). A third dog was treated at 2 mg/kg/day NaCN (1.1 mg/kg/day CN^-) for 14.5 months. One untreated dog served as a control. At greater than 1 mg/kg/day NaCN, acute signs of toxicity were observed immediately after dosing, with recovery in <0.5 h. All dogs treated with NaCN exhibited degenerative changes in CNS ganglion cells, especially in the Purkinje cells of the cerebellum. These changes included necrosis, reduced RNA content, and inflammation. In addition to CNS effects, dogs treated at >1 mg/kg/day showed decreased serum albumin levels and increased hemoglobin levels.

Dermal, human. Studies describing adverse neurological effects in humans following exposure to cyanides were not found in the available literature.

Dermal, animal. In previously reported studies by Walton and Witherspoon (1963) and Fairley et al. (1934), neurotoxic effects such as convulsions and coma preceded death in guinea pigs exposed to HCN dermally for acute exposure periods.

General discussion. The nervous system is the most sensitive end point of cyanide toxicity, partly because of its high metabolic demands. High doses of cyanide can result in death via central nervous system

effects, which can cause respiratory arrest. In humans, chronic low-level cyanide exposure through cassava consumption (and possibly through tobacco smoke inhalation) has been associated with tropical neuropathy, tobacco amblyopia, and Leber's hereditary optic atrophy. It has been suggested that defects in the metabolic conversion of cyanide to thiocyanate, as well as nutritional deficiencies of protein and vitamin B_{12}, play a role in the development of these disorders (Wilson 1965).

In a study by Lessell (1971), rats treated with NaCN by subcutaneous injection at time-weighted average doses of 0.61, 1.31, and 1.72 mg/kg/day CN^-, 3 days/week for 3 months, developed necrotic lesions of the corpus callosum and optic nerve. High mortality was observed at all dose levels. Additional inhalation and oral studies in animals have shown that cyanide exposure leads to encephalopathy in both white and gray matter. In particular, damage has been observed in regions such as the deep cerebral white matter, the corpus callosum, hippocampus, corpora striata, palladium, and the substantia nigra. White matter may be more sensitive because of its relatively low cytochrome oxidase content. These effects have been observed following acute exposures (Levine and Stypulkowski 1959a,b) and longer-term exposures (Hertting et al. 1960). Investigators have suggested that the topographic selectivity of cyanide-induced encephalopathy is related to the depth of acute intoxication and the distribution of the cerebral vascular system, which may result in selected regions of vascular insufficiency (Levine 1967).

Additional mechanisms of cyanide action on neurons have also been suggested. Brierley et al. (1976), after conducting a study in which rats were infused intravenously with NaCN, suggested that cyanide induces cytotoxic damage to brain neurons via secondary effects on circulation and respiration. They measured arterial pO_2 and CO_2 levels and found that in intoxicated rats, pO_2 levels rose while CO_2 levels fell. It was suggested that the low levels of CO_2 may have led to vasoconstriction and reduction in brain blood flow; therefore, brain damage may have been due to both cytoxic and anoxic anoxia.

Several recent studies have suggested that a disruption in neuronal calcium regulation may be an important factor in the manifestation of cyanide-induced neurotoxic events following acute exposure. The predominance of anaerobic metabolism in a cyanide-poisoned cell induces a decrease in the ATP/ADP ratio, or energy charge (Isom et al. 1975), and thus alters energy-dependent processes such as cellular calcium homeostasis (Johnson et al. 1986). An in vitro study, Adams et al. (1985), showed elevated levels of intracellular calcium in a cyanide-exposed, presynaptic squid neuron. Calcium is thought to block the release of neurotransmitters from the presynaptic terminal and thus block neurotransmission (Adams et al. 1985). Increases in the levels of whole-brain calcium were observed when KCN was administered subcutaneously to mice. These increases were correlated with cyanide-induced tremors (Johnson et al. 1986). Increases in intracellular calcium have also been associated with cyanide-induced effects on vascular smooth muscle and cardiac muscle, possibly inducing cell damage (Allen and Smith 1985, Robinson et al. 1985a). These effects may result from ischemia-induced increases in extracellular potassium, which in turn enhance cellular permeabilities to cyanide (Robinson et al. 1985b).

4.3.3.2 Cardiovascular and/or respiratory effects

Indicators of cardiovascular and respiratory effects have been observed in humans and animals following exposure to cyanides. However, these effects are predominantly secondary to effects on the central nervous system.

Inhalation, human. Acute exposure to HCN at high concentrations results in hyperventilation followed by unconsciousness and often death. These effects are secondary to effects on the central nervous system.

In an epidemiology study (El Ghawabi et al. 1975), 16 of 36 male electroplaters from three factories in Egypt complained of breathing difficulty. The workers were all nonsmokers who had been exposed to cyanide at concentrations of ~6.4 to 10.3 ppm (7.1 to 11.4 mg/m^3) for 5 to 15 years. Carmelo (1955) reported EKG abnormalities in 11 of 13 fumigation workers who had all experienced episodes of acute HCN intoxication. Exposure concentrations were not reported.

Inhalation, animal. O'Flaherty and Thomas (1982) exposed a group of four male rats to HCN at 200 ppm (220 mg/m^3) for five 12.5-min periods at 4-day intervals. Four rats exposed to air served as controls. Two hours after the first, third, and fifth exposures, cardiac-specific creatine phosphokinase in blood samples was determined. The results indicated increased activity of the phosphokinase in the exposed rats, an indication of myocardial damage. The changes were consistently independent of the number of previous exposures. After the fifth exposure, the number of ectopic heart beats generated during the first 2 min after an injection of norepinephrine into the tail vein was increased in exposed rats compared with controls. HCN exposure via the described regimen did not increase microscopic lesions of the heart. Treatment of rats with chlorpromazine and sodium thiosulfate before HCN exposure sharply reduced or abolished the increase in plasma cardiac-specific creatine phosphokinase activity and the number of ectopic heart beats induced by norepinephrine injection.

Purser et al. (1984) exposed a total of seven cynomolgus monkeys (*Macaca fascilaris*) for 30 min to HCN or to atmospheres containing HCN, which were produced by the pyrolysis of polyacrylonitrile (PAN). HCN concentrations during both types of exposures ranged from 87 to 196 ppm (96 to 217 mg/m^3). Physiological effects observed included bradycardia with arrhythmias, T-wave abnormalities, hyperventilation, and loss of consciousness. After the exposures, recovery was rapid.

Matijak-Schaper and Alarie (1982) exposed mice to several concentrations of HCN for 30 min and reported data on the decrease in respiratory rate. A "DC_{50}" value of 63 ppm HCN (70 mg/m^3) was presented as the concentration that resulted in a 50% decrease in average respiratory rate because of depression of the respiratory centers. Some sensory irritation was also reported in these experiments. Sato et al. (1955) observed rough respiration and hindered mobility in mice exposed to HCN at 10 ppm for 2 h.

Hugod (1981) exposed groups of 22 Danish rabbits to HCN at 0 or 0.55 mg/m^3 (0.5 ppm) continuously for 28 days. Electron microscopic examination of the myocardium did not reveal a significant difference

between control and exposed rabbits. No other parameters were examined in this study.

Oral. Studies describing cardiovascular or respiratory effects in humans and animals following oral exposure were not found in the available literature.

Dermal, human. Pontal et al. (1982) and Trapp (1970) described cases in which humans fell or jumped into vats containing silver cyanide and potassium cyanide. Doses were not determined in these cases, and concomitant oral and inhalation exposures were likely. In both cases, acute effects, such as loss of consciousness, were observed, with respiratory failure noted in the Pontal et al. (1982) case. Treatment was immediate and recovery was complete.

Dermal, animal. Studies regarding respiratory and cardiovascular effects in animals following dermal exposure to cyanides were not found in the available literature.

General discussion. Clinical signs and symptoms of cardiovascular and respiratory effects induced by cyanides, such as EKG abnormalities, increased blood levels of cardiac-specific creatine phosphokinase, and altered cardiac and respiratory rates, have been reported (Purser et al. 1984, O'Flaherty and Thomas 1982, Martijak and Alarie 1982, El Ghawbi et al. 1975, Carmello 1955, Wexler et al. 1947). In most cases, these effects can be attributed to early cyanide-induced effects on the cardiac and vasomotor centers of the brain, and the reflex stimulation of the cardioinhibitory, cardioaccelerator, and vasomotor centers via the carotid artery and aortic bodies (Wexler et al. 1947). These conclusions were reported by Wexler et al. (1947) based on observations following the intravenous administration to 16 human volunteers of doses of NaCN that were just sufficient to stimulate respiration (0.15 to 0.2 mg/kg NaCN). Typically, the effects noted were a sinus pause, followed by irregularity and a slowing of the heart rate from a few seconds to as long as 2 min. The heart rate accelerated to above normal control levels; however, rate and rhythm were restored after 3 min.

Support for cyanide-induced, neurogenic-mediated effects on the cardiovascular and respiratory systems, rather than direct effects, comes from data showing that the responses of these systems to sublethal doses of cyanide appear to be reversible (Purser et al. 1984) and that microscopic examinations of myocardial tissue taken from cyanide-exposed animals have been largely negative even when animals have been repeatedly exposed to cyanide over several weeks (Hugod 1981, O'Flaherty and Thomas 1982). Furthermore, Wexler et al. (1947), citing unpublished data, reported that the early changes in heart rhythm and rate in dogs treated with cyanide, which were similar to changes seen in humans after cyanide, could be diminished by atropine or abolished by bilateral vagotomy and denervation of the carotid body.

Limited data suggest that cyanide has direct effects on the heart. Wexler et al. (1947) studied the effect of lethal doses of cyanide on the electrocardiograms of four men executed by the inhalation of HCN. From these studies, the authors suggested that the later, more pronounced electrocardiographic and rhythm changes observed in these

individuals were the result of a direct action of cyanide on the heart plus the effect of anoxia.

Vick and Froehlich (1985) studied the effectiveness of several antidotes for acute cyanide toxicity produced in dogs treated intravenously with NaCN (2.5 mg/kg). From their studies, they suggested that the early cardiovascular-respiratory difficulties observed in these cyanide-poisoned dogs was due in part to a shock-like state that was not related to the effects of cyanide on cytochrome oxidase. These investigators reported that histamine levels were elevated following the injection of cyanide, and that phenoxybenzamine, an alpha-adrenergic blocker, partially prevented these early cardiovascular changes and markedly increased the percent survival. The mechanism for this effect was not elucidated, although relatively high doses of haloalkylamine-type alpha-adrenergic blocking agents such as phenoxybenzamine can inhibit histamine responses (Gilman et al. 1985). However, additional studies would be necessary to support their hypothesis and to determine the mechanism of phenoxybenzamine's prevention of cyanide-induced death under the experimental conditions. Furthermore, these authors proposed that the early effectiveness of amyl nitrite in preventing deaths of the animals in these studies was due in part to amyl nitrite's ability to cause vasodilation, thus reversing "early cyanide-induced vasoconstriction" and restoring normal cardiac function. Experimental data supporting this conclusion were not presented.

Several in vitro studies indicate that cyanide could produce direct effects on the cardiovascular system.

An interaction between calcium ions and cyanide in cardiovascular effects has been suggested by the results of in vitro studies. Allen and Smith (1985) demonstrated that exposure to cyanide in a metabolically depleted ferret papillary muscle eventually results in elevated intracellular calcium levels, but only after a substantial contracture developed. They proposed that intracellular calcium may precipitate cell damage and arrhythmias. The mechanism by which calcium levels were raised was not determined.

Robinson et al. (1985a) used isolated strips of aorta from rabbits, dogs, and ferrets to determine the effects of cyanide on vascular smooth muscle. Cyanide was found to cause small contractions in the isolated rabbit aorta beginning at ~10×10^{-11} *M* cyanide, reaching a maximum response at 10×10^{-5} *M* cyanide. At higher cyanide concentrations (10×10^{-5} to 10×10^{-3} *M*), relaxation occurred. Robinson et al. (1985b) found that 10×10^{-4} *M* chlorpromazine or 4,4'-diisothiocyano-2,2'-stilbene disulfonic acid (DIDS) reduced the contractions, perhaps by blocking anionic channel mechanisms that would ordinarily facilitate the entry of cyanide into vascular smooth muscle cells.

4.3.3.3 Thyroid effects

Inhalation, human. In an epidemiology study by El Ghawabi et al. (1975), 36 exposed workers and 20 controlsfrom three electroplating factories were studied (all were nonsmokers). The exposed workers had worked for 5 to 15 years with mean cyanide levels ranging from 6.4 to 10.4 ppm (7.1 to 11.5 mg/m^3). Examinations revealed that 56% of the exposed workers had enlarged thyroid glands. There was no quantification

of the extent of enlargement or information regarding when the thyroid glands first became enlarged. The exposed group also had significantly elevated hemoglobin and lymphocyte counts. Additional signs and symptoms reported at 6.4 to 10.4 ppm include breathing difficulty, headache, throat irritation, weakness, changes in taste and smell, abdominal pain, vomiting, and nervous instability. Factors that make interpretation of this study difficult include the potential exposure of workers to other volatiles, a range of exposure levels, and unmatched controls.

Blanc et al. (1985) studied 36 former HCN-exposed workers from a silver-reclaiming facility on the average of 10.5 months after they had stopped working. Relative exposure levels were estimated from information concerning work habits. Results of a questionnaire concerning symptoms indicated dose-response trends in reported symptoms including headache, dizziness, nausea, and a bitter almond taste. Biochemical data indicated low vitamin B_{12} and folic acid levels. No palpable abnormalities of the thyroid gland were noted. Serum levels of thyroid-stimulating hormone (TSH) were within the range of normal limits, although the mean TSH level of the highest exposed workers was significantly ($P < 0.05$) different from the laboratory mean. The exposure concentration measured 1 day after the plant stopped operations indicated a time-weighted average HCN concentration of 15 ppm (16.6 mg/m^3). This measurement shows that exposures were high, but actual exposure levels could not be determined.

Inhalation, animal. Studies describing thyrotoxicity following inhalation exposure of animals to cyanide were not found in the available literature.

Oral, human. Qualitative data suggest that chronic exposure to cyanogens in cassava results in thyroid abnormalities (Ermans et al. 1972, 1980). Surveys in communities in Africa where cassava is a staple crop show a strong correlation between cassava consumption and endemic goiter and cretinism. Dietary deficiencies, especially low intake of iodine, contribute to these effects.

Oral, animal. In a 14-day study by Kreutler et al. (1978), groups of at least 10 young male rats were fed a basal, low-iodine diet that varied in the amount of protein. Three groups were fed a low-protein diet (2% casein); one group served as a control, along with a 0.2% KCN (2,000 ppm) group and a 0.2% KCN and KI (added to drinking water) group. Two additional groups were fed diets containing 20% casein: one group with 0.2% KCN and the other group without. The level of KCN added to the diet corresponded to a dose of ~100 mg/kg/day KCN (40 mg/kg/day CN^-). The results of the study showed a significant increase in absolute and relative thyroid weights, along with increased plasma thyroid-stimulating hormone only in the KCN low-protein group. These effects were not observed when protein levels were increased or when iodine was added to the drinking water of rats fed a low-protein diet.

Philbrick et al. (1979) administered diets supplemented with 1,500 mg/kg KCN (75 mg/kg/day KCN or 30 mg/kg/day CN^-) to four groups of 10 rats for 11.5 months. KCN was added to each of two basal diets, and test animals were compared with appropriate control animals, which were fed only the basal diet. At 4 months into the study, both KCN groups had significant decreases in plasma thyroxine and in thyroxine-secretion

rates, indicating depressed thyroid gland function. At 11 months, both KCN test groups had significant decreases in thyroxine secretion rates and significant increases in relative thyroid weight.

In a developmental study in pigs (Tewe and Maner 1981b), histopathological changes were observed in the thyroid glands of sows fed a cassava diet (30.3 mg/kg/day CN^-) with KCN added at 500 mg CN^- per kg of food through the first 110 days of gestation. No histopathological effects on the thyroid were observed in pigs fed diets containing an additional 250 mg CN^- per kg of food. Because only two pigs per dose group were examined, this study will not be used to determine a significant exposure level.

Dermal. Studies describing thyrotoxicity in humans or animals following dermal exposure to cyanides were not found in the available literature.

General discussion. Thiocyanate, a metabolite of cyanide, is goiterogenic in animals and humans (VanderLaan and Bissel 1946). In studies previously described, Kreutler et al. (1978) and Philbrick et al. (1979) orally administered cyanide and thiocyanate to rats and produced effects on the thyroid gland.

The mechanisms of cyanide-induced effects on the thyroid gland are discussed in several studies. VanderLaan and Bissell (1946) demonstrated that thiocyanate markedly inhibits the accumulation of iodine by the thyroid gland, thus decreasing the ability of the gland to maintain a concentration of iodine above that of the blood. In addition, thiocyanate may inhibit the iodination process, thus interfering with the organic binding of glandular iodine (Ermans et al. 1972).

A discussion of effects on the thyroid in animals exposed to thiocyanate in utero is presented in Sect. 4.3.3.

4.3.3.4 Other effects

Sodium cyanide dust is reported to be irritating to the eyes (NIOSH/OSHA 1981). Contact with tears may result in the liberation of HCN, which can be absorbed and produce systemic intoxication. Skin irritation may also occur from contact with cyanide dust, and exposure of skin to strong cyanide solutions can result in ulcerations that are slow to heal.

4.3.4 Developmental Toxicity

4.3.4.1 Inhalation

Human. Studies concerning developmental effects in humans following inhalation exposure to cyanides were not found in the available literature.

Animal. Willhite (1981) exposed pregnant hamsters (number unspecified), during the early primitive streak stage of gestation, to acetonitrile at 0, 1,800, 3,800, 5,000, or 8,000 ppm for 60 min. Concentration-related increases in maternal mortality, fetal resorptions, and fetal malformations were observed. The most common malformations observed were exencephaly, exencephalocoele, and fused and

bifurcated ribs. Cyanide and thiocyanate were found in tissues sampled 2.5 h after acetonitrile exposure. In addition, incubation of liver slices in vitro with acetonitrile resulted in the production of cyanide, leading the authors to state that the toxicity of acetonitrile was due to the metabolic liberation of cyanide.

4.3.4.2 Oral

Human. Epidemiological surveys in Zaire in areas where cassava is a staple food indicate that congenital hypothyroidism is present in 15% of newborns, an incidence ~500 times that observed in industrialized countries (Ermans 1980). High chronic thiocyanate levels, as a result of cassava consumption, and iodine deficiency probably contribute to this condition. Additional studies describing developmental effects in humans following oral exposure to cyanide were not found in the available literature.

Animal. In a study by Singh (1981), pregnant rats were fed milled cassava powder as 50 or 80% of their diets on gestation days 1 to 15. Control rats received commercial rat food. During the study, a dose-related decrease in maternal weight gain was observed. Fetuses were collected on gestation day 20. Rats fed cassava as 80% of the diet showed a high incidence of embryo-lethality (19%), and 28% of the fetuses were abnormal. Abnormalities included limb defects, open eyes, microcephaly, and retarded growth. At 50% cassava, the only effect noted was low fetal body weight. No resorptions or malformations were found in the control group. Paula and Rangel (1939) reported that cassava flour contains ~0.001 to 0.02% HCN. Singh (1981) points out that the role of cassava in the induction of congenital anomalies remains controversial, and the results of this study should be interpreted cautiously. Given this and the lack of specific cyanide dose information, no level of significant exposure was calculated.

In a study by Tewe and Maner (1981a), female Wistar rats were fed a basal cassava diet containing 12 mg/kg HCN or the basal diet with 500 ppm cyanide added (as 1.25 g KCN per kg diet). The rats were fed the diets from 20 days before mating through lactation. During gestation, feed intake of controls was limited to the level consumed by rats fed the diet containing additional cyanide. Fetuses were not examined for abnormalities. At weaning, two female pups from each litter were randomly allotted to the experimental diets for 28 days, whereas the remaining pups were examined for serum thiocyanate levels. Significant decreases in food consumption and growth rate were observed in weanlings fed KCN-enhanced diets during the 28-day postweaning period, regardless of previous cyanide exposure. Those weanlings exposed to higher levels of cyanide in utero and during the 28-day postweaning period had significantly reduced protein efficiency ratios. Serum thiocyanate was significantly increased in lactating rats and offspring during lactation and in the postweaning phase in rats fed KCN-enhanced diets. Kidney and liver rhodanese activities were not affected. If it is estimated that a rat consumes food the equivalent of 10% of its body weight per day (Lehman 1959), the "control" rats consumed ~1.2 mg/kg/day CN^- and rats fed diets with added KCN consumed ~51.2 mg/kg/day CN^-. The doses of cyanide from the KCN-enhanced diet will be considered a LOAEL for

developmental effects in rats. Because there were no untreated controls, it is not clear if the low dose was truly a NOAEL.

In a similar study, Tewe and Maner (1981b) fed groups of six pregnant Yorkshire pigs either a low-cyanide (30.3 mg/kg CN^- diet) cassava (control) diet or the cassava diet with added cyanide for total cyanide levels of either 276 or 520.7 mg/kg CN^-. Each pig was fed 3.72 kg of diet per day. The sows were fed these diets from the day after breeding until parturition. On gestation day 110, two sows per group were sacrificed; the fetuses were weighed and thiocyanate levels were determined. The treatment had no significant effect on either the number or the weight of 110-day-old fetuses. Serum thiocyanate levels were slightly increased in the sows and fetuses of the 520.7-mg/kg added cyanide group, with serum-bound iodine decreased during gestation in all groups. Histopathological examination of tissues of the sows showed proliferation of glomerular cells of the kidney in all groups and reduced activity of the thyroid gland in dams fed at 520.7 mg/kg. The remaining sows were fed their respective diets through parturition, at which time their diets were changed to corn and soybeans. After 21 days of lactation, the sows and piglets were bled for thiocyanate, protein, and protein-bond iodine determinations. The results showed significantly ($P < 0.05$) higher levels of serum thiocyanate in sows but not in piglets from sows fed diets containing 500 ppm added cyanide, in comparison with other groups. Protein and protein-bond iodine levels were not significantly different. The authors concluded that cyanide at a level of 520.7 mg/kg in the diet did not interfere with the production of the first litter of sows; however, metabolic and pathological differences did occur.

Willhite (1982) treated groups of at least five pregnant hamsters orally with D,L-amygdalin (the most common constituent of laetrile) at 200, 225, 250, or 275 mg/kg on the morning of gestation day 8. Additional groups were treated with an oral dose of D,L-amygdalin at 275 mg/kg (plus intraperitoneal treatment with sodium thiosulfate at 300 mg/kg), an oral dose of D-amygdalin at 300 mg/kg, or an intravenous dose of D,L-amygdalin at 275 mg/kg. Control hamsters were given oral or intravenous doses of saline. Signs of maternal toxicity were observed in dams dosed orally at 250 mg/kg and greater. Dams treated with sodium thiosulfate were protected from toxicity. The hamsters were sacrificed on gestation day 14 and the fetuses were collected. Examination of fetuses revealed a dose-related increase in abnormalities in hamsters treated orally with D- and D,L-amygdalin. The malformations most frequently observed were exencephaly, encephalocele, and rib anomalies. In the group treated with D,L-amygdalin and sodium thiosulfate, there were 2/123 fetuses with malformations compared with 32/68 malformed fetuses from dams receiving similar levels of D,L-amygdalin without thiosulfate treatment. Intravenous treatment with D,L-amygdalin resulted in no abnormal fetuses. From these results, the authors concluded that the teratogenic effects observed after oral amygdalin exposure were due to cyanide released by bacterial beta glucosidase in the gastrointestinal lumen. Levels of cyanide exposure could not be calculated from this study.

4.3.4.3 Dermal

Studies describing developmental effects in humans or animals following dermal exposure to cyanide were not found in the available literature.

4.3.4.4 General discussion

Parenteral studies also provide evidence that cyanide and cyanide-containing compounds can result in developmental effects. In a study by Doherty et al. (1983), groups of 3 to 20 pregnant hamsters were treated with a single intraperitoneal injection of succinonitrile (SN) at 0.78 to 6.24 mmol/kg, or with tetramethyl succinonitrile (TMSN) at 0.036 to 0.147 mmol/kg, on gestation day 8. Other groups of hamsters received 8.06 mmol/kg thiosulfate (cyanide antagonist) or 3.49 mmol/kg of trimethadione (an anticonvulsant) in addition to SN or TMSN treatment. On gestation day 11, the dams were sacrificed and the fetuses were examined. The results of the study showed that SN treatment was associated with exencephaly and encephalocoele and/or runting at a dose of 3.02 mmol/kg, with maternal toxicity (dyspnea, hypothermia, ataxia) observed in 20% of the dams at the teratogenic doses. Thiosulfate protected both fetuses and dams against SN teratogenicity and toxicity; trimethadione was ineffective. TMSN was not teratogenic; however, it produced maternal toxicity (clonic-tonic convulsions and death) in 37% of the dams treated with 0.147 mmol/kg. Thiosulfate did not protect against maternal toxicity as did trimethadione. Nonpregnant hamsters injected with SN showed dose-related levels of cyanide in their blood, whereas only trace amounts of cyanide were found in TMSN-treated hamsters. The authors concluded that SN effects are produced as a result of metabolically released cyanide, whereas TMSN toxicity is caused by the parent compound or by a metabolite not identified in this study.

In a second study, Doherty et al. (1982) administered sodium cyanide to groups of 5 to 7 pregnant hamsters via infusion from minipumps implanted subcutaneously at the back of the neck. The pumps were implanted under anesthesia (sodium pentobarbitol) on gestation day 6, and the dams were treated until gestation day 9 when the pumps were removed. Controls were treated in a similar manner, although they were dosed with distilled water. The hamsters were treated at NaCN infusion rates of 0.126, 0.1275, or 0.1295 mmol/kg/h. Two additional groups of hamsters were simultaneously infused with sodium thiosulfate. Mild maternal toxicity was observed in about half of the hamsters in the lower dose rate groups. At 0.1295 mmol/kg/h, signs of toxicity including dyspnea, incoordination, and hypothermia were observed in all dams. On gestation day 11, the dams were sacrificed and the fetuses were examined. Malformations were observed at all dose rates, with the incidence of resorptions increasing with the level of NaCN infusion. The predominant malformations observed were neural tube defects, including nonclosure, encephalocoele, and exencephaly. Hydropericardium, crooked tail, and small limbs were also noted. The simultaneous infusion of sodium thiosulfate protected the fetus and dam against the adverse effects of cyanide. The authors concluded that cyanide was teratogenic to the hamster over a narrow dose range. In a preliminary study, using three hamsters per group, no anomalies were found at an infusion rate of 0.125 mmol/kg/h, but 100% resorptions and some maternal deaths occurred

at 0.133 mmol/kg/h. The level of 0.126 mmol/kg/h NaCN, which corresponds to a dose of 78.6 mg/kg/day CN^-, was the lowest that produced an adverse effect. The authors cautioned that a dose-response relationship cannot be implied from this study; the variability in certified pump rates was larger than the percentage difference among doses, and the pumping rates could not be verified in vivo.

Thiocyanate administration during gestation has been reported to result in thyroid effects in the offspring. In a study by Kreutler et al. (1978), young rats developed goiter following thiocyanate exposure in utero and during the first 10 days of lactation. Piironen and Virtanen (1963) found that thiocyanate transfers to the milk of mammals. They noticed that the iodine content of the milk was consistently lower in thiocyanate-fed mothers. Apparently, thiocyanate ingestion inhibits iodine absorption by the mammary gland; this decrease in iodine may contribute to thyroid effects observed in the young.

4.3.5 Reproductive Toxicity

Data concerning reproductive effects in humans or animals following exposure to cyanides by all routes were not found in the available literature.

4.3.6 Genotoxicity

In vitro genotoxicity studies are summarized in Table 4.6. Cyanides have tested negative for mutagenicity and effects on DNA synthesis except for a study by Kushi et al. (1983), in which a marginally mutagenic response for HCN in *S. typhimurium* strain TA100 was reported.

No in vivo genotoxicity studies were found in the available literature.

4.3.7 Carcinogenicity

There is no evidence to suggest that cyanide produces carcinogenic effects in humans or animals.

4.4 INTERACTIONS WITH OTHER CHEMICALS

4.4.1 Synergistic/Additive Interactions

A number of compounds have been found to act in synergy with cyanide to produce toxic effects. In an in vitro study by Gray et al. (1986), the addition of sodium cyanide and tributyltin to human erythrocyte suspensions resulted in a synergistic increase in tributyltin-induced hemolysis. The investigators believed that tributyltin aggregates transport cyanide anions across erythrocyte cell membranes. The cyanide anions then increase lysis through enzyme inhibition or the cross-linking of protein sulfhydryl groups.

Synergism has also been observed between cyanide and ascorbic acid. Basu (1983) found that guinea pigs exhibited increased toxic effects when treated with ascorbic acid prior to the oral administration of KCN. When guinea pigs were treated with KCN only, 38% exhibited slight tremors, whereas 100% of those treated with both compounds exhibited severe tremors, ataxia, muscle twitches, paralysis, and convulsions.

Table 4.6. Genotoxicity of cyanides

End point	In vitro species (test system)	Results: Without activation	Results: With activation	References
Gene mutation	*Salmonella typhimurium* TA1535	–	–	DeFlora 1981
	S. typhimurium TA1537	–	–	DeFlora 1981
	S. typhimurium TA1538	–	–	DeFlora 1981
	S. typhimurium TA97	–	–	DeFlora et al. 1984
	S. typhimurium TA98	–	–	DeFlora 1981
	S. typhimurium TA100	–	–	DeFlora 1981
	S. typhimurium TA102	–	–	DeFlora et al. 1984
	S. typhimurium TA100	+	–	Kushi et al. 1983
	S. typhimurium DW379	–	–	Owais et al. 1985
DNA damage	*Escherichia coli* WP67, CM871, WP2	–	–	DeFlora et al. 1984
Chromosome aberration	Chinese hamster cells	–	–	Sofuni et al. 1985

+ = Positive results; – = negative results.

This synergistic effect appears to result from the ability of ascorbic acid to compete with cyanide for cystine, thus diminishing the detoxication of cyanide (Basu 1983).

Compounds such as sulfide or azide, which share cyanide's ability to inhibit cytochrome oxidase, are also potential synergists with cyanide (Smith and Gosselin 1979, Smith et al. 1977).

The possible interaction of HCN with other toxicants in fire environments has been discussed by Birky and Clarke (1981), who reported that when high blood cyanide levels were found in fire victims, the carboxyhemoglobin levels were also high. Thus, it is difficult to assess the significance of HCN toxicity. The authors suggested that sublethal concentrations of HCN may interact with other toxicants and cause death. They also speculated that cyanide could lead to incapacitation, preventing escape, so that the victim could be exposed to high levels of carbon monoxide.

Levin et al. (1987) examined the effects of exposure to a variety of combinations of gases and low oxygen levels that could be produced by fires. Thirty-minute studies on the lethal effects of carbon monoxide and HCN indicated that they act in additive fashion. Exposure to 5% carbon dioxide reduced the 30-min LC_{50} value (including postexposure deaths) in rats from 110 to 75 ppm.

4.4.2 Antagonistic Interactions

The antagonists of cyanide have been intensively studied and reviewed in detail by Way (1984). Cyanide antagonists are used in the treatment of cyanide intoxication.

Cyanide antagonists can be classified into two general groups: those that act as sulfur donors for rhodanese-catalyzed cyanide detoxification and those that induce the chemical binding of cyanide. Sulfur donors include sodium thiosulfate, polythionates, and thiosulfates.

Antagonists that induce the chemical binding of cyanide include sodium nitrite, amyl nitrite, hydroxylamine, and methylene blue. These compounds generate methemoglobin, which competes with cytochrome oxidase for cyanide-forming cyanomethemoglobin (Way 1984). Cobalt-containing compounds may also function as binders by forming a stable complex with cyanide (Way 1984). Isom and Way (1974) reported the dramatic antagonism of the lethal effects of KCN when cobaltous chloride was administered to mice along with sodium thiosulfate. The authors suggested that this synergistic antidotal effect of cobaltous chloride may be associated with the physiological disposition of the cobaltous ion and its ability to chelate both thiocyanate and cyanide ions.

O'Flaherty and Thomas (1982) found that pretreatment of rats with chlorpromazine (10 mg/kg intramuscularly) and sodium thiosulfate (1,000 mg/kg intraperitoneally) greatly decreased or abolished the increase in plasma creatine kinase observed in rats exposed to HCN at 200 ppm for 12.5 min. In an in vitro study, Robinson et al. (1985a) found that chlorpromazine and 4,4'-diisothiocyano-2,2'-stilbene disulfonic acid reduced cyanide-induced contractions in vascular smooth muscle. It was

suggested that the compounds may block ionic channels that would otherwise facilitate the entry of cyanide into the muscle cells.

Several papers discuss the antagonism of cyanide intoxication by oxygen alone or with other compounds. Sheey and Way (1968) reported that oxygen alone results in minimal antagonism in mice injected with KCN and only slightly enhances the antagonistic effects of sodium nitrite. The antidotal effect of sodium thiosulfate alone or in combination with sodium nitrite, however, was strongly enhanced by oxygen.

Isom et al. (1982) found that oxygen-treated mice did not show behavioral signs of cyanide intoxication below doses of 6 mg/kg KCN, whereas air-treated animals showed effects such as gasping, irregular breathing, and convulsions at levels as low as 3 mg/kg KCN. When mice were pretreated with sodium nitrite and sodium thiosulfate, and either air or oxygen, the dose of KCN needed to cause a 59% inhibition of brain cytochrome oxidase was more than doubled in mice in an oxygen atmosphere, with all points on the oxygen curve significantly different from the air-treatment curve.

Isom and Way (1974) reported a "striking enhancement" of the oxidation of glucose to CO_2 when oxygen, sodium nitrite, and sodium thiosulfate were given to mice dosed at 45 mg/kg KCN; no enhancement was noticed at 10 or 15 mg/kg KCN. The authors did not attribute the synergistic effect of oxygen on the antidotal combination of sodium nitrite and sodium thiosulfate to enhanced cyanide detoxication.

Purser et al. (1984) compared in monkeys the toxicity of pure HCN gas with the complex, HCN-containing atmospheres generated by pyrolyzing polyacrylonitrile (PAN). It was found that for a given chamber HCN concentration, the smoke atmospheres generated from pyrolyzed PAN, which also contained other nitriles as well as carbon monoxide (CO), were less toxic than HCN gas alone, both in time to incapacitation and the severity of clinical signs. This discovery was surprising since it was expected that the presence of organic nitriles such as acetonitrile, benzonitrile, and unreacted acrylonitrile, although less toxic than HCN on a molar basis, would produce an additive effect. In addition, the presence of relatively high concentrations of CO in the PAN atmospheres should also have increased the toxicity. The investigators suggested, without any supporting experimental evidence, that some form of metabolic competition between the less toxic organic nitriles and HCN prevented HCN from exerting its full effect. From these studies, the authors suggested that when death occurs in humans following fires, the initial rapid incapacitation may be caused by cyanide, whereas the actual cause of death may be sometime later due to CO poisoning.

5. MANUFACTURE, IMPORT, USE, AND DISPOSAL

5.1 OVERVIEW

Hydrogen cyanide is produced at 14 locations in the United States, and there are numerous suppliers of cyanide salts. The demand for hydrogen cyanide in the United States during 1987 is projected to be 1.03 billion lb. This compound is produced primarily as a by-product during the production of acrylonitrile. The major uses of hydrogen cyanide are as an intermediate in the production of adiponitrile (for nylon 6/6), methyl methacrylate, cyanuric acid, chelating agents, sodium cyanide, methionine, and nitriloacetic acid. The two most important uses for cyanide salts are in electroplating and in metal treatment.

5.2 PRODUCTION

The demand for hydrogen cyanide in the United States during 1986 was 1.01 billion lb, and the demand for 1987 is projected to be 1.03 billion lb (CMR 1987). Manufacturers and production sites are as follows (CMR 1987): Ciba-Geigy (St. Gabriel, Louisiana, and Glens Falls, New York), Cyanamid (Fortier, Louisiana), Degussa/Du Pont (Theodore, Alabama), Dow (Freeport, Texas), Du Pont (Memphis, Tennessee; Orange, Texas; Theodore, Alabama; and Victoria, Texas), Monsanto (Chocolate Bayou, Texas), Rohm and Haas (Deer Park, Texas), Standard Oil (Green Lake, Texas, and Lima, Ohio), and Sterling (Texas City, Texas). The combined annual capacity of these plants is 1.358 billion lb (CMR 1987). In addition to these companies, there are numerous suppliers of cyanide salts (American Chemical Society 1986, OPD Chemical Buyers Directory 1987, Chemical Week Buyers' Guide 1986).

There are two common methods of manufacturing hydrogen cyanide: (1) formation as a by-product during the synthesis of acrylonitrile from the reaction of propylene and ammonia with air and (2) direct synthesis by the reaction of methane and ammonia with air over platinum metals as catalysts (Jenks 1979, 1985; CMR 1987). The manufacture of acrylonitrile accounts for ~81% of the hydrogen cyanide produced; direct synthesis accounts for the remaining 19% (CMR 1987).

5.3 IMPORT

Approximately 410,000 lb of potassium cyanide was imported during 1984 and ~15.4 million lb of sodium cyanide was imported during 1982 through principal U.S. customs districts (HSDB 1987). More complete data on the import of hydrogen cyanide and cyanide salts into the United States were not available.

5.4 USES

The use pattern for hydrogen cyanide is as follows (CMR 1987): adiponitrile (for nylon 6/6), 40%; methyl methacrylate, 30%; cyanuric acid, 10%; chelating agents, 7%; sodium cyanide, 7%; miscellaneous, including methionine and nitriloacetic acid, 6%. Miscellaneous applications also include the use of hydrogen cyanide as an insecticide and rodenticide for fumigating enclosed spaces (e.g., stored grain areas) and its use in the manufacture of ferrocyanides, acrylates, lactic acid, pharmaceuticals, and specialty chemicals (Worthing 1987, Jenks 1979). Cyanide salts have a variety of uses. The two most important applications are in electroplating and metal treatment (Towill et al. 1978). Minor applications include use in analytical chemistry as radioactive tracers, as insecticides and rodenticides, and in the manufacture of dyes and pigments (Sax and Lewis 1987, O'Brien 1982, Worthing 1987).

5.5 DISPOSAL

Alkaline chlorination with Cl_2 plus NaOH or hypochlorite is by far the most widely used commercial method for treating cyanides. This method results in the conversion of the cyanide solution to the less toxic cyanate. Some other possible treatment techniques available include large-scale outdoor burning following special precautions; ozonation; decontamination by treatment with caustic followed by addition to ferrous sulfate solution (nontoxic ferrocyanide forms); peroxidation to cyanate; electrolysis to CO_2, NH_3, and cyanate; and biological decomposition to CO_2 and N_2. It can be seen from these examples that typical treatments involve the decomposition of cyanides to less toxic compounds by physical or chemical processes. After using an appropriate treatment method, cyanide wastes may be disposed of in a secured sanitary landfill (U.S. Department of Health and Human Services/U.S. Department of Labor 1978).

6. ENVIRONMENTAL FATE

6.1 OVERVIEW

The major sources of cyanide releases to water are reported to be discharges from metal finishing industries, iron and steel mills, and organic chemical industries. Effluents from the cyanidation process used in precious metal extraction contain high amounts of cyanide. The major source of the cyanide released to air is vehicle exhaust, and the major sources of cyanide releases to soil appear to be disposal of cyanide wastes in landfills and the use of cyanide-containing road salts. Cyanide released to air is expected to exist almost entirely as hydrogen cyanide gas. This compound has the potential to be transported over long distances before reacting with photochemically generated hydroxyl radicals. The residence time of HCN in the troposphere has been estimated to be 1.4 to 4.3 years. Neither photolysis nor deposition by rainwater is expected to be an important removal mechanism. Only 2% of tropospheric HCN is expected to be transported to the stratosphere. In water, cyanide occurs most commonly in the form of hydrogen cyanide. Hydrogen cyanide is expected to be removed from water primarily by volatilization. At low concentrations, some hydrogen cyanide may also be removed by aerobic or anaerobic biodegradation. At soil surfaces with pH <9.2, volatilization of hydrogen cyanide is expected to be an important loss mechanism for cyanides. In subsurface soil, cyanide present at low concentrations would probably biodegrade. In cases where levels of cyanide are toxic to microorganisms (i.e., landfills, spills), hydrogen cyanide may leach into groundwater.

6.2 RELEASES TO THE ENVIRONMENT

There are numerous sources from which cyanide is released to the environment. The major point sources of cyanide releases to water are discharges from publicly owned treatment works (POTWs), iron and steel production, and the organic chemicals industries (Fiksel et al. 1981, Rohmann et al. 1985, Ohio River Valley Water Sanitation Committee 1982). Estimates based on data from the mid-to-late 1970s indicate that these sources account for ~89% of the estimated 31 million lb of cyanide discharged annually to surface waters. Since metal finishing and organic chemicals industries are estimated to account for 90% of the influent to POTWs, they are the dominant sources of both direct and indirect aqueous discharge (Fiksel et al. 1981). Another important source of direct release to surface waters is the nonpoint runoff from the use of cyanide as an anti-caking agent in road salts (Fiksel et al. 1981, Cole et al. 1984). The effluents from the cyanidation process used in the extraction of precious metals from their ores may contain high levels of cyanide (Huiatt 1985, Scott 1985). The total cyanide content of typical tailing

pond effluents from gold mill tailings ponds may range from 0.3 to 61 mg/L (Scott 1985).

Cyanide emissions to air have been conservatively estimated to be 44 million lb/year based on data from the mid-to-late 1970s. Over 90% of these emissions are attributed to releases in automobile exhaust (Fiksel et al. 1981). Other sources of release may be emissions from chemical processing industries, steel and iron industries, metallurgical industries, metal-plating and finishing industries, and petroleum refineries; emissions from municipal solid waste incinerators; the combustion of polyurethane, acrylonitriles, polyamides, silk, wool, and paper during fires; cigarette smoke; volatilization from cyanide waste disposed of in landfills; and direct release to the atmosphere during fumigation (Fiksel et al. 1981, Towill et al. 1978, Carotti and Kaiser 1972, Bourbon et al. 1979, Sklarew and Hayes 1984).

The largest sources of cyanide releases to soil are probably from the disposal of cyanide wastes in landfills and the use of cyanide-containing road salts.

6.3 ENVIRONMENTAL FATE

6.3.1 Air

Most cyanide in the atmosphere is expected to exist almost entirely as hydrogen cyanide gas, although small amounts of metal cyanides may be present as particulate matter in air (EPA 1984). The reaction of hydrogen cyanide with photochemically generated hydroxyl radicals proceeds fairly slowly. Based on a reaction rate constant of 3×10^{-14} $cm^3/(molecule\text{-}s)$ at 25°C, and assuming an ambient hydroxyl radical concentration of 8×10^5 $molecules/cm^3$, the half-life for the reaction of hydrogen cyanide vapor with hydroxyl radicals in the atmosphere has been calculated to be ~334 days (Fritz et al. 1982). The fate of HCN in air was studied by Cicerone and Zellner (1983), who showed that the rate of hydroxyl radical reaction with HCN in air is dependent on the altitude and that the reaction is slightly faster at lower altitudes. The estimated residence time of HCN in air due to hydroxyl radical reaction varies between 1.4 and 4.3 years. Cicerone and Zellner (1983) estimated that the atmospheric residence time for HCN due to reaction with singlet oxygen (O 1D) is 634 years. Therefore, this reaction is not important in the troposphere. It was also reported that the removal of tropospheric HCN by photolysis and washout by rainwater are not important and that only 2% of tropospheric HCN is transferred to the stratosphere. The relatively slow rate of degradation of hydrogen cyanide suggests that this compound has the potential to be transported over long distances before being removed by physical or chemical processes. Metal cyanide particles are expected to be removed from air by both wet and dry deposition.

6.3.2 Water

Cyanide occurs most commonly in the form of hydrogen cyanide in water, although it can also occur as the cyanide ion, alkali metal cyanides (i.e. KCN, NaCN), relatively stable metallocyanide complexes (i.e., $[Fe(CN)_6]^{-3}$), moderately stable metallocyanide complexes

(i.e., copper cyanide), or easily decomposable metallocyanide complexes [i.e., $Zn(CN)_2$]. The environmental fate of these cyanide compounds can vary widely (Callahan et al. 1979).

The alkali metal salts are very soluble in water, and as a result, they readily dissociate into their respective anions and cations upon release to water. The resulting cyanide ion may then form hydrogen cyanide or react with various metals present in natural water. If the cyanide ion is present in excess, complex metallocyanides may form; however, if metals are prevalent, simple metal cyanides may form. In clear water or at water surfaces, some metallocyanides, such as ferrocyanides and ferricyanides, may decompose to the cyanide ion by photodissociation and subsequently form hydrogen cyanide. Unlike easily decomposed water-soluble metal cyanides, insoluble metal cyanides are not expected to degrade to hydrogen cyanide. Rather, the insoluble cyanide compounds are expected to adsorb to sediment, possibly bioaccumulate in aquatic organisms, or biodegrade (Callahan et al. 1979, Towill et al. 1978).

Volatilization is expected to be an important (if not dominant) fate process for hydrogen cyanide. At pH <9.2, most of the free cyanide should exist as hydrogen cyanide, a volatile form of cyanide. Wide variations in the rate of volatilization are expected since this process is affected by a number of parameters including temperature, pH, wind speed, and cyanide concentration (Callahan et al. 1979). Because of the lack of data on this topic, the half-life for this process could not be determined. Biodegradation is also expected to be an important fate process in natural water systems. A number of microorganisms have been shown to degrade low concentrations of cyanide under both aerobic and anaerobic conditions (Towill et al. 1978, Callahan et al. 1979). Acclimation appears to increase tolerance to this compound (Raef et al. 1977). Hydrogen cyanide is not expected to undergo direct photolysis, to chemically hydrolyze, to adsorb significantly to suspended solids and sediments, or to bioaccumulate significantly in aquatic organisms (Callahan et al. 1979).

6.3.3 Soil

By analogy to the fate of cyanides in water, it is predicted that the fate in soil would be pH dependent. Cyanide may occur in the form of hydrogen cyanide, alkali metal salts, or immobile metallocyanide complexes. At soil surfaces with pH <9.2, it is expected that volatilization of hydrogen cyanide would be an important loss mechanism for cyanides. In subsurface soil, cyanide present at low concentrations would probably biodegrade. In soil with pH <9.2, hydrogen cyanide is expected to be highly mobile, and in cases where cyanide levels are toxic to microorganisms (i.e., landfills, spills), this compound may leach into groundwater (EPA 1984).

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7. POTENTIAL FOR HUMAN EXPOSURE

7.1 OVERVIEW

Anthropogenic sources are responsible for much of the cyanide found in the environment. According to the VIEW Data Base (1989), cyanide has been found at 134 evaluated sites on the National Priorities List of 1,177 hazardous waste sites in the Unites States. Cyanide also occurs naturally in fruits, roots, and leaves of numerous plants. Cyanides may also be present in the liver and excreta of some animals (Howe 1985). A few examples of natural cyanides are given in Sect. 7.2.4.

Despite the variety of sources from which cyanide may be released to the environment, there are limited monitoring data available. It appears that the general population may be exposed to cyanide by inhalation of contaminated air, ingestion of contaminated drinking water, and/or consumption of many foods; however, because of the lack of data, the average daily intake of this compound could not be estimated.

A 1981-1983 NIOSH survey estimated that a combined total of 143,720 workers are potentially exposed to the cyanide ion, hydrogen cyanide, sodium cyanide, potassium cyanide, cyanogen chloride, zinc cyanide, copper cyanide, silver cyanide, and potassium silver cyanide in the United States (NIOSH 1985). Workers in a wide variety of occupations may be exposed to cyanides, including workers involved in electroplating, metallurgy, pesticide application, firefighting, steel manufacturing, gas works operations, and metal cleaning (Fiksel et al. 1981). Exposure is expected to occur primarily through inhalation and less frequently by absorption through the skin.

7.2 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

7.2.1 Air

Monitoring data for cyanide in air were not located in the available literature.

7.2.2 Water

Cyanide has been detected in surface waters throughout the United States, in groundwater below landfills and disposal sites, and in drinking water, sediments, and urban runoff (Ohio River Valley Water Sanitation Committee 1982, Myers 1983, Great Lakes Water Quality Board 1983, Towill et al. 1978, Cole et al. 1984, Bedding et al. 1982, Fiksel et al. 1981, Schuckrow et al. 1982); however, monitoring data for cyanide within each segment of the media are quite limited. This may be because of the short lifetime of cyanide in the environment. It appears that many discharges or pulse inputs to water supplies may not be

detected by the periodic sampling methods commonly used for monitoring surface or drinking waters (Fiksel et al. 1981).

Based on data obtained from the EPA STORET Data Base, it appears that the cyanide concentration in most of the surface waters tested over time in the United States does not exceed 3.5 μg/L (Fiksel et al. 1981); however, 37 out of 50 states (74%) have locales where cyanide concentrations in ambient water are <3.5 μg/L, which is the lowest criterion recommended to protect freshwater aquatic life as a 24-h average (Fiksel et al. 1981). Data from the Nationwide Urban Runoff Program (as of 1982) indicate that cyanide was found in 16% of the urban runoff samples collected in 19 cities across the United States. In positive samples, the concentration of cyanide ranged from 2 to 33 μg/L (Cole et al. 1984).

A 10-city survey done as part of the 1974 EPA National Organics Reconnaissance Survey (NORS) revealed that cyanogen chloride occurred in 8 out of the 10 drinking water supplies analyzed (Bedding et al. 1982). In another EPA survey, a study of drinking water supplies serving interstate carriers revealed that 21 of 297 samples contained cyanide at a concentration >10 μg/L (Towill et al. 1978). Because of the limited amount of monitoring data, the average daily intake of cyanide through drinking water could not be estimated.

7.2.3 Soil

Monitoring data for cyanide in soil were not found in the available literature.

7.2.4 Other

The primary source of cyanide in food is glycogenic glycosides. Plants containing these natural compounds can produce hydrogen cyanide by acid hydrolysis or by the action of the enzyme glucosidases (EPA 1980, Fiksel et al. 1981). As many as 1,000 plants, including edible items such as almonds, pits from stone fruits (i.e., apricots, peaches, plums, apples, cherries), sorghum, cassava, soybeans, spinach, lima beans, sweet potatoes, maize, millet, sugarcane, and bamboo shoots have the capability of producing hydrogen cyanide (Honig et al. 1983, Fiksel et al. 1981, Lasch and El Shawa 1981). Levels of cyanide monitored in some of these foods are as follows: cereal grains and their products, 0.001 to 0.45 μg/g; soy protein products, 0.07 to 0.3 μg/g; cassava, 1 mg/g; lima beans, 3 mg/g (Honig et al. 1983). The analysis of 233 samples of commercially available and homemade stone-fruit juices showed that pitted-fruit juices contained much less cyanide than nonpitted or partially pitted fruit juices (Stadelmann 1976). This indicates that the pits are the primary sources of cyanides in these juices. For example, the HCN content of a homemade mixed cherry juice from pitted fruits was 5.3 mg/L, compared to a value of 23.5 mg/L in a cherry juice containing 100% crushed pits. This study also reported the following levels (median concentrations in mg/L) of HCN in commercial fruit juices: cherry, 4.6; apricot, 2.2; prune, 1.9; and peach, 2.9. From a toxicological consideration, the author recommended that the HCN content allowed in fruit juices should be set at 5 mg/L. Cyanide can also occur in foodstuffs in the form of residues present from cyanide fumigation

(Way 1984). Sufficient data are not available to estimate the average daily intake of cyanide. It has been speculated that human exposure in the United States to naturally occurring cyanide in foods would generally be low (Fiksel et al. 1981).

Laetrile (a drug used in the treatment of cancer), sodium nitroprusside (a drug used to reduce high blood pressure), and impure phencyclidine (PCP) (an illicit drug), all of which release cyanide on metabolism, have been associated with human exposure (Khandekar and Edelman 1979, Aitken et al. 1977, Soine et al. 1979).

Cyanide levels in mainstream (inhaled) smoke from U.S. commercial cigarettes vary from 10 to 400 μg per cigarette; levels in sidestream smoke vary between 0.6 and 27% of those in mainstream smoke (Fiksel et al. 1981). Based on these data, it appears that 25 to 30% of the population in the United States is exposed to between 250 and >10,000 μg cyanide per day from smoking cigarettes.

Cyanides have been detected in automobile exhaust. The average rate of emission was reported to be 11 to 14 mg per mile for cars not equipped with catalytic converters and on the order of 1 mg per mile for cars with catalytic converters operating under optimum conditions. Cars with malfunctioning catalytic converters may emit as much (or more) hydrogen cyanide as cars without such equipment (Fiksel et al. 1981).

7.3 OCCUPATIONAL EXPOSURES

A National Occupational Exposure Survey (NOES) conducted by NIOSH between 1981 and 1983 estimated that the number of workers potentially exposed to cyanide compounds in the United States is as follows (NIOSH 1985): cyanide ion, 367; hydrogen cyanide, 3,769; sodium cyanide, 49,243; potassium cyanide, 43,780; cyanogen chloride, 2,275; zinc cyanide, 14,570; copper cyanide, 15,929; silver cyanide, 13,064; and potassium silver cyanide, 793. These numbers do not include exposure to trade name compounds that contain cyanides. Workers in a wide variety of occupations may be exposed to cyanides, for example, workers involved in electroplating, metallurgy, pesticide application, firefighting, steel manufacturing, gas works operations, and oil shale retort processing; in the manufacture of cyanides, adiponitrile, methyl methacrylate, cyanuric acid, dyes, pharmaceuticals, or chelating agents; and in tanneries, blacksmithing, metal cleaning, photoengraving, or photography (Fiksel et al. 1981, CMR 1987). In a survey of the plating facility of a national airline conducted by NIOSH in December 1981, the concentrations of HCN in three work areas were found to range from 0.001 to 0.002 mg/m^3 (NIOSH 1987).

Exposure is expected to occur primarily through inhalation and less frequently by absorption through the skin.

7.4 POPULATIONS AT HIGH RISK

Persons with a metabolic disturbance in the conversion of cyanide to thiocyanate may be at greater risk. A defect in the rhodanese system and vitamin B_{12} deficiency have been associated with tobacco amblyopia and Leber's hereditary optic atrophy in persons exposed to cyanide in tobacco smoke (Wilson 1983).

A number of dietary deficiencies may increase the risk of cyanide exposure. Iodine deficiency, along with excess exposure to cyanide, may be involved in the etiology of such thyroid disorders as goiter and cretinism (Delange and Ermans 1971, Ermans et al. 1972). Protein deficiencies and vitamin B_{12} and riboflavin deficiencies may subject people in the tropics who eat cassava to increased risks of tropical neuropathies (Osuntokun 1972 Osuntokun et al. 1969, Makene and Wilson 1972). Studies that have uncovered more severe effects in nutritionally deprived animals (Philbrick et al. 1979, Kreutler et al. 1978, Rutkowski et al. 1985) provide support to the observations in humans.

In areas where cassava is a staple food, congenital hypothyroidism is present in 15% of newborns (Ermans 1980), indicating that fetuses may be at a higher risk. Animal studies provide further evidence that fetuses may be at a higher risk than the general population. Teratogenic effects have been observed in rodents following inhalation, oral, and parenteral exposure to cyanide-containing compounds (Willhite 1981, 1982; Singh 1981; Doherty et al. 1982, 1983).

An additional group of people who may be at greater risk are those who are exposed to cyanide but are unable to smell the chemical (EPA 1987a).

8. ANALYTICAL METHODS

8.1 ENVIRONMENTAL MEDIA

The long history of cyanide poisoning has led to a substantial number of reports in the literature dealing with the identification and quantification of cyanide in air, water, and other environmental media. One of the most significant problems in cyanide monitoring is the instability of the collected samples (Cassinelli 1986). The sample handling and preservation methods have been discussed by several investigators (Egekeze and Oehme 1979; EPA 1982a, 1983a; Cassinelli 1986). Inorganic cyanides in water can be present both as complexed and as free cyanide. Cyanide in water is usually determined in three different forms: free cyanide, cyanide amenable to chlorination, and total cyanide. Free cyanides such as NaCN, KCN, and HCN are readily ionized to the cyanide ion under the conditions used in most common analytical techniques. Methods for determining cyanide amenable to chlorination measure simple metal cyanides and most complex cyanides with the exception of iron cyanides. Total cyanide is a measure of all cyanides including iron cyanide complexes.

Table 8.1 lists the analytical methods for determining cyanides that may be present in three different forms. EPA Method 335.2 is required by the EPA Contract Laboratory Program (EPA 1987c) for the analysis of total cyanide in water, soil, and sediment. Cyanide determination in air, as given in Table 8.1, is usually performed by distinguishing between two forms of cyanides (i.e., hydrogen cyanide gas and particulate cyanides). Mixed cellulose ester membrane filters are usually used to collect particulate cyanides, and the HCN gas that passes through the membrane is trapped in NaOH for HCN determination. The collected particulate cyanides can be quantified separately after acid distillation. Many particle cyanides, however, decompose in moist air with the liberation of HCN, thereby giving erroneously higher values for HCN by this method. The decomposition of particle cyanide is dependent on the relative humidity of air, the particle size, and the total surface area of the collected particles (Cassinelli 1986). Almost all the methods available for determining cyanide in water can be applied to the analysis of cyanides in air, because most quantification methods for air samples ultimately involve the determination of the cyanide ion in solution. The three commonly used methods (colorimetric, titrimetric, and electrochemical) may all suffer from interference problems unless proper precautions are taken. Methods using specific ion electrodes (electrochemical) respond to numerous interferences (S, Cl, I, Br, Cd, Ag, Zn, Cu, Ni, and Hg) (Cassinelli 1986). Sulfide, certain oxidizing agents, nitrate or nitrite, thiocyanate, aldehydes, and ketones may interfere under acid distillation conditions, thus producing erroneous results from both colorimetric and titrimetric methods. In

Table 8.1. Analytical methods for the determination of cyanide

Sample matrix	Sample preparation	Quantification method	Detection limit	Accuracy/ % recovery	References
Occupational air	Filtered air passed through midget impinger containing NaOH. Sulfide interference removed by addition of H_2O_2	Specific ion electrode (HCN only)	0.01 ppm (for 200 L of air)	NR[a]	NIOSH 1976, 1978
Aerosol and gas	Pass aerosol or gas through cellulose ester membrane filter and NaOH bubbler, extract filter with KOH, and range bubbler with KOH	Specific ion electrode (HCN and salts)	2.5 μg CN^-	Not significant at 3–21 mg/m^3	NIOSH 1984
Air	Cellulose-ester-membrane-filtered air passed through midget impinger containing $Cd(NO_3)/_2/$ Na_2CO_3/NaH_2BO_3/ethylenediamine	Ion-chromatography/amperometric detection (HCN only)	0.04 ppm (for 2.6 L of air)	91%	Cassinelli 1986
Air	Cellulose-ester-membrane-filtered air passed through midget impinger containing NaOH. Solution heated at 110°C to convert NaCN to sodium formate	Ion-chromatography/amperometric detector	NR	100–109% at 5–20 ppm	Dolzine et al. 1982
Water (drinking, surface, saline, and domestic and industrial waste)/ soil-sediment	Sample acidified and reflux-distilled; released HCN absorbed in NaOH scrubber. Absorbing solution treated with chloramine-T and pyridine-pyrazolone or pyridine-barbituric acid	Spectrophotometric (EPA CLP Method 335.2) (total cyanide)	0.02 ppm	85–102% at 0.28–0.62 ppm	EPA 1983a, 1987c
Water (drinking, surface, saline, domestic and industrial waste)	Sample chlorinated with calcium hypochlorite at pH 11–12 and ClCN driven off. Residual sample acidified and reflux-distilled; released HCN absorbed in NaOH. Absorbing solution treated with chloramine-T and pyridine-pyrazolone or pyridine-barbituric acid	Spectrophotometric (EPA Method 9010 and Method 335.1) (cyanide amenable to chlorination)	NR	NR	EPA 1982a, 1983a
Water (drinking, surface, saline, domestic and industrial waste)/ soil-sediment	Sample acidified and reflux-distilled; released HCN absorbed in NaOH. Absorbing solution titrated with $AgNO_3$ in presence of *p*-dimethylamino-benzal-rhodanine indicator.	Titrimetric (EPA CLP Method 335.2) (total cyanide)	1 ppm	NR	EPA 1983a, 1987c

Table 8.1 (continued)

Sample matrix	Sample preparation	Quantification method	Detection limit	Accuracy/ % recovery	References
Water	None	Ion-chromatography/amperometric detector (free and a few complexed cyanides)	2 ppb	100–112%	Rocklin and Johnson 1983
Waste or leachate	Sample acidified and reflux-distilled; released HCN absorbed in NaOH. Absorbing solution titrated with $AgNO_3$ in presence of *p*-dimethylaminobenzal-rhodanine indicator	Titrimetric (EPA Method 9010) (total cyanide)	NR	NR	EPA 1982a
Food (cereal and other foodstuffs)	Extract with water/acetonitrile. Dry extract	GC/ECD at low detection voltage (free cyanide)	~0.1 ppm	90%	Heuser and Scudmore 1969
Food (soybean and soybean products)	Sample mixed with water, lead nitrate, tartaric acid, and antifoaming agent. Mixture acidified with H_2SO_4 and distilled. Distillate complexed with pyridine-barbituric acid	Spectrophotometric (total cyanide)	NR	32–80%	Honig et al. 1983
Plasma	De-proteinized by adding trichloroacetic acid. Supernatant brominated and treated with pyridine-*p*-phenylenediamine	Spectrophotometric (thiocyanate-cyanide determination)	~0.07 ppm	96% at 0.14 ppm	Pettigrew and Fell 1972
Urine	Diluted sample brominated with Br_2 and treated with pyridine *p*-phenylendiamine	Spectrophotometric (thiocyanate-cyanide determination)	~0.07 ppm	88% at 0.6 ppm	Pettigrew and Fell 1972
Blood	Acidified (pH 5.2) sample in a Conway microdiffusion cell is absorbed in NaOH. NaOH solution treated with chloramine T-phosphate and pyridine-pyrazolone reagent	Spectrophotometric (total cyanide)	0.1 ppm	NR	Morgan and Way 1980, Way 1984
Blood	Acidified (buffered at pH 5.2) sample in a Conway microdiffusion cell is absorbed in NaOH. NaOH solution buffered at pH 7.5 mixed with pyridoxal-HCl. Solution heated to 50°C or mixed with *p*-benzoquinone in dimethyl sulfoxide	Spectrophotofluorometric (total cyanide)	0.025 ppm	NR	Ganjeloo et al. 1980, Morgan and Way 1980, Way 1984
Biological fluids	Acidified (buffered at pH 5.2) sample in a Conway microdiffusion cell is absorbed in NaOH	Specific ion electrode (total cyanide)	0.03 ppm	NR	Way 1984
Blood and liver	Homogenized sample acid digested at 90°C. Released HCN swept by air is passed through a lead acetate and a NaOH absorption tube	Specific ion electrode (total cyanide)	NR	100–109% at 0.3–130 ppb	Egekeze and Oehme 1979

[a]NR = Not reported.

addition, fatty acids in samples may distill over and form soaps under alkaline titration conditions, thus causing interference in the titrimetric method (EPA 1982a, 1983a). Of the commonly used methods, the colorimetric method and the electrochemical (specific ion electrode) method have satisfactory sensitivity for cyanide determination. The more recently developed ion-chromatographic/amperometric determination may have higher sensitivity. A collaborative study conducted by Britton et al. (1984) to determine the most reliable method among the three most commonly used methods (two colorimetric methods and the electrode method) showed that both pyridine-barbituric acid and pyridine-pyrazolone have similar statistical accuracy. The pyridine-barbituric acid method was preferred by Britton et al. (1984) over the pyridine-pyrazolone method for its convenience (quicker analysis time) rather than the statistical accuracy of data. The electrode method was reported to have higher data variability.

Several less commonly used methods are available for the quantification of cyanides. One of these methods uses chloramine-T to oxidize cyanide to cyanogen chloride for subsequent extraction with hexane for quantification by electron capture detection (detection limit of 0.25 ppm) (Way 1984). In one of the indirect methods, cyanide is measured indirectly after the precipitation of silver cyanide with excess $AgNO_3$ and then determining the excess silver in the supernatant by atomic absorption spectrometry (NIOSH 1976, Way 1984). Continuous monitoring instruments based on diffusion and amperometric methods for the quantification of diffused HCN are also available (NIOSH 1976).

8.2 BIOLOGICAL MEDIA

Some of the common methods available for determining cyanide in biological media are given in Table 8.1. Cyanide in the body is biotransformed to thiocyanate rather quickly. The relative proportion of cyanide to thiocyanate in body fluids is about 1:1,000 (Pettigrew and Fell 1973). Some authors have determined thiocyanate in body fluids as a measure of cyanide exposure. The determination of cyanide in body fluids requires the separation of cyanide from thiocyanate, usually by distillation of cyanides. Sodium thiosulfates, a common cyanide antagonist that acts as an interference, can be eliminated by using a buffered solution at a pH of 5.2 as the acidifying agent for cyanide microdiffusion (Way 1984, Sylvester et al. 1982). The microdiffusion technique, when employed with spectrophotofluorimetric methods for quantification, provides one of the most sensitive methods for determining cyanides in biological fluids (Way 1984).

9. REGULATORY AND ADVISORY STATUS

9.1 INTERNATIONAL

The World Health Organization (WHO) has established an interim acceptable daily intake (ADI) for cyanide in food of 3.5 mg/person/day for a 70-kg human. The WHO (1971) drinking water standard for cyanide is 0.05 mg/L.

9.2 NATIONAL

9.2.1 Regulations

9.2.1.1 Air

Agency	Standard
OSHA	Permissible limit for occupational exposure, cyanide--5 mg/m^3; hydrogen cyanide--10 ppm or 11 mg/m^3; both values have skin designations (OSHA 1985)

9.2.1.2 Water

Hydrogen cyanide, potassium cyanide, calcium cyanide, barium cyanide, zinc cyanide, and silver cyanide are designated as hazardous substances under Sect. 311(b) (2) (A) of the Federal Water Pollution Control Act and are regulated by the Clean Water Act Amendments of 1977 and 1978 (discharge regulated) (EPA 1983b).

Cyanide is regulated under the Clean Water Act Effluent Guidelines for the following industrial point sources: electroplating, organic chemicals, inorganic chemicals, iron and steel manufacturing, nonferrous metals manufacturing, steam electric, ferroalloy, asbestos manufacturing, timber products processing, metal finishing, mineral mining, pharmaceuticals, paving and roofing, paint formulating, ink formulating, gum and wood, carbon black, photographic, battery manufacturing, coil coating, aluminum forming, and nonferrous metal forming (EPA 1988a).

9.2.1.3 Food

Agency	Standard
EPA	Tolerances for hydrogen cyanide in foods when used as a postharvest fumigant range from 25 ppm in dried beans, peas, and nuts to 250 ppm in spices (EPA 1982b)

9.2.1.4 Nonmedia specific

Agency	Standard
EPA	Reportable quantities (RQ) for potassium silver cyanide and silver cyanide--1 lb (EPA 1985a)
	RQs for hydrogen cyanide, sodium cyanide, potassium cyanide, calcium cyanide, barium cyanide, cyanogen chloride, copper cyanide, and zinc cyanide--10 lb (EPA 1985a)
	RQ for cyanogen--100 lb (EPA 1985a)
EPA	Federal law (Sect. 302 of SARA) requires any facility where an extremely hazardous substance is present in excess of the threshold planning quantity (TPQ) to notify the state emergency planning commission. TPQs for cyanide compounds are 100 pounds for hydrocyanic acid, potassium cyanide, and sodium cyanide and 500 pounds for potassium silver cyanide (EPA 1987d).

9.2.2 Advisory Guidance

9.2.2.1 Air

Agency	Advisory
NIOSH	Hydrogen cyanide and cyanide salts, 10-min ceiling level--4.7 ppm (5 mg/m^3) (NIOSH 1976). Hydrogen cyanide at 50 ppm is considered immediately dangerous to life or health (IDLH) (NIOSH 1981).
Other	ACGIH: hydrogen cyanide, ceiling limit--10 ppm (11 mg/m^3); cyanogen, TLV-TWA--10 ppm (20 mg/m^3)
	Cyanogen chloride, ceiling limit--0.3 ppm (0.6 mg/m^3) (ACGIH 1986)

9.2.2.2 Water

Agency	Advisory
PHS	Cyanide levels in water should not exceed 0.2 mg/L (U.S. Public Health Service 1962)
EPA	Ambient water quality criteria to protect human health, cyanides--3.77 mg/L CN^-; criteria to protect aquatic life, cyanides--3.5 μg/L as a 24-h average and the concentration should not exceed 52 μg/L at any time (EPA 1980)
EPA	Health advisories (HA) for cyanides (HCN, NaCN, and KCN); 1-day, 10-day, and longer-term--220 μg/L; lifetime HA--154 μg/L (EPA 1987b)

9.2.3 Data Analysis

9.2.3.1 Reference doses (RfDs)

Oral RfDs for free cyanide, hydrogen cyanide, sodium cyanide, potassium cyanide, calcium cyanide, barium cyanide, cyanogen, chlorine cyanide, copper cyanide, zinc cyanide, silver cyanide, and potassium silver cyanide have been verified and are available on IRIS (EPA 1985b,c,d,e,f,g,h,i; EPA 1987e; EPA 1985j,k,l). The RfD for barium cyanide, 0.07 mg/kg/day (EPA 1985g), is based on the toxicity of barium; therefore, its derivation will not be presented here. The RfD for copper cyanide, 0.005 mg/kg/day (EPA 1987e), is based on the study by ITT Research Institute (1986). As discussed in Sect. 4.3.2.2, signs of classical copper-induced toxicity were observed in this study and were not considered to be cyanide induced. All the remaining RfDs are based on the study by Howard and Hanzal (1955), in which no effects were observed in rats fed HCN in the diet for 2 years at a level that provided females a dose of 10.8 mg/kg/day CN^- (highest NOAEL). The RfD for free cyanide (EPA 1985b) was calculated as follows:

$$\text{RfD} = 10.8 \text{ mg/kg/day}/(100)(5) = 0.02 \text{ mg/kg/day} ,$$

where

10.8 mg/kg/day = NOAEL dose calculated in EPA (1985b) from data provided by the authors;
100 = uncertainty factor, 10 for interspecies extrapolation, 10 to protect sensitive individuals;
5 = modifying factor to account for the apparent tolerance to cyanide when it is ingested with food rather than when it is administered by gavage or in drinking water.

The RfDs for other cyanide compounds (listed below) were calculated in a similar manner, using the appropriate molecular weights presented in Sect. 3.1.

Compound	RfD (mg/kg/day)	Reference
Hydrogen cyanide	0.02	EPA 1985c
Sodium cyanide	0.04	EPA 1985d
Potassium cyanide	0.05	EPA 1985e
Calcium cyanide	0.04	EPA 1985f
Cyanogen	0.04	EPA 1985h
Chlorine cyanide	0.05	EPA 1985i
Zinc cyanide	0.05	EPA 1985j
Silver cyanide	0.1	EPA 1985k
Potassium silver cyanide	0.2	EPA 19851

9.2.3.2 Carcinogenic potency

There are no data indicating that cyanides are carcinogenic. Cyanide has been assigned an EPA classification of D - not classifiable as to human carcinogenicity (EPA 1988b).

9.3 STATE

The only states listed by FSTRAC (1988) with drinking water guidelines for cyanide are Arizona (160 μg/L) and Kansas (220 μg/L).

10. REFERENCES

ACGIH (American Conference of Governmental Industrial Hygienists). 1986. Documentation of the Threshold Limit Values and Biological Exposure Indices. 5th ed. Cincinnati, Ohio: ACGIH, pp. 154, 155, 314.

Adams DJ, Takeda K, Umbach JA. 1985. Inhibitors of calcium buffering depress evoked transmitter release at the squid giant synapse. J Physiol 369:145-159.

Aitken D, West D, Smith F, et al. 1977. Cyanide toxicity following nitroprusside-induced hypotension. Can Anaesth Soc J 24(6):651-660.

Allen DG, Smith GL. 1985. Intracellular calcium in metabolically depleted ferret ventricular muscle during exposure to cyanide and its removal. In: Meeting of the Physiological Society and the Societa Italiana di Fisiological (Italian Physiological Society), Oxford, England, July 11-13. J Physiol 269:1-92.

American Chemical Society. 1986. Chemcyclopedia 87. Washington D.C.: American Chemical Society, pp. 181, 194, 204.

Amoore JE, Hautala E. 1983. Odor as an aid to chemical safety: Odor thresholds compared with threshold limit values and volatilities for 214 industrial chemicals in air and water dilution. J Appl Toxicol 3(6):272-290.

* Ansell M, Lewis FAS. 1970. A review of cyanide concentrations found in human organs--A survey of literature concerning cyanide metabolism, "normal," nonfatal, and fatal body cyanide levels. J Forensic Med 17(4):148-155.

Arrington LR. 1972. Introductory Laboratory Animal Science. The Breeding, Care, and Management of Experimental Animals. Danville, Ill: The Interstate Printers & Publishers, Inc.

Ballantyne B. 1983. Acute systemic toxicity of cyanides by topical application to the eye. J Toxicol: Cut Ocular Toxicol 2(2&3):119-129.

Ballantyne B, Bright J, Swanston DW, Williams PW. 1971. Toxicity of cyanides given intramuscular injection. Br J Pharmacol 41:423-424.

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* Key studies.

Ballantyne B, Bright J, Swanston DW, Williams PW. 1972. Toxicity and distribution of free cyanides given intramuscularly. Med Sci Law 12: 209-219.

Basu TK. 1983. High-dose ascorbic acid decreases detoxification of cyanide derived from amygdalin (Laetrile): Studies in the guinea pig. Can J Physiol Pharmacol 61(11):1426-1430.

Barnes D, Bellin J, DeRosa C, et al. 1987. Reference dose (RfD): Description and use in health risk assessments. Appendix A in Integrated Risk Information System Supportive Documentation, Vol. I. Washington, D.C.: Office of Health and Environmental Assessment, Environmental Protection Agency. EPA-600/8-86-032a.

Bedding ND, McIntyre AE, Perry R, Lester JN. 1982. Organic contaminants in the aquatic environment. I. Sources and occurrence. Sci Total Environ 25:143-167.

Berlin C. 1977. Editorial. Cyanide poisoning: A challenge. Arch Intern Med 137(8):993-994.

Birky MM, Clark FB. 1981. Inhalation of toxic products from fires. Bull NY Acad Med 57:997-1013.

Blanc P, Hogan M, Mallin K, Hryhorczuk D, Hessl S, Bernard B. 1985. Cyanide intoxication among silver-reclaiming workers. J Am Med Assoc, 253(3):367-371.

Bourbon I, Alary J, Esclassans JF, Lepert JC. 1979. Evaluation of some elements found in the effluent of a municipal incinerator. CYP 8:9-14. (From Chem Abstr 93:78569g.)

Brierley JB, Brown AW, Calverley J. 1976. Cyanide intoxication in the rat: Physiological and neuropathological aspects. J Neurol Neurosurg Psychiatry 39:129-140.

Britton P, Winter J, Kroner RC. 1984. EPA Method Study 12. Cyanide in Water. Environmental Protection Agency. EPA-600/4-84-045, NTIS PB84-196674.

Callahan MA, Slimak MW, Gabel NW, May IP. 1979. Water-Related Environmental Fate of 129 Priority Pollutants, Vol. 1. Office of Water Planning and Standards, Office of Water and Waste Management, Environmental Protection Agency, Washington, D.C.

Carmelo S. 1955. New contributions to the study of subacute-chronic hydrocyanic acid intoxication in men. Rass Med Ind 24:254-271 (in Italian) (cited in NIOSH 1976).

Carotti AA, Kaiser ER. 1972. Concentrations of twenty gaseous chemical species in the flue gas of a municipal incinerator. J Air Pollut Control Assoc 22:224-253.

Cassinelli ME. 1986. Progress Toward Developing a Monitoring Method for Hydrogen Cyanide in Air. National Institute for Occupational Safety and Health, Division of Physical Sciences and Engineering, Method Research Branch, Cincinnati, Ohio. NTIS PB86-236171.

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

Chatwin TD, Trepanowski JJ. 1987. Utilization of soils to mitigate cyanide releases. In: Proceedings of the 3rd Western Regional Conference on Precious Metal, Coal and Environment, Rapid City, S.D., September 23-26, pp. 151-170.

Chemical Week Buyer's Guide. 1986. New York, N.Y.: McGraw-Hill, Inc., pp. 166, 218, 288, 480, 534.

Cicerone RJ, Zellner R. 1983. The atmospheric chemistry of hydrogen cyanide (HCN), J Geophys Res 88:10689-10696.

CMR (Chemical Marketing Reporter). 1987. Chemical Profile: Hydrogen Cyanide. June 22, 1987. New York, N.Y.: Schnell Publishing Co.

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

Cole RH, Frederick RE, Healy RP, Rolan RG. 1984. Preliminary findings of the priority pollutant monitoring project of the Nationwide Urban Runoff Program. J Water Pollut Control Fed 56(7):898-908.

Conn EE. 1973. Cyanogenetic glycosides. Washington, D.C.: National Academy of Sciences 14:299-308.

Courville CB. 1963. Forensic neuropathy. X. Common chemical, metallic, and metalloid poisons. J Forensic Sci 8:481-502 (cited in NIOSH 1976).

DeFlora S. 1981. Study of 106 organic and inorganic compounds in the *Salmonella*/microsome test. Carcinogenesis 2(4):283-298.

DeFlora S, Camoirano A, Zanacchi P, Bennicelli C. 1984. Mutagenicity testing with TA97 and TA102 of 30 DNA-damaging compounds, negative with other *Salmonella* strains. Mutat Res 134(2-3):159-165.

Delange F, Ermans AM. 1971. Role of dietary goitrogen in the etiology of endemic goiter in Idjwi Island. Am J Clin Nutr 24:1354-1360 (cited in EPA 1985a).

DiPalma JR. 1971. Noxious gases and vapors: I. Carbon monoxide, cyanides, methemoglobin and sulfhemoglobin. In: Drill's Pharmacol Med 4th ed. p. 1205.

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

* Doherty PA, Smith RP, Ferm VH. 1983. Comparison of the teratogenic potential of two aliphatic nitriles in hamsters: Succinonitrile and tetramethylsuccinonitrile. Fundam Appl Toxicol 3:41-48.

Dolzine TW, Esposito GG, Rinehart DS. 1982. Determination of hydrogen cyanide in air by ion chromatography. Anal Chem 54:470-473.

Drinker P. 1932. Hydrocyanic acid gas poisoning by absorption through the skin. J Ind Hyg 14:1-2.

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

Egekeze JO, Oehme FW. 1979. Direct potentiometric method for the determination of cyanide in biological materials. J Anal Toxicol 3:119-124.

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

EPA (Environmental Protection Agency). 1980. Ambient Water Quality Criteria for Cyanides, with Errata for Ambient Water Quality Criteria Documents dated June 9, 1981 (Updated February 23, 1982). Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, Ohio, for the Office of Water Regulations and Standards, Criteria and Standards Division, Washington, D.C. EPA-440/5-80-035, NTIS PB81-1117483.

EPA (Environmental Protection Agency). 1982a. Test Methods for Evaluating Solid Waste. Physical/Chemical methods. Method 9010. Total and Amenable Cyanide. Office of Solid Waste and Emergency Response, Washington, D.C.

EPA (Environmental Protection Agency). 1982b. Code of Federal Regulations. 40 CFR 180.130 (cited in HSDB 1987).

EPA (Environmental Protection Agency). 1983a. Methods for Chemical Analysis of Water and Wastes. Method 335.2. Cyanide, Total. Environmental Monitoring and Support Laboratory, Cincinnati, Ohio.

EPA (Environmental Protection Agency). 1983b. Code of Federal Regulations. 40 CFR 116.4 (cited in HSDB 1987).

EPA (Environmental Protection Agency). 1984. Health Effects Assessment for Cyanide. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH, for the Office of Solid Waste and Emergency Response. EPA-540/1-86-011.

EPA (Environmental Protection Agency). 1985a. Notification requirements; reportable quantity adjustments; final rule and proposed rule. 40 CFR 117 and 302. Fed Regist 50(65):13456-13522.

EPA (Environmental Protection Agency). 1985b. Integrated Risk Information System (IRIS): Reference dose (RfD) for oral exposure for cyanide (free). Online. (Verification date, 8/5/85.) Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, Ohio.

EPA (Environmental Protection Agency). 1985c. Integrated Risk Information System (IRIS): Reference dose (RfD) for oral exposure for hydrogen cyanide. Online. (Verification date, 8/5/85.) Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, Ohio.

EPA (Environmental Protection Agency). 1985d. Integrated Risk Information System (IRIS): Reference dose (RfD) for oral exposure for sodium cyanide. Online. (Verification date, 8/5/85.) Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, Ohio.

EPA (Environmental Protection Agency). 1985e. Integrated Risk Information System (IRIS): Reference dose (RfD) for oral exposure for potassium cyanide. Online. (Verification date, 8/5/85.) Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, Ohio.

EPA (Environmental Protection Agency). 1985f. Integrated Risk Information System (IRIS): Reference dose (RfD) for oral exposure for calcium cyanide. Online. (Verification date, 8/5/85.) Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, Ohio.

EPA (Environmental Protection Agency). 1985g. Integrated Risk Information System (IRIS): Reference dose (RfD) for oral exposure for barium cyanide. Online. (Verification date, 8/5/85.) Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, Ohio.

EPA (Environmental Protection Agency). 1985h. Integrated Risk Information System (IRIS): Reference dose (RfD) for oral exposure for cyanogen. Online. (Verification date, 8/5/85.) Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, Ohio.

EPA (Environmental Protection Agency). 1985i. Integrated Risk Information System (IRIS): Reference dose (RfD) for oral exposure for chlorine cyanide. Online. (Verification date, 8/5/85.) Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, Ohio.

EPA (Environmental Protection Agency). 1985j. Integrated Risk Information System (IRIS): Reference dose (RfD) for oral exposure for zinc cyanide. Online. (Verification date, 8/5/85.) Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, Ohio.

EPA (Environmental Protection Agency). 1985k. Integrated Risk Information System (IRIS): Reference dose (RfD) for oral exposure for silver cyanide. Online. (Verification date, 8/5/85.) Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, Ohio.

EPA (Environmental Protection Agency). 1985l. Integrated Risk Information System (IRIS): Reference dose (RfD) for oral exposure for potassium silver cyanide. Online. (Verification date, 8/5/85.) Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, Ohio.

* EPA (Environmental Protection Agency). 1987a. Drinking Water Criteria Document for Cyanide. External review draft. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, Ohio, for the Office of Drinking Water, Washington, D.C.

EPA (Environmental Protection Agency). 1987b. Cyanide: Health Advisory. Office of Drinking Water, Washington, D.C.

EPA (Environmental Protection Agency). 1987c. Statement of Work for organics analysis, multi-media, multi-concentration. U.S. EPA Contract Laboratory Program.

EPA (Environmental Protection Agency). 1987d. Extremely hazardous substances list and threshold planning quantities; Emergency planning and release notification requirements. Fed Regist 52(77):13378-13410.

EPA (Environmental Protection Agency). 1987e. Integrated Risk Information System (IRIS): Reference dose (RfD) for oral exposure for copper cyanide. Online. (Verification date, 8/5/85.) Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, Ohio.

EPA (Environmental Protection Agency). 1988a. Analysis of Clean Water Act Effluent Guidelines for Pollutants. Summary of the Chemicals Regulated by Industrial Point Source Category 40 CFR Parts 400-475. Draft. Prepared by the Industrial Technology Division (WH 552). Office of Water Regulations and Standards, Office of Water, Washington, D.C.

EPA (Environmental Protection Agency). 1988b. Integrated Risk Information System (IRIS). Risk estimate for carcinogenicity for cyanide, free. Online. (Revised verification date, 9/7/88.) Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, Ohio.

* Ermans AM. 1980. General conclusions. In: Ermans AM, Mbulamoko NM, Delange F, Ahlvaratia R. Role of Cassava in the Etiology of Endemic Goiter and Cretinism. Ottawa, Canada: International Development Research Centre, pp. 147-152.

Ermans AM, Delange F, Van Der Velden M, Kinthaert J. 1972. Possible role of cyanide and thiocyanate in the etiology of endemic cretinism. Adv Exp Med Biol 30:455-486.

Ermans AM, Mbulamoko NM, Delange F, Ahlvaratia R. 1980. Role of Cassava in the Etiology of Endemic Goiter and Cretinism. Ottawa, Canada: International Development Research Centre, p. 182.

Fairley A, Linton EC, Wild FE. 1934. The absorption of hydrocyanic acid vapour through the skin--hydrocyanic acid, prussic acid, with notes on other matters related to acute cyanide poisoning. J Hyg 34:283-294 (cited in NIOSH 1976).

Feldstein M, Klendshaj. 1954. The determination of cyanide in biological fluids by microdiffusion analysis. J Lab Clin Med 44:166-170 (cited in NIOSH 1976).

* Ferguson HC. 1962. Dilution of dose and acute oral toxicity. Toxicol Appl Pharmacol 4:759-762.

Fiksel J, Cooper C, Eschenroeder A, Goyer M, Perwak J. 1981. Exposure and Risk Assessment for Cyanide. Environmental Protection Agency. EPA-440/4-85/008. NTIS PB85-220572.

Finck PA. 1969. Postmortem distribution studies of cyanide. A report of three cases. Med Ann DC 38:357-358.

Foulds WS, Cant JS, Chisholm IA, Bronte-Stewart J, Wilson J. 1968. Hydroxocobalamin in the treatment of Leber's hereditary optic atrophy. Lancet 1:896-897 (Great Britain).

Friedberg KD, Schwarzkopf HA. 1969. Blausaureexhalation bei der cyanidvergiftung. Arch Toxicol 24:235-248.

Fritz B, Lorenz K, Steinert W, Zellner R. 1982. Laboratory kinetic investigation of the tropospheric oxidation of selected industrial emissions. In: Comm. Eur. Communities, Eur 7624, Phys Chem Behav Atmos Pollut, pp. 92-202.

FSTRAC. 1988. Summary of State and Federal Drinking Water Standards and Guidelines. Chemical Communication Subcommittee. Federal State Toxicology and Regulatory Alliance Committee (FSTRAC).

Ganjeloo A, Isom GE, Morgan RL, Way JL. 1980. Fluorometric determination of cyanide in biological fluids with *p*-benzoquinone. Toxicol Appl Pharmacol 55:103-107.

* Gettler AO, Baine JO. 1938. The toxicology of cyanide. Am J Med Sci 195:182-198.

Gilman AG, Goodman LS, Rall TW, Murad F. 1985. The Pharmacological Basis of Therapeutics. 7th ed. New York, N.Y.: Macmillan Publishing Co., pp. 185, 1323-1332.

Gosselin RE, Hodge HC, Smith RP, Gleason MN. 1976. Clinical Toxicology of Commercial Products. 4th ed. Baltimore, Md.: Williams and Wilkins Co., pp. 105-112.

Grant WM. 1980. Peripheral visual system as a target. In: Spencer PS, Schaumburg HH, eds. Experimental and Clinical Neurotoxicology. Baltimore, Md.: Williams and Wilkins, pp. 77-91.

Gray BH, Porvaznik M, Lee LH. 1986. Cyanide stimulation of tri-N-butyltin mediated hemolysis. J Appl Toxicol 6(4):263-269.

Great Lakes Water Quality Board. 1983. An Inventory of Chemical Substances Identified in the Great Lakes Ecosystem. Vol. 1. Summary. Report to the Great Lakes Water Quality Board. Windsor, Ontario, Canada, p. 195.

* Hartung R. 1981. Cyanides and nitriles. In: Patty's Industrial Hygiene and Toxicology. Vol. 10, 3rd ed. New York, N.Y.: John Wiley and Sons, Inc., pp. 4845-4900.

Hasen BA, Dekker EE. 1976. Inactivation of bovine liver 2-keto-4-hydroxyglutarate aldolase by cyanide in the presence of aldehydes. Biochemistry 15:2912-2917 (cited in Way 1984).

Hawley GG. 1981. The Condensed Chemical Dictionary. 10th ed. New York, N.Y.: Van Nostrand Reinhold Co., pp. 106, 180-181, 275, 294-295, 542, 847-848, 924, 937-938, 1108.

* Hayes WJ Jr. 1967. The 90-day LD_{50} and a chronicity factor as measure of toxicity. Toxicol Appl Pharmacol 11:327-335.

* Haymaker W, Ginzler AM, Ferguson RL. 1952. Residual neuropathological effects of cyanide poisoning--A study of central nervous system of 23 dogs exposed to cyanide compounds. Mil Surg 3(4):231-246.

Hertting GO, Kraupp E, Schnetz E, Wieketich ST. 1960. Untersuchungen uber die folgen einer chronischen verabreichung akut toxishen dosen von natriumcyanid an hunden. Acta Pharmacol Toxicol 17:27-43 (cited in EPA 1985a).

Heuser SG, Scudmore KA. 1969. Determination of fumigant residues in cereals and other foodstuffs: A multidetection scheme for gas chromatography of solvent extracts. J Sci Food Agric 20:566-572.

Higgins EA, Fiorca V, Thomas AA, Davis HV. 1972. Acute toxicity of brief exposures to HF, HCI, NO_2, and HCN with and without CO. Fire Technol 8:120-130 (cited in NIOSH 1976).

Himwich WA, Saunders JP. 1948. Enzymatic conversion of cyanide to thiocyanate. Am J Physiol 153:348-354.

Hirano AL, Levine S, Zimmerman HM. 1967. Experimental cyanide encephalopathy: Electron-microscopic observations of early lesions in white matter. J Neuropathol Exp Neurol 26:200-213.

Honig DH, Hockridge ME, Gould RM, Rackis JJ. 1983. Determination of cyanide in soybeans and soybean products. J Agric Food Chem 31:272-275.

* Howard JW, Hanzal RF. 1955. Chronic toxicity for rats of food treated with hydrogen cyanide. J Agric Food Chem 3(4):325-329.

Howe RHL. 1985. The presence of cyanide in nature. In: Conference on Cyanide and the Environment, Tucson, Ariz., December 1984. Fort Collins, Colo.: Department of Geochemical Engineering. Program, Colorado State University, pp. 331-339.

HSDB (Hazardous Substance Data Bank). 1987. Online: September 1987.

Hugod C. 1981. Myocardial morphology in rabbits exposed to various gas phase constituents of tobacco smoke: An ultrastructural study. Atherosclerosis 40:181-190 (Shannon, Ireland).

Huiatt JL. 1985. Cyanide from mineral processing: Problems and research needs. In: Conference on Cyanide and the Environment, Tucson, Ariz., December 1984. Fort Collins, Colo.: Geochemical Engineering Program, Colorado State University, pp. 65-81.

Hurst EW. 1940. Experimental demyelination of the central nervous system: 1. The encephalopathy produced by potassium cyanide. Aust J Exp Biol Med Sci 18:201-223 (cited in EPA 1987a).

IIT Research Institute. 1986. Ninety-Day Oral Toxicity Study of Copper Cyanide (CuCN) in Sprague-Dawley Rats. Draft final report. IITRI Project No. L06183, Study No. 3, 2 vols. Prepared for the Dynamac Corp.

IIT Research Institute. 1987. Ninety-Day Oral Toxicity Study of Potassium Silver Cyanide [$KAg(CN_2)$] in Sprague-Dawley Rats. Draft final report. IITRI Project No. L06183, Study No. 4, 2 vols. Prepared for the Dynamac Corp.

Isom G, Way JL. 1973. Cyanide intoxication: Protection with cobaltous chloride. Toxicol Appl Pharmacol 24:449-456.

Isom G, Way JL. 1974. Effect of oxygen on cyanide intoxication. VI. Reactivation of cyanide inhibited glucose metabolism. J Pharmacol Exp Ther 189(1):235-243.

Isom GE, Liu PHW, Way JL. 1975. Effect of sublethal doses of cyanide on glucose catabolism. Biochem Pharmacol 24:871-875 (cited in Johnson et al. 1986).

Isom G, Burrows GE, Way JL. 1982. Effects of oxygen on the antagonism of cyanide intoxication cytochrome oxidase, in vivo. Toxicol Appl Pharmacol 65:250-256.

Jenks WR. 1979. Cyanides. In: Kirk-Othmer Encyclopedia of Chemical Technology. New York, N.Y.: John Wiley and Sons, Inc., Vol. 7, pp. 307-334.

Jenks WR. 1985. Acrylonitrile. In: Kirk-Othmer Concise Encyclopedia of Chemical Technology. New York, N.Y.: John Wiley and Sons, Inc., pp. 31-32.

Johnson JD, Meisenheimer TL, Isom GE. 1986. Cyanide-induced neurotoxicity: Role of neuronal calcium. Toxicol Appl Pharmacol 84(3):464-469.

Khandekar JD, Edelman H. 1979. Studies of amygdalin (laetrile) toxicity in rodents. J Am Med Assoc 242(2):169-171.

Kreutler PA, Varbanov V, Goodman W, Olaya G, Stanbury JB. 1978. Interactions of protein deficiency, cyanide and thiocyanate of thyroid function in neonatal and adult rats. Am J Clin Nutr 31:282-289.

Kushi A, Matsumoto T, Yoshida D. 1983. Mutagen from the gaseous phase of protein pyrolyzate. Agric Biol Chem 47(9):1979-1982.

* Landahl HD, Herrmann RG. 1950. Retention of vapors and gases in the human nose and lung. Arch Ind Hyg Occup Med 1:36-45.

Lasch EE, El Shawa R. 1981. Multiple cases of cyanide poisoning by apricot kernels in children from Gaza. Pediatrics 68(1):5-7.

Lehman AJ. 1959. Appraisal of the safety of chemicals in food, drugs, and cosmetics. Association of Food and Drug Officials in the United States.

Lessell S. 1971. Experimental cyanide optic neuropathy. Arch Ophthalmol 86:194-204.

Levin B. 1987. Review of second draft of Toxicological Profile for Cyanide.

Levin BC, Paabo M, Gurman JL, Harris SE. 1987. Effects of exposure to single or multiple combinations of the predominant toxic gases and low oxygen atmospheres produced in fires. Fundam Appl Toxicol (in press).

Levine S. 1967. Experimental cyanide encephalopathy. J Neuropathol Exp Neurol 26:214-222.

Levine S, Stypulkowski W. 1959a. Experimental cyanide encephalopathy. Arch Pathol 67:306-323.

Levine S, Stypulkowski W. 1959b. Effect of ischemia on cyanide encephalopathy. Neurology 9:407-411.

Liebowitz D, Schwartz H. 1948. Cyanide poisoning. Am J Clin Pathol 18:965-970.

Makene WJ, Wilson J. 1972. Biochemical studies in Tanzanian patients with ataxic tropical neuropathy. J Neurol Neurosurg Psychiatry 35:31-33.

Marsho TV, Kung SD. 1976. Oxygenase properties of crystallized fraction 1 protein from tobacco. Arch Biochem 173:341-346 (cited in Way 1984).

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

Ministry of Health, Mozambique. 1984. Mantakassa: An epidemic of spastic paraparesis associated with chronic cyanide intoxication in a cassava staple area of Mozambique. 1. Epidemiology and clinical and laboratory findings in patients. Bull WHO 62(3):477-484.

Monekosso GL, Wilson J. 1966. Plasma thiocyanate and vitamin B_{12} in Nigerian patients with degenerative neurological disease. Lancet 14:1062-1064 (Great Britain).

Money GL. 1958. Endemic neuropathies in the Epe district of southern Nigeria. West Afr Med J 7:58-62.

Morgan RL, Way JL. 1980. Fluorometric determination of cyanide in biological fluids with pyridoxal. J Anal Toxicol 4:78-81.

Myers VB. 1983. Remedial activities at the Miami Drum site, Florida. Proceedings of the National Conference on the Management of Uncontrolled Hazardous Waste Sites. pp. 354-357.

* NIOSH (National Institute for Occupational Safety and Health). 1976. Occupational Exposure to Hydrogen Cyanide and Cyanide Salts. Rockville, Md.: Department of Health, Education, and Welfare, Public Health Service, Centers for Disease Control, Publ. 1-191.

NIOSH (National Institute for Occupational Safety and Health). 1978. NIOSH Manual of Analytical Methods. Hydrogen Cyanide. Methods 288, Vol. 4. 2nd ed. Cincinnati, Ohio: NIOSH Publication 78-175.

NIOSH (National Institute for Occupational Safety and Health). 1981. Pocket Guide to Chemical Hazards. Department of Health, Education, and Welfare, (NIOSH) Pub. 78-210, p. 112 (cited in HSDB 1987).

NIOSH (National Institute for Occupational Safety and Health). 1984. NIOSH Manual of Analytical Methods, Method No. 7904, Vol 1. 3rd ed. Department of Health and Human Services, NIOSH, Cincinnati, Ohio.

NIOSH (National Institute for Occupational Safety and Health). 1985. National Institute for Occupational Safety and Health. National Occupational Exposure Survey (NOES), September 23, 1985.

NIOSH (National Institute for Occupational Safety and Health). 1987. In-depth Survey Report, American Airlines Plating Facility, December 7-10, 1981. NTIS PB83-187799.

NIOSH/OSHA (National Institute for Occupational Safety and Health/Occupational Safety and Health Administration). 1981. Occupational Health Guideline for Cyanide. In: Mackinson FW, Stricoff RS, eds. Occupational Health Guidelines for Chemical Hazards. Department of Health and Human Services (NIOSH) Publ. 81-123.

NTIS (National Technical Information Service). 1987. Federal Research in Progress. Online.

NTP (National Toxicology Program). 1987. Management Status Report. July 1987.

O'Brien RE. 1982. Radioactive tracers. In: Kirk-Othmer Encyclopedia of Chemical Technology, Vol. 19. New York, N.Y.: John Wiley and Sons, Inc., pp. 633-634.

* O'Flaherty EJ, Thomas WC. 1982. The cardiotoxicity of hydrogen cyanide as a component of polymer pyrolysis smoke. Toxicol Appl Pharmacol 63:373-381.

Ohio River Valley Water Sanitation Commission. 1982. Assessment of the Water Quality Conditions: Ohio River Mainstream 1980-81. Cincinnati, Ohio: Ohio River Valley Water Sanitation Commission.

OPD Chemical Buyer's Directory. 1987. New York, N.Y.: Schnell Publishing Co. pp. 162, 270, 409, 570, 634-635.

OSHA (Occupational Safety and Health Administration). 1985. Occupational Standards Permissible Exposure Limits. 29 CFR 1910.1000.

Osuntokun BO. 1972. Chronic cyanide neurotoxicity and neuropathy in Nigerians. Plant Food Human Nutr 2:215-266.

Osuntokun BO. 1980. A degenerative neuropathy with blindness and chronic cyanide intoxication of dietary origin: The evidence in Nigerians. Toxicol Tropics, pp. 16-52.

Osuntokun BO, Monekosso ML, Wilson J. 1969. Relationship of a degenerative tropical neuropathy to diet: Report of a field study. Br Med J 1:547-550.

Owais WM, Janakat, Hunaiti A. 1985. Conversion of cyanide to a toxic and nonmutagenic metabolite in *Salmonella typhimurium*. Environ Mutagenesis 7(Supple. 3):16-17.

Owasoyo JO, Iramain CA. 1980. Acetylcholinesterose activity in rat brain: Effect of acute cyanide intoxication. Toxicol LEH 6(1):1-3.

Paula de GRD, Rangel J. 1939. HCN or the poison of bitter or sweet manioc. Rev Aliment 29:215-217 (in Spanish) (taken from Chemical Abstracts 39:2161).

Pettigrew AR, Fell GS. 1972. Simplified colorimetric determination of thiocyanate in biological fluid and its application to investigation of toxic amblyopias. Clin Chem (Winston-Salem, NC) 18(9):996-1000.

Pettigrew AR, Fell GS. 1973. Microdiffusion method for estimation of cyanide in whole blood and its application to the study of conversion of cyanide to thiocyanate. Clin Chem (Winston-Salem, NC) 19(5):466-471.

* Philbrick DJ, Hopkine JB, Hill DC, Alexander JC, Thomson RG. 1979. Effect of prolonged cyanide and thiocyanate feeding in rats. J Toxicol Environ Health 5:579-592.

Piironen E, Virtanen AI. 1963. The effect of thiocyanate in nutrition on the iodine content of cow's milk. Z Ernaehrungswiss 3:140-147 (cited in Ermans 1972).

Pontal PG, Bismuth C, Garnier R, Pronszuck de Garbine J. 1982. Therapeutic attitude in cyanide poisoning retrospective study of 24 nonlethal cases. Vet Hum Toxicol Supp pp. 90-94.

Potter AL. 1950. The successful treatment of two recent cases of cyanide poisoning. Br J Ind Med 7:125-130.

* Purser DA, Grimshaw P, Berrill KR. 1984. Intoxication by cyanide in fires: A study in monkeys using polyacrylonitrile. Arch Environ Health 39(6):394-400.

Radojicic B. 1973. Determining thiocyanate in urine of workers exposed to cyanides. Arh Hig Rada 24:227-232 (in Yugoslavian) (cited in Hartung 1981).

Raef SF, Characklis WG, Kessick MA, Ward CH. 1977. Fate of cyanide and related compounds in aerobic microbial systems--II. Microbial degradation. Water Res 11:485-492.

Reiders F. 1971. Noxious gases and vapors. I. Carbon monoxide, cyanides, methemoglobin, and sulfhemoglobin. In: DiPalma JR, ed. Drill's Pharmacol Med 4th Ed, pp. 1180-1205.

Robinson CP, Baskin SI, Visnich N Jr, Franz DR. 1985a. The effects of cyanide and its interactions with norepinephrine on isolated aorta strips from the rabbit, dog, and ferret. Toxicology 35(1):59-72.

Robinson CP, Baskin SI, Franz DR. 1985b. The mechanisms of action of cyanide on the rabbit aorta. J Appl Toxicol 5(6):372-377.

Rocklin RD, Johnson DL. 1983. Determination of cyanide, sulfide, iodide, and bromide by ion chromatography with electrochemical detection. Anal Chem 55:4-7.

Rohmann SO, Miller RL, Scott EA, Muir WR. 1985. Tracing a river's toxic pollution: A case study of the Hudson. McCook AS, ed. INFORM. New York, N.Y., p. 154.

Rutkowski JV, Roebuck BD, Smith RP. 1985. Effects of protein-free diet and food deprivation on hepatic rhodanese activity, serum protein and acute cyanide lethality in mice. J Nutr 115:132-137.

Salvato JA. 1982. Environmental Engineering and Sanitation. New York, N.Y.: John Wiley & Sons Inc., p. 186.

Sandberg CG. 1967. A case of chronic poisoning with potassium cyanide. Acta Med Scand 181(2):233-236 (cited in NIOSH 1976).

* Sato T, Fukyama T, Yamada M. 1955. The allowable concentration of hydrogen cyanide in air. Bull Inst Public Health Tokyo 4:3-5 (cited in NIOSH 1976).

Sax NI. 1984. Dangerous Properties of Industrial Materials. New York, N.Y.: Van Nostrand Reinhold Co., pp. 2282, 2403.

Sax NI, Lewis RD, eds. 1987. Hawley's Condensed Chemical Dictionary. 11th ed. New York, N.Y.: Van Nostrand Reinhold Co.

Schneider JF, Westley J. 1969. Metabolic interrelations of sulfur in proteins, thiosulfate, and cystine. J Biol Chem 244:5735-5744.

Schubert J, Brill WA. 1968. Antagonism of experimental cyanide toxicity in relation to the in vivo activity of cytochrome oxidase. J Pharmacol Exp Ther 162:352-359 (cited in NIOSH 1976).

Schuckrow AJ, Pajak AP, Touhill CP. 1982. Hazardous Waste Leachate Management Manual. Park Ridge, N.J.: Noyes Data Corp., pp. 50-52.

Scott JS. 1985. An overview of cyanide treatment methods for gold mill effluents. In: Conference on Cyanide and the Environment, Tucson, Ariz., December 1984, Fort Collins, Colo.: Geochemical Engineering Program, Colorado State University, pp. 307-328.

* Sheehy M, Way JL. 1968. Effect of oxygen on cyanide intoxication. III. Mithridate. J Pharmacol Exp Ther 161(1):163-168.

* Singh JD. 1981. The teratogenic effects of dietary cassava on the pregnant albino rat: A preliminary report. Teratology 24:289-291.

Sklarew DS, Hayes DJ. 1984. Trace nitrogen-containing species in the offgas from 2 oil shale retorting processes. Environ Sci Technol 18:600-603.

Smith L, Kruszyna H, Smith RP. 1977. The effect of methemoglobin on the inhibition of cytochrome c oxidase by cyanide, sulfide or azide. Biochem Pharmacol 26:2247-2250 (cited in EPA 1985a).

Smith RP, Gosselin RE. 1979. Hydrogen sulfide poisoning. J Occup Med 21:93-97 (cited in EPA 1985a).

Smyth HF, Carpenter CP, Weil CS, Pozanni UC, Striegel JA, Nycum JS. 1969. Range-finding toxicity data: List VII. J Am Ind Hyg Assoc 30:470-476.

Sofuni T, Hayashi M, Matsuoka A, Sawada M, Hatanaka M, Ishidate M Jr. 1985. Mutagenicity tests on organic chemical contaminants in city water and related compounds. I. Chromosome aberration tests in cultured mammalian cells. Bull Natl Inst Hyg Sci Tokyo 103:64-75.

Soine WH, Vincek WC, Agee DT. 1979. Phencyclidine contaminant generates cyanide. N Engl J Med 301:438.

Stadelmann W. 1976. The hydrocyanic acid content in juices from pitted fruit. Fluess Obst 43:45-48 (English translation).

Sylvester DM, Holmes RK, Sander C, Way JL. 1982. Interference of thiosulfate with potentiometric analysis of cyanide in blood and its elimination. Toxicol Appl Pharmacol 65:116-121.

ten Berge WF, Zwart A, Appelman LM. 1986. Concentration-time mortality response relationship of irritant and systemically acting vapour and gases. J Hazard Mat 13:301-309.

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

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

Thomas TA, Brooks JW. 1970. Accidental cyanide poisoning. Anaesthesia 25:110-114 (cited in NIOSH 1976).

Towill LE, Drury JS, Whitfield BL, Lewis EB, Galyan EL, Hammons AS. 1978. Reviews of the environmental effects of pollutants. V. Cyanide. EPA Health Effects Research Laboratory, Office of Research and Development, Cincinnati, Ohio. NTIS PB28-9920.

Trapp WG. 1970. Massive cyanide poisoning with recovery: A Boxing-Day story. Can Med Assoc J 102:517.

* Uitti RJ, Rajput AH, Ashenhurst EM, Rozdilsky B. 1985. Cyanide-induced Parkinsonism: A clinicopathologic report. Neurology 35(6):291-295.

U.S. Department of Health and Human Services/U.S. Department of Labor. 1978. Occupational Health Guideline for Cyanide. In: NIOSH/OSHA Occupational Health Guidelines for Chemical Hazards. Washington, D.C.

U.S. Public Health Service. 1962. Drinking Water Standards. U.S. Government Printing Office, Washington, D.C. Public Health Service Publ. 956 (cited in EPA 1985a).

* Valade MP. 1952. Lesions du systeme nerveux central dans les intoxications chroniques experimentals par l'acide cyanhydrique gazeux. (Injuries to the central nervous systems in chronic experimental poisoning by hydrocyanic acid gas). Bull Acad Natl Med Paris 136:280-285 (cited in NIOSH 1976).

VanderLaan WP, Bissell A. 1946. Effects of propylthiouracil and of potassium thiocyanate on the uptake of iodine by the thyroid gland of the rat. Endocrinology 39:157-160.

* Vick JA, Froehlich HL. 1985. Studies of cyanide poisoning. Arch Int Pharmacodyn Ther 273:314-322.

VIEW Data Base. 1989. Agency for Toxic Substances and Disease Registry (ATSDR), Office of External Affairs, Exposure and Disease Registry Branch, Atlanta, Ga. June 20, 1989.

Vogel SN, Sultan TR, Ten Eyck RP. 1981. Cyanide poisoning. Clin Toxicol 18(3):367-383.

Walton DC, Witherspoon MG. 1926. Skin absorption of certain gases. J Pharmacol Exp Ther 26:315-324.

Way JL. 1984. Cyanide intoxication and its mechanism of antagonism. Ann Rev Pharmacol Toxicol 24:451-481.

Way JL, End E, Sheehy MH, et al. 1972. Effect of oxygen on cyanide intoxication: lV. Hyperbaric oxygen. Toxicol Appl Pharmacol 22:415-421.

Weast RC, ed. 1985. CRC Handbook of Chemistry and Physics, 66th ed., CRC Press, Inc., Boca Raton, Fla., pp. B-75, B-82, B-93, B-95, B-100, B-127, B-139, B-142, B-159.

Westley J. 1981. Cyanide and sulfane sulfur. In: Vennesland B, Conn EE, Knowles CJ, Westley J, Wissing F, eds. Cyanide in Biology. London, UK: Academic pp. 61-76.

* Wexler J, Whittenberger JL, Dumke PR. 1947. The effect of cyanide on the electrocardiogram of man. Am Heart J 34:163-173.

WHO (World Health Organization). 1971. International Standard for Drinking-Water, p. 31 (cited in Salvato 1982).

Willhite CC. 1981. Malformations induced by inhalation of acetonitrile vapors in the golden hamster. Teratology 23(2):69A (abstract).

Willhite CC. 1982. Congenital malformations induced by laetrile. Science 215:1513.

Wilson J. 1965. Leber's hereditary optic atrophy: A possible defect of cyanide metabolism. Clin Sci 29:505-515.

Wilson J. 1983. Cyanide in human disease: A review of clinical and laboratory evidence. Fundam Appl Toxicol 3(5):397-399.

Wilson J, Matthews DM. 1966. Metabolic interrelationships between cyanide, thiocyanate and Vitamin B_{12} in smokers and non-smokers. Clin Sci 31:1-7.

Windholz M, ed. 1983. The Merck Index, 10th ed. Rahway, N.J., Merck and Co., Inc., pp. 140, 229, 385, 696, 1100, 1104, 1222, 1233, 1456.

Wokes F, Moore DF. 1958. Tobacco amblyopia. Lancet 2:526-527 (Great Britain).

Wolnik KA, Fricke FL, Bonnin E, Gaston CM, Satzger RD. 1984. The Tylenol tampering incident--Tracing the source. Anal Chem 56(3):466A-468A, 470A, 474A.

Wood JL, Cooley SL. 1956. Detoxification of cyanide by cystine. J Biol Chem 218:449-457.

Worthing CR. 1987. The Pesticide Manual, 8th ed. British Crop Protection Council, Thornton Heath, UK.

* Yamamoto KY, Yamamoto H, Hattori H, Samori T. 1982. Effects of routes of administration on the cyanide concentration distribution in the various organs of cyanide-intoxicated rats. Tohoku J Exp Med 137:73-78.

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11. GLOSSARY

Acute Exposure--Exposure to a chemical for a duration of 14 days or less, as specified in the Toxicological Profiles.

Bioconcentration Factor (BCF)--The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same time period.

Carcinogen--A chemical capable of inducing cancer.

Ceiling value (CL)--A concentration of a substance that should not be exceeded, even instantaneously.

Chronic Exposure--Exposure to a chemical for 365 days or more, as specified in the Toxicological Profiles.

Developmental Toxicity--The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

Embryotoxicity and Fetotoxicity--Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the insult occurred. The terms, as used here, include malformations and variations, altered growth, and in utero death.

Frank Effect Level (FEL)--That level of exposure which produces a statistically or biologically significant increase in frequency or severity of unmistakable adverse effects, such as irreversible functional impairment or mortality, in an exposed population when compared with its appropriate control.

EPA Health Advisory--An estimate of acceptable drinking water levels for a chemical substance based on health effects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

Immediately Dangerous to Life or Health (IDLH)--The maximum environmental concentration of a contaminant from which one could escape within 30 min without any escape-impairing symptoms or irreversible health effects.

Intermediate Exposure--Exposure to a chemical for a duration of 15-364 days, as specified in the Toxicological Profiles.

Immunologic Toxicity--The occurrence of adverse effects on the immune system that may result from exposure to environmental agents such as chemicals.

In vitro--Isolated from the living organism and artificially maintained, as in a test tube.

In vivo--Occurring within the living organism.

Key Study--An animal or human toxicological study that best illustrates the nature of the adverse effects produced and the doses associated with those effects.

Lethal Concentration(LO) (LC_{LO})--The lowest concentration of a chemical in air which has been reported to have caused death in humans or animals.

Lethal Concentration(50) (LC_{50})--A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

Lethal Dose(LO) (LD_{LO})--The lowest dose of a chemical introduced by a route other than inhalation that is expected to have caused death in humans or animals.

Lethal Dose(50) (LD_{50})--The dose of a chemical which has been calculated to cause death in 50% of a defined experimental animal population.

Lowest-Observed-Adverse-Effect Level (LOAEL)--The lowest dose of chemical in a study or group of studies which produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

Lowest-Observed-Effect Level (LOEL)--The lowest dose of chemical in a study or group of studies which produces statistically or biologically significant increases in frequency or severity of effects between the exposed population and its appropriate control.

Malformations--Permanent structural changes that may adversely affect survival, development, or function.

Minimal Risk Level--An estimate of daily human exposure to a chemical that is likely to be without an appreciable risk of deleterious effects (noncancerous) over a specified duration of exposure.

Mutagen--A substance that causes mutations. A mutation is a change in the genetic material in a body cell. Mutations can lead to birth defects, miscarriages, or cancer.

Neurotoxicity--The occurrence of adverse effects on the nervous system following exposure to a chemical.

No-Observed-Adverse-Effect Level (NOAEL)--That dose of chemical at which there are no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Effects may be produced at this dose, but they are not considered to be adverse.

No-Observed-Effect Level (NOEL)--That dose of chemical at which there are no statistically or biologically significant increases in frequency or severity of effects seen between the exposed population and its appropriate control.

Permissible Exposure Limit (PEL) -An allowable exposure level in workplace air averaged over an 8-h shift.

q_1^*--The upper-bound estimate of the low-dose slope of the dose-response curve as determined by the multistage procedure. The q_1^* can be used to calculate an estimate of carcinogenic potency, the incremental excess cancer risk per unit of exposure (usually μg/L for water, mg/kg/day for food, and $\mu g/m^3$ for air).

Reference Dose (RfD)--An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure of the human population to a potential hazard that is likely to be without risk of deleterious effects during a lifetime. The RfD is operationally derived from the NOAEL (from animal and human studies) by a consistent application of uncertainty factors that reflect various types of data used to estimate RfDs and an additional modifying factor, which is based on a professional judgment of the entire database on the chemical. The RfDs are not applicable to nonthreshold effects such as cancer.

Reportable Quantity (RQ)--The quantity of a hazardous substance that is considered reportable under CERCLA. Reportable quantities are: (1) 1 lb or greater or (2) for selected substances, an amount established by regulation either under CERCLA or under Sect. 311 of the Clean Water Act. Quantities are measured over a 24-h period.

Reproductive Toxicity--The occurrence of adverse effects on the reproductive system that may result from exposure to a chemical. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

Short-Term Exposure Limit (STEL)--The maximum concentration to which workers can be exposed for up to 15 min continually. No more than four excursions are allowed per day, and there must be at least 60 min between exposure periods. The daily TLV-TWA may not be exceeded.

Target Organ Toxicity--This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

Teratogen--A chemical that causes structural defects that affect the development of an organism.

Threshold Limit Value (TLV)--A concentration of a substance to which most workers can be exposed without adverse effect. The TLV may be expressed as a TWA, as a STEL, or as a CL.

Time-weighted Average (TWA)--An allowable exposure concentration averaged over a normal 8-h workday or 40-h workweek.

Uncertainty Factor (UF)--A factor used in operationally deriving the RfD from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of humans, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using LOAEL data rather than NOAEL data. Usually each of these factors is set equal to 10.

APPENDIX: PEER REVIEW

A peer review panel was assembled for cyanide. The panel consisted of the following members: Dr. Yves Alarie, University of Pittsburgh; Dr. Barbara C. Levin, National Bureau of Standards; Dr. R. Craig Schnell, University of North Dakota; and Dr. Roger Smith, Dartmouth Medical School. These experts collectively have knowledge of cyanide's physical and chemical properties, toxicokinetics, key health end points, mechanisms of action, human and animal exposure, and quantification of risk to humans. All reviewers were selected in conformity with the conditions for peer review specified in the Superfund Amendments and Reauthorization Act of 1986, Section 110.

A joint panel of scientists from ATSDR and EPA has reviewed the peer reviewers' comments and determined which comments will be included in the profile. A listing of the peer reviewers' comments not incorporated in the profile, with a brief explanation of the rationale for their exclusion, exists as part of the administrative record for this compound. A list of databases reviewed and a list of unpublished documents cited are also included in the administrative record.

The citation of the peer review panel should not be understood to imply their approval of the profile's final content. The responsibility for the content of this profile lies with the Agency for Toxic Substances and Disease Registry.

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