TOXICOLOGICAL PROFILE FOR CYANIDE

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Agency for Toxic Substances and Disease Registry

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DISCLAIMER

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UPDATE STATEMENT

A Toxicological Profile for Cyanide, Draft for Public Comment was released in September 2004. This edition supersedes any previously released draft or final profile.

Toxicological profiles are revised and republished as necessary. For information regarding the update status of previously released profiles, contact ATSDR at:

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FOREWORD

This toxicological profile is prepared in accordance with guidelines developed by the Agency for Toxic Substances and Disease Registry (ATSDR) and the Environmental Protection Agency (EPA). The original guidelines were published in the *Federal Register* on April 17, 1987. Each profile will be revised and republished as necessary.

The ATSDR toxicological profile succinctly characterizes the toxicologic and adverse health effects information for the hazardous substance described therein. Each peer-reviewed profile identifies and reviews the key literature that describes a hazardous substance's toxicologic properties. Other pertinent literature is also presented, but is 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.

The focus of the profiles is on health and toxicologic information; therefore, each toxicological profile begins with a public health statement that describes, in nontechnical language, a substance's relevant toxicological properties. Following the public health statement is information concerning 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. Data needs that are of significance to protection of public health are identified by ATSDR and EPA.

Each profile includes the following:

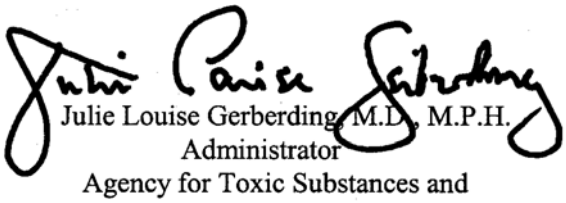
(A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a hazardous substance to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects;

(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 that present a significant risk to human health of acute, subacute, and chronic health effects; and

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

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.

This profile reflects ATSDR's assessment of all relevant toxicologic testing and information that has been peer-reviewed. Staff of the Centers for Disease Control and Prevention and other Federal scientists have also reviewed the profile. In addition, this profile has been peer-reviewed by a nongovernmental panel 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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Disease Registry

*Legislative Background

The toxicological profiles are developed in response to the Superfund Amendments and Reauthorization Act (SARA) of 1986 (Public Law 99 499) which amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund). This public law directed ATSDR to prepare toxicological profiles for hazardous substances most commonly found at facilities on the CERCLA National Priorities List and that pose the most significant potential threat to human health, as determined by ATSDR and the EPA. The availability of the revised priority list of 275 hazardous substances was announced in the Federal Register on December 7, 2005 (70 FR 72840). For prior versions of the list of substances, see Federal Register notices dated April 17, 1987 (52 FR 12866); October 20, 1988 (53 FR 41280); October 26, 1989 (54 FR 43619); October 17,1990 (55 FR 42067); October 17, 1991 (56 FR 52166); October 28, 1992 (57 FR 48801); February 28, 1994 (59 FR 9486); April 29, 1996 (61 FR 18744); November 17, 1997 (62 FR 61332); October 21, 1999(64 FR 56792); October 25, 2001 (66 FR 54014) and November 7, 2003 (68 FR 63098). Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list.

QUICK REFERENCE FOR HEALTH CARE PROVIDERS

Toxicological Profiles are a unique compilation of toxicological information on a given hazardous substance. Each profile reflects a comprehensive and extensive evaluation, summary, and interpretation of available toxicologic and epidemiologic information on a substance. Health care providers treating patients potentially exposed to hazardous substances will find the following information helpful for fast answers to often-asked questions.

Primary Chapters/Sections of Interest

Chapter 1: Public Health Statement: The Public Health Statement can be a useful tool for educating patients about possible exposure to a hazardous substance. It explains a substance's relevant toxicologic properties in a nontechnical, question-and-answer format, and it includes a review of the general health effects observed following exposure.

Chapter 2: Relevance to Public Health: The Relevance to Public Health Section evaluates, interprets, and assesses the significance of toxicity data to human health.

Chapter 3: Health Effects: Specific health effects of a given hazardous compound are reported by type of health effect (death, systemic, immunologic, reproductive), by route of exposure, and by length of exposure (acute, intermediate, and chronic). In addition, both human and animal studies are reported in this section.
NOTE: Not all health effects reported in this section are necessarily observed in the clinical setting. Please refer to the Public Health Statement to identify general health effects observed following exposure.

Pediatrics: Four new sections have been added to each Toxicological Profile to address child health issues:

Section 1.6	**How Can (Chemical X) Affect Children?**
Section 1.7	**How Can Families Reduce the Risk of Exposure to (Chemical X)?**
Section 3.7	**Children's Susceptibility**
Section 6.6	**Exposures of Children**

Other Sections of Interest:

Section 3.8	**Biomarkers of Exposure and Effect**
Section 3.11	**Methods for Reducing Toxic Effects**

ATSDR Information Center

Phone: 1-888-42-ATSDR or (404) 498-0110 ***Fax:*** (770) 488-4178
E-mail: atsdric@cdc.gov ***Internet***: http://www.atsdr.cdc.gov

The following additional material can be ordered through the ATSDR Information Center:

Case Studies in Environmental Medicine: Taking an Exposure History—The importance of taking an exposure history and how to conduct one are described, and an example of a thorough exposure history is provided. Other case studies of interest include *Reproductive and Developmental*

Hazards; Skin Lesions and Environmental Exposures; Cholinesterase-Inhibiting Pesticide Toxicity; and numerous chemical-specific case studies.

Managing Hazardous Materials Incidents is a three-volume set of recommendations for on-scene (prehospital) and hospital medical management of patients exposed during a hazardous materials incident. Volumes I and II are planning guides to assist first responders and hospital emergency department personnel in planning for incidents that involve hazardous materials. Volume III—*Medical Management Guidelines for Acute Chemical Exposures*—is a guide for health care professionals treating patients exposed to hazardous materials.

Fact Sheets (ToxFAQs) provide answers to frequently asked questions about toxic substances.

Other Agencies and Organizations

The National Center for Environmental Health (NCEH) focuses on preventing or controlling disease, injury, and disability related to the interactions between people and their environment outside the workplace. Contact: NCEH, Mailstop F-29, 4770 Buford Highway, NE, Atlanta, GA 30341-3724 • Phone: 770-488-7000 • FAX: 770-488-7015.

The National Institute for Occupational Safety and Health (NIOSH) conducts research on occupational diseases and injuries, responds to requests for assistance by investigating problems of health and safety in the workplace, recommends standards to the Occupational Safety and Health Administration (OSHA) and the Mine Safety and Health Administration (MSHA), and trains professionals in occupational safety and health. Contact: NIOSH, 200 Independence Avenue, SW, Washington, DC 20201 • Phone: 800-356-4674 or NIOSH Technical Information Branch, Robert A. Taft Laboratory, Mailstop C-19, 4676 Columbia Parkway, Cincinnati, OH 45226-1998 • Phone: 800-35-NIOSH.

The National Institute of Environmental Health Sciences (NIEHS) is the principal federal agency for biomedical research on the effects of chemical, physical, and biologic environmental agents on human health and well-being. Contact: NIEHS, PO Box 12233, 104 T.W. Alexander Drive, Research Triangle Park, NC 27709 • Phone: 919-541-3212.

Referrals

The Association of Occupational and Environmental Clinics (AOEC) has developed a network of clinics in the United States to provide expertise in occupational and environmental issues. Contact: AOEC, 1010 Vermont Avenue, NW, #513, Washington, DC 20005 • Phone: 202-347-4976 • FAX: 202-347-4950 • e-mail: AOEC@AOEC.ORG • Web Page: http://www.aoec.org/.

The American College of Occupational and Environmental Medicine (ACOEM) is an association of physicians and other health care providers specializing in the field of occupational and environmental medicine. Contact: ACOEM, 25 Northwest Point Boulevard, Suite 700, Elk Grove Village, IL 60007-1030 • Phone: 847-818-1800 • FAX: 847-818-9266.

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THE PROFILE HAS UNDERGONE THE FOLLOWING ATSDR INTERNAL REVIEWS:

1. Health Effects Review. The Health Effects Review Committee examines the health effects chapter of each profile for consistency and accuracy in interpreting health effects and classifying end points.

2. Minimal Risk Level Review. The Minimal Risk Level Workgroup considers issues relevant to substance-specific Minimal Risk Levels (MRLs), reviews the health effects database of each profile, and makes recommendations for derivation of MRLs.

3. Data Needs Review. The Research Implementation Branch reviews data needs sections to assure consistency across profiles and adherence to instructions in the Guidance.

4. Green Border Review. Green Border review assures the consistency with ATSDR policy.

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PEER REVIEW

A peer review panel was assembled for cyanide. The panel consisted of the following members:

1. Dr. Arthur Gregory, President, Techto Enterprises, Luray, Virginia;

2. Dr. Maryce Jacobs, President, Health Sciences Institute, Incorporated, Solomons, Maryland; and

3. Dr. James Withey, Environmental Health Center Canada, Retired, Ottawa, Ontario, Canada.

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 Section 104(I)(13) of the Comprehensive Environmental Response, Compensation, and Liability Act, as amended.

Scientists from the Agency for Toxic Substances and Disease Registry (ATSDR) have 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.

The citation of the peer review panel should not be understood to imply its approval of the profile's final content. The responsibility for the content of this profile lies with the ATSDR.

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1. PUBLIC HEALTH STATEMENT

This public health statement tells you about cyanide and the effects of exposure to it.

The Environmental Protection Agency (EPA) identifies the most serious hazardous waste sites in the nation. These sites are then placed on the National Priorities List (NPL) and are targeted for long-term federal clean-up activities. Cyanide has been found in at least 471 of the 1,662 current or former NPL sites. Although the total number of NPL sites evaluated for this substance is not known, the possibility exists that the number of sites at which cyanide is found may increase in the future as more sites are evaluated. This information is important because these sites may be sources of exposure and exposure to this substance may harm you.

When a substance is released either from a large area, such as an industrial plant, or from a container, such as a drum or bottle, it enters the environment. Such a release does not always lead to exposure. You can be exposed to a substance only when you come in contact with it. You may be exposed by breathing, eating, or drinking the substance, or by skin contact.

If you are exposed to cyanide, many factors will determine whether you will be harmed. These factors include the dose (how much), the duration (how long), and how you come in contact with it. You must also consider any other chemicals you are exposed to and your age, sex, diet, family traits, lifestyle, and state of health.

1.1 WHAT IS CYANIDE?

Cyanide is a chemical group consisting of one atom of carbon connected to one atom of nitrogen by three molecular bonds (C≡N) and cyanides are compounds (substances formed by the joining of two or more atoms) that contain a cyanide group (typically shown as CN). Cyanides can both occur naturally or be man-made and many are powerful and rapid-acting poisons. Hydrogen cyanide (HCN), which is a gas, and the simple cyanide salts (sodium cyanide and potassium cyanide) are common examples of cyanide compounds. Certain bacteria, fungi, and algae can

produce cyanide, and cyanide is found in a number of foods and plants. In certain plant foods, including almonds, millet sprouts, lima beans, soy, spinach, bamboo shoots, and cassava roots (which are a major source of food in tropical countries), cyanides occur naturally as part of sugars or other naturally-occurring compounds. However, the edible parts of plants that are eaten in the United States, including tapioca which is made from cassava roots, contain relatively low amounts of cyanide.

Many of the cyanides in soil and water come from industrial processes. The major sources of cyanides in water are discharges from some metal mining processes, organic chemical industries, iron and steel plants or manufacturers, and publicly owned wastewater treatment facilities. Other cyanide sources include vehicle exhaust, releases from certain chemical industries, burning of municipal waste, and use of cyanide-containing pesticides. Much smaller amounts of cyanide may enter water through storm water runoff where road salts are used that contain cyanide. Cyanide in landfills can contaminate underground water. Hydrogen cyanide, sodium cyanide, and potassium cyanide are the forms of cyanide most likely to be in the environment as a result of industrial activities. Hydrogen cyanide is a colorless gas with a faint, bitter, almond-like odor. Sodium cyanide and potassium cyanide are both white solids with a slight, bitter, almond-like odor in damp air. Cyanide salts and hydrogen cyanide are used in electroplating, metallurgy, organic chemicals production, photographic developing, manufacture of plastics, fumigation of ships, and some mining processes. Hydrogen cyanide has also been used in gas-chamber executions and as a war gas. Chlorination of water contaminated with cyanide produces the compound cyanogen chloride. Four incidents of cyanide in soil resulted from disposal of cyanide-containing wastes in landfills and use of cyanide-containing road salts. See Chapters 4 and 5 for more information about physical and chemical properties and about production and use of cyanide.

Thiocyanates are a group of compounds formed from a combination of sulfur, carbon, and nitrogen. Thiocyanates are found in various foods and plants; they are produced primarily from the reaction of free cyanide with sulfur. This reaction occurs in the environment (for example, in industrial waste streams that contain cyanide) and in the human body after cyanide is swallowed or absorbed. Thiocyanate is the major product formed from cyanide that passes into the body as

the body attempts to rid itself of cyanide. Although thiocyanates are less harmful than cyanide in humans, they are known to affect the thyroid glands, reducing the ability of the gland to produce hormones that are necessary for the normal function of the body.

Ammonium thiocyanate is used in antibiotic preparations, pesticides, liquid rocket fuels, adhesives, and matches. It also is used in photographic processes, to improve the strength of silks, and as a weed killer.

Thiocyanates are present in water primarily because of discharges from coal processing, extraction of gold and silver, and mining industries. Thiocyanates in soil result from direct application of herbicides (weed killers), insecticides, and rodenticides and from disposal of byproducts from industrial processes. Less important sources include release from damaged or decaying tissues of certain plants, such as mustard, kale, and cabbage.

1.2 WHAT HAPPENS TO CYANIDE WHEN IT ENTERS THE ENVIRONMENT?

Cyanide enters air, water, and soil from both natural processes and industrial activities. Airborne cyanide is generally far below levels that would cause concern. In air, cyanide is present mainly as gaseous hydrogen cyanide. A small amount of cyanide in air is present as fine dust particles. This dust eventually settles over land and water. Rain and snow help remove cyanide particles from air. The gaseous hydrogen cyanide is not easily removed from the air by settling, rain, or snow. The half-life (the time needed for half of the material to be removed) of hydrogen cyanide in the atmosphere is about 1–3 years. Most cyanide in surface water will form hydrogen cyanide and evaporate. However, the amount of hydrogen cyanide formed is generally not enough to be harmful to humans. Some cyanide in water will be transformed into less harmful chemicals by microorganisms (plants and animals of very small size), or will form a complex with metals, such as iron. The half-life of cyanide in water is not known. Cyanide in water does not build up in the bodies of fish.

Cyanides are fairly mobile in soil. Once in soils, cyanide can be removed through several processes. Some cyanide compounds in soil can form hydrogen cyanide and evaporate, whereas

some cyanide compounds will be transformed into other chemical forms by microorganisms in soil. Consequently, cyanides usually do not seep into underground water. However, cyanide has been detected in underground waters of a few landfills and industrial waste disposal sites. At the high concentrations found in some landfill leachates (water that seeps through landfill soil) and in the wastes stored in some disposal sites, cyanide becomes toxic to soil microorganisms. Because these microorganisms can no longer change cyanide to other chemical forms, cyanide is able to passes through soil into underground water. See Chapters 5 and 6 for more information about what happens to cyanide in the environment.

Less is known about what happens to thiocyanate when it enters the environment. In soil and water, thiocyanate is changed into other chemical forms by microorganisms. This occurs in soil mainly at temperatures up to 86 °F (30 °C). At these temperatures, thiocyanate in soil does not undergo much evaporation or sorption (binding to soil). See Chapters 5 and 6 for more information about what happens to thiocyanate in the environment.

1.3 HOW MIGHT I BE EXPOSED TO CYANIDE?

You can be exposed to cyanides by breathing air and drinking water, touching soil or water containing cyanide, or eating foods that contain cyanide. Many plant materials, such as cassava roots, lima beans, and almonds, naturally contain low-to-moderate levels of cyanide. The concentration of hydrogen cyanide in unpolluted air is less than 0.2 parts of hydrogen cyanide per million (ppm; 1 ppm is equivalent to 1 part by volume of hydrogen cyanide in a million parts by volume of air). The concentration of cyanide in drinking water ranges from 0.001 to 0.011 ppm (1 ppm is equivalent to 1 part by weight in 1 million parts by volume of water) in the United States and Canada. Cyanogen chloride, which can be formed in the process of water chlorination, has been found at concentrations ranging from 0.00045 to 0.0008 ppm in drinking water from 35 U.S. cities. We do not know how many people in the general population of the United States are exposed to significant amounts of cyanide from eating foods that naturally contain it. Smoking is probably one of the major sources of cyanide exposure for people who do not work in cyanide-related industries. Breathing smoke-filled air during fires also may be a

major source of cyanide exposure. People who live near hazardous waste sites that contain cyanide may be exposed to higher amounts of cyanide than the general population.

Cyanide is used or produced in various occupational settings where activities include electroplating, some metal mining processes, metallurgy, metal cleaning, certain pesticide applications, tanning, photography and photoengraving, firefighting, and gas works operations. Cyanide also is used in some dye and pharmaceutical industries. The National Occupational Exposure Survey (NOES) has estimated the numbers of workers potentially exposed to the following cyanides: 4,005 to hydrogen cyanide; 66,493 to sodium cyanide; 64,244 to potassium cyanide; 3,215 to potassium silver cyanide; 3,606 to calcium cyanide; 22,339 to copper (I) cyanide; and 1,393 to cyanogen chloride. See Chapter 6 for more information about exposure to cyanide.

You can be exposed to thiocyanate in the same ways that you can be exposed to cyanide. Exposure to cyanide will expose you to thiocyanate because your body changes toxic cyanide to the much less toxic thiocyanate. Many foods (plants, dairy products, meat) contain thiocyanate. People who work in cyanide-related industries, such as the manufacture of electronic computing equipment, commercial printing, photographic processes, hospitals, production of adhesives, and construction and furniture manufacture, may be exposed to thiocyanate. No information is available about the concentrations of thiocyanate in unpolluted air or drinking water. We do not know how many people in the general U.S. population are exposed to significant amounts of thiocyanate from eating foods that contain thiocyanate. People who smoke or breathe tobacco smoke in the environment can be exposed to high levels of thiocyanate. People who live near hazardous waste sites that contain thiocyanate potentially can be exposed to higher amounts of thiocyanate compared with nonsmokers in the general population. The National Occupational Exposure Survey (NOES) estimates that 90,599 workers potentially are exposed to ammonium thiocyanate.

1.4 HOW CAN CYANIDE ENTER AND LEAVE MY BODY?

Cyanide can enter your body if you breathe air, eat food, or drink water that contains it. Cyanide can enter your body through the skin, but this may occur only in people who work in cyanide-related industries without adequate protective gear. You can be exposed to contaminated water, air, or soil at hazardous waste sites. Once it is in your lungs or stomach, cyanide can quickly enter the bloodstream. Some of the cyanide is changed to thiocyanate, which is less harmful and leaves the body in the urine. A small amount of cyanide is converted in the body to carbon dioxide, which leaves the body in the breath. At low levels of exposure to cyanide compounds, most of the cyanide and its products leave the body within the first 24 hours after exposure. The way cyanide enters and leaves the body is similar in people and animals. You can find more information about the movement of cyanide in the body in Chapter 3.

1.5 HOW CAN CYANIDE AFFECT MY HEALTH?

Scientists use many tests to protect the public from harmful effects of toxic chemicals and to find ways for treating persons who have been harmed.

One way to learn whether a chemical will harm people is to determine how the body absorbs, uses, and releases the chemical. For some chemicals, animal testing may be necessary. Animal testing may also help identify health effects such as cancer or birth defects. Without laboratory animals, scientists would lose a basic method for getting information needed to make wise decisions that protect public health. Scientists have the responsibility to treat research animals with care and compassion. Scientists must comply with strict animal care guidelines because laws today protect the welfare of research animals.

Exposure to small amounts of cyanide can be deadly regardless of the route of exposure. The severity of the harmful effects depends in part on the form of cyanide, such as hydrogen cyanide gas or cyanide salts. Exposure to high levels of cyanide for a short time harms the brain and heart and can even cause coma and death. Cyanide produces toxic effects at levels of 0.05 milligrams of cyanide per deciliter of blood (mg/dL) or higher, and deaths have occurred at

levels of 0.3 mg/dL and higher (a deciliter equals 100 milliliters). People who breathed 546 ppm of hydrogen cyanide have died after a 10-minute exposure; 110 ppm of hydrogen cyanide was life-threatening after a 1-hour exposure. People who eat small amounts of cyanide compounds in a short time may die unless they quickly receive antidote therapy.

Some of the first indications of cyanide poisoning are rapid, deep breathing and shortness of breath, followed by convulsions (seizures) and loss of consciousness. These symptoms can occur rapidly, depending on the amount eaten. The health effects of large amounts of cyanide are similar, whether you eat, drink, or breathe it; cyanide uptake into the body through the skin is slower than these other types of exposure. Skin contact with hydrogen cyanide or cyanide salts can irritate and produce sores. Workers who breathed in amounts of hydrogen cyanide as low as 6–10 ppm over a period of time developed breathing difficulties, chest pain, vomiting, blood changes, headaches, and enlargement of the thyroid gland.

Use of cassava roots as a primary food source has led to high blood cyanide levels in some people in tropical countries. Some of them suffered harmful effects to the nervous system, including weakness of the fingers and toes, difficulty walking, dimness of vision, and deafness, but chemicals other than cyanide also could have contributed to these effects. Cyanide exposure from cassava was linked to poor functioning and later enlargement of the thyroid gland; this is because in the body, cyanide is converted to thiocyanate, which is toxic to the thyroid gland. These effects have not been seen at levels of cyanide usually found in foods in the United States. Cyanide has not been reported to directly cause reproductive problems in people. Harmful effects on the reproductive system occurred in rats and mice that drank water containing sodium cyanide. Other cyanide effects in animal studies were similar to those observed in people. Cyanide has not been reported to cause cancer in people or animals. EPA has determined that cyanide is not classifiable as to its human carcinogenicity (ability to cause cancer in humans).

Vitamin B_{12}, a natural chemical containing cyanide, is beneficial to your body because it prevents anemia (iron-poor blood). The cyanide binds in vitamin B_{12} so that it does not serve as a source of cyanide exposure and cannot harm you. You can find more information about the harmful effects of cyanide in Chapter 3.

1.6 HOW CAN CYANIDE AFFECT CHILDREN?

This section discusses potential health effects in humans from exposures during the period from conception to maturity at 18 years of age.

Like adults, children can be exposed to cyanide by breathing air, drinking water, touching soil or water, or eating foods that contain cyanide, but the amounts are usually low. Breathing second-hand tobacco smoke is a more important source of cyanide exposure for children. Serious exposures can occur when children accidentally eat certain fruit pits, such as apricot kernels, containing a cyanide-releasing substance. A high blood level of thiocyanate is a sign of cyanide exposure in children, as well as adults. If a pregnant mother is exposed to cyanide, for example, by exposure to tobacco smoke, the fetus will be exposed to both cyanide and thiocyanate crossing the placenta. Animal studies show that cyanide and thiocyanate can be transferred into milk and pass to nursing baby animals, and suggest that this may also occur in humans.

Effects reported in exposed children are like those seen in exposed adults. Children who ate large quantities of apricot pits, which naturally contain cyanide as part of complex sugars, had rapid breathing, low blood pressure, headaches, and coma, and some died. Cyanide has not been reported to directly cause birth defects in people. However, among people in the tropics who eat cassava root, children have been born with thyroid disease because of the mothers' exposure to cyanide and thiocyanate during pregnancy. Birth defects occurred in rats that ate cassava root diets, and harmful effects on the reproductive system occurred in rats and mice that drank water containing sodium cyanide.

More information on the effects of cyanide exposure in children can be found in Section 3.7.

1.7 HOW CAN FAMILIES REDUCE THE RISK OF EXPOSURE TO CYANIDE?

If your doctor finds that you have been exposed to cyanide, ask whether your children might also have been exposed. Your doctor might need to ask your state health department to investigate.

Families can reduce their exposure to cyanide by not breathing in tobacco smoke, which is the most common source of cyanide exposure for the general population. In the event of a building fire, families should evacuate the building immediately, because smoke from burning plastics contains cyanide (and carbon monoxide). Breathing this smoke can lead to unconsciousness or death. Cyanide in smoke can arise from the combustion of certain plastics (e.g., polyacryl-amines, polyacrylics, polyurethane, etc.).

Compounds that release cyanide are naturally present in plants. The amounts are usually low in the edible portion but are higher in cassava. Pits and seeds of common fruits, such as apricots, apples, and peaches, may have substantial amounts of cyanide-releasing chemicals, so people should avoid eating these pits and seeds to prevent accidental cyanide poisoning. Parents should teach their children not eat fruit pits and seeds. People should be aware that taking high levels of vitamin C may increase the danger of cyanide poisoning from fruit pits, because more cyanide is released from the pits.

Studies have shown that the effects of cyanide are worse in humans and animals with poor nutrition. Diets containing adequate amounts of protein should improve recovery from cyanide exposure incidents.

1.8 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO CYANIDE?

Blood and urine levels of cyanide and thiocyanate can be measured, and small amounts of these compounds are always detectable in blood and urine because of natural processes. After cyanide poisoning, increased blood levels of cyanide and thiocyanate are detectable. Harmful effects can occur when blood levels of cyanide are higher than 0.05 parts per million (ppm), but some

effects can occur at lower levels. Tissue levels of cyanide can be measured if cyanide poisoning is suspected. However, cyanide and thiocyanate are cleared rapidly from the body in urine or exhaled breath; for that reason, blood measurements are only useful for detecting recent exposure. A bitter, almond-like odor in the breath may alert a physician that a person was exposed to cyanide, but this is not always found. In general, if cyanide exposure is suspected, treatment should be started immediately without waiting for the results of blood cyanide measurements. For more information about the health effects of cyanide and how it can be detected in the environment, see Chapters 3 and 7.

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

The federal government develops regulations and recommendations to protect public health. Regulations *can* be enforced by law. The EPA, the Occupational Safety and Health Administration (OSHA), and the Food and Drug Administration (FDA) are some federal agencies that develop regulations for toxic substances. Recommendations provide valuable guidelines to protect public health, but *cannot* be enforced by law. The Agency for Toxic Substances and Disease Registry (ATSDR) and the National Institute for Occupational Safety and Health (NIOSH) are two federal organizations that develop recommendations for toxic substances.

Regulations and recommendations can be expressed as "not-to-exceed" levels, that is, levels of a toxic substance in air, water, soil, or food that do not exceed a critical value that is usually based on levels that affect animals; they are then adjusted to levels that will help protect humans. Sometimes these not-to-exceed levels differ among federal organizations because they used different exposure times (an 8-hour workday or a 24-hour day), different animal studies, or other factors.

Recommendations and regulations are also updated periodically as more information becomes available. For the most current information, check with the federal agency or organization that provides it. Some regulations and recommendations for cyanide include the following:

EPA sets regulations for the amount of cyanide allowed in drinking water. The highest amount allowed is 200 micrograms of cyanide per liter of water (µg/L or 0.2 ppm). EPA also sets limits for amounts of hydrogen cyanide in stored foods that have been treated with cyanide to control pests. The maximum amount allowed on citrus fruits is 50 ppm. EPA also requires industries to report spills of 1 pound or more of potassium silver cyanide and 10 pounds or more of hydrogen cyanide, potassium cyanide, sodium cyanide, calcium cyanide, or copper cyanide.

OSHA sets levels of cyanide that are allowable in workplace air. The permissible exposure limit for hydrogen cyanide (HCN) and most cyanide salts is 10 ppm or 11 milligrams of cyanide per cubic meter of air (mg/m^3) averaged over an 8-hour workday and 40-hour workweek. NIOSH sets guidelines (recommended exposure limits or RELs) for chemicals in workplace air. The short-term REL for hydrogen cyanide is 4.7 ppm or 5 mg/m^3, averaged over 15 minutes and not to be exceeded at any time in the workday. There is a 10-minute ceiling limit for most cyanide salts of 4.7 ppm or 5 mg/m^3. NIOSH also determines levels that are immediately dangerous to life and health (IDLH) if a worker is exposed for more than half an hour. IDLH levels are 50 ppm for hydrogen cyanide or 25 mg/m^3 as cyanide for most cyanide salts.

For more information about regulations and advisories for cyanide in the environment or workplace, see Chapter 8.

1.10 WHERE CAN I GET MORE INFORMATION?

If you have any more questions or concerns, please contact your community or state health or environmental quality department, or contact ATSDR at the address and phone number below.

ATSDR can also tell you the location of occupational and environmental health clinics. These clinics specialize in recognizing, evaluating, and treating illnesses that result from exposure to hazardous substances.

Toxicological profiles are also available on-line at www.atsdr.cdc.gov and on CD-ROM. You may request a copy of the ATSDR ToxProfiles™ CD-ROM by calling the toll-free information and technical assistance number at 1-888-42ATSDR (1-888-422-8737), by e-mail at atsdric@cdc.gov, or by writing to:

Agency for Toxic Substances and Disease Registry
Division of Toxicology and Environmental Medicine
1600 Clifton Road NE
Mailstop F-32
Atlanta, GA 30333
Fax: 1-770-488-4178

Organizations for-profit may request copies of final Toxicological Profiles from the following:

National Technical Information Service (NTIS)
5285 Port Royal Road
Springfield, VA 22161
Phone: 1-800-553-6847 or 1-703-605-6000
Web site: http://www.ntis.gov/

2. RELEVANCE TO PUBLIC HEALTH

2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO CYANIDE IN THE UNITED STATES

Cyanides, a diverse family of compounds containing the highly reactive cyanide anion (CN^-), are produced from both anthropogenic and natural sources. The cyanide compounds most commonly found in the environment include sodium cyanide, potassium cyanide, and gaseous hydrogen cyanide, the latter being the main form present in air. The use of the term 'cyanide' in this section refers to the cyanide ion or the cyanogen radical (CN) in a compound. Cyanides may be released into the environment during the course of industrial usage or from smoke or vehicle exhaust containing the incomplete combustion products of nitrogen-containing organic polymers. Numerous plant species contain cyanogen glycosides that can release hydrogen cyanide upon biodegradation or ingestion. The edible portions of dietary plant species commonly used in the United States contain relatively low levels of cyanogen glycosides, although some pits and seeds of common fruits (e.g., apple, apricot, peach) contain significantly higher concentrations. The cassava root (tapioca), which is a major dietary staple in tropical countries, contains a sufficient amount of cyanogen glycosides to require special processing to reduce the danger of toxicity.

The general population is exposed to cyanides primarily by ingestion of food and water, and to a lesser degree, by inhalation. The cyanide content in unpolluted air averages 0.160–0.166 ppm (0.180–0.187 mg/m^3). Cyanide levels in smoke from U.S. commercial cigarettes range from 10 to 400 μg/cigarette for mainstream (inhaled) smoke and from 0.006 to 0.27 μg/cigarette for sidestream smoke. The cyanide content in 99.8% of public water systems using groundwater in the United States between 1993 and 1998 did not exceed the maximum concentration limit of 0.2 mg/L. Mean cyanide concentrations have been reported for some food products: cereal grains (0.002–0.45 μg/g), soy protein products (0.07–0.3 μg/g), canned unpitted fruits (0–4 μg/g), commercial fruit juices (1,900–4,600 μg/L), and U.S. lima beans (100–170 μg/g). There are no comprehensive data on the cyanide content of total diet samples in the United States, so it is not possible to estimate the average daily intake from foods.

See Chapter 6 for more detailed information regarding concentrations of cyanide and cyanogenic compounds in environmental media.

2.2 SUMMARY OF HEALTH EFFECTS

The toxicity of individual cyanide compounds is dependent on the ease with which they release cyanide anion (CN^-). For example, cyanide radicals have a low affinity for alkali metals and a high affinity for ferric iron (Fe^{3+}) and other metals; therefore, simple cyanide salts (for example, sodium cyanide or potassium cyanide) are toxic, whereas certain iron-containing cyanide compounds do not release CN^- readily and are nearly nontoxic. Cyanide exerts its primary toxicological effects by binding to the metallic cofactor in metalloenzymes, thereby impairing enzyme and cell function. Cytochrome c oxidase (an enzyme in the mitochondrial respiratory chain) is the most significant target of cyanide exposure since its inhibition prevents tissues from using oxygen. The result is a reduction in oxygen sufficient to cause tissue damage (histiotoxic hypoxia) throughout the body, with the most vulnerable tissues being those with high oxygen demands and/or a deficiency in detoxifying enzymes such as rhodanese. The inhibition of oxygen use 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, which is one biomarker of cyanide exposure. In addition to binding to cytochrome c oxidase, cyanide inhibits catalase, peroxidase, hydroxocobalamin, phosphatase, tyrosinase, ascorbic acid oxidase, xanthine oxidase, and succinic dehydrogenase activities, which may also contribute to the signs of cyanide toxicity.

Although the entire body is affected by cyanide exposure, adverse effects on the central nervous system are of the most consequence to the organism because of the high metabolic demand for oxygen in neurons and its control of respiratory function. Initial stimulation of carotid and aortic bodies and effects on the central nervous system adversely affect the function of the respiratory system, which contributes to the global histiotoxic hypoxia leading to death. Thus, the adverse affect of cyanide on respiration operates on both the cellular and physiological levels. High inhalation, oral, or dermal exposure levels result in convulsions, unconsciousness, and death due to inactivation of the centers controlling respiration. Lower exposures may result in headache or dizziness.

The signs of cyanide toxicity at concentrations leading to death in humans are well described. Intoxication at ≥2,000 ppm hydrogen cyanide 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, follows the first breath. In <1 minute, apnea, a few gasps, loss of consciousness, and convulsions occur. Cardiovascular failure may also occur, although the heart may continue to beat for 3–4 minutes after the last breath. Reported signs sometimes include a bitter almond-like odor on the breath and (in light-toned individuals) a rose-colored hue of the skin. The total absorbed dose of hydrogen

cyanide in such rapid deaths can be as low as 0.7 mg/kg. Dyspnea has been observed in survivors of inhalation poisoning incidents, and renal dysfunction (anuria followed by polyuria) was observed in one fatal inhalation exposure case. Similar signs of respiratory distress and renal dysfunction (albuminuria) were reported following ingestion of high doses of cyanide salts. Within a few minutes after swallowing the toxicant, the victim collapses, frequently with a scream. Dyspnea, convulsions, and death from asphyxia follow. Dermal exposure to cyanide results in comparable effects, but at higher doses. Based on case report studies, the following acute median lethal exposure levels for humans were estimated: an LC_{50} of 524 ppm for a 10-minute inhalation exposure to hydrogen cyanide, an LD_{50} of 1.52 mg/kg for the oral route, and an LD_{50} of 100 mg/kg for the dermal route, assuming that CN^- is readily released from the compound. Animal studies also report dyspnea, convulsions, and asphyxiation as effects of high-acute exposure to cyanide by any route of exposure.

Nonlethal exposures to hydrogen cyanide gas produces upper respiratory irritation, cough, altered sense of smell, nasal congestion, epistaxis, hemoptysis, and dyspnea in exposed workers. Workers acutely exposed to cyanogen, which dissociates into hydrogen cyanide and hydrocyanic acid, experienced nasal irritation. Other effects observed at nonlethal exposure levels include hypotension, heart palpitations, precordial pains, nausea and vomiting resulting from central nervous system stimulation or direct contact with cyanide, and albinuria. Animal studies also report bradycardia, arrhythmia, and T-wave abnormalities, vomiting, increased blood urea nitrogen, and histopathology of the renal proximal tubular epithelium and glomeruli. Hepatic effects have not been reported in humans, but have been observed in some animal studies.

Thyroid effects following cyanide exposure result from the interference of thiocyanate, a metabolite of cyanide, with iodine uptake and utilization in the thyroid gland. Reduced thyroid hormone levels, increasingly elevated levels of thyroid stimulating hormone, and goiter are typical sequelae of chronic cyanide exposure observed in tropical populations reliant on cassava as the main staple of the diet. The effects in these populations are intensified since cassava is a poor source of dietary protein. These conditions may not apply to populations in the United States since the varied diets provide levels of protein intake and general nutrition that are much higher than in countries using cassava as a food staple. Enlargement of the thyroid gland and increased levels of thyroid stimulating hormone were observed in workers exposed by inhalation to 6.4–15 ppm hydrogen cyanide. Thyroid toxicity was also reported in intermediate-duration oral studies in rats and pigs, but not in dogs because they are deficient in the enzyme rhodanese, which promotes thiocyanate formation.

In tropical countries, maternal ingestion of cassava during pregnancy has been associated with congenital hypothryoidism in some of the offspring. No other conclusive studies were located regarding developmental and reproductive effects in humans after exposure to cyanide or ingestion of foods containing cyanogenic plant material. Oral studies in animals indicate adverse effects on male reproduction (discussed below) and possible developmental toxicity. Studies in goats indicate that maternal exposure to cyanide can result in the transfer of cyanide and its metabolite, thiocyanate, through milk to offspring, but the relevance of goat data for humans is not established.

There is no evidence that cyanide exposure is correlated with carcinogenicity in humans or animals. Cyanide has only an indirect genotoxic effect *in vitro* and *in vivo* in that dying cells release endonucleases into the cytosol, ultimately resulting in DNA fragmentation.

The following sections discuss significant neurotoxic and reproductive effects resulting from exposure to cyanide in greater detail.

Neurological Effects. The most significant effects of cyanide exposure occur in the nervous system, especially in the brain (encephalopathy). Acute-duration inhalation of high concentrations of cyanide provokes a brief central nervous system stimulation followed by depression, convulsions, coma, and death in humans and animals. The effects are probably due to rapid biochemical changes in the brain, such as changes in ion flux, neurotransmitter release, and possibly peroxide formation. Death in acute cases is associated with effects on neurological centers controlling respiration. Convulsions and coma were also reported in humans and animals following acute dermal exposure to cyanide. It is likely that absorption of hydrogen cyanide vapor by the inhalation route also occurred in the human cases. Pathological changes that may occur in the central nervous system during acute exposure to high doses may complicate recovery. Severe Parkinsion-like symptoms have been noted in several cases of severe acute oral exposure to lethal amounts of cyanide (after antidotes were administered), often becoming more severe in the weeks following the initial exposure. Tremor and headache are milder symptoms of neurotoxicity in humans. Extensive degenerative changes have been produced experimentally in the brain by cyanide treatment, at 149–633 ppm for 2–10 minutes for dogs, the most sensitive species, and at higher levels in other species. In rats, cyanide-induced histopathological damage was observed in deep cerebral white matter, the corpus callosum, hippocampus, corpora striata, pallium, and substantia nigra following acute inhalation exposures to hydrogen cyanide lasting less than 2 hours. Partial remyelination after cessation of exposure has been reported, but it is apparent that this process is slow and incomplete. The topographic selectivity of cyanide-induced encephalopathy may be related to the depth of acute

intoxication and the distribution of the blood flow, which may result in selected regions of vascular insufficiency.

No data were available for cyanide-induced neurotoxicity in humans following intermediate-duration exposures by any route, but a number of animal studies are available, none of which, however, systematically evaluated neurotoxicity using a neurobehavioral test battery. Following repeated inhalation exposure to cyanide, transitory neurobehavioral effects (increased response rates without encephalopathy) were observed in monkeys at 12.5 ppm and more serious effects (tremors, rigidity, ataxia, atrophy of Purkinje cells, and vasodilation and hemorrhage in the brain) were observed in dogs, the most sensitive species tested, at 45 ppm. Oral exposure studies administered cyanide salts by oral gavage, in drinking water, or diet. In oral gavage studies in pigs or rats, behavioral changes (reduced activity) were observed at doses between 0.14 and 0.8 mg cyanide/kg/day and more serious effects (tremors, convulsions) were observed at 7.8 mg CN^-/kg/day, a lethal dose. No encephalopathy or overt signs of neurotoxicity were observed following repeated exposure via drinking water to doses as high as 12.5 mg CN^-/kg/day in rats or 28.8 mg CN^-/kg/day in mice. Myelin degeneration of spinal cord tracts was observed in rats receiving 30 mg CN^-/kg/day via dietary exposure.

Chronic exposure to lower cyanide concentrations in occupational settings causes a variety of symptoms from fatigue, dizziness, and headaches to ringing in the ears, paresthesias of extremities, and syncopes, or even hemiparesis and hemianopia. In addition, behavioral changes were reported following prolonged cyanide exposure in workers and animals, and loss of memory and decreases in visual acuity, psychomotor ability, and visual learning were reported in workers. It is possible, however, that during occupational exposure, such as electroplating operations, chemicals other than cyanide may have contributed to the effects observed. Chronic neurological effects are exacerbated by nutritional deficiencies or other disorders that provide inadequate levels of thiosulfate needed to detoxify cyanide. Chronic exposure to cyanogenic glycosides in certain cassava diets may lead to multiple neuropathies in exposed populations. Among those observed were hyperreflexia or spastic paraparesis of the extremities, spastic dysarthria, visual and hearing difficulties, and cerebellar signs. In addition, epidemics of Konzo, a neurological disease characterized by the sudden onset of varying degrees of symmetric, isolated, nonprogressive spastic paraparesis, have occurred in Africa and have been associated with high dietary cyanide exposure from “bitter” cassava that was not fully processed. Scopoletin, a potent hypotensive and spasmolytic agent, has been isolated from cassava roots and may contribute to the tropical ataxic neuropathy observed among cassava eaters. No chronic-duration data were available for neurotoxicity in exposed animals.

Reproductive Effects. No studies were located regarding reproductive effects in humans after any route of exposure, but a few studies reported reproductive effects in animals exposed via the oral route. Reproductive effects were the only adverse effects observed in rats and mice ingesting, respectively, 12.5 or 24.3 mg CN^-/kg/day as sodium cyanide in the drinking water for 13 weeks. In male rats, decreases in the caudal epididymal weight, epididymis weight, testis weight, spermatid heads, and spermatid counts were noted, whereas in male mice, significant decreases in the epididymal and caudal epididymal weights were noted without changes in sperm parameters. Alterations in the estrus cycle (longer duration of proestrus and diestrus stages compared to estrus and metestrus stages) were observed in female rats, but were not considered biologically significant. Several other studies support the observation of effects on the male reproductive system. Increased gonadal weight was observed in male rats exposed by oral gavage to copper cyanide or potassium silver cyanide for 90 days. A reduction in the spermatogenic cycle, testicular germ cell sloughing and degeneration, and occasional abnormal cells were noted in dogs ingesting 1.04 mg CN^-/kg/day as sodium cyanide in a rice diet or as the equivalent cassava diet. In contrast, no effects on reproductive organs were reported in hamsters exposed to cassava during gestation. Increased resorptions were noted following oral exposure of rats to cyanogenic glycosides in a cassava diet. The results of one study suggest that exposure to cyanide could lead to reproductive effects in humans.

2.3 MINIMAL RISK LEVELS (MRLs)

Estimates of exposure levels posing minimal risk to humans (MRLs) have been made for cyanide. An MRL is defined as an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (noncarcinogenic) over a specified duration of exposure. MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration within a given route of exposure. MRLs are based on noncancerous health effects only and do not consider carcinogenic effects. MRLs can be derived for acute, intermediate, and chronic duration exposures for inhalation and oral routes. Appropriate methodology does not exist to develop MRLs for dermal exposure.

Although methods have been established to derive these levels (Barnes and Dourson 1988; EPA 1990a), uncertainties are associated with these techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of the procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for health effects that are delayed in development

or are acquired following repeated acute insults, such as hypersensitivity reactions, asthma, or chronic bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

In the discussions of available toxicity data, results for dogs are included as supporting data, but these studies were not considered for MRL derivations because their intrinsic levels of the detoxifying enzyme rhodanese are lower than in other mammals, resulting in relatively greater sensitivity to cyanide exposures than in humans.

Inhalation MRLs

No MRLs were derived for inhalation exposure to cyanide because the available data indicated serious adverse effects occurring even at the lowest reported exposure levels. The acute inhalation toxicity database for humans includes case reports of lethality, serious neurological effects (coma with slight loss of peripheral vision after recovery, brain death), and/or metabolic effects (lactic acidosis indicative of impaired respiration) following brief exposure to 200–452 ppm hydrogen cyanide (Bonsall 1984; Singh et al. 1989). Acute hydrogen cyanide inhalation studies in laboratory rodents reported nonlethal acute inhalation effects following 30-minute exposures to hydrogen cyanide, including a 50% reduction in the respiratory rate in mice exposed at 63 ppm (Matijak-Schaper and Alarie 1982) and neurological (semiconsciousness, changes in electroencephalograph results), respiratory (severe dyspnea), and cardiological effects (bradycardia, arrhythmia, and T-wave abnormalities) in cynomolgous monkeys at 100 ppm (Purser et al. 1984). Cynomolgous monkeys exposed at 60 ppm for 30 minutes exhibited abnormal delta wave activity in electroencephalograms but no other abnormalities (Purser et al. 1984). A study of auditory function and histology in rats reported a no-observed-adverse-effect level (NOAEL) of 50 ppm hydrogen cyanide for a 3.5-hour exposure, but these data are not suitable for derivation of an MRL because the ear was the only organ evaluated in this study (Fechter et al. 2002). As none of these acute-duration studies observed the animals after the day of exposure, it is not known whether effects would have persisted or worsened over time. Since human case reports have mentioned increasing degradation of neurological status over a period of weeks (Carella et al. 1988; Chin and Calderon 2000; Feldman and Feldman 1990; Grandas et al. 1989; Rachinger et al. 2002; Rosenberg et al. 1989; Rosenow et al. 1995; Uitti et al. 1985), the available animal data showing minimal or no effects (Fechter et al. 2002; Purser 1984) are not reliable as points of departure for the derivation of an acute-duration inhalation MRL for cyanide.

No data are available for the intermediate-duration inhalation toxicity of cyanide in humans and only inadequate data are available for animals. One study reported 25% lethality, and serious neurological effects (tremors, ataxia, and atrophy of Purkinje and glial cells), respiratory effects (dsypnea), and gastrointestinal effects (vomiting, tenesmus, and diarrhea) in dogs exposed to 45 ppm hydrogen cyanide for 30 minutes/day, every other day for 28 days (Valade 1952). Another study reported increased creatine phosphokinase activity in the hearts of rats exposed to 200 ppm for 12.5 minutes/day, every fourth day for 20 days, but did not find evidence of cardiac histopathology or evaluate effects in other organ systems (O'Flaherty and Thomas 1982). As these studies reported serious effects in dogs, a sensitive species, or were limited in scope, neither are adequate for the derivation of an intermediate-duration MRL for cyanide.

The database for chronic-duration inhalation toxicity of cyanide consists of several occupational studies in workers in electroplating jobs. These studies described serious neurological effects (paresthesia, hallucination, weakness) as well as respiratory (dyspnea), cardiovascular (palpitations and chest pain), and thyroid effects (enlargement of thyroid gland or increased levels of thyroid stimulating hormone) following exposure to 6.4–15 ppm (Blanc et al. 1985; El Ghawabi et al. 1975). These studies were limited in either the lack of information about exposure levels, the small size of the cohorts, or the probable dermal contact with cyanide in liquid. Neurological effects were noted in workers who received multiple exposures (to gasoline, hydrochloric acid, and copper cyanide) (El Ghawabi et al. 1975). These studies are not adequate for deriving a chronic-duration inhalation MRL for cyanide because the lowest-observed-adverse-effect level (LOAEL) effects were serious, and because of the likelihood of multiple exposures and possible skin contact with liquid cyanide.

Oral MRLs

The database for acute-duration oral toxicity of cyanide consists of a few studies on human poisoning incidents and a limited number of studies in laboratory animals exposed to single doses of cyanide salts. In humans ingesting 4.6–15 mg CN^-/kg as potassium cyanide, serious adverse effects were observed in the nervous system (brain lesions, Parkinsonian-like signs, decreased verbal fluency, reduced information processing, coma), respiratory system (hyperventilation), cardiovascular system (shallow pulse, enlarged heart, and inaudible heart sounds), gastrointestinal system (nausea and vomiting), renal system (albinuria), and musculoskeletal system (generalized muscular rigidity) (Feldman and Feldman 1990; Liebowitz and Scharetz 1948; Rosenow et al. 1995). In rodents, single doses of 4–22 mg CN^-/kg as potassium, sodium, or calcium cyanide resulted in 50–90% lethality (Ferguson 1962; Smyth et al. 1969).

Developmental effects (delayed ossification and 23% reduction in fetal weight) were observed in the offspring of hamsters that ingested 1 mg CN^-/kg/day in cassava on gestational days 3–14 (Frakes et al. 1986a). Fetal effects occurred despite the absence of overt toxicity in dams at doses as high as 10.4 mg/kg/day. The presence of other chemicals such as scopoletin in cassava (Obidoa and Obasi 1991; see Section 3.2.2.4) confound the assessment of the dose-response for cyanide toxicity from the Frakes et al. (1986a) developmental toxicity study. No acute-duration oral MRL was derived for cyanide because of the serious effects observed at the lowest doses or because of uncertainties as to the dose-response for cyanide following ingestion of cassava.

- An MRL of 0.05 mg CN^-/kg/day has been derived for intermediate-duration oral exposure (15–364 days) to cyanide compounds.

There are no data for the intermediate-duration oral toxicity of cyanide in humans, but there are a number of studies in animals exposed to sodium or potassium cyanide. As discussed in Section 3.2.2, a number of animal studies examined the toxicity of cyanide following intermediate-duration oral exposure. However, not all studies are suitable for establishing dose-response relationships. Several studies (Gerhart 1986, 1987; Jackson 1988: Soto-Blanco et al. 2002a) in rats and pigs report neurological, thyroid, and gastrointestinal effects following gavage administration of cyanide; however, their usefulness for dose-response assessment is limited because the bolus dosing may overwhelm the detoxification process and is not characteristic of typical general population exposures to cyanide in drinking water. Similarly, although a toxicity study in dogs receiving sodium cyanide reported effects in the male reproductive system, adrenal gland, and kidney, the lower levels of the detoxifying enzyme rhodanese in this species both increases the sensitivity to cyanide and prevents the production of the metabolite thiosulfate to levels that would be toxic to the thyroid as seen in humans and other animals (Kamalu 1993). Additionally, studies involving exposure to cyanide via a cassava diet (Tewe and Maner 1981a, 1981b) were not considered as the basis of an MRL because there is evidence suggesting that other toxic compounds, such as scopoletin, may contribute to the observed toxic effects (Kamalu 1993).

In rat and mice exposed to sodium cyanide in drinking water for 13 weeks (NTP 1993), reproductive effects in males were the only adverse effects observed. Effects on male reproduction included reductions in epididymal weights (13%), testicular weights (8%), and spermatid counts (13.6%) in F344 rats exposed to 12.5 mg CN^-/kg/day, and 10–18% reductions in epididymal/caudal epididymal weights in B6C3F1 mice exposed to 24.3 mg CN^-/kg/day. In rabbits exposed to sodium cyanide in the diet at doses of 15 mg CN^-/kg/day for 4 weeks or 20 mg CN^-/kg/day for 40 weeks, hepatic toxicity (fatty degeneration and necrosis of the liver, increased serum levels of succinate dehydrogenase, alanine aminotransferase, and

alkaline phosphatase) and renal toxicity (tubular necrosis) were observed (Okolie and Iroanya 2003; Okolie and Osagie 1999). Neurotoxicity (myelin degeneration in the spinal cord) was observed in rats exposed at 30 mg CN^-/kg/day as potassium cyanide in food for 11.5 months (Philbrick et al. 1979). Effects on male reproduction were severe in dogs (germ cell sloughing and degeneration, reduced spermatogenesis cycle) (Kamalu 1993) and also observed in rats and mice in studies in which no other systemic effects were observed. Hepatic, renal, and body weight effects were reported in Wistar rats that received doses of 3.6 mg CN^-/kg/day as potassium cyanide in drinking water for 15 days (Sousa et al. 2002a). However, the reliability of these findings is questionable because of the lack of incidence data for the histopathological lesions and because no body weight effects were noted in other rat studies with exposures for longer durations and at higher doses. On the basis of these considerations, reproductive toxicity in males is selected as the critical effect of cyanide toxicity. The NTP (1993) bioassay in rats is selected as the principal study because it provided the lowest LOAEL and a NOAEL for the critical effect and examined the full range of tissues with extensive interim hematological, clinical chemistry, and urinalyses.

The intermediate-duration oral MRL was based on a NOAEL of 4.5 mg CN^-/kg/day and a LOAEL of 12.5 mg CN^-/kg/day in rats exposed for 13 weeks (NTP 1993). In this study, groups of 10 male and 10 female F344/N rats were given sodium cyanide in drinking water at concentrations of 0, 3, 10, 30, 100, or 300 ppm. The reported average cyanide intakes were 0, 0.2, 0.5, 1.4 (males), 1.7 (females), 4.5 (males), 4.9 (females), or 12.5 mg/kg/day, respectively). At the end of the study, the animals were evaluated for histopathology, hematology, clinical chemistry, urine chemistry, and reproductive toxicity; a satellite set of 10 males/group were also evaluated for hematology, clinical chemistry, and urinalyses at about 1, 3, 6, and 11 weeks. Exposure to cyanide had no significant effect on survival, body weight gain, the incidence of clinical signs, nonreproductive organ weights (absolute or relative to body weight), hematology, or clinical chemistry parameters, or histopathology. Dose-related reduced water intake and concomitant increased urine density were attributed to palatability effects at the higher doses. Some cyanide-related effects were observed in the study of reproductive parameters. Statistically significant decreases, compared to controls, were observed in the absolute weights of the left epididymis (7%), left cauda epididymis (13%), and left testis (7.6%) of rats treated at 12.5 mg/kg/day. In addition, 13.6% reductions compared to controls were observed in spermatid heads per testis and spermatid counts per mL suspension in rats treated at 12.5 mg/kg/day. The authors considered these to be evidence of a mild adverse effect of cyanide on the male reproductive system. The statistically significant reductions (7.4–8.6% lower than controls) in left cauda epididymis weights observed at 1.4 and 4.5 mg/kg/day were not considered biologically significant in the absence of any other significant effect. The small (<4%),

statistically significant, but not dose-related, reductions observed in spermatozoa motility in the 1.4, 4.5, and 12.5 mg/kg/day groups were within the range of normal values and were not considered biologically significant by the study investigators. For females, significantly ($p=0.03$, Wilk's Criterion) more time was spent in proestrus and diestrus stages and less time in estrus and metestrus stages in the 4.9 and 12.5 mg/kg/day dose groups than in controls, but a dose-relationship was not observed. For this reason, the study investigators did not consider these results unequivocal proof that cyanide adversely affects the female reproductive system. The intermediate-duration oral MRL of 0.05 mg/kg/day is based on a NOAEL of 4.5 mg/kg/day and a LOAEL of 12.5 mg/kg/day for reductions in the number of spermatid heads and sperm counts. The NOAEL was divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability) to derive the MRL.

A chronic oral MRL was not derived for cyanides because of the lack of suitable data in humans and animals. Studies of populations that customarily eat cassava are not appropriate for MRL derivations because some neurological effects may have resulted from scopoletin rather than released cyanide (Obidoa and Obasi 1991). One chronic-duration oral study found no significant cyanide-dependent effects in rats exposed to hydrogen cyanide in the diet for 2 years at doses as high as 7.8 mg/kg/day for males or 10.4 mg/kg/day for females (Howard and Hanzal 1955). However, the reliability of this study is low because evaporation of the cyanide from the feed resulted in unstable cyanide levels throughout the experiment and uncertainties as to the dose-response for cyanide. Since the human data are confounded by exposure to cassava and no LOAEL was identified in the only available animal study, no MRL was derived for chronic-duration oral exposure to cyanide.

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3. HEALTH EFFECTS

3.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective on the toxicology of cyanide. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health.

A glossary and list of acronyms, abbreviations, and symbols can be found at the end of this profile.

3.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

To help public health professionals and others address the needs of persons living or working near hazardous waste sites, the information in this section is organized first by route of exposure (inhalation, oral, and dermal) and then by health effect (death, systemic, immunological, neurological, reproductive, developmental, genotoxic, and carcinogenic effects). These data are discussed in terms of three exposure periods: acute (14 days or less), intermediate (15–364 days), and chronic (365 days or more).

Levels of significant exposure for each route and duration are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELs have been classified into "less serious" or "serious" effects. "Serious" effects are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). "Less serious" effects are those that are not expected to cause significant dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether an end point should be classified as a NOAEL, "less serious" LOAEL, or "serious" LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify these end points. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between "less serious" and "serious" effects. The distinction between "less serious" effects and "serious" effects is

considered to be important because it helps the users of the profiles to identify levels of exposure at which major health effects start to appear. LOAELs or NOAELs should also help in determining whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

The significance of the exposure levels shown in the Levels of Significant Exposure (LSE) tables (Tables 3-1 to 3-3) and figures (Figures 3-1 and 3-2) may differ depending on the user's perspective. Public health officials and others concerned with appropriate actions to take at hazardous waste sites may want information on levels of exposure associated with more subtle effects in humans or animals (LOAELs) or exposure levels below which no adverse effects (NOAELs) have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels or MRLs) may be of interest to health professionals and citizens alike.

This section provides information regarding known health effects of cyanide exposure. Exposure to hydrogen cyanide gas is most common by inhalation. In the discussion below, inhalation exposures are expressed as ppm hydrogen cyanide for a defined period of time. Exposure to cyanide can also occur by inhalation of cyanogen gas, a dimer of cyanide. However, cyanogen breaks down in aqueous solution into cyanide ion (CN^{-1}) and OCN^- ions (Cotton and Wilkinson 1980). The rate of the breakdown depends on pH and is faster in basic media (e.g., hydrogen cyanide is in equilibrium as H^+ and CN^- in blood with a pH of 7.38–7.44) than in acidic media (e.g., hydrogen cyanide is the only species in stomach contents at a pH of 3). The amount of cyanide ion formed within a body tissue or fluid as a result of exposure to cyanogen has been reported; however, the amount varies with type of body tissue and fluid. Thus, it is difficult to estimate cyanide levels in body tissues after cyanogen exposure. Therefore, studies regarding exposure to cyanogen are discussed in the text as ppm cyanogen, but are not included in LSE tables or figures.

Oral exposure to cyanide usually results from accidental, homicidal, or suicidal ingestion of cyanide salts. Sodium cyanide and potassium cyanide are the most frequently studied cyanide compounds. Copper cyanide, potassium silver cyanide, silver cyanide, and calcium cyanide are other compounds that humans could encounter through oral or dermal exposure; some data for cyanide compounds containing copper or silver are omitted from the LSE tables and figures because the toxicological effects may have been caused by the metal, rather than or in addition to CN^-. Similarly, toxicological data for ferricyanide compounds are omitted from the LSE tables and figures because CN^- remains tightly bound to iron and is therefore much less bioavailable than CN^- in soluble cyanide compounds. Cassava roots and certain fruit pits

contain compounds that can be broken down in the gastrointestinal tract to form cyanide. Cassava roots form the staple diet of some populations in Africa, Central and South America, and Asia. However, it must be noted that cassava roots are notoriously deficient in protein and other nutrients and contain many other compounds, in addition to cyanide, that could be responsible for some of the observed toxic effects. Thiocyanate, a metabolite of cyanide that is formed in the body after exposure to cyanide compounds, is responsible for toxic effects to the thyroid gland. When possible, all oral exposures are expressed as mg CN^-/kg/day.

A User's Guide has been provided at the end of this profile (see Appendix B). This guide should aid in the interpretation of the tables and figures for Levels of Significant Exposure and the MRLs.

3.2.1 Inhalation Exposure

3.2.1.1 Death

Inhalation of sufficient concentrations of hydrogen cyanide gas can rapidly cause death, which has led to the use of hydrogen cyanide in gas chamber executions (Wexler et al. 1947). An average fatal concentration for humans was estimated as 546 ppm hydrogen cyanide after a 10-minute exposure (DOA 1976, as cited in Ballantyne 1988). In one case, a worker exposed to 200 ppm hydrogen cyanide in a silver plating tank became unconscious and eventually died even though he had received antidotal therapy in a hospital (Singh et al. 1989). In other cases, exposure to 270 ppm hydrogen cyanide led immediately to death, 181 ppm hydrogen cyanide exposure was fatal after 10 minutes, and 135 ppm hydrogen cyanide was fatal after 30 minutes in humans (Dudley et al. 1942). Three deep-sea trawler men died when exposed to toxic fumes (containing lethal concentrations of hydrogen cyanide, carbon dioxide and hydrogen sulfide) from spoiled fish (Cherian and Richmond 2000); all three men collapsed within 1 minute of exposure, and cyanide exposure was confirmed in one man post-mortem by a blood cyanide concentration of 0.05 mg/L.

Levels of acute exposure resulting in animal deaths were reported in numerous studies and LC_{50} (lethal concentration, 50% death) values were provided for several species. Inhalation LC_{50} values of hydrogen cyanide in rats ranged from 143 ppm for 60 minutes to 3,417 ppm for 10 seconds (Ballantyne 1983a). Five-minute LC_{50} values of 503 ppm for the rat and 323 ppm for the mouse were reported by DiPasquale and Davis (1971). At lethal concentrations, animals exhibited hyperactivity and asphyxial convulsions with death occurring within 20 minutes of exposure; gross pathology findings included pulmonary

hemorrhage and congestion of the liver and kidney. Exposure to cyanide resulted in similar LC_{50} values in mice (Higgins et al. 1972; Matijak-Schaper and Alarie 1982). LC_{50} values for hydrogen cyanide in rabbits ranged from 188 ppm for 30 minutes to 2,200 ppm for 45 seconds (Ballantyne 1983a). Lethal concentrations were also reported in experiments with dogs exposed for acute (Haymaker et al. 1952) and intermediate durations (Valade 1952). Both studies used a small number of dogs for different exposure regimens so that statistical significance could not be evaluated.

The LC_{50} values in each species and LOAEL values for death in humans in the acute-, and intermediate-duration category are recorded in Table 3-1 and plotted in Figure 3-1. Lethality data for dogs have been omitted from Table 3-1 and Figure 3-1 because that species has a relatively low amount of the detoxifying enzyme rhodanese and is unusually susceptible to cyanide exposure compared to humans or other mammals (see Sections 3.4.3 and 3.5.3).

3.2.1.2 Systemic Effects

The systemic effects observed in humans and animals after inhalation exposure to cyanide are discussed below. The highest NOAEL values and all reliable LOAEL values for each systemic effect in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1. Systemic toxicity data for dogs have been omitted from Table 3-1 and Figure 3-1 because that species has a relatively low amount of the detoxifying enzyme rhodanese and is unusually susceptible to cyanide exposure compared to humans or other mammals (see Sections 3.4.3 and 3.5.3).

Respiratory Effects. Initially, respiration is stimulated, but later, dyspnea occurs in patients admitted to a hospital after acute hydrogen cyanide exposure (Chen and Rose 1952; Peden et al. 1986; Potter 1950). The levels of exposure in these accidental poisonings were not provided. Nasal irritation was reported in volunteers exposed to 16 ppm cyanogen (8 ppm cyanide) for 6–8 minutes (McNerney and Schrenk 1960). No effects were reported at 8 ppm cyanogen (4 ppm cyanide).

Dyspnea was observed in workers chronically exposed (5–15 years) to 6.4–10.4 ppm of an unspecified cyanide form evolved from sodium cyanide and copper cyanide during electroplating (El Ghawabi et al. 1975) and in workers exposed to 15 ppm hydrogen cyanide in a silver-reclaiming facility (Blanc et al. 1985). Other complaints included cough, sore throat, altered sense of smell, nasal congestion, epistaxis, and hemoptysis. However, exposure to other chemicals such as cleaners and cutting oils also occurs in electroplating operations.

Table 3-1 Levels of Significant Exposure to Cyanide - Inhalation

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
ACUTE EXPOSURE								
Death								
1	Human	10 min				546 (LC50)	DOA 1976 HCN	
2	Human	NS				200 M (fatal after 3 days)	Singh et al. 1989 HCN	
3	Rat (Wistar)	5 min				503 M (5-min LC50)	AMRL 1971 HCN	
4	Rat (NS)	60 min				143 (LC50 in 60 min)	Ballantyne 1983a HCN	
5	Rat (Wistar)	5 min				503 (LC50)	Higgins et al. 1972 HCN	
6	Mouse (ICR)	5 min				323 M (5-min LC50)	AMRL 1971 HCN	
7	Mouse (ICR)	5 min				323 (LC50)	Higgins et al. 1972 HCN	
8	Mouse (ICR)	3 min				400 M (90% lethality)	Hume et al. 1995 HCN	
9	Mouse (Swiss-Webster)	30 min				166 M (LC50)	Matijak-Schaper and Alarie 1982 HCN	
10	Rabbit (NS)	35 min				188 (LC50 in 35 min)	Ballantyne 1983a HCN	

Table 3-1 Levels of Significant Exposure to Cyanide - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
Systemic								
11	Human	13 min	Ocular		452 M (slight loss of peripheral vision after recovery)		Bonsall 1984 HCN	
12	Monkey (Cynomolgus)	30 min	Resp			100 (severe dyspnea)	Purser et al. 1984 HCN	
			Cardio			100 (bradycardia, arrhythmia, T-wave abnormalities)		
13	Mouse (Swiss-Webster)	30 min	Resp			63 M (DC50)	Matijak-Schaper and Alarie 1982 HCN	
Neurological								
14	Human	13 min				452 M (coma)	Bonsall 1984 HCN	
15	Monkey (Cynomolgus)	30 min				100 (semiconsciousness, disrupted respiration, EEG changes)	Purser et al. 1984 HCN	
16	Rat (Long- Evans)	3.5 hr		50 M			Fechter et al. 2002 HCN	
INTERMEDIATE EXPOSURE								
Systemic								
17	Rat (Long- Evans)	20 d 4 d intervals 12.5 min/d	Cardio			200 M (increased creatine phosphokinase activity)	O'Flaherty and Thomas 1982 HCN	

Table 3-1 Levels of Significant Exposure to Cyanide - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
CHRONIC EXPOSURE								
Systemic								
18	Human	NS (occup)	Resp		15 M (dyspnea)		Blanc et al. 1985 HCN	
			Cardio		15 M (palpitations, chest pain)			
			Gastro		15 M (nausea)			
			Endocr		15 M (increased mean thyroid stimulating hormone levels)			
			Dermal		15 M (rash)			
			Ocular		15 M (eye irritation)			
			Bd Wt		15 M (approximately 8% weight loss)			
19	Human	5-15 yr (occup)	Resp		6.4 M (dyspnea, irritation of throat)		El Ghawabi et al. 1975 NaCN	
			Cardio		6.4 M (precordial pain)			
			Gastro		6.4 M (vomiting)			
			Hemato		6.4 M (increased hemoglobin and lymphocytes)			
			Endocr		6.4 M (thyroid enlargement)			
			Dermal	10.4 M				
			Ocular		6.4 M (lacrimation)			

Table 3-1 Levels of Significant Exposure to Cyanide - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
Neurological								
20	Human	NS (occup)				15 M (persistent headache, dizziness, paresthesia)	Blanc et al. 1985 HCN	
21	Human	5-15 yr (occup)				6.4 M (confusion, hallucination, headache, dizziness, weakness)	El Ghawabi et al. 1975 NaCN	

a The number corresponds to entries on Figure 3-1.

Bd Wt = body weight; Cardio = cardiovascular; d = day(s); DC50 = concentration that resulted in 50% decrease in average respiratory rate; EEG = electroencephalogram; Endocr = endocrine; F = female; Gastro = gastrointestinal; HCN = hydrogen cyanide; Hemato = hematological; LC50 = lethal concentration, 50%kill; LOAEL = lowest-observed-adverse-effect level; M = male; min = minutes; NaCN = sodium cyanide; NOAEL = no-observed-adverse-effect level; NS = not specified; (occup) = occupational; Resp = respiratory; sec = second(s); yr = year(s); x = time(s)

Figure 3-1 Levels of Significant Exposure to Cyanide - Inhalation

Acute (≤14 days)

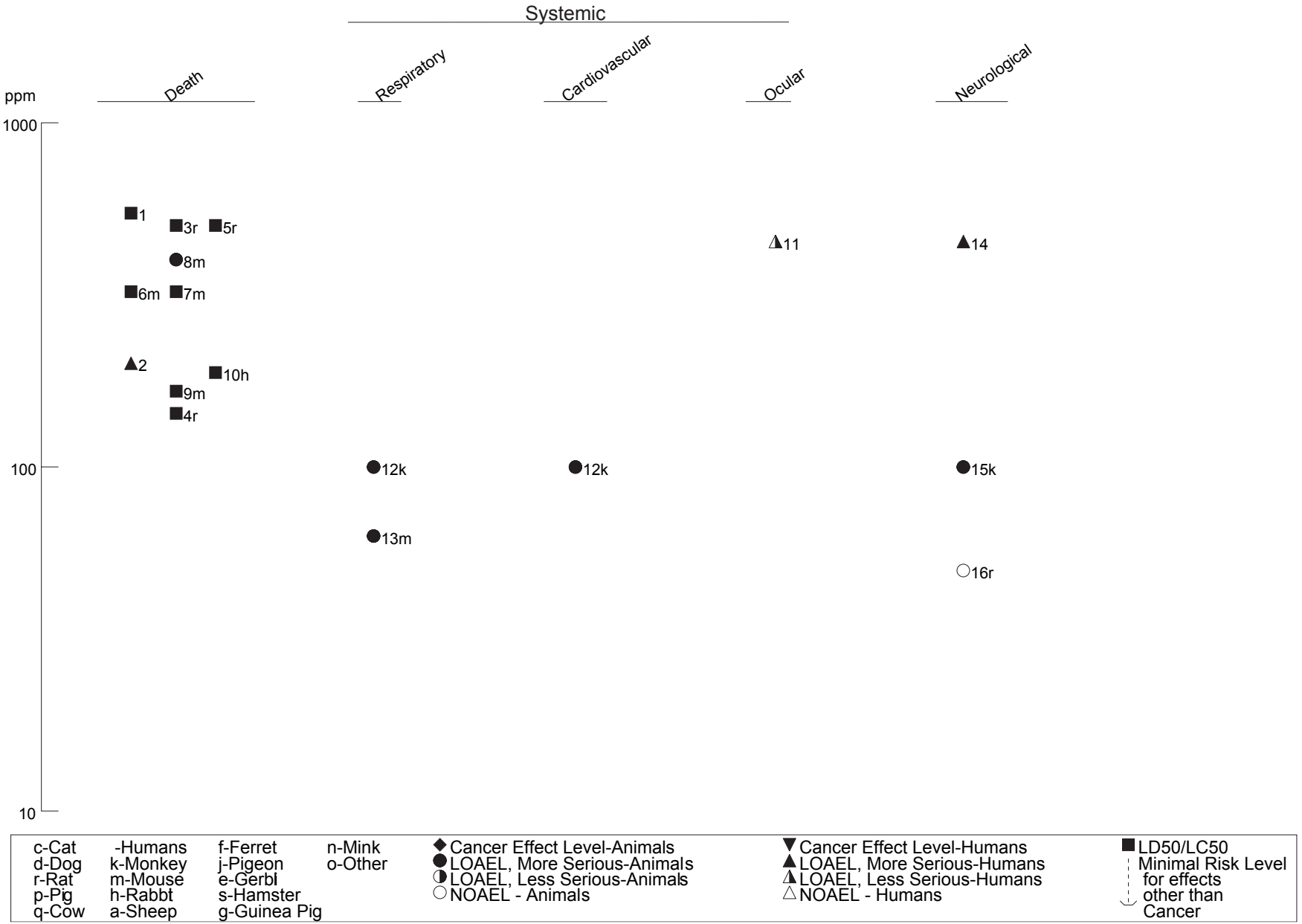


Figure 3-1 Levels of Significant Exposure to Cyanide - Inhalation (*Continued*)

Intermediate (15-364 days)

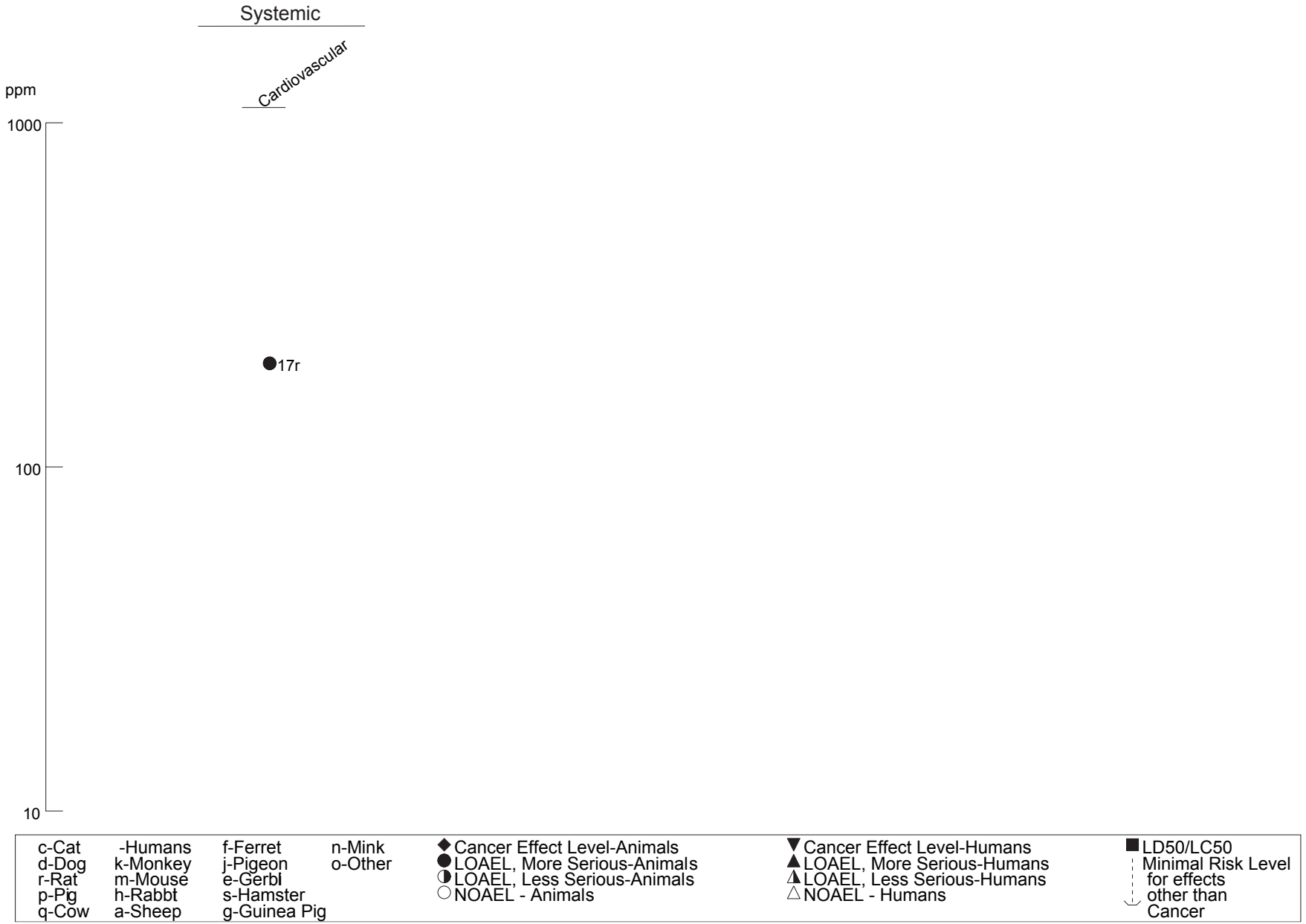
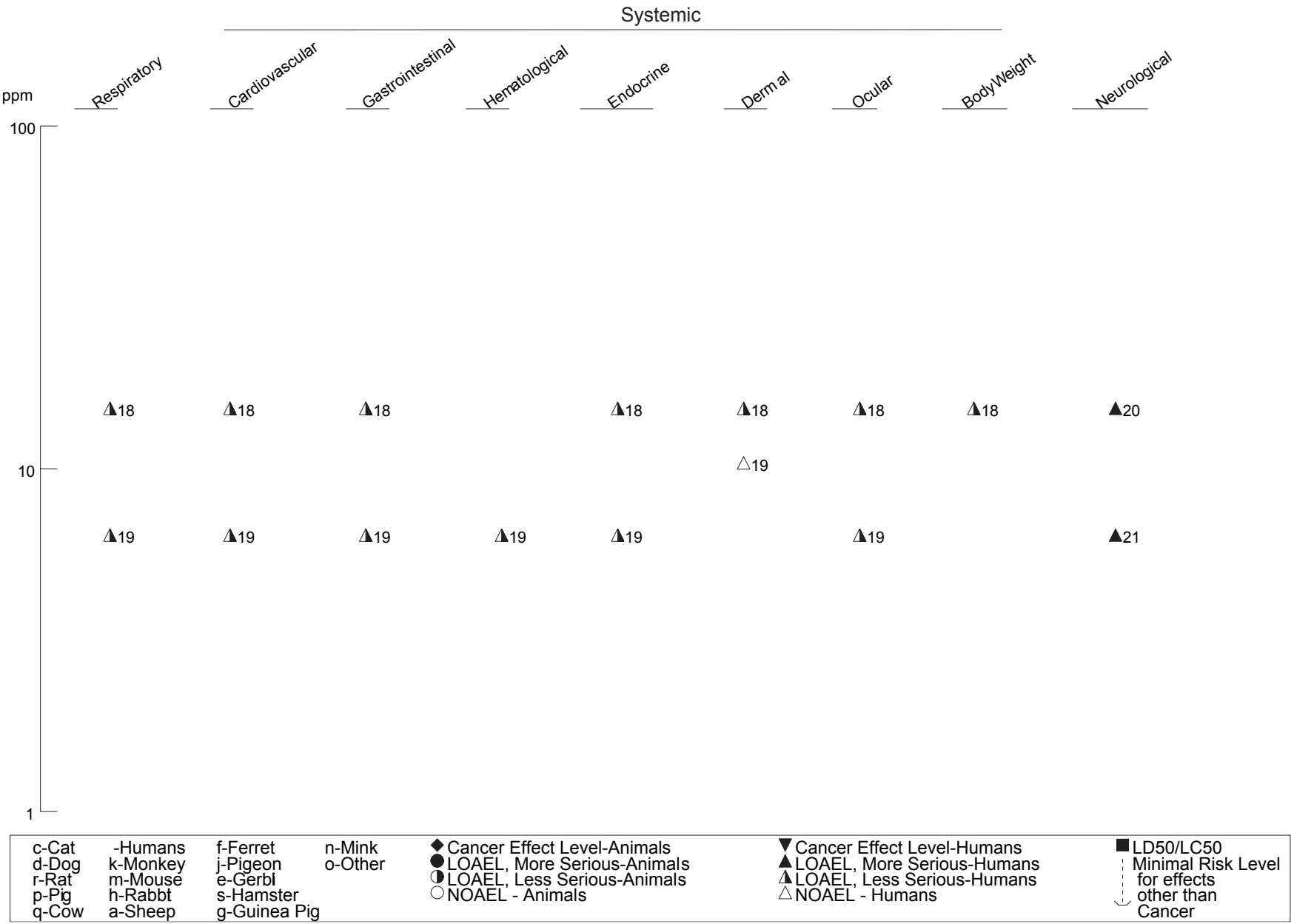


Figure 3-1 Levels of Significant Exposure to Cyanide - Inhalation (*Continued*)

Chronic (≥365 days)



Asphyxia has been observed in rats exposed to 250 ppm cyanogen (125 ppm cyanide) for 7.5–120 minutes (McNerney and Schrenk 1960), asphyxia and pulmonary edema were observed in dogs exposed to concentrations ranging from 149 to 633 ppm hydrogen cyanide for 2–10 minutes (Haymaker et al. 1952), while severe dyspnea was observed in monkeys exposed to 100 ppm hydrogen cyanide for 30 minutes (Purser et al. 1984). Exposure to 63 ppm hydrogen cyanide for 30 minutes resulted in a 50% decrease in respiratory rate of mice due to depression of the respiratory center (Matijak-Schaper and Alarie 1982).

In intermediate-duration studies, no respiratory effects were reported in rats exposed to 25 ppm cyanogen (12.5 ppm cyanide) for 6 months, and a decrease in total lung moisture content was the only finding in monkeys exposed to 11 ppm cyanogen (5.5 ppm cyanide), also for 6 months (Lewis et al. 1984). Dyspnea was found in dogs exposed to 45 ppm hydrogen cyanide for 30 minutes a day at 2–8-day intervals for 28–96 days (Valade 1952).

Cardiovascular Effects. Wexler (1947) reported on four men who were executed by inhalation of hydrogen cyanide gas (concentration not reported). He reported a distinct slowing of the heart rate within 1–3 minutes of exposure, with further changes in the heart rate, sinus irregularities, and audio-visual dissociation. Palpitations and hypotension were the most frequently reported cardiovascular effects in patients after accidental inhalation poisoning with cyanide; however, exact exposure levels were not known (Peden et al. 1986). Workers occupationally exposed to 6.4–10.4 ppm cyanide for 5–15 years, which evolved from sodium cyanide and copper cyanide during electroplating, complained of precordial pain (El Ghawabi et al. 1975). About 14% of workers exposed to 15 ppm hydrogen cyanide in a silver-reclaiming facility reported palpitations and 31% reported chest pain (Blanc et al. 1985). Exposure to other chemicals such as cleaners and cutting oils may have also occurred during electroplating operations.

Bradycardia, arrhythmias, and T-wave abnormalities were observed in monkeys exposed to 100 ppm hydrogen cyanide for 30 minutes (Purser et al. 1984). Increased cardiac-specific creatinine phosphokinase activity was measured in blood samples from rats 2 hours after 12.5 minutes of exposure to 200 ppm hydrogen cyanide for 20 days at 4-day intervals (O'Flaherty and Thomas 1982). However, no treatment-related changes were found in the hearts at histopathology. In addition, no cardiovascular effects were reported at necropsy in rats and monkeys exposed to 25 ppm cyanogen (12.5 ppm cyanide) for 6 months (Lewis et al. 1984).

Gastrointestinal Effects. Nausea or vomiting was reported in 69% of workers exposed to 15 ppm hydrogen cyanide in a silver reclaiming facility (Blanc et al. 1985). Vomiting was also reported in workers exposed to 6.4–10.4 ppm cyanide evolved from sodium cyanide and copper cyanide during electroplating (El Ghawabi et al. 1975), but exposure to other chemicals such as cleaners and cutting oils may have also contributed to the effects. The gastrointestinal effects resulting from cyanide exposure are probably provoked by central nervous system effects and/or by irritation of the gastric mucosa in cases in which the gas is swallowed during breathing.

Information regarding gastrointestinal effects in animals is limited to a report of vomiting in dogs exposed to 45 ppm hydrogen cyanide for 28–96 days (Valade 1952).

Hematological Effects. Increased hemoglobin and lymphocyte count were observed in workers exposed to 6.4–10.4 ppm of an unspecified cyanide form during electroplating (El Ghawabi et al. 1975). The results were significantly different from controls. Furthermore, punctate basophilia of erythrocytes, which indicated toxic poisoning, was present in 28 of 36 subjects. However, exposure to copper, a known hematotoxic agent, also occurred during the electroplating operations. In another study (Kumar et al. 1992), an increase in neutrophil values, an increase in erythrocyte sedimentation rate, and a decrease in hemoglobin levels were noted in male workers exposed to unspecified concentrations of cyanide for an unspecified duration during case hardening and electroplating.

In animals, no hematological effects were found in rats and monkeys exposed to 25 ppm cyanogen (12.5 ppm cyanide) 6 hours/day, 5 days/week, for 6 months (Lewis et al. 1984).

Musculoskeletal Effects. No studies were located regarding musculoskeletal effects in humans after inhalation exposure to cyanide.

No musculoskeletal effects were observed in rats or monkeys exposed to 25 ppm cyanogen (12.5 ppm cyanide) for 6 hours/day, 5 days/week for 6 months (Lewis et al. 1984).

Hepatic Effects. An increase in serum alkaline phosphatase was noted in workers exposed to unspecified levels of cyanide; however, serum bilirubin was found to be within the normal range in these workers (Kumar et al. 1992).

Only one study reported on pathological and histopathological examinations of the liver in animals. No changes were found in rats and monkeys exposed to 25 ppm cyanogen (12.5 ppm cyanide) for 6 months (Lewis et al. 1984).

Renal Effects. One study was located regarding renal effects in humans after inhalation exposure to cyanide. Singh et al. (1989) reported anuria followed by polyuria in a man who was occupationally exposed to 200 ppm hydrogen cyanide) for an unspecified length of time.

No histopathological changes were observed in kidneys of rats and monkeys exposed to 25 ppm cyanogen (12.5 ppm cyanide) 6 hours/day, 5 days/week for 6 months (Lewis et al. 1984).

Endocrine Effects. Mean thyroid stimulating hormone (TSH) levels were significantly higher (although within normal limits) in a group of 36 workers exposed to 15 ppm hydrogen cyanide for an unspecified duration in a silver-reclaiming facility than in unexposed individuals ($p<0.05$). T_3 levels in high exposure workers were also elevated relative to unexposed workers ($p<0.01$). Data for T_4 were not presented, but the investigators indicated that the absence of T_4 abnormalities could be accounted for by the time lapse between exposure and examination (median 10.5 months) (Blanc et al. 1985). Similarly, thyroid enlargement was present in 20 of 36 workers exposed for 5–15 years to 6.4–10.4 ppm cyanide evolved from sodium cyanide and copper cyanide. The endocrine effect may be due to formation of thiocyanate, a metabolite of cyanide. However, exposure to other chemicals such as cleaners and cutting oils also occurs during electroplating operations. Thyroid ^{131}I uptake was significantly higher when compared with the control group. This may be due to thiocyanate's ability to block iodine uptake and also compete with I^- as a substrate for the thyroid peroxidase, resulting in less "organification" of I_2 (decreasing the iodination of tyrosine to form iodotyrosine) by the thyroid gland. Since the workers were away from work on the 2 days preceding the test, the results may be explained on the basis of acute cyanide withdrawal, as with other anti-thyroid agents, where sudden cessation of the drug leads to rapid accumulation of iodine in the iodine-depleted gland (El Ghawabi et al. 1975).

No studies were located regarding endocrine effects in animals after inhalation exposure to cyanide.

Dermal Effects. Cyanide caused a rash in 42% of workers exposed to 15 ppm hydrogen cyanide (Blanc et al. 1985). Brick-red chemical burns on the skin were observed in a man who was occupationally exposed to 200 ppm hydrogen cyanide for an unspecified length of time (Singh et al.

1989). No dermatitis was reported in workers exposed to 6.4–10.4 ppm cyanide evolved from sodium cyanide and copper cyanide (El Ghawabi et al. 1975).

No studies were located regarding dermal effects in animals after inhalation exposure to cyanide.

Ocular Effects. Cyanogen caused eye irritation in volunteers during acute exposure to 16 ppm (8 ppm cyanide) (McNerney and Schrenk 1960). No effect was observed in those exposed to 8 ppm cyanogen (4 ppm cyanide). Slight loss of peripheral vision was the only persistent finding from a case report of a man who had been exposed to 452 ppm hydrogen cyanide (for 13 minutes while cleaning a chemical tank (Bonsall 1984). During chronic occupational exposure, eye irritation occurred in workers of two electroplating factories (exposure levels not specified) (Chandra et al. 1988). In other studies, cyanide caused eye irritation in 58% of workers exposed to 15 ppm hydrogen cyanide (Blanc et al. 1985) and lacrimation in workers exposed to 6.4 ppm cyanide (El Ghawabi et al. 1975). The eye irritation may not be due solely to cyanide exposure, as electroplating workers may be exposed to a variety of chemicals that are irritating to the eyes.

Information regarding ocular effects in animals after inhalation exposure is limited to a report of eye irritation in rats acutely exposed (7.5–120 minutes) to 250 ppm cyanogen (125 ppm cyanide) (McNerney and Schrenk 1960).

Body Weight Effects. In an occupational setting, loss of appetite was reported in 58% and weight loss (approximately 8%) in 50% of workers exposed to 15 ppm hydrogen cyanide (for an unspecified duration in a silver-reclaiming facility (Blanc et al. 1985).

Decreased body weight was reported in rats exposed to 25 ppm cyanogen (12.5 ppm cyanide) 6 hours/day, 5 days/week for 6 months (Lewis et al. 1984).

3.2.1.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological effects in humans or animals after inhalation exposure to cyanide.

3.2.1.4 Neurological Effects

The central nervous system is a primary target for cyanide toxicity. Acute exposure of humans to fatal levels of hydrogen cyanide causes a brief stage of central nervous system stimulation followed by depression, convulsions, coma with abolished deep reflexes and dilated pupils, paralysis, and in some cases, death (Bonsall 1984; Chen and Rose 1952; Peden et al. 1986; Potter 1950; Singh et al. 1989). Though clinical symptoms of cyanide poisoning are well recognized, specific dose-response data are generally not known. Acute exposure to lower concentrations can cause lightheadedness, breathlessness, dizziness, numbness, and headaches (Lam and Lau 2000; Peden et al. 1986). Impaired short-term memory was reported as a delayed effect in a female 1 year after treatment for convulsions following acute exposure to cyanide gas (Lam and Lau 2000).

Chronic exposure of humans to potassium cyanide and other chemicals may have produced severe neurological effects such as hemiparesis and hemianopia (Sandberg 1967). During chronic occupational exposure, workers exposed to 15 ppm hydrogen cyanide for an unspecified duration reported fatigue, dizziness, headaches, disturbed sleep, ringing in ears, paresthesias of extremities, and syncopes (Blanc et al. 1985). A dose-effect was demonstrated on high- and low-exposure jobs; however, exact cyanide concentrations in the air were not known. Neurological effects persisted in some workers even after a 10-month nonexposure period. Similar effects were observed in workers exposed to 6.4 ppm cyanide (El Ghawabi et al. 1975). Clinical symptoms included headaches, weakness, changes in taste and smell, dizziness, disturbances of accommodation, and psychosis. Loss of delayed and immediate memory and decreases in visual ability, psychomotor ability, and visual learning were reported in workers exposed to unspecified levels of hydrogen cyanide for an unspecified duration (Kumar et al. 1992). In another study, chronic occupational exposure of workers (5–19 years) to hydrogen cyanide (exposure levels not specified) resulted in headaches and dizziness in workers (Chandra et al. 1988). Furthermore, when behavioral functions were tested in this cohort, an alteration of delayed memory and/or visual impairment was found in 31.5% of workers. However, exposure to other chemicals, such as cleaners and cutting oils, also occurs during electroplating operations.

The central nervous system is also a primary target for cyanide toxicity in animals. Following acute exposure, neurological effects before death included restless and panic movements, poor coordination, tremor, and lethargy in rats exposed to 250 ppm cyanogen (125 ppm cyanide) for 1.5–120 minutes (McNerney and Schrenk 1960). When rats were exposed to unspecified concentrations of hydrogen cyanide and kept unconscious for 20–60 minutes, lesions of various degrees developed in the brain

(Hirano et al. 1967; Levine 1969; Levine and Stypulkowski 1959a). Necrosis was found mainly in the mid-sagittal sections of the brain. Demyelination was also reported and morphological signs indicative of remyelination were reported in rats several months after cyanide intoxication (Hirano et al. 1968), but it was apparent that this process was slow and incomplete. Acute exposure of dogs for 2–10 minutes, each to a different concentration ranging from 149 to 633 ppm hydrogen cyanide resulted in motor incoordination, muscular rigidity, and coma (Haymaker et al. 1952). Extensive necrosis in the grey matter of the neural system was observed at necropsy. After acute exposure (up to 30 minutes) to 60–100 ppm hydrogen cyanide, increased delta activity was observed in electroencephalograms of cynomolgus monkeys, but those exposed at the higher level experienced semiconsciousness within 20 minutes (Purser 1984; Purser et al. 1984). Cyanide exposure levels in most acute-duration studies were relatively high and usually caused death in some animals. Only transitory behavioral changes were reported in monkeys exposed to 25 ppm cyanogen (12.5 ppm cyanide) for 6 months (Lewis et al. 1984). No effects were found at 11 ppm cyanogen (5.5 ppm cyanide) exposure. Exposure of dogs to 45 ppm hydrogen cyanide for 28–96 days caused tremors, convulsions, and coma (Valade 1952). Vascular and cellular lesions were found in the central nervous system.

In rats exposed to 10–50 ppm hydrogen cyanide for 3.5 hours, there was no adverse effect 4 weeks later on hearing or the histology of cochlear hair cells (Fechter et al. 2002). However, co-administration for 2 hours of 100 dB broadband noise (13.6 kHz) caused an hydrogen cyanide-dose-related increase in auditory compound action potential thresholds compared with noise administered alone that was statistically significant at 30 ppm hydrogen cyanide; a loss of outer hair cells of the cochlea was noted in rats exposed to hydrogen cyanide and noise.

The highest NOAEL value and all reliable LOAEL values for neurological effects in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1. Neurotoxicity data for dogs have been omitted from Table 3-1 and Figure 3-1 because that species has a relatively low amount of the detoxifying enzyme rhodanese and is unusually susceptible to cyanide exposure compared to humans or other mammals (see Sections 3.4.3 and 3.5.3).

No studies were located regarding the following health effects in humans or animals after inhalation exposure to cyanide:

3.2.1.5 Reproductive Effects

3.2.1.6 Developmental Effects

3.2.1.7 Cancer

3.2.2 Oral Exposure

3.2.2.1 Death

An average fatal dose of 1.52 mg/kg cyanide for humans has been calculated from case report studies of intentional or accidental poisonings (EPA 1987a). The lowest fatal oral dose reported in humans was estimated as 0.56 mg/kg cyanide (form not specified) (Gettler and Baine 1938). However, these data were obtained from the case history; furthermore, analytical measurements of the time lack the precision of current technology.

Oral LD_{50} (lethal dose, 50% death) values for sodium cyanide were calculated as 3 mg CN^-/kg for unfasted rats, and 2.7 mg CN^-/kg/day for rats that fasted for 24 hours before exposure and for unfasted rabbits (Ballantyne 1988); initial signs of toxicity appeared sooner in rats (1 minute for both groups) than in rabbits (4 minutes) and the time to death was shorter in the fasted rats than in the unfasted rats or rabbits (17 rather than 22 minutes). In rats, the acute LD_{50} was 8 mg CN^-/kg as sodium cyanide, but 22 mg CN^-/kg as calcium cyanide (Smyth et al. 1969). Acute LD_{50} values in rabbits were similar (2.34–2.7 mg CN^-/kg/day) regardless of whether the source was hydrocyanic acid, sodium cyanide, or potassium cyanide (Ballantyne 1983a). Mortality was 95% in rats and mice that received a single dose of 4 and 6 mg CN^-/kg, respectively, in the form of potassium cyanide in a volume of water equivalent to 5% of body weight (Ferguson 1962); mortality was lower (50% in rats and 35% in mice) when the same doses were delivered in a volume of water equivalent to 1.25% of body weight. Increased mortality was observed in rats exposed to 14.5 mg CN^-/kg/day as copper cyanide for 90 days (Gerhart 1986) and to 2.6 mg CN^-/kg/day as potassium silver cyanide for 90 days (Gerhart 1987); these data are omitted from Table 3-2 because of the possible confounding effect of the metals. Hemolytic anemia, which probably resulted from copper toxicity, caused death in rats exposed to copper cyanide (Gerhart 1986). No deaths

were reported in male and female rats exposed to 0.2–12.5 mg CN^-/kg/day in the drinking water for 13 weeks (NTP 1993).

The LD_{50} and minimum lethal dose (LD_{LO}) values in each species and all reliable LOAEL values for death in each species and duration category are recorded in Table 3-2 and plotted in Figure 3-2.

3.2.2.2 Systemic Effects

The systemic effects observed in humans and animals after oral exposure to cyanide are discussed below. The highest NOAEL values and all reliable LOAEL values for each systemic effect in each species and duration category are recorded in Table 3-2 and plotted in Figure 3-2. Studies on dogs have been omitted because that species has a relatively low amount of the detoxifying enzyme rhodanese and is unusually susceptible to cyanide exposure compared to humans or other mammals (see Sections 3.4.3 and 3.5.3). Studies involving ingestion of cassava have also been omitted because of the confounding effects of malnutrition noted in human studies and because of the presence of other toxic compounds besides cyanogenic glycosides that might contribute to toxicity (e.g., scopoletin; see Section 3.10). Intermediate-duration studies that employed oral gavage dosing are omitted because bolus administration may overwhelm detoxification processes in a manner not typical of gradual exposures in drinking water for the general population.

Respiratory Effects. Breathing irregularities occur after cyanide poisoning through oral exposure. Stertorous, deep, and rapid breathing was reported in a man who ingested ≈15 mg CN^-/kg as potassium cyanide in a suicide attempt (Liebowitz and Schwartz 1948). Shortness of breath and dyspnea were observed in two reports of suicide attempts; one man ingested 7.6 mg CN^-/kg (Goodhart 1994) and the other man ingested 0.57 mg CN^-/kg (Saincher et al. 1994), both as potassium cyanide. A man admitted to a hospital after ingesting an unknown amount of sodium cyanide ceased breathing (Grandas et al. 1989). A woman who ingested an unknown amount of cyanide developed acute respiratory distress syndrome and arteriolization (elevated oxyhemoglobin saturation) of the ventral venous blood (Martin-Bermudez et al. 1997). Dyspnea developed in a woman 20 minutes after eating 30 apricot pits (~15 g), resulting in an estimated cyanide exposure between 0.026 and 0.234 mg CN^-/kg (Suchard et al. 1998). Tachypnea was also reported in children who were poisoned by cyanide after ingesting apricot pits (Lasch and El Shawa 1981).

Table 3-2 Levels of Significant Exposure to Cyanide - Oral

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
ACUTE EXPOSURE								
Death								
1	Rat (Sprague-Dawley)	once (GW)				4 (19/20 died)	Ferguson 1962 KCN	
2	Rat (NS)	once (GW)				22 (LD50)	Smyth et al. 1969 Ca(CN)2	
3	Rat (NS)	once (GW)				8 (LD50)	Smyth et al. 1969 NaCN	
4	Mouse (Swiss-Webster)	once (GW)				6 (19/20 died)	Ferguson 1962 KCN	
Systemic								
5	Human	once (IN)	Resp			15 M (hyperventilation)	Liebowitz and Schwartz 1948 KCN	
			Cardio			15 M (shallow pulse, inaudible heart sounds, enlarged heart)		
			Gastro		15 M (vomiting and nausea)			
			Hemato	15 M				
			Musc/skel		15 M (generalized muscular rigidity)			
			Renal			15 M (albuminuria)		

Table 3-2 Levels of Significant Exposure to Cyanide - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
Neurological								
6	Human	once (IN)				15 M (coma)	Liebowitz and Schwartz 1948 KCN	
7	Human	once (IN)				7.4 M (brain lesions, Parkinsonian-like signs, decreased verbal fluency and speed of information processing)	Rosenow et al. 1995 KCN	
INTERMEDIATE EXPOSURE								
Systemic								
8	Rat (Fischer- 344)	13 wk (W)	Resp	12.5			NTP 1993 NaCN	
			Cardio	12.5				
			Hemato	12.5				
			Hepatic	12.5				
			Renal	12.5				
			Endocr	12.5				
			Bd Wt	12.5				
9	Rat (NS)	11.5 mo (F)	Endocr		30 M (decreased plasma thyroxine at 4 months, increased thyroid weight at 11 months)		Philbrick et al. 1979 KCN	
			Bd Wt			30 M (38% decreased weight gain)		

Table 3-2 Levels of Significant Exposure to Cyanide - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
10	Rat (NS)	11.5 mo (F)	Endocr		67 M (decreased plasma thyroxine and thyroxine secreting rate, increased thyroid weight at 11 mo)		Philbrick et al. 1979 KSCN	
			Bd Wt	67 M				
11	Mouse (B6C3F1)	13 wk (W)	Cardio	24.3[b] M			NTP 1993 NaCN	
				28.8 F				
			Hemato	24.3[b] M				
				28.8 F				
			Hepatic	24.3[b] M				
				28.8 F				
			Renal	24.3[b] M				
				28.8 F				
			Endocr	28.8 F				
			Bd Wt	24.3[b] M				
				28.8 F				

Table 3-2 Levels of Significant Exposure to Cyanide - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
12	Rabbit (New Zealand)	4 wk (F)	Resp			15 M (pulmonary edema)	Okolie and Iroanya 2003 NaCN	
			Hepatic			15 M (fatty degeneration and necrosis)		
			Renal			15 M (tubular necrosis)		
			Bd Wt	15 M				
13	Rabbit (New Zealand)	40 wk (F)	Hepatic			20 M (focal congestion and necrosis, increased serum SDH, ALT, AP)	Okolie and Osagie 1999 KCN	
			Renal			20 M (tubular/glomerular necrosis)		
			Bd Wt	20 M				
14	Rabbit (New Zealand)	40 wk (F)	Resp			20 M (focal pulmonary edema and necrosis)	Okolie and Osagie 2000 KCN	
			Cardio	20 M				
			Endocr	20 M				
Immuno/ Lymphoret								
15	Rat (Fischer- 344)	13 wk (W)		12.5			NTP 1993 NaCN	

Table 3-2 Levels of Significant Exposure to Cyanide - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
16	Mouse (B6C3F1)	13 wk (W)		24.3[b] M 28.8 F			NTP 1993 NaCN	
Neurological								
17	Rat (Fischer- 344)	13 wk (W)		12.5			NTP 1993 NaCN	
18	Rat (NS)	11.5 mo (F)				30 M (modest myelin degeneration in spinal cord)	Philbrick et al. 1979 KCN	
19	Rat (NS)	11.5 mo (F)				67 M (modest myelin degeneration in spinal cord)	Philbrick et al. 1979 KSCN	
20	Mouse (B6C3F1)	13 wk (W)		24.3[b] M 28.8 F			NTP 1993 NaCN	

Table 3-2 Levels of Significant Exposure to Cyanide - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
Reproductive								
21	Rat (Fischer- 344)	13 wk (W)		4.5 M[b,c] 12.5 F	12.5 M (decreased left epididymal [7%], left caudal epididymal [13%], and testes weights [8%], number of spermatid heads per testis [14%], and spermatid count [14%])		NTP 1993 NaCN	
22	Mouse (B6C3F1)	13 wk (W)		8.6 M[b] 28.8 F	24.3 M (10 and 18% decrease in left epididymus and caudal epididymus weights)		NTP 1993 NaCN	

a The number corresponds to entries on Figure 3-2.

b Differences in levels of health effects and cancer effects between male and females are not indicated in Figure 3-2. Where such differences exist, only the levels of effect for the most sensitive gender are presented.

c Used to derive intermediate oral minimal risk level (MRL) of 0.05 mg/kg/day; dose divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans, and 10 for human variability).

ATP = adenosine triphosphate; Bd Wt = body weight; BUN = blood urea nitrogen; Cardio = cardiovascular; Ca(CN)2 = calcium cyanide; d = day(s); Endocr = endocrine; F = female; (G) = gavage; Gastro = gastrointestinal; Gd = gestation day; (GW) = gavage in water; HCN = hydrogen cyanide; Hemato = hematological; (IN) = ingestion; KAgCN2 = potassium silver cyanide; KCN = potassium cyanide; KSCN = potassium thiocyanate; LD50 = lethal dose, 50% kill; Ld = lactation day; LDlo = lowest lethal dose; LOAEL = lowest-observed-adverse-effect level; M = male; mo = month(s); NaCN = sodium cyanide; NOAEL = no-observed-adverse-effect level; NS = not specified; NTP = National Toxicology Program; prox = proximal; Resp = respiratory; SDH = sorbital dehydrogenase; T3 = triiodothyronine; T4 = thyroxine; (W) = water; wk = week(s); x = time(s)

Figure 3-2 Levels of Significant Exposure to Cyanide - Oral

Acute (≤14 days)

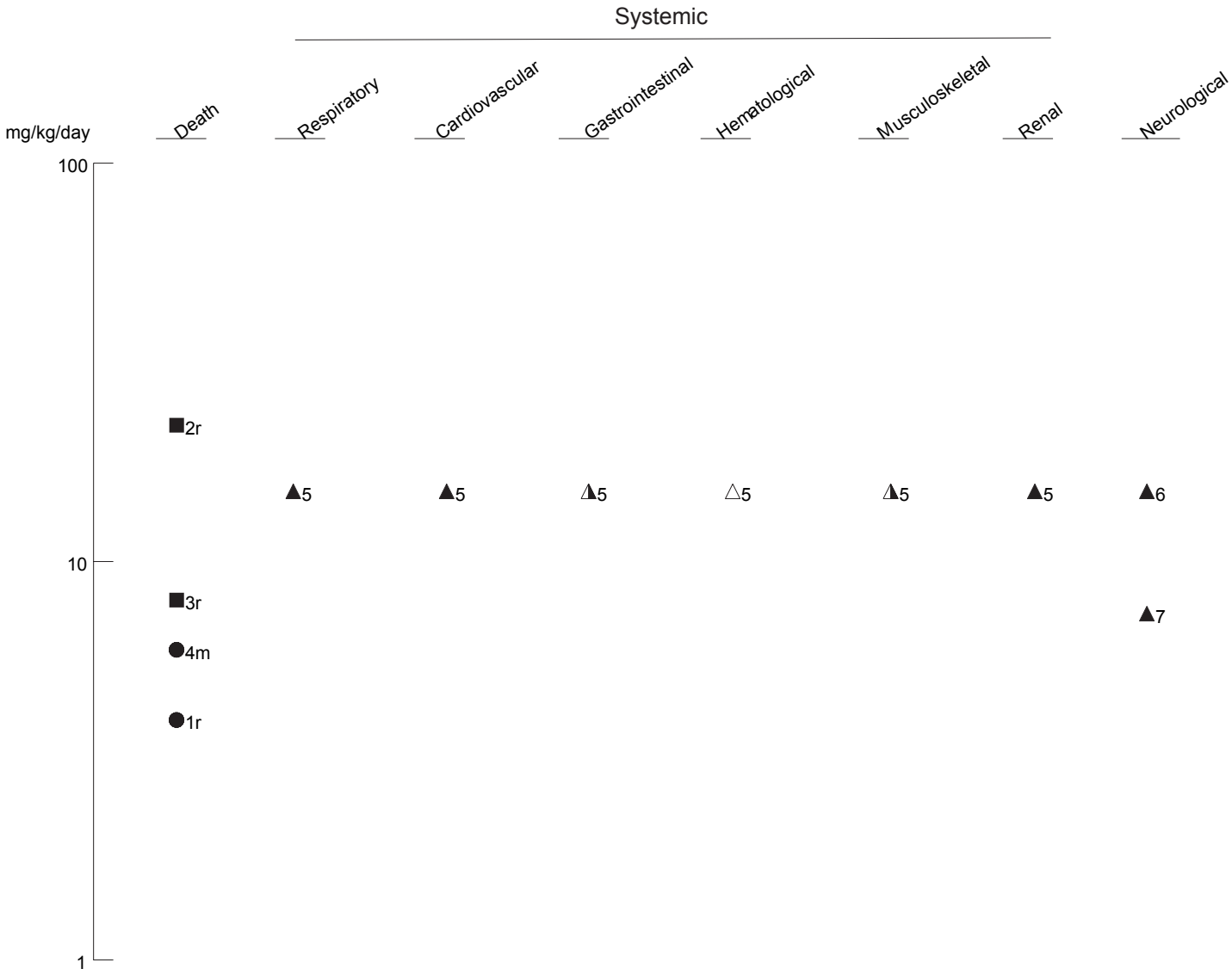
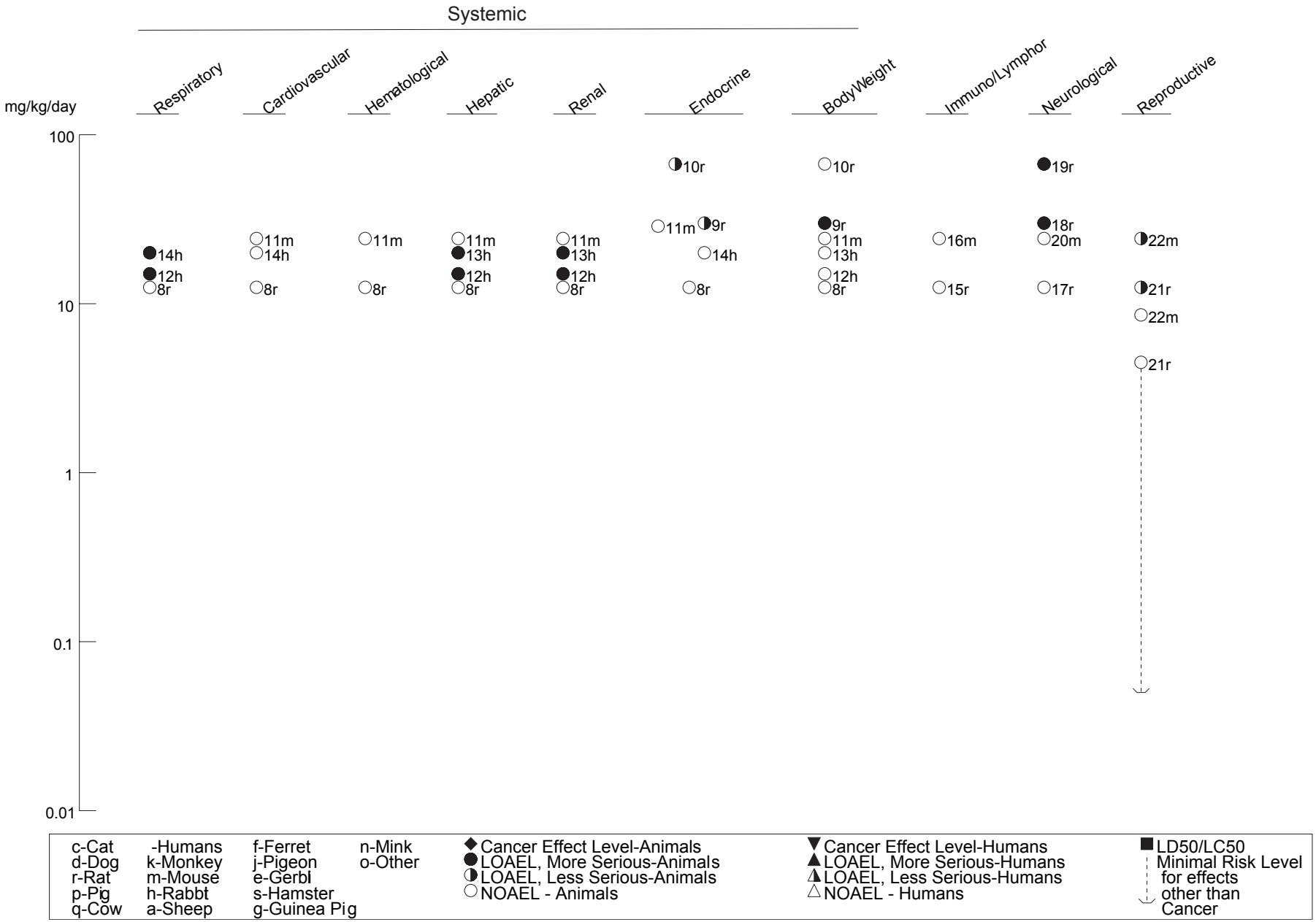


Figure 3-2 Levels of Significant Exposure to Cyanide - Oral (*Continued*)

Intermediate (15-364 days)



Respiratory effects were also observed in animals exposed to cyanide. Alveolar congestion, pulmonary edema, and significant decreases in activities of superoxide dismutase, catalase, and alkaline phosphatase were observed in the lungs of male rabbits that ingested 15 mg/kg/day of cyanide from sodium cyanide in feed for 4 weeks (Okolie and Iroanya 2003). Labored respiration was reported in rats treated with 4.35 mg CN^-/kg/day as copper cyanide by gavage for 90 days (Gerhart 1986). No effects were reported at 1.45 mg CN^-/kg/day. Labored respiration occurred in rats exposed at a lower dose of 0.8 mg CN^-/kg/day when administered in a form of potassium silver cyanide for 90 days (Gerhart 1987). Lung congestion and hemorrhage seen at necropsy were attributed to asphyxia rather than to a direct effect of cyanide. In another study, rats were exposed to 0.2–12.5 mg CN^-/kg/day as sodium cyanide in the drinking water for 13 weeks. Changes in absolute lung weight were seen, but they were minor and sporadic, and the authors did not consider them to be treatment related (NTP 1993). No respiratory effects were reported in rats exposed to a target dose of 10.4 mg CN^-/kg/day as hydrogen cyanide in their feed for 2 years (Howard and Hanzal 1955). The actual dose, however, may have been considerably lower than 10.4 mg/kg/day due to evaporation of hydrogen cyanide from the food.

Cardiovascular Effects. Several case studies reported cardiovascular effects in humans after oral exposure to cyanide. Weak, shallow pulse and inaudible heart sounds were observed in a comatose man on hospital admission after ingestion of ≈15 mg CN^-/kg as potassium cyanide (Liebowitz and Schwartz 1948). Following gastric lavage and glucose infusion, the pulse rate and blood pressure became elevated. An enlarged heart was noted. No cardiovascular effects were reported during the recovery. In another study, children poisoned by apricot pits had hypotension upon hospital admission (Lasch and El Shawa 1981).

After intermediate- or chronic-duration oral exposure to inorganic cyanides, cardiovascular effects in animals, if any, are minimal. No significant histopathological changes were observed in rats exposed to 2.6 or 7.8 mg CN^-/kg/day as potassium silver cyanide for 90 days (Gerhart 1987). No treatment-related effects on heart histopathology or tissue levels of aspartate aminotransferase (AST) or alkaline phosphatase were observed in male rabbits that ingested 20 mg CN^-/kg/day as potassium cyanide via the diet for 10 months (Okolie and Osagie 2000). Changes in absolute heart weight were seen in male and female mice exposed to 0.3–28.8 mg CN^-/kg/day as sodium cyanide in the drinking water for 13 weeks, but they were minor and sporadic, and the authors did not consider them to be treatment related (NTP 1993). Dogs fed a diet of cassava ingested an estimated 1.04 mg CN^-/kg/day for 14 weeks and exhibited hemorrhage, pyknotic nuclei, and swelling of muscle fibers in the myocardium, while dogs fed rice to which 1.04 mg CN^-/kg food was added as sodium cyanide did not show any cardiovascular effects

(Kamalu 1993). Furthermore, no cardiovascular effects were observed in rats exposed to an estimated dose of 10.4 mg CN^-/kg/day as hydrogen cyanide in their feed for 2 years (Howard and Hanzal 1955). The actual dose, however, may have differed from 10.4 mg/kg/day due to evaporation of hydrogen cyanide from the food.

Gastrointestinal Effects. Vomiting was reported in children who ingested a large number of apricot pits (Lasch and El Shawa 1981) and in a man who ingested 7.6 mg CN^-/kg in a suicide attempt (Goodhart 1994). Gastrointestinal spasms were reported in a man who accidentally ingested (and inhaled) an unknown amount of potassium cyanide (Thomas and Brooks 1970). Gastric surgery for extensive necrosis had to be performed in a man after he ingested an unknown amount of sodium cyanide (Grandas et al. 1989). The alkaline properties of solutions of sodium and potassium cyanide cause the corrosive responses in the stomach following ingestion.

Diarrhea was observed in rats treated orally with 14.5 mg CN^-/kg/day copper cyanide for 90 days (Gerhart 1986). No effects were observed at 4.35 mg/kg/day. However, as the diarrhea was probably due to the toxicity of copper, these data are omitted from Table 3-2. No gastrointestinal effects were found in rats exposed to 7.8 mg CN^-/kg/day as potassium silver cyanide for 90 days (Gerhart 1987). However, increased vomiting was reported in pigs in a dose as low as 0.7 mg CN^-/kg/day given as potassium cyanide for 24 weeks by gavage (Jackson 1988). Chronic intestinal inflammation occurred in dogs exposed to ≥0.27 mg CN^-/kg/day for 14.5 months (Hertting et al. 1960).

Hematological Effects. Information regarding hematological effects in humans after oral exposure to cyanide is limited. No adverse hematologic effects were reported in a man who ingested 15 mg CN^-/kg as potassium cyanide (Liebowitz and Schwartz 1948).

In animals, hematological effects were observed in studies with copper cyanide, potassium cyanide, potassium silver cyanide, and sodium cyanide. Hemolytic anemia was diagnosed in the group of rats treated by gavage for 90 days with 14.5 mg CN^-/kg/day as copper cyanide (Gerhart 1986). Decreased erythrocytes were reported together with decreased hemoglobin concentrations and decreased hematocrit. The diagnosis of anemia was supported by microscopic findings of pigmentation of the spleen and liver, presence of hemoglobin in the cytoplasm of the renal convoluted tubule epithelium, and by hyperplasia of hematopoietic tissue (spleen and bone marrow). Decreased hemoglobin was observed also at 4.35 mg CN^-/kg/day after 90 days. Since hemolytic anemia is characteristic of copper toxicity; the hematological effects can be partially attributed to copper toxicity rather than to cyanide toxicity, and the data are

omitted from Table 3-2; other anions of tested cyanide compounds are not known to contribute to hematological effects. Increased mean corpuscular volume, mean corpuscular hemoglobin concentration, and spleen weight indicated hematological effects in rats exposed to 7.8 mg CN^-/kg/day as potassium silver cyanide for 90 days by gavage. No effects were found at 2.6 mg CN^-/kg/day (Gerhart 1987). The contribution of silver to the hematological effects is not known. In another study, minimal changes were observed in hematology in rats and mice exposed to sodium cyanide in the drinking water for 13 weeks and the authors did not consider them to be treatment related (NTP 1993).

Musculoskeletal Effects. Muscular rigidity was observed in humans after acute cyanide poisoning (Grandas et al. 1989) and rhabdomyolysis, a clinical syndrome characterized by skeletal muscle injury, was observed in a man who ingested 0.57 mg CN^-/kg as potassium cyanide in a suicide attempt (Saincher et al. 1994).

No studies were located regarding musculoskeletal effects in animals after oral exposure to cyanide.

Hepatic Effects. Increased serum creatinine and serum creatinine kinase were observed in a man who ingested 0.57 mg CN^-/kg as potassium cyanide in a suicide attempt (Saincher et al. 1994).

In animals, hepatotoxicity was observed after ingestion of copper cyanide. Male rats treated for 90 days by gavage with 14.5 mg CN^-/kg/day as copper cyanide had increased levels of serum glutamic oxaloacetic transaminase (SGOT) and serum glutamic pyruvic transaminase (SGPT) levels, increased bilirubin and alkaline phosphatase, and decreased globulin levels in the blood (Gerhart 1986). Liver necrosis was observed in the group of female rats treated with 4.35 mg CN^-/kg/day. However, blood chemistry did not reveal any changes. The hepatic effects of copper cyanide are possibly due to the toxicity of copper rather than of cyanide and are therefore omitted from Table 3-2.

Changes in absolute and relative liver weights were reported in rats exposed to 0.2–12.5 mg CN^-/kg/day and mice exposed to 0.3–28.8 mg CN^-/kg/day, both as sodium cyanide in the drinking water for 13 weeks, but they were minor and sporadic, and the authors did not consider them to be treatment related (NTP 1993). Severe cytoplasmic vacuolization of hepatocytes was observed in male rats that ingested 3.6 mg CN^-/kg/day as potassium cyanide in drinking water for 15 days (Sousa et al. 2002); hepatic effects were minimal at 0.36–1.2 mg CN^-/kg/day and absent at 0.12 mg CN^-/kg/day. In this study, serum AST was significantly higher than the control (by 21–33%) at the three lower doses, but was lower than the control at the highest dose. The hepatic toxicity data from Sousa et al. (2002) are omitted from Table 3-2

and Figure 3-2 because no incidence data were provided for the lesions and the elevation in AST occurred with an inverse dose response in treated groups. Liver histopathology (necrosis, fatty degeneration, and congestion), decreased hepatic enzyme activities (for superoxide dismutase, catalase, and alkaline phosphatase), and increased serum enzyme activities (lactate dehydrogenase and alanine aminotransferase) indicative of liver damage were observed in male rabbits that ingested 15 mg CN^-/kg/day from sodium cyanide in feed for 4 weeks (Okolie and Iroanya 2003). In another study, periportal vacuolation and congestion were observed in the livers of dogs fed 1.04 mg CN^-/kg/day, as cassava, while no hepatic effects were observed in dogs fed rice containing the same concentration of cyanide, as sodium cyanide, for 14 weeks (Kamalu 1993). Focal congestion and necrosis were observed in the livers of male rabbits that ingested 20 mg CN^-/kg/day as potassium cyanide via the diet for 10 months (Okolie and Osagie 1999). No hepatic effects were reported in rats exposed by gavage to 7.8 mg CN^-/kg/day as potassium silver cyanide for 90 days (Gerhart 1987) or in rats exposed to an estimated dose of 10.4 mg CN^-/kg/day as hydrogen cyanide in their feed for 2 years (Howard and Hanzal 1955). The actual dose, however, may have differed from 10.4 mg/kg/day due to evaporation of hydrogen cyanide from the food.

Renal Effects. Information regarding renal effects of cyanide in humans is limited to one report. Albuminuria was found in a man during the first 2 days after ingestion of 15 mg CN^-/kg as potassium cyanide in a suicide attempt (Liebowitz and Schwartz 1948).

In male rabbits that ingested 15 mg CN^-/kg/day from sodium cyanide in feed for 4 weeks, renal histopathology (tubular and glomerular necrosis) and decreases in renal activities of superoxide dismutase and catalase were observed (Okolie and Iroanya 2003). In rats, decreased kidney weight was observed in rats treated with 14.5 mg CN^-/kg/day as copper cyanide for 90 days (Gerhart 1986); no changes were reported at 4.35 mg/kg/day exposure. However, as copper toxicity was probably responsible for the kidney effects, these data are omitted from Table 3-2. Increased blood urea nitrogen was found at 7.8 mg CN^-/kg/day, but not at 2.6 mg CN^-/kg/day, as potassium silver cyanide (Gerhart 1987). The contribution of silver to this effect is not known. No significant changes indicating renal effects were found on analysis of blood samples taken at the end of the experiment. Changes in absolute and relative kidney weights were observed in rats and mice exposed to 0.2–12.5 mg CN^-/kg/day and mice exposed to 0.3–28.8 mg CN^-/kg/days sodium cyanide in the drinking water for 13 weeks, but they were minor and sporadic, and the authors did not consider them to be treatment related (NTP 1993).

Histopathological lesions of the kidney have been reported in animals exposed to cyanide. Congestion and cytoplasmic vacuolization of the proximal tubular epithelium (moderate-to-severe) were observed in male rats exposed to 1.2–3.6 mg CN^-/kg/day as potassium cyanide in drinking water for 15 days (Sousa et al. 2002); lesions were minimal in severity at 0.3 mg CN^-/kg/day and absent at 0.12 mg CN^-/kg/day. However, as no incidence data were provided for these lesions, they are omitted from Table 3-2 and Figure 3-2. Proliferation of glomerular cells in the kidney was observed in pigs exposed to 0.64 mg CN^-/kg/day in cassava feed for 110 days (Tewe and Maner 1981b). In another study, vacuolation, swelling, and proximal tubule damage with desquamation of the epithelium and casts were observed in kidneys of dogs fed 1.04 mg CN^-/kg/day as cassava, while increased urinary protein, casts, and some desquamation, but no damage in proximal tubules, were observed in dogs fed rice with the same concentration of cyanide, as sodium cyanide, for 14 weeks (Kamalu 1993). Renal tubular and glomerular necrosis were observed in male rabbits that were exposed to 20 mg CN^-/kg/day as potassium cyanide via the diet for 10 months (Okolie and Osagie 1999). However, no renal effects were observed in rats exposed to an estimated dose of 10.4 mg CN^-/kg/day as hydrogen cyanide in their feed for 2 years (Howard and Hanzal 1955); in this study, however, the actual dose may have been different due to evaporation of hydrogen cyanide from the food. Cloudy swelling of epithelial cells of renal tubules was reported in three dogs; each dog was exposed to a different dose of sodium cyanide (ranging from 0.27 to 1.68 mg CN^-/kg/day) for 14.5 months (Hertting et al. 1960).

Endocrine Effects. Cyanide occurs naturally in several plants, such as cassava, soybeans, spinach, and bamboo shoots, in which it is generated after ingestion from cyanogenic glycosides. Chronic oral exposure to cyanide in humans who eat cassava as a main carbohydrate source of their diet has been associated with thyroid toxicity. The effects are probably caused by thiocyanate, a metabolite of cyanide that reduces iodine uptake by the thyroid. The incidence of endemic goiter correlated with cassava intake in the Congo, where thyroid uptake of radioiodine was decreased in the goitrous area, compared with the controls (Delange and Ermans 1971). In another study, altered thyroid hormone parameters were measured in a village in Mozambique where an epidemic of spastic paraparesis was found, which was related to ingestion of cassava (Cliff et al. 1986). Increases in thyroid stimulating hormone levels and the ratio of triiodothyronine to thyroxine (T_3/T_4) were detected in serum; consistent with these measurements, the authors calculated a decrease in the index of free thryroxine (FT_4I) and an increase in free triiodothyronine (FT_3I). However, the incidence of endemic goiter was not elevated in this village. Examined individuals also had very high levels of thiocyanate in serum and urine (Cliff et al. 1986).

Thyroid effects were also found in animals exposed to cyanide. Dose-related increases in the number of histological lesions of the thyroid gland (reabsorption vacuoles) were observed in all male rats that ingested 0.12–3.6 mg CN^-/kg/day as potassium cyanide in drinking water for 15 days (Sousa et al. 2002). These data are omitted from Table 3-2 and Figure 3-2 because plasma levels of T_3 and T_4 were unaffected by treatment and longer exposures in other studies found no effect on the thyroid. For example, daily exposure of male rats by gavage to 0.02–0.24 mg CN^-/kg/day as potassium cyanide for 3 months had no effect on plasma a levels of T_3 and T_4 or thyroid histology (Soto-Blanco et al. 2002a). Rats fed a diet containing 30 mg CN^-/kg/day as potassium cyanide for 4 months had a significant decrease in plasma thyroxine levels and thyroxine secretion rates; at 11 months, treated rats showed no significant decreases in thyroxine concentrations, but had significant increases in relative thyroid weight (Philbrick et al. 1979). When pigs were fed cassava diets with or without additional potassium cyanide during pregnancy, an increase in the maternal thyroid weight and thyroid gland hypofunction were observed after ingestion of 11.3 mg CN^-/kg/day, but not at 5.6 mg CN^-/kg/day (Tewe and Maner 1981b). This study is omitted from Table 3-2 and Figure 3-2 because it did not include a control group fed a cyanide-free diet. In another study, no effects on the thyroid gland were noted at 12.5 mg CN^-/kg/day in rats given sodium cyanide in drinking water for 13 weeks or in mice given 24.3–28.8 mg CN^-/kg/day (NTP 1993). However, thyroid effects have been reported at low doses in another study. Decreased thyroid function was found in pigs exposed to 0.4 mg CN^-/kg/day as potassium cyanide for 24 weeks by gavage (Jackson 1988). The pancreas showed no histopathology in this study. The histology of the pancreas was unaffected in male rabbits that ingested 20 mg CN^-/kg/day as potassium cyanide via the diet for 10 months (Okolie and Osagie 2000).

Effects on the adrenal gland, including swelling of the adrenal cortex, hemorrhage, and fibrosis, were observed in dogs fed 1.04 mg CN^-/kg/day as cassava, as well as in dogs fed rice with the same concentration of cyanide, as sodium cyanide, for 14 weeks (Kamalu 1993).

Dermal Effects. No studies were located regarding dermal effects in humans after oral exposure to cyanide.

During intermediate-duration exposure, discolored inguinal fur was found in rats exposed for 90 days to 14.5 mg CN^-/kg/day by gavage as copper cyanide (Gerhart 1986) and to 2.6 mg CN^-/kg/day as potassium silver cyanide (Gerhart 1987). As no dermal effects were described in animals exposed to cyanide compounds that did not include heavy metals, these data are omitted from Table 3-2 and Figure 3-2.

Ocular Effects. Macular degeneration and optic atrophy were reported in 20 West Africans who ingested cassava over an unspecified period (van Heijst et al. 1994). The mean levels of thiocyanate and cyanide in these patients were elevated, but were not statistically different from controls (hospital staff). Individuals with other neurological lesions in addition to ocular effects had significantly elevated serum levels of thiocyanate and cyanide. The authors indicated that nutritional deficiencies contributed to neuropathy.

Ocular opacity was noted in rats exposed to 2.6 mg CN^-/kg/day as potassium silver cyanide for 90 days (Gerhart 1987); since it is likely that opacity resulted from deposition of silver, these data are omitted from Table 3-2 and Figure 3-2. No pathological findings were observed during ophthalmological examination of rats exposed to 14.5 mg CN^-/kg/day as copper cyanide for 90 days (Gerhart 1986).

Body Weight Effects. No studies were located regarding body weight effects in humans after oral exposure to cyanide.

Decreased body weight gain was cited as one of the effects of exposure to copper cyanide, potassium cyanide, and potassium silver cyanide. Terminal body weights were significantly reduced by 18% in male rats that ingested 3.6 mg CN^-/kg/day as potassium cyanide in drinking water for 15 days, but were unaffected at 0.12–1.2 mg CN^-/kg/day (Sousa et al. 2002); the effect in high dose rats was significant as early as the first week of treatment. The significance of these results are uncertain given the lack of body weight effects in other studies. For example, no effect on body weight gain was observed in male rats exposed by gavage to 0.02–0.24 mg CN^-/kg/day as potassium cyanide for 3 months (Soto-Blanco et al. 2002a). In addition, there was no statistically significant or dose-related effect on body weight gain in rats exposed to doses as high as 12.5 mg CN^-/kg/day or in mice exposed to doses as high as 28.8 mg CN-/kg/day as sodium cyanide in drinking water for 13 weeks (NTP 1993). Reduced body weight gain was reported in male rats exposed for 90 days to 4.35 mg CN^-/kg/day as copper cyanide, but not in those exposed to 1.45 mg CN^-/kg/day for 90 days (Gerhart 1986). Furthermore, decreased weight gain was found in male rats exposed to 2.6 mg CN^-/kg/day as potassium silver cyanide for 90 days (Gerhart 1987). Since the presence of the copper or silver may have contributed to the observed decreased body weight, these data are omitted from Table 3-2 and Figure 3-2. Pregnant hamsters fed 1.0 mg CN^-/kg/day in cassava for 10 days during gestation had decreased body weight gain (Frakes et al. 1986a). No body weight effects were noted in male rabbits that ingested 15 mg CN^-/kg/day from sodium cyanide in the diet for 4 weeks (Okolie and Iroanya 2003). Body weight gain was significantly reduced in

male rabbits that ingested 20 mg CN^-/kg/day as potassium cyanide via the diet for 10 months (Okolie and Osagie 1999).

Metabolic Effects. Yen et al. (1995) reported metabolic acidosis in 67% of patients acutely poisoned by unknown concentrations of cyanide. Metabolic acidosis was observed in a woman who received an estimated dose of cyanide between 0.026 and 0.234 mg CN^-/kg from ingesting 30 apricot kernels (approximately 15 g) (Suchard et al. 1998). An apparent attempted homicide victim developed metabolic acidosis after ingesting an unknown quantity of cyanide (Chin and Calderon 2000).

In one animal study mentioning metabolic effects, decreased serum albumin and lowered calcium and potassium levels were observed in dogs fed 1.04 mg CN^-/kg/day as cassava or sodium cyanide for 14 weeks (Kamalu 1993). Statistically significant reductions in mitochondrial respiratory control ratios (by 17–22%) and tissue ATP levels (by 23–28%) were reported in the liver and heart, but not the brain of female rats receiving 3.7 mg CN^-/kg/day as potassium cyanide in drinking water for 30 days (Pritsos 1996). As no data were provided to confirm whether these biochemical findings were mirrored by adverse effects on oxygen usage at the physiological level, these data are omitted from Table 3-2 and Figure 3-2.

3.2.2.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological effects in humans after oral exposure to cyanide.

No significant changes in absolute or relative thymus weight were noted in rats and mice exposed to up to 12.5 and 28.8 mg CN^-/kg/day as sodium cyanide, respectively, in drinking water for 13 weeks (NTP 1993).

3.2.2.4 Neurological Effects

Neurologic toxicity following cyanide ingestions differs depending on length of exposure and the rate at which treatment is administered. Neurological effects of cyanide poisoning in humans may correlate with the amount ingested; however, the exact doses consumed by the victims are usually not known. Tremors were reported in a patient who accidentally ingested an unknown amount of fluid containing 2.3% silver cyanide and 6.9% sodium cyanide (Chen and Rose 1952). Children who ingested a large number of

apricot pits experienced various neurological effects ranging in severity from headaches to coma (Lasch and El Shawa 1981). The severity of effects corresponded with the amount of ingested pits. Comatose patients were admitted to a hospital after ingesting 15 mg CN^-/kg (Liebowitz and Schwartz 1948), 7.6 mg CN^-/kg (Goodhart 1994), 114–229 mg CN^-/kg (Kasamo et al. 1993), and 5.7 mg CN^-/kg (Valenzuela et al. 1992), all as potassium cyanide. A cancer patient who ingested 3,000 mg of amygdalin soon became comatose and had two general tonic-clonic seizures (Bromley et al. 2005). Although the dose is generally nontoxic, hydrolysis would potentially release 180 mg of cyanide. It was suggested that the patient's high daily intake of ascorbic acid (4,800 mg/day) may have elevated the rate of hydrolysis in the gut, resulting in increased release of cyanide. Histopathological effects in the brain were noted in an individual who died 4 days after being poisoned with potassium cyanide (Riudavets et al. 2005). Effects included autolysis in several regions of the brain (basal ganglia, thalamus, hypothalamus, and cerebellum), acute hypoxic/ischemic changes (neuronal necrosis) in the cerebellum (Purkinje and granule cells), basal ganglia, hypothalamus, and deep cortical layers (manifest as pseudolaminar necrosis), and apoptosis of glial cells in the white matter.

Several reports were located regarding development of Parkinsonism-like signs in patients after cyanide ingestion. A man who received emergency treatment for ingestion of 320 mg CN^- as potassium cyanide in a suicide attempt developed extrapyramidal signs in the weeks following his medical discharge, including drooling, marked micrographia, masked facies, mild intention tremor, and cogwheel rigidity. Magnetic resonance imaging of the brain revealed bilateral, symmetrical abnormalities of the basal ganglia, particularly the globus pallidus (Feldman and Feldman 1990). A woman in a light coma had positive Babinski's sign on the right with slight right hemiparesis and dysphonia within 2 weeks after acute cyanide poisoning (dose and form of cyanide not reported) (Carella et al. 1988). Within 5 years, progressive Parkinsonism, dystonia, and apraxia of the right eye opening was present. Atrophy of the cerebellum and distinct ventricular enlargement in cerebral hemispheres were revealed by computed tomography and magnetic resonance image examinations. Another female developed Parkinsonian-like signs (intermittent stiffness with bradykinesia of the limbs) 5 months after ingesting an unknown amount of an unspecified cyanide compound (Chin and Calderon 2000). In another case, a man went into a coma after ingesting an unknown amount of sodium cyanide (Grandas et al. 1989). He later regained consciousness, but was apathetic with reduced speech and a loss of balance; dystonia and severe Parkinsonism developed during subsequent years. Computed tomography scan revealed bilateral luciencies in the putamen and external globus pallidus. Similar effects were observed in a 35-year-old female who was promptly treated after ingestion of a potentially lethal dose of potassium cyanide (Zaknun et al. 2005). Five days after an initial period of coma, she presented with agitation and

involuntary movements of the trunk and extremities, but in the third week, she developed akinetic mutism and loss of muscle strength; damage to central axonal auditory and somatosensory signal propagation was detected. Other effects included alterations in signalling in the superior pre-central cortex, disruptions of the blood-brain barrier, pseudolaminar cortical necrosis, and progressive loss (between days 18 and 54) of nigro-striatal dopaminergic neurons. Severe Parkinsonism also developed in two men who ingested ≈5.57 mg CN^-/kg (Uitti et al. 1985) and 8.57 mg CN^-/kg (Rosenberg et al. 1989), respectively, as potassium cyanide in suicide attempts. Lesions were reported in the globus pallidus and putamen in both cases. Parkinsonian-like symptoms, including severe bradykinesia, postural instability, delay in initiating movement, hypokinetic dysarthria, axial cogwheel rigidity, or hand tremor, developed in two men several weeks after ingesting potassium cyanide—amounts unknown in one and 7.4 mg CN^-/kg in the other (Rosenow et al. 1995). The latter individual exhibited delays in information processing and motor reactions as well as reduced verbal fluency when examined 5 weeks after the incident. Magnetic resonance imaging detected lesions of the pallidum, posterior putamen, and substantia nigra in both patients; deficits in subthalamic nucleus, temporal and occipital cortex, and cerebellum were noted in the patient who ingested 7.4 mg CN^-/kg. Reduced uptake of labeled dopamine in the putamen and caudate and in glucose metabolism in the temporo-parieto-occipital cortex, cerebellum, and posterior putamen were detected by positron emission tomography in this patient. In another study, enhanced magnetic resonance imaging detected lesions in the brain of a woman who became comatose after ingesting an unknown quantity of an unspecified cyanide compound (Rachinger et al. 2002). Three weeks after the suicide attempt, pseudolaminar necrosis was detected along the sensorimotor cortex and lesions were detected in the lentiform nuclei and caudate nuclei. Six weeks after the poisoning incident, hemorrhagic necrosis was detected in the striatum and globus pallidus, as well as in the basal ganglia and sensorimotor cortex. It must be noted that these studies do not necessarily demonstrate a true cause and effect relationship between cyanide exposure and Parkinsonism. However, these nine reports of such a relationship are indicative of the need for further research on the subject. In addition, other chemicals, such as manganese and carbon monoxide, and therapy with certain drugs may result in Parkinsonism.

Memory impairment has been reported as a delayed effect in individuals who survived a cyanide poisoning incident with antidotal treatment. A female developed difficulties with short-term memory 5 months after ingesting an unknown amount of an unspecified cyanide compound (Chin and Calderon 2000).

The effects of chronic oral exposure of humans to cyanogenic glucosides were studied in regions of Africa with populations that consume a high level of cassava roots (Howlett et al. 1990; Ministry of

Health, Mozambique 1984; Monekosso and Wilson 1966; Money 1958; Osuntokun 1968, 1972; Osuntokun et al. 1969; Tylleskar et al. 1994). In some cases, the diet consisted almost exclusively of cassava roots, due to failure of other food crops (Howlett et al. 1990). A variety of neuropathies have been observed in these regions and the findings correlated with increased blood thiocyanate levels, all collectively termed "tropical ataxic neuropathy" (Osuntokun 1973). Symmetrical hyperreflexia of the upper limbs, symmetrical spastic paraparesis of the lower limbs, spastic dysarthria, diminished visual acuity, peripheral neuropathy, cerebellar signs, and deafness were among the clinical findings (Ministry of Health, Mozambique 1984). Decreased plasma vitamin B_{12} levels were also detected in affected individuals (Monekosso and Wilson 1966). Konzo, a distinct upper motor neuron disease characterized by the sudden onset of varying degrees of symmetric, isolated, nonprogressive spastic paraparesis, has occurred in rural areas of Africa and has been associated with high dietary cyanide exposure from the consumption of insufficiently processed bitter cassava (Tylleskar et al. 1994). However, scopoletin, a potent hypotensive and spasmolytic agent, has also been isolated from cassava roots (Obidoa and Obasi 1991). This substance, which remains in cassava during processing, rather than cyanide, was suggested to be the etiological agent in the tropical ataxic neuropathy observed among cassava eaters (Obidoa and Obasi 1991). In addition, protein and vitamin deficiencies may subject people in the tropics who eat cassava to increased risks of tropical neuropathies (Makene and Wilson 1972; Osuntokun 1972; Osuntokun et al. 1969). Until it can be shown that scopoletin is the etiological agent, cyanide must be considered the primary cause of these neuropathies.

The central nervous system is also a primary target of orally administered cyanide in animals. Tremors, convulsions, recumbency, and lethargy were observed in rats exposed to 7.8 mg CN^-/kg/day as potassium silver cyanide for 90 days by gavage (Gerhart 1987). Since 28 of 40 rats died at this dose level, some of the effects described may represent nonspecific signs that precede death. Hypoactivity was observed in all exposed groups starting at a dose of 0.8 mg CN^-/kg/day. Similarly, hypoactivity was reported in rats exposed to ≥0.14 mg CN^-/kg/day as copper cyanide for 90 days by gavage (Gerhart 1986). At 4.35 mg CN^-/kg/day, fixed posture occurred, while pronounced lethargy was noted at 14.5 mg CN^-/kg/day. Decreased brain weight was reported at 14.5 mg CN^-/kg/day cyanide (Gerhart 1987). The severity of effects increased as the dose increased in both of these studies and males seemed to be more sensitive to cyanide toxicity than females.

Male rats receiving 0.24 mg CN^-/kg/day as potassium cyanide by gavage for 3 months showed increases in histopathological lesions of the spinal cord (axonal "spheroids" or swellings), hippocampus (neuronal loss), and cerebellum (damage to Purkinje cells and loss of white matter) (Soto-Blanco et al. 2002a).

Since the original study did not report results quantitatively, this study is omitted from Table 3-2 until dose-incidence data can be obtained from the study authors. Rats fed a diet containing 30 mg CN^-/kg/day as potassium cyanide and 67 mg CN^-/kg/day as potassium thiocyanate for 11.5 months had myelin degeneration in the spinal cord (Philbrick et al. 1979). The authors mentioned that tissues from exposed animals were more subject to autolysis, so the strength of the association between neurological histopathology and cyanide exposure in this study is uncertain; vitamin B12 deficiency was ruled out as a cause in this study. In a behavioral study, exposure to 0.4 mg CN^-/kg/day as potassium cyanide by gavage for 24 weeks in pigs led to slower reaction time, reduced exploratory behavior, and increased victimization behavior in pigs (Jackson 1988). In contrast, no neurological effects were reported in rats fed an estimated dose of 10.4 mg CN^-/kg/day as hydrogen cyanide in their feed for 2 years (Howard and Hanzal 1955). The actual dose, however, may have been considerably lower than 10.4 mg/kg/day due to evaporation of hydrogen cyanide from the food. No histopathological changes to the brain were noted in rats and mice exposed to up to 12.5 and 28.8 mg CN^-/kg/day, as the sodium salt, respectively, in the drinking water for 13 weeks (NTP 1993); the spinal cord was not examined for histopathology in this study. Degenerative changes in ganglion cells were reported in three dogs that were exposed to 0.27–1.68 mg CN^-/kg/day as sodium cyanide in capsules for 14.5 months (Hertting et al. 1960).

The highest NOAEL value and all reliable LOAEL values for neurological effects in each species and duration category are recorded in Table 3-2 and plotted in Figure 3-2. Studies that employed oral gavage dosing are omitted because bolus administration may overwhelm detoxification processes in a manner not typical of gradual exposures in drinking water for the general population

3.2.2.5 Reproductive Effects

No studies were located regarding reproductive effects in humans after oral exposure to cyanide.

Increased early embryonic deaths were reported in rats fed a diet containing 80% cassava powder during gestation, but no reproductive effects were found in a group fed with 50% cassava powder (Singh 1981). Furthermore, no changes were observed in the number of implantations or resorptions in hamsters fed a cassava diet that provided 10.4 mg CN^-/kg/day during gestation (Frakes et al. 1986a). Increased gonadal weight was observed in male rats exposed by oral gavage to 14.5 mg CN^-/kg/day as copper cyanide (Gerhart 1986) or 2.6 mg CN^-/kg/day, as potassium silver cyanide, for 90 days (Gerhart 1987). The NOAEL values were 4.35 mg CN^-/kg/day (Gerhart 1986) and 0.8 mg CN^-/kg/day (Gerhart 1987), respectively. No effects were observed in female rats in either study. A reduction in the spermatogenic

cycle, testicular germ cell sloughing and degeneration, and occasional abnormal cells were noted in dogs fed 1.04 mg CN^-/kg/day as cassava and in dogs fed rice containing the same concentration of cyanide, as sodium cyanide, for 14 weeks (Kamalu 1993).

A number of reproductive effects were observed following exposure of rats and mice to sodium cyanide in the drinking water for 13 weeks (NTP 1993). This study was used as the basis for the intermediate-duration oral MRL as described in the footnote to Table 3-2 and Appendix A. In male rats, reproductive effects including decreased left epididymis weight, left cauda epididymis weight, left testis weight, spermatid heads, and spermatid counts were observed at 12.5 mg CN^-/kg/day. In female rats, significantly more time was spent in proestrus and diestrus stages, and less time was spent in estrus and metestrus stages in the 4.9 and 12.5 mg CN^-/kg/day groups, but these effects were not considered to be adverse. In male mice, a significant decrease in the left epididymal and caudal epididymal weights was noted at 24.3 mg CN^-/kg/day, but no changes in sperm motility or spermatid head density were observed. No changes were noted on the estrus cycle length in female mice.

The highest NOAEL value and all reliable LOAEL values for reproductive effects in each species and duration category are recorded in Table 3-2 and plotted in Figure 3-2. Studies on dogs have been omitted because that species has a relatively low amount of the detoxifying enzyme rhodanese and is unusually susceptible to cyanide exposure compared to humans or other mammals (see Sections 3.4.3 and 3.5.3). Studies involving ingestion of cassava have also been omitted because of the confounding effects of malnutrition noted in human studies and because of the presence of other toxic compounds besides cyanogenic glycosides that might contribute to toxicity (e.g., scopoletin; see Section 3.10). Studies that employed oral gavage dosing are omitted because bolus administration may overwhelm detoxification processes in a manner not typical of gradual exposures in drinking water for the general population.

3.2.2.6 Developmental Effects

No studies were located regarding developmental effects in humans after oral exposure to cyanide.

Developmental abnormalities (microcephaly with open eyes, limb defects, and growth retardation) were observed in 28% of the fetuses of rats exposed to feed containing 80% cassava powder during gestation (Singh 1981). Teratogenic effects (encephalocele and rib abnormalities) were reported in hamsters exposed to a single oral dose of amygdalin during gestation, but these changes were found only at maternally toxic doses (Willhite 1982). Fetotoxicity (reduced fetal weight and ossification) were found in

the offspring of hamsters fed a cassava diet providing 1.0 mg CN^-/kg/day during pregnancy (Frakes et al. 1986a) or to the cyanogenic glucoside linamarin at 120 or 140 mg/kg (Frakes et al. 1985). Blood cyanide increased to a peak of 110 nmol/mL at 3 hours after such a dose of linamarin or to 140 nmol/mL after amygdalin (Frakes et al. 1986b). In contrast, no major developmental effects were observed in rats that were fed a basal cassava diet providing ≈1.2 mg CN^-/kg/day or in rats whose cassava feed was supplemented with potassium cyanide bringing the total dose to 51 mg CN^-/kg/day (assuming young growing rats and pregnant rats consume food each day equivalent to 10% of their body weight) (Tewe and Maner 1981a). The rats were exposed to cyanide during gestation days 16–20 and then for 21 days during lactation. When their offspring were exposed to similar diets providing doses of ≈1.2 and 51 mg CN^-/kg/day, decreased growth was observed in the higher dosed weanlings regardless of the exposure *in utero*. When pigs were fed a cassava diet alone or one supplemented with potassium cyanide for 110 gestation days, no effects on number of fetuses or upon fetal weight were observed in the 11.3 mg CN^-/kg/day cyanide exposed group (Tewe and Maner 1981b). The rat and pig studies by Tewe and Maner (1981a, 1981b) are not presented in Table 3-2 or Figure 3-2 because they did not include control groups fed cyanide-free diets.

The highest NOAEL value and all reliable LOAEL values for developmental effects in each species and duration category are recorded in Table 3-2 and plotted in Figure 3-2. Studies for dogs have been omitted because that species has a relatively low amount of the detoxifying enzyme rhodanese and is unusually susceptible to cyanide exposure compared to humans or other mammals (see Sections 3.4.3 and 3.5.3). Studies involving ingestion of cassava have also been omitted because of the confounding effects of malnutrition noted in human studies and because of the presence of other toxic compounds besides cyanogenic glycosides that might contribute to toxicity (e.g. scopoletin; see Section 3.10). Studies that employed oral gavage dosing are omitted because bolus administration may overwhelm detoxification processes in a manner not typical of gradual exposures in drinking water for the general population.

3.2.2.7 Cancer

No studies were located regarding cancer effects in humans or animals after oral exposure to cyanide.

3.2.3 Dermal Exposure

Chronic dermal exposure of humans to cyanide can occur in occupational settings. However, the main route of exposure is considered to be inhalation and, therefore, the occupational exposure studies are discussed in Section 3.2.1. Studies involving conjunctival exposure are discussed in this section, although not strictly involving the dermal route.

3.2.3.1 Death

An average LD_{50} value for dermal exposure of 100 mg CN^-/kg as hydrogen cyanide was estimated for humans (Rieders 1971).

LD_{50} values calculated for dermal exposure to cyanides in rabbits were 6.7 mg CN^-/kg when applied as hydrogen cyanide, 7.7 mg CN^-/kg as sodium cyanide, and 8.9 mg CN^-/kg as potassium cyanide (Ballantyne 1983a). The dermal LD_{50} of cyanide as sodium cyanide was slightly lowered by moistening the skin and substantially lowered by abrading the skin (Ballantyne 1988). Similar differences in toxicity of various chemical forms of cyanide were observed after cyanide was applied to the inferior conjunctival sac of one eye (Ballantyne 1983a, 1983b, 1988). Transocular LD_{50} values were 1.0 mg CN^-/kg as hydrogen cyanide, 2.68 mg CN^-/kg as sodium cyanide, and 3.2 mg CN^-/kg as potassium cyanide. The deaths occurred within 3–12 minutes. Deaths occurred also in guinea pigs when their skin was exposed to hydrogen cyanide; however, the doses could not be quantified (Fairley et al. 1934; Walton and Witherspoon 1926). The LD_{50} values for death are recorded in Table 3-3.

It should be noted that none of the studies in this section reported the surface area to which the cyanide was applied.

3.2.3.2 Systemic Effects

No studies were located regarding hematological, musculoskeletal, hepatic, endocrine, or body weight effects in humans or animals after dermal exposure to cyanide. The systemic effects observed in humans and animals after dermal exposure to cyanide are discussed below. The highest NOAEL values and all reliable LOAEL values for each systemic effect in each species and duration category are recorded in Table 3-3.

Table 3-3 Levels of Significant Exposure to Cyanide - Dermal

Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL	LOAEL Less Serious	LOAEL Serious	Reference Chemical Form	Comments
ACUTE EXPOSURE							
Death							
Rabbit (NS)	once				7.7 F mg/kg (dermal LD50)	Ballantyne 1983a NaCN	
Rabbit (NS)	once				6.7 F mg/kg (dermal LD50)	Ballantyne 1983a HCN	
Rabbit (NS)	once				8.9 F mg/kg (dermal LD50)	Ballantyne 1983a KCN	
Rabbit (albino)	once				1 F mg/kg (transocular LD50)	Ballantyne 1983a, 1983b HCN	
Rabbit (albino)	once				3.2 F mg/kg (transocular LD50)	Ballantyne 1983a, 1983b KCN	
Rabbit (New Zealand)	once				2.4 F mg/kg (transocular LD50)	Ballantyne 1988 NaCN	
Rabbit (New Zealand)	once				4.1 F mg/kg (dermal LD50 -abraded skin)	Ballantyne 1988 NaCN	
Rabbit (New Zealand)	once				6.3 F mg/kg (dermal LD50 -moist skin)	Ballantyne 1988 NaCN	

Table 3-3 Levels of Significant Exposure to Cyanide - Dermal (continued)

Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL	LOAEL Less Serious		LOAEL Serious		Reference Chemical Form	Comments
Systemic									
Human	8-10 min	Cardio		20000 M ppm	(palpitations)			Drinker 1932 HCN	
Rabbit (albino)	once	Resp		0.9 F mg/kg	(rapid breathing)			Ballantyne 1983b HCN	
		Ocular				0.9 F mg/kg	(corneal opacity, keratitis)		
Rabbit (albino)	once	Resp		2.5 F mg/kg	(rapid breathing)			Ballantyne 1983b KCN	
		Ocular				2.5 F mg/kg	(corneal opacity, keratitis)		
Rabbit (albino)	once	Resp	1.69 F mg/kg	2.1 F mg/kg	(rapid breathing)			Ballantyne 1983b NaCN	
		Ocular	1.69 F mg/kg			2.1 F mg/kg	(corneal opacity, keratitis)		
Neurological									
Human	8-10 min			20000 M ppm	(dizziness, weakness, headache)			Drinker 1932 HCN	

Table 3-3 Levels of Significant Exposure to Cyanide - Dermal (continued)

Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL	LOAEL			Reference Chemical Form	Comments
				Less Serious		Serious		
Rabbit (albino)	once				0.9 F mg/kg	(convulsions and loss of consciousness)	Ballantyne 1983b HCN	
Rabbit (New Zealand)	once				2.5 F mg/kg	(convulsions and loss of consciousness)	Ballantyne 1983b KCN	
Rabbit (albino)	once		1.7 F mg/kg		2.1 F mg/kg	(convulsions and loss of consciousness)	Ballantyne 1983b NaCN	

Cardio= cardiovascular; d = day(s); F = female; HCN = hydrogen cyanide; KCN = potassium cyanide; LD50 = lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male; min = minutes; NaCN = sodium cyanide; NOAEL = no-observed-adverse-effect level; NS = not specified; Resp = respiratory

Respiratory Effects. Breathing irregularities including Cheyne-Stokes respiration developed in two persons who fell into cisterns containing copper cyanide or potassium cyanide (Dodds and McKnight 1985; Trapp 1970) and one person whose hands were exposed to hydrogen cyanide (Potter 1950). The effects reflect the central nervous system toxicity of cyanide.

Rapid breathing was reported as the first sign of toxicity in rabbits that received 0.9 mg CN^-/kg as hydrogen cyanide, 1.69 and 2.1 mg CN^-/kg as sodium cyanide, and 2.5 mg CN^-/kg as potassium cyanide in their conjunctival sacs (Ballantyne 1983b, 1988). Similarly, labored or rapid breathing preceded coma and death in guinea pigs exposed dermally to unknown doses of hydrogen cyanide (Fairley et al. 1934; Walton and Witherspoon 1926).

Cardiovascular Effects. Peripheral vasoconstriction and gross plasma extravasation were reported in a man who accidentally fell into a cistern with hot copper cyanide (Dodds and McKnight 1985). Palpitations were recorded in three men who wore respiratory masks while working in an atmosphere containing 20,000 ppm hydrogen cyanide for 8–10 minutes (Drinker 1932). The masks were reported to give excellent respiratory protection. Therefore, the effects seen in these men may have been due to dermal exposure.

No studies were located regarding cardiovascular effects in animals after dermal exposure to cyanide.

Gastrointestinal Effects. No studies were located regarding gastrointestinal effects in humans after dermal exposure to cyanide.

Acute dermal exposure of guinea pigs to an unknown concentration of hydrogen cyanide resulted in submucous hemorrhages in the stomach as observed at necropsy (Fairley et al. 1934).

Renal Effects. The information regarding renal effects following dermal exposure to cyanide in humans is limited to one case report. Transitory oliguria (scanty urination) was observed in a patient who accidentally fell into a cistern containing 1,000 gallons of hot copper cyanide and remained there for 3 minutes before being rescued (Dodds and McKnight 1985).

No studies were located regarding renal effects in animals after dermal exposure to cyanide.

Dermal Effects. No studies were located regarding dermal effects in humans after dermal exposure to cyanide.

When the skin of rabbits was exposed to 5,000 ppm cyanide as cyanogen for 8 hours, no dermal lesions were found (McNerney and Schrenk 1960). Vascular congestion was reported in the skin of guinea pigs after exposure to unknown doses of hydrogen cyanide for 65 minutes (Fairley et al. 1934).

Ocular Effects. No studies were located regarding ocular effects in humans after dermal exposure to cyanide.

Cyanide toxicity was tested in rabbits by applying 1.69–5.28 mg CN^-/kg/day as sodium cyanide to the inferior conjunctival sac of one eye (Ballantyne 1983b, 1988). Irritation, lacrimation, and conjunctival hyperemia were present immediately after the treatment. Keratitis developed in some rabbits after a cyanide application of 0.9 mg CN^-/kg as hydrogen cyanide, 2.1 mg CN^-/kg as sodium cyanide, and 2.5 mg CN^-/kg as potassium cyanide.

3.2.3.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological effects in humans or animals after dermal exposure to cyanide.

3.2.3.4 Neurological Effects

Deep coma developed in two persons who accidentally fell into cisterns containing copper cyanide (Dodds and McKnight 1985) and potassium cyanide, respectively (Trapp 1970). Similarly, a worker, whose hand was exposed to liquid hydrogen cyanide, fell into a coma, lost deep reflexes, and showed dilated pupils within 5 minutes (Potter 1950). Men working in an atmosphere containing 20,000 ppm hydrogen cyanide for 8–10 minutes experienced dizziness, weakness, and headaches (Drinker 1932). The workers wore masks that were reported to give excellent respiratory protection. However, exposure to such high concentrations is not safe because the gas is absorbed through the unprotected skin. The effects seen in these men may have been due to dermal exposure.

Weakness and ataxic movements, convulsions, and coma developed in rabbits that received 0.9 mg CN^-/kg as hydrogen cyanide, 2.1 mg CN^-/kg as sodium cyanide, and 2.5 mg CN^-/kg as potassium cyanide into their conjunctival sacs (Ballantyne 1983b, 1988). Rabbits exposed dermally to 1.92 mg CN^-/kg as hydrogen cyanide, 4.0 mg CN^-/kg as potassium cyanide or 2.6 mg CN^-/kg as sodium cyanide exhibited tremors, retrocolic spasms, and convulsions (Ballantyne 1994). Similarly, convulsions and coma preceded death in guinea pigs exposed dermally to unknown doses of hydrogen cyanide (Fairley et al. 1934; Walton and Witherspoon 1926).

All reliable LOAEL values for neurological effects in each species for acute duration are recorded in Table 3-3.

No studies were located regarding the following health effects in humans or animals after dermal exposure to cyanide:

3.2.3.5 Reproductive Effects

3.2.3.6 Developmental Effects

3.2.3.7 Cancer

3.3 GENOTOXICITY

In vivo. No studies were located regarding genotoxic effects in humans after oral or inhalation exposure to cyanide.

A single oral dose of 1 mg CN^-/kg as potassium cyanide did not inhibit testicular deoxyribonucleic acid (DNA) synthesis in mice (Friedman and Staub 1976).

Increased DNA fragmentation was electrophoretically detectable in mitochondria isolated from the brains of male ddy mice that had received a subcutaneous injection of 2.8 mg CN (as potassium cyanide) per kg (Yamamoto and Mohanan 2002). DNA fragmentation was detected by *in situ* terminal deoxynucleotide transferase nick-end labeling (TUNEL) in the parietal and suprrhinal regions of the motor cortex in mice injected with potassium cyanide (2.4 mg CN/kg/day) for 1–12 days (Mills et al. 1999).

In vitro. *In vitro* genotoxicity studies are summarized in Table 3-4. Cyanide in the form of potassium cyanide tested negative in *Salmonella typhimurium* strains TA1535, TA1537, TA1538, TA98, TA100 (De Flora 1981), TA97, and TA102 (De Flora et al. 1984). A positive mutagenic response was reported for hydrogen cyanide in strain TA100 without metabolic activation (Kushi et al. 1983). Adding S-9 mix to the culture decreased the induction of reverse mutations by cyanide to 40% of the nonactivated reaction. Negative results were also obtained in the DNA repair test in *Escherichia coli* WP67, CM871, and WP2 with potassium cyanide (De Flora et al. 1984). Cyanide in the form of sodium cyanide tested negative in

S. typhimurium strains TA97, TA98, TA100, and TA1535, with and without metabolic activation (NTP 1993). Potassium cyanide tested at 0.01 or 1.0 mM failed to induce reverse mutations in *S. typhimurium* strains TA98 or TA100 with or without metabolic activation (Kubo et al. 2002).

The Vitotox test is a screening assay for genotoxicity and cytotoxicity (Meriläinen and Lampinen 2004). The genotoxicity component is based on a recombinant *S. typhimurium* TA104 with a reporter luciferase operon under control of a *rec*N promoter. In this system, damaged DNA interacts with the *rec*A regulator protein, initiating the SOS response that derepresses the *rec*N promoter, allowing luciferase expression. Sodium cyanide tested at concentrations up to 0.8 mM without metabolic activation yielded negative results for genotoxicity in this system.

Potassium cyanide did not inhibit DNA synthesis in cultured HeLa cells (Painter and Howard 1982).

In cultured A549 human epithelial-like lung carcinoma cells, ≥1 mM potassium cyanide induced dose-related reductions in cell viability by 8 hours and dose-dependent increases in electrophoretically-detectable double-strand DNA breaks by 24 hours (Vock et al. 1998). Based on this temporal relationship and the fact that the induced DNA fragments were smaller than 0.5 Mbp, the authors concluded that the genotoxic effect of cyanide was indirect and based on the activation of endonucleases by calcium entering the damaged cells. Dose-related increases in DNA breaks were induced in rat thymocytes treated for 6 hours with ≥1.25 mM potassium cyanide or in baby hamster kidney (BHK-21) cells at 5 mM (Bhattacharya and Lakshmana Rao 1997). Incubation of cells in calcium-free medium significantly reduced the level of DNA damage, supporting the hypothesis that a cytotoxic-related calcium-influx contributes to this fragmentation of DNA.

Storer et al. (1996) evaluated 81 chemicals for genotoxicity in an *in vitro* alkaline elution assay for DNA strand breaks in primary cultures of rat hepatocytes. The study included a battery of assays for

Table 3-4. Genotoxicity of Cyanide *In Vitro*

Species (test system)	End point	Results		Reference	Form
		With activation	Without activation		
Prokaryotic organisms:					
Salmonella typhimurium					
TA82, TA102	Reverse mutation	–	Not tested	De Flora et al. 1984	KCN
S. typhimurium					
TA98, TA100, TA1535, TA1537, TA1538	Reverse mutation	–	–	De Flora 1981	KCN
S. typhimurium					
TA98	Reverse mutation	–	–	Kushi et al. 1983	HCN
TA100		(+)	+		
S. typhimurium					
TA98, TA100	Reverse mutation	–	–	Kubo et al. 2002	KCN
Escherichia coli					
WP67, CM871, WP2	DNA repair test	–	–	De Flora et al. 1984	KCN
S. typhimurium					
TA97, TA98, TA 100, TA 1535	Reverse mutation	–	–	NTP 1993	NaCN
Eukaryotic organisms:					
HeLa cells	DNA synthesis inhibition	–	–	Painter and Howard 1982	KCN
Human A549 lung carcinoma cells	DNA breakage		$+^{cyt}$	Vock et al. 1998	KCN
Human TK6 lymphoblastoma cells	DNA breakage		$+^{cyt}$	Henderson et al. 1998	KCN
Rat thymocytes	DNA breakage		$+^{cyt}$	Bhattacharya and Lakshmana Rao 1997	KCN
Hamster BHK-21 cells	DNA breakage		$+^{cyt}$	Bhattacharya and Lakshmana Rao 1997	KCN
Rat hepatocytes	DNA breakage		$+^{cyt}$	Storer et al. 1996	KCN
Mitochondrial fraction from brain of male ddy mice	Mitochondrial DNA breakage		+	Yamamoto and Mohanan 2002	KCN

– = negative result; + = positive result; (+) = weakly positive result; $+^{cyt}$ = DNA breakage associated with cytotoxicity; DNA = deoxyribonucleic acid; HCN = hydrogen cyanide; KCN = potassium cyanide; NaCN = sodium cyanide

cytotoxicity (including tetrazolium dye reduction, trypan blue dye exclusion after 3 hours of recovery, ATP content, K+ content, and cell blebbing) to distinguish between genotoxicity and false-positive results resulting from the loss of membrane integrity in damaged cells. DNA strand breakage following treatment with ≥6 mM potassium cyanide was determined to be associated with the induction of endonucleolytic DNA degradation caused by cytotoxicity (ATP content ≤5% of control, increased cell blebbing). Henderson et al. (1998) electrophoretically detected significant DNA breakage (DNA migration) in TK6 human lymphoblastoma cells treated with potassium cyanide at 2 mg CN^-/mL a concentration reducing cell survival (as measured by trypan blue exclusion) by 30%.

Dose-related increases in electrophoretically detectable DNA breaks were induced by potassium cyanide (0.1–2 mM) in a crude mitochondrial fraction isolated from the brains of male ddy mice (Yamamoto and Mohanan 2002).

3.4 TOXICOKINETICS

Cyanide gas and salts such as sodium cyanide or potassium cyanide are rapidly absorbed following inhalation or oral exposure, but are more slowly absorbed by dermal exposure. Following inhalation, cyanide is rapidly distributed throughout the body, with measurable levels detected in all organs studied to date. Cyanide can be distributed in the body within seconds and death can occur within minutes. Following oral exposure, the highest levels have been detected in the lungs and blood. Animal studies have shown that cyanide does not accumulate in the blood and tissues following chronic oral exposure. Cyanide is transformed to thiocyanate in the body, with a plasma half-life of 20 minutes to 1 hour. Cyanide metabolites are excreted primarily in the urine, with small amounts excreted through the lungs.

3.4.1 Absorption

3.4.1.1 Inhalation Exposure

Cyanide as hydrogen cyanide is rapidly absorbed (within seconds) following inhalation exposure. Humans retained 58% of hydrogen cyanide in the lungs after inhaling the gas through normal breathing (Landahl and Herrmann 1950).

Quantitative data on the absorption of hydrogen cyanide by inhalation were reported in dogs (Gettler and Baine 1938). During exposure to an unknown concentration of hydrogen cyanide, one dog reportedly

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 minutes, respectively. More recent quantitative data were not available.

3.4.1.2 Oral Exposure

Information regarding the rapid lethal effects following oral intake of cyanide as soluble cyanide salts in humans indicates that cyanide is rapidly absorbed from the gastrointestinal tract. In a case study, an 80-kg male ingested an estimated 15–25 mg CN^-/kg as potassium cyanide in a suicide attempt (Liebowitz and Schwartz 1948). Based on a concentration of 200 mg hydrogen cyanide/L in the blood 2 hours after ingestion, it was estimated that the patient had 1.2 g hydrogen cyanide in the blood, with ≈2.3 g CN^- in the body, after 2 hours.

The gastrointestinal absorption of cyanide following ingestion of certain complex iron-containing cyanide compounds is low because cyanide binds with high affinity to iron. In three volunteers (study authors), each of whom ingested a capsule containing 500 mg labeled potassium ferric hexacyanoferrate ($KFe[Fe(CN)_6]$), equivalent to a lethal dose of 3.14–3.64 mg CN^-/kg, only 0.03 mg of free CN^-/kg were absorbed (Nielsen et al. 1990). From the mild toxicological effects, minimal absorption of free cyanide was suspected to have occurred in a woman who attempted suicide by ingesting a coffee spoonful of potassium ferricyanide ($K_3Fe(CN)_6$ or Prussian red) (Hantson et al. 1996). Low bioavailability of cyanide was deduced in the case of a man who attempted suicide by ingesting an unknown amount of cyanide in the form of potassium ferrocyanide (Laforge et al. 1999). Despite an initial toxic blood cyanide concentration of 0.3 mg/100 mL, there were no clinical signs of toxicity and blood chemistry was otherwise normal. (Since free cyanide absorption and toxicity is unusually low for these iron compounds, the data are not discussed in Section 3.2.2).

Three dogs were given lethal doses of hydrogen cyanide by gavage. The amount of cyanide absorbed was determined by the difference between the cyanide given and the cyanide left in the stomach and intestines (Gettler and Baine 1938). The dogs dosed with 8.4, 4.4, or 1.6 mg HCN/kg, died 8, 21, and 155 minutes after treatment and had absorbed 17, 24, and 72%, respectively, of the dose given. Rats excreted 47% of a dose of radioactivity in the urine during 24 hours following gavage treatment with 2 mg CN^-/kg as radiolabeled potassium cyanide (Farooqui and Ahmed 1982), indicating that at least 53% of the cyanide was absorbed in 24 hours.

Sousa et al. (2003) compared the absorption of cyanide in male Wistar rats and Landrace-Large White pigs that were given a single dose of 1.2 mg CN^-/kg as potassium cyanide by aqueous gavage. The peak blood concentration (Cmax) of cyanide was reached within 15 minutes in rats and by 30 minutes in pigs. The peak plasma cyanide concentrations were 0.23 and 0.15 mg/100 mL for rats and pigs, respectively. In this study, the peak blood concentration of thiocyanate was reached within 6 hours in rats and pigs. The peak plasma thiocyanate concentrations were 42.8 and 58.1 µmol/L for pigs and rats, respectively. More detail on the mechanism of absorption is provided in Section 3.5.1.

3.4.1.3 Dermal Exposure

No studies were located regarding quantitative absorption in humans after dermal exposure to cyanide gases or common inorganic salts. Evidence that cyanide can be absorbed through the skin of humans is provided in case reports of toxic effects in humans after accidental dermal contact with cyanide (see Section 3.2.3).

Information regarding dermal absorption of cyanide in animals was provided in studies of guinea pigs and dogs (Walton and Witherspoon 1926). When a small area of the shaved abdomen of guinea pigs was exposed to hydrogen cyanide vapor for 30–60 minutes, signs of cyanide toxicity observed included rapid respiration followed by general twitching of muscles, convulsions, and death. In a similar experiment, shaved and unshaved dogs were placed in a chamber in which their bodies, with the exception of the head and neck, were exposed to hydrogen cyanide vapor. No signs of toxicity were reported after exposure to 4,975 ppm hydrogen cyanide for 180 minutes. Deaths occurred after exposure to 13,400 ppm hydrogen cyanide for 47 minutes and suggested dermal absorption. Further indirect evidence regarding dermal absorption of cyanide as hydrogen cyanide or its salts (Ballantyne 1983a, 1983b, 1988) can be found in Section 3.2.3.

3.4.2 Distribution

3.4.2.1 Inhalation Exposure

Once cyanide is absorbed, it is rapidly distributed by the blood throughout the body. Tissue levels of hydrogen cyanide were 0.75, 0.42, 0.41, 0.33, and 0.32 mg/100 g of tissue in the lung, heart, blood, kidney, and brain, respectively, in a man who died following inhalation exposure to hydrogen cyanide gas. In one case of death due to cyanide oral exposure, it was estimated that 30 mg of hydrogen cyanide

had been ingested and that 3 hours had elapsed before death (Gettler and Baine 1938). In another case, tissue cyanide levels from a man who died from inhalation of hydrogen cyanide were reported as 0.5 mg per 100 mL of blood and 0.11, 0.07, and 0.03 mg/100 g in the kidney, brain, and liver, respectively. Urinary cyanide levels were reported as 0.2 mg/100 mL, and 0.03 mg/100 g were found in the gastric contents (Finck 1969). Following chronic occupational exposure to 0.19–0.75 ppm hydrogen cyanide, 56.0 and 18.3 µg CN^-/100 mL were found in the blood of smokers and nonsmokers, respectively (Chandra et al. 1980). The cyanide levels in control groups were 4.8 µg/mL for smokers and 3.2 µg/mL for nonsmokers.

In two dogs exposed to unspecified fatal concentrations of hydrogen cyanide, the highest cyanide levels were found in the lungs, blood, and heart (Gettler and Baine 1938). Rats exposed to hydrogen cyanide gas at 356 or 1,180 ppm died within 10 and 5 minutes, respectively (Yamamoto et al. 1982). Samples taken immediately after respiration stopped showed that the pattern of tissue distribution of cyanide did not vary with the concentration used. In averaging data for both dose groups, tissue concentrations, reported as µg/g wet weight (ww), were 4.4 in the lungs, 3.0 in the blood, 2.15 in the liver, 1.4 in the brain, and 0.68 in the spleen. Thus, the highest cyanide concentrations were observed in the lung. Rabbits exposed to hydrogen cyanide at 2,714 ppm for 5 minutes had cyanide levels of 170/100 mL in blood and 48 µg/100 mL in plasma, and tissue levels (in units of µg/100 g) of 0 in the liver, 6 in the kidney, 50 in the brain, 62 in the heart, 54 in the lung, and 6 in the spleen (Ballantyne 1983a).

3.4.2.2 Oral Exposure

Small but significant levels of cyanide are present in normal blood plasma at concentrations of 0–14 µg % (Feldstein and Klendshoj 1954). Vitamin B_{12} contains cyanide, with the source of cyanide attributed to breakdown of cyanogenic foods by bacteria in the gut.

Cyanide levels in a woman who died 30 minutes after ingesting ≈1,325 mg cyanide as sodium cyanide were, in mg %: 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). The mean organ levels of cyanide ion in cases of fatal poisoning in 17–58 cases were, in mg %: stomach contents, 160; spleen, 3.77; blood, 2.39; liver, 1.62; brain, 1.2; kidney, 0.61; and urine, 0.06 (Ansell and Lewis 1970). Brain cyanide levels ranged from 0.06 to 1.37 mg hydrogen cyanide/100 g of tissue in four humans who ingested fatal doses of cyanide (Gettler and Baine 1938). Cyanide levels in the livers of six humans ranged from 0.22 to 0.91 mg hydrogen cyanide/100 g of tissue. In two cases in which men died from ingestion of unknown quantities of unspecified cyanide

salts, cyanide levels were highest in the gastric contents, and next highest in the lungs and blood (Finck 1969).

Combined data from 9 to 10 rats that died 3.3 and 10.3 minutes after gavage doses of 7 or 21 mg CN^-/kg as sodium cyanide showed average tissue concentrations of cyanide in µg/g of: liver, 8.9; lung, 5.8; blood, 4.9; spleen, 2.1; and brain, 1.5 (Yamamoto et al. 1982). When six rats were treated with 4 mg CN^-/kg as potassium cyanide, signs of central nervous system toxicity were observed (Ahmed and Farooqui 1982), and cyanide levels 1 hour after exposure were 3,380 µg/g in liver, 748 µg/g in brain, and 550 µg/g in kidney. Forty minutes after male Wistar rats received an oral dose of 1.2 mg CN^-/kg as potassium cyanide, the tissue levels of cyanide were 1.04 µg/mL in blood, 0.54 µg/g in liver, 0.20 µg/g in brain, 0.29 µg/g in kidney, and 0.07 µg/g in stomach (Saito et al. 2000). Two-fold increases in the administered dose (2.4 or 4.8 mg CN^-/kg) resulted in approximate 2-fold increases in the cyanide content of these tissues, except for the liver, which showed 3-fold increases. In a study using orally administered radioactively labeled potassium cyanide, the radioactivity detected in whole blood or plasma decreased rapidly within 6 hours. Of the low levels of radioactivity detected in red blood cells, about 94% of the radioactivity recovered was found in the hemolysate, of which 70, 14–25, and 5–10% was detected in the heme fraction, globin, and cell membranes, respectively (Farooqui and Ahmed 1982). Rabbits treated by gavage with 11.9–20.3 mg CN^-/kg as hydrogen cyanide had cyanide levels of 480 µg/100 mL in blood, 252 µg/100 mL in serum, and tissue levels (µg/100 g wet tissue) of 512 in liver, 83 in kidney, 95 in brain, 105 in the heart, 107 in the lung, and 72 in the spleen at necropsy (Ballantyne 1983a).

Cyanide has not been shown to accumulate in the blood and tissues following chronic oral exposure to inorganic cyanides. Following the treatment of groups of 10 male and 10 female rats with hydrogen cyanide in the diet at ≤10.4 mg CN^-/kg/day for 2 years, virtually no cyanide was found in plasma or kidneys (Howard and Hanzal 1955). Low levels were found in erythrocytes (mean of 1.9 µg/100 g). Levels of thiocyanate, the less toxic primary metabolite of cyanide, increased 3.5-fold in plasma, 3.3-fold in erythrocytes, 1.3-fold in liver, and 2.5-fold in kidney. Evaporation of hydrogen cyanide from the feed was thought to have occurred in this study, resulting in lower exposure levels than stated.

3.4.2.3 Dermal Exposure

No studies were located regarding distribution in humans after dermal exposure to cyanide.

Six rabbits exposed dermally (area not reported) to 33.75 mg CN^-/kg as hydrogen cyanide had blood and serum cyanide levels of 310 and 144 µg/dL, respectively, and tissue levels (µg/100 g) of 26 in liver, 66 in kidney, 97 in brain, 110 in heart, 120 in lungs, and 21 in the spleen (Ballantyne 1983a). Cyanide concentrations were measured immediately after rabbits died, 3–12 minutes after administration of 5.25 mg CN^-/kg as hydrogen cyanide, sodium cyanide, or potassium cyanide to their conjunctival sac (Ballantyne 1983b). Higher cyanide levels were observed in whole blood than in serum in all three groups. However, blood and serum cyanide levels were significantly lower in sodium cyanide and potassium cyanide groups than in the hydrogen cyanide group. Hydrogen cyanide-treated rabbits also had higher concentrations of cyanide in myocardium, lungs, and brain than rabbits from the other two groups. In all groups, the least amount of cyanide was found in the liver and kidney.

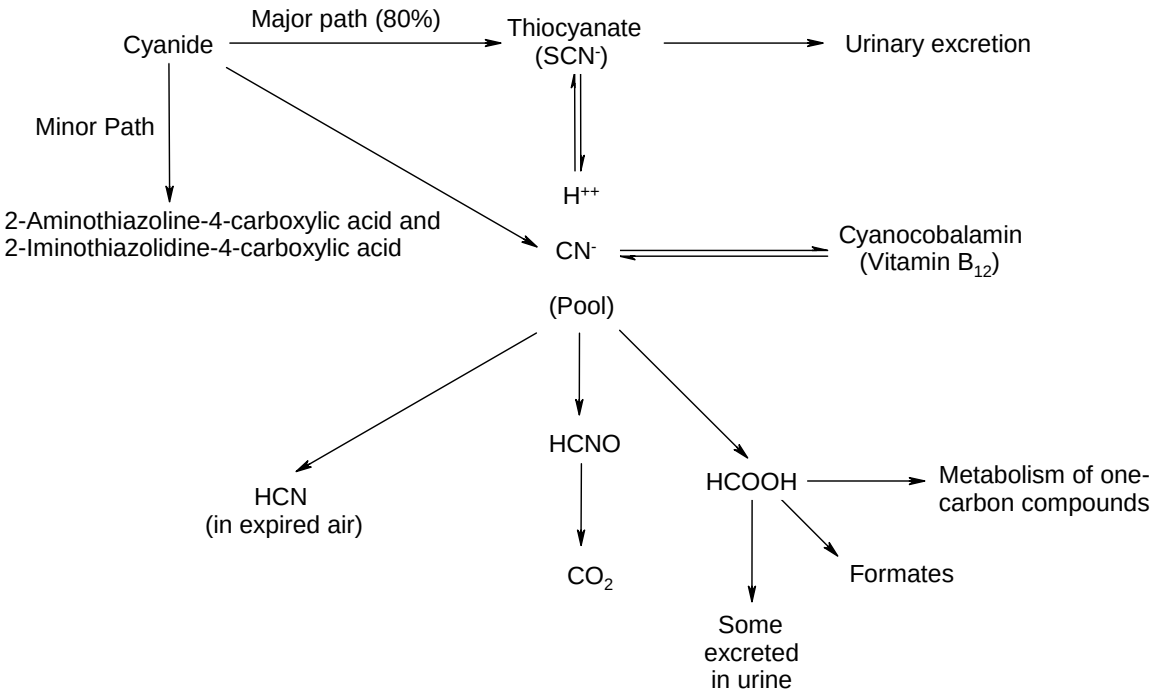
3.4.3 Metabolism

Reports of ingestion of cyanides by humans and reports of occupational exposure (see Section 3.8.1) indicate that cyanide is transformed into thiocyanate. A plasma half-life of 20 minutes to 1 hour has been estimated for cyanides in humans after nonlethal exposures (Hartung 1982).

Sousa et al. (2003) conducted a toxicokinetic study in male Wistar rats and Landrace-Large White pigs that were given a single dose of 1.2 mg CN^-/kg as potassium cyanide by aqueous gavage. In this study, the peak blood concentration of thiocyanate, the main metabolite of cyanide, was reached within 6 hours in rats and pigs. The peak plasma thiocyanate concentrations were 0.11 and 0.15 mg/100 mL for pigs and rats, respectively.

The metabolism of cyanide has been studied in animals. The proposed metabolic pathways shown in Figure 3-3 are (1) the major pathway, conversion to thiocyanate by either rhodanese or 3-mercapto-pyruvate sulfur transferase; (2) conversion to 2-aminothiazoline-4-carboxylic acid (Wood and Cooley 1956); (3) incorporation into a 1-carbon metabolic pool (Boxer and Richards 1952); or (4) combining with hydroxocobalamin to form cyanocobalamin (vitamin B_{12}) (Ansell and Lewis 1970). Thiocyanate has been shown to account for 60–80% of an administered cyanide dose (Blakley and Coop 1949; Wood and Cooley 1956) while 2-aminothiazoline-4-carboxylic acid accounts for about 15% of the dose (Wood and Cooley 1956). The conversion of cyanide to thiocyanate was first demonstrated in 1894. Conversion of cyanide to thiocyanate is enhanced when cyanide poisoning is treated by intravenous administration of a sulfur donor (Smith 1996; Way 1984). The sulfur 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

Figure 3-3. Basic Processes Involved in the Metabolism of Cyanide



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 as the major metabolite. Once thiocyanate is formed, it is not converted back to cyanide.

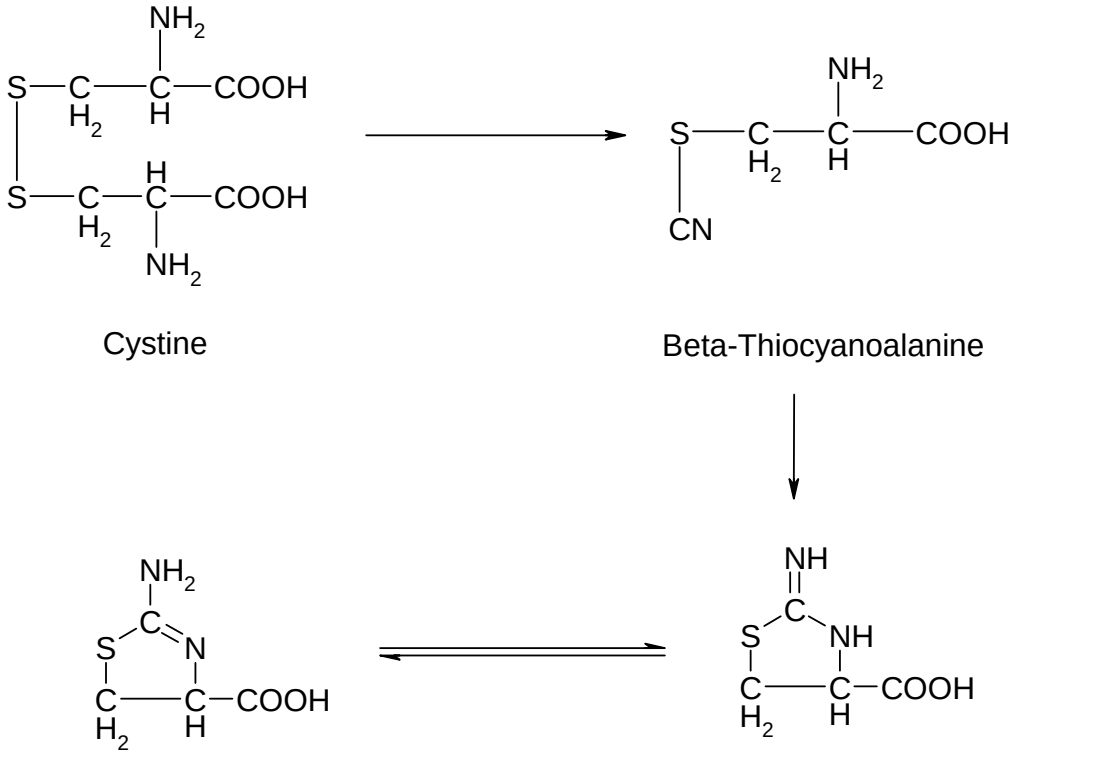
Radioisotopic studies showed that albumin interacts with the sulfane pool and that the serum albumin-sulfane sulfur carrier complex can react with cyanide (Schneider and Westley 1969). Higher hepatic rhodanese and lower serum albumin levels were found in mice fed a protein-free diet for 14 days compared with mice fed a control diet (Rutkowski et al. 1985). Despite the higher rhodanese levels, mortality following an intraperitoneal injection of sodium cyanide 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 also higher compared with controls, but only at high cyanide doses when thiosulfate was also administered. However, the pharmacokinetic studies in dogs, in which thiosulfate administration increased the rate of elimination of cyanide, suggest that the sulfane sulfur pool may play an important role as the central compartment for cyanide detoxification (Sylvester et al. 1983; Way 1984).

The species and tissue distribution of rhodanese is highly variable (Himwich and Saunders 1948). In dogs, the highest activity (conversion of cyanide to thiocyanate) 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 in dogs, which is consistent with the greater susceptibility of dogs to the acute effects of cyanide. Similar low levels of activity of the enzyme were found for the brain, testes, lungs, spleen, and muscle among various species.

In vitro studies with rat tissues indicated that rhodanese activity was ≈7 times higher in the nasal mucosa than in the liver (Dahl 1989). Furthermore, kinetic constants for rhodanese in mitochondria were higher in nasal than in liver tissue.

Figure 3-4 illustrates the minor pathway for metabolism of cyanide in mammalian systems in which cyanide chemically combines with the amino acid cystine. This chemical reaction yields cysteine and β-thiocyanoalanine that is further converted to form 2-aminothiazoline-4-carboxylic acid and its tautomer, 2-iminothiazolidiene-4-carboxylic acid (Wood and Cooley 1955).

Figure 3-4. Minor Path for the Removal of Cyanide from the Body



Cystine

Beta-Thiocyanoalanine

2-Aminothiazoline-4-carboxylic acid

2-Imino-4-thiazolidine-carboxylic acid

Source: Ansell and Lewis 1970

Reactions of cyanide with the salts or esters of some amino acids (e.g., pyruvate, α-ketoglutarate, oxaloacetate) lead to formation of cyanohydrin intermediates and their incorporation into intermediary metabolism.

The ability of cyanide to form complexes with some metallic ions such as cobalt is the basis for the reaction with hydroxocobalamin that yields cyanocobalamin. Cyanocobalamin (vitamin B_{12}), which contains cyanide and cobalt, is essential for the health of mammalian organisms.

3.4.4 Elimination and Excretion

3.4.4.1 Inhalation Exposure

Following chronic occupational exposure to 0.19–0.75 ppm hydrogen cyanide, 24-hour urinary levels of thiocyanate were 6.23 (smokers) and 5.4 µg/mL (nonsmokers) in exposed workers as compared with 3.2 (smokers) and 2.15 µg/mL (nonsmokers) in the controls (Chandra et al. 1980). This study demonstrates that tobacco smoking contributes to higher thiocyanate levels excreted in the urine. No studies were located regarding excretion of cyanide in animals after inhalation exposure to cyanide.

3.4.4.2 Oral Exposure

Cyanide metabolites are normally excreted in urine (Vassel et al. 1944) with small amounts eliminated through the lungs. Urinary excretion of thiocyanate was monitored in a man after ingestion of ≈3–5 g potassium cyanide (15–25 mg CN^-/kg) (Liebowitz and Schwartz 1948). The results indicated that the patient excreted 237 mg of thiocyanate over a 72-hour period. This quantity was substantially more than the normal average amount of thiocyanate in urine, which varies between 0.85 and 14 mg/24 hours. Thirty-one children who had consumed flour made from insufficiently processed cassava had mean urinary thiocyanate levels of 757 µmol/L, compared with 50 µmol/L in those children who had consumed sufficiently processed cassava (Tylleskar et al. 1992). In another study (Mlingi et al. 1993), mean urinary thiocyanate was 490 µmol/L in a village affected by Konzo disease and 350 µmol/L in an unaffected village, with the villages being comparable in all other respects.

When male Sprague-Dawley rats were given 2 mg CN^-/kg [^{14}C] potassium cyanide, urinary excretion of radioactivity reached 47% of the dose within 24 hours following administration (Farooqui and Ahmed 1982). When [^{14}C] sodium cyanide was injected subcutaneously into rats at a level of 8.3 µmol, no

difference in radioactivity eliminated was observed between the group pretreated for 6 weeks with a diet containing 0.7 mg CN^-/kg as potassium cyanide and their matching controls (Okoh 1983). Most of the radioactivity was detected in the urine (89% by 24 hours). Thiocyanate was the major metabolite. About 4% of the radioactivity was expired, mostly as carbon dioxide.

Sousa et al. (2003) compared toxicokinetic parameters in male Wistar rats and Landrace-Large White pigs that were given 1.2 mg CN^-/kg as potassium cyanide by aqueous gavage. The half-lives of elimination of cyanide from the blood were 0.54 hours for pigs and 0.64 hours for rats. The half-lives of elimination of thiocyanate from the blood were 4.95 hours in pigs and 5.8 hours in rats. The overall clearance of cyanide from the blood was reported as 0.367, and 0.379 mL/minute per kg for pigs and rats, respectively; the clearance of thiocyanate was reported as 0.135 and 0.061 mL/minute per kg for pigs and rats, respectively.

Orally administered cyanide and its metabolite thiocyanate were eliminated in the breast milk of lactating goats (Soto-Blanco and Gorniak 2003). The relevance of the goat data to humans is not established.

3.4.4.3 Dermal Exposure

No studies were located regarding excretion in humans or animals after dermal exposure to cyanide.

3.4.5 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models

Physiologically based pharmacokinetic (PBPK) models use mathematical descriptions of the uptake and disposition of chemical substances to quantitatively describe the relationships among critical biological processes (Krishnan et al. 1994). PBPK models are also called biologically based tissue dosimetry models. PBPK models are increasingly used in risk assessments, primarily to predict the concentration of potentially toxic moieties of a chemical that will be delivered to any given target tissue following various combinations of route, dose level, and test species (Clewell and Andersen 1985). Physiologically based pharmacodynamic (PBPD) models use mathematical descriptions of the dose-response function to quantitatively describe the relationship between target tissue dose and toxic end points.

PBPK/PD models refine our understanding of complex quantitative dose behaviors by helping to delineate and characterize the relationships between: (1) the external/exposure concentration and target

tissue dose of the toxic moiety, and (2) the target tissue dose and observed responses (Andersen and Krishnan 1994; Andersen et al. 1987). These models are biologically and mechanistically based and can be used to extrapolate the pharmacokinetic behavior of chemical substances from high to low dose, from route to route, between species, and between subpopulations within a species. The biological basis of PBPK models results in more meaningful extrapolations than those generated with the more conventional use of uncertainty factors.

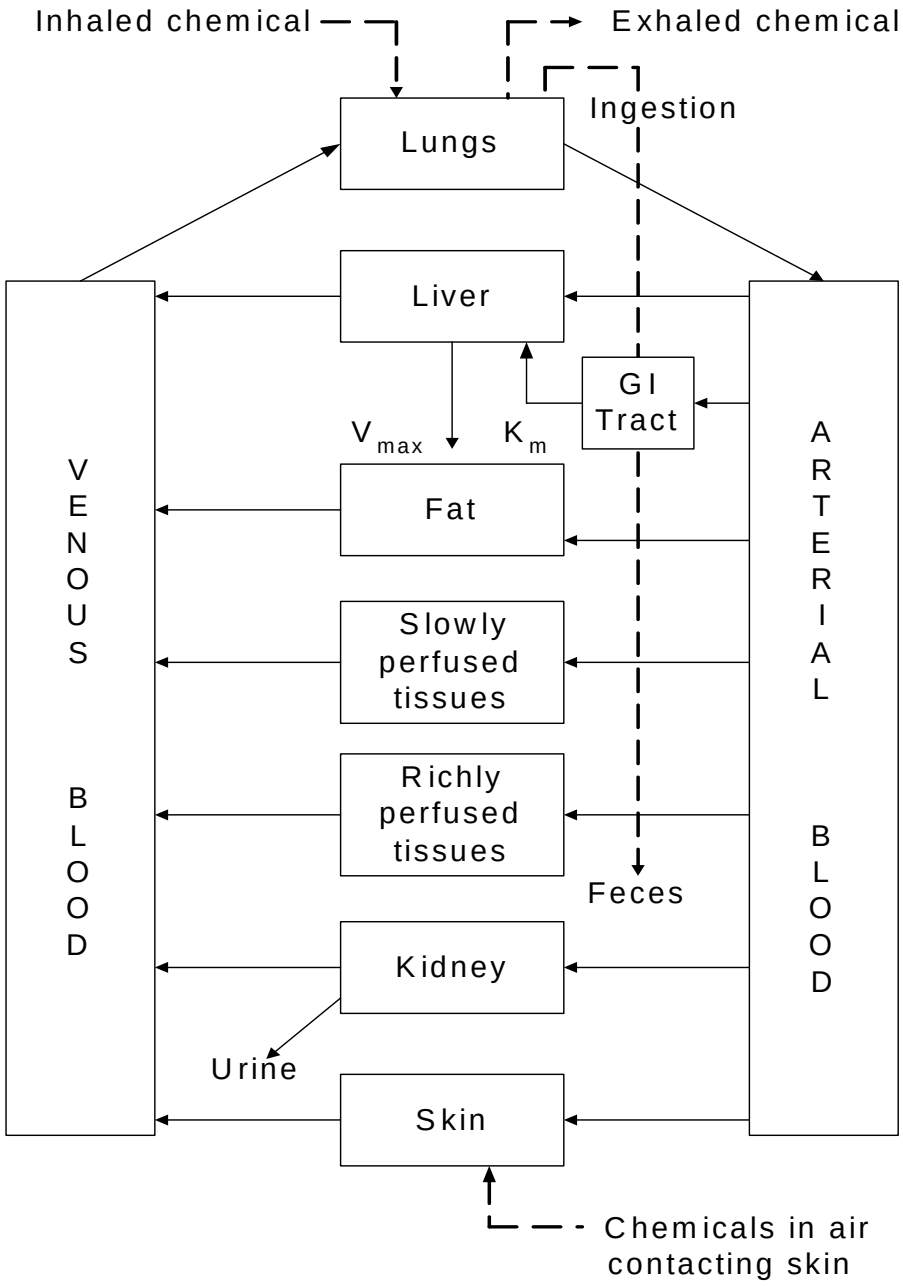
The PBPK model for a chemical substance is developed in four interconnected steps: (1) model representation, (2) model parameterization, (3) model simulation, and (4) model validation (Krishnan and Andersen 1994). In the early 1990s, validated PBPK models were developed for a number of toxicologically important chemical substances, both volatile and nonvolatile (Krishnan and Andersen 1994; Leung 1993). PBPK models for a particular substance require estimates of the chemical substance-specific physicochemical parameters, and species-specific physiological and biological parameters. The numerical estimates of these model parameters are incorporated within a set of differential and algebraic equations that describe the pharmacokinetic processes. Solving these differential and algebraic equations provides the predictions of tissue dose. Computers then provide process simulations based on these solutions.

The structure and mathematical expressions used in PBPK models significantly simplify the true complexities of biological systems. If the uptake and disposition of the chemical substance(s) are adequately described, however, this simplification is desirable because data are often unavailable for many biological processes. A simplified scheme reduces the magnitude of cumulative uncertainty. The adequacy of the model is, therefore, of great importance, and model validation is essential to the use of PBPK models in risk assessment.

PBPK models improve the pharmacokinetic extrapolations used in risk assessments that identify the maximal (i.e., the safe) levels for human exposure to chemical substances (Andersen and Krishnan 1994). PBPK models provide a scientifically sound means to predict the target tissue dose of chemicals in humans who are exposed to environmental levels (for example, levels that might occur at hazardous waste sites) based on the results of studies where doses were higher or were administered in different species. Figure 3-5 shows a conceptualized representation of a PBPK model.

No PBPK models were located for cyanide.

Figure 3-5. Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance



Source: adapted from Krishnan et al. 1994

Note: This is a conceptual representation of a physiologically based pharmacokinetic (PBPK) model for a hypothetical chemical substance. The chemical substance is shown to be absorbed via the skin, by inhalation, or by ingestion, metabolized in the liver, and excreted in the urine or by exhalation.

3.5 MECHANISMS OF ACTION

This section presents a brief overview of any known mechanisms of metabolism, absorption, distribution, and excretion including substance reactions or physiological processes that lead to or comprise the mechanism(s) of toxic effect.

3.5.1 Pharmacokinetic Mechanisms

Absorption. Absorption of cyanide across the gastrointestinal mucosa depends on the pH of the gut and the pKa and lipid solubility of the particular cyanide compound. Hydrogen cyanide is a weak acid with a pKa of 9.2 at 25 °C. The acidic environment in the stomach favors the non-ionized form of hydrogen cyanide and facilitates absorption. Information regarding the rapid lethal effects following oral intake of cyanide in humans (Gosselin et al. 1984) indicates that cyanide is rapidly absorbed from the gastrointestinal tract.

Hydrogen cyanide is moderately lipid-soluble, which, along with its small size, allows it to rapidly cross mucous membranes and to be taken up instantly across the alveolar epithelium of the lung after inhalation; penetration across the epidermis is less rapid. In addition, some cyanide compounds, such as potassium cyanide, have a corrosive effect on the skin that can increase the rate of percutaneous absorption (NIOSH 1976). Information regarding dermal absorption in animals and evidence that cyanide can be absorbed through the skin of humans is provided in Sections 3.4.1.3 and 3.2.3, respectively.

Distribution. Cyanide is rapidly distributed by the blood throughout the body. In a study using orally administered radioactively labeled potassium cyanide, radioactivity detected in whole blood or plasma decreased rapidly within 6 hours. Of the low levels of radioactivity detected in the red blood cells, about 94% of the radioactivity recovered was found in the hemolysate; of which 70% was detected in the heme fraction, 14–25% in globin, and only 5–10% in cell membranes (Farooqui and Ahmed 1982). Yamamoto et al. (1982) determined that the pattern of distribution of cyanide did not vary with the concentration used. Ballantyne (1983b) observed higher cyanide levels in whole blood than in serum in rabbits exposed dermally to hydrogen cyanide, potassium cyanide, and sodium cyanide. See Section 3.4.2.1 for specific studies on cyanide tissue distribution.

Cyanide is a reactive chemical substance and has the potential to form a variety of adducts in biological systems. A study of radiolabeled cyanide binding to mouse brain parts revealed that the hypothalamus accumulated more label than cerebral cortex, hippocampus, or cerebellum (Borowitz et al. 1994). Similarly, Baskin et al. (1987) found that the left ventricle of the guinea pig heart contained nearly twice as much as the right ventricle after a brief exposure to cyanide. Binding to certain tissue constituents may be important for decreasing the actions of cyanide and protecting cells from cyanide toxicity (Devlin et al. 1989b).

Storage. Cyanide does not accumulate in blood and tissues following chronic oral exposure. In a study with rats administered hydrogen cyanide in the diet at <10.4 mg CN^-/kg/day for 2 years, virtually no cyanide was found in plasma or kidneys (Howard and Hanzal 1955).

Metabolism. See Section 3.4.5.

Excretion. Cyanide metabolites (of which thiocyanate is the major component) are excreted primarily in urine, with small amounts of the metabolites eliminated through the lungs. When radioactively labeled cyanide is administered, most of the radioactivity is detected in the urine within 24 hours (Farooqui and Ahmed 1982; Okoh 1983). Boxer and Richards (1952) were the first to show that cyanide was oxidized to CO_2 and in the Okoh (1983) study, about 4% of the radioactivity was expired, mostly as carbon dioxide. See Section 3.4.3.4 for information on studies examining elimination and excretion.

Effect of Dose and Duration of Exposure on Toxicity. The severity of neurological effects in humans and animals after acute oral exposure to cyanide is dose-related (Chen and Rose 1952; Lasch and El Shawa 1981). Central nervous system effects have been observed following acute-duration exposures (Levine and Stypulkowski 1959a) and chronic-duration exposures (Hertting et al. 1960), via the inhalation and oral routes. Necrosis is the most prevalent central nervous system effect following acute-duration exposure to high concentrations of cyanide, whereas demyelination is observed in animals that survive repeated exposure protocols (Bass 1968; Ibrahim et al. 1963).

Increased duration of exposure to inhaled cyanide in mice resulted in lower LC_{50} values (Higgins et al. 1972; Matijak-Schaper and Alarie 1982). Additionally, cyanide toxicity was influenced by dilution of the gavage dose. Greater dilution resulted in higher mortality for the same total dose (Ferguson 1962).

Tylleskar et al. (1992) studied a population in rural Zaire that was affected with Konzo. Konzo is characterized by symmetric isolated bilateral involvement of upper motor neurons of abrupt onset; the damage is permanent, but not progressive. The Konzo patients had serum thiocyanate concentrations below those of the controls. The authors suggest that the combination of high exposure and a decreased conversion rate because of a deficiency in suitable sulfur substrates might explain this difference. Thus, daily exposure and decreased conversion rates may lead to high blood concentrations of cyanide that may then lead to upper motor neuron damage. 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 central nervous system disorders such as tropical ataxic neuropathy, tobacco amblyopia, and Leber's hereditary optic atrophy.

Route-Dependent Toxicity. A great similarity exists among cyanide-induced effects following inhalation, oral, and dermal exposure. Signs of toxicity in target organs from acute cyanide exposure (primarily central nervous system and heart), and chronic exposure (including central nervous system and thyroid gland), are similar in both humans and animals regardless of route. In general, the latency of effects is shortest by the inhalation route, similar for the oral route, but longer for the dermal route, since the skin is a thicker barrier to penetration. The rate of cyanide absorption and, therefore, latency of toxic effects is decreased in fasting animals.

3.5.2 Mechanisms of Toxicity

Effects of Metabolism on Toxicity. Cyanide (as hydrogen cyanide), originating *in vivo* by dissociation of potassium cyanide, sodium cyanide, and other cyanogenic compounds or arising from catabolism of cyanogenic glycosides, exerts its acute toxic effects by complexing with the ferric iron atom in metalloenzymes, resulting in histotoxic anoxia through inhibition of cytochrome c oxidase (Rieders 1971; Way 1984), metalloenzymes that function as the terminal oxidase of the inner mitochondrial membrane respiratory chain. A two-step process has been proposed: cyanide as hydrogen cyanide first penetrates a protein crevice of cytochrome c oxidase and binds to the protein (Stannard and Horecker 1948). Hydrogen cyanide then binds to the trivalent iron ion of the enzyme, forming a relatively stable (but reversible) coordination complex. One mole of hydrogen cyanide is bound to one mole of cytochrome c oxidase (Van Buuren et al. 1972). 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 resultant reduction in or cessation of aerobic metabolism (Rieders 1971; Way 1984). Glucose catabolism then shifts from the aerobic pathway to anaerobic metabolism including the pentose

phosphate pathway, resulting in increased blood glucose, pyruvic acid, lactic acid, and nicotinamide adenine dinucleotide (NADPH) levels, and a decrease in the adenosine triphosphate/adenosine diphosphate (ATP/ADP) ratio (Rieders 1971; Way 1984). Wilson et al. (1994) suggest that it is the binding of cyanide to oxidized Cu_B, the copper ion that is part of the dioxygen binding-site that leads to the inhibition of cytochrome c oxidase.

The inhibition of oxygen use by cells (termed histoxic hypoxia) causes oxygen tensions to rise in peripheral tissues (Smith 1996). This results in a decrease in the unloading gradient for oxyhemoglobin; thus, oxyhemoglobin is carried in the venous blood (Rieders 1971). Inhibition of oxygen utilization is thought to occur rapidly after cyanide exposure. Tadic (1992) determined that inhibition of cytochrome c oxidase activity in rat brains was most pronounced between 15 and 20 minutes after administration of sodium cyanide (12 mg/kg or $1.3xLD_{50}$). In addition to binding to cytochrome c oxidase, cyanide also binds to catalase, peroxidase, methemoglobin, hydroxocobalamin, phosphatase, tyrosinase, ascorbic acid oxidase, xanthine oxidase, and succinic dehydrogenase. These reactions may also contribute to the classic signs of cyanide toxicity (Ardelt et al. 1989; Rieders 1971). Information on mechanisms of toxicity in target organs is presented below.

Target Organ Toxicity. The central nervous system is the primary target for cyanide toxicity in humans and animals. Acute inhalation of high concentrations of cyanide provokes a brief central nervous system stimulation followed by depression, convulsions, coma, and death in humans (Bonsall 1984; Chen and Rose 1952; Peden et al. 1986; Potter 1950; Singh et al. 1989) and in animals (Haymaker et al. 1952; McNerney and Schrenk 1960; Purser et al. 1984). The effects are probably due to rapid biochemical changes in the brain, such as changes in ion flux, neurotransmitter release, and possibly peroxide formation (Johnson and Isom 1985; Kanthasamy et al. 1991a, 1994; Persson et al. 1985). In both *in vivo* and *in vitro* studies using brain tissue, the sensitivity of mitochondrial cytochrome c oxidase activity to inhibition by cyanide was greater than the inhibition of mitochondrial respiratory activity. Only after cytochrome c oxidase activity was depressed by >50% was a large decrease in respiratory activity detected, suggesting that a large portion of cytochrome c oxidase may serve as a functional reserve. Cyanide poisoning likely involves mechanisms in addition to inhibition of cytochrome c oxidase activity (Pettersen and Cohen 1993). Cyanide is a strong nucleophile with multiple effects including release of secondary neurotransmitters, release of catecholamines from adrenal glands and adrenergic nerves, and inhibition of antioxidant enzymes in the brain (Smith 1996). However, the extremely low concentration of cyanide required to inhibit the oxidase, the rapid interaction of hydrogen cyanide with the enzyme, and the key role of cytochrome c oxidase in aerobic metabolism all combine to make cyanide inhibition of the

terminal step of electron transport (Chance and Erecinsk 1971; Gibson and Greenwood 1963), the key molecular target in cyanide poisoning.

Inhalation and oral studies in animals have shown that acute or chronic 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, corpus callosum, hippocampus, corpora striata, pallium, and substantia nigra. White matter may be more sensitive because of its relatively low cytochrome c oxidase content. Rats injected subcutaneously with daily maximal doses between >3.7 and 9.2 mg CN^-/kg/day (not averaged) 3 days/week for 3 months developed necrotic lesions of the corpus callosum and optic nerve, but there was not a consistent dose-response (Lessell 1971); this may reflect variability in diffusion of cyanide into the systemic circulation by the subcutaneous injection route. High mortality was observed among exposed animals. These effects have been observed following acute-duration exposures (Levine and Stypulkowski 1959a) and chronic-duration exposures (Hertting et al. 1960). Necrosis is a prevalent central nervous system effect following acute exposure to high concentrations of cyanide, whereas demyelination is observed in animals that survive repeated exposure protocols (Bass 1968; Ibrahim et al. 1963). The mechanism of cyanide-induced demyelination is not completely understood, but the evidence suggests that a direct effect of cyanide on white matter may not be necessary. It has been suggested that local edema affecting the oligodendrocytes and caused by vascular changes triggered by cyanide represent a primary event in demyelination (Bass 1968; Ibrahim et al. 1963). Aitken and Braitman (1989) determined that cyanide has a direct effect on neurons not mediated by its inhibition of metabolism. Consistent with the view that cyanide toxicity is due to the inability of tissue to utilize oxygen is a report that in cyanide-intoxicated rats, arterial pO_2 levels rose, while carbon dioxide levels fell (Brierley et al. 1976). The authors suggested that the low levels of carbon dioxide may have led to vasoconstriction and reduction in brain blood flow; therefore, brain damage may have been due to both histotoxic and anoxic effects. Partial remyelination after cessation of exposure has been reported, but it is apparent that this process, unlike that in the peripheral nervous system, is slow and incomplete (Hirano et al. 1968). The topographic selectivity of cyanide-induced encephalopathy may be related to the depth of acute intoxication and distribution of blood flow, which may result in selected regions of vascular insufficiency (Levine 1969).

Several 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 decreases 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). Elevated levels of intracellular calcium in a cyanide-exposed, presynaptic squid neuron were observed in an *in vitro* study (Adams et al. 1985). Elevated levels of neuronal calcium may initiate release of neurotransmitters from the presynaptic terminal, which can activate the nervous system (Maduh et al. 1990a). Levels of whole-brain calcium increased when potassium cyanide was administered subcutaneously to mice. These increases were correlated with cyanide-induced tremors (Johnson et al. 1986). Brain injury may be associated with cyanide-induced endogenous glutamate release, mediated by both calcium dependent and independent mechanisms, which in turn produce excitotoxic responses in select brain areas (Patel et al. 1991, 1992, 1993). In examining receptor subtypes involved in mediating cyanide-induced toxicity, sodium cyanide-induced cytotoxicity was found to be mediated primarily by activation of the N-methyl-D aspartate (excitatory amino acid) receptor. Sturm et al. (1993) examined the ability of adenosine to attenuate the excitotoxicity secondary to glutamate receptor activation following potassium cyanide exposure in hippocampal neuronal cell cultures. The authors concluded that neuronal cell death was mediated at least in part by glutamate and that the cell death was attenuated by adenosine via the A_1-specific receptor. 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 calcium (Robinson et al. 1985b). Furthermore, changes in cytosolic pH and dysfunction of hydrogen ion handling mechanisms were observed in neuronal cells exposed *in vitro* to cyanide (Maduh et al. 1990b). Pazdernik et al. (1994) reported an increase of local cerebral glucose utilization (LCGU) in many regions of the brain within a minute after sublethal exposure to 2.7–5 mg CN^-/kg as sodium cyanide by controlled intravenous infusion over 1 hour. However, by 1 hour, there was a global increase in LCGU in almost every region of the brain. LCGU values returned to normal in all regions except the choroid plexus by 6 hours and in that region as well by 24 hours. These results support the expectation that cyanide causes a shift from aerobic to anaerobic metabolism, as illustrated by increases in extracellular lactate and pyruvate and in LCGU.

When cyanide blocks oxidative metabolism in mitochondria, cells shift their metabolism and enhanced glucose utilization occurs. One consequence of this altered metabolic pattern is accumulation of nicotinamide adenine dinucleotide (NADH), which is a powerful stimulant of calcium mobilization from cell stores through "inositol triphosphate receptors." Elevated calcium damages cells. Increase in cellular NADH, therefore, is an important event in the toxic action of cyanide (Kaplin et al. 1996).

Studies have shown that cyanide releases catecholamines from rat pheochromocytoma cells and brain slices (Kanthasamy et al. 1991b), from isolated bovine adrenal glands (Borowitz et al. 1988), and from adrenals of mice following subcutaneous injection of high doses of potassium cyanide (Kanthasamy et al. 1991b). Thus, it was proposed that the cardiac and peripheral autonomic responses to cyanide are partially mediated by an elevation of plasma catecholamines (Kanthasamy et al. 1991b). Dopamine levels in potassium cyanide-treated animals were significantly decreased in striatum and hippocampus, and somewhat decreased in cerebral cortex of mice (Kanthasamy et al. 1994), while extracellular levels of dopamine and homovanillic acid were increased in the brain of rats treated with sodium cyanide (Cassel et al. 1995). Kiuchi et al. (1992) suggested that suppression of ATP production by sodium cyanide induces an abrupt and remarkable increase in dopamine release from the nerve terminal in the striatum. Kanthasamy et al. (1994) also observed that in striatal and hippocampal tissues, but not in cerebral cortex, malondialdehyde levels increased indicating the occurrence of lipid peroxidation in these brain regions. In addition, reduced numbers of tyrosine hydroxylase (TH) positive cells indicated a loss of dopaminergic neurons (Kanthasamy et al. 1994). Behavioral effects seen in the mice were reversed by administration of l-DOPA (treatment for dopamine-deficiency). Ardelt et al. (1994) also evaluated hydroperoxide generation as a potential mechanism of cyanide neurotoxicity. Increased lipid peroxidation was observed in brain and kidney, but not in liver or heart. It was also determined that calcium plays a critical role in lipid peroxidation in neuronal cells. Subcellular fractionation of brain tissue showed an increase in lipid peroxidation in the microsomal but not mitochondrial fraction. Matsumoto et al. (1993) evaluated the involvement of extracellular calcium in dopamine release from rat striatum resulting from cyanide exposure. A gradual increase in intracellular calcium was observed during incubation of sodium cyanide with striatal slices. The excessive influx of extracellular calcium during sodium cyanide perfusion may contribute to the changes in dopamine levels in striatum and to the observed suppression of dopamine release in response to high potassium stimulation. Release of dopamine was not suppressed by perfusion with a calcium-free solution; thus, additional mechanisms other than the opening of calcium channels must also be involved in dopamine release by cyanide. Decreased dopamine uptake has been suggested as an explanation for this increase in dopamine, since dopamine uptake is driven by a sodium gradient that is maintained by the Na/K ATPase and could be reduced if ATP is depleted. Cyanide did not affect monamine oxidase or catechol-o-methyl transferase, suggesting that a disturbance in dopamine metabolism did not lead to extracellular dopamine elevation (Matsumoto et al. 1993).

Mills et al. (1999) reported that there is more than one mode of cell death operating in the brains of mice injected with potassium cyanide. Extensive DNA fragmentation, pyknosis, and chromosome condensation, all characteristics of apoptosis, were observed in the parietal and suprarhinal regions of the

motor cortex of treated mice. However, necrotic lesions with astrocytic gliosis were found in the substantia nigra. Pretreatment with the antioxidant alpha-phenyl-tert-butyl nitrone reduced cortical DNA fragmentation, but had no effect on the necrotic lesions produced in the substantia nigra.

Prabhakaran et al. (2002) similarly reported different modes of death induced by cyanide in primary cultures of rat cortical or mesencephalic neurons; the mode of cell death and the reactive oxygen species generated differed in the two kinds of cells. Cortical neurons exhibited apoptosis, with increases in hydrogen peroxide and superoxide, and a moderate change in mitochondrial membrane potential, leading to release of cytochrome c and activation of caspase-3-like protease (a cysteine protease associated with apoptosis). Mesencephalic neurons exhibited necrosis involving excess nitric oxide and superoxide, with a more pronounced reduction in mitochondrial membrane potential. Additional studies demonstrated that necrosis of exposed mesencephalic cells or cortical neurons exposed to 0.5–0.6 mM KCN was induced by the upregulation of uncoupling protein 2 (UCP-2), a protein of the inner mitochondrial membrane (Li et al. 2005; Prabhakaran et al. 2005). UCP-2 increases proton leak across the inner mitochondrial membrane, dissociating respiration from ATP synthesis. In experiments preventing the expression of UCP-2, the necrotic death of cultured mesencephalic cells exposed to cyanide was also prevented (Prabhakaran et al. 2005).

The mediation of cyanide-induced apoptosis has been studied in cultured cortical neurons exposed to 0.3 mM cyanide (Shou et al. 2002, 2003). Treatment with cyanide activated p38 mitogen-activated protein (MAP) kinase within 30 minutes, an upstream event necessary for the translocation of Bax protein from the cytosol to mitochondria 2.5 hours later (Shou et al. 2003). Translocation of Bax protein to mitochondria is a required step in the release of cytochrome c from mitochondria as well as the caspase cascade that regulates apoptosis. Cyanide treatment of cortical neurons also results in the activation of the redox-sensitive transcription factor NF-κB, and its translocation to the nucleus, where it upregulates expression of the pro-apoptotic proteins Bax and Bcl-X_S (Shou et al. 2002). Increased cytosolic calcium levels also contribute to apoptosis of cyanide-treated cortical neurons (Shou et al. 2004). Increased calcium activates cellular calcineurin, which stimulates the activation of the protein known as BAD (Bcl-2/Bcl-X_L-antagonist, causing cell death) and its translocation to mitochondria within 1 hour of treatment with cyanide. The net effect of BAD is to selectively inhibit proteins (Bcl-1/Bcl-X_L) that are antagonists to apoptosis (Shou et al. 2004).

It has been noted that survivors of cyanide poisoning incidents may develop Parkinsonian-like signs, with lesions in the substantia nigra, a dopaminergic center, confirmed by MRI (Carella et al. 1988; Chin and

Calderon 2000; Grandas et al. 1989; Feldman and Feldman 1990; Rachinger et al. 2002; Rosenberg et al. 1989; Rosenow et al. 1995; Uitti et al. 1985; Zaknun et al. 2005). Jones et al. (2000, 2003) have presented evidence based on experiments on PC12 cells (a pheochromocytoma cell line that can be induced to differentiate as neurons) and fetal rat mesencephalic cells indicating that cyanide toxicity is exacerbated by the oxidation of dopamine. Increases in apoptosis and reactive oxygen species occurred at higher levels in PC12 cells incubated in dopamine plus potassium cyanide compared to those incubated in either chemical separately; concentrations of potassium cyanide that had no effect on fetal rat midbrain cells significantly increased the adverse effects of added dopamine. Toxicity in one or both systems was reduced by preincubation with antioxidants (superoxide dismutase, glutathione catalase), an inhibitor to nitric oxide synthase (N^{omega}-nitro-L-arginine methyl ester), and the peroxynitrite scavenger uric acid. The authors suggest that the inactivation of antioxidant enzymes by cyanide as described by Ardelt et al. (1989) may render neurons more vulnerable to the adverse effects of dopamine oxidation. Dopaminergic brain centers would therefore be more sensitive to cyanide neurotoxicity. In cultured cerebellar granule cells taken from 8-day-old rat pups, cyanide treatment generated nitric oxide and reactive oxygen species concurrently, resulting in lipid peroxidation (Gunasekar et al. 1996).

Chao et al. (1996) investigated the possibility that cyanide had an effect on motor neurons that was independent of respiratory impairment. In mouse triangularis sterni and diaphragm nerve-muscle preparations under glucose-free conditions, 10 μM sodium cyanide increased spontaneous transmitter release. This was correlated with a depression of ATP-sensitive potassium currents, an effect that was antagonized by diazoxide, an opener of ATP-sensitive K^+ channels. The authors suggest that cyanide causes depolarization of motor nerve terminals via its effect on the ATP-sensitive K^+ channels. Cassel et al. (1994) examined the *in vitro* effects of sodium cyanide on two forms of monoamine oxidase (MAO), an enzyme important in regulation of biogenic amines in the brain and peripheral tissue. In striatal tissue, cyanide produced a dose-dependent increase in the activity of MAO-A but not MAO-B. Greer and Carter (1995) investigated the effects of hydrogen cyanide on the neural mechanisms controlling breathing. Cyanide, at concentrations considered lethal *in vivo*, caused a modest depression of the frequency and amplitude of inspiratory rhythmic discharge. The neuronal network underlying respiration continued to function for hours in the presence of very high concentrations of cyanide. The authors hypothesized that the rapid suppression of breathing caused by cyanide *in vivo* is due to changes in neuronal excitability in respiratory centers in the central nervous system.

Results of *in vitro* studies suggest an interaction between calcium ions and cyanide in cardiovascular effects (Allen and Smith 1985; Robinson et al. 1985a). It has been demonstrated that exposure to cyanide

in metabolically depleted ferret papillary muscle eventually results in elevated intracellular calcium levels, but only after a substantial contracture develops (Allen and Smith 1985). The authors proposed that intracellular calcium may precipitate cell damage and arrhythmias. The mechanism by which calcium levels are raised was not determined. Franchini and Krieger (1993) produced selective denervation of the aortic and carotid bifurcation areas, and confirmed the carotid body chemoreceptor origin of cardiovascular, respiratory, and certain behavioral responses to cyanide in rats. Bradycardia and hyperventilation induced by cyanide are typical responses evoked by carotid body chemoreceptor stimulation (Franchini and Krieger 1993).

The respiratory effects of cyanide include dyspnea, asphyxia, and a decrease in respiratory rate (Blanc et al. 1985; Matijak-Schaper and Alarie 1982; McNerney and Schrenk 1960). A recent study (Bhattacharya et al. 1994) demonstrated an initial increased air flow, transthoracic pressure, and tidal volume accompanied by a significant decrease in pulmonary phospholipids following inhalation of hydrogen cyanide in rats. This study also showed that hydrogen cyanide exhibited a direct effect on pulmonary cells in rats.

Cyanide-induced effects on the thyroid gland are particularly important in chronic cyanide exposures and are discussed in several studies. Thiocyanate markedly inhibits accumulation of iodine by the thyroid gland, thus decreasing the ability of the gland to maintain a concentration of iodine above that of blood (VanderLaan and Bissell 1946). In addition, thiocyanate may inhibit the iodination process, thus interfering with the binding of glandular iodine and reducing the formation of thyroxine (Ermans et al. 1972). Changes in thyroid chemistry reported in individuals chronically exposed to cyanide have not been accompanied by manifestations of hypothyroidism. Fukayama et al. (1992) studied the antithyroid action of thiocyanate in a culture system of thyroid follicles. Thiocyanate concentrations equivalent to serum levels in smokers showed three independent antithyroid actions, including inhibition of iodide transport, inhibition of binding of iodide in the thyroid, and increased iodide efflux. The discrepancy in the potency of the antithyroid activity of thiocyanate *in vivo* and *in vitro* appears to be due to the presence of iodide and moieties such as the perchlorate ion, which is known to alter the effect of thiocyanate on the thyroid (Van Middlesworth 1986).

Persons with a metabolic disturbance in the conversion of cyanide to thiocyanate may be at greater risk from the toxic effect of cyanide. A defect in the rhodanese system and vitamin B_{12} deficiency have been noted in persons with tobacco amblyopia and Leber's hereditary optic atrophy exposed to tobacco smoke which contains cyanide (Wilson 1983). Iodine deficiency, along with excess chronic exposure to cyanide,

may, in certain cases, be involved in the etiology of such thyroid disorders as goiter and cretinism (Delange and Ermans 1971; Ermans et al. 1972). Also, protein deficiencies and vitamin B_{12} and riboflavin, and other deficiencies may subject people who eat foods high in cyanogenic glycosides to increased risk of neuropathies (Makene and Wilson 1972; Osuntokun 1972; Osuntokun et al. 1969). Patients with motor neuron disease (amyotrophic lateral sclerosis) possess a disorder in cyanide metabolism that may result in higher susceptibility to cyanide (Kato et al. 1985).

Carcinogenesis. No studies were located regarding carcinogenic effects of cyanide exposure in humans or animals following any route of exposure. Therefore, no mechanism of carcinogenesis can be discussed.

Caveat Regarding in vitro Studies. During a study of the effect of sodium cyanide on cultured SH-SY5Y human neuroblastoma cells, Arun et al. (2005) observed that no significant toxicity was observed up to concentrations of 10 mM and conducted further experiments to determine the cause of the apparent resistance to cyanide. Culturing at 37 °C for 2 hours resulted in variable depletion of cyanide from the medium, depending on the type of vessel: by 3.9% using 15-mL capped polypropylene tubes, by 22.4% using vented cap 25-cm^2 culture flasks, and by 57.2–86.7% using unsealed multiwell plates (12-, 24-, or 96-well). Cyanide loss from standard Dulbecco's monified Eagle's/Ham's F12 medium (DMEM) with 10% fetal bovine serum (FBS) was compared to the loss from individual constituents of medium tested after 2-hour culturing at room temperature. Cyanide loss from solution was 68.6% from an amino acid mixture, 47.9% from glucose solution, 36.3% from phenol red (typically included as a pH indicator), and 81.1% from standard DMEM plus 10% FBS. Arun et al. (2005) measured a 10% loss of sodium cyanide from deionized water (0.2 mL volume) over a 2-hour period at room temperature and higher losses when a protein donor (alanine) was present. Release of HCN by outgassing accompanied cyanide depletion from the medium. The results of these experiments indicate there is measurable loss of cyanide from solution where vessels are not sealed. This may result in an underestimate of the toxicity of cyanide in *in vitro* culture experiments.

3.5.3 Animal-to-Human Extrapolations

Biological effects of cyanide in humans have been demonstrated (Smith 1996; Wexler et al. 1947). However, no studies directly comparing the cytotoxicity of similar animal and human cells were available. However, a difference in species susceptibility to cyanide poisoning was indicated by slightly lower lethal concentrations in rabbits compared to rats (Ballantyne 1983a). Additionally, mortality from cyanides applied dermally varied depending on the cyanide compound used. In the Ballantyne (1983a)

study, dermal application resulted in cyanide levels in blood and serum that were lower after topical sodium cyanide and potassium cyanide exposure than from hydrogen cyanide; however, oral exposure in rabbits produced an LD_{50} of 2.3–2.7 mg CN^-/kg/day, regardless of whether the source was hydrocyanic acid, sodium cyanide, or potassium cyanide (Ballantyne 1983a).

Species and tissue distribution of rhodanese (thiosulfate sulfurtransferase), an enzyme important in metabolizing cyanide, is highly variable (Drawbaugh and Marrs 1987; Himwich and Saunders 1948). In dogs, the highest activity of rhodanese was found in the adrenal gland, ≈2.5 times greater than the activity in the liver (Himwich and Saunders 1948). Monkeys, rabbits, and rats had the highest rhodanese activity in liver and kidney, with relatively low levels in adrenals. It should be noted that total rhodanese activity in other species was higher than in dogs, which is consistent with the greater susceptibility of dogs to the acute effects of cyanide. Thus, dogs may not be a good model from which to extrapolate the toxicity of cyanide to humans. Similar activities of the enzyme among the species were found for the brain, testes, lungs, spleen, and muscle. Plasma activities of rhodanese in rats, hamsters, rabbits, and guinea pigs ranged from 14 to 20 Units/mL compared to 31 Units/mL for Beagle dogs (Drawbaugh and Marrs 1987).

In an effort to identify appropriate animal models for testing the efficacy of methemoglobin-forming cyanide antidotes, Rockwood et al. (2003) compared the endogenous activities of the erythrocyte NADH-dependent enzyme methemoglobin reductase (ferricyanide reductase) in several species. Two strains of beagles had enzyme activities roughly 40–50% lower than the mean for humans and with no overlap to the range for the human data. The enzyme activities of the other tested species had higher means than the human, but the ranges for the Rhesus and Aotus monkeys were similar to the human, indicating that these would be appropriate models. Data for the marmoset, Cynomolgus monkey, and African green monkey showed less overlap to the human data, whereas data for the ferret, chimpanzee, and baboon showed no overlap.

3.6 TOXICITIES MEDIATED THROUGH THE NEUROENDOCRINE AXIS

Recently, attention has focused on the potential hazardous effects of certain chemicals on the endocrine system because of the ability of these chemicals to mimic or block endogenous hormones. Chemicals with this type of activity are most commonly referred to as *endocrine disruptors*. However, appropriate terminology to describe such effects remains controversial. The terminology *endocrine disruptors*, initially used by Thomas and Colborn (1992), was also used in 1996 when Congress mandated the EPA to develop a screening program for "...certain substances [which] may have an effect produced by a

naturally occurring estrogen, or other such endocrine effect[s]...". To meet this mandate, EPA convened a panel called the Endocrine Disruptors Screening and Testing Advisory Committee (EDSTAC), and in 1998, the EDSTAC completed its deliberations and made recommendations to EPA concerning *endocrine disruptors*. In 1999, the National Academy of Sciences released a report that referred to these same types of chemicals as *hormonally active agents*. The terminology *endocrine modulators* has also been used to convey the fact that effects caused by such chemicals may not necessarily be adverse. Many scientists agree that chemicals with the ability to disrupt or modulate the endocrine system are a potential threat to the health of humans, aquatic animals, and wildlife. However, others think that endocrine-active chemicals do not pose a significant health risk, particularly in view of the fact that hormone mimics exist in the natural environment. Examples of natural hormone mimics are the isoflavinoid phytoestrogens (Adlercreutz 1995; Livingston 1978; Mayr et al. 1992). These chemicals are derived from plants and are similar in structure and action to endogenous estrogen. Although the public health significance and descriptive terminology of substances capable of affecting the endocrine system remains controversial, scientists agree that these chemicals may affect the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body responsible for maintaining homeostasis, reproduction, development, and/or behavior (EPA 1997). Stated differently, such compounds may cause toxicities that are mediated through the neuroendocrine axis. As a result, these chemicals may play a role in altering, for example, metabolic, sexual, immune, and neurobehavioral function. Such chemicals are also thought to be involved in inducing breast, testicular, and prostate cancers, as well as endometriosis (Berger 1994; Giwercman et al. 1993; Hoel et al. 1992).

Nishihara et al. (2000) screened a large number of industrial chemicals for estrogenic activity *in vitro* using a two-hybrid expression system: *Saccharomyces cerivisiae* Y190 containing expression plasmids for the estrogen receptor alpha and the coactivator TIF-2. At concentrations as high as 1 mM, potassium cyanide did not induce estrogenic expression in this assay (defined as 10% of the agonist activity of 10^{-7} M 17-beta-estradiol). No other reports of cyanides modulating estrogen hormonal levels were located.

3.7 CHILDREN'S SUSCEPTIBILITY

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans, when all biological systems will have fully developed. Potential effects on offspring resulting from exposures of parental germ cells are considered, as well as any indirect

effects on the fetus and neonate resulting from maternal exposure during gestation and lactation. Relevant animal and *in vitro* models are also discussed.

Children are not small adults. They differ from adults in their exposures and may differ in their susceptibility to hazardous chemicals. Children's unique physiology and behavior can influence the extent of their exposure. Exposures of children are discussed in Section 6.6, Exposures of Children.

Children sometimes differ from adults in their susceptibility to hazardous chemicals, but whether there is a difference depends on the chemical (Guzelian et al. 1992; NRC 1993). Children may be more or less susceptible than adults to health effects, and the relationship may change with developmental age (Guzelian et al. 1992; NRC 1993). Vulnerability often depends on developmental stage. There are critical periods of structural and functional development during both prenatal and postnatal life, and a particular structure or function will be most sensitive to disruption during its critical period(s). Damage may not be evident until a later stage of development. There are often differences in pharmacokinetics and metabolism between children and adults. For example, absorption may be different in neonates because of the immaturity of their gastrointestinal tract and their larger skin surface area in proportion to body weight (Morselli et al. 1980; NRC 1993); the gastrointestinal absorption of lead is greatest in infants and young children (Ziegler et al. 1978). Distribution of xenobiotics may be different; for example, infants have a larger proportion of their bodies as extracellular water, and their brains and livers are proportionately larger (Altman and Dittmer 1974; Fomon 1966; Fomon et al. 1982; Owen and Brozek 1966; Widdowson and Dickerson 1964). The infant also has an immature blood-brain barrier (Adinolfi 1985; Johanson 1980) and probably an immature blood-testis barrier (Setchell and Waites 1975). Many xenobiotic metabolizing enzymes have distinctive developmental patterns. At various stages of growth and development, levels of particular enzymes may be higher or lower than those of adults, and sometimes unique enzymes may exist at particular developmental stages (Komori et al. 1990; Leeder and Kearns 1997; NRC 1993; Vieira et al. 1996). Whether differences in xenobiotic metabolism make the child more or less susceptible also depends on whether the relevant enzymes are involved in activation of the parent compound to its toxic form or in detoxification. There may also be differences in excretion, particularly in newborns who all have a low glomerular filtration rate and have not developed efficient tubular secretion and resorption capacities (Altman and Dittmer 1974; NRC 1993; West et al. 1948). Children and adults may differ in their capacity to repair damage from chemical insults. Children also have a longer remaining lifetime in which to express damage from chemicals; this potential is particularly relevant to cancer.

Certain characteristics of the developing human may increase exposure or susceptibility, whereas others may decrease susceptibility to the same chemical. For example, although infants breathe more air per kilogram of body weight than adults breathe, this difference might be somewhat counterbalanced by their alveoli being less developed, which results in a disproportionately smaller surface area for alveolar absorption (NRC 1993).

From the few oral studies available, the effects of cyanide on children appear to be like those of similarly exposed adults. This is expected based on cyanide's inhibition of mitochondrial respiration in all cells. Neurological (headache and coma), respiratory (tachypnea), cardiovascular (hypotension), and gastrointestinal effects (vomiting) have been reported in children who have been poisoned by eating apricot pits (Lasch and El Shawa 1981). Congenital hypothyroidism has been observed in some children who were exposed to increased thiocyanate levels because of the maternal cassava diet during pregnancy (Ermans et al. 1980).

Developmental studies in animals (rats or hamsters) orally exposed to potassium cyanide, cassava diets, or one of the cyanogenic glycosides (amygdalin, linamarin) reported fetal toxicity (reduced fetal weight, delayed ossification) and developmental anomalies (microcephaly, limb defects, encephalocele, and rib abnormalities) in offspring (Frakes et al. 1986a; Singh 1981; Tewe and Maner 1981a; Willhite 1982). These effects occurred at exposure levels that were toxic to the dam. A developmental study in pigs indicates that this species is less sensitive than rodents to gestational exposure to cyanide (Tewe and Maner 1981b). Results of a study in lactating goats indicate that cyanide and thiocyanate can be transferred through milk to nursing offspring (Soto-Blanco and Gorniak 2003).

It is likely that the observed adverse effects on fetal growth and the timing of ossification following maternal exposure to cyanide has multiple sources. In addition to a direct action of cyanide on mitochondrial respiration in fetal cells, the reduction in oxygen-carrying capacity of the maternal blood would also be expected to result in lower metabolic rates in fetuses. Furthermore, hypothyroidism, characterized by reductions in thyroid hormone levels, would also adversely affect rates of cell metabolism.

In goats, maternal co-administration of sodium thiocyanate prevented the rise in erythrocyte cyanide levels caused by sodium nitroprusside (Curry et al. 1997). Sodium nitroprusside is infused intravenously as a vasodilator for the treatment of hypertensive emergencies (Agarwal and Kumari 2003; Curry et al. 1997; Przybylo et al. 1995; Randall and St. Louis 1996; Sipe et al. 2001). In the blood, sodium

nitroprusside nonenzymatically receives one electron from oxyhemoglobin, forming the nitroprusside radical, which dissociates to nitric oxide (the vasodilator) and five cyanide ions (Przybylo et al. 1995). In practice, sodium thiocyanate is co-administered to prevent cyanide toxicity. Curry et al. (1997) infused sodium nitroprusside into gravid ewes, resulting in elevations of erythrocyte cyanide concentrations that caused the death of one ewe and one fetus from cardiac toxicity. Co-administration of sodium thiocyanate to gravid ewes prevented the elevation in erythrocyte cyanide levels in ewes and fetuses. Curry et al. (1997) conclude that sodium thiocyanate, like cyanide and sodium nitroprusside, cross the placenta in goats. The relevance of the goat study to humans is not known.

3.8 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility (NAS/NRC 1989).

Due to a nascent understanding of the use and interpretation of biomarkers, implementation of biomarkers as tools of exposure in the general population is very limited. A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself, substance-specific metabolites in readily obtainable body fluid(s), or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to cyanide are discussed in Section 3.8.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial

cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by cyanide are discussed in Section 3.8.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 3.10, Populations That Are Unusually Susceptible.

3.8.1 Biomarkers Used to Identify or Quantify Exposure to Cyanide

Methods are available to measure levels of cyanide and its metabolite, thiocyanate, in blood and urine. High blood cyanide levels of 250–300 µg/100 mL were reported in cases of death from cyanide poisoning (Vogel et al. 1981). The relationship between increased exposure and increased urine levels of thiocyanate was demonstrated in workers exposed occupationally to 6.4–10.3 ppm cyanide in air (El Ghawabi et al. 1975). In another study, blood cyanide concentrations varied from 0.54 to 28.36 µg/100 mL in workers exposed to ≈0.2–0.8 ppm cyanide in air and from 0.0 to 14.0 µg/100 mL in control workers (Chandra et al. 1988). Correspondingly, blood thiocyanate concentrations were 0.05–2.80 mg/100 mL in exposed workers and 0.02–0.88 mg/100 mL in control workers, respectively. Data obtained from the controls indicate that cyanide can be detected in populations exposed to low cyanide levels in the environment. Cyanide-containing food, metabolism of certain drugs, and combustion of nitrogenous polymers are among several sources of cyanide exposure. Furthermore, industrially polluted air, soil, and water may contribute to higher environmental cyanide levels.

Several studies showed increased cyanide and thiocyanate levels in body fluids of smokers. The difference between smokers and nonsmokers can be quite distinct (Maliszewski and Bass 1955). Mean thiocyanate levels in smokers and nonsmokers, respectively, were found to be 7.1 and 2.0 µg/mL in plasma, 75.7 and 20.3 µg/mL in saliva, and 12.3 and 2.1 µg/mL in urine. A more recent study also reported on mean thiocyanate levels in smokers and nonsmokers, respectively (Jarvis 1989). Levels reported were 7.1 and 2.9 µg/mL in plasma, 142 and 76 µg/mL in saliva, and 9.0 and 5.8 µg/mL in urine. Another study found a correlation between the number of cigarettes smoked per day and the thiocyanate levels in plasma and in saliva (Yamanaka et al. 1991). Based on changes in salivary thiocyanate in six

smokers who stopped smoking, this study estimated the half-life of salivary thiocyanate to be 9.5 days. In addition, infants living in homes with family members who smoked heavily were found to have significantly higher serum thiocyanate levels than those infants who were not exposed to cigarette smoke in the home (Chen et al. 1990). It is unclear whether passive smoking (exposure of a nonsmoker to air contaminated with tobacco smoke) is a factor in elevated fetal serum thiocyanate levels. In one study, fetal thiocyanate levels were increased in association with passive smoking in the home (Bottoms et al. 1982), while another study did not report an association (Hauth et al. 1984).

Whether it is more appropriate to use whole blood or plasma for measuring cyanide concentrations has been the subject of several reports. Cyanide plasma levels are usually about one-third to one-half, depending on the species, those found in whole blood (Ballantyne 1983a). However, they can more closely reflect the actual tissue dose. Furthermore, cyanide was found to attach more readily to plasma albumin than to hemoglobin (McMillan and Svoboda 1982). It was suggested that hemoglobin in erythrocytes binds cyanide molecules, but does not play any role in their metabolism. Some authors argue that cyanide in red blood cells may be biologically active (Way 1984). In addition, it is known that cyanide rapidly leaves serum and plasma, especially in the first 20 minutes. It may be appropriate to measure cyanide in both whole blood and plasma. Whole blood samples can be stored at 4 °C for several weeks with little change in cyanide content.

In cyanide-poisoning cases, any blood levels of cyanide >0.02 mg/100 mL indicate a toxic situation (Berlin 1977). However, because cyanide binds tightly to cytochrome c oxidase, serious effects can also occur at lower levels; therefore, the clinical condition of the patient should be considered when determining proper therapy. Linden and Lovejoy (1998) presented a rough estimate of blood cyanide levels at which symptoms appear: flushing and tachycardia at 0.05–0.1 mg/100 mL, obtundation (dulled sensibility) at 0.1–0.25 mg/100 mL, coma and respiratory depression at 0.25–0.3 mg/100 mL, and death at >0.3 mg/100 mL.

An almond-like smell in the breath of a poisoned patient can warn a physician that the individual may be suffering from cyanide poisoning. Approximately 60–70% of the population can detect the bitter almond odor of hydrogen cyanide. The odor threshold for those sensitive to the odor is estimated to be 1–5 ppm in the air. However, even at high toxic concentrations, up to 20% of all individuals are genetically unable to smell hydrogen cyanide (Snodgrass 1996). Some effects of cyanide that can also be used to monitor exposure are discussed in Section 3.8.2.

3.8.2 Biomarkers Used to Characterize Effects Caused by Cyanide

Cyanide can inhibit enzymatic activity by binding to some metallic moieties in metalloenzymes (Ardelt et al. 1989; Way 1984) and cytochrome c oxidase is especially sensitive to cyanide inhibition. Dose-related reductions in cytochrome c oxidase activity were detected in various organs of rats exposed to oral doses of potassium cyanide (Ikegaya et al. 2001); this marker was suggested as a method of diagnosis for samples taken within 2 days post-mortem. Consequent to the inhibition of cytochrome c oxidase, theoretically, oxygen cannot be used and histotoxic anoxia occurs. Elevated plasma lactate concentrations, resulting from the shift to anaerobic metabolism, have been used to assess the severity of cyanide poisoning in humans (Baud et al. 1996, 2002). Death is caused by respiratory failure. Dyspnea, palpitations, hypotension, convulsions, and vomiting are among the first effects of acute cyanide poisoning (see Section 3.2). Ingestion of amounts ≥50–100 mg sodium or potassium cyanide may be followed by almost instantaneous collapse and cessation of respiration (Hartung 1982). Data summarized by Hartung (1982) indicate that exposure to a concentration in air of 270 ppm causes immediate death; concentrations of 181 and 135 ppm are fatal after 10 and 20 minutes of exposure, respectively; concentrations between 45 and 55 ppm can be tolerated for 30–60 minutes with immediate or late effects; and 18–36 ppm may produce slight symptoms after several hours of exposure. Following chronic exposure, cyanide has been associated with the development of tropical neuropathy, tobacco amblyopia, and Leber's hereditary optic atrophy (Wilson 1965). Chronic exposure to cyanide arising from consumption of cyanogenic plant foods has also been connected with the occurrence of endemic goiter (Delange and Ermans 1971).

Neuropathological sequelae of acute cyanide poisoning have been detected in the brain by magnetic resonance imaging (MRI) and positron emission tomography (PET). MRI techniques identified brain lesions that developed in the weeks following a poisoning event, typically in the globus pallidus, putamen, substantia nigra, and cerebellum (Rosenberg et al. 1989; Rosenow et al. 1995). PET has been used to localize deficiencies in dopa uptake in the striatum and reduced glucose metabolism in the cerebral cortex and other brain regions affected by cyanide (Rosenow et al. 1995). These imaging methods cannot determine that cyanide was the cause of the lesions, but provide a means of monitoring changes in the extent of brain lesions following cyanide exposure.

In the development of antidotes to cyanide, the following neurochemical biomarkers of cyanide toxicity have been considered (Isom and Borowitz 1995): inhibition of cytochrome c oxidase, activation of voltage sensitive calcium channels, activation of receptor operated calcium channels, elevation of

cytosolic free Ca^{2+}, activation of intracellular calcium cascades, inhibition of antioxidant enzymes (superoxide dismutase, catalase, and glutathione peroxidase), peroxidation of membrane lipids, and generation of reactive oxygen species.

Genetic markers for cyanide-induced hypoxia have been identified in several human cell lines (human intestinal epithelial T84 cells and Jurkat T cells) exposed to sodium cyanide *in vitro* (Kiang et al. 2003). Cyanide treatment upregulated the expression of inducible nitric oxide synthase (iNOs) and heat shock protein-70 (HSP-70) in both cell types, p53 in T84 cells and the protooncogene Bcl-2 in Jurkat T cells. Cellular caspase-3 activity, indicative of apoptosis, was also significantly increased in both cell types. An inhibitor to iNOs (N^{omega}-nitro-L-arginine or LNNA) abolished the cyanide-induced increase in iNOs, HSP-70, and Bcl-2 and the increase in caspase-3 activity. These studies indicate genetic responses to cyanide exposure *in vitro* and could provide a strategy for comparing tissue-specific responses to cyanide and developing therapeutic interventions following cyanide exposure *in vivo*.

For more information on biomarkers for renal and hepatic effects of chemicals see ATSDR/CDC Subcommittee Report on Biological Indicators of Organ Damage (1990) and for information on biomarkers for neurological effects see OTA (1990).

3.9 INTERACTIONS WITH OTHER CHEMICALS

Interactions in the context of this profile refer to modifications in toxic responses when an organism is exposed to another compound in addition to cyanide. A number of compounds act in synergy with cyanide to produce toxic effects. In smoke, both hydrogen cyanide and carbon monoxide would potentially increase central nervous system effects in exposed individuals (Birky and Clarke 1981). High blood cyanide levels were found in fire victims; however, the carboxyhemoglobin levels were also high. Thus, it is difficult to assess the relative significance of hydrogen cyanide in the toxicity from smoke inhalation.

In an investigation to examine toxicological interactions of the primary fire gases, the additive, synergistic, or antagonistic effects of combinations of hydrogen cyanide with carbon monoxide or with carbon dioxide on the 30-minute LC_{50} value for hydrogen cyanide alone were determined in rats (Levin et al. 1987). Co-exposure of rats to hydrogen cyanide (LC_{50}=110 ppm) and carbon monoxide (LC_{50}=4,600 ppm) resulted in lethal effects of these two gases that were additive. In contrast, co-exposure to hydrogen cyanide and 5% carbon dioxide (not lethal by itself) resulted in an increase in

lethality of hydrogen cyanide, reflected as a decrease of the hydrogen cyanide LC_{50} value to 75 ppm. Dodds et al. (1992) also investigated the effect of simultaneous exposure to cyanide and carbon monoxide in rats, and found an additive effect on certain parameters, including lactate elevation and neurologic index. Norris et al. (1986) reported a synergistic effect on lethality in mice that were injected with potassium cyanide and exposed to carbon monoxide atmospheres.

Synergism has also been observed between cyanide and ascorbic acid. Guinea pigs exhibited increased toxic effects when treated with ascorbic acid prior to oral administration of potassium cyanide (Basu 1983). When guinea pigs were treated solely with 3.2 mg CN^-/kg as potassium cyanide, 38% exhibited slight tremors, whereas 100% of those pre-treated on 3 consecutive days with 1.3 g/kg ascorbic acid before potassium cyanide was administered exhibited severe tremors, ataxia, muscle twitches, paralysis, and convulsions. It has been suggested that this synergistic effect results from the ability of ascorbic acid to compete with cyanide for cysteine, thus diminishing the detoxication of cyanide.

Antidotes for cyanide poisoning have been intensively studied and reviewed (Way 1984). Cyanide antagonists can be classified into two general groups: those that act as sulfane sulfur donors for rhodanese-catalyzed cyanide detoxification and those that induce chemical binding of cyanide. Sulfur donors include sodium thiosulfate, polythionates, and thiosulfates. Sodium thiosulfate has been successfully used as an antidote against cyanide poisoning in humans for decades (Way 1984). A pharmacokinetic study in dogs demonstrated that intravenous administration of thiosulfate increased the detoxification rate of intravenously given cyanide to thiocyanate over 30 times (Sylvester et al. 1983). In this study, pretreatment with thiosulfate decreased the biological half-life of cyanide from ≈39 to ≈15 minutes and also decreased the volume of distribution of cyanide from 498 to 204 mL/kg. Thiosulfate pretreatment had prophylactic effects in guinea pigs exposed to cyanide by intravenous infusion (Mengel et al. 1989). The protection lasted for several hours depending on the dose of thiosulfate administered.

Antagonists that induce the chemical binding of cyanide to sites other than cytochrome c oxidase include sodium nitrite, amyl nitrite, and hydroxylamine. These compounds generate methemoglobin, which competes with cytochrome c oxidase for cyanide to form cyanmethemoglobin (Way 1984). Sodium nitrite has been effectively used in the therapy of cyanide intoxication in humans especially in combination with sodium thiosulfate (Smith 1996; Way 1984). Studies in mice demonstrated that intraperitoneal pretreatment with sodium nitrite more than doubled the LD_{50} value of intraperitoneally administered sodium cyanide from 3.18 to 7.95 mg CN^-/kg (Kruszyna et al. 1982). Peak

methemoglobinemia was 35% at 40 minutes. Other methemoglobin generating agents seemed to be less effective. 4-Dimethylaminopropiophenol enhanced the LD_{50} value to 6.36 mg CN^-/kg and hydroxylamine to 4.66 mg CN^-/kg with peak methemoglobinemia being 40 and 36%, respectively, at 7 minutes. The data suggested that sodium nitrite, a slow methemoglobin former, gave prolonged protection against cyanide, while animals treated with fast methemoglobin formers died later on, probably due to the cyanide release from the cyanmethemoglobin pool. An improvement of cyanide-altered cerebral blood flow was observed in dogs treated with sodium nitrite or 4-dimethylaminophenol following intravenous injection of hydrogen cyanide (Klimmek et al. 1983). However, neither treatment prevented the progression of lactic acidosis.

Cobalt-containing compounds may also function as binders by forming a stable complex with cyanide. A dramatic antagonism of the lethal effects of potassium cyanide was reported when cobaltous chloride was administered to mice along with sodium thiosulfate (Isom and Way 1973). 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. This ability is also utilized when dicobalt ethylenediamine tetra-acetate acid (Co_2EDTA) is used as a cyanide antidote. An improvement of cerebral aerobic metabolism and blood flow was observed in dogs treated with 10 mg/kg Co_2EDTA intravenously following intravenous application of 1.6 mg CN^-/kg as potassium cyanide (Klimmek et al. 1983). A lower molecular weight porphyrin cobalt compound than hydroxocobalamin (CoTPPS) was used as an antidote to the lethal effects of cyanide (McGuinn et al. 1994). The interaction with hydroxocobalamin (see Section 3.4.3) was also proposed as a mechanism for cyanide detoxification in cases of acute poisoning. It was demonstrated that intravenous administration of hydroxocobalamin (50–250 mg/kg) prior to or after intraperitoneal injection of potassium cyanide prevented lethality and decreased cyanide-induced toxic effects in mice (Mushett et al. 1952).

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 hydrogen cyanide at 200 ppm for 12.5 minutes (O'Flaherty and Thomas 1982). In an *in vitro* study, chlorpromazine and 4,4'-diisothiocyano-2,2'-stilbene disulfonic acid reduced cyanide-induced contractions in vascular smooth muscle (Robinson et al. 1985a). It was suggested that chlorpromazine prevents cyanide-induced calcium influx and reduces peroxidation of membrane lipids (Maduh et al. 1988).

The ability of cyanide to combine with carbonyl groups of some intermediary metabolites (e.g., sodium pyruvate, α-ketoglutarate) to form cyanohydrin has been used for antidotal purposes. Pretreatment of mice with 1 g/kg sodium pyruvate intraperitoneally prior to subcutaneous injection of potassium cyanide caused a statistically significant increase in the LD_{50} values from 3.1 to 5 mg CN^-/kg (Schwartz et al. 1979). Sodium pyruvate also prevented the development of convulsions in cyanide-exposed mice. Similarly, intraperitoneal pretreatment of mice with 2 g/kg α-ketoglutarate before the intraperitoneal injection of potassium cyanide increased the LD_{50} value from 2.68 to 13.32 mg CN^-/kg (Moore et al. 1986). It was further demonstrated that both sodium pyruvate and α-ketoglutarate enhanced the antidotal effects of other cyanide antagonists (e.g., sodium thiosulfate, sodium nitrite) (Moore et al. 1986; Schwartz et al. 1979).

A striking protection against cyanide can be elicited by a new conceptual approach, employing carrier erythrocytes containing highly purified rhodanese (thiosulfate sulfur transferase). Several studies have shown that resealed erythrocytes containing rhodanese and sodium thiosulfate rapidly metabolize cyanide to the less toxic thiocyanate (Cannon et al. 1994; Petrikovic et al. 1995). Maduh and Baskin (1994) showed that rhodanese may be regulated by protein phosphorylation and treatments that alter the phosphorylation state of rhodanese may affect cyanide detoxification via formation of thiocyanate.

Several papers discuss the effects of oxygen alone or with other compounds on cyanide toxicity. Oxygen alone results in minimal antagonism in mice injected with potassium cyanide and only slightly enhances the antagonistic effects of sodium nitrite on cyanide (Sheehy and Way 1968). The antidotal effect of sodium thiosulfate alone or in combination with sodium nitrite, was enhanced by oxygen. Oxygen-treated mice did not show behavioral signs of cyanide intoxication below doses of 2.4 mg CN^-/kg as potassium cyanide, whereas air-treated animals showed effects such as gasping, irregular breathing, and convulsions at levels as low as 1.2 mg CN^-/kg as potassium cyanide (Isom et al. 1982). When mice were pretreated with sodium nitrite and sodium thiosulfate and either air or oxygen, the dose of potassium cyanide needed to cause a 59% inhibition of brain cytochrome c oxidase more than doubled in mice in an oxygen atmosphere; all points on the oxygen curve differed significantly from the air-treatment curve.

A striking enhancement of the oxidation of glucose to carbon dioxide was observed when oxygen, sodium nitrite, and sodium thiosulfate were given to mice dosed at 18 mg CN^-/kg as potassium cyanide; no enhancement was noticed at 4 or 6 mg CN^-/kg as potassium cyanide (Isom and Way 1974). These studies indicate that oxygen can be used in supporting classical cyanide antagonists in the therapy of cyanide poisoning, but even hyperbaric oxygen alone had no effect on cyanide poisoning in mice (Way et al.

1972). The mechanism of the action is not known, since cyanide inhibits the cellular utilization of oxygen through inhibiting cytochrome c oxidase and, theoretically, the administration of oxygen should have no effect or useful purpose (Smith 1996).

Propargylglycine, which is an inhibitor of the enzyme cystathionine gamma-lyase, significantly lowered the LD_{50} for sodium cyanide intraperitoneally injected into rats (Porter et al. 1996). The authors suggested that the enzyme contributes to cyanide detoxification, possibly through the pathway that provides sulfur donors for the enzyme rhodanese.

3.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to cyanide than will most persons exposed to the same level of cyanide in the environment. Reasons may include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters result in reduced detoxification or excretion of cyanide, or compromised function of organs affected by cyanide. Populations who are at greater risk due to their unusually high exposure to cyanide are discussed in Section 6.7, Populations with Potentially High Exposures.

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). Individuals with preterminal chronic renal failure have elevated serum thiocyanate levels because of impaired clearance of thiocyanate, increasing their vulnerability to cyanide exposure (Koyama et al. 1997).

A number of dietary deficiencies may increase the risk of deleterious cyanide effects. Iodine deficiency is involved in the etiology of such thyroid disorders as goiter and cretinism. These disorders may be exacerbated by excess exposure to cyanide (Delange and Ermans 1971; Ermans et al. 1972). Protein deficiencies and vitamin B_{12}, riboflavin, and other vitamin and elemental deficiencies may subject people in the tropics who eat cassava to increased risks of tropical neuropathies (Makene and Wilson 1972; Osuntokun 1972; Osuntokun et al. 1969). However, a recent study reported that scopoletin, a potent hypotensive and spasmolytic agent found in cassava roots, may be the etiological agent in the tropical neuropathies observed among cassava eaters, rather than cyanide (Obidoa and Obasi 1991). Furthermore, children and women seem to be more susceptible to the endemic spastic paraparesis in the cassava-

consumption regions (Rosling 1988). Studies that have uncovered more severe effects from cyanides in nutritionally deprived animals provide support to the observations in humans (Kreutler et al. 1978; Rutkowski et al. 1985).

In areas where cassava is a staple food, congenital hypothyroidism is present in 15% of newborns (Ermans et al. 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. Developmental toxicity has been observed in rodents following inhalation, oral, and parenteral exposure to cyanide-containing compounds (Doherty et al. 1982, 1983; Frakes et al. 1985, 1986a; Singh 1981; Willhite 1982).

One group of people who may be at greater risk are those who are exposed to cyanide but are unable to smell the chemical (Kirk and Stenhouse 1953; Snodgrass 1996). Patients with motor neuron disease (amyotrophic lateral sclerosis) possess a disorder in cyanide detoxification that may result in their higher susceptibility to cyanide (Kato et al. 1985).

3.11 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to cyanide. However, because some of the treatments discussed may be experimental and unproven, this section should not be used as a guide for treatment of exposures to cyanide. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice. The following texts provide specific information about treatment following exposures to cyanide:

Ellenhorn MJ, Barceloux DG. 1997. Medical toxicology, diagnosis and treatment of human poisoning. New York, NY: Elsevier Publishing.

Goldfrank LR, Flomenbaum NE, Lewin NA, et al., eds. 1998. Goldfranks toxicologic emergencies. 6th edition. Stamford, CT: Appleton and Lange, 1569-1585.

Gosselin RE, Smith RP, Hodge HC. 1984. Clinical toxicology of commercial products. 5th edition. III-123-130. Baltimore, MD: Williams and Wilkins.

IPCS/CEC. 1993. Evaluation of antidotes series. Vol. 2. Antidotes for poisoning by cyanide. International Program on Chemical Safety/Commission of the European Communities http://www.inchem.org/documents/antidote/antidote/ant02.htm. June 16, 2004.

3.11.1 Reducing Peak Absorption Following Exposure

Human exposure to cyanide may occur by inhalation, ingestion, or by dermal contact, but the general population is more likely to be exposed by inhaling air or ingesting food or water contaminated with cyanide. General recommendations for reducing absorption of cyanide from inhalation and dermal exposure include removing the exposed individual from the contaminated area and removing the contaminated clothing (Ellenhorn and Barceloux 1997; Goldfrank et al. 1990; Stutz and Janusz 1988). If the eyes and skin are exposed, they should be flushed with water. However, in order not to become secondary victims, rescuers may enter potentially contaminated areas only with self-contained breathing apparatus and protective clothing. Speed is essential during a rescue operation.

In order to reduce absorption of ingested cyanide, gastric lavage with activated charcoal may be performed immediately after ingestion. Individuals exposed by any route are commonly administered 100% oxygen and assisted ventilation, including endotracheal intubation, as needed. Hyperbaric oxygen has been advocated when patients do no respond to standard therapy (Litovitz et al. 1983); however, studies in laboratory animals suggest that hyperbaric oxygen is no more effective than normobaric oxygen (Way 1984). An antidotal combination of inhaled amyl nitrate and intravenous sodium nitrite and sodium thiosulfate are often indicated. The IPCS/CEC (1993) review of antidotes for cyanide poisoning noted that individuals deficient in glucose-6-phosphate-dehyrogenase are at risk of severe hemolysis from sodium nitrite therapy because of the resulting high plasma methemoglobin concentrations. Monitoring for metabolic acidosis, cardiac dysrhythmias, and possible pulmonary edema is suggested.

3.11.2 Reducing Body Burden

The primary target for cyanide toxicity is the central nervous system following both acute and chronic exposure. Exposure to high doses of cyanide can rapidly lead to death (see Section 3.2). Cyanide is not stored in the organism and one study indicates that, under the stated parameters, >50% of the received dose can be eliminated within 24 hours (Okoh 1983). However, because of the rapid toxic action of cyanide, therapies that enhance metabolism and elimination of cyanide are warranted immediately.

Cyanide is metabolized in the body by two metabolic pathways that have been identified (Ansell and Lewis 1970). The first and major metabolic pathway involves the transfer of sulfane sulfurs from a donor to cyanide to yield thiocyanate (see Section 3.4). The reaction employs the enzyme rhodanese as a catalyst. Thiocyanate is a fairly stable compound and is excreted predominately in urine. Serum proteins

(especially albumin) are a major internal pool of sulfane sulfurs. Their protective role against cyanide toxicity was confirmed in tests with laboratory animals (Rutkowski et al. 1985; Tewe and Maner 1980, 1982). Cyanide antagonists help convert cyanide to thiocyanate. Sodium thiosulfate is commonly used in cases of cyanide poisoning (Bonsall 1984; Mengel et al. 1989; Schubert and Brill 1968; Sylvester et al. 1983). Sodium thiocyanate is also used to prevent toxicity resulting from the cyanide released from sodium nitroprusside during infusion therapy for hypertensive emergencies (see Section 3.7) (Agarwal and Kumari 2003; Curry et al. 1997; Przybylo et al. 1995; Randall and St. Louis 1996; Sipe et al. 2001). This usage has been shown to be effective in preventing cyanide toxicity in the fetuses of gravid ewes infused with sodium nitroprusside (Curry et al. 1997). An increase in antidotal effect was noted when rhodanese was combined with thiosulfate (Frankenberg 1980). Similarly, other sulfane sulfur donors and disulfides such as 2-aminoethyl-4-methoxyphenyl disulfide hydrochloride have protective effects against cyanide toxicity (Baskin et al. 1999; Petrikovics et al. 1995; Ternay et al. 2000).

The second and minor metabolic pathway consists of the reaction of cyanide with cystine to yield cysteine and β-thiocyanoalanine (Wood and Cooley 1955). The latter is then converted to 2-imino-4-thiazolidine-carboxylic acid and excreted in urine. Cystine has not been used for the purpose of mitigation of cyanide effects because its contribution to detoxification via this pathway is minor.

3.11.3 Interfering with the Mechanism of Action for Toxic Effects

The mechanism of acute cyanide toxicity is well understood (see Section 3.5). Cyanide inhibits the activity of some enzymes by binding to their metallic moiety. By blocking the action of cytochrome c oxidase, histotoxic hypoxia/anoxia develops rapidly in exposed organisms (Smith 1996). The ability of cyanide to bind to some metallic ions is utilized with antidotes that induce methemoglobinemia in exposed organisms. Cyanide binds to the ferric ion of methemoglobin to form inactive cyanmethemo-globin (see Section 3.9). Antidotes utilized for this purpose either clinically or experimentally include amyl nitrite, sodium nitrite, hydroxylamine, p-aminopropiophenone, p-aminoheptanophenone, 8-[(4-amino-1-methylbutyl)amino]-5-1-hexyloxy)-6-methoxy-4-methylquinoline-DL-tartrate (WR242511), 4-dimethylaminophenol, and primaquine (Bhattacharya 1995; Bhattacharya et al. 1991, 1993; Bright and Marrs 1987; Hall et al. 1987; Kampe et al. 2000; Kruszyna et al. 1982; Menton et al. 1996, 1997; Scharf et al. 1992; Schubert and Brill 1968; USAMRICD 1994; Vick and Von Bredow 1996). The disadvantage of these antidotes is that the methemoglobinemia further aggravates the depletion of oxygen from tissues; therefore, antidote-induced methemoglobin levels need to be closely followed in clinical practice. Prophylactic administration of stroma-free methemoglobin preserved cardiovascular and metabolic

function in dogs exposed to cyanide intravenously (Breen et al. 1996); the additional methemoglobin traps cyanide in the blood, thereby protecting tissues. Experimentally, the antagonistic effect of sodium nitrite is improved by co-administration with atropine, an effect attributed to the suppression of bradycardia (Vick and Von Bredow 1996; Yamamoto 1995). A complex of diethylamine/nitric oxide reduced the toxicity of cyanide in mice (Baskin et al. 1996); the beneficial effect was attributed to methemoglobin-forming activity at higher doses and the vasodilation activity of nitric oxide.

Cyanide's binding to metallic ions is also employed in a reaction with cobalt-containing compounds that yields cyanocobalamin (see Section 3.9). Cobalt compounds generally are not used because of their toxicity; however, Co_2EDTA (Klimmek et al. 1983) and hydroxocobalamin (Benabid et al. 1987; Mannaioni et al. 2002; Mengel et al. 1989; Mushett et al. 1952) have been used as antidotes both in clinical and laboratory trials. Cardiac toxicity from Co_2EDTA use under clinical conditions has raised caution in its clinical use, as the cardiac toxicity of cobalt is well known (Way 1984). Both of these antidotes have the advantage of not inducing methemoglobinemia. One study (McGuinn et al. 1994) used a lower molecular weight cobalt porphyrin compound (CoTPPS) as an antidote to the lethal effects of cyanide. This compound was found to have a high affinity for cyanide due to its low molecular weight, and it allows administration in 3-fold molar excess of binding sites over a lethal dose of cyanide. Similarly, cyanide forms stable complexes with selenite (Palmer and Olson 1979).

In an effort to find additional antidotes that would not produce methemoglobinemia, compounds such as sodium pyruvate, dihydroxyacetone, α-ketoglutarate (Niknahad and O'Brien 1996), oxaloacetate, pyridoxal 5'-phosphate, chlorpromazine, and naloxone (Way 1984) have been introduced (see Section 3.9). Interactions of cyanide with carbonyl groups of these compounds lead to formation of inert cyanohydrin intermediates (Bhattacharya and Vijayaraghavan 2002; Hume et al. 1995; Keniston et al. 1987; Moore et al. 1986; Schwartz et al. 1979; Yamamoto 1989). Niknahad et al. (1994) demonstrated that dihydroxyacetone and glyceraldehyde are much more effective than pyruvate and α-ketoglutarate as cyanide antagonists. Dihydroxyacetone and sodium thiosulfate together had synergistic effects against potassium cyanide (Niknahad and Ghelichkani 2002); a combination of pretreatment with dihydroxyacetone and post-treatment with sodium thiosulfate increased the LD_{50} of potassium cyanide (subcutaneous) in mice by nearly 10-fold. In rabbits injected (subcutaneous) with high doses of potassium cyanide, the beneficial effect of dihydroxyacetone and sodium thiosulfate diminished after 1 hour, which the authors attributed to metabolism of dihydroxyacetone with concomitant release of bound cyanide; additional treatment with dihydroxyacetone was needed to prevent the death of the animals. Several studies have shown that α-ketoglutaric acid has a synergistic antidotal effect against

hydrogen cyanide, sodium cyanide, or potassium cyanide when administered with sodium nitrite and/or sodium thiosulfate. These studies did not address the problem of lactic acidosis that follows cyanide exposure.

Pharmacological approaches to finding antidotes for cyanide are also under investigation. Maduh et al. (1995) examined the effects of a protein kinase C inhibitor, 1-5-(isoquinolinesulfonyl)-2 methylpiperazine (H-7), on cellular energy depletion caused by sodium cyanide. They reported that H-7 partially prevented cellular energy depletion and increased the number of surviving cells.

Neurological damage following exposure to cyanide has been associated with an influx of calcium ions and the subsequent release of biogenic amines. Accordingly, calcium channel blockers have been tested for their efficacy in preventing typical cyanide-induced changes. Diltiazem pretreatment, but not co-treatment prevented a cyanide-induced decrease in dopamine (and increase in L-dopa) in the corpus striatum of rats (Mathangi and Namasivayam 2004b). The calcium channel blockers procaine (also an anesthetic) and verapamil antagonized the toxicity of potassium cyanide in mice (Jiang et al. 1998). Both compounds extended the time to death of a lethal dose of potassium cyanide and prevented the cyanide-induced rise in total brain calcium. Procaine increased the LD_{50} for potassium cyanide and its protective effect was synergistic in mice treated with sodium nitrite and/or sodium thiosulfate. The antioxidants, Trolox® (6-hydroxy-2,5,7,8-tetramethylchroman 2-carboxylic acid) and EGTA, and the Ca^{2+}/Mg^{2+}-dependent endonuclease inhibitor, aurintricarboxylic acid, all increased the LD_{50} for potassium cyanide subcutaneously injected into mice (Bhattacharya and Lakshamana Rao 2001). However, mean survival time was not significantly increased compared to mice receiving a lethal dose (LD_{50}x8).

Several antioxidants have been shown to reduce some effects of cyanide toxicity. Dietary supplementation with antioxidant vitamins A, C, and E partially antagonized cyanide-induced reductions in superoxide dismutase in the liver, kidney, and lung and catalase in the kidney and lung of rabbits (Okolie and Iroanya 2003). Cyanide-induced histopathology was ameliorated by vitamin treatment; vitamin supplementation eliminated hepatic congestion in the liver (but not necrosis or fatty degeneration), eliminated glomerular, but not tubular necrosis in the kidney, and eliminated alveolar congestion and pulmonary edema in cyanide-treated rabbits. These results, along with the study by Basu (1983, see Section 3.9) that employed "megadoses" of vitamin C, suggest that the effect of vitamins on cyanide toxicity may be sensitive to dose and may be tissue-specific. Vitamin C reduced peroxide accumulation and cell death in rat pheochromocytoma cells (PC12 cells) exposed to potassium cyanide (Kanthasamy et al. 1997). Ibuprofen (Lambat et al. 2000) and aspirin (Daya et al. 2000) reduced the

production of superoxide radicals in rat brain homogenates treated with potassium cyanide. Melatonin and 6-hydroxymelatonin protect against cyanide-induced neurotoxicity (seizures, neuronal cell death) by suppressing the formation of superoxide anion radicals and lipid peroxidation (Choi and Han 2002; Maharaj et al. 2003; Yamamoto and Tang 1996a, 1996b, 1996c, 1998).

Some antidotes have been tested in cultured hepatocytes. Glycine reduces cyanide-induced mortality of hepatocytes *in vitro* by countering the influx of sodium ions that occurs from metabolic acidosis as ATP is depleted by mitochondrial poisoning (Carini et al. 1997); sodium overload can lead to irreversible cell injury from osmotic swelling. L- and D-cysteine reduce the toxicity of cyanide to hepatocytes by increasing the pool of thiosulfate available for thiocyanate formation (Huang et al. 1998). Dexamethasone retarded hepatocyte toxicity by reducing the hydrolysis of membrane phospholipids induced by cyanide (Pastorino et al. 1995).

Sun et al. (1995) reported that the nitric oxide generator, isosorbide dinitrate, is an effective cyanide antidote in mice. They showed that the mechanism does not involve methemoglobin formation and suggested that nitric oxide might antagonize the respiratory depressant effects of cyanide. Other more efficient nitric oxide generators may be very useful cyanide antidotes.

Myers et al. (1995) investigated the effect of transfection with the protooncogene Bcl-2 on survival of GT1-7 hypothalamic tumor cells exposed to potassium cyanide under aglycemic conditions *in vitro*. Transfectants were protected against delayed (24–72-hour) cell death, ATP depletion, lipid oxidation, and impaired mitochondrial respiration. The authors suggest that Bcl-2 may operate by an antioxidant mechanism.

Fructose, but not glucose, protected primary cultures of rat hepatocytes against time-dependent toxicity of 2.5 mM sodium cyanide for up to 4 hours (Thompson et al. 2003). The difference in efficacy between the two glycolytic substrates was attributed to fact that fructokinase has a low K_m for the phosphorylation of fructose compared to the relatively high K_m for hepatic glucokinase. Therefore, fructose, but not glucose, provides an alternate source of ATP during cyanide exposure *in vitro*.

In addition, other chemicals such as α-adrenergic blocking agents like chlorpromazine (O'Flaherty and Thomas 1982; Way and Burrows 1976) or oxygen (Burrows et al. 1973; Sheehy and Way 1968; Way et al. 1966) may be used to enhance the protective action of other antidotes. However, the mechanism of

their action is not well understood. Further research for a potent and safe antidote to mitigate cyanide toxicity is desirable, particularly among smoke inhalation victims who have carbon monoxide poisoning.

In summary, the efficacy and safety of experimental treatments discussed in this section have not been compared systematically and therefore, do not replace the current therapeutic practice. It must be stressed that the therapeutic value of the antidotes mentioned above is heavily dependent on the time lapse between exposure and their use, since the usual course of inorganic cyanide poisoning is acute and proceeds at very high rates.

3.12 ADEQUACY OF THE DATABASE

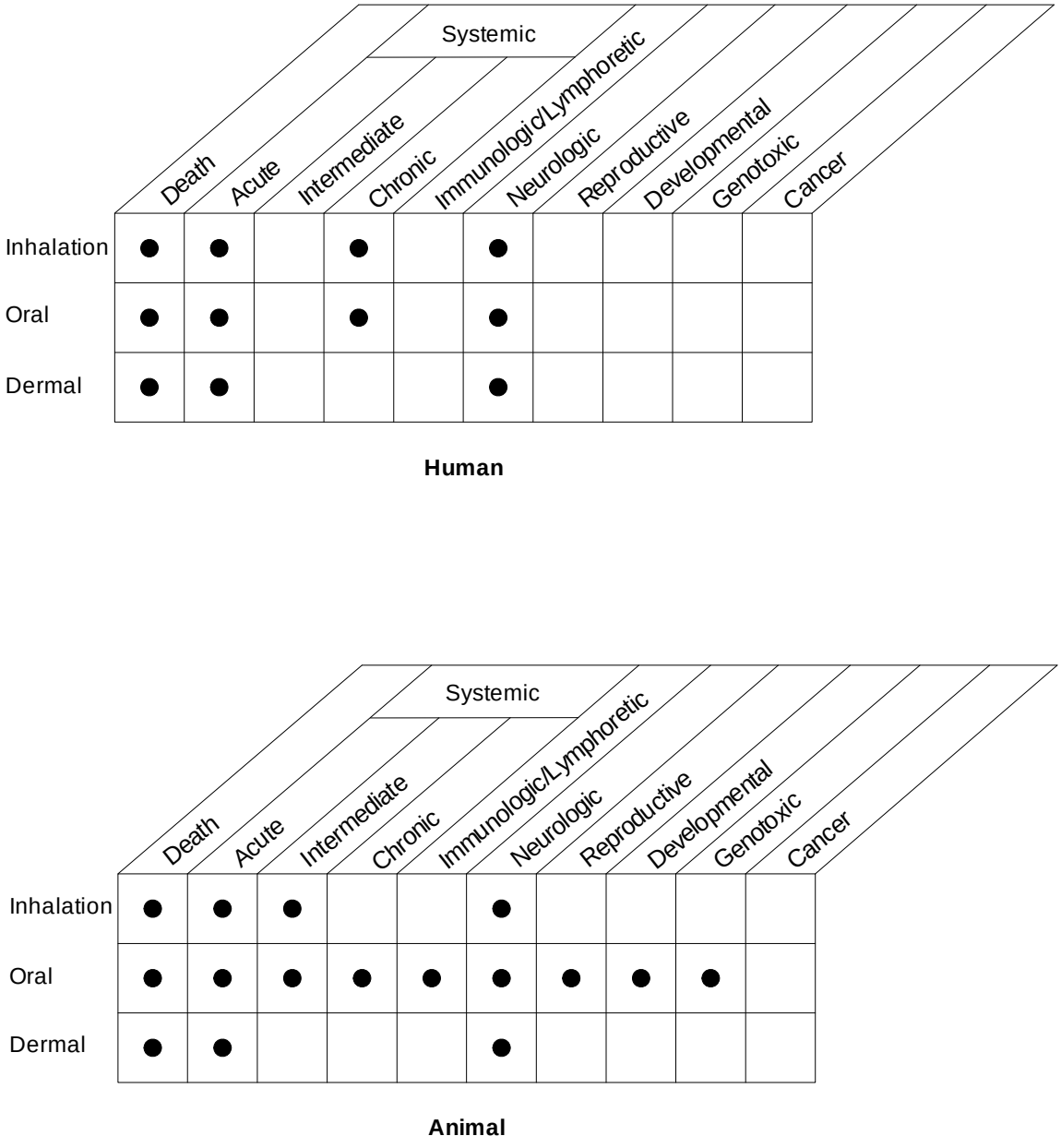
Section 104(I)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of cyanide is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of cyanide.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

3.12.1 Existing Information on Health Effects of Cyanide

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to cyanide are summarized in Figure 3-6. The purpose of this figure is to illustrate the existing information concerning the health effects of cyanide. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not necessarily imply anything about the quality of the study or studies, nor should missing information in this figure be interpreted as a "data need". A data need, as defined in ATSDR's *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (Agency for Toxic Substances and Disease Registry 1989b), is

Figure 3-6. Existing Information on Health Effects of Cyanide



substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

In the section that follows, data needs are identified for cyanide forms for which toxicity data were available and were, therefore, summarized in Section 3.2. These forms include primarily sodium cyanide, potassium cyanide, and hydrogen cyanide. As seen from Figure 3-6, information is available regarding death, systemic effects of acute exposure, and neurological effects in humans after inhalation, oral, and dermal exposure to cyanide. In addition, information is available regarding chronic systemic effects in humans after inhalation and oral exposure.

Data regarding death, systemic effects of acute exposure, and neurological effects were obtained for animals following inhalation, oral, and dermal exposure to cyanide. Furthermore, information was obtained regarding systemic effects after intermediate-duration inhalation and oral exposure, and chronic oral exposure. In addition, information exists regarding developmental and reproductive effects after oral exposure of animals to cyanide. Studies involving cassava are omitted from consideration in this figure because they do not provide quantitative dose-response information for cyanide.

3.12.2 Identification of Data Needs

Acute-Duration Exposure. The target organs of acute cyanide exposure are the central nervous system, respiratory system, and cardiovascular system. Exposure to high levels of cyanide leads rapidly to death. Lethality data are available in humans for acute inhalation (Dudley et al. 1942; Singh et al. 1989), oral (Gettler and Baine 1938), and dermal (Rieders 1971) exposures to hydrogen cyanide; however, specific exposure levels are often not available. Neurological sequelae (see Neurotoxicity below) were reported as long-term, sometimes delayed effects such as Parkinsonism in survivors of acute poisoning incidents following inhalation (Lam and Lau 2000) or oral exposure (Carella et al. 1988; Chin and Calderon 2000; Rachinger et al. 2002; Rosenberg et al. 1989; Rosenow et al. 1995). Lethality studies were performed in several animal species, and LC_{50} and LD_{50} values were derived for inhalation (hydrogen cyanide and cyanogen) (Ballantyne 1983a), oral (potassium cyanide and sodium cyanide) (Ballantyne 1983a, 1988), and dermal (hydrogen cyanide, potassium cyanide, and sodium cyanide) (Ballantyne 1983a, 1988) exposures. The systemic effects observed in animals included serious impairments in the central nervous system (semiconsciousness), lung (dyspnea), and heart (arrhythmia). These effects were also seen in humans regardless of route of cyanide exposure. Since most of the animal

studies only reported lethality as an end point and the only other effects were serious, there is no suitable NOAEL or LOAEL values to serve as the basis for acute MRLs. Additional acute studies by all routes using several dose levels and examining comprehensive end points would help to determine thresholds for known target organs and for any new target organs that might be identified. The information would be useful to populations living near hazardous waste sites that can be exposed to cyanide in contaminated water or soil for a short time.

Intermediate-Duration Exposure. No intermediate-duration studies were located regarding cyanide effects in humans. A few inhalation (Valade 1952) and oral (Jackson 1988; Kamalu 1993; Okolie and Osagie 1999; Philbrick et al. 1979; Sousa et al. 2002; Tewe and Maner 1981b) studies in animals indicated the central nervous system is an important target organ of intermediate-duration exposure to cyanide toxicity (potassium cyanide and hydrogen cyanide). In addition, hematological, hepatic, renal, and reproductive effects may be caused by oral exposure. Studies on cyanide compounds containing metals such as copper and silver (Gerhart 1986, 1987) are inappropriate for establishing dose-responses for cyanide because the metals may contribute to toxicity. An oral rat study by Soto-Blanco et al. (2002a), which employed the lowest exposure levels, did not report dose-response results in sufficient detail to serve as a basis for an MRL. The extensive oral study on sodium cyanide by NTP (1993) did not evaluate neurohistopathology in the spinal cord. No intermediate-duration dermal studies were available. It is known, however, that cyanides can rapidly penetrate the skin and similar toxic effects are presumed. No intermediate-duration inhalation MRL could be derived because of the lack of data. An intermediate oral MRL of 0.05 mg/kg/day was derived from a study showing reproductive effects in rats exposed in drinking water to 12.5 mg CN^-/kg/day as sodium cyanide for 3 months (NTP 1993). This study is further described in the Reproductive Toxicity section below. Additional intermediate-duration inhalation studies using several dose levels would be useful to determine threshold levels for neurotoxicity. The information would be useful to populations living near hazardous waste sites that can be repeatedly exposed to cyanide in contaminated water or soil for periods of <1 year.

Chronic-Duration Exposure and Cancer. Some reports of occupationally exposed workers indicated that low concentrations of hydrogen cyanide may have caused neurological, respiratory, and cardiovascular effects (Blanc et al. 1985; Chandra et al. 1980, 1988; El Ghawabi et al. 1975; Kumar et al. 1992). The route of exposure was predominantly inhalation, although dermal exposure can also occur in the work place. The studies, however, lacked either information about exposure levels or used small cohorts of workers. Studies in populations that used cassava roots as a main source of their diet described the neurological effects of cyanide consumption (Osuntokun 1972, 1980). However, these effects may be

due to a recently identified substance, scopeletin, rather than to cyanide (Obidoa and Obasi 1991). For chronic exposure in animals, only one oral study in rats (hydrogen cyanide) was located (Howard and Hanzal 1955). However, the reliability of this study is low because of the unstable cyanide levels in their feed throughout the experiment due to evaporation of cyanide. Furthermore, no effects were found in the study besides nondose-related changes in weight gain in female rats, but not in male rats. No chronic studies in animals were located for the inhalation and dermal routes. Therefore, data are not sufficient to derive MRL values for chronic exposure. Additional chronic-duration studies in animals would be helpful to determine thresholds for target organs.

No studies were located regarding carcinogenicity of cyanide in humans or animals. The chronic toxicity studies suggested above should be designed to also analyze the carcinogencity of cyanide.

The results of chronic toxicity and carcinogenicity studies would be useful to populations living near hazardous waste sites that can be repeatedly exposed to cyanide in contaminated water or soil for periods exceeding 1 year.

Genotoxicity. No human data are available on the genotoxicity of cyanide. No genotoxicity was found in one *in vivo* study in mice exposed orally to potassium cyanide (Friedman and Staub 1976). However, DNA fragmentation has been detected in DNA from the brains of mice injected with potassium cyanide (Mills et al. 1999; Yamamoto and Mohanan 2002). The relevance of this fragmentation to genotoxicity is not known. *In vitro* studies with cyanide in the form of potassium cyanide did not show any mutagenic activity in *S. typhimurium* or *E. coli* (De Flora 1981; De Flora et al. 1984; Kubo et al. 2002), and cyanide in the form of sodium cyanide tested negative in *Salmonella* strains TA97, TA98, TA100, and TA1535, with and without metabolic activation (NTP 1993). One study in *S. typhimurium* suggested that hydrogen cyanide may be mutagenic (Kushi et al. 1983); an increase in the induction of reverse mutations was noted without metabolic activation. A number of *in vitro* studies on cultured cells, including A549 human epithelial-like lung carcinoma cells, as well as various animal cell types, reported DNA fragmentation following exposure to potassium cyanide (Bhattacharya and Lakshmana Rao 1997; Henderson et al. 1998; Storer et al. 1996; Vock et al. 1998). These studies indicate that the DNA fragmentation is secondary to the general cytotoxicity of cyanide, which results in the release of endonucleases by the dying cells. As there are no structural reasons to suggest that cyanide may be genotoxic and fragmentation is secondary to cytotoxicity, it does not appear that further genotoxicity studies are needed at this time, until the Kushi reverse mutation data can be replicated independently.

Reproductive Toxicity. No data were located regarding reproductive effects of cyanide in humans. One animal study reported increased resorptions in rats following oral exposure to a cassava diet (Singh 1981). Because some human populations use cassava roots as the main source of their diet, further information regarding this observation would be useful for these populations, but this is probably not a concern for people living in the United States. Increased gonadal weight was found in male rats in 90-day oral studies of copper cyanide and potassium silver cyanide (Gerhart 1986, 1987), but the possible contribution of the metals to the dose-response cannot be discounted. A number of reproductive effects, including decreases in left cauda epididymal weight, left testis weight, spermatid heads, and spermatid counts were noted in rats exposed to sodium cyanide in the drinking water for 13 weeks (NTP 1993). This study was used as the basis for the intermediate oral MRL (see Intermediate-Duration Exposure above and Appendix A). Thus, it appears that only limited value would be associated with further reproductive studies at this time.

Developmental Toxicity. No studies were located regarding teratogenic effects in humans exposed to cyanide by any route, although hypothyroidism, attributed to elevated thiocyanate levels, has been observed in offspring as a result of maternal dietary consumption of cassava during pregnancy (Ermans et al. 1980). Developmental studies in animals were performed only following oral exposure and contradictory results were obtained. Teratogenic effects of cyanide exposure were observed in rats and hamsters fed a cassava diet (Frakes et al. 1986a; Singh 1981), while no effects were found in rats and pigs fed cassava diets alone or supplemented with potassium cyanide (Tewe and Maner 1981a, 1981b). However, the latter studies are flawed in that they did not include a control group not exposed to cyanide. Furthermore, growth retardation was the only effect in weanling rats in the second generation of a two-generation oral exposure study with potassium cyanide. More data regarding developmental toxicity in experimental animals would be useful to identify the possible risk for humans. Studies on developmental neurotoxiocology, including postnatal behavior analysis, would provide significant information relative to child development for populations living near hazardous waste sites containing cyanide.

Immunotoxicity. No data were located regarding immunological effects in humans or animals after inhalation, oral, or dermal exposure to cyanide. A battery of immune function tests has not been performed in humans or animals; testing in animals under low-level exposure conditions would be useful to clarify whether cyanide is an immunotoxicant.

Neurotoxicity. The central nervous system is an important target for cyanide toxicity in humans and animals following exposure by all three routes. Acute inhalation exposure to high levels of cyanide,

regardless of the form, leads quickly to death that is preceded by dyspnea, convulsions, and central nervous system depression (Bonsall 1984; Chen and Rose 1952; Peden et al. 1986; Potter 1950; Singh et al. 1989). Neurological and behavioral effects were observed in humans after chronic inhalation exposure to hydrogen cyanide in the workplace (Blanc et al. 1985; Chandra et al. 1988; El Ghawabi et al. 1975; Lam and Lau 2000). Oral exposure to cyanide led to the development of severe peripheral neuropathies, and hearing and visual problems in those who used cassava as a staple in the diet (Osuntokun 1980). However, these effects may be due to a recently identified substance, scopeletin, rather than due to cyanide (Obidoa and Obasi 1991). Some neurological effects (memory loss and a Parkinsonian-type syndrome have been reported as delayed effects following accidental acute ingestion of soluble cyanide compounds (Chin and Calderon 2000; Grandas et al. 1989; Rachinger et al. 2002; Rosenberg et al. 1989; Rosenow et al. 1995; Uitti et al. 1985). Experimental studies in animals exposed to hydrogen cyanide or cyanide compounds by the inhalation (Purser et al. 1984; Valade 1952), oral (Philbrick et al. 1979), or dermal routes (Ballantyne 1983b), have found neurological effects similar to those seen in humans. Behavioral changes were reported in pigs after oral exposure to potassium cyanide (Jackson 1988). Additional studies for neurological effects for all routes and durations would be useful for determining the NOAEL values for this most sensitive end point. Of particular value would be studies in animals that correlate morphological changes, such as demyelination, with changes in higher functions, such as learning and memory.

Epidemiological and Human Dosimetry Studies. Human exposure to low levels of cyanide is quite common. Cigarette and fire smoke contain cyanide (EPA 1981e); cyanide is used as a postharvest pesticide fumigant (Jenks 1979) and can be detected at low levels in drinking water supplies (EPA 1981e). Workers are exposed to cyanide in several industries, but usually only when not using personal protective gear (Blanc et al. 1985). Although several studies reported neurological and thyroid effects in workers chronically exposed occupationally, dose relationships of these effects are not known, and the effects may have been confounded by simultaneous exposure to other chemicals. Similarly, exact correlations between environmental exposures and cyanide levels in blood or urine were not established. Therefore, occupational and environmental studies that would provide data on exposure levels and concentrations found in body fluids would be useful. These studies might be useful for establishing cause/effect relationships that might lead to future monitoring of populations exposed to low levels of cyanide from dietary sources or contaminated waste sites. Furthermore, studies regarding the health status, including significant elevations in urinary thiocyanate as a biomarker, of such populations would be informative. Studies examining exposure to cyanide via cassava consumption would not be useful,

since cassava is not normally consumed in the United States and it contains another substance rather than cyanide which may contribute to neurotoxicity (Obidoa and Obasi 1991).

Biomarkers of Exposure and Effect.

Exposure. Concentrations of cyanide can be measured in the blood, urine, and tissues, and the metabolite thiocyanate can be measured in blood and urine (Ballantyne 1983a; Berlin 1977; Chandra et al. 1988; El Ghawabi et al. 1975; Jarvis 1989; Maliszewski and Bass 1955; Vogel et al. 1981; Yamanaka et al. 1991). Since certain amounts of cyanide can always be found in the human tissues, urine, and expired air, only exposure to high doses can be detected by this way. Cyanide is metabolized in the body to thiocyanate in a reaction that is catalyzed by the enzymes rhodanese and mercaptopyruvate sulfur transferase (Ansell and Lewis 1970). Significant elevations in thiocyanate levels have been detected in cassava-eating populations (Ermans et al. 1980; Mlingi et al. 1993; Tylleskar et al. 1992) and in animals (Blakely and Coop 1949; Himwich and Saunders 1948; Howard and Hanzal 1955; Okoh 1983; Smith 1996; Sousa et al. 2003; Way 1984; Wood and Cooley 1956) and can serve as a reasonable marker of exposure. Since cyanide is eliminated from the body relatively rapidly, but thiocyanate levels are sustained for longer periods, other biomarkers of low-level exposure would be useful.

Effect. The target organs of cyanide toxicity are the central nervous system and the cardiovascular system, but exposure to other chemicals may have similar effects. Reductions in cytochrome c oxidase activity in specific organs and elevations in plasma lactate concentrations have been used as measures of cyanide toxicity following acute exposure (Baud et al. 1996, 2002; Ikegaya et al. 2001). Imaging techniques, such as MRI and PET, have been use to follow the course of brain injury or monitor changes in glucose utilization by specific brain regions, respectively, following acute exposure to cyanide (Carella et al. 1988; Chin and Calderon 2000; Grandas et al. 1989; Feldman and Feldman 1990; Rachinger et al. 2002; Rosenberg et al. 1989; Rosenow et al. 1995; Uitti et al. 1985; Zaknun et al. 2005). The features examined in these studies are not specific to cyanide exposure. Thus, there is a need for studies evaluating characteristic changes in the brain following exposure to cyanide under different exposure conditions (routes of exposure, dose levels, frequency, durations, and form administered). Evaluating differences in the effect of metal cyanide compounds (copper cyanide or silver cyanide) versus the soluble cyanides would help evaluate the contribution of the metal to toxicity. These kinds of studies could also serve as a basis for evaluating the efficacy of antidotes.

Some genetic markers for cyanide-induced hypoxia have been identified in some human cell lines with or without the use of biologically relevant inhibitors (Kiang et al. 2003). These kinds of studies could be expanded to evaluate tissue-specific (cell-type-specific) differences in responses to cyanide exposure. More studies to identify subtle biochemical changes to serve as biomarkers of effects of low cyanide exposure would be useful and could also serve as a platform for the development of new antidotes.

Absorption, Distribution, Metabolism, and Excretion. Hydrogen cyanide, sodium cyanide, and potassium cyanide are readily absorbed following inhalation, oral, and dermal exposures (Ballantyne 1983a; Sousa et al. 2003). Inhalation exposure provides the most rapid route of entry. Cyanide is distributed throughout the body and detoxified by a mitochondrial enzyme, rhodanese (Ansell and Lewis 1970). Other minor detoxification pathways include spontaneous reaction with cystine and the reaction with hydroxo-cobalamin (Ansell and Lewis 1970). The severity and rapidity of the onset of effects depend on the route, dose, duration of exposure, and the cyanide compound administered. Certain iron-containing cyanide compounds exhibit very low bioavailability by the oral route (Nielsen et al. 1990) as suggested by the absence of toxicity among attempted suicides of people who ingested these compounds (Hantson et al. 1996; Laforge et al. 1999). Once cyanides have been absorbed, excretion is similar in humans (Chandra et al. 1980; Liebowitz and Schwartz 1948) and animals (Farooqui and Ahmed 1982; Okoh 1983; Sousa et al. 2003). Cyanide metabolites are excreted primarily in urine, and small amounts of hydrogen cyanide are eliminated through the lungs (Farooqui and Ahmed 1982; Okoh 1983). Additional quantitative data on the toxicokinetics of cyanide would be useful, because there are few studies available that quantitate absorption, distribution and excretion following acute inhalation exposure. The only studies reporting the transfer of cyanide or thiocyanate into breast milk or across the placenta were conducted in goats (Soto-Blanco and Gorniak 2003), which are not an appropriate animal model for humans. Such studies need to be conducted in a more appropriate animal model. No data were found that dealt with saturation kinetics in cyanide metabolism, since cyanide is fatal long before saturation is reached.

Comparative Toxicokinetics. Several studies on cyanide lethality and toxicity indicate that the central nervous system (Blanc et al. 1985; Bonsall 1984; Chandra et al. 1988; Chen and Rose 1952; Dodds and McKnight 1985; El Ghawabi et al. 1975; Fairley et al. 1934; Haymaker et al. 1952; Hirano et al. 1967; Jackson 1988; Kumar et al. 1992; Lasch and El Shawa 1981; Levine 1969; Levine and Stypulkowski 1959a; Lewis et al. 1984; McNerney and Schrenk 1960; Peden et al. 1986; Potter 1950; Purser et al. 1984; Singh et al. 1989; Trapp 1970; Valade 1952; Walton and Witherspoon 1926), the reproductive system (Kamalu 1993; NTP 1993; Singh 1981), and the thyroid gland (Blanc et al. 1985; El

Ghawabi et al. 1975; Gerhart 1986, 1987; Jackson 1988; Philbrick et al. 1979; Soto-Blanco et al. 2002a; Tewe and Maner 1981a, 1981b) are target organs in both humans and animals. Toxicokinetic studies cannot be performed in humans; however, data regarding cyanide distribution have been obtained during autopsies in several lethal cases of poisoning following inhalation or oral exposure to hydrogen cyanide, sodium cyanide, or potassium cyanide (Finck 1969; Gettler and Baine 1938). A large proportion of the toxicokinetic studies in animals was published between 1935 and 1965 (Blakely and Coop 1949; Boxer and Rickards 1952; Gettler and Baine 1938; Howard and Hanzal 1955; Walton and Witherspoon 1926; Wood and Cooley 1956). As a result, much of the information is descriptive rather than quantitative, and the quantitative data presented were generated with inaccurate analytical equipment and methodologies. However, more recent studies in rats with hydrogen cyanide, sodium cyanide, and potassium cyanide indicate a pattern of distribution that is similar to that in humans (Ballantyne 1983a, 1983b; Sousa et al. 2003; Yamamoto et al. 1982). Furthermore, a study regarding transocular exposure showed that tissue concentrations of cyanide in rabbits varied depending on the cyanide compound used (Ballantyne 1983a, 1983b). Detailed pharmacokinetic studies on cyanide and its interaction with thiosulfate have been conducted in dogs (Sylvester et al. 1983). A comparative quantitative toxicokinetic study in male rats and pigs exposed to a single dose of potassium cyanide focused on the plasma concentration of cyanide and thiocyanate (Sousa et al. 2003). Additional toxicokinetic data in several species would be needed to identify the best model for assessing human risk. On account of the relatively low hepatic content of the detoxifying enzyme rhodanese compared to other species (Drawbaugh and Marrs 1987; Himwich and Saunders 1948), dogs do not appear to be the optimal model species for extrapolation to humans.

Methods for Reducing Toxic Effects. This discussion presumes that cyanide exposure was not prevented by the use of protective gear, which, if possible, should be the major strategy for avoiding toxic effects. The mechanism by which cyanide enters the blood stream in humans is not known, but due to the relatively small size of the molecule, it is likely that cyanide simply follows a concentration gradient. Some of the mechanisms of toxic action of cyanide are known: the compound inhibits the activity of various enzymes by binding to their metallic moiety. Cyanide antagonists, such as sodium thiosulfate, have been used as antidotes to cyanide poisoning by aiding in the conversion of the cyanide ion to thiocyanate (Bonsall 1984; Mengel et al. 1989; Schubert and Brill 1968; Sylvester et al. 1983). Other antidotes such as amyl nitrite, sodium nitrite, hydroxylamine, p-aminopropiophenone, 4-dimethyl-aminophenol, and primaquine work by binding to iron ions and increase the levels of methemoglobin to which cyanide can bind (Bright and Marrs 1987; Kruszyna et al. 1982; Schubert and Brill 1968). In practice, antidote therapy is continued until serum parameters (blood oxygen and serum pH) indicate that no additional cyanide is impairing mitochondrial function. Additional research has been carried out on

antidotes that would not produce methemoglobinemia (Bhattacharya and Vijayaraghavan 2002; Keniston et al; 1987; Moore et al. 1986; Klimmek et al. 1983; Niknahad and O'Brien 1996; Schwartz et al. 1979; Yamamoto 1989). Synergistic effects of supplemental therapies such as alpha-ketoglutaric acid along with conventional antidotes have been examined (Hume et al. 1995; Niknahad et al. 1994). Pharmacological approaches have been employed to find antidotes for cyanide (Isom and Borowitz 1995; Maduh et al. 1995). Other types of compounds that have been tested include calcium-channel blockers (Jiang et al. 1998; Mathangi and Namisivayam 2004a), antioxidants (Choi and Han 2002; Kanthasamy et al. 1997; Maharaj et al. 2003; Okolie and Iroanya 2003; Yamamoto and Tang 1996a, 1996b, 1996c, 1998), anti-inflammatory drugs (Daya et al. 2000; Lambat et al. 2000), and certain amino acids (Carini et al. 1997). Evaluations of antidotes need to consider the progression of lactate acidosis.

Children's Susceptibility. Data needs relating to both prenatal and childhood exposures, and developmental effects expressed either prenatally or during childhood, are discussed in detail in the Developmental Toxicity subsection above.

There is some evidence from the cassava-eating populations that hypothyroidism may occur from gestational exposure to cyanide (Ermans et al. 1980) and from lactating ewes that cyanide can be transferred in milk of exposed goats (Soto-Blanco and Gorniak 2003). In general, the effects in children are not expected to differ from adults. However, there is no study that has yet examined possible neurological or neurobehavioral deficits in offspring following gestational exposure to cyanide. This would appear to be a significant issue, given the report suggesting that neurohistopathology is the most sensitive effect in rats (Soto-Blanco et al. 2002a). Studies evaluating the different sensitivity of young organisms to side effects of cyanide antidotes would be useful in establishing suitable dose levels of antidotes for children.

Child health data needs relating to exposure are discussed in Section 6.8.1, Identification of Data Needs: Exposures of Children.

3.12.3 Ongoing Studies

A number of ongoing studies concerning health effects and mechanisms of action associated with cyanide have been identified in the 2005 version of the Federal Research In Progress (FEDRIP) database (FEDRIP 2005).

In a project supported by the National Institute for Occupational Safety and Health, Dr. Laurence D. Fechter, of the Loma Linda Veterans Association, Redlands, California, is investigating the effect of hydrogen cyanide exposure on noise-induced hearing loss in rats.

Dr. Gary E. Isom of Purdue University, West Lafayette, Indiana, is evaluating necrotic and apoptopic mechanisms of neuronal cell death caused by cyanide in a project supported by the National Institute of Environmental Health Sciences.

Under the auspices of the National Cancer Institute, Dr. Timothy R. Fennell, of Research Triangle Institute, North Carolina, is investigating methods for the analysis of adducts formed between hemoglobin and reactive chemicals, including cyanide. The study aims to understand the basis for selective vulnerability of specific brain regions to cyanide.

Dr. Julia A. Kovacs of the University of Washington, Seattle, Washington, is evaluating the inhibitory effect of cyanide on superoxide reductases as part of a project on structure-reactivity relationships for metalloenzymes; this project is supported by the National Institute of General Medical Sciences.

Dr. Herbert T. Nagasawa of the Department of Veterans Affairs, Medical Center, Minneapolis, Minnesota, is evaluating the efficacy of derivatives of 2-mercaptopyruvic acid as antidotes for cyanide in mice.

Dr. Arne Slungaard of the University of Minnesota, is investigating the effect of thiocyanate on eosinophil peroxidase-mediated oxidative damage, inflammation, and apoptosis. The study is supported by the National Heart, Lung and Blood Institute.

Dr. Patricia Sonsalla of the University of Medicine and Dentistry of New Jersey, R.W. Johnson Medical School, is investigating a number of mitochondrial toxins, including cyanide, to establish their effect on dopamine homeostasis, the function of dopamine vesicles, and the role of dopamine in modulating neurodegeneration. This study is supported by the National Institute of Neurological Disorders and Stroke.

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4. CHEMICAL AND PHYSICAL INFORMATION

4.1 CHEMICAL IDENTITY

Information regarding the chemical identity of the most common cyanides is located in Table 4-1. Hydrogen cyanide is a toxic gas that may enter the environment from both natural processes and human industrial activities. It may exist in polymeric forms. The cyanide compounds in which cyanide can be obtained as CN^- are classified as simple and complex cyanides. Some simple cyanides are soluble in water (sodium cyanide, NaCN; potassium cyanide, KCN; and calcium cyanide, $Ca(CN)_2$), while others are sparingly soluble or almost insoluble (copper (I) cyanide, CuCN). Cyanogen (NC-CN) and cyanogen chloride (CNCl) are highly toxic gases that are soluble in water. At neutral pH, cyanogen undergoes a slow hydrolysis to form hydrogen cyanide, cyanic acid (HOCN), and other products. At alkaline pH, CNCl hydrolyzes to CNO^-, which has only limited toxicity. Alkaline chlorination of water containing cyanide produces cyanogen chloride. Thiocyanate (SCN^-) is an oxidation product of the cyanide anion (CN^-), produced in the presence of a sulfur donor.

4.2 PHYSICAL AND CHEMICAL PROPERTIES

Information regarding the physical and chemical properties of cyanide is located in Table 4-2. Cyanides form strong complexes with many metals, particularly those of the transition series. One example of such complex formation is the reaction of cyanide with iron in the formation of ferrocyanide and ferricyanide complexes. Solutions of ferrocyanides and ferricyanides can form hydrogen cyanide and cyanide ions when exposed to sunlight or ultraviolet radiation. Cyanogenic glycosides are cyanide compounds produced naturally in many plants (Jones 1998). These glycosides produce hydrogen cyanide when hydrolyzed (EPA 1978c) or digested (Ellenhorn and Barceloux 1997; WHO 2004b). For example, in the human gut, the cyanogenic glycoside amygdalin, which is found in bitter almonds and in apricot pits and is the active ingredient in the drug Laetrile, undergoes two enzymatically catalyzed hydrolysis steps (Ellenhorn and Barceloux 1997). The first step involves the removal of one of the two β-D-gluco-pyranosyl groups from amygdalin through the action of beta-glucosidase to form the cyanogenic glycoside, prunasin. The enzyme, emulsion, then hydrolyzes prunasin to form hydrogen cyanide, glucose, and benzaldehyde.

Table 4-1. Chemical Identity of Cyanide and Compounds[a]

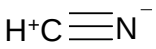
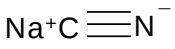
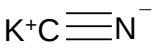
Characteristic	Hydrogen cyanide	Sodium cyanide	Potassium cyanide
Synonym(s)	Formonitrile; hydrocyanic acid; prussic acid	Cyanide of sodium; hydrocyanic acid; sodium salt	Cyanide of potassium; hydrocyanic acid; potassium salt
Registered trade name(s)	Cyclone B; Cyclon[b]	Cyanogran[c]	Carswell No. 688A
Chemical formula	HCN	NaCN	KCN
Chemical structure			
Identification numbers:			
CAS registry	74-90-8	143-33-9	151-50-8
NIOSH RTECS	MW6825000	VZ7530000	TS8750000
EPA hazardous waste	P063; D003	P106; D003	P098; D003
OHM/TADS	7216749	7216892	7216862
DOT/UN/NA/IMCO shipping	UN1051; IMO 6.1 UN1614; NA 1051	UN1689; IMO 6.1	UN1680; IMO 6.1
HSDB	165	734	1245
NCI	No data	No data	No data

Table 4-1. Chemical Identity of Cyanide and Compounds[a]

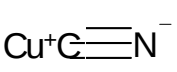
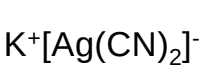
Characteristic	Calcium cyanide	Copper(I) cyanide	Potassium silver cyanide
Synonym(s)	Calcid; calcyan; cyanide of calcium	Cuprous cyanide[c]; cupricin[c]	Potassium argentocyanide; potassium dicyanoargentate
Registered trade name(s)	Caswell No. 142; Cyanogas[c]	AI3–28745	No data
Chemical formula	$Ca(CN)_2$	CuCN	$KAg(CN)_2$
Chemical structure			
Identification numbers:			
CAS registry	592-01-8	544-92-3	506-61-6
NIOSH RTECS	EW0700000	GL7150000	TT5775000
EPA hazardous waste	P021; D003	P029; D003	P099; D003; D011
OHM/TADS	7216626	No data	No data
DOT/UN/NA/IMCO shipping	UN1575; IMO 6.1	UN1587; IMO 6.1	No data
HSDB	242	1438	6053
NCI	No data	No data	No data

Table 4-1. Chemical Identity of Cyanide and Compounds[a]

Characteristic	Cyanogen	Cyanogen chloride	Ammonium thiocyanate
Synonym(s)	Carbon nitride; dicyanogen; ethanedinitrile	Chlorine cyanide; chlorocyan	Thiocyanic acid, ammonium salt; ammonium rhodanide; ammonium sulfocyanate[c]
Registered trade name(s)	No data	Caswell No. 267	Trans-Aid[b]
Chemical formula	$(CN)_2$	CNCl	NH_4SCN
Chemical structure	$N\equiv C-C\equiv N$	$Cl-C\equiv N$	$NH_4^+S-C\equiv N^-$
Identification numbers:			
CAS registry	460-19-5	506-77-4	1762-95-4
NIOSH RTECS	GT1925000	GT2275000	XK7875000
EPA hazardous waste	P031; D003	P033; D003	No data
OHM/TADS	7216656	7216658	721218
DOT/UN/NA/IMCO shipping	UN1026; IMO 2.3	UN1589; IMO 2.3	NA9092
HSDB	2130	917	701
NCI	No data	No data	No data

[a]All data are from HSDB 2004 unless otherwise noted.
[b]Crop Protection Handbook 2004
[c]Budavari 1989

CAS = Chemical Abstracts Service; DOT/UN/NA/IMO = Department of Transportation/United Nations/North America/International Maritime Dangerous Goods Code; EPA = Environmental Protection Agency; HSDB = Hazardous Substances Data Bank; NCI = National Cancer Institute; NIOSH = National Institute for Occupational Safety and Health; OHM/TADS = Oil and Hazardous Materials/Technical Assistance Data System; RTECS = Registry of Toxic Effects of Chemical Substances

Table 4-2. Physical and Chemical Properties of Cyanide and Compounds

Property	Hydrogen cyanide	Sodium cyanide
Molecular weight	27.03[a]	49.01[a]
Color	Colorless[b]	White[b]; colorless[a]
Physical state	Gas or liquid[b]	Solid[b]
Melting point, °C	-13.4[b]	563.7[a]
Boiling point, °C	25.70[c]	1496[a]
Density, g/cm^3	0.6884 (liquid at 20 °C)[c]	1.60 (for cubic form)[c]
Odor	Faint bitter almond odor[d]	Odorless when dry, emits slight odor of HCN in damp air[b]
Odor threshold:		
Water	0.17 ppm (w/v)[e]	No data
Air	0.58 ppm (v/v)[e]; 0.8–4.4 ppm[f]	No data
Solubility:		
Water	Miscible[a]	48 g/100 mL at 10 °C[c]
Organic solvent(s)	Soluble in ethanol, ether[a]	Slightly soluble in ethanol[a] and formamide[c]
Partition coefficients:		
Log K_{ow}	0.66[g]; 1.07 (calc.)[h]	0.44[g]
Log K_{oc}	No data	No data
Vapor pressure, mm Hg	630 (at 20 °C)[f]	0.76 at 800 °C[c]
Henry's law constant	5.1x10^{-2} atm-m^3/mol[i]	No data
Autoignition temperature	538[c]	No data
Flashpoint, °C	-17.8 (closed cup)[c]	No data
Flammability limits	5.6–40%[j]	Not combustible[j]
Conversion factors:		
mg/m^3 to ppm in air, 20 °C	1 mg/m^3 = 0.890 ppm	NA[k]
ppm to mg/L in water	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
Explosive limits	Upper, 40%; lower, 5.6%[f]	No data

Table 4-2. Physical and Chemical Properties of Cyanide and Compounds

Property	Potassium cyanide	Calcium cyanide
Molecular weight	65.12[a]	92.12[a]
Color	White[b]; colorless[a]	White[a]
Physical state	Solid[b]	Solid[a]
Melting point, °C	634.5[a]	Decomposes at >350 °C[a]
Boiling point, °C	No data	No data
Density, g/cm^3	1.553 (for cubic form)[c]	1.8–1.9 (commercial product)[c]
Odor	Faint bitter almond odor[b]	Faint bitter almond odor[b]
Odor threshold:		
Water	No data	No data
Air	No data	No data
Solubility:		
Water	71.6 g/100 mL at 25 °C[c]	Soluble in water with gradual liberation of HCN[b]
Organic solvent(s)	Slightly soluble in ethanol[c] and methanol[b]	
Partition coefficients:		
Log K_{ow}	No data	No data
Log K_{oc}	3.0 (calculated)[l]	No data
Vapor pressure, mm Hg	No data	No data
Henry's law constant	No data	No data
Autoignition temperature	No data	No data
Flashpoint, °C	No data	No data
Flammability limits	Not combustible[j]	Not combustible[j]
Conversion factors:		
mg/m^3 to ppm in air, 20 °C	NA[k]	NA[k]
ppm to mg/L in water	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	
Explosive limits	No data	No data

Table 4-2. Physical and Chemical Properties of Cyanide and Compounds

Property	Potassium silver cyanide	Cyanogen
Molecular weight	199.01[b]	52.04[a]
Color	White[b]	Colorless[a]
Physical state	Solid[b]	Gas[a]
Melting point, °C	No data	-27.9[a]
Boiling point, °C	No data	-20.7[a]
Density, g/cm^3	2.36[a]	0.9577 at -21.17 °C[a]
Odor	No data	Almond-like odor[b]
Odor threshold:		
Water	No data	No data
Air	No data	230 ppm; irritating at 15 ppm[f]
Solubility:		
Water	Soluble[b]; 250 g/L (25 °C)[m]	450 cc/100 cc (20 °C)[a]
Organic solvent(s)	Slightly soluble in ethanol[a]	Soluble in ethanol and ethyl ether[a]
Partition coefficients:		
Log K_{ow}	No data	0.07[n]
Log K_{oc}	No data	No data
Vapor pressure, mm Hg	No data	3,800 at 20 °C[o]
Henry's law constant	No data	No data
Autoignition temperature	No data	No data
Flashpoint, °C	No data	No data
Flammability limits	No data	6.6–32% in air[j]
Conversion factors:		
mg/m^3 to ppm in air, 20 °C	NA[k]	1 mg/m^3 = 0.462 ppm
ppm to mg/L in water	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
Explosive limits	No data	No data

Table 4-2. Physical and Chemical Properties of Cyanide and Compounds

Property	Cyanogen chloride	Copper(I) cyanide
Molecular weight	61.47[a]	89.56[a]
Color	Colorless[d]	White to cream-colored[b]
Physical state	Gas[d]	Solid[a]
Melting point, °C	-6[a]	473 (in N_2)[a]
Boiling point, °C	13.8[b];12.7[a]	Decomposes[a]
Density, g/cm^3	1.186[b]	2.92[a]
Odor	Highly irritating[h]	No data
Odor threshold:		
Water	No data	No data
Air	1 ppm[f]	No data
Solubility:		
Water	Soluble[b]; 27.5 mg/L (25 °C)[m]	2.6 mg/L (25°C)[m]
Organic solvent(s)	Soluble in ethanol and ethyl ether[b]	Insoluble in alcohol[f]
Partition coefficients:		
Log K_{ow}	No data	No data
Log K_{oc}	No data	No data
Vapor pressure, mm Hg	760 at 13.8 °C	No data
Henry's law constant	3.2x10^{-3} atm-m^3/mol[m]	No data
Autoignition temperature	No data	No data
Flashpoint, °C	No data	No data
Flammability limits	Not combustible[f]	Does not readily ignite[f]
Conversion factors:		
mg/m^3 to ppm in air, 20 °C	1 mg/m^3 = 2.5 ppm	NA[k]
ppm to mg/L in water	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
Explosive limits	No data	No data

Table 4-2. Physical and Chemical Properties of Cyanide and Compounds

Property	Ammonium thiocyanate
Molecular weight	76.12[a]
Color	Colorless[a]
Physical state	Solid[a]
Melting point, °C	149.6[a]
Boiling point, °C	170 decomposes[a]
Density, g/cm^3	1.305[a]
Odor	Odorless[b]
Odor threshold:	
Water	No data
Air	No data
Solubility:	
Water	128 g/100 cc at 0 °C[a]; Very soluble in hot water[a]; 181 g/100 cc at 25 °C[p]
Organic solvent(s)	Very soluble in ethanol; soluble in acetone and methanol; insoluble in ethyl acetate and chloroform[b]
Partition coefficients:	
Log K_{ow}	No data
Log K_{oc}	No data
Vapor pressure, mm Hg	No data
Henry's law constant	No data
Autoignition temperature	No data
Flashpoint, °C	No data
Flammability limits	May be combustible[f]
Conversion factors:	
mg/m^3 to ppm in air, 20 °C	NA[k]
ppm to mg/L in water	ppm (w/v) = mg/L = µg/mL
ppm to mg/kg in soluble samples	ppm (w/w) = mg/kg = µg/g
Explosive limits	No data

[a]Lide 1990
[b]Budavari 1989
[c]Jenks 1979
[d]Hawley 1981
[e]Amoore and Hautala 1983
[f]HSDB 2004
[g]EPA 1984a
[h]Verschueren 1983
[i]Yoo et al. 1986; value at 25 °C and saturation pressure
[j]NFPA 1994
[k]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).
[l]Kenaga 1980
[m]EPA 1985f
[n]Hansch et al. 1995
[o]EPA 1978c
[p]Lide 2005

EPA = Environmental Protection Agency; HCN = hydrogen cyanide; HSDB = Hazardous Substances Data Bank; NA = not applicable

Hydrogen cyanide has a pK_a of 9.2 (Smith and Martell 1989); therefore, solutions of cyanide compounds in water (such as from sodium cyanide and potassium cyanide) can form hydrogen cyanide at acid and neutral pHs. Alkaline solutions with pH >12 are practical for preventing significant outgassing of hydrogen cyanide.

Hydrogen cyanide is a fire hazard and may be explosive when an excess of a strong acid is added to confined hydrogen cyanide. Solutions of some cyanide compounds are not stable and may decompose upon exposure to air or light.

5. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

5.1 PRODUCTION

The demand for hydrogen cyanide in the United States during 2000 was 1.615 billion pounds, up slightly from 1.605 billion pounds in 1999 (CMR 2001). Production of hydrogen cyanide in 2003 was 2.019 billion pounds in the United States (FAS 2005). The demand for hydrogen cyanide was projected to be 1.838 billion pounds in 2004 (CMR 2001; NYSDOH 2005). Major producers of hydrogen cyanide are Adisseo USA, Inc. (Institute, West Virginia); Cyanco Co. (Winnemucca, Nevada); Cytec Industries (Waggoman, Louisiana); Degussa Corp. (Theodora, Alabama); The Dow Chemical Company (Freeport, Texas); E.I. du Pont de Neumours and Company (Memphis, Tennessee; Beaumont, Texas); Innovene (Green Lake, Texas and Lima, Ohio); Invista, Inc. (Orange, Texas and Victoria, Texas); Rhom and Haas Texas Inc. (Deer Park, Texas); Solutia, Inc. (Alvin, Texas); Sterling Chemicals, Inc. (Texas City, Texas); and Syngenta Crop Protection (St. Garbiel, Louisiana) (SRI 2005). The combined annual production capacity of these plants is approximately 2.036 billion pounds (SRI 2005).

As of February 2005, the following companies produced other cyanide compounds in the United States (SRI 2005):

ammonium thiocyanate:	Crompton, Taft, Louisiana; and Mallinckrodt, Inc., St. Louis, Missouri
cyanogen:	Matheson Gas Products, Inc., Gloucester, Massachusetts
potassium cyanide:	DuPont Chemical Company, Memphis, Tennessee; and The Dow Chemical Company, Nashua, New Hampshire
potassium silver cyanide:	Engelhard Corporation, Union, New Jersey; and Metalor Technologies USA, North Attleboro, Massachusetts

Facilities in the United States producing sodium cyanide and their annual capacity (in millions of pounds) in 2005 include: Cyanco Co., Winnemucca, Nevada (86); and E.I. du Pont de Neumours and Company, Memphis, Tennessee (200) (SRI 2005). Two production facilities, E.I. du Pont de Neumours and Company, Texas City, Texas, and CyPlus, Theodore, Alabama, with production capacities of 85 and 60 million pounds per year, respectively, were idle in 2005 (SRI 2005).

Facilities in each state that manufactured or processed hydrogen cyanide or cyanide compounds in 2002, the range of the maximum amounts stored on site, and the types of production or use activities (e.g.,

production for sale or on-site use in processing) are shown in Tables 5-1 and 5-2, respectively (TRI03 2005). The information in Tables 5-1 and 5-2 is derived from the Toxics Release Inventory (TRI). The TRI data should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list. No information is available in the TRI database for thiocyanate compounds in this profile because these compounds are not included under SARA, Title III and, therefore, are not among the chemicals that facilities are required to report (EPA 2004q).

There are two common methods of manufacturing hydrogen cyanide. The first consists of the formation of hydrogen cyanide as a byproduct during the synthesis of acrylonitrile from the reaction of propylene and ammonia with air. The second method involves direct synthesis by the reaction of methane and ammonia with air over platinum catalysts, otherwise known as the Andrussow process (CMR 1993; Curry 1992; Homan 1987). Another less common manufacturing method, the Shawinigan process, is being applied in Spain and Australia that involves the reaction of ammonia with propane or butane in a fluidized bed of coke particles (Homan 1987; Shine 1971). Other methods of production include the dehydration of formamide and the reaction of sodium carbonate with coke-oven gas (Curry 1992; Sittig 1980). The formamide method of production has now been replaced by direct synthesis from methane and ammonia (Homan 1987). Of the total production capacity in the United States, direct synthesis and other routes of primary production accounts for 77% of the hydrogen cyanide produced; byproduct of acrylonitrile production accounts for the remaining 23% (CMR 1993; SRI 1995). The methods of commercial production of potassium and sodium cyanide include reacting potassium or sodium carbonate with carbon and ammonia, and reacting hydrogen cyanide with potassium or sodium hydroxide (Curry 1992; Homan 1987; HSDB 2004). Sodium cyanide can also be prepared by heating sodium amide with carbon or by melting sodium chloride and calcium cyanamide together in an electric furnace (Hartung 1982). Potassium silver cyanide is manufactured by adding silver chloride to a solution of potassium cyanide (Sax and Lewis 1987). Calcium cyanide is manufactured by heating calcium cyanamide with a source of carbon in electric furnaces at temperatures >1,000 °C (Curry 1992; Homan 1987). It may also be produced by neutralization of lime with hydrogen cyanide (Homan 1987).

Cyanogen is usually prepared by adding an aqueous solution of sodium or potassium cyanide to an aqueous solution of copper (II) sulfate or chloride (Homan 1987; Windholz 1983). It may also be produced by heating mercury cyanide, or by heating hydrogen cyanide in the presence of a catalyst (Homan 1987). Cyanogen chloride is produced by the action of chlorine on hydrogen cyanide or by the action of chlorine on moist sodium cyanide suspended in carbon tetrachloride and kept cooled to -3 °C (Homan 1987; Windholz 1983). Ammonium thiocyanate is produced by boiling an aqueous solution of

Table 5-1. Facilities that Produce, Process, or Use Hydrogen Cyanide

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
AK	2	0	99,999	1, 5
AL	11	0	999,999	1, 3, 4, 5, 6, 12, 14
AR	1	1,000	9,999	12
CA	8	0	999,999	1, 5, 13
CO	4	0	99,999	1, 3, 5, 12
DE	1	1,000	9,999	1, 3, 5, 12
ID	3	0	9,999	1, 5, 6
IL	9	0	9,999,999	1, 3, 5, 6, 7, 11, 12, 13, 14
IN	3	0	999,999	1, 5
KY	6	0	999	1, 5, 13
LA	19	0	9,999,999	1, 3, 4, 5, 6, 12, 13, 14
MA	2	0	999	1, 5
MD	1	10,000	99,999	1, 5
MI	1	100,000	999,999	1, 5
MN	3	100	999	1, 5, 13
MS	2	100	9,999	1, 5
MT	2	0	999	1, 5
NH	4	100,000	49,999,999	2, 3, 6
NJ	3	0	99	1, 5
NV	10	0	9,999,999	1, 3, 5, 6, 13
NY	4	0	9,999,999	1, 3, 5, 6, 13
OH	6	1,000	9,999,999	1, 4, 5, 6
OK	3	0	999	1, 5, 12, 14
PA	9	100	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 13
SC	6	0	999,999	1, 3, 5, 6
SD	1	10,000	99,999	1, 5
TN	7	0	99,999,999	1, 3, 4, 5, 6, 13, 14
TX	43	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 12, 13, 14
UT	4	0	999	1, 3, 5, 6, 12
WA	2	0	999	1, 5
WI	1	0	99	1, 5
WV	10	0	49,999,999	1, 3, 5, 6, 7, 8, 10, 12
WY	2	0	999	1, 3, 5, 6

[a]Post office state abbreviations used
[b]Amounts on site reported by facilities in each state
[c]Activities/Uses:

1. Produce
2. Import
3. Onsite use/processing
4. Sale/Distribution
5. Byproduct
6. Impurity
7. Reactant
8. Formulation Component
9. Article Component
10. Repackaging
11. Chemical Processing Aid
12. Manufacturing Aid
13. Ancillary/Other Uses
14. Process Impurity

Source: TRI03 2005 (Data are from 2003)

Table 5-2. Facilities that Produce, Process, or Use Cyanide Compounds

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
AK	2	100,000	9,999,999	1, 5, 10
AL	27	0	9,999,999	1, 3, 4, 5, 6, 7, 8, 10, 11, 12, 13
AR	16	0	99,999	2, 3, 6, 7, 10, 11, 12
AZ	14	100	9,999,999	1, 6, 10, 11, 12
CA	60	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
CO	12	100	999,999	1, 2, 3, 5, 6, 7, 9, 10, 11, 13, 14
CT	40	100	999,999	1, 2, 3, 4, 6, 7, 8, 9, 10, 11, 12, 13
DE	1	1,000	9,999	1, 3, 5, 12
FL	8	100	99,999	3, 6, 7, 10, 11, 12, 13
GA	20	100	999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
IA	6	100	99,999	1, 3, 5, 6, 8
ID	10	1,000	999,999	1, 2, 3, 5, 6, 7, 10, 12
IL	85	0	999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
IN	51	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
KS	10	0	99,999	1, 3, 6, 7, 8, 10, 11, 12, 13
KY	25	0	999,999	1, 5, 6, 7, 8, 10, 11, 12, 13
LA	18	0	9,999,999	1, 3, 4, 5, 6, 10, 12, 13, 14
MA	25	0	999,999	1, 2, 3, 4, 5, 6, 7, 10, 11, 12
MD	14	100	99,999,999	1, 2, 3, 5, 6, 7, 10, 11, 12
ME	7	100	99,999	5, 10, 11, 12
MI	72	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
MN	30	100	999,999	1, 3, 5, 6, 8, 10, 11, 12
MO	14	100	999,999	1, 3, 4, 5, 6, 8, 9, 10, 12, 13
MS	11	0	99,999	1, 5, 6, 7, 9, 10, 12
MT	6	0	999,999	1, 5, 10, 13
NC	13	0	99,999	7, 8, 10, 11, 12
NE	5	0	99,999	7, 10, 12
NH	13	0	9,999,999	1, 3, 4, 5, 6, 8, 10, 11
NJ	47	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
NV	39	100	49,999,999	1, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
NY	43	0	999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
OH	66	0	999,999	1, 2, 3, 4, 5, 6, 7, 8, 10, 11, 12, 13, 14
OK	8	1,000	99,999	1, 3, 5, 6, 10, 11, 12
OR	10	100	99,999	1, 2, 3, 5, 7, 10, 11, 12, 13
PA	61	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 10, 11, 12, 13
PR	13	100	999,999	6, 7, 8, 10, 11, 12, 13
RI	28	0	99,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12
SC	15	100	9,999,999	1, 3, 5, 6, 7, 10, 11, 12

Table 5-2. Facilities that Produce, Process, or Use Cyanide Compounds

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
SD	5	100	9,999,999	1, 2, 3, 5, 6, 7, 10, 11, 12
TN	25	100	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
TX	54	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
UT	8	100	999,999	1, 3, 5, 6, 10, 12
VA	17	0	99,999	1, 3, 5, 6, 8, 10, 11, 12
WA	8	100	999,999	1, 2, 3, 5, 8, 10, 11, 12
WI	36	0	999,999	1, 2, 3, 5, 6, 7, 8, 10, 11, 12, 13
WV	10	0	9,999,999	1, 5, 11, 13
WY	2	100,000	9,999,999	1, 4

[a]Post office state abbreviations used
[b]Amounts on site reported by facilities in each state
[c]Activities/Uses:

1. Produce
2. Import
3. Onsite use/processing
4. Sale/Distribution
5. Byproduct
6. Impurity
7. Reactant
8. Formulation Component
9. Article Component
10. Repackaging
11. Chemical Processing Aid
12. Manufacturing Aid
13. Ancillary/Other Uses
14. Process Impurity

Source: TRI03 2005 (Data are from 2003)

ammonium cyanide with sulfur or polysulfides or by reaction of ammonia and carbon disulfide (Homan 1987; Sax and Lewis 1987).

5.2 IMPORT/EXPORT

The imports and exports of hydrogen cyanide through principal U.S. customs districts are negligible (CMR 2001). Recent import and export data for some of the cyanide compounds included in this profile are summarized in Table 5-3 for 2004 (USDOC 2004). Import volumes were greatest for thiocyanates, cyanates, and fulminates at 11.6 millions pounds followed by cyanides and cyanide oxides of sodium at 4.71 million pounds. China, Germany, Japan, Czech Republic, and the United Kingdom were the primary exporters of these cyanide chemicals to the United States in 2004 (USDOC 2004). Recent import data could not be found in the available literature for potassium silver cyanide, cyanogen, or cyanogen chloride.

Cyanides and cyanide oxides of sodium comprise the majority of exports for cyanide compounds with a volume of 147 million pounds. The second largest export item among the cyanide compounds was potassium cyanide at 3.82 million pounds. The most recent import data that could be found for copper (I) cyanide indicate that 0.52 and 0.26 million pounds of this compound were imported into the United States in 1984 and 1986, respectively (HSDB 2004). Export data could not be found in the available literature for calcium cyanide, potassium silver cyanide, cyanogen, or cyanogen chloride.

5.3 USE

The predominant users of cyanides are the steel, electroplating, mining, and chemical industries. The principal cyanide compounds used in industrial operations are potassium and sodium cyanide and calcium cyanide, particularly in metal leaching operations (Curry 1992; EPA 1993g). Cyanides have been well established in uses as insecticides and fumigants; in the extraction of gold and silver ores; in metal cleaning; in the manufacture of synthetic fibers, various plastics, dyes, pigments, and nylon; and as reagents in analytical chemistry (EPA 1978c, 1993g; HSDB 2004). Cyanides are present in some foods, but this presence is due mainly to the production of hydrogen cyanide from naturally-occurring cyanogenic compounds in foods (see Sections 6.4.4 and 6.5). Cyanogen has been used as a high-energy fuel in the chemical industry and as a rocket or missile propellant; cyanogen and its halides are used in organic syntheses, as pesticides and fumigants, and in gold-extraction processes (EPA 1978c; HSDB

Table 5-3. Import and Export Volumes of Cyanide Compounds in 2004[a]

Compounds	Millions of pounds
Imports:	
Potassium cyanide	0.954
Calcium cyanide	0.006
Cyanides and cyanide oxides of sodium	4.71
Other cyanides and cyanide oxides	No data
Thiocyanates, cyanates, and fulminates	11.6
Exports:	
Potassium cyanide	3.82
Calcium cyanide	No data
Cyanides and cyanide oxides of sodium	147
Other cyanides and cyanide oxides	1.59
Thiocyanates, cyanates, and fulminates	1.56

[a]USDOC (2004)

2004). When used in pesticidal applications and in accordance with the product label, cyanide compounds are registered and regulated by the EPA under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) (EPA 1998, 2004d).

As a commercially available product, hydrogen cyanide is sold as a gas and is also available as a technical grade liquid in concentrations of 5, 10, and 96–99.5%. Almost all grades of hydrogen cyanide contain a stabilizer such as phosphoric acid to prevent decomposition and explosion (Curry 1992). In recent years, the use of hydrogen cyanide in the nylon and methyl methacrylate production processes has produced a strong demand. The use pattern for hydrogen cyanide is the following: adiponitrile (for nylon 6/6), 47%; methyl methacrylate, 27%; sodium cyanide, 8%; methionine, 6%; chelating agent, 2%; cyanuric chloride, 2%; and miscellaneous uses, including nitriloacetic acid and salts, 8% (CMR 2001). Miscellaneous applications also include the use of hydrogen cyanide as an insecticide and rodenticide for fumigating enclosed spaces (grain storage, etc.) (Worthing 1987) and its use in the manufacture of ferrocyanides, acrylates, lactic acid, pharmaceutical, and specialty chemicals (Worthing 1987).

Cyanide salts have various uses. The most significant applications of compounds included in this profile are uses in electroplating and metal treatment, as an anti-caking agent in road salts, and in gold and silver extraction from ores. Minor applications include use as insecticides and rodenticides, as chelating agents, and in the manufacture of dyes and pigments (EPA 1978c; Pesce 1993; Sax and Lewis 1987; Worthing 1987). Calcium cyanide is used as a cement stabilizer (Curry 1992; Windholz 1983) and has had limited use in rodent control and as a beehive fumigant (Lowe and Sullivan 1992). Formerly used as a polymerization catalyst and as an antifouling agent in marine paints, copper (I) cyanide continues to be used in plating baths for silver, brass, and copper-tin alloy plating. Many metal polishes contain potassium or sodium cyanide. Potassium cyanide has a primary use in silver plating and is also used as a reagent in analytical chemistry. Potassium and sodium cyanide are used in combination for nitriding steel (HSDB 2004). One method of achieving hardened, weather-resistant metal surfaces uses a process known as cyaniding, which involves heating the metal in a liquid solution of sodium cyanide, sodium chloride, and sodium carbonate in the presence of atmospheric oxygen (Curry 1992). Fumigation of fruit trees, railway cars, and warehouses, and treatment of rabbit and rat burrows and termite nests are included among the former uses for sodium cyanide (HSDB 2004).

Cyanogen, a colorless gas with an almond-like odor, is used in organic syntheses, as a fumigant, as a fuel gas for welding and cutting heat-resistant metals, and as a rocket and missile propellant with ozone or fluorine (Sax and Lewis 1987; HSDB 2004). Applications of cyanogen chloride include use in chemical

syntheses, as a military poison gas, as a metal cleaner, in ore refining, and in the production of triazine herbicides, optical brighteners, dyestuffs, and synthetic rubber (Hartung 1982; Homan 1987; HSDB 2004; Sine 1994; Windholz 1983). Cyanogen chloride has also been used a warning agent in fumigant gases due to the fact that at low concentrations, it has strong lacrimatory effects (Homan 1987).

Ammonium thiocyanate is used as an ingredient in antibiotic fermentations, pesticides, liquid rocket propellants, adhesives, and matches; in photographic processes; to improve the strength of silks; in the manufacture of transparent artificial resins; and as a weed killer and defoliant (Sax and Lewis 1987; Weil and Sandler 1997; Windholz 1983).

5.4 DISPOSAL

It has been estimated that 4.7 billion gallons of cyanide-containing wastes and 0.8 billion gallons of reactive wastes containing cyanide compounds were generated in the United States in 1983 (Grosse 1986). Regulations governing the treatment and disposal of cyanide-containing wastes are detailed in Chapter 8. Cyanide is listed among the 65 toxic pollutants regulated by the Effluent Guidelines and Standards given in Title 40, Sections 400–475, of the Code of Federal Regulations. The pretreatment standards established for point source categories such as hydrogen peroxide manufacturing, electroplating, metal finishing, and ferroalloy manufacturing, regulate emissions of cyanides based on either total amount of cyanide or as cyanide that is amenable to chlorination in waste streams. Under the Resource Conservation and Recovery Act (RCRA), cyanide is listed as a hazardous waste when it is a discarded as a commercial chemical product, off-specification species, container residue, or spill residue; a waste from non-specific sources; or a waste from specific sources (EPA 1980a). Cyanide salts and complexes are the basis for listing 11 solid waste streams as hazardous wastes under RCRA (EPA 1986b). According to RCRA, cyanide-containing wastes are required to be treated by the best available technology before the wastes are disposed of in land. Cyanogen- and cyanogen chloride-containing waste, for example, are assigned the hazardous waste codes P031 and P033, respectively, and must be treated by chemical or electrolytic oxidation employing specific oxidizing reagents (e.g., hypochlorite, peroxides, ozone, or ultraviolet light assisted ozone) or other reagents of equivalent efficiency; wet air oxidation incorporating a surrogate or indicator parameter; or treatment by incineration in units operated in compliance with RCRA standards (EPA 1986b). The concentration of cyanide permissible in wastes for land disposal is described in the Land Disposal Restriction in Title 40 Section 268, of the Code of Federal Regulations and varies according to the nature of wastes. The maximum concentration in treated waste (i.e., non-waste water) should not exceed 590 mg/kg for total cyanides and 30 mg/kg for cyanides

amenable to chlorination (EPA 1988c). While liquids are prohibited from land disposal, the maximum concentrations allowable in most treated waste waters, with the exception of the bottom streams from the acetonitrile column and the waste water stripper used in the production of acrylonitrile, are 1.9 mg/L for total cyanides and 0.86 mg/kg for cyanides amenable to chlorination (EPA 1988c).

Conducted in the presence of sodium hydroxide and sodium hypochlorite, the chemical oxidation method commonly referred to as alkaline chlorination is the most widely used commercial method for treating cyanide-containing wastes. This method results in the conversion of the cyanide solution to the less toxic cyanate. Depending on the cyanides present, the product will be a sludge or solution, which when sufficient reaction time has been allowed, will largely be devoid of free cyanide (IRPTC 1985).

The alkaline chlorination process has been applied to the removal of cyanide from waste waters and slurries generated as a consequence of cyanide heap leaching gold and other precious metals from low grade ores (EPA 1994c). However, few mining sites currently use this technology. Instead, cyanide in waste water or spent ore heaps is converted to cyanate through reactions with sulfur dioxide, ferrous sulfate, or hydrogen peroxide. These processes have been shown to effectively lower cyanide concentrations to levels that are within federal and state limits for discharge from the mining site (EPA 1994c). A limitation of the technique is that it does not remove free chlorine, chloramines, or iron cyanides, which are toxic to fish. Other approaches that have demonstrated good efficiencies for removing cyanide from spent ore heaps and waste water include precipitate from leachate through reaction with cuprous ions, reaction of cyanide ion with sulfur dioxide, or biodegradation of cyanide (Akcil and Mudder 2003; EPA 1994c). The sulfur dioxide method is limited by an inability to remove thiocyanate, cyanate, and ammonia, which are toxic to fish, and may not provide sufficient removal efficiencies to meet local permit requirements (EPA 1994c). Biodegradation of cyanide in waste water and leachate is effective on soluble forms of cyanide, but may not be effective on degrading cyanide bound in metal complexes (EPA 1994c).

Cyanide salts should not be treated with acid in preparation for disposal or flushed into drains that may contain or subsequently receive acid waste. Acidification is not a recommended method of treatment prior to disposal because of the liberation of hydrogen cyanide. Similarly, incineration of cyanides must proceed with caution and is not recommended unless extensive equipment capable of safely handling liberated hydrogen cyanide is available (IRPTC 1985). Of the cyanide compounds included in this profile, only hydrogen cyanide and cyanogen chloride are listed as potential candidates for rotary kiln incineration or fluidized bed incineration (HSDB 2004).

The biodegradation of cyanides has been investigated, with varying results, for several industrial processes, and additional research in this area would be valuable. While investigations of the potential for microbial species found in mineral processing waste waters demonstrate effective removal of cyanide, metal complexed cyanide, and thiocyanate (Boucabeille 1994b; EPA 1994c), complex cyanides did not appear amenable to biodegradation at gasworks sites (Thomas and Lester 1993). Application of formaldehyde to electroplating waste under basic conditions can convert the cyanide anion to substituted acetates in addition to recovering copper and silver as free metals with formaldehyde reduction (Tucker and Carson 1985). Calcium or sodium polysulfide treatment converts some cyanide wastes into less toxic thiocyanate (Higgins and Desher 1988). These examples suggest that typical treatments involve the decomposition of cyanides to less toxic compounds by physical or chemical processes. More than 97% of cyanide is typically removed from waste waters by alkaline chlorination, electrolysis, or ozonation process. Cyanide from some wastes can be removed by ion-exchange resins. After using an appropriate treatment method such as those described above, cyanide wastes may be disposed of in a secured sanitary landfill (Grosse 1986; Higgins and Desher 1988; Tucker and Carson 1985). Disposal by injection of high-pH cyanide wastes into sandstone was investigated by Scrivner et al. (1986). Currently, the injection of waste water containing hydrogen cyanide and cyanide compounds through underground injection is a major method for disposal of these wastes. The available data indicate that in 2003, 1.56 million pounds of hydrogen cyanide and 2.94 million pounds of cyanide compounds were disposed of by underground injection (see Section 6.2 and Tables 6-1 and 6-2) (TRI03 2004).

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6. POTENTIAL FOR HUMAN EXPOSURE

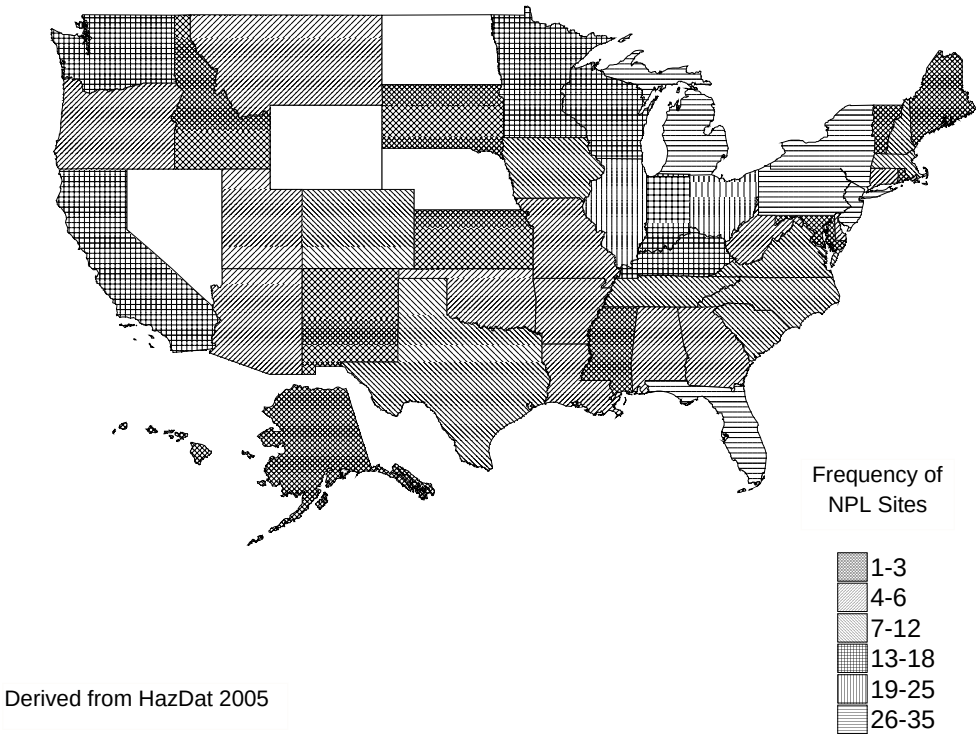
6.1 OVERVIEW

The term cyanide in this Toxicological Profile means a compound that contains the cyanogen (CN) radical. Since the CN portion of the compound is of concern in poisons, any reference to the amount present in air, water, soil, sediments, or other media refers only to this part of the compound. The term free cyanide refers to hydrogen cyanide and cyanide ion (CN^-) (EPA 1981e; Oudjehani et al. 2002; Shifrin et al. 1996; WHO 2004b).

Cyanide (reported as cyanide, hydrogen cyanide, sodium cyanide, potassium cyanide, or copper (I) cyanide) has been identified in at least 464 of the 1,662 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (HazDat 2005). However, the number of sites evaluated for cyanide is not known. The frequency of these sites can be seen in Figure 6-1. Of these sites, 462 are located within the United States, 1 is located in Guam (not shown), and 1 is located in the Commonwealth of Puerto Rico (not shown).

Anthropogenic (of human origin) sources are responsible for much of the cyanide in the environment. Cyanide-containing substances also occur naturally in the fruits, seeds, roots, and leaves of numerous plants, and are released to the environment from natural biogenic processes from higher plants, bacteria, and fungi (Cicerone and Zellner 1983; Crutzen and Carmichael 1993; EPA 1981e; Jones 1998; Knowles 1988; Mudder and Botz 2000). However, an estimate of the amount of cyanide released to the environment from natural biogenic processes is not available. The major cyanide releases to water are discharges from metal-finishing industries, iron and steel mills, and organic chemical industries (EPA 1981e). Effluents from the cyanidation process used in precious metal extraction contain high amounts of cyanide (EPA 1994c; Huiatt 1985; Scott 1985). The contribution of this source to the total cyanide discharge in water is insignificant on average (EPA 1981e). However, large, short-term releases can occur from the failure of tailing ponds resulting in the introduction of high concentrations of cyanide into local surface waters and subsoils (Fields 2001; Mudder and Botz 2000). Vehicle exhaust (EPA 1981e) and biomass burning (Crutzen and Carmichael 1993; Lobert and Warnatz 1993) are major sources of cyanide released into the air. The major sources of simple and complex cyanide releases to soil appear to be from the disposal of cyanide wastes in landfills and the use of cyanide-containing road salts (EPA 1981e; Gaffney et al. 1987). Cyanogen chloride is formed in drinking water from reaction of humic

Figure 6-1. Frequency of NPL Sites with Cyanide Contamination



substances with chloramine produced during chlorination (Jacangelo et al. 1989; Ohya and Kanno 1987). Thiocyanate is released to water primarily from discharges of industrial waste waters from coal processing and extraction of gold and silver (Boucabeille et al. 1994a); the thiocyanate is formed from the reaction of sulfur donors that are present in coal and crushed rock with the cyanide that is used in the processing of these materials. Thiocyanate is also found in mining waste waters where it results from the interaction of the cyanide anion (CN^-) with sulphur (Boucabeille et al. 1994b). Releases of thiocyanate to soil result from anthropogenic and natural sources. Anthropogenic releases occur primarily from direct application in herbicidal formulations and from disposal as byproducts from industrial processes. Nonanthropogenic sources include damaged or decaying tissues of plants from the family *Brassica* (e.g., cabbage, mustard, kale) (Brown and Morra 1993).

Cyanide is released into air mainly as hydrogen cyanide gas and, to a lesser extent, as particulate cyanides. Hydrogen cyanide can potentially be transported over long distances before reacting with photochemically generated hydroxyl radicals. The residence time of hydrogen cyanide in the atmosphere has been estimated to be approximately 2.5 years, with a range of 1.3–5.0 years, depending on the hydroxyl radical concentration (Cicerone and Zellner 1983). Neither photolysis nor deposition by rainwater is expected to be a significant removal mechanism. Only 2% of the tropospheric hydrogen cyanide is expected to be transported to the stratosphere (Cicerone and Zellner 1983). In water, cyanide occurs most commonly as hydrogen cyanide. Hydrogen cyanide is expected to be removed from water primarily by volatilization. Cyanide may also be removed by aerobic or anaerobic biodegradation (Akcil and Mudder 2003; EPA 1979, 1994c). At soil surfaces, volatilization of hydrogen cyanide is a significant loss mechanism for cyanides. In subsurface soil, cyanide at low concentrations would probably biodegrade under both aerobic and anaerobic conditions. In cases where cyanide levels are toxic to microorganisms (i.e., landfills, spills), the concentrations of water-soluble cyanides may be sufficiently high to leach into groundwater.

The environmental fate of thiocyanate has not been thoroughly investigated. Aerobic and anaerobic biodegradation are significant transformation processes for thiocyanates in water (Boucabeille et al. 1994a, 1994b; Shivaraman et al. 1985) and soil (Brown and Morra 1993). At near-ambient temperatures, sorption and volatilization are not significant partitioning processes for thiocyanate in soil (Brown and Morra 1993).

Despite the various ways cyanide is thought to be released into the environment, available monitoring data are limited. The available data indicate that the general population is exposed to cyanide primarily

by ingestion of foods that contain substances that release cyanides when ingested and through smoking, and to a lesser extent, by consumption of contaminated drinking water and inhalation of contaminated air. Dermal absorption is not a significant exposure route for the general population. The concentration of cyanide in the northern hemisphere's non-urban troposphere ranges from 160 to 166 ppt (ppt = parts per trillion) (Cicerone and Zellner 1983; Jaramillo et al. 1989). The mean cyanide concentration in most surface waters is not greater than 3.5 μg/L (EPA 1981e). The cyanide content in certain varieties of lima beans can be as high as 3 mg/g (Honig et al. 1983), although values between 0.10 and 0.17 mg/g are common in U.S. lima beans (EPA 1978c). Much lower cyanide concentrations in various cereal grains and cereal products have been reported, ranging from 0.001 to 0.45 μg/g (Honig et al. 1983). Mean cyanide concentrations in soybean products have been found to range from 0.07 to 0.3 μg/g, whereas the mean cyanide concentration in soybean hulls was 1.24 μg/g (Honig et al. 1983). Due to the lack of data on cyanide content in total diet samples, the average daily intake could not be estimated.

Cyanogen chloride has been measured in drinking water with a concentration ranging between 0.45 and 0.80 μg/L (Krasner et al. 1989).

Available monitoring data on thiocyanate are also very limited. No information was found in the available literature on major routes of exposure among the general population or on estimates of exposure. Because thiocyanate is a major metabolite of cyanide in the body, exposure to cyanide is a source of thiocyanate exposure. Thiocyanate occurs naturally in many edible plants. Vegetables in the family *Brassica* contain high levels of thiocyanate with concentrations ranging up to 660 μg/g, whereas other commonly consumed vegetables (e.g., spinach, radishes, celery) generally contain thiocyanates at concentrations <2 μg/g. Thiocyanate concentrations in milk and other dairy products and in meat have been reported to be <1–9.0 and 0.5–0.7 μg/g, respectively (Weuffen et al. 1984). Thiocyanate concentrations in coal plant waste waters (Jensen and Tuan 1993) and mining waste waters (Boucabeille et al. 1994b) have been found to be 100–1,500 and 300–450 mg/L, respectively. No data were found in the available literature on thiocyanate concentrations in surface, ground, or drinking waters. Soils treated with rapeseed meal (from the family *Brassica*) contained thiocyanate at concentrations on the order of 6 μg/g (Brown et al. 1991).

It should be noted that the amounts of cyanide or thiocyanate found by chemical analysis are not necessarily the amounts that are bioavailable.

Among the general population, subpopulations with the most likely potential of exposure to cyanide at concentrations higher than background levels include active and passive tobacco smokers (EPA 1981e) and individuals who are exposed to house fires or other types of building fires (Andrews et al. 1989; Bolstad-Johnson 2000). Subpopulations with potential for exposure to cyanides or thiocyanates are residents who live near industrial sites releasing these compounds to the environment, residents who live near cyanide- or thiocyanate-containing hazardous waste sites, and people who consume foods high in cyanogenic glycosides. Fetuses of smoking mothers or mothers exposed to high levels of environmental smoke may also be at risk of exposure to relatively high concentrations of cyanide and thiocyanate (Bottoms et al. 1982; EPA 1992f; Hauth et al. 1984). For example, mean thiocyanate concentrations of 88.6 and 32.0 μg/L have been measured in fetal blood of mothers who smoked or were exposed to passive smoke, as compared to a mean thiocyanate concentration of 24.3 μg/L in unexposed mothers (Bottoms et al. 1982).

Occupational exposures to cyanide occur primarily through inhalation and, less frequently, through dermal absorption. Estimates from the National Occupational Exposure Survey (NOES) conducted by the National Institute for Occupational Safety and Health (NIOSH) indicate that over 250,000 workers are potentially exposed to cyanide compounds, including cyanogen chloride (NIOSH 1989a). Workers may be exposed to cyanides in various occupations, including electroplating, metallurgy, pesticide application, firefighting, steel manufacturing, gas works operations, and metal cleaning (EPA 1981e; WHO 2004b). The manufacture of industrial inorganic chemicals may be a potential source of occupational exposure to cyanogen chloride (NIOSH 1989a). Potential sources of occupational exposure to ammonium thiocyanate include the manufacture of electronic computing equipment, research and development laboratories, newspaper and other commercial printing, general medical and surgical hospitals, production of adhesives and sealants, and the construction and furniture industries (NIOSH 1989a). Potential occupational exposures may also occur during the direct application of herbicidal formulations (e.g., amitrol-T, a mixture of ammonium thiocyanate and amino-1,2,4-triazole) and from handling, treatment, or disposal of thiocyanate-containing wastes from industrial processes (Brown and Morra 1993).

6.2 RELEASES TO THE ENVIRONMENT

The Toxics Release Inventory (TRI) data should be used with caution because only certain types of facilities are required to report (EPA 2005b). This is not an exhaustive list. Manufacturing and processing facilities are required to report information to the TRI only if they employ 10 or more full-time employees; if their facility is included in Standard Industrial Classification (SIC) Codes 10 (except 1011,

1081, and 1094), 12 (except 1241), 20–39, 4911 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4931 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4939 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4953 (limited to facilities regulated under RCRA Subtitle C, 42 U.S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited to facilities primarily engaged in solvents recovery services on a contract or fee basis); and if their facility produces, imports, or processes ≥25,000 pounds of any TRI chemical or otherwise uses >10,000 pounds of a TRI chemical in a calendar year (EPA 2005b).

6.2.1 Air

Cyanide emissions into the air have been conservatively estimated at 44 million pounds/year based on data obtained during the mid-to-late 1970s. Over 90% of these emissions were attributed to releases from automobile exhaust. The second largest source of cyanide emission to the air was reported to be from the manufacture of methyl methacrylate, acrylonitrile, and hydrogen cyanide (EPA 1981e). From data acquired from the California Air Resources Board (ARB), it is estimated that 1.2 million pounds of hydrogen cyanide were released into air from industrial sources (CEPA 1997). Other smaller sources of cyanide release include emissions from iron and steel production, coal combustion (EPA 1981e), petroleum refineries (EPA 1981e), oil shale retorting processes (Hargis et al. 1986; Sklarew and Hayes 1984), municipal solid waste incinerators (Carotti and Kaiser 1972; Greim 1990), the combustion of acrylonitriles or other nitrogen-containing plastics (Brandt-Rauf et al. 1988; EPA 1981e), cigarette smoke (Baker and Proctor 1990; EPA 1981e; Guerin et al. 1987), volatilization from cyanide waste disposed of in landfills, and direct release to the atmosphere from certain agricultural pest control activities (EPA 1981e). In 1976, an estimated 137,000 pounds of cyanide was released in the air from agricultural pest control, 18,000–180,000 pounds from incineration, and 13,000–750,000 pounds from cigarette smoke (EPA 1981e). The production of coke or other coal carbonization processes also release hydrogen cyanide into the atmosphere (Cicerone and Zellner 1983). Release of hydrogen cyanide from cyanidation processes used in the extraction of precious metals from their ores was estimated to be 22 tons/year in the United States in 1992, or 20,000 tons worldwide (Korte and Coulston 1995). Hydrogen cyanide is also released into the atmosphere from natural biogenic processes from higher plants, bacteria, and fungi (Cicerone and Zellner 1983; Crutzen and Carmichael 1993; EPA 1981e; Knowles 1988; Mudder and Botz 2000; WHO 2004b). However, an estimate of the amount of hydrogen cyanide released from natural biogenic sources is not available (Cicerone and Zellner 1983; WHO 2004b). Crutzen and Carmichael

(1993) have recently suggested that biomass burning represents an important source of atmospheric hydrogen cyanide. The combined worldwide emissions of hydrogen cyanide and acetonitrile due to biomass burning have been estimated to range from 0.5 to $1.7x10^{12}$ g of N/year (≈1.1–3.7 billion pounds per year) (Crutzen and Andreae 1990). These estimates were based in part on highly uncertain global estimates of worldwide amounts of burned fuel and area and, consequently, have a high degree of uncertainty. Lobert and Warnatz (1993) have estimated that low molecular weight nitriles, primarily hydrogen cyanide and acetonitrile, represent about 4% of the nitrogen balance of biomass fires and contribute a major amount to their global atmospheric source.

The amount of hydrogen cyanide released to the atmosphere in 2003 by U.S. industrial facilities sorted by state is given in Table 6-1 (TRI03 2005). According to TRI03 (2005), an estimated total of 1.14 million pounds (approximately 517 metric tons) of hydrogen cyanide was discharged into air, amounting to approximately 42.2% of the total amount of hydrogen cyanide released into the environment from manufacturing and processing facilities in the United States in 2003. The release of cyanide compounds (as X^+CN^-, where $X^+=H^+$ or any group where formal dissociation can occur; for example, KCN or $Ca(CN)_2$) into air by U.S. industrial facilities is given in Table 6-2 and sorted by state (TRI03 2005). According to the data given in Table 6-2, it is estimated that 0.313 million pounds (approximately 142 metric tons) of cyanide compounds were released into air in 2003, which amounts to approximately 4.97% of the total environmental release. The TRI data should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list. No information is available in the TRI database for other cyanide and thiocyanate compounds in this profile because these compounds are not included under SARA, Title III, and therefore, are not among the chemicals that facilities are required to report (EPA 1993g, 2001).

6.2.2 Water

There are numerous sources that release cyanide into water. Cyanide is released into water from both point and nonpoint sources. The major point sources of cyanide released to water are discharges from publicly owned treatment works (POTWs), iron and steel production, and organic chemical industries (EPA 1981e). Estimates based on data from the mid-to-late 1970s indicate that these sources account for ≈89% of the estimated 31 million pounds of total cyanide discharged annually to surface waters. Since metal finishing and organic chemical industries are estimated to account for 90% of the influent to POTWs, they are the dominant sources of both direct and indirect discharge of cyanide to water (EPA 1981e). The amount of cyanide released to surface water by U.S. industrial facilities that manufactured or

Table 6-1. Releases to the Environment from Facilities that Produce, Process, or Use Hydrogen Cyanide[a]

		Reported amounts released in pounds per year[b]						
						Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	On-site[j]	Off-site[k]	On- and off-site
AK	1	12,477	0	0	0	12,477	0	12,477
AL	2	5,735	0	0	0	5,735	0	5,735
AR	1	0	0	0	0	0	0	0
CA	6	20,719	0	0	0	20,719	0	20,719
CO	2	8,119	0	0	1	8,120	0	8,120
DE	1	7,100	960	0	0	8,060	0	8,060
ID	1	15,000	0	0	0	15,000	0	15,000
IL	2	8,178	0	0	842	8,178	842	9,020
IN	2	2,963	0	0	0	2,963	0	2,963
KY	1	250	0	0	0	250	0	250
LA	9	64,664	59	0	0	64,723	0	64,723
MA	1	4,241	0	0	0	4,241	0	4,241
MI	1	1,155	0	0	0	1,155	0	1,155
MS	1	28,000	0	0	0	28,000	0	28,000
MT	2	720	0	0	510	1,230	0	1,230
NC	1	0	0	0	0	0	0	0
NH	1	74	0	0	0	74	0	74
NJ	1	290	0	0	0	290	0	290
NV	13	154,182	0	0	320	154,502	0	154,502
OH	2	20,910	0	1,219	0	20,910	1,219	22,129
OK	1	3,409	0	0	0	3,409	0	3,409
PA	1	5,402	0	0	0	5,402	0	5,402
SC	3	31,005	136	0	0	31,141	0	31,141
TN	4	146,700	0	0	0	146,700	0	146,700
TX	23	531,144	452	1,554,533	573	2,086,507	195	2,086,702
UT	1	26,342	0	0	0	26,342	0	26,342
WA	1	440	110	0	0	550	0	550

Table 6-1. Releases to the Environment from Facilities that Produce, Process, or Use Hydrogen Cyanide[a]

		Reported amounts released in pounds per year[b]						
						Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	On-site[j]	Off-site[k]	On- and off-site
WV	2	40,496	0	0	0	40,496	0	40,496
Total	87	1,139,715	1,717	1,555,752	2,246	2,697,174	2,256	2,699,430

[a]The TRI data should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list. Data are rounded to nearest whole number.
[b]Data in TRI are maximum amounts released by each facility.
[c]Post office state abbreviations are used.
[d]Number of reporting facilities.
[e]The sum of fugitive and point source releases are included in releases to air by a given facility.
[f]Surface water discharges, waste water treatment-(metals only), and publicly owned treatment works (POTWs) (metal and metal compounds).
[g]Class I wells, Class II-V wells, and underground injection.
[h]Resource Conservation and Recovery Act (RCRA) subtitle C landfills; other on-site landfills, land treatment, surface impoundments, other land disposal, other landfills.
[i]Storage only, solidification/stabilization (metals only), other off-site management, transfers to waste broker for disposal, unknown
[j]The sum of all releases of the chemical to air, land, water, and underground injection wells.
[k]Total amount of chemical transferred off-site, including to POTWs.

RF = reporting facilities; UI = underground injection

Source: TRI03 2005 (Data are from 2003)

Table 6-2. Releases to the Environment from Facilities that Produce, Process, or Use Cyanide Compounds[a]

		Reported amounts released in pounds per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
AK	4	0	0	0	540,718	0	540,718	0	540,718
AL	6	930	1,569	65	23,000	0	25,499	65	25,564
AR	3	746	0	0	21,955	0	22,701	0	22,701
AZ	3	20	0	0	0	119	20	119	139
CA	15	1,288	533	560	16,501	11	1,821	17,072	18,893
CO	1	10	0	0	3	0	13	0	13
CT	6	945	149	0	0	297	1,094	297	1,391
DE	1	7,100	960	0	0	0	8,060	0	8,060
FL	4	0	0	0	0	0	0	0	0
GA	4	36	9	0	261	0	45	261	306
IA	1	0	0	0	0	0	0	0	0
ID	1	255	5	0	0	0	260	0	260
IL	28	5,521	422	0	35	3,587	5,944	3,621	9,565
IN	14	6,442	13,585	39,006	430,760	0	489,787	6	489,793
KY	7	1,189	337	0	5	0	1,526	5	1,531
LA	3	4	65	605,383	4	0	605,456	0	605,456
MA	4	255	0	0	18	355	255	373	628
MD	1	168	0	0	0	0	168	0	168
ME	2	736	0	0	0	0	736	0	736
MI	15	3,189	6	11,953	12,667	1,325	25,398	3,742	29,140
MN	5	1,841	0	0	0	0	1,841	0	1,841
MO	5	487	5	0	5	0	497	0	497
MS	2	28,000	0	0	0	0	28,000	0	28,000
MT	2	0	0	0	71,000	0	71,000	0	71,000
NC	3	250	0	0	0	250	250	250	500
NH	1	0	47	0	0	0	47	0	47
NJ	5	11,922	1,312	0	20,400	4	14,220	19,418	33,638
NV	21	37,473	0	0	1,416,272	1,025	1,453,745	1,025	1,454,770
NY	10	2,475	270	0	0	0	2,745	0	2,745
OH	22	14,709	168	450,025	1,133	26,900	464,877	28,058	492,936
OK	2	500	5	0	5	250	510	250	760
OR	3	162	5	0	150	0	167	150	317
PA	8	80,089	17,519	0	4,350	0	97,608	4,350	101,958
PR	1	250	0	0	0	0	250	0	250
RI	6	250	250	0	0	746	500	746	1,246
SC	4	512	0	0	0	7,938	512	7,938	8,450

Table 6-2. Releases to the Environment from Facilities that Produce, Process, or Use Cyanide Compounds[a]

		Reported amounts released in pounds per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
SD	2	255	500	0	500	0	1,005	250	1,255
TN	7	2,091	1,135	0	15	0	3,226	15	3,241
TX	18	80,533	1,725	1,829,872	936	0	1,912,143	923	1,913,066
UT	4	16,304	1,300	0	177,278	117	194,882	117	194,999
VA	3	232	190	0	0	8	422	8	430
WA	3	892	110	0	281	0	1,283	0	1,283
WI	6	272	0	0	0	0	272	0	272
WV	2	5,120	9,061	0	221,163	0	14,181	221,163	235,344
Total	268	313,453	51,243	2,936,864	2,959,415	42,931	5,993,686	310,222	6,303,907

[a]The TRI data should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list. Data are rounded to nearest whole number.
[b]Data in TRI are maximum amounts released by each facility.
[c]Post office state abbreviations are used.
[d]Number of reporting facilities.
[e]The sum of fugitive and point source releases are included in releases to air by a given facility.
[f]Surface water discharges, waste water treatment-(metals only), and publicly owned treatment works (POTWs) (metal and metal compounds).
[g]Class I wells, Class II-V wells, and underground injection.
[h]Resource Conservation and Recovery Act (RCRA) subtitle C landfills; other on-site landfills, land treatment, surface impoundments, other land disposal, other landfills.
[i]Storage only, solidification/stabilization (metals only), other off-site management, transfers to waste broker for disposal, unknown
[j]The sum of all releases of the chemical to air, land, water, and underground injection wells.
[k]Total amount of chemical transferred off-site, including to POTWs.

RF = reporting facilities; UI = underground injection

Source: TRI03 2005 (Data are from 2003)

processed cyanide compounds ranged from approximately 0 to 150,000 and 1,100 to 1,090,000 pounds, respectively (TRI88 1990). These data indicate that the industrial discharge of cyanides into surface water and POTWs decreased substantially in 1988 in comparison to the estimated discharge during the 1970s.

The amount of hydrogen cyanide and cyanide compounds released to surface water in 2003 by U.S. industrial facilities sorted by state is shown in Tables 6-1 and 6-2 (TRI03 2005). According to TRI03 (2005), estimated totals of 1,717 and 51,200 pounds of hydrogen cyanide and cyanide compounds, respectively, were discharged to surface water in 2003. These releases amount to approximately 0.064 and 0.81% of the total environmental release of hydrogen cyanide and cyanide compounds, respectively. Hydrogen cyanide and cyanide compounds were also released through underground injection wells at estimated totals of 1,560,000 and 2,940,000 pounds, respectively. These releases amount to 57.7 and 46.6% of the total environmental release of hydrogen cyanide and cyanide compounds, respectively. The TRI data should be used with caution since only certain facilities are required to report. This is not an exhaustive list. No information is available in the TRI database for other cyanide and thiocyanate compounds in this profile because these compounds are not included under SARA, Title III, and therefore, are not among the chemicals that facilities are required to report (EPA 1993g, 2001).

The effluents from the cyanidation process used in the extraction of precious metals from their ores may contain high levels of cyanide (Huiatt 1985; Korte and Coulston 1995; Mudder and Botz 2000; Scott 1985). The total cyanide content of typical tailing pond effluents from gold mill tailing ponds has been reported to range from 0.3 to 310 mg/L (EPA 1994c; Scott 1985). Although the contribution from this source to the total discharge of cyanide into the environment has been estimated to be negligible on average (EPA 1981e), large, short-term releases can occur from the failure of tailing ponds, resulting in the introduction of high concentrations of cyanide into local surface waters and subsoils (Fields 2001; Mudder and Botz 2000). Normally, these cyanide wastes undergo decontamination through the conversion of cyanide to the less toxic cyanate in a chemical oxidation methods commonly referred to as alkaline chlorination. In the method, the cyanide wastes are treated with sodium hydroxide or sodium hypochlorite. Alkaline chlorination is the most widely used commercial method for treating cyanide-containing wastes. Depending on the cyanides present, the product will be a sludge or solution, which, when sufficient reaction time has been allowed, will, in time, largely be devoid of free cyanide (IRPTC 1985). Leachates from solid waste disposal sites are point sources of cyanide release to groundwater (Myers 1983; Venkataramani et al. 1984). No quantitative estimate of the amount of cyanide entering the

groundwater from this point source was located. The nonpoint sources of cyanide released to water are comprised of agricultural and road runoff and atmospheric fallout and washout. The predominant sources of cyanides found in urban runoff samples were reported to be products of gasoline combustion and anticaking ingredients in road salts (Cole et al. 1984). It has been estimated that a maximum of ≈2 million pounds of sodium ferrocyanide, which is used as an anticaking agent in road salts during the winter in the northeastern United States, are washed off from roads into streams and storm sewers (EPA 1981e; Gaffney et al. 1987).

Thiocyanate is released to water primarily from discharges of industrial waste waters from coal processing and extraction of gold and silver (Boucabeille et al. 1994a). Thiocyanate is also found in mining waste waters where it results from the reaction of the cyanide anion (CN^-) with sulphur (Boucabeille et al. 1994b). Thiocyanate has been detected in surface water samples at one of eight hazardous waste sites, and in groundwater samples at five of eight hazardous waste sites where thiocyanate has been detected in some environmental medium (HazDat 2005). The HazDat information used includes data from both NPL and other Superfund sites.

6.2.3 Soil

Estimates of amounts of cyanide released to soil from anthropogenic sources are limited. The largest anthropogenic sources of cyanide releases to soil probably result from the disposal of cyanide wastes in landfills and the use of cyanide-containing road salts (EPA 1981e; Gaffney et al. 1987). In 77 of 124 hazardous waste sites in the United States, the median cyanide concentration in subsoil samples was 0.8 mg/kg (HazDat 2005; WHO 2004b). In the same study, topsoil samples taken from 51 of 91 had median cyanide concentrations of 0.4 mg/kg. In the soils of former manufactured gas plant sites, the concentrations of cyanide compounds in the United States are below 2,000 mg/kg (Shifrin et al. 1996; WHO 2004b). The cyanides in these soils are predominately (97%) in the form of ferrocyanides.

The amount of hydrogen cyanide and cyanide compounds released to land in 2003 by U.S. industrial facilities sorted by state is shown in Tables 6-1 and 6-2 (TRI03 2005). According to TRI03 (2005), an estimated total of only 2,250 pounds of hydrogen cyanide was discharged to land from U.S. manufacturing or processing facilities in 2003. Conversely, an estimated 2.96 million pounds of cyanide compounds were discharged to land in 2003, which amounts to 46.9% of the total release to the environment. An estimated 2,260 and 310,000 pounds of hydrogen cyanide and cyanide compound wastes were transferred off-site (see Tables 6-1 and 6-2) and may be ultimately disposed of on land. The

TRI data should be used with caution since only certain facilities are required to report. This is not an exhaustive list. No information is available in the TRI database for other cyanide and thiocyanate compounds in this profile because these compounds are not included under SARA, Title III, and therefore, are not among the chemicals that facilities are required to report (EPA 1993g, 2001).

Natural biogenic processes of bacteria, fungi, and cyanogenic plants such as sorghum, soybeans, and cassava, also release cyanide into the soil (EPA 1978c; Knowles 1988; WHO 1992, 2004).

Releases of thiocyanate to soil result from anthropogenic and natural sources. Anthropogenic releases occur primarily from direct application in herbicidal formulations (e.g., amitrol-T, a mixture of ammonium thiocyanate and amino-1,2,4-triazole) and from disposal as byproducts from industrial processes. Nonanthropogenic sources include damaged or decaying tissues of plants from the family *Brassica* (e.g., mustard, rape) (Brown and Morra 1993).

6.3 ENVIRONMENTAL FATE

6.3.1 Transport and Partitioning

Because hydrogen cyanide is a gas and has a relatively slow degradation rate in air (see Section 6.3.2), the atmosphere will be the ultimate sink for this compound. Almost all of the hydrogen cyanide released to the atmosphere remains in the lower altitudes (troposphere); only 2% of tropospheric hydrogen cyanide is transferred to the stratosphere (Cicerone and Zellner 1983). Cyanide has the potential to be transported over long distances from its emission source. Despite higher water solubility at saturated pressure, the removal of hydrogen cyanide by rainwater appears to be a negligible partitioning pathway (Cicerone and Zellner 1983). Because hydrogen cyanide is a gas, its removal from air by dry deposition is also likely to be negligible. However, metal cyanide particles, particularly water-soluble cyanide particles, are expected to be removed from the air by both wet and dry deposition.

Volatilization and sorption are the two physical processes that contribute to the loss of cyanide from water. At pH <9.2, most of the free cyanide in solution should exist as hydrogen cyanide, a volatile cyanide form (EPA 1978c). On the basis of Henry's law constant (see Table 4-2) and the volatility characteristics associated with various ranges of Henry's law constant (Thomas 1982), volatilization is a significant and probably dominant fate process for hydrogen cyanide in surface water (EPA 1992f). The most common alkali metal cyanides (e.g., sodium and potassium cyanide) may also be lost from surface

water primarily through volatilization; whereas, the sparingly soluble metal cyanides such as copper (I) cyanide are removed from water predominantly by sedimentation and biodegradation (see Section 6.3.2.2) (EPA 1992f). Variations in the volatilization rate are expected because this process is affected by several parameters including temperature, pH, wind speed, and cyanide concentration (EPA 1979). EPA (1979) summarized the unpublished results of a laboratory study that indicated that the volatilization half-life of hydrogen cyanide from solutions at concentrations of 25–200 µg/L ranged from 22 to 110 hours. First-order kinetics were observed. In outdoor experiments with moderate winds, the rate of hydrogen cyanide loss increased by a factor of 2–2.5. In a study to evaluate the effect of cyanide on biochemical oxidation, there was a 50% loss of 6 ppm (mg/L) cyanide in river water kept in open biochemical oxygen demand bottles (without aeration) at pH 7.4 within ≈10 days (Ludzack et al. 1951). When the bottles were aerated (rate of aeration not given), 50% loss occurred in only ≈10 hours. The kinetics of the rate of loss due to volatilization were not rigorously investigated. The volatilization rate was pH-dependent, with the rate faster at a lower pH. Data indicated that cyanide volatilization is a more important fate process than cyanide loss due to chemical and biodegradation reactions (see Section 6.3.2.2) (Ludzack et al. 1951; Raef et al. 1977a). Because volatilization is not an important fate process for cyanide in groundwater, cyanide would be expected to persist for considerably longer periods of time in underground aquifers than in surface water.

Cyanides are sorbed by various natural media, including clays (Cruz et al. 1974), biological solids (Raef et al. 1977b), and sediments (EPA. 1979). However, additional data are necessary to assess the significance of cyanide sorption to suspended solids and sediments in water. Hydrogen cyanide and the alkali metal cyanides are not likely to be strongly sorbed onto sediments and suspended solids because of their high water solubilities (see Table 4-2). Soluble metal cyanides may show somewhat stronger sorption than hydrogen cyanide, with the extent of sorption increasing with decreasing pH and increasing iron oxide, clay, and organic material contents of sediment and suspended solids (EPA 1979). However, sorption is probably insignificant even for metal cyanides when compared to volatilization and biodegradation (EPA 1979, 1992f).

There are no data available to indicate that simple metal cyanides and hydrogen cyanide bioconcentrate in aquatic organisms (EPA 1979, 1980a, 1985a, 1992f). Bioconcentration factors (BCFs) of 0.73 and 1.62 can be calculated for hydrogen cyanide, using the equation of Veith et al. (1979) for the BCF of a chemical in whole fish (log BCF, 0.85; log K_{ow}, -0.70) and the log K_{ow} values in Table 4-2. Similarly, the calculated BCF for sodium cyanide is 0.47. There is some evidence that certain metal cyanide complexes bioaccumulate in aquatic organisms. Fish from water with soluble silver and copper cyanide complexes

were found to have metal cyanides in their tissues at concentrations ranging up to 168 and 304 µg/g, respectively (wet or dry weight not specified) (EPA 1979). It is difficult to evaluate the toxicologic significance of bioaccumulation of metal cyanide complexes because these compounds are much less toxic than soluble hydrogen cyanide, sodium cyanide, or potassium cyanide (EPA 1992f). There is no evidence of biomagnification of cyanides in the food chain (EPA 1978c). Accumulation of cyanide in food webs is not expected, considering the rapid detoxification of cyanide by most species and the lethal effects of large doses of cyanide (EPA 1978c).

Volatilization of hydrogen cyanide would be a significant loss mechanism for cyanides from soil surfaces at a pH <9.2. Cyanides are fairly mobile in soil. Mobility is lowest in soils with low pH and high concentrations of free iron oxides, positively charged particles, and clays (e.g., chlorite, kaolin, gibbsite), and highest in soils with high pH, high concentrations of free $CaCO_3$ and negatively charged particles, and low clay content (EPA 1979). Although cyanide has a low soil sorption capability, it is usually not detected in groundwater, probably because of fixation by trace metals through complexation or transformation by soil microorganisms (see Section 6.3.2.3) (EPA 1978c). In soils where cyanide levels are high enough to be toxic to microorganisms (i.e., landfills, spills), this compound may leach into groundwater (EPA 1984a). Also, leaching of cyanide into a shallow aquifer can occur, as demonstrated by the high concentration of cyanide (1,200 µg/L) in groundwater sampled from the Biscayne Aquifer in Dade County, Florida, which lies below a solid waste site (Myers 1983).

No information could be found in the available literature on the transport and partitioning of cyanogen chloride in the environment, or its partitioning coefficients (K_{oc}, K_{ow}) or Henry's law constants (see Table 4-2). Like cyanogen, cyanogen chloride is a highly volatile gas (see Table 4-2). Therefore, it would be expected that volatilization from water and soil would be a primary route of environmental partitioning for both cyanogen and cyanogen chloride.

Similarly, little information could be found in the available literature on the environmental transport and partitioning of thiocyanate in the environment. At near ambient temperatures (≈30 °C), it appears that sorption and volatilization are not significant partitioning processes for thiocyanate in soil, with thiocyanate losses due primarily to microbial degradation (see Section 6.3.2.3) (Brown and Morra 1993).

6.3.2 Transformation and Degradation

The various cyanide compounds included in this profile undergo a number of different transformation and degradation reactions in the environment as discussed in the following sections. The resulting environmental transformation products within different media are shown in Table 6-3.

6.3.2.1 Air

Most cyanide in the atmosphere exists almost entirely as hydrogen cyanide gas, although small amounts of metal cyanides may be present as particulate matter in the air (EPA 1984a). Hydrogen cyanide is very resistant to photolysis at wavelengths of normal sunlight (EPA 1979). The most important reaction of hydrogen cyanide in air is the reaction with photochemically-generated hydroxyl radicals and subsequent rapid oxidation to carbon monoxide (CO) and nitric oxide (NO); photolysis and reaction with ozone are not important transformation processes, and reaction with singlet oxygen ($O\ ^1D$) is not a significant transformation process except at stratospheric altitudes where singlet oxygen is present in significant concentrations (Cicerone and Zellner 1983). The rate of hydroxyl radical reaction with hydrogen cyanide in the atmosphere depends on the altitude, and the rate of the reaction is at least an order of magnitude faster at lower tropospheric altitudes (0–8 km) than at upper tropospheric altitudes (10–12 km) (Cicerone and Zellner 1983). Based on a reaction rate constant of $3x10^{-14}$ cm^3/(molecule-sec) at 25 °C (Fritz et al. 1982) and assuming an average hydroxyl radical concentration of $5x10^5$ molecules/cm^3, the residence time for the reaction of hydrogen cyanide vapor with hydroxyl radicals in the atmosphere is ≈2 years. This value compares well with the atmospheric residence time derived by Cicerone and Zellner (1983) of approximately 2.5 years, with a range of 1.3–5.0 years, depending on the hydroxyl radical concentrations assumed. Using the equation $t_{½} = 0.693\tau$ for converting residence time (τ) to half-life ($t_{½}$) (Lyman 1982) and an estimated atmospheric residence time for hydrogen cyanide of 2–3 years, and assuming first-order kinetics for the reaction of hydrogen cyanide with hydroxyl radicals, an atmospheric half-life of 1.4–2.9 years can be calculated for hydrogen cyanide.

Cyanogen is reactive and does not persist in the environment unchanged (EPA 1978c). Cyanogen reacts slowly with water to yield hydrogen cyanide and cyanic acid (HOCN) among other products (EPA 1979) and this hydrolysis reaction may be a possible atmospheric degradation pathway. Cyanogen has also been shown to react with hydroxyl radicals in the gas phase (Atkinson 1989). Based on a rate constant of $2.5x10^{-15}$ cm^3/(molecule-sec) at 27 °C and assuming an average hydroxyl radical concentration of $5x10^5$ molecules/cm^3, the residence time for the reaction of hydrogen cyanide vapor with hydroxyl

Table 6-3. Environmental Transformation Products of Cyanide Compounds by Medium

Parent compound	Product(s)	Comments	Reference
Air			
HCN	$HOCN + HO_2$ (unlikely) $NO + CHO^-$ (formed in minutes)	HNC-OH intermediate	Cicerone and Zellner 1983
	$NO + CHO^-$ (formed in minutes)	HCN-OH intermediate	Cicerone and Zellner 1983
Cyanogen	HCN, cyanic acid (NCOH), and other compounds	In the presence of water; slow reaction	EPA 1979
Water			
HCN	$NH_4^+ + HCOO^-$ in equilibrium with $H_2NCHO + H_2$	pH dependent (pH <1, $t_{1/2}$=10–1,000 hours)	EPA 1979
	$NH_4^+ + HCOO^-$	Alkaline hydrolysis; very slow reaction	
CN^-	Metal cyanides	In the presence of excess metals; alkali metal cyanides very soluble; alkaline earth metal cyanides not very soluble	EPA 1979, 1992f
	Complex metallocyanides	Excess CN^- in the presence of metals; solubilities of metallocyanides vary	EPA 1979, 1992f
	>99% HCN	pH<7	EPA 1978c
CN^-	$NH_3 + CO_2$ (NH_3 converted to nitrite and nitrate in presence of nitrifying bacteria)	Aerobic biotransformation	Richards and Shieh 1989
	$N_2 + CO_2$	Anaerobic biotransformation under denitrification conditions	Richards and Shieh 1989
HCN/CN^- salts	Thiocyanate (SCN^-), $NH_3 + CO_2$, $CHOO^-$	Biotransformation	EPA 1978c
Cyanogen	HCN, cyanic acid (NCOH), and other compounds	Slow reaction at pH 7; 5.25 hours at pH 8.5	EPA 1979; Munro et al. 1999; U.S. Army 1989
Metallocyanides	CN^- (possibly)	Photolysis	EPA 1979
	Isocyanate (OCN^-)	Oxidation	EPA 1992f
	$CO_2 + N_2$	In the presence of strong oxidizing agents	EPA 1992f
SCN^-	HCN	In acidic media	EPA 1979

Table 6-3. Environmental Transformation Products of Cyanide Compounds by Medium

Parent compound	Product(s)	Comments	Reference
Sediment and Soil			
CN^-	Metallocomplexes	Abiotic transformation in the presence of metals	EPA 1978c
	$NH_3 + CO_2$ (NH_3 converted to nitrite and nitrate in presence of nitrifying bacteria)	Aerobic biotransformation (predicted from fate in waste water)	Richards and Shieh 1989
	$N_2 + CO_2$	Aerobic biotransformation under denitrification conditions (predicted from fate in waste water)	Richards and Shieh 1989
SCN^-	COS (possibly; microbial degradation pathway not known)	Microbial degradation	Brown and Morra 1993
Waste water/sludge			
CN^-	$NH_3 + CO_2$ (NH_3 converted to nitrite and nitrate in presence of nitrifying bacteria)	Aerobic biotransformation	Richards and Shieh 1989
	$N_2 + CO_2$	Anaerobic biotransformation under denitrification conditions	Richards and Shieh 1989
CN^-/metallo-cyanides (including cuprocyanide)	$NH_3 + CO_2$	Microbial degradation in mining waste waters	Boucabeille et al. 1994b
SCN^-	$NH_3 + CO_2 + SO_4^=$	Microbial degradation in mining waste waters	Boucabeille et al. 1994a
	$COS + NH_3$	Microbial degradation in activated sludge	Katayama et al. 1993

radicals in the atmosphere is ≈25 years. Therefore, the reaction of cyanogen with photochemically-induced hydroxyl radicals will not play a significant role in the degradation of this compound in air.

No specific information was found in the available literature on the transformation and degradation of cyanogen chloride or thiocyanates in air. However, cyanogen chloride has been shown to undergo slow hydrolysis in neutral aqueous solution (rate constant at pH 7 of 6.45×10^{-5} $mol^{-1}sec^{-1}$) (U.S. Army 1989). Therefore, hydrolysis of this compound may be a possible atmospheric degradation pathway in air.

6.3.2.2 Water

Cyanide occurs most commonly as hydrogen cyanide in water, although it can also occur as the cyanide ion, alkali and alkaline earth metal cyanides (potassium cyanide, sodium cyanide, calcium cyanide), relatively stable metallocyanide complexes (ferricyanide complex $[Fe(CN)_6]^{-3}$), moderately stable metallocyanide complexes (complex nickel and copper cyanide), or easily decomposable metallocyanide complexes (zinc cyanide $[Zn(CN)_2]$, cadmium cyanide $[Cd(CN)_2]$). The environmental fate of these cyanide compounds varies widely (EPA 1979).

Oxidation, hydrolysis, and photolysis are the three predominant chemical processes that may cause loss of simple cyanides in aquatic media. Certain cyanides are oxidized to isocyanates by strong oxidizing agents; the isocyanates may be further hydrolyzed to ammonia and carbon dioxide (EPA 1978c). However, it has not yet been determined whether such oxidation and subsequent hydrolysis of isocyanate is a significant fate process in natural waters known to contain peroxy radicals (EPA 1992f).

In water, hydrogen cyanide and cyanide ion exist in equilibrium with their relative concentrations primarily dependent on pH and temperature. At pH <8, >93% of the free cyanide in water will exist as undissociated hydrogen cyanide (EPA 1978c). Hydrogen cyanide can be hydrolyzed to formamide, which is subsequently hydrolyzed to ammonium and formate ions (EPA 1979). However, the relatively slow rates of hydrolysis reported for hydrogen cyanide in acidic solution (Krieble and McNally 1929; Krieble and Peiker 1933) and of cyanides under alkaline conditions (Wiegand and Tremelling 1972) indicate that hydrolysis is not competitive with volatilization and biodegradation for removal of free cyanide from ambient waters (EPA 1979).

The alkali metal cyanides are very soluble in water. As a result, they readily dissociate into their respective anions and cations when released into water. Depending on the pH of the water, the resulting

cyanide ion may then form hydrogen cyanide or react with various metals in natural water. The proportion of hydrogen cyanide formed from soluble cyanides increases as the water pH decreases. At pH <7, >99% of the cyanide ions in water are converted to hydrogen cyanide (EPA 1978c). As the pH increases, cyanide ions in the water may form complex metallocyanides in the presence of excess cyanides; however, if metals are prevalent, simple metal cyanides are formed. Unlike water-soluble alkali metal cyanides, insoluble metal cyanides are not expected to degrade to hydrogen cyanide (EPA 1979).

The significance of photolysis in the fate of cyanides in water has not been fully investigated. Hydrogen cyanide and cyanide ions in aqueous solution have been found to be very resistant to photolysis by natural sunlight, except under heterogeneous photocatalytic conditions (EPA 1979; Frank and Bard 1977). Photocatalytic oxidation may not be significant in natural waters, however, because of significant light reduction at increasingly greater depths (EPA 1992f). 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. For example, diurnal changes in free cyanide concentrations in the drainage from spent precious metal ore heaps were found to maximize around mid-day due to the photodissociation of iron and cobalt cyanocomplexes (Johnson et al. 2002). Because of adsorption of ferrocyanide onto soil surfaces and sediment of surface waters, and light scattering in turbid waters in the field, the rate of free cyanide formation from the photolysis of ferrocyanide in runoff and surface water from washout of ferrocyanide in de-icing salt will be slower than from laboratory photolysis with clean water (EPA 1979).

Biodegradation is an important transformation process for cyanide in natural surface waters, and is dependent on such factors as cyanide concentrations, pH, temperature, availability of nutrients, and acclimation of microbes. However, additional data are needed to assess the relative significance of this process in determining the fate of aquatic cyanides (EPA 1979). Although the cyanide ion is toxic to microorganisms at concentrations as low as 5–10 mg/L (Klecka et al. 1985; Malaney et al. 1959), acclimation increases tolerance to this compound (Raef et al. 1977a). A number of pure cultures of microorganisms degrade low concentrations of cyanide under both aerobic and anaerobic conditions (EPA 1978c, 1979, 1992f). However, biodegradation data derived from use of a pure culture are not strictly relevant to natural waters that contain mixed cultures. Mixed microorganisms in sewage sludge or activated sludge acclimated to cyanide also significantly biodegrade concentrations ≤100 mg/L of most simple and complex cyanides (Gaudy et al. 1982; Pettet and Mills 1954; Richards and Shieh 1989; Shivaraman et al. 1985). In a study to evaluate the effect of the cyanide ion on biochemical oxidation conducted in sealed vessels, a 50% loss of cyanide at concentrations ≤6 mg/L in two natural river waters

occurred at times estimated to range from <10 to 24 days (Ludzack et al. 1951). The rate of loss appeared to be linear within this time frame. These data may represent a biodegradation half-life; however, the possibility of loss by chemical reaction was not addressed in this study.

Most of the available information on the mechanisms of biodegradation of cyanides in water comes from studies on the evaluation and use of this process as a means of detoxicifying cyanide-containing wastes (Akcil and Mudder 2003; EPA 1994c; Raybuck 1992). It is known that there is a natural attentuation of the cyanide ion and thiocyanide concentrations in waste waters, for example those obtained gold mill tails, that is due the acclimation of indigenous microflora in the tailings (Akcil and Mudder 2003; Oudjehani et al. 2002; Zagury et al. 2004). A number of microorganisms have been identified that are capable of uptake, conversion, sorption, and/or precipitation of the cyanide ion, cyanate, and thiocyanate, including species of the genera, *Actinomyces, Alcaligenes, Arthrobacter, Bacillus, Micrococcus, Neisseria, Paracoccus, Pseudomonas*, and *Thiobacillus* (Akcil and Mudder 2003). Some of these species, for example *Pseudomonas*, are capable of using the cyanide ion and thiocyanate as the sole source of carbon and nitrogen and therefore, are particularly effective at cyanide degradation. In fact, *Pseudomonas* is the basis of commercial applications for degrading the cyanide ion to ammonia and carbonate in waste waters generated in mining operations that use the cyanide ion to leach gold and other precious metals for low-grade ores (Akcil and Mudder 2003).

Raybuck (1992) has recently reviewed the role of microbes in cyanide degradation and has categorized the microbial enzymes that use the cyanide ion as a substrate according to the following types of reactions: substitution/addition, hydrolysis, oxidation, and reduction. Sulfur transferases such as rhodanese are involved in substitution reactions that result in the conversion of the cyanide ion to the less toxic thiocyanate, whereas pyridoxal phosphate enzymes are involved in substitution/addition reactions that result in production of nitrile derivatives of α-amino acids. These organic nitriles may then be ultimately degraded via enzyme catalyzed hydrolysis to either the corresponding amino acid and ammonia (without formation of the free amide) or the carboxylic acid and ammonia (via formation of the free amide). The cyanide hydratase and cyanidase enzymes catalyze the hydrolysis of the cyanide ion to formamide or formic acid and ammonia, respectively. A strain of *Alcaligenes xylosoxidans subsp. denitrificans* has been found to effectively hydrolyze the cyanide ion concentrations up to 300 mg/L down to very low levels (0.01–0.02 mg/L) and to be resistant to inactivation by chloride, sulfate, iodide, Fe^{+2}, Zn^{+2}, or Ni^{+2} at concentrations of 70 mg/L (Basheer et al. 1992). Thus, these hydrolytic systems are some of the most promising for detoxification of cyanide-containing waste waters (Raybuck 1992). A number of microbial systems have been identified that are capable of direct oxidation or reduction of the cyanide

ion. *Bacillus pumulus*, *Pseudomonas fluorescens*, and *Pseudomonas paucimobili* have all been found to oxidize the cyanide ion to ammonia and carbon dioxide (Meyers et al. 1993). In an aerobic batch bioreactor experiment, *Pseudomonas putida* was found to significantly degrade 4 mM sodium cyanide (cyanide concentration approximately 100 mg/L) to ammonia and carbon dioxide (Chapatwala et al. 1993). Other evidence indicates that formamide and formate are additional transformation products in microbial oxidation of the cyanide ion by this species, inferring that there may be more than one pathway of cyanide biotransformation involved (Kunz et al. 1992; White et al. 1988). Several bacterial species have been identified that are capable of oxidative degradation of metallocyanides (Silva-Avalos et al. 1990). The cyanide oxygenase system involved in this process offers a new technology for the treatment of metal cyanide wastes (Raybuck 1992).

The ferrocyanide complex is not easily biodegradable (Belly and Goodhue 1976; Pettet and Mills 1954). However, when an aqueous solution of potassium ferrocyanide was seeded with pure culture of *Pseudomona aeruginosa*, or *E. coli*, or a mixture of the two bacteria, formation of free cyanide was observed after a delay period of ≈2 days (Cherryholmes et al. 1985). The rate of free cyanide formation, when measured as CN^-, increased with addition of nutrient in water, and a free cyanide concentration ≤4,000 µg/L was detected at the end of 25 days. It was shown that the free cyanide formation was due to biodegradation and not to either photolysis or hydrolysis. The relevance of this study to the fate of ferrocyanide complexes in natural water or industrial effluents is difficult to assess because ferrocyanide concentrations used in these experiments (3,300 mg/L) are rarely encountered in these media.

Biodegradation is also a significant transformation process for thiocyanates in natural waters; however, additional data are needed to assess the relative importance of this process. Like the cyanide ion, thiocyanate is toxic to microorganisms at high concentrations and acclimated cultures have increased tolerance to this compound (Boucabeille et al. 1994a). Laboratory studies have shown that at concentrations up to at least 1.42 g/L, thiocyanate was completely degraded within 4 days to ammonia and sulfate ion (SO_4^{-2}) by an acclimatized co-culture of two bacteria (*Acinetobacter johnsonii* and *Pseudomonas diminuta*) isolated from sludge from an urban sewage treatment plant (Boucabeille et al. 1994a). Thiosulfate ion ($S_2O_3^{-2}$) was identified as the intermediate in this degradation pathway.

Several studies document the biodegradation of mixtures of cyanides and thiocyanate in waste waters (e.g., Akcil and Mudder 2003; Boucabeille et al. 1994b; EPA 1994c; Mudder and Whitlock 1984; Paruchuri et al. 1990; Shivaraman et al. 1985). Under aerobic conditions, the biodegradation of the cyanide ion and thiocyanate initially produces ammonia, which is converted to nitrite and nitrate in the

presence of nitrifying bacteria, whereas anaerobic biodegradation under denitrification conditions may produce nitrogen (Richards and Shieh 1989). Complete biodegradation of simple and metal complexed cyanides and thiocyanate from mining waste waters by various bacteria belonging to the families Pseudomonadaceae, Vibrioniaceae, and Enterobacteriaceae has recently been reported (Boucabeille et al. 1994b). Biodegradation of cyanide and thiocyanate resulted in the formation of ammonia, with or without accumulation of nitrite and/or nitrate, depending on whether a batch, fed-batch, or continuous treatment process was used. Sulphate ions were produced from thiocyanate degradation. Shivaraman et al. (1985) reported the uninhibited microbial degradation of thiocyanate and the cyanide ion to ammonia by acclimatized mixed cultures at cyanide concentrations up to 22.40±1.34 mg/L, whereas Paruchuri et al. (1990) have reported the complete inhibition of microbial degradation of thiocyanate in the presence of 10 mg/L cyanide ion.

Cyanogen reacts slowly with water to produce hydrogen cyanide, cyanic acid, and other compounds (EPA 1979). Cyanogen chloride also hydrolyzes slowly to cyanic acid and hydrochloric acid in water at pH 7, with a rate constant of 6.45×10^{-5} $mol^{-1}sec^{-1}$ (U.S. Army 1989). Hydrolysis of cyanogen chloride is more rapid under acidic and basic conditions, with rate constants of 2×10^{-2} and $6–8 \times 10^{2}$ $mol^{-1}sec^{-1}$ (pH 10), respectively (U.S. Army 1989). The half-life of cyanogen chloride at neutral pH ranges between 1 minute at 45 °C and 10 hours at 5 °C (Opresko et al. 1998). However, volatilization would be expected to be the predominant fate process for both cyanogen chloride and cyanogen in water and, therefore, these compounds are not expected to persist in water.

6.3.2.3 Sediment and Soil

Analogous to the fate of cyanides in water, it is predicted that the fate of cyanides in soil would be dependent on cyanide concentrations, pH, temperature, metal content, concentration of microbes, availability of nutrients, and acclimation of microbes. Cyanide may occur as hydrogen cyanide, alkali metal salts, or as immobile metallocyanide complexes. In soil, cyanide present at low concentrations would biodegrade under aerobic conditions with the initial formation of ammonia, which would be converted to nitrite and nitrate in the presence of nitrifying bacteria. Under anaerobic conditions, the cyanides ion will denitrify to gaseous nitrogen (Richards and Shieh 1989). Upper limits of 200 and 2 ppm (mg/kg CN^-), respectively, have been reported for uninhibited aerobic and anaerobic biodegradation of cyanide in soil (Fueller 1985); however, these limits have not been confirmed in other studies (Thomas and Lester 1993). Cyanide ions in soil are not involved in oxidation-reduction reactions but may undergo complexation reactions with metal ions in soil (EPA 1978c).

No information could be found in the available literature on the transformation of cyanogen or cyanogen chloride in soil or sediment. However, because these compounds are highly volatile gases they are not expected to persist in soils. Additionally, biotic or abiotic degradation would not be expected to be significant fate processes compared to volatilization.

Although the fate of thiocyanate in soil is largely uncharacterized, there is evidence to suggest that thiocyanate is not persistent in soils. Early studies have shown that thiocyanate can undergo both aerobic (Betts et al. 1979) and anaerobic microbial degradation (Betts et al. 1979; Stafford and Callely 1969; Youatt 1954); however, the degradation pathway has not been defined (Brown and Morra 1993). Saturated soils treated with thiocyanate were found to emit carbonyl sulfide (COS) (Minami 1982; Minami and Fukushi 1981). Katayama et al. (1992, 1993) have reported the formation of carbonyl sulfide from the biodegradation of thiocyanate by pure and mixed cultures of *Thiobacillus thioparus.* These species are ubiquitous in soil (Kelly and Harrison 1989). In a recent laboratory investigation of the fate of ionic thiocyanate in six different soils, Brown and Morra (1993) concluded that microbial degradation is the primary mechanism for thiocyanate disappearance at or below 30 °C, with carbonyl sulfide proposed as a possible hydrolysis product. Loss of thiocyanate at higher temperatures (50–60 °C) did not appear to result from microbial degradation; the observed decreases in thiocyanate concentrations of soil extracts with incubation time at elevated temperatures were postulated to result primarily from increased sorption or increased sorption kinetics, but abiotic catalysis of thiocyanate degradation was also noted as a possible cause.

6.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

Reliable evaluation of the potential for human exposure to cyanide depends in part on the reliability of supporting analytical data from environmental samples and biological specimens. Concentrations of cyanide in unpolluted atmospheres and in pristine surface waters are often so low as to be near the limits of current analytical methods. Where levels have been measured in the environment, the values reported for cyanide and thiocyanate must be interpreted with caution. Methods for the analysis of cyanide and thiocyanate have many interferences (EPA 1978d, 1980e, 1996). In addition, samples containing cyanide and/or thiocyanate may not be stable if the samples are not carefully preserved (EPA 1978d, 1980e, 1996; Keith 1991; WHO 2004b). In reviewing data on cyanide levels monitored or estimated in the environment, it should also be noted that the amount of chemical identified analytically is not necessarily

equivalent to the amount that is bioavailable (Oudjehani et al. 2002; Zagury et al. 2004). The analytical methods available for monitoring cyanide in a variety of environmental media are detailed in Chapter 7.

6.4.1 Air

The concentration of hydrogen cyanide in the northern hemisphere's non-urban troposphere ranges from 160 to 166 ppt (Cicerone and Zellner 1983; Jaramillo et al. 1989). Although ambient monitoring data regarding cyanide in air near source areas (e.g., hydrogen cyanide manufacturing industries, coke production industries, waste disposal sites) were not located in the available literature, the hydrogen cyanide concentration in the vicinity of the source areas would be expected to be higher than the non-urban tropospheric concentration. The semiquantitatively measured hydrogen cyanide concentrations in the offgas from shale oil retorting processes ranged from 6 to 39 ppm in one retort at one site; however, hydrogen cyanide was not detected in retorts at another site (Sklarew and Hayes 1984).

Cyanides (reported as cyanide, hydrogen cyanide, sodium cyanide, potassium cyanide, calcium cyanide, or copper(I) cyanide) have been detected at concentrations (measured as cyanide) between 0.00797 and 0.032 mg/m^3 in 6 air samples collected at 5 of 464 hazardous waste sites where cyanides have been detected in some environmental medium (HazDat 2005). The HazDat information used includes data from both NPL and other Superfund sites. No information was found on the detection of cyanogen, cyanogen chloride, or thiocyanates in air at any NPL or other Superfund hazardous waste sites (HazDat 2005). No information could be found in the available literature on the concentrations of cyanogen, cyanogen chloride, or thiocyanates in air at other locations in the United States.

6.4.2 Water

Cyanide has been detected in waste waters from plating industries at concentrations up to 100 g/L (Chen et al. 1994; Grosse 1986); from a textile industry at a maximum concentration of 0.2 mg/L (Rawlings and Samfield 1979); in the primary and secondary effluents from a Los Angeles City waste water treatment plant at mean concentrations of 29±4 and 10±6 µg/L (0.03 and 0.01 mg/L), respectively (Young 1978); and in the final effluent from a Los Angeles County waste water treatment plant at a mean concentration of 240 µg/L (0.24 mg/L) (Young 1978). Waste waters from a mining site storage basin were found to contain cyanide at concentrations of >10 mg/L as simple cyanides; 20–80 mg/L as combined simple cyanides and copper(I) cyanide; 20–190 mg/L as combined simple cyanides, copper(I) cyanide, and

ferrocyanide; and 300–450 mg/L as thiocyanate (Boucabeille et al. 1994b). Waste waters from gold mines have been reported to contain total cyanide and thiocyanate concentrations ranging from 0.5 to 10 mg/L and from 45 to 75 mg/L, respectively (Mudder and Whitlock 1984). Weak acid dissociable (WAD) cyanide was measured in tailing ponds at several Nevada gold mines in 1990; the concentrations ranged from 8.4 to 216 mg/L at the discharge pipe and from 7.8 to 11.3 mg/L at the reclaim area (Henny et al. 1994). In New York State alone, 47 industries discharged 3,877 pounds of cyanide into streams in 1982 (Rohmann et al. 1985). Cyanide has also been found in groundwater below landfills and disposal sites (Agency for Toxic Substances and Disease Registry 1989a; Myers 1983; Venkataramani et al. 1984). A maximum cyanide concentration of 1,200 µg/L (1.2 mg/L) was found in shallow groundwater ≤3 meters below an inactive drum recycling facility in Miami, Florida (Myers 1983). In another example, a maximum cyanide concentration of 52,000 µg/L (52 mg/L) in shallow groundwater (≈3 meters) was measured below an inactive detinning plant near Tampa, Florida (Agency for Toxic Substances and Disease Registry 1998). Cyanide concentrations were found to range from 0.005 to 14.0 mg/L in the leachates from 14 of 43 U.S. landfills with industrial wastes; the "typical" cyanide concentration was reported to be 0.008 mg/L (Venkataramani et al. 1984). Data from the Nationwide Urban Runoff Program as of 1982 indicate that cyanide was found in urban runoff samples collected in 4 of 15 urban areas across the United States: Denver, Colorado; Long Island, New York; Austin Texas; and Bellevue, Washington. Overall, cyanide was detected in 16% of the urban runoff samples collected, at concentrations ranging from 2 to 33 µg/L (Cole et al. 1984).

Cyanide concentrations in run-off obtained from an area that had been burned in a 2000 wildfire that occurred in Tennessee and North Carolina near the Smokey Mountains National Park averaged 49 µg/L (Barber et al. 2003). This is equal to the LC_{50} for cyanide in rainbow trout and is more than an order magnitude greater than the cyanide concentration measured in run-off obtained from unburned areas surrounding the wildfire site. Higher cyanide concentrations were reported in run-off from the Cerro Grande fire that occurred near Los Alamos, New Mexico in 2000 with an average value of 80 µg/L.

Based on data obtained from the EPA STORET database, the mean cyanide concentration in 61% of surface waters tested in the United States is ≤3.5 µg/L and 35 % of surface waters contained cyanide (as CN^-) at concentrations of 3.5–52 µg/L (EPA 1981e). The data also show that 37 of 50 states (74%) have locales where cyanide concentrations in ambient water are >3.5 µg/L. Areas with levels >200 µg/L include portions of southern California, North Dakota, South Dakota, Iowa, northwest Georgia, western New York, and western Pennsylvania (EPA 1981e). It should be noted that these results are applicable only to the period from the late 1970s to the early 1980s. Furthermore, the reliability of some of these

early STORET data may be questionable. Analyses of more recent STORET cyanide data could not be found. Cyanide at a concentration >1 µg/L was detected in water from the Great Lakes (Great Lakes Water Quality Board 1983). The concentration of cyanide in 104 samples collected during 1980 and 1981 at various points on the Ohio River and its tributaries was reported to range from <5 to 80 µg/L (Ohio River Valley Sanitation Commission 1982). The highest concentration was detected in water from Beaver Falls, Pennsylvania.

A survey of 969 water supply systems in the United States in 1970 found the concentration of cyanide to be at or below 0.008 mg/L (EPA 1981e). In 1975, a survey of interstate water supply systems found that in 21 of 297 analyses (7.1%), the concentration of cyanide exceeded the maximum concentration limit (MCL) of 0.2 mg/L (EPA 1981e). In more recent data from the EPA taken from 1993–1998, only 0.2% of public water systems using groundwater exceeded the MCL of 0.2 mg/L (EPA 1999). For public water systems using surface water, there were no reported cyanide concentrations in excess of the MCL. In a nationwide survey of Canadian water supplies, it was found that in 70 cities, the concentration of cyanide was <0.001 mg/L, whereas water samples taken from two cities had a cyanide concentration of 0.011 mg/L (Meranger and Lo 1992).

Cyanides (reported as cyanide, hydrogen cyanide, sodium cyanide, potassium cyanide, calcium cyanide, or copper(I) cyanide) have been detected in surface water samples at 243 of 464 hazardous waste sites (HazDat 2005). Cyanide concentrations in 70 surface water (lake, streams, ponds, etc.) samples ranged between 0.0012 and 120 mg/L with mean and median values of 2.67 and 0.0385 mg/L, respectively. Cyanides have also been detected in groundwater samples at 120 of the 464 hazardous waste sites. Cyanide concentrations in 19 groundwater samples taken from private and public wells ranged between 0.00002 and 300 mg/L with mean and median values of 16.0 and 0.0292 mg/L, respectively (HazDat 2005). Cyanides have also been identified in leachate samples at 43 of 406 hazardous waste sites at concentrations ranging from 0.0017 to 400 mg/L (HazDat 1996). The HazDat information used includes data from both NPL and other Superfund sites.

Cyanogen chloride is formed in drinking water from the reaction of humic substances with chloramine used during chlorination (Jacangelo et al. 1989; Ohya and Kanno 1987). In a mid-1970s EPA survey, cyanogen chloride was detected in drinking water from 8 of 10 U.S. cities (Fielding and Packham 1977). No information could be found in the available literature on the release of cyanogen to water. No information was found on detections of cyanogen or cyanogen chloride in surface water or groundwater at any NPL or other Superfund hazardous waste sites (HazDat 2005).

Cyanogen chloride is formed in drinking water due to reaction of humic substances with chloramine formed during chlorination (Ohya and Kanno 1987). It has been reported that the concentration of cyanogen chloride in drinking water is most influenced by the final disinfectant. The use of chloramine as a final disinfectant produces levels of cyanogen chloride that are 4–15 times higher than levels produced when chlorine is used (Jacangelo et al. 1989; Krasner et al. 1989). Cyanogen chloride was qualitatively detected during a 1975 survey of Cincinnati, Ohio drinking water (Kopfler et al. 1977). A 10-city survey that was conducted as part of the 1974 EPA National Organics Reconnaissance Survey revealed that cyanogen chloride was present in 8 of 10 drinking water supplies analyzed (no quantitative concentration values given) (Bedding et al. 1982). In a 1988 survey of 35 water utilities, the quarterly median cyanogen chloride concentrations in drinking water ranged from 0.45 to 0.80 µg/L (Krasner et al. 1989).

No information could be found in the available literature on the levels of thiocyanate in ground, surface, or drinking water. Thiocyanate is found in concentrations ranging from 100 to 1,500 mg/L in coal plant waste waters (Ganczarczyk 1979; Jensen and Tuan 1993), and from 300 to 450 mg/L in mining (gold extraction) waste waters (Boucabeille et al. 1994b).

6.4.3 Sediment and Soil

Limited information was found in the available literature on concentrations of cyanides in soil or sediments at several hazardous waste sites; however, no information could be found for cyanogen or cyanogen chloride. Maximum total cyanide concentrations in soil, subsoil, and sediments at an inactive detinning plant located near Tampa, Florida, were measured at 1.5, 19, and 0.87 µg/L, respectively (Agency for Toxic Substances and Disease Registry 1998). At the Greenwood Chemical Site in Albemarle, Virginia, a maximum concentration of total cyanides of 2,870 mg/kg soil was measured in 1989 along with a maximum concentration of 84.0 mg/kg in sediments obtained from abandoned waste lagoons (Agency for Toxic Substances and Disease Registry 1999a). The maximum total cyanide concentrations in soil samples taken from the Byron Salvage Yard NPL site and neighboring Dirk Farm waste disposal site were measured at 133 ppm and between 1 and 835 ppm, respectively (Agency for Toxic Substances and Disease Registry 1999b). In general, though, the highly volatile gases hydrogen cyanide, cyanogen, and cyanogen chloride (see Table 4-2) would not be expected to be present in sediment or soil in any appreciable amounts. Also, degradation by microorganisms in soil can convert

cyanide to carbon dioxide, ammonia, and other nitrogen compounds that will rapidly volatilize from soils (CEPA 1997).

Cyanides (reported as cyanide, hydrogen cyanide, sodium cyanide, potassium cyanide, calcium cyanide, or copper(I) cyanide) have been detected at 225 of 464 hazardous waste sites (HazDat 2005). Cyanide concentrations in 60 topsoil (<3 inches depth) samples ranged between 0.0022 and 18,000 mg/kg, with mean and median values of 1,017 and 4.02 mg/kg, respectively. Cyanide concentrations in 91 subsurface soil (>3 inches depth) samples ranged between 0.00024 to 32,300 mg/kg, with mean and median values of 813 and 15.4 mg/kg, respectively. Cyanides were also detected at 118 of 464 hazardous waste sites where cyanides have been detected in some environmental medium (HazDat 2005). Cyanide concentrations in 40 sediment samples (lakes, streams, ponds, etc.) ranged between 0.00006 and 30,700 mg/kg, with mean and median values of 777 and 1.15 mg/kg, respectively. The HazDat information used includes data from both NPL and other Superfund sites.

Cyanogen has been detected in soil samples taken from one hazardous waste site at a concentration of 0.063 ppm (HazDat 2005). Measurements of cyanogen chloride in soil samples at two hazardous waste sites have been conducted; however, concentrations of cyanogens chloride were not reported (HazDat 2005). The HazDat information used includes data from both NPL and other Superfund sites. No other information could be found in the available literature on the concentration of cyanogen or cyanogen chloride in soil.

Monitoring data on thiocyanate concentrations in soils are scarce. Concentrations of thiocyanate in soils amended with defatted seed meal of *Brassica napus L.* (rapeseed) were reported to be on the order of 6 μg/g (Brown et al. 1991). Thiocyanate has been detected in soil samples collected at three of eight hazardous waste sites, and in sediment samples at three of eight hazardous waste sites where thiocyanate has been detected in some medium (HazDat 2005). The HazDat information used includes data from both NPL and other Superfund sites. No information could be found in the available literature on thiocyanate concentrations in sediments.

6.4.4 Other Environmental Media

The primary cyanide source in food is cyanogenic glycosides. Plants containing cyanogenic glycosides can produce hydrogen cyanide by acid hydrolysis or by the action of the enzyme β-glucosidase (EPA 1980a, 1981e; Jones 1998; Seigler 1991). Hydrogen cyanide release can occur either during maceration,

which activates the intracellular β-glucosidase, or in the gut by the action of β-glucosidase produced by microflora. The level of activity of β-glucosidase in the gut depends on the bacterial composition and the pH level (WHO 1992, 2004). There are approximately 60 known cyanogenic glycosides, which differ in their bioavailability (Seigler 1991). For example, cyanide production from the ingestion of seeds containing prunasin does not occur unless the seeds have been crushed. The potential toxicity of cyanogenic plants depends on their ability to release hydrogen cyanide during preparation or digestion at concentrations high enough to be of concern for human health (WHO 1992, 2004).

Over 2,650 plant species can produce hydrogen cyanide (Seigler 1991; Swain et al. 1992). These include edible plants such as almonds, pits from stone fruits (e.g., apricots, peaches, plums, cherries), sorghum, cassava, soybeans, spinach, lima beans, sweet potatoes, maize, millet, sugarcane, and bamboo shoots (EPA 1981e). The cyanogenic glycoside content of a foodstuff is usually expressed as the amount of cyanide released by acid hydrolysis; glycoside concentrations are rarely reported (WHO 1992).

Cyanide levels measured in some foods are as follows: cereal grains and their products, 0.001–0.45 μg/g; soy protein products, 0.07–0.3 μg/g; and lima beans, 0.1–3 mg/g (EPA 1978c; Honig et al. 1983). The cyanide equivalent of total cyanogenic content (i.e., cyanogenic glycosides, cyanohydrins, and hydrogen cyanide) of cassava root has been reported to range from 91 to 1,515 mg/kg hydrogen cyanide (86–1,458 μg/g CN^-) dry weight (d/w) (O'Brien et al. 1992). Cassava is the major starchy food for more than 300 million people in many tropical countries of the world, and many cultivars are toxic (Seigler 1991). Effective processing can reduce the amount of total cyanogen in fresh cassava roots to significantly lower levels in foods ready for consumption (Mlingi et al. 1993; O'Brien et al. 1992). For example, the mean cyanide content in garri (a flour product of grated, pressed, and fermented cassava root pulp) from a city market in Nigeria ranged from 10.6 to 22.1 μg/g dry weight (d/w) (Ukhun and Dibie 1989). A somewhat wider distribution of results was obtained in another recent evaluation of commercial garri from three main garri-producing Nigerian communities (Aletor 1993). The mean total cyanide content (glucosidic plus non-glucosidic) of 38.8% of all samples (n=108) ranged from 0 to 10 mg/kg hydrogen cyanide (0–9.6 μg/g CN^-), whereas 40.7, 12.9, and 7.4% of the samples had mean total cyanide contents of 10–20, 20–30, and 30–40 mg/kg hydrogen cyanide (9.6–19, 19–29, and 29–39 μg/g CN^-), respectively. The mean cyanide content of domestic samples of “sweet” to “bitter” cassava food products in Cameroon was reported to range from 18.6 to 94.9 mg/kg hydrogen cyanide (17.9–91.4 μg/g CN^-) d/w for a dried cassava flour, and from 0.0 to 0.9 mg/kg hydrogen cyanide (0.0–0.9 μg/g CN^-) d/w for a cassava paste (O'Brien et al. 1992). Improper processing of cassava roots may result in maintenance of cyanogenic content of cassava food products at levels that are toxic (Mlingi et al. 1992, 1993; O'Brien et al. 1992).

Cassava is a starch staple, but it is low in protein (Gomez et al. 1988). Low protein intake results in a decrease in available sulfur for conversion of cyanide to thiocyanate (Mlingi et al. 1993; Tylleskar et al. 1992). Hydrogen cyanide concentrations in sorghum leaves have been reported to range from approximately 200 to 1,300 ppm (192–1,250 μg/g CN^-) wet weight (w/w), with higher concentrations observed in early growth stages and at lower levels of phosphorus fertilization (Chand et al. 1992).

In apricot pits, the cyanide concentration may vary from 8.9 to 217 mg/100 g (89–2,170 μg/g) w/w, depending on the type of cultivar, season, and geographic area (Lasch and El Shawa 1981). Swain et al. (1992) reported a mean cyanide concentration in black cherry (*Prunus serotina Ehrh.*) fruits somewhat greater than 3 μmol/seed at maturity, which is equivalent to a mean cyanide content of 78 μg/seed; insufficient information was provided to allow conversion of these results to weight per weight (w:w) units. In a recent laboratory study, Voldrich and Kyzlink (1992) reported cyanide concentrations in canned unpitted fruits (peaches, apricots, plums, and cherries) ranging from 0 to 4 mg/kg (μg/g) w/w, depending on the glycoside content of the raw fruits and the conditions of heat processing. These authors noted that the observed cyanide levels were not negligible relative to an allowable daily intake (ADI) value for cyanide of 0.05 mg/kg body weight. An adult (70 kg body weight) could consume approximately 1 kg of canned fruits with a cyanide content of 4 mg/kg without exceeding this ADI value; however, a safe portion for a child (15 kg body weight) would be only about 180 grams (12 mg/kg). The analysis of 233 samples of commercially available and homemade stone-fruit juices showed that pitted fruit juices had lower cyanide concentrations than unpitted or partially pitted fruit juices, indicating that the pits are the primary sources of cyanides in these juices (Stadelmann 1976). For example, the hydrogen cyanide content of a home-made mixed cherry juice from pitted fruits was 5.3 mg/L, compared to 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 hydrogen cyanide in commercial fruit juices: cherry, 4.6; apricot, 2.2; prune, 1.9; and peach, 2.9. Stadelmann (1976) recommended that the maximum hydrogen cyanide content allowed in fruit juices should be set at a level of 5 mg/L.

Cyanide can also be present in foodstuffs as residues from cyanide fumigation (EPA 1981e). Human exposure to naturally occurring cyanide in foods in the United States is expected to be low compared to certain populations in the Third World that subsist on cassava and similar crops (EPA 1981e).

Edible plants such as kale, cabbage, radishes, broccoli, brussels sprouts, cauliflower, collards, mustard greens, turnips, and kohlrabi contain glucosinolates, are hydrolysed by the endogenous enzyme myrosinase to produce toxic products, including thiocyanate (Abukutsa et al. 1993; Bible and Chong

1975; Bible et al. 1980; Carlson et al. 1985, 1987; Olea and Parras 1992; Olea-Serano et al. 1988). Vegetables from the *Brassica* family (e.g., cabbages, kohlrabi, kale) contain high levels of thiocyanate ranging from 5 to 660 µg/g w/w (Weuffen et al. 1984). Kale leaves have been reported to contain concentrations of potassium thiocyanate at harvest ranging from 447 to 5,067 ppm (µg/g) d/w (equivalent to thiocyanate concentrations of 267–3,035 µg/g d/w) depending on the fertilizer nitrogen source (Abukutsa et al. 1993). Other commonly consumed vegetables (e.g., lettuce, spinach, radishes) have been found to contain thiocyanate at concentrations ranging from approximately 0.1–5.0 µg/g w/w, with concentrations usually <2.0 µg/g w/w (Weuffen et al. 1984). Milk and other dairy products have been reported to contain thiocyanate at concentrations ranging from <1 to 9.0 µg/g, whereas concentrations in meat products have been reported to range from only 0.5 to 0.7 µg/g (Weuffen et al. 1984).

Laetrile (amygdalin), a drug formerly used in clinical trials for the treatment of cancer (Khandekar and Edelman 1979); sodium nitroprusside, a drug used to reduce high blood pressure (Aitken et al. 1977; Vesey et al. 1976); and a series of commercially important, simple, aliphatic nitriles (e.g., acetonitrile, propionitrile, acrylonitrile, n-butyronitrile, maleonitrile, succinonitrile) (Willhite and Smith 1981) release cyanide upon metabolism. These drugs and industrial chemicals have been associated with human exposure to cyanide and have caused serious poisoning and, in some cases, death.

Reported levels of cyanide in tobacco smoke are quite variable. Cyanide levels in mainstream (inhaled) smoke from U.S. commercial cigarettes have been reported to range from 10 to 400 µg per cigarette, with the ratio of cyanide concentration in sidestream smoke to mainstream smoke ranging from 0.006 to 0.27 per cigarette (Chepiga et al. 2000; EPA 1981e). In studies that have included non-U.S. commercial cigarettes, hydrogen cyanide concentrations in mainstream and sidestream smoke ranging from 280 to 550 µg/cigarette and from 53 to 111 µg/cigarette, respectively, have been reported; sidestream/ mainstream ratios of hydrogen cyanide concentrations ranged from 0.06 to 0.50 (Baker and Proctor 1990; Guerin et al. 1987).

Cyanides have been detected in automobile exhaust. The average emission rate was 11–14 mg/mile for cars not equipped with catalytic converters and 1 mg/mile for cars with catalytic converters operating under optimum conditions. Cars with malfunctioning catalytic converters may emit as much or more hydrogen cyanide than cars without such equipment (EPA 1981e).

6.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

The general population may be exposed to cyanide from inhaling air and ingesting food and drinking water contaminated with it. Since most of the cyanide in the air will be present as hydrogen cyanide (see Section 6.3.2.1), the primary inhalation exposure to cyanide will occur from hydrogen cyanide. The concentration of hydrogen cyanide in the air of non-urban areas is ≈160–166 ppt (see Section 6.4.1). Based on an atmospheric hydrogen cyanide concentration of 170 ppt (0.191 mg/m^3) and an average daily inhalation volume of 20 m^3, the inhalation exposure of the general U.S. non-urban, nonsmoking population to hydrogen cyanide is estimated to be 3.8 µg/day. In drinking water, cyanide may be present as cyanogen chloride (see Section 6.4.2). In 1988, the quarterly median cyanogen chloride concentration in drinking water from 35 U.S. water utilities ranged from 0.45 to 0.8 µg/L (0.19–0.3 µg/L cyanide) (Krasner et al. 1989). Based on a daily drinking water consumption of 2 L for a 70-kg adult, the daily intake of cyanogen chloride is estimated to be 0.9–1.6 µg, which is equivalent to 0.4–0.7 µg of hydrogen cyanide. The concentration of cyanide in drinking water in the United States in 1970 was <0.008 mg/L (EPA 1981e). In more recent data obtained from water supply systems in Canada, the concentration of cyanide was below 0.001 mg/L in 70 cities with two cities reporting concentrations of 0.011 mg/L (Meranger and Lo 1992). Using the range of cyanide concentrations given in the Canadian study (0.001–0.011 mg/L) as representative of the general population in the United States and assuming a daily water consumption of 2 L for a 70-kg adult, the daily intake of cyanide is estimated to be 0.002–0.22 mg. EPA has established an MCL of 0.2 mg/L for cyanide in drinking water (see Chapter 8), which is equivalent to a daily intake of 0.4 mg, based on a daily drinking water consumption rate of 2 L for a 70-kg adult (EPA 1991a). Estimates of the cyanide concentration in the total diet of a U.S. adult were not located in the available literature. Therefore, no estimate of daily cyanide intake from food can be made. In the United States, human exposure to cyanide from foods in which it occurs naturally is expected to be low, but is likely to exceed cyanide intake from inhalation of air and ingestion of drinking water (CEPA 1997; EPA 1981e). The EPA has established tolerances for hydrogen cyanide in various foods ranging from 25 to 250 ppm (EPA 1975b) and from 5 to 25 ppm (see Chapter 8). Poitrast et al. (1988) have estimated an overall allowable daily intake of 0.6 mg for cyanide, incorporating an uncertainty factor of 100–1,000 to ensure that the potential for an infant receiving a toxic dose of cyanide from breast milk is quite low.

The dietary cyanide intake of Tukanoan Indians in northwest Amazonia who rely heavily on high (>70% of all foods) cyanide-containing varieties of cassava was estimated to be >20 mg/day (Dufour 1988). Yet, Dufour (1988) did not find physical disorders in Tukanoan Indians attributable to high cassava diets, in contrast to observations related to cassava-consuming populations in Africa. One reason that has been

suggested is that the cassava processing techniques of the Tukanoans are very sophisticated and very effective in reducing the cyanide concentration in the crop. Indeed, it has been shown in several studies of cassava processing techniques used in Africa that the level of hydrogen cyanide can be effectively and reliably reduced by allowing sufficient time for the hydrolysis of cyanogenic glucosides and evaporation of hydrogen cyanide (Ojo and Dean 2002; Onabolu et al. 2002). Another reason that may account for the observed differences in toxicity among different populations is that the variety of cassava may differ between geographical areas (Rosling 1988). When outbreaks of acute cyanide intoxications do occur in African populations that have been found to result from incomplete processing of cassava, resulting in highly elevated cyanide levels in combination with chronic dietary protein malnutrition (WHO 2004b). This occurred when, due to a food shortage, the lengthy sun drying normally used to remove cyanogenic glucosides was replaced by repeated pounding and drying to obtain flour for consumption in 1 day (Mlingi et al. 1992, 1993; Tylleskar et al. 1992).

The primary route of exposure to thiocyanates for the general population appears to be from ingestion of foods in which thiocyanate occurs naturally (e.g., cabbage, kale, spinach, kohlrabi). Estimates of the thiocyanate concentration in the total diet of an adult in the United States were not located in the available literature; however, these would be expected to be quite low. Exposure to cyanide also is a source of thiocyanate exposure because thiocyanate is a major metabolite of cyanide in the human body.

Occupational exposures to cyanide are expected to occur primarily through inhalation and, less frequently, through skin absorption. Preliminary data from the NOES conducted by NIOSH from 1980 to 1983 estimated that the number of workers potentially exposed to cyanide compounds in the United States in 1981–1983 are as follows (NIOSH 1989a): cyanide, 367; hydrogen cyanide, 4,005; sodium cyanide, 66,493; potassium cyanide, 64,244; potassium silver cyanide, 3,215; calcium cyanide, 3,606; copper (I) cyanide, 22,339; ammonium thiocyanate, 90,599; and cyanogen chloride, 1,393. Thiocyanate and cyanogen were not included in the NOES (NIOSH 1989a). These numbers do not include workers potentially exposed to trade-name compounds that contain cyanides or thiocyanates. Workers in various occupations may be exposed to cyanide compounds. People possibly exposed to cyanide include workers involved in electroplating, metallurgy, cyanotype printing, pesticide application, firefighting, steel manufacturing, and gas works operations; workers involved in the manufacture of cyanides, adiponitrile and other simple, aliphatic nitriles, methyl methacrylate, cyanuric acid, dyes, pharmaceuticals, or chelating agents; and people who work in tanneries, blacksmithing, metal cleaning, and photoengraving or photography industries (EPA 1981e; Lucas 1992; WHO 2004b; Willhite and Smith 1981). Workers in the oil shale retorting industry may be exposed to cyanide because the offgas from the retorting process

contains hydrogen cyanide (see Section 6.2.1). There is a reported case of the fatal poisoning of three trawler crew members as they entered a refrigerated compartment containing spoiled fish in which cyanide, in addition to methane and hydrogen sulfide, have been implicated in their deaths (Cherian and Richmond 2000). Medical and emergency personnel (e.g., police and firefighters) who may be involved in resuscitation efforts or removal of gastric contents of postmortem victims of cyanide poisoning are potentially exposed to higher levels of cyanide (Andrews et al. 1989; Bolstad-Johnson et al. 2000; Nolte and Dasgupta 1996). Workers involved in large-scale processing of cassava have been shown to have thiocyanate levels in urine that are 2.2–2.6 times the levels found in individuals who regularly consume cassava products (Okafor et al. 2002). The increased thiocyanate levels in cassava processors are due to inhalation of hydrogen cyanide that is discharged to air during the processing of cassava. The manufacture of industrial inorganic chemicals may be a significant potential source of occupational exposure to cyanogen chloride (NIOSH 1989a). Potential sources of occupational exposure to ammonium thiocyanate include the manufacture of electronic computing equipment, research and development laboratories, newspaper and other commercial printing, general medical and surgical hospitals, production of adhesives and sealants, and the construction and furniture industries (NIOSH 1989a).

In a survey of the plating facility of a national airline conducted by NIOSH in December 1981, the concentrations of hydrogen cyanide in three work areas ranged from 0.001 to 0.004 mg/m^3 (0.0009–0.004 ppm) (NIOSH 1982). The cyanide concentrations in four work areas in a plating facility of an electrical and electronic company in Waynesboro, Virginia, ranged from 0.07 mg/m^3 (0.07 ppm hydrogen cyanide) in a salt pot room to 4.3 mg/m^3 (4.0 ppm hydrogen cyanide) beside a stripping tank (NIOSH 1976). Similarly, the concentration of cyanide in the breathing zone air of workers in a plating facility in Galion, Ohio, was 1.7 mg/m^3 (1.6 ppm hydrogen cyanide) (NIOSH 1978). In a NIOSH survey of a university art department foundry, hydrogen cyanide was detected in the smoke produced during pouring and knockout of castings at a concentration of approximately 4 ppm; hydrogen cyanide was not detected in personal breathing zone samples taken during knockout of castings (Lucas and Salisbury 1992). These levels are all below the NIOSH recommended ceiling limit of 4.7 ppm (NIOSH 1992).

Levels of cyanide and its metabolite thiocyanate in blood serum and plasma, urine, and saliva have been used as indicators of cyanide exposure in humans, particularly in workers at risk of occupational exposures, in smokers or nonsmokers exposed to sidestream or environmental tobacco smoke, in populations exposed to high dietary levels of cyanide, and in other populations with potentially high exposures (see Section 6.7). The correlation between increased cyanide exposure and urinary thiocyanate

levels was demonstrated in workers exposed to 6.4–10.3 ppm cyanide in air (El Ghawabi et al. 1975). In another study, blood cyanide concentrations were found to vary from 0.54 to 28.4 µg/100 mL in workers exposed to approximately 0.2–0.8 ppm cyanide in air, and from 0.0 to 14.0 µg/100 mL in control workers (Chandra et al. 1988). Similar elevations in urinary thiocyanate levels were observed, with concentrations for exposed workers and controls ranging from 0.05 to 2.80 and from 0.02 to 0.88 mg/mL, respectively.

A study of tissue distributions of cyanide in five victims of acute cyanide poisoning found that cyanide concentrations are highest in blood (Zhang et al. 2005). Blood had the highest concentration of cyanide in all the victims, ranging between 0.65 and 30.6 µg/mL. Normalizing cyanide concentrations in liver, kidney, brain, and urine samples to cyanide concentrations in blood, it was found that liver had the next highest concentrations of cyanide, with S/B ratios ranging from 0.24 to 0.35.

The results of several studies that have shown elevated cyanide or thiocyanate concentrations in body fluids of smokers are summarized in Table 6-4. In general, these results indicate that serum cyanide levels (Cardeal et al. 1993; Symington et al. 1987; Tsuge et al. 2000) and plasma, serum, and saliva thiocyanate levels (Banerjee and Muthu 1994; Jarvis 1989; Maliszewski and Bass 1955; Pre and Vassy 1992, 1993; Tsuge et al. 2000; Waage et al. 1992; Yamanaka et al. 1991) could distinguish smokers from nonsmokers and/or light smokers. Pre and Vassy (1992) found that plasma thiocyanate was an indicator of smoking status that was not sensitive to light or passive smoking. However, inhaling smokers were easily distinguished from noninhaling smokers. The authors concluded that a plasma thiocyanate concentration below 20 µmol/L (1,200 µg/L) indicated that passive smoking was very unlikely, whereas concentrations above 80–85 µmol/L (4,600–4,900 µg/L) were a reliable indication of an active inhalation of smoke. Yamanaka et al. (1991) found a correlation between the number of cigarettes smoked per day and the thiocyanate levels in plasma and saliva; however, in apparent contrast to results obtained by Maliszewski and Bass (1955), thiocyanate concentrations in urine of smokers and nonsmokers were not found to be significantly different.

Data on elevated levels of thiocyanate in body fluids resulting from consumption of cyanide-containing foods come primarily from populations in tropical regions that may consume large quantities of improperly processed cyanogenic plants such as cassava (WHO 2004b). Among four populations in Africa known to be exposed to high levels of dietary cyanide because of incomplete processing of cassava during drought periods, urinary thiocyanate concentrations (mean±SE) ranged from 350±39 to 1,120±75 µmol/L (20±2–65±4 mg/L), compared to urinary thiocyanate levels in the normal population of <100 µmol/L (5.8 µg/L) (Mlingi et al. 1992, 1993; Tylleskar et al. 1992). The mean plasma thiocyanate

Table 6-4. Cyanide and Thiocyanate Concentrations (µg/mL)[a] in Smokers and Nonsmokers

	Plasma/Blood		Serum		Saliva		Urine		
Compound	S[b]	NS[b]	S	NS	S	NS	S	NS	Reference
Cyanide									
			2.11 (1.42–3.67)	0.78 (0.44–1.15)					Cardeal et al. 1993[c]
			6.8 (1.3–19.4)	2.9 (0.0–11.7)					Symington et al. 1987[c,d]
	0.27 (0.14–0.41)[e]	0.17 (0.11–0.25)[e]			0.66 (0.13–2.07)[e]	0.38 (0.05–1.20)[e]			Tsuge et al. 2000
Thiocyanate									
			232 (10)	92 (9)					Banerjee and Muthu 1994[f]
	7.1	2.9			142	76	9.0	5.8	Jarvis 1989[g]
	7.1 (6.2–8.6)	2.0 (1.2–2.8)			75.7 (48.4–112.2)	20.3 (9.71–28.7)	12.3 (7.8–17.2)	2.1 (1.1–3.9)	Maliszewski and Bass 1955[c]
	8.7[h] (4.4–21.5)	1.8[i] (0.5–4.4)							Pré and Vassy 1992[f]
	3.3[j] (1.0–4.6)								
			6.6 (1.5)	1.2 (0.3)					Pré and Vassy 1993[f]
	111.2 (1.7–290)[e]	33.5 (6.3–94)[e]			1,655 (270–2,940)[e]	542 (13–1,630)[e]			Tsuge et al. 2000
			(<0.05–0.35)	(<0.05–0.08)					Waage et al. 1992[f,k]
	2.1	3.7			88	33	18	19	Yamanaka et al. 1991[k,l]

[a]Values are means; values in parentheses are ranges or standard deviations
[b]S = smoker; NS = nonsmoker
[c]No statistics reported
[d]As cited in Cardeal et al. 1993
[e]Values are expressed as µM; values in parentheses are ranges.
[f]Results significantly different
[g]Results not significantly different
[h]Inhaling smokers
[i]Nonsmokers including passive smokers
[j]Noninhaling smokers
[k]Values estimated from graphical presentation of data
[l]All results, except urine, are significantly different.

concentration in one of these populations was 335±12 µmol/L (19±1 µg/L), compared to 28±4 µmol/L (1.6±0.2 µg/L) in a control population (Mlingi et al. 1992). Elevated mean serum thiocyanate concentrations (11±3 µg/L compared to reference values of 0.5–4 µg/L) were observed in only one of two populations in which this biomarker was measured (Tylleskar et al. 1992, 1994). There was no apparent explanation for this difference.

High serum thiocyanate concentrations (>180 µmol/L) have been found in Tukanoan Indians on traditional diets. However, the levels of residual cyanide appear to be tolerated well (Dufour 1988).

6.6 EXPOSURES OF CHILDREN

This section focuses on exposures from conception to maturity at 18 years in humans. Differences from adults in susceptibility to hazardous substances are discussed in Section 3.7, Children's Susceptibility.

Children are not small adults. A child's exposure may differ from an adult's exposure in many ways. Children drink more fluids, eat more food, breathe more air per kilogram of body weight, and have a larger skin surface in proportion to their body volume. A child's diet often differs from that of adults. The developing human's source of nutrition changes with age: from placental nourishment to breast milk or formula to the diet of older children who eat more of certain types of foods than adults. A child's behavior and lifestyle also influence exposure. Children crawl on the floor, put things in their mouths, sometimes eat inappropriate things (such as dirt or paint chips), and spend more time outdoors. Children also are closer to the ground, and they do not use the judgment of adults to avoid hazards (NRC 1993).

Information on exposures of cyanide to children living in the United States is mainly limited to studies on side-stream smoke. These studies show that this is an important route of exposure to cyanide for children in households with a resident smoker. Chen et al. (1990) found that serum thiocyanate concentrations of 18-month-old infants heavily exposed to environmental tobacco smoke (>20 cigarettes a day smoked in the home) were significantly higher than those of unexposed infants ($p<0.05$). Mean concentrations (±standard deviation [SD]) in these respective groups were 36.2±14.88 µmol/L (2.1±0.9 µg/mL) and 27.7±10.7 µmol/L (1.6±0.6 µg/mL). Positive correlations between fetal umbilical serum thiocyanate levels and serum thiocyanate levels of smoking mothers (Bottoms et al. 1982; Hauth et al. 1984) and mothers exposed to environmental tobacco smoke in the home (Bottoms et al. 1982) have been reported. Hauth et al. (1984) found that the mean serum thiocyanate concentration (95 µmol/L; 5.5 µg/mL) was significantly higher ($p<0.001$) in smokers than in passive smokers (35.9 µmol/L; 2.1 µg/mL) or

nonsmokers (32.3 µmol/L; 1.9 µg/mL). Similarly, the mean umbilical thiocyanate concentration in the newborn infants of smoking mothers (72 µmol/L; 4.8 µg/mL) was significantly higher than those in newborn infants of passive smokers (26 µmol/L; 1.5 µg/mL) and nonsmokers (23 µmol/L; 1.3 µg/mL). In contrast, Bottoms et al. (1982) found that among newborn infants of nonsmoking mothers, fetal umbilical thiocyanate concentrations increased with passive smoking in the home ($p<0.05$).

For children without exposures to side-steam smoke, their main cyanide exposures are expected to be similar to those noted for the general population in Section 6.5 in air and water. Estimates of the cyanide concentration in the total diet of children in the United States were not located in the available literature. Therefore, no estimate of daily cyanide intake from food can be made. However, in the United States, exposure of children to cyanide from foods in which it occurs naturally is expected to be low, but, as noted for Section 6.5 for the general population, it is likely to exceed cyanide intake from inhalation of air and ingestion of drinking water (EPA 1981e). Based on a concentration of cyanide in U.S. and Canadian drinking water of 0.001–0.011 mg/L, the daily intake of cyanide in children is estimated to be 0.001–0.011 mg, assuming a daily consumption of 1 L of water (EPA 1981e; Meranger and Lo 1992). For cyanide as cyanogen chloride, the daily intake is estimated to be 0.5–0.8 µg, which is equivalent to 0.2–0.4 µg of hydrogen cyanide. This estimate is based on the quarterly median cyanogen chloride concentration in drinking water from 35 U.S. water utilities ranged from 0.45 to 0.8 µg/L (0.19–0.3 µg/L cyanide) (Krasner et al. 1989) and the daily consumption of 1 L of drinking water.

Accidental cyanide poisonings in children are rare and are usually associated with exposures to combustion products in smoke (Riordan et al. 2002). Poisonings have been reported for ingestion of apricot kernels or seeds or candy made from apricot kernels. Because of their lower body weight, children tend to be more susceptible to consumption of apricot kernels than adults, with 10 or more seeds being fatal to a child (WHO 2004b).

6.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Among the general population, subpopulations with the most likely potential for exposure to cyanide and thiocyanate include active and passive smokers (EPA 1981e) and people who are exposed to house or other building fires (Andrews et al. 1989; Ballantyne 1987a; Bolstad-Johnson et al. 2000). Other subpopulations with potentially high cyanide or thiocyanate exposures are residents who live near industrial sites releasing cyanides or thiocyanates into the environment, residents who live near cyanide- or thiocyanate-containing hazardous waste sites, and people who consume foods high in cyanogenic

glycosides. The fetuses of pregnant women who smoke or who are exposed to high levels of environmental smoke (i.e., passive smokers) may be subjected to potentially high exposures of cyanide and thiocyanate (Bottoms et al. 1982; EPA 1992f; Hauth et al. 1984). Workers involved in electroplating, metallurgy, pesticide application, firefighting, gas works operations, tanning, blacksmithing, metal cleaning, photoengraving, photography, cyanotype printing, the manufacture of steel, cyanides, adiponitrile and other nitriles, methyl methacrylate, cyanuric acid, dyes, pharmaceuticals, or chelating agents have the potential to be occupationally exposed to higher concentrations of cyanide than the general population (EPA 1981e; NIOSH 1989a). Workers in the following industries may also be exposed to higher concentrations of thiocyanate than the general population: manufacture of electronic computing equipment, research and development laboratories, newspaper and other commercial printing, general medical or surgical hospitals, production of adhesives and sealants, pesticide application, building and furniture construction, and handling, treatment, or disposal of thiocyanate-containing wastes from industrial processes (Brown and Morra 1993; NIOSH 1989a; WHO 2004b). Two additional groups of people who may be at greater risk for cyanide exposure are those who are exposed to cyanide but are unable to smell the chemical (EPA 1987a) and patients with motor neuron disease (see Section 3.10).

Data related to the levels of cyanide or thiocyanate exposure in several of these population groups have been presented in Section 6.5. No data were found related to the levels of cyanide or thiocyanate exposure in cassava eaters in the United States. Also, no data were located in the available literature related to the levels of cyanide and thiocyanate exposure of people who live near industrial sites releasing cyanides or thiocyanates to the environment, or near hazardous waste sites. Cyanides (reported as cyanide, hydrogen cyanide, sodium cyanide, potassium cyanide, calcium cyanide, or copper (I) cyanide) have been detected in air, surface and groundwater, and soil samples at NPL hazardous waste sites; cyanogen and cyanogen chloride have been detected in soil samples at NPL hazardous waste sites; and thiocyanates have been detected in surface and groundwater, and soil samples at NPL sites (see Section 6.2) (HazDat 2005). There is a need for reliable data on the levels at which these substances are found in various media at these sites in order to estimate potential exposures of people living near hazardous waste sites.

6.8 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of cyanide is available. Where adequate information is not

available, ATSDR, in conjunction with NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of cyanide.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

6.8.1 Identification of Data Needs

Physical and Chemical Properties. As reported in Section 4.2, most of the relevant physical and chemical properties of cyanide compounds are known. Except for soil partition (K_{oc}) coefficient, data for the physical and chemical properties of hydrogen cyanide are available to estimate its environmental fate. Additional data are needed to estimate the environmental fate of the other cyanides covered in this profile. Although qualitative information is available, quantitative data are needed for the solubility of calcium cyanide in water. Octanol/water partition coefficient (K_{ow}) data are needed for cyanogen chloride. Certain physical parameters, such as K_{ow} and K_{oc}, are not available nor are they useful for predicting the environmental fate and transport of the ionic cyanide compounds. These partition coefficients are generally used to assess the partitioning of neutral organic compounds between organic matter and water and are not good at describing the varying ionic or complexation interactions of ionic compounds, such as the simple and metal complexed cyanides and thiocyanate, with water, aquatic biota, soil, or sediments.

Production, Import/Export, Use, Release, and Disposal. According to the Emergency Planning and Community Right-to-Know Act of 1986, 42 U.S.C. Section 11023, industries are required to submit substance release and off-site transfer information to the EPA. The TRI, which contains this information for 2003, became available in May of 2005. This database is updated yearly and should provide a list of industrial production facilities and emissions.

Knowledge of a chemical's production volume is important because it may indicate the magnitude of environmental contamination and human exposure. Data regarding the production, trend, use pattern, and disposal of commercially significant cyanide compounds are available (CMR 2001; Curry 1992; Homan 1987; HSDB 2004; Sittig 1980; SRI 2005; TRI03 2005). It is known that the import and export of

hydrogen cyanide is insignificant compared to its production; however, except for potassium, sodium and calcium cyanide salts, recent import and export data for other individual cyanide compounds are difficult to obtain (USDOC 2004). There are some less recent data regarding the release of cyanides in air (EPA 1981e; TRI88 1990) but, except for hydrogen cyanide (TRI03 2005), more recent quantitative data regarding the release of individual cyanide compounds in air, water, and particularly soil and sediment are unavailable and would be useful for assessing current human exposures to cyanides.

Cyanide is naturally present in many foods high in cyanogenic glycosides (EPA 1978c, 1981e; Honig et al. 1983; Jones 1998). No information was located in the available literature to indicate that cyanide enters foods during processing or that elevated cyanide concentrations are present in any consumer products. The two most likely sources of general population exposure to cyanide include people who inhale cigarette smoke (EPA 1981e) or individuals who are exposed to a house or other type of building fire (Andrews et al. 1989; Ballantyne 1987a; Bolstad-Johnson et al. 2000). There are EPA regulations regarding the disposal of cyanide wastes or OSHA and NIOSH regulations regarding the levels of hydrogen cyanide in workplaces (see Chapter 8). Data is available on chemical and biological processes for degrading cyanide in leachate and waste water generated during the extraction of gold and other precious metals from low grade ore (Akcil and Mudder 2003; EPA 1994c). Additional research is needed on improved methods of pollution prevention and biodegradation to reduce or eliminate releases of cyanide compounds to the environment from industrial processes.

Environmental Fate. The environmental fate of hydrogen cyanide gas in air is well studied (Cicerone and Zellner 1983; Fritz et al. 1982); however, it would be useful if the role of particulate cyanides (e.g., sodium cyanide, potassium cyanide) in determining the fate of total cyanides in the air was known. Given that hydrogen cyanide occurs in the atmosphere from both natural and anthropogenic processes (Cicerone and Zellner 1983; Crutzen and Andreae 1990; Crutzen and Carmichael 1993; EPA 1981e; Knowles 1988; Lobert and Warnatz 1993), it would be useful if an estimate were available for the contribution of anthropogenic processes to the overall hydrogen cyanide burden in the atmosphere. It is generally known that volatilization and biodegradation will be important processes for the loss of cyanides in water (EPA 1978c, 1979; Ludzack et al. 1951; Raef et al. 1977a), but no experimental or estimated values for the half-life of cyanides in ambient water are available. No comprehensive data regarding the role of sorption in determining the fate of cyanides in water are available. It is generally known that volatilization from soil surfaces and biodegradation play significant roles in the loss of cyanides in soil (EPA 1978c), but no quantitative data regarding the half-life of cyanides in ambient soil are available. Additional data on the relative importance of volatilization and biodegradation in

determining the fate of cyanides in soils are needed. The elucidation of the role of cyanide complexation by metals in soil and sediment in controlling the fate of cyanide would be useful.

Both cyanogen and cyanogen chloride are highly volatile gases, indicating that volatilization would be the major transport pathway for these compounds from surface water and soils. Cyanogen is reactive and does not persist in the environment unchanged (EPA 1979). It also has been reported to react slowly with water to yield hydrogen cyanide and cyanic acid, among other products (EPA 1979), and this hydrolysis reaction may be a possible degradation pathway. Likewise, cyanogen chloride has also been shown undergo slow hydrolysis at neutral pH to form cyanic acid and hydrogen chloride (U.S. Army 1989). Additional information on the environmental fate of cyanogen and cyanogen chloride is needed.
There is almost no available information on the environmental transport and partitioning of thiocyanate in the environment. At ambient temperatures, it appears that sorption and volatilization are not significant partitioning processes for thiocyanate in soil, with thiocyanate losses due primarily to microbial degradation (Brown and Morra 1993); however, additional research is needed in this area. Although biodegradation is a significant transformation process for thiocyanate in water, additional data are needed on the relative importance of this process in determining the fate of thiocyanates in natural water systems.

Bioavailability from Environmental Media. Cyanide is known to be absorbed following inhalation, oral, and dermal contact (Gosselin et al. 1984; Rieders 1971). The environmental factors that may influence the bioavailability of cyanide from contaminated air, water, soil, or plant material have not been studied. Since cyanides are not strongly sorbed to soil and sediments (EPA 1979), the role of sorption may not be significant in determining the bioavailability of cyanides from different soils or waters. The bioavailability of cyanide from an environmental medium is expected to increase if the cyanide is present in water-soluble forms, such as ions or soluble complexes. The pH of a medium may also be significant in determining the bioavailability because hydrogen cyanide gas may be released as the pH of the medium decreases (EPA 1978c, 1979). Data delineating the factors affecting the bioavailability of cyanide compounds from soil and other environmental media need further development, since the absorption studies discussed in Section 3.4.1 have been performed with the pure chemical.

The factors that may influence the bioavailability of thiocyanate from various foods and other environmental media have not been investigated. There is no data need at this time because exposure to thiocyanate from environmental media is expected to be low.

Food Chain Bioaccumulation. Simple cyanide compounds do not bioconcentrate in fish (EPA 1979, 1985a). There is evidence suggesting that the bioconcentration of cyanide metal complexes in fish (EPA 1979). Therefore, it would be useful to determine the bioconcentration potential for cyanide in fish from water exposed to less toxic and water-soluble cyanide complexes. There is no indication of biomagnification of cyanides in aquatic and terrestrial food chains (EPA 1978c). Because of the high toxicity of cyanides at high doses and rapid metabolism at low doses, biomagnification of cyanide in animals seems unlikely.

No information could be found in the available literature on the potential of thiocyanates for bioconcentration or biomagnification in the food web. In the absence of this information, data would be useful to determine the potential for thiocyanate to bioconcentrate and/or biomagnify in a food chain.

Exposure Levels in Environmental Media. Reliable monitoring data for the levels of cyanide in contaminated media at hazardous waste sites are needed so that the information obtained on levels of cyanide in the environment can be used in combination with the known body burden of cyanide to assess the potential risk of adverse health effects in populations living in the vicinity of hazardous waste sites.

Data exist regarding the levels of cyanide in air and drinking water, and these data have been used to estimate human exposure. The concentration of hydrogen cyanide in the air of non-urban areas is ≈160–166 ppt (Cicerone and Zellner 1983; Jaramillo et al. 1989) and the inhalation exposure of the general U.S. non-urban, nonsmoking population to hydrogen cyanide was estimated to be 3.8 µg/day. The chlorination of public drinking water supplies may result in the formation of cyanogen chloride (Jacangelo et al. 1989; Ohya and Kanno 1987). In 1988, the quarterly median cyanogen chloride concentration in drinking water from 35 U.S. water utilities ranged from 0.45 to 0.8 µg/L (Krasner et al. 1989). Based on a daily drinking water consumption of 2 L for a 70-kg adult, the daily intake of cyanogen chloride is estimated to be 0.9–1.6 µg. These data are sufficient to estimate human exposure from air and drinking water, although continued monitoring data in these environmental media would be useful. Cyanide and thiocyanate concentrations in certain foods are known (Abukutsa et al. 1993; EPA 1978c, 1981e; Honig et al. 1983; Pre and Vassy 1992); however, a data need exists to estimate the dietary exposures for the general population to cyanide and thiocyanate from food sources. It will also be useful to develop data that would clearly establish whether cyanides or thiocyanates pose acute or chronic exposure hazards for residents in the vicinity of hazardous waste sites. This information should include data on background concentrations in all media to which a resident might be exposed.

Information on the consumption of cassava in the United States could not be located in the available literature. Therefore, an assessment of cassava consumption in the United States would be needed before recommending a need for data relating to exposure levels of cyanide in cassava consumers.

Exposure Levels in Humans. The levels of cyanide and thiocyanate in various human tissues and body fluids of both control and occupationally exposed groups and of smokers and nonsmokers are available (see Sections 3.4.4, 3.8.1, and 6.5). Although no specific data need exists regarding levels of cyanide and thiocyanate in human biological samples, continued monitoring data are recommended in order to assess current human exposure. Data are available that describe the levels of these chemicals in humans consuming foods containing cyanogenic materials (WHO 2004b). These data are mainly limited to cyanide exposures that result from the consumption of cassava (Dufour 1988; Mlingi et al. 1992; Ojo and Dean 2002; Okafor et al. 2002; Onabolu et al. 2002; Tylleskar et al. 1992, 1994).

This information is necessary for assessing the need to conduct health studies on these populations.

Exposures of Children. Data regarding the exposure of children to side-stream (second-hand) cigarette smoke are available (Bottoms et al. 1982; Chen et al. 1990; Hauth et al. 1984). There are no comprehensive data on the cyanide or thiocyanate content of total diet samples in the United States, so it is not possible to estimate the average daily intake from foods. This is a data need for both children and adult exposures.

Data on exposures of children to cyanides and thiocyanates in the vicinity of hazardous waste sites would be useful to clearly establish whether cyanides or thiocyanates pose acute or chronic exposure hazards to children living near these sites. This information should include data on background concentrations in all media.

Child health data needs relating to susceptibility are discussed in Section 3.12.2, Identification of Data Needs: Children's Susceptibility.

Exposure Registries. No exposure registries for cyanide were located. This substance is not currently one of the compounds for which a sub-registry has been established in the National Exposure Registry. The substance will be considered in the future when chemical selection is made for sub-registries to be established. The information that is amassed in the National Exposure Registry facilitates

the epidemiological research needed to assess adverse health outcomes that may be related to exposure to this substance.

6.8.2 Ongoing Studies

No new or ongoing studies of release, environmental fate and transport, levels monitored in the environment, or human exposures were identified for cyanide or cyanide compounds in the Federal Research in Progress (FEDRIP 2005) database.

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7. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting, measuring, and/or monitoring cyanide, its metabolites, and other biomarkers of exposure and effect to cyanide. The intent is not to provide an exhaustive list of analytical methods. Rather, the intention is to identify well-established methods that are used as the standard methods of analysis. Many of the analytical methods used for environmental samples are the methods approved by federal agencies and organizations such as EPA and the National Institute for Occupational Safety and Health (NIOSH). Other methods presented in this chapter are those that are approved by groups such as the Association of Official Analytical Chemists (AOAC) and the American Public Health Association (APHA). Additionally, analytical methods are included that modify previously used methods to obtain lower detection limits and/or to improve accuracy and precision.

7.1 BIOLOGICAL MATERIALS

Humans may be exposed to cyanide from dietary, industrial, environmental, and other sources. Inhalation of tobacco smoke is an important source of cyanide, and exposure may occur from smoke due to fires. After absorption, cyanide is rapidly distributed in the body through blood. Some of the common methods available for determining cyanide in biological media are reported in Table 7-1. Since cyanide forms volatile hydrogen cyanide gas, tissue sampling techniques, storage, and cyanide analysis must be done with caution. The choice of tissues and the factors influencing measured cyanide concentrations are also important (Ballantyne 1983c, 1987a).

The determination of cyanide in body fluids requires the separation of cyanide from thiocyanate, usually by distillation of cyanides or microdiffusion into an absorber solution. The cyanide is measured spectrophotometrically after a colorimetric reaction involving the cyanide ion and chloramines-T plus pyridine-pyrazolone, *p*-benzoquinone, or *p*-phenylene diamine (see Table 7-1). Detection limits are in the low to mid ppb range (µg/L) (Cruz-Landeira et al. 2000; Ganjeloo et al. 1980; Laforge et al. 1994). Most of these techniques are time-consuming, and some lack specificity or sensitivity. Cyanide in blood is almost exclusively localized to the erythrocytes, whereas thiocyanate is confined to plasma (Lundquist and Sorbo 1989); thus, some researchers recommend analysis of erythrocytes (McMillan and Svoboda 1982; Sano et al. 1992). Some interferences can be mitigated. For example, sodium thiosulfate, a

Table 7-1. Analytical Methods for Determining Cyanide in Biological Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Blood	Separation in a microdiffusion cell; treatment of absorber solution with chloramine T-phosphate and pyridine-pyrazolone reagent	Spectrophotometry (total cyanide)	0.1 ppm	No data	Morgan and Way 1980
Blood	Separation in a microdiffusion cell; treatment of absorber solution with *p*-benzoquinone	Spectrofluorometry (total cyanide)	0.025 ppm	No data	Ganjeloo et al. 1980
Plasma	Deproteinization with trichloroacetic acid; bromination of supernatant and treatment with pyridine-*p*-phenylene diamine	Spectrophotometry (thiocyanate-cyanide determination)	0.07 ppm	96 (thio-cyanate)	Pettigrew and Fell 1972
Erythrocyte suspension	Sample purged; absorption of hydrogen cyanide in sodium hydroxide; conversion of thiocyanate to cyanide by potassium permanganate oxidation	Spectrophotometry (thiocyanate-cyanide determination)	No data	93–97	McMillan and Svoboda 1982
Blood cells	Separation of cells by centrifugation; extraction; derivitization	HPLC with fluorescence detection	2 ng/mL	83	Sano et al. 1992
Blood	Lysis of blood; extraction; derivatization NDA and taurine	Capillary electrophoresis with fluorescence detection	0.1 ng/mL	No data	Chinaka et al. 2001
Blood	Acidification of sample in a sealed vial	Headspace GC/NPD	0.3 µg/mL	No data	Levin et al. 1990
Blood	Acidification of sample; incubation with chloramine-T in sealed vial	Headspace GC/ECD	100 µg/L	No data	Odoul et al. 1994
Blood	Acidification of sample containing $K^{13}C^{15}N$ in a sealed vial; micro-diffusion to NDA derivatization solution	HPLC-MS	5 ng/mL	88.0 (100 ng/mL); 85.7 (500 ng/mL)	Tracqui et al. 2002
Blood	Separation by diffusion; color development	Spectrophotometry	0.07 µg/mL	No data	Laforge et al. 1994

Table 7-1. Analytical Methods for Determining Cyanide in Biological Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Blood	Incubation of acidified sample	GC/NPD	1 ng/mL	No data	Seto et al. 1993
Blood	Separation in a microdiffusion cell; absorption in methemoglobin solution	Spectrophotometric (free cyanide determination)	0.4 µg/mL	80	Tomoda and Hashimoto 1991
Blood	Add $K^{13}C^{15}N$ to blood sample; acidify with phosphoric acid and incubate at 60 °C for 15 minutes	GC/MS	0.008 µg/mL	98	Dumas et al. 2005
Blood and liver	Treatment of HCN released from sample digestion with lead acetate and absorption with NaOH	Specific ion electrode (total cyanide)	5 µg/L	100–109 (whole blood, 0.3–130 ppb)	Egekeze and Oehme 1979
Blood and urine	Separation in a Conway microdiffusion cell; treatment of absorber solution with naphthalene-2,3-dialdehyde and taurine	Spectrophotofluoro-metric	0.8 ppb	66–82.6 at 0.0013–0.13 ppm (blood); 75.6–82 at 0.0013–0.13 ppm (urine)	Sano et al. 1989
Plasma and urine	Sample is acidified with HCl and extracted on a mixed cation exchange column; analyte is eluted from column, lyophilized, and derivatized by reaction with 30% MSTFA in hexane	GC/MS (2-aminothiazoline-4-carboxylic acid)	25 ng/mL	100% (plasma); 84% (urine)	Logue et al. 2005
Urine	Dilution of sample; bromination and treatment with pyridine-*p*-phenylenediamine	Spectrophotometric (thiocyanate-cyanide determination)	0.07 ppm	88 (thiocyanate at 0.6 ppm)	Pettigrew and Fell 1972
Urine	Sample acidified and purged; absorbed and reacted in hydroxycobalamine solution	Spectrophotometry (total cyanide)	28 ng/mL	50	Cruz-Landeira et al. 2000

Table 7-1. Analytical Methods for Determining Cyanide in Biological Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Saliva	Derivatization	HPLC/UV (thiocyanate)	2 ng (instrumental)	95–99	Liu and Yun 1993

ECD = electron capture detector; GC = gas chromatography; GC/MS = gas chromatography/mass spectrometry; HCN = hydrogen cyanide; HPLC = high performance liquid chromatography; HPLC-MS = high performance liquid chromatography coupled with mass spectrometric detector; MSTFA = N-methyl-N-trimethylsilyltrifluoroacetamide; NaOH = sodium hydroxide; NDA = naphthalenedialdehyde; NPD = nitrogen-phosphorus detector; UV = ultraviolet detector

common cyanide antagonist that acts as an interference, can be eliminated by using a buffered solution at pH 5.2 as the acidifying agent for cyanide microdiffusion (Sylvester et al. 1982; Way 1984).

Low detection limits (low ng/mL) have been achieved using a headspace/gas chromatographic (GC) technique (Dumas et al. 2005; Seto et al. 1993) with good precision in the measurements reported (Dumas et al. 2005; Levin et al. 1990; Seto et al. 1993). The sample is acidified and incubated, and the headspace analyzed by GC with a nitrogen-specific detector (NPD) (Levin et al. 1990; Seto et al. 1993) or mass spectrometer (Dumas et al. 2005). Cryogenic oven-trapping techniques have been used to trap volatiles from blood, such as cyanide, at the head of the GC column before analysis, thus eliminating problems of sample foaming that are encountered in traditional head-space analysis methods. Detection limits of 2 ng/mL (2 µg/L) have been reported with extraction efficiencies of 3.22% from blood (Watanabe-Suzuki et al. 2002). Blood samples may be treated with chloramine-T prior to incubation to produce a derivative which can be determined by GC with electron capture detection (ECD). Cyanate and thiocyanate do not interfere with the detection of cyanide in this method (Odoul et al. 1994). The detection limit is 5 µg/L (ppb); precision is good (<15% relative standard deviation [RSD]) (Odoul et al. 1994).

Trace amounts of cyanide in blood cells may be determined using a liquid chromatographic technique with fluorescence detection (Felscher and Wulfmeyer 1998; Sano et al. 1992). The blood cells are extracted and the cyanide derivatized prior to chromatography. The detection limit is 2 ng/mL. Recovery is acceptable (>80%), and precision is good (<15% RSD) (Felscher and Wulfmeyer 1998; Sano et al. 1992). Coupling the liquid chromatography technique to a mass spectrometric detector also provides good detection sensitivities (limit of detection=5 ng/mL) and recoveries (>85%) (Tracqui et al. 2002). Using an ion liquid chromatography method coupled with fluorescence detection, Chinaka et al. (1998) were able to achieve detection limits down to 3.8 pmoles/mL (0.10 ng/mL) of cyanide and 86 pmoles/mL (5.1 ng/mL) of thiocyanate in blood.

Cyanide in biological tissue and fluids can be measured spectrophotometrically after reaction with methemoglobin (Tomoda and Hashimoto 1991). The detection limit is 0.4 µg/mL. Other performance data were not reported (Tomoda and Hashimoto 1991). Cyanide in urine has been determined using microdiffusion separation and fluorimetric determination (Sano et al. 1989). The detection limit of the assay is reported to be 30 ng/L with recoveries of 75.6–82.6% (Sano et al. 1989).

Cyanide in the body is biotransformed to thiocyanate quickly. People may also be exposed to thiocyanate from dietary, industrial, and medical sources. The plasma concentration of thiocyanate has also been used

as an index of long-term exposure to cigarette smoke (Liu and Yun 1993). Some authors have determined thiocyanate in body fluids as a measure of cyanide exposure, while others measure cyanide concentrations in body fluids directly.

Serum levels of thiocyanate are usually determined spectrophotometrically after a colorimetric reaction of thiocyanate with ferric nitrate or barbituric acid and pyridine (Li et al. 1993; Olea et al. 1992). Ion exchange resin chromatography has been used to isolate thiocyanate from serum (Olea et al. 1992). Detection limits are in the ppb range (Li et al. 1993; Olea et al. 1992). Recovery and precision, where reported, are good (recovery >90%; precision <15% RSD) (Li et al. 1993). Methods are available for measuring thiocyanate in saliva by high performance liquid chromatography (HPLC) (Liu and Yun 1993) and in saliva and blood spectrophotometrically (Tominaga et al. 1991; Yamanaka et al. 1991). Table 7-2 lists representative analytical methods for determining thiocyanides in biological matrices.

In addition to thiocyanate, another cyanide metabolite, 2-aminothiazoline-4-carboxylic acid (ATCA), is being used as a biomarker of cyanide exposures. This biomarker is formed through the reaction of cyanide with *l*-cystine and accounts for 20% of cyanide metabolism in the human body (Logue et al. 2005). Unlike cyanide, ATCA is stable for months in biological samples stored at freezing or ambient temperatures. ATCA is readily recovered from plasma or urine by first acidifying the sample and then extracting the compound on to a mixed, cation exchange column. The ACTA is eluted from the column and coverted to the trimethylsilyl derivative through reaction with 30% N-methyl-N-trimethylsilyl-trifluoroacetamide (MSTFA) in hexane before analysis by gas chromatography/mass spectrometry (GC/MS). The assay method provides for good detection limits (25 ng/mL) and recoveries (100% from plasma and 84% from urine).

7.2 ENVIRONMENTAL SAMPLES

Hydrogen cyanide and cyanide salts are important environmental contaminants, and there are numerous reports dealing with the identification and quantification of cyanide in air, water, and other environmental media. Representative examples of monitoring methods for cyanide are included in Table 7-3.

Hydrogen cyanide in environmental or workplace air is usually collected in sodium hydroxide solution, then measured spectrophotometrically after color development (Agrawal et al. 1991; NIOSH 1989b). One of the most significant problems in cyanide monitoring is the instability of the collected samples (NIOSH 1986b). The collection solution is pH ≥11 to avoid volatilization loss of molecular hydrogen

Table 7-2. Analytical Methods for Determining Biomarkers for Cyanide

Analyte	Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Thiocyanate	Human serum, urine, saliva	Extraction of buffered (pH 7) 2-benzoyl pyridine thiosemi-carbazone and sample with isoamyl acetate	Flame atomic absorption spectrometry	4 ng/mL	96–102	Chattaraj and Das 1992
Thiocyanate	Serum	Addition of acetonitrile, centrifugation, separation	Spectro-photometry	0.3 µg/mL	94	Li et al. 1993
Thiocyanate	Human urine, saliva	Derivatization of basic pH sample with pentafluorobenzyl bromide in the presence of Kryptofix 222 B polymer and extraction into methylene chloride then back extraction into isooctane	GC with ECD	0.0115 nmol (in 0.2 mL)	83–106	Chen et al. 1994
Thiocyanate	Human urine, saliva	Dilution with water then filtration (0.45 µm)	Ion chromatography utilizing ODS column coated with cetyl-dimethylamine and with UV absorbance (210 nm) detection	20 ng/mL	95–101	Michigami et al. 1992
Thiocyanate	Urine	Ion chromatography using weakly basic resin; acidification of eluate with HCl; addition of bromine water, arseneous oxide and pyridine-*p*-phenylene diamine	Spectro-photometry	2.5 µmol/L (lowest reported)	No data	Tominaga and Midio 1991
Thiocyanate	Human urine	Dilution with water then passage through disposable Toyo pack ODS and IC-SP columns	Suppressed ion chromatography with conductivity detection	200 nM	No data	Miura and Koh 1991

ECD = electron capture detector; GC = gas chromatography; IC/SP = ion chromatography/sulfopropyl type column; ODS = octadecyl silane; nM = nanomolar

Table 7-3. Analytical Methods for Determining Cyanide in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Occupational air (NIOSH Method 7904)	Filtered air collected in midget impinger containing NaOH; extraction of filter with NaOH; sulfide removed	Specific ion electrode (HCN cyanide salts)	2.5 µg CN^{-}[a]	96.7 at 5–21 mg/m^3	NIOSH 1989a
Occupational air (NIOSH Method 6010)	Collection of breathing zone air samples on adsorbent; extraction with water; treatment with barbituric acid/ pyridine reagent	Spectrophotometry (HCN)	1 µg CN^{-}[b]	~100	NIOSH 1989b
Occupational air	Passage of filtered air through midget impinger containing NaOH; conversion of NaCN to sodium formate; optional ion exchange clean-up	Ion-chromatography/ amperometric detector (HCN)	5–10 ppm	100–109 at 5–20 ppm	Dolzine et al. 1982
Air	Filtered air collected in midget impinger	Ion-chromatography/ amperometric detection (HCN only)	0.04 ppm (for 2.6 L of air)	91 at air flow rate of 0.171 L/minute	NIOSH 1986b
Water (drinking, surface, saline, domestic, and industrial waste) (EPA Method 335.1)	Chlorination of sample at pH 11–12 and ClCN driven off; reflux-distillation of residual sample; absorption of released HCN in NaOH; treatment with chloramine-T and pyridine-pyrazolone or pyridine-barbituric acid	Spectrophotometry (cyanide amenable to chlorination)	No data	No data	EPA 1983a
Water (drinking, surface, saline, domestic, and industrial waste) (EPA Method 335.2)	Reflux-distillation of sample; absorption of released HCN in NaOH scrubber; treatment of absorbing solution with chloramine-T and pyridine-pyrazolone or pyridine barbituric acid	Spectrophotometry (total cyanide)	0.02 ppm	85–102 at 0.28–0.62 ppm	EPA 1983a

Table 7-3. Analytical Methods for Determining Cyanide in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Water (drinking, surface, saline, domestic, and industrial waste) (EPA Method 335.2) (EPA Method 335.3)	Reflux-distillation of sample; absorption of released HCN in NaOH; titration of absorbing solution with $AgNO_3$ in presence of *p*-dimethylamino-benzalrhodanine indicator	Titrimetric (total cyanide)	1 ppm	No data	EPA 1983a
Water (drinking, surface, saline, domestic, and industrial waste) (EPA Method 335.4)	Reflux-distillation of sample; absorption of released HCN in NaOH; treatment with chloramine-T, pyridine barbituric acid	Semi-automated spectrophotometry (total cyanide)	~0.02 ppm	95 (ave.)	EPA 1993h
Water	None	Ion-chromatography/ amperometric detection (free and a few complexed cyanides)	2 ppb	100–112	Rocklin and Johnson 1983
Water	Separation of acidified sample in a microdiffusion cell; absorption in NaOH	Potentiometric (free cyanide)	0.018 mg/L CN^-	96.5–103.9 at 0.037–3.49 mg/L	Rubio et al. 1987
Water (ASTM Method D2036A)	Separation of acidified sample in a microdiffusion cell; absorption in NaOH	Potentiometric (total cyanides)	0.03 mg/L	99.0–111	ASTM 1999
Water	None	FIA; spectrophotometric detection (free cyanide)	20 ng/mL	88–107	Ma and Liu 1992
Water	None	FIA; amperometric detection (free cyanide)	2.6 ng/mL	99–103	Nikolić et al. 1992
Water	Sample shaken in presence of quinoline and benzoyl chloride at pH 7	HPLC with spectrophotometric detection (free CN^-)	26 pg/mL	No data	Madungwe et al. 1991

Table 7-3. Analytical Methods for Determining Cyanide in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Water	None	Ion chromatography with postcolumn derivatization and fluorimetric detection (free cyanide)	0.1 ng/mL	94–96	Gamoh and Imamichi 1991
Water	Treatment of sample with NaOH and hypophosphite; passage through silver filter (free cyanide); treatment in photo cell prior to filter for total cyanide and selective oxidation for cyanides not amenable to chlorination (CNATC)	Flame AAS or graphite furnace AAS	2 ng/mL (flame AAS); 0.06 ng/mL (graphite furnace AAS	107 (free cyanide), 90.4 (CNATC), 98.1 (total cyanide)	Rosentreter and Skogerboe 1992
Water	Samples sealed in vials with nitrogen	Headspace GC/ECD (cyanogen chloride)	0.04 ng/mL	91 average	Xie and Reckhow 1993
Water	Absorption on to SPME fiber; thermal desorption in GC	GC/ECD (cyanogen chloride or bromide)	77 ng/L (cyanogen chloride) 41 ng/L (cyanogen bromide)	No data	Cancho et al. 2000
Water (APHA Method 4500-CN^- J)	Adjustment of sample pH to 8.0–8.5 using phosphate buffer; addition of pyridine-barbituric acid	Spectrophotometry (cyanogen chloride)	0.02 µg/mL (as CN^-) (lowest calibration)	No data	APHA 1992
Water and waste water (APHA Method 4500-CN^- M)	Filtration of sample; optional treatment with resin; treatment with ferric nitrate solution	Colorimetric detection (thiocyanate)	No data	71–99, 0.07–1.42 mg/L	APHA 1992

Table 7-3. Analytical Methods for Determining Cyanide in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Waste or leachate (EPA Method 9012A)	Reflux-distillation of acidified sample; absorption of released HCN in NaOH; treatment with $AgNO_3$ and an indicator (titrimetric) or chloramine-T/pyridine-barbituric acid (colorimetric)	Titrimetric or colorimetric detection (total and amenable cyanide)	0.1–0.2 mg/L (titrimetric) 0.02 mg/L (colorimetric)	(titrimetric) 94–99 (total cyanide), 87–97 (amenable cyanide)	EPA 1996
Waste water	Addition of sample to buffered methemoglobin	Spectrophotometry (free cyanide)	0.2 µg/mL	No data	Tomoda and Hashimoto 1991
Waste water	None	FIA with spectrophotometric detection	3 ng/mL	98	Kubáň 1992
Waste water	Sample acidified and irradiated with UV; microdiffusion and absorption in NaOH solution	FIA with amperiometric detection (total cyanide)	0.5 µg/L	99.5 (2 µg/L) 99 (30 µg/L)	Weinberg and Cook 2002
Waste water	Complexation of sample with 2-benzoyl-pyridine thiosemi-carbazone; solvent extraction	Flame AAS (free cyanide)	4.8 ng/mL	97–101	Chattaraj and Das 1991
Solid waste or oil waste (EPA Method 9013)	Extraction of solid component with water at pH 10 and hexane	Titrimetric or colorimetric detection (soluble cyanides)	No data	60–90 (solid) 88–92 (oil)	EPA 1992e
Soils/ sediments (USGS Method I6302)	Reflux-distillation of sample; absorption of released HCN in NaOH; treatment with chloramine-T, pyridine barbituric acid	Colorimetric detection (recoverable simple cyanides)	0.5 mg/kg	No data	USGS 1985
Food (cereal and other foodstuffs)	Extraction of sample with water/ acetonitrile, dried	GC/ECD at low detection voltage (free cyanide)	0.1 ppm	90	Heuser and Scudmore 1969

Table 7-3. Analytical Methods for Determining Cyanide in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Food (soybean and soybean products)	Sample mixed with water, lead nitrate, tartaric acid, and anti-forming agent; acidification and distillation; treatment of distillate with pyridine-barbituric acid	Spectrophoto-metry (total cyanide)	No data	32–80	Honig et al. 1983

[a]Method detection limits depend upon the volume of air sampled; the working range is 5–20 mg/m^3 for a 10-L air sample.
[b]Method detection limits depend upon the volume of air sampled; the working range is 1–333 mg/m^3 for a 3-L sample.

AAS = atomic absorption spectroscopy; $AgNO_3$ = silver nitrate; ASTM = American Society for Testing and Materials; ClCN = cyanogen chloride; CN^- = cyanide ion; CNATC = cyanides not amenable to chlorination (Rosentreter and Skogerboe 1992); EPA = Environmental Protection Agency; FIA = flow injection analysis; GC/ECD = gas chromatograph/electron capture detector; HCN = hydrogen cyanide; NaOH = sodium hydroxide; NIOSH = National Institute for Occupational Safety and Health; USGS = United States Geological Survey; UV = ultraviolet

cyanide. However, carbon dioxide from air may react with the solution during storage, thereby lowering the pH and releasing hydrogen cyanide gas, making the reading for cyanide lower than actually presented. Oxidizing agents in solution may transform cyanide during storage and handling. Ferrocyanide and ferricyanide complexes of cyanide undergo photodecomposition with ultraviolet light. Particulate cyanides are known to decompose in moist air with the liberation of hydrogen cyanide and cyanic acid (HOCN). The recommended method for the storage of cyanide samples is to collect the samples at pH 12–12.5 in closed, dark bottles and store them in a cool, dark place. It is also recommended that the samples be analyzed immediately upon collection. The sample handling and preservation methods have been discussed (NIOSH 1986b; Egekeze and Oehme 1979). Cyanide determination in air usually distinguishes between two forms of cyanides: hydrogen cyanide gas and particulate cyanides. Filters are usually used to collect particulate cyanides, and the hydrogen cyanide gas that passes through the membrane is trapped in sodium hydroxide. The collected particulate cyanides can be quantified separately after acid distillation. Detection limits are in the ppm range for occupational air (Dolzine et al. 1982; NIOSH 1989a, 1989b) and sub-ppm range for ambient air (NIOSH 1986b). Reported recovery is good (>90%) (Dolzine et al. 1982; NIOSH 1986b, 1989a, 1989b).

Inorganic cyanides in water can be present both as complexed and 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 sodium cyanide, potassium cyanide, and hydrogen cyanide 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 7-3 lists representative analytical methods for determining cyanides that may be present in various forms. A number of standard methods are available (APHA 1992; ASTM 1999; EPA 1983a, 1996; NIOSH 1989a, 1989b). An ion-exchange chromatography method has been developed to separate and quantify cyano complexes of gold, silver, iron, nickel, cobalt, and copper using a UV detection technique (Karmarkar 2002). Minimum detection limits of 0.07–0.83 mg/L and recoveries of 99.8–118.8% were reported, both of which varied considerably depending on the cyano metal complex.

Procedures for extracting cyanide from aqueous matrices usually involve acidifying the sample followed by heating and refluxing to evolve hydrogen cyanide, which is then trapped in an impinger containing absorption media. Complex cyanides and metal cyanide complexes can be degraded to free cyanide through UV irradiation (314 nm) of an acidified sample (Weinberg and Cook 2002). Cyanide is usually measured by colorimetric, titrimetric, or electrochemical methods (for example, APHA 1992). All are

subject to interference problems. 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 addition, fatty acids in samples may distill over and form soaps under alkaline titration conditions, thus causing interference in the titrimetric method (EPA 1983a, 1996). Colorimetric methods may be based on pyridine with chloramine-T as the oxidizing agent and barbituric acid as the coupling component (EPA 1996) or pyrazolone as the coupling agent (EPA 1983a). Low detection limits are attained (10–20 µg/L), but sulfide and thiocyanate are common interferents (Csikal and Barnard 1983; Drikas and Routley 1988). Titrimetric methods usually employ silver nitrate (EPA 1983a, 1996); however, the detection limits are in the low mg/L range. Methods using specific ion electrodes (electrochemical) respond to numerous interferences (sulfur, chlorine, iodine, bromine, cadmium, silver, zinc, copper, nickel, and mercury) (NIOSH 1986b).

Continuous monitoring methods based on amperometric (Nikolić et al. 1992) or spectrophotometric (Kubáň 1992; Ma and Liu 1992) techniques for the quantification of free cyanide are also available. Ion chromatography with amperometric determination provides good sensitivity (2 ppb) and selectivity for free cyanide and for the weak complexes of cadmium and zinc (Rocklin and Johnson 1983). Postcolumn derivatization and fluorescence detection provides low detection limits as well (0.1 ppb) (Gamoh and Imamichi 1991).

Methods were identified in the available literature for the determination of the concentrations of cyanides and thiocyanates present in soils at low levels. A colorimetric method (USGS 1985) is used to quantify simple cyanides in soils and sediments (see Table 7-3). A reflux-distillation of soil or sediment samples converts CN^- to hydrogen cyanide, which is released from the sample and then absorbed in a 1 M NaOH solution. The absorbed cyanide is chlorinated with Chloramine-T and then reacted with pyridine-barbituric acid to form the chromophore. Detection limits of >0.5 mg/kg are reported; no recovery data were given. The method will decompose thiocyanate in the samples to cyanide and sulfide, resulting in a concentration of cyanide that is higher than was originally present in the sample. Sulfide concentrations of >10 mg/kg will greatly interfere with the quantification of cyanide in the assay. In addition to simple cyanides, complex cyanides can also be measured in soil and sediment samples utilizing a modified sample preparation procedure that uses an ultraviolet digestion-distillation method to break down the complex cyanides to the cyanide ion. Brown and Morra (1991) extracted simple cyanides from soils using a calcium chloride solution followed by analysis by ion-chromatography (see Table 7-4). The assay provided a detection limit of 0.02 µg/L with a recovery averaging 94%, depending on soil type.

Table 7-4. Analytical Methods for Determining Environmental Degradation Products of Cyanide

Analyte	Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
SCN^-	Water	Filtration (0.45 µm)	Reversed-phase ion-pair chromatography with amperometric detection	104 ng/mL	No data	Xu et al. 1993
SCN^-	Water/waste water	Filtration; acidification; reaction with ferric chloride	Colorimetric	0.1 mg/L	No data	ASTM 1994a
SCN^-	Soil	Extraction of soil with calcium chloride solution	Ion chromatography with conductivity detection	0.02 µg/g	83; avg. 94, depending on soil type	Brown and Morra 1991

SCN^- = thiocyanate ion

Recent method development strategies for quantifying cyanide in water are using biological sensing elements (i.e., organisms, enzyme, receptor, antibody, etc.) coupled to an electronic signal-transducing element. With respect to organisms, the assay takes advantage of the effect that cyanide has on respiration and metabolism. For example, Karube et al. (1998) use yeast in a flow-through reactor setup where river water containing cyanide is pumped through the reactor and the oxygen concentration in the effluent stream is measured using an oxygen electrode. When cyanide passes through the reactor, it inhibits yeast respiration and therefore decreases oxygen consumption, resulting in an increase in the current at the oxygen electrode. A detection limit of 0.2 ppm (3μM) was reported for the assay with a linear response to 1 ppm. In another approach, Nikolelis et al. (1997) use a lipid bilayer embedded with methemoglobin to detect and quantify cyanide in water samples. The binding of cyanide to the methemoglobin causes a change in the electrochemical potential across the membrane that is measured with an electrometer. A detection limit of 4.9 nM (0.0032 ppm) was reported with a relative standard deviation (RSD) of 5.2% at cyanide concentration of 150 nM.

Few methods are available for the determination of cyanogen and cyanogen chloride in environmental matrices. Methods available include gas chromatographic-flame ionization detection of cyanogen chloride and cyanogen (Brown et al. 1986), headspace gas chromatography with electron capture detection (GC/ECD) (Cancho et al. 2000; Xie and Reckhow 1993) and colorimetric detection (APHA 1992). Detection limits are in the low ppb range for the colorimetric method (APHA 1992) and in the sub-ppb range for the GC/ECD method (Xie and Reckhow 1993).

Recent work by Yang and Shang (2005) reports the development of a membrane introduction mass spectrometry (MIMS) technique for quantifying cyanogens chloride in environmental samples. Non-polar, low molecular weight, volatile and semi-volatile organics in aqueous samples are introduced direct to a mass spectrometer through pervaporation as the sample passes through a permeable silicone membrane. Linear responses over three orders of magnitude of concentrations of cyanogens chloride were obtained with a detection limit of 1.7 μg/L and a recovery of 98.5%. The presence of organics, such as dichloroethene, acetophenone, benzaldehyde, and benzyl alcohol, can interfere with the quantification of cyanogen chloride. However, these compounds are generally industrial chemicals that are typically not detected in drinking water, most surface waters, or domestic waste water.

Standard methods are available for measuring thiocyanate in aqueous matrices (APHA 1992; ASTM 1994a). These are colorimetric methods and are subject to interferences. In addition, thiocyanate is biodegradable; thus, care must be exercised in sample collection, preservation, and storage. The detection

limit is 100 ppb (ASTM 1994a). An automated method with good sensitivity (0.5 ppb) is available for determining thiocyanate in water and waste water (ASTM 1994b). Various methods have been reported for determination of thiocyanate in soils; however, ion chromatographic determination provides good selectivity and sensitivity (20 ppb) (Brown and Morra 1991). Representative examples of monitoring methods for thiocyanate are included in Table 7-4.

7.3 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of cyanide is available. Where adequate information is not available, ATSDR, in conjunction with NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of cyanide.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

7.3.1 Identification of Data Needs

Methods for Determining Biomarkers of Exposure and Effect.

Exposure. Besides environmental exposure, exposure to cyanide can also occur from consumption of cyanide-containing food and smoking cigarettes. Since so many factors can influence cyanide exposure, the exact correlation between cyanide concentrations in the body and its level in the environment has not been made. Therefore, measuring cyanide and/or thiocyanate levels in blood and urine cannot be used as a biomarker for exposure to low cyanide concentrations. Reliable analytical methods are available for the detection of cyanide and thiocyanate in blood, plasma, and urine of both unexposed and exposed persons are available, as summarized in Tables 7-1 and 7-2. Further studies determining biomarkers for exposure to low cyanide concentrations would be useful since current methods that are used to measure cyanide

and/or thiocyanate in blood and urine are not effective at assessing exposures to low concentrations of cyanide.

The International Programme on Chemical Safety, in its document regarding the antidotes for poisoning by cyanide, has identified several analytical data needs related to the detection of cyanide in biological matrices (IPCS/CEC 1993). Analytical techniques available for the measurement of methemoglobin do not permit accurate estimation of the amount of free hemoglobin available for oxygen transport because cyanmethemoglobin cannot be quantified. A rapid and accurate technique for measuring methemoglobin and cyanmethemoglobin concentrations in conjunction is therefore needed to monitor the use of methemoglobin-generating cyanide antidotes. Reliable quantitative analytical methods for cyanide in whole blood in the presence of one or more antidotes are also needed.

Effect. Although certain effects, such as cyanosis and endemic goiter, have been associated with cyanide exposure (see Section 3.8.2), a positive correlation between cyanide exposure and one of its effects has not yet been established. Additional studies establishing a correlation between cyanide exposure and one of its effects will be useful in diagnosing cyanide exposure.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. The concentration of hydrogen cyanide in most ambient air is so low that it is beyond the detection limit of the standard analytical methods. An infrared absorption method of a large vertical tropospheric column was used to measure the hydrogen cyanide concentration in the troposphere (Cicerone and Zellner 1983). Similarly, ground-based millimeter wave emission spectroscopy was used to measure stratospheric concentration of hydrogen cyanide (Jaramillo et al. 1989). Also, the level of cyanogen chloride in drinking water ranges from 0.45 to 0.80 ppb (Krasner et al. 1989), which is beyond the detection limit of the standard analytical methods without concentration and trapping procedures. Cyanogen chloride in water was determined by a purge and trap GC/MS method (Krasner et al. 1989) and an MIMS-based method (Yang and Shang 2005), methods that are not available to many laboratories. There is, therefore, a need to develop standard analytical methods capable of quantifying hydrogen cyanide in air and cyanogen chloride in water at levels that are generally found in these media.

Cyanide metabolizes in the human body to thiocyanate, and its biodegradation products include ammonia, carbon dioxide, nitrate, or nitrogen (Richards and Shieh 1989). The detection of thiocyanate or 2-aminothiazoline-4-carboxylic acid in body fluids may indicate cyanide exposure (Logue et al. 2005). Similarly, the amounts of cyanide degradation products formed in an environmental medium could be

used to measure cyanide's biodegradation rate. A summary of methods for determining environmental degradation products is shown in Table 7-4. Suitable analytical methods are available to detect all of these compounds (Pettigrew and Fell 1973; Richards and Shieh 1989). No additional information is needed at this time.

7.3.2 Ongoing Studies

The Federal Research in Progress (FEDRIP 2005) database provides additional information obtainable from a few ongoing studies that may fill in some of the data needs identified in Section 7.3.1 and provides examples of new methods used in the detection and quantification of cyanide or thiocyanide. Only one study was identified. Dr. Fennell at Research Triangle Institute is developing liquid-chromatography/ mass spectrometry based analytical methods for the detection and quantification of adducts formed between hemoglobin and reactive chemicals such as cyanide.

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8. REGULATIONS AND ADVISORIES

The international, national, and state regulations and guidelines regarding cyanide in air, water, and other media are summarized in Table 8-1.

ATSDR has derived an intermediate oral MRL of 0.05 mg/kg/day for cyanide based on a NOAEL of 4.5 mg/kg/day and a LOAEL of 12.5 mg/kg/day from a study in which 10 male and 10 female rats were given 0.2–12.5 mg/kg/day cyanide, as sodium cyanide, in the drinking water for 13 weeks (NTP 1993).

EPA reference doses (RfDs) have been established for chronic oral exposure to cyanide and its compounds. These RfDs range from $2x10^{-1}$ mg/kg/day for potassium silver cyanide to $5x10^{-3}$ mg/kg/day for copper cyanide. The RfD for potassium silver cyanide was based on weight loss and thyroid effects in several rat studies (Howard and Hanzel 1955; Philbrick et al. 1979), while the RfD for copper cyanide was based on decreased body and organ weights and liver and kidney effects in an intermediate-duration rat study (Gerhart 1987). An EPA reference concentration (RfC) exists only for chronic inhalation exposure to hydrogen cyanide; this RfC is $3x10^{-3}$ mg/m^3. The RfC was based on central nervous system and thyroid effects in a human occupational study (El Ghawabi et al. 1975).

The EPA has determined that cyanide is not classifiable as to its human carcinogenicity (Group D). No cancer classifications exist for the National Toxicology Program, IRIS, or IARC (no available data).

Several cyanide compounds are on the list of chemicals regulated under "The Emergency Planning and Community Right-to-Know Act of 1986" (EPCRA) (EPA 2004d). Section 313 of Title III of EPCRA requires owners and operators of certain facilities that manufacture, import, process, or otherwise use the chemicals on this list to report annually their release of those chemicals to any environmental media.

OSHA requires employers of workers who are occupationally exposed to cyanide to institute engineering controls and work practices to reduce and maintain employee exposure at or below permissible exposure limits (PELs). The employer must use engineering and work practice controls, if feasible, to reduce exposure to or below an 8-hour time-weighted average (TWA) of 10 ppm (11 mg/m^3) as cyanide. Respirators must be provided and used during the time period necessary to install or implement feasible engineering and work practice controls (OSHA 2004d). NIOSH (2004) recommends a 10-minute ceiling of 5 mg/m^3 for cyanide in compounds such as sodium cyanide or potassium cyanide.

Table 8-1. Regulations and Guidelines Applicable to Cyanide and Cyanide Compounds

Agency	Description	Information	Reference
INTERNATIONAL			
Guidelines:			
IARC	Carcinogenicity classification	No data	IARC 2004
WHO	Air quality guideline value	No data	WHO 2000
	Drinking water guideline value		WHO 2004
	Cyanide	0.07 mg/L	
	Cyanogen chloride (for cyanide as total cyanogenic compounds)	0.07 mg/L	
NATIONAL			
Regulations and Guidelines:			
a. Air			
ACGIH	TLV (8-hour TWA)		ACGIH 2003
	Cyanogen	10 ppm	
	Cyanogen chloride (ceiling limit)	0.3 ppm	
	Hydrogen cyanide (ceiling limit)[a]	4.7 ppm	
EPA	Hazardous air pollutant		EPA 2004j 42USC7412
	Cyanide compounds		
	Regulated toxic and flammable substances and threshold quantities for accidental release prevention		EPA 2005a 40CFR68.130
	Cyanogen (toxic)	10,000 pounds	
	Cyanogen chloride (flammable)	10,000 pounds	
NIOSH	REL (10-hour TWA)		NIOSH 2005
	Cyanogen	10 ppm	
	Cyanogen chloride (10-minute ceiling limit)	0.3 ppm	
	Hydrogen cyanide (short-term limit)[a]	4.7 ppm	
	Potassium cyanide (10-minute ceiling limit)	4.7 ppm	
	Sodium cyanide (10-minute ceiling limit)	4.7 ppm	
	IDLH		
	Cyanogen	No data	
	Cyanogen chloride	No data	
	Hydrogen cyanide	50 ppm	
	Potassium cyanide (as cyanide)	25 mg/m^3	
	Sodium cyanide (as cyanide)	25 mg/m^3	
OSHA	PEL (8-hour TWA) for general industry		OSHA 2004d 29CFR1910.1000, Table Z-1
	Hydrogen cyanide[a]	10 ppm	
	PEL (8-hour TWA) for construction industry		OSHA 2004c 29CFR1926.55, Appendix A
	Cyanogen	10 ppm	
	Hydrogen cyanide[a]	10 ppm	
	PEL (8-hour TWA) for shipyard industry		OSHA 2004a 29CFR1915.1000, Table Z
	Cyanogen	10 ppm	
	Hydrogen cyanide[a]	10 ppm	

Table 8-1. Regulations and Guidelines Applicable to Cyanide and Cyanide Compounds

Agency	Description	Information	Reference
NATIONAL *(cont.)*			
OSHA	Highly hazardous chemicals which present a potential for a catastrophic event at or above the threshold quantity listed		OSHA 2004b 29CFR1910.119, Appendix A
	Cyanogen	2,500 pounds	
	Cyanogen chloride	500 pounds	
	Hydrogen cyanide, anhydrous	1,000 pounds	
b. Water			
EPA	Drinking water standards and health advisories		EPA 2004a
	Cyanide		
	1-day HA for a 10-kg child	0.2 mg/L	
	10-day HA for a 10-kg child	0.2 mg/L	
	DWEL	0.8 mg/L	
	Lifetime HA (70-kg adult)	0.2 mg/L	
	Cyanogen chloride		
	1-day HA for a 10-kg child	0.05 mg/L	
	10-day HA for a 10-kg child	0.05 mg/L	
	DWEL	2.0 mg/L	
	Designated as a hazardous substances pursuant to Section 311(b) of the Clean Water Act		EPA 2004t 40CFR116.4
	Ammonium thiocyanate	Yes	
	Calcium cyanide		
	Cyanogen chloride		
	Hydrogen cyanide		
	Potassium cyanide		
	Sodium cyanide		
	National primary drinking water standards and public notification		EPA 2004h 40CFR141.32
	Cyanide[b]	0.2 ppm	
	Reportable quantities of hazardous substances designated pursuant to Section 311(b) of the Clean Water Act		EPA 2004k 40CFR117.3
	Ammonium thiocyanate	5,000 pounds	
	Calcium cyanide	10 pounds	
	Cyanogen chloride	10 pounds	
	Hydrogen cyanide	10 pounds	
	Potassium cyanide	10 pounds	
	Sodium cyanide	10 pounds	
	National primary drinking water regulations (MCL)		EPA 2004g 40CFR141.62
	Cyanide	0.2 mg/L	
FDA	Bottled water		FDA 2003 21CFR165.110
	Cyanide	0.2 mg/L	

Table 8-1. Regulations and Guidelines Applicable to Cyanide and Cyanide Compounds

Agency	Description	Information	Reference
NATIONAL *(cont.)*			
c. Food			
EPA	Tolerance for residues of hydrogen cyanide from postharvest fumigation as a result of application of sodium cyanide on citrus fruits	50 ppm	EPA 2004m 40CFR180.130
	Exemptions from the requirement of a tolerance when used in accordance with good agricultural practices in pesticide formulations applied to growing crops; and when used as an adjuvant or intensifier for defoliation and weed control on cotton and soybeans	Ammonium thiocyanate	EPA 2004n 40CFR180.920
FDA	Indirect food additive for use only as a component of adhesives	Ammonium thiocyanate	FDA 2003 21CFR175.105
d. Other			
EPA	Carcinogenicity classification		IRIS 2004
	Calcium cyanide	No data	
	Chlorine cyanide	No data	
	Copper(I) cyanide	No data	
	Cyanide	Group D[c]	
	Cyanogen	No data	
	Hydrogen cyanide	No data	
	Potassium cyanide	No data	
	Potassium silver cyanide	No data	
	Sodium cyanide	No data	
	RfC[d]		
	Calcium cyanide	No data	
	Chlorine cyanide	No data	
	Copper(I) cyanide	No data	
	Cyanide	No data	
	Cyanogen	No data	
	Hydrogen cyanide	$3x10^{-3}$ mg/m^3	
	Potassium cyanide	No data	
	Potassium silver cyanide	No data	
	Sodium cyanide	No data	
	RfD[e]		
	Calcium cyanide	$4x10^{-2}$ mg/kg/day	
	Chlorine cyanide	$5x10^{-2}$ mg/kg/day	
	Copper(I) cyanide	$5x10^{-3}$ mg/kg/day	
	Cyanide	$2x10^{-2}$ mg/kg/day	
	Cyanogen	$4x10^{-2}$ mg/kg/day	
	Hydrogen cyanide	$2x10^{-2}$ mg/kg/day	
	Potassium cyanide	$5x10^{-2}$ mg/kg/day	
	Potassium silver cyanide	$2x10^{-1}$ mg/kg/day	
	Sodium cyanide	$4x10^{-2}$ mg/kg/day	

Table 8-1. Regulations and Guidelines Applicable to Cyanide and Cyanide Compounds

Agency	Description	Information	Reference
NATIONAL *(cont.)*			
EPA	Hazardous waste identification		EPA 2004f 40CFR261, Appendix VIII
	Calcium cyanide	P021	
	Copper(I) cyanide	P029	
	Cyanides (soluble salts and complexes)	P030	
	Cyanogen	P031	
	Cyanogen chloride	P033	
	Hydrogen cyanide	P063	
	Potassium cyanide	P098	
	Potassium silver cyanide	P099	
	Sodium cyanide	P106	
	Pesticide (sodium cyanide) classified as restricted use and limited to use by or under the direct supervision of a certified applicator	All capsules and all ball formulations for all uses[f]	EPA 2004i 40CFR152.175
	Superfund; emergency planning and notification of extremely hazardous substances and their threshold quantities		EPA 2004e 40CFR355, Appendix A
	Hydrogen cyanide	100 pounds	
	Potassium cyanide	100 pounds	
	Potassium silver cyanide	500 pounds	
	Sodium cyanide	100 pounds	
	Superfund; designation of hazardous substances and their reportable quantities		EPA 2004d 40CFR302.4
	Ammonium thiocyanate[g]	5,000 pounds	
	Calcium cyanide[h]	10 pounds	
	Copper cyanide[i]	10 pounds	
	Cyanides (soluble salts and complexes)	10 pounds	
	Cyanogen[i]	100 pounds	
	Cyanogen chloride[h]	10 pounds	
	Hydrogen cyanide[h]	10 pounds	
	Potassium cyanide[h]	10 pounds	
	Potassium silver cyanide[i]	1 pound	
	Sodium cyanide[h]	10 pounds	
	Tolerances for pesticide chemicals in food; when calcium cyanide and hydrogen cyanide are on the same agricultural commodity, the total amount shall not yield more residue than the larger of the two tolerances, calculated as hydrogen cyanide		EPA 2004o 40CFR180.3
	Toxic chemical release reporting; community right-to-know; effective date for hydrogen cyanide	01/01/1987	EPA 2004p 40CFR372.65
	TSCA chemical information rules; manufacturers reporting period for sodium cyanide		EPA 2004r 40CFR712.30
	Effective date	10/29/1990	
	Reporting date	12/27/1990	

Table 8-1. Regulations and Guidelines Applicable to Cyanide and Cyanide Compounds

Agency	Description	Information	Reference
NATIONAL *(cont.)*			
EPA	TSCA health and safety data reporting for sodium cyanide		EPA 2004s 40CFR716.120
	Effective date	10/29/1990	
	Sunset date	12/19/1995	
STATE			
a. Air			
	No data		
b. Water			
	Drinking water standards and guidelines		HSDB 2004
Arizona	Calcium cyanide	220 µg/L	
	Copper(I) cyanide	1,300 µg/L	
	Potassium cyanide	220 µg/L	
	Potassium silver cyanide	50 µg/L	
	Sodium cyanide	220 µg/L	
Connecticut	Potassium silver cyanide	50 µg/L	
Florida	Cyanogen	10,000 µg/L	
	Cyanogen chloride	350 µg/L	
	Hydrogen cyanide	10,000 µg/L	
Maine	Potassium cyanide	154 µg/L	
	Potassium silver cyanide	50 µg/L	
	Sodium cyanide	154 µg/L	
Minnesota	Potassium cyanide	100 µg/L	
	Potassium silver cyanide	30 µg/L	
	Sodium cyanide	100 µg/L	
Wisconsin	Potassium silver cyanide	50 µg/L	
c. Food			
	No data		

Table 8-1. Regulations and Guidelines Applicable to Cyanide and Cyanide Compounds

Agency	Description	Information	Reference
STATE *(cont.)*			
d. Other			
	No data		

[a]Skin designation: Potential significant contribution to the overall exposure by the cutaneous route, including mucous membranes and the eyes, either by contact with vapors, or of probable greater significance, by direct skin contact with the substance.
[b]EPA sets drinking water standards and has determined that cyanide is a health concern at certain levels of exposure. This inorganic chemical is used in electroplating, steel processing, plastics, synthetic fabrics, and fertilizer products; it usually gets into water as a result of improper waste disposal. This chemical has been shown to damage the spleen, brain, and liver of humans fatally poisoned with cyanide. EPA has set the drinking water standard for cyanide at 0.2 ppm to protect against the risk of these adverse health effects. Drinking water that meets the EPA standard is associated with little to none of this risk and should be considered safe with respect to cyanide (EPA 2004h).
[c]Group D: Not classifiable as a human carcinogen.
[d]An estimate (with uncertainty spanning an order of magnitude) of a daily inhalation exposure concentration that is likely to be without significant risk of adverse effects during a lifetime (chronic exposure).
[e]An estimate (with uncertainty spanning an order of magnitude) of a daily oral exposure dose that is likely to be without significant risk of adverse effects during a lifetime (chronic exposure).
[f]The criteria influencing the restriction of sodium cyanide is based on the inhalation hazard to humans. Also, sodium cyanide capsules may only be used by certified applicators who have also taken the required additional training.
[g]Designated as a hazardous substance pursuant to Section 311(b)(2) of the Clean Water Act.
[h]Designated as a hazardous substance pursuant to Section 311(b)(2) of the Clean Water Act and Section 3001 of RCRA.
[i]Designated as a hazardous substance pursuant to Section 3001 of RCRA.

ACGIH = American Conference of Governmental Industrial Hygienists; CFR = Code of Federal Regulations; DWEL = drinking water equivalent level; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; HA = health advisory; HSDB = Hazardous Substances Data Bank; IARC = International Agency for Research on Cancer; IDLH = immediately dangerous to life or health; IRIS = Integrated Risk Information System; MCL = maximum contaminant level; NIOSH = National Institute for Occupational Safety and Health; OSHA = Occupational Safety and Health Administration; PEL = permissible exposure limit; RCRA = Resource Conservation and Recovery Act; REL = recommended exposure limit; RfC = reference concentration; RfD = reference dose; TLV = threshold limit values; TSCA = Toxic Substances Control Act; TWA = time-weighted average; USC = United States Codes; WHO = World Health Organization

Cyanide is regulated by the Clean Water Effluent Guidelines as stated in Title 40, Sections 400–475, of the Code of Federal Regulations. For each point source category, cyanide may be regulated as amenable or total cyanide. The point source categories for which cyanide is controlled include electroplating; metal finishing; organic chemicals; plastics and synthetic fibers; hydrogen peroxide manufacturing; iron and steel; nonferrous metals; steam electri-power; ferroalloy manufacturing; pharmaceuticals; battery manufacturing; aluminum forming; nonferrous metal forming; and coil coating.

Under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), food tolerance restrictions (see Table 8-1) apply to various cyanide compounds when applied to growing crops (EPA 2004m, 2004n, 2004o).

Under the Resource Conservation and Recovery Act (RCRA), cyanide is listed as a hazardous waste when it is a discarded commercial chemical product, off-specification species, container residue, or spill residue (EPA 1980c); a waste from non-specific sources (EPA 1981c); or a waste from specific sources (EPA 1981c).

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10. GLOSSARY

Absorption—The taking up of liquids by solids, or of gases by solids or liquids.

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

Adsorption—The adhesion in an extremely thin layer of molecules (as of gases, solutes, or liquids) to the surfaces of solid bodies or liquids with which they are in contact.

Adsorption Coefficient (K_{oc})—The ratio of the amount of a chemical adsorbed per unit weight of organic carbon in the soil or sediment to the concentration of the chemical in solution at equilibrium.

Adsorption Ratio (Kd)—The amount of a chemical adsorbed by sediment or soil (i.e., the solid phase) divided by the amount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed in micrograms of chemical sorbed per gram of soil or sediment.

Amygdalin—A naturally occurring cyanogenic glucoside found in almonds and apricot pits. It is also the active ingredient in the drug Laetrile, which has been formerly used to treat cancer. The hydrolysis of amgydalin releases hydrogen cyanide.

Benchmark Dose (BMD)—Usually defined as the lower confidence limit on the dose that produces a specified magnitude of changes in a specified adverse response. For example, a BMD10 would be the dose at the 95% lower confidence limit on a 10% response, and the benchmark response (BMR) would be 10%. The BMD is determined by modeling the dose response curve in the region of the dose response relationship where biologically observable data are feasible.

Benchmark Dose Model—A statistical dose-response model applied to either experimental toxicological or epidemiological data to calculate a BMD.

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 period.

Biomarkers—Broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility.

Cancer Effect Level (CEL)—The lowest dose of chemical in a study, or group of studies, that produces significant increases in the incidence of cancer (or tumors) between the exposed population and its appropriate control.

Carcinogen—A chemical capable of inducing cancer.

Case-Control Study—A type of epidemiological study that examines the relationship between a particular outcome (disease or condition) and a variety of potential causative agents (such as toxic chemicals). In a case-controlled study, a group of people with a specified and well-defined outcome is identified and compared to a similar group of people without outcome.

Case Report—Describes a single individual with a particular disease or exposure. These may suggest some potential topics for scientific research, but are not actual research studies.

Case Series—Describes the experience of a small number of individuals with the same disease or exposure. These may suggest potential topics for scientific research, but are not actual research studies.

Ceiling Value—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.

Cohort Study—A type of epidemiological study of a specific group or groups of people who have had a common insult (e.g., exposure to an agent suspected of causing disease or a common disease) and are followed forward from exposure to outcome. At least one exposed group is compared to one unexposed group.

Cross-sectional Study—A type of epidemiological study of a group or groups of people that examines the relationship between exposure and outcome to a chemical or to chemicals at one point in time.

Data Needs—Substance-specific informational needs that if met would reduce the uncertainties of human health assessment.

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.

Dose-Response Relationship—The quantitative relationship between the amount of exposure to a toxicant and the incidence of the adverse effects.

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 occurs. The terms, as used here, include malformations and variations, altered growth, and *in utero* death.

Environmental Protection Agency (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.

Epidemiology—Refers to the investigation of factors that determine the frequency and distribution of disease or other health-related conditions within a defined human population during a specified period.

Genotoxicity—A specific adverse effect on the genome of living cells that, upon the duplication of affected cells, can be expressed as a mutagenic, clastogenic, or carcinogenic event because of specific alteration of the molecular structure of the genome.

Half-life—A measure of rate for the time required to eliminate one half of a quantity of a chemical from the body or environmental media.

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

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

Immunological Effects—Functional changes in the immune response.

Incidence—The ratio of individuals in a population who develop a specified condition to the total number of individuals in that population who could have developed that condition in a specified time period.

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

***In Vitro*—**Isolated from the living organism and artificially maintained, as in a test tube.

***In Vivo*—**Occurring within the living organism.

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

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

Lethal Time(50) (LT_{50})—A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

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

Lymphoreticular Effects—Represent morphological effects involving lymphatic tissues such as the lymph nodes, spleen, and thymus.

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

Minimal Risk Level (MRL)—An estimate of daily human exposure to a hazardous substance that is likely to be without an appreciable risk of adverse noncancer health effects over a specified route and duration of exposure.

Modifying Factor (MF)—A value (greater than zero) that is applied to the derivation of a Minimal Risk Level (MRL) to reflect additional concerns about the database that are not covered by the uncertainty factors. The default value for a MF is 1.

Morbidity—State of being diseased; morbidity rate is the incidence or prevalence of disease in a specific population.

Mortality—Death; mortality rate is a measure of the number of deaths in a population during a specified interval of time.

Mutagen—A substance that causes mutations. A mutation is a change in the DNA sequence of a cell's DNA. Mutations can lead to birth defects, miscarriages, or cancer.

Necropsy—The gross examination of the organs and tissues of a dead body to determine the cause of death or pathological conditions.

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

No-Observed-Adverse-Effect Level (NOAEL)—The dose of a chemical at which there were 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.

Octanol-Water Partition Coefficient (K_{ow})—The equilibrium ratio of the concentrations of a chemical in *n*-octanol and water, in dilute solution.

Odds Ratio (OR)—A means of measuring the association between an exposure (such as toxic substances and a disease or condition) that represents the best estimate of relative risk (risk as a ratio of the incidence among subjects exposed to a particular risk factor divided by the incidence among subjects who were not exposed to the risk factor). An OR of greater than 1 is considered to indicate greater risk of disease in the exposed group compared to the unexposed group.

Organophosphate or Organophosphorus Compound—A phosphorus-containing organic compound and especially a pesticide that acts by inhibiting cholinesterase.

Permissible Exposure Limit (PEL)—An Occupational Safety and Health Administration (OSHA) allowable exposure level in workplace air averaged over an 8-hour shift of a 40-hour workweek.

Pesticide—General classification of chemicals specifically developed and produced for use in the control of agricultural and public health pests.

pH—The negative logarithim (base 10) of the hydrogen ion concentration; expressed as $pH \equiv -\log_{10} [H^+]$.

Pharmacokinetics—The dynamic behavior of a material in the body, used to predict the fate (disposition) of an exogenous substance in an organism. Utilizing computational techniques, it provides the means of studying the absorption, distribution, metabolism, and excretion of chemicals by the body.

Pharmacokinetic Model—A set of equations that can be used to describe the time course of a parent chemical or metabolite in an animal system. There are two types of pharmacokinetic models: data-based and physiologically-based. A data-based model divides the animal system into a series of compartments,

which, in general, do not represent real, identifiable anatomic regions of the body, whereas the physiologically-based model compartments represent real anatomic regions of the body.

Physiologically Based Pharmacodynamic (PBPD) Model—A type of physiologically based dose-response model that quantitatively describes the relationship between target tissue dose and toxic end points. These models advance the importance of physiologically based models in that they clearly describe the biological effect (response) produced by the system following exposure to an exogenous substance.

Physiologically Based Pharmacokinetic (PBPK) Model—Comprised of a series of compartments representing organs or tissue groups with realistic weights and blood flows. These models require a variety of physiological information: tissue volumes, blood flow rates to tissues, cardiac output, alveolar ventilation rates, and possibly membrane permeabilities. The models also utilize biochemical information, such as air/blood partition coefficients, and metabolic parameters. PBPK models are also called biologically based tissue dosimetry models.

pK—The negative logarithim (base 10) of the dissociation constant of a weak acid or base.

Prevalence—The number of cases of a disease or condition in a population at one point in time.

Prospective Study—A type of cohort study in which the pertinent observations are made on events occurring after the start of the study. A group is followed over time.

q1*—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 µg/m^3 for air).

Recommended Exposure Limit (REL)—A National Institute for Occupational Safety and Health (NIOSH) time-weighted average (TWA) concentration for up to a 10-hour workday during a 40-hour workweek.

Reference Concentration (RfC)—An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious noncancer health effects during a lifetime. The inhalation reference concentration is for continuous inhalation exposures and is appropriately expressed in units of mg/m^3 or ppm.

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 no-observed-adverse-effect level (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 the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA). Reportable quantities are (1) 1 pound or greater or (2) for selected substances, an amount established by regulation either under CERCLA or under Section 311 of the Clean Water Act. Quantities are measured over a 24-hour 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.

Retrospective Study—A type of cohort study based on a group of persons known to have been exposed at some time in the past. Data are collected from routinely recorded events, up to the time the study is undertaken. Retrospective studies are limited to causal factors that can be ascertained from existing records and/or examining survivors of the cohort.

Risk—The possibility or chance that some adverse effect will result from a given exposure to a chemical.

Risk Factor—An aspect of personal behavior or lifestyle, an environmental exposure, or an inborn or inherited characteristic that is associated with an increased occurrence of disease or other health-related event or condition.

Risk Ratio—The ratio of the risk among persons with specific risk factors compared to the risk among persons without risk factors. A risk ratio greater than 1 indicates greater risk of disease in the exposed group compared to the unexposed group.

Short-Term Exposure Limit (STEL)—The American Conference of Governmental Industrial Hygienists (ACGIH) maximum concentration to which workers can be exposed for up to 15 minutes continually. No more than four excursions are allowed per day, and there must be at least 60 minutes between exposure periods. The daily Threshold Limit Value-Time Weighted Average (TLV-TWA) may not be exceeded.

Standardized Mortality Ratio (SMR)—A ratio of the observed number of deaths and the expected number of deaths in a specific standard population.

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)—An American Conference of Governmental Industrial Hygienists (ACGIH) concentration of a substance to which most workers can be exposed without adverse effect. The TLV may be expressed as a Time Weighted Average (TWA), as a Short-Term Exposure Limit (STEL), or as a ceiling limit (CL).

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

Toxic Dose(50) (TD50)—A calculated dose of a chemical, introduced by a route other than inhalation, which is expected to cause a specific toxic effect in 50% of a defined experimental animal population.

Toxicokinetic—The absorption, distribution, and elimination of toxic compounds in the living organism.

Uncertainty Factor (UF)—A factor used in operationally deriving the Minimal Risk Level (MRL) or Reference Dose (RfD) or Reference Concentration (RfC) 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 human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using lowest-observed-adverse-effect level (LOAEL) data rather than no-observed-adverse-effect level (NOAEL) data. A default for each individual UF is 10; if complete certainty in data exists, a value of 1 can be used; however, a reduced UF of 3 may be used on a case-by-case basis, 3 being the approximate logarithmic average of 10 and 1.

Xenobiotic—Any chemical that is foreign to the biological system.

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APPENDIX A. ATSDR MINIMAL RISK LEVELS AND WORKSHEETS

The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) [42 U.S.C. 9601 et seq.], as amended by the Superfund Amendments and Reauthorization Act (SARA) [Pub. L. 99–499], requires that the Agency for Toxic Substances and Disease Registry (ATSDR) develop jointly with the U.S. Environmental Protection Agency (EPA), in order of priority, a list of hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL); prepare toxicological profiles for each substance included on the priority list of hazardous substances; and assure the initiation of a research program to fill identified data needs associated with the substances.

The toxicological profiles include an examination, summary, and interpretation of available toxicological information and epidemiologic evaluations of a hazardous substance. During the development of toxicological profiles, Minimal Risk Levels (MRLs) are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified duration of exposure. MRLs are based on noncancer health effects only and are not based on a consideration of cancer effects. These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.

MRLs are derived for hazardous substances using the no-observed-adverse-effect level/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1–14 days), intermediate (15–364 days), and chronic (365 days and longer) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive chemical-induced end point considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as 100-fold below levels that have been shown to be nontoxic in laboratory animals.

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology and Environmental Medicine, expert panel peer reviews, and agency-wide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published levels. For additional information regarding MRLs, please contact the Division of Toxicology and Environmental Medicine, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop F-32, Atlanta, Georgia 30333.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Cyanide and compounds
CAS Numbers:
Date: March 2006
Profile Status: Post Public, Final
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Graph Key: 21
Species: Rat

Minimal Risk Level: 0.05 [X] mg/kg/day [ ] ppm

Reference: NTP. 1993. NTP technical report on toxicity studies of sodium cyanide administered in drinking water to F344/N rats and B6C3F1 mice. Toxicity Report No. 37. National Toxicology Program, U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health. NIH Publication 94-3386.

Experimental design: For the main study, 10 male and 10 female rats were given drinking water containing sodium cyanide at concentrations of 0, 3, 10, 30, 100, or 300 ppm for 13 weeks. A supplemental set of 10 males/group was assigned for interim examinations of hematology, clinical chemistry, and urinalysis examinations. The intakes of cyanide during that period averaged 0, 0.2, 0.5, 1.4 (males) or 1.7 (females), 4.5 (males) or 4.9 (females), or 12.5 mg/kg/day, respectively. Rats in the base study were observed twice daily. Body weights were recorded at the start of the study, weekly thereafter, and at necropsy. Clinical observation were recorded weekly. Water consumption by cage was measured weekly. Blood from the base study rats was collected on days 86 (males) and 93 (females), and from the supplemental study rats on days 5, 25, 45, and 92 for hematology and clinical chemistry. Urinalysis samples were collected from the supplemental rats on days 8, 22, 43, and 88. Complete necropsies were performed for all rats in the base study. The heart, kidneys, liver, lung, testes, and thymus were weighed. Complete histopathologic examinations of all gross lesions, tissue masses, and more than 35 tissues were performed on all animals in the 0 and 12.5 mg/kg/day dose groups. In the other exposed groups, all gross lesions, the liver (males only), spleen, and urinary bladder were examined for histopathology. Functional reproductive parameters were evaluated in main study rats in the 0, 30, 100, and 300 ppm groups. Vaginal cytology and sperm motility evaluations were performed for 12 days prior to sacrifice. Numbers of leukocytes, nucleated epithelial cells, and large squamous epithelial cells were determined from vaginal swabs to ascertain estrous cycle stage and the percentage of cycle spent in the various stages; the vagina in these rats was examined for histopathology. At necropsy, reproductive tissue weights were recorded for males, and data were recorded for epididymal sperm motility, density, and spermatogenesis.

Effects noted in study and corresponding doses: Exposure to cyanide had no significant effect on survival, body weight gain, the incidence of clinical signs, nonreproductive organ weights (absolute or relative to body weight), hematology, or clinical chemistry parameters. Water consumption was about 10% lower in the two highest exposure groups, and concomitantly, urine volume was decreased and urine specific density was increased; the authors suggested that these findings indicated a palatability problem at the two highest doses. Urinary thiocyanate levels were increased in most exposed groups, indicative of biotransformation of ingested cyanide. No treatment-related gross or histopathologic lesions were observed in rats, including potential target tissues such as the corpus callosum of the brain and the follicular epithelium of the thyroid gland (susceptible to the anti-thyroid effects of the metabolite thiocyanate).

Some cyanide-related effects were observed in the study of reproductive parameters. Statistically significant decreases compared to controls were observed in the absolute weights of the left epididymis (-7%), left cauda epididymis (-13%), and left testis (-7.6%) of rats treated at 12.5 mg/kg-day. In addition, 13.6% reductions compared to controls were observed in spermatid heads per testis and and spermatid counts per mL suspension in rats treated at 12.5 mg/kg/day. The authors considered these to be evidence of a mild adverse effect of cyanide on the male reproductive system. The statistically significant reductions (7.4–8.6% lower than controls) in left cauda epididymis weights observed at 1.4 and 4.5 mg/kg/day were not considered biologically significant in the absence of any other significant effect. The small (<4%), statistically significant, but not dose-related, reductions observed in spermatozoa motility in the 1.4, 4.5, and 12.5 mg/kg/day groups were within the range of normal values and were not considered biologically significant by the authors. For females, significantly (p=0.03, Wilk's Criterion) more time was spent in proestrus and diestrus stages and less time in estrus and metestrus stages in the 4.9 and 12.5 mg/kg/day dose groups than in controls, but a dose-relationship was not observed. For this reason, the authors did not consider these results unequivocal proof that cyanide adversely affects the female reproductive system.

Dose and end point used for MRL derivation: 4.5 mg/kg/day, based on the NOAEL for no reproductive effects in male rats.

[X] NOAEL [ ] LOAEL

Uncertainty Factors used in MRL derivation: 100

[ ] 00 for use of a LOAEL
[X] 10 for extrapolation from animals to humans
[X] 10 for human variability

MRL = 4.5 mg/kg/day/100 = 0.05 mg/kg/day

Was a conversion factor used from ppm in food or water to a mg/body weight dose? Yes.
If so, explain: The doses based on water consumption as reported by NTP (1993) were 0, 0.3, 0.9, 1.0, 2.7, 3.2, 8.5, 9.2, 23.5, and 23.6 mg NaCN/kg/day. These doses were converted from sodium cyanide to cyanide by multiplying each dose by 0.53 (CN^-/NaCN); resulting in dose levels of 0, 0.2, 0.5, 1.4 (males), 1.7 (females), 4.5 (males), 4.9 (females), or 12.5 mg/kg/day cyanide.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: NA

Was a conversion used from intermittent to continuous exposure? NA

Other additional studies or pertinent information that lend support to this MRL: No studies are available for the intermediate-duration oral toxicity of humans exposed to known quantities of cyanide, but there are a number of studies in animals exposed to sodium or potassium cyanide (as discussed in Section 3.2.2). However, not all studies are suitable for establishing dose-response relationships. Several studies (Gerhart 1986, 1987; Jackson 1988: Soto-Blanco et al. 2002a) in rats and pigs report neurological, thyroid, and gastrointestinal effects following gavage administration of cyanide; however, their usefulness for dose-response assessment is limited because the bolus dosing may overwhelm the detoxification process and is not characteristic of typical general population exposures to cyanide in drinking water. Similarly, although a toxicity study in dogs receiving sodium cyanide reported effects in the male reproductive system, adrenal gland, and kidney, the lower levels of the detoxifying enzyme rhodanese in this species both increases the sensitivity to cyanide and prevents the production of the metabolite

thiosulfate to levels that would be toxic to the thyroid as seen in humans and other animals (Kamalu 1993). Additionally, studies involving exposure to cyanide via a cassava diet (Tewe and Maner 1981a, 1981b) were not considered as the basis of an MRL because there is evidence suggesting that other toxic compounds, such as scopoletin, may contribute to the observed toxic effects (Kamalu 1993).

In rat and mice exposed to sodium cyanide in drinking water for 13 weeks (NTP 1993), reproductive effects in males were the only adverse effects observed. Effects on male reproduction included reductions in epididymal weights (-13%), testicular weights (-8%), and spermatid counts (-13.6%) in F344 rats exposed to 12.5 mg CN^-/kg/day, and 10–18% reductions in epididymal/caudal epididymal weights in B6C3F1 mice exposed to 24.3 mg CN^-/kg/day. In rabbits exposed to sodium cyanide in the diet at doses of 15 mg CN^-/kg/day for 4 weeks or 20 mg CN^-/kg/day for 40 weeks, hepatic toxicity (fatty degeneration and necrosis of the liver, increased serum levels of succinate dehydrogenase, alanine aminotransferase, and alkaline phosphatase) and renal toxicity (tubular necrosis) were observed (Okolie and Iroanya 2003; Okolie and Osagie 1999). Neurotoxicity (myelin degeneration in the spinal cord) was observed in rats exposed at 30 mg CN^-/kg/day as potassium cyanide in food for 11.5 months (Philbrick et al. 1979). Effects on male reproduction were severe in dogs (germ cell sloughing and degeneration, reduced spermatogenesis cycle) (Kamalu 1993) and also observed in rats and mice in studies in which no other systemic effects were observed. Hepatic, renal, and body weight effects were reported in Wistar rats that received doses of 3.6 mg CN^-/kg/day as potassium cyanide in drinking water for 15 days (Sousa et al. 2002a). However, the reliability of these findings is questionable because of the lack of incidence data for the histopathological lesions and because no body weight effects were noted in other rat studies with exposures for longer durations and at higher doses. On the basis of these considerations, reproductive toxicity in males is selected as the critical effect of cyanide toxicity. The NTP (1993) bioassay in rats is selected as the principal study because it provided the lowest LOAEL and a NOAEL for the critical effect and examined the full range of tissues with extensive interim hematological, clinical chemistry, and urinalyses.

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APPENDIX B. USER'S GUIDE

Chapter 1

Public Health Statement

This chapter of the profile is a health effects summary written in non-technical language. Its intended audience is the general public, especially people living in the vicinity of a hazardous waste site or chemical release. If the Public Health Statement were removed from the rest of the document, it would still communicate to the lay public essential information about the chemical.

The major headings in the Public Health Statement are useful to find specific topics of concern. The topics are written in a question and answer format. The answer to each question includes a sentence that will direct the reader to chapters in the profile that will provide more information on the given topic.

Chapter 2

Relevance to Public Health

This chapter provides a health effects summary based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information. This summary is designed to present interpretive, weight-of-evidence discussions for human health end points by addressing the following questions:

1. What effects are known to occur in humans?

2. What effects observed in animals are likely to be of concern to humans?

3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

The chapter covers end points in the same order that they appear within the Discussion of Health Effects by Route of Exposure section, by route (inhalation, oral, and dermal) and within route by effect. Human data are presented first, then animal data. Both are organized by duration (acute, intermediate, chronic). *In vitro* data and data from parenteral routes (intramuscular, intravenous, subcutaneous, etc.) are also considered in this chapter.

The carcinogenic potential of the profiled substance is qualitatively evaluated, when appropriate, using existing toxicokinetic, genotoxic, and carcinogenic data. ATSDR does not currently assess cancer potency or perform cancer risk assessments. Minimal Risk Levels (MRLs) for noncancer end points (if derived) and the end points from which they were derived are indicated and discussed.

Limitations to existing scientific literature that prevent a satisfactory evaluation of the relevance to public health are identified in the Chapter 3 Data Needs section.

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information is available, ATSDR has derived MRLs for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not

meant to support regulatory action, but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans.

MRLs should help physicians and public health officials determine the safety of a community living near a chemical emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Chapter 2, "Relevance to Public Health," contains basic information known about the substance. Other sections such as Chapter 3 Section 3.9, "Interactions with Other Substances," and Section 3.10, "Populations that are Unusually Susceptible" provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology that the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses (RfDs) for lifetime exposure.

To derive an MRL, ATSDR generally selects the most sensitive end point which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen end point are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest no-observed-adverse-effect level (NOAEL) that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor (UF) of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MRL are provided in the footnotes of the levels of significant exposure (LSE) tables.

Chapter 3

Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

Tables and figures are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species, MRLs to humans for noncancer end points, and EPA's estimated range associated with an upper- bound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. Use the LSE tables and figures for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of NOAELs, LOAELs, or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE Table 3-1 and Figure 3-1 are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

LEGEND

See Sample LSE Table 3-1 (page B-6)

(1) Route of Exposure. One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. Typically when sufficient data exist, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure, i.e., inhalation, oral, and dermal (LSE Tables 3-1, 3-2, and 3-3, respectively). LSE figures are limited to the inhalation (LSE Figure 3-1) and oral (LSE Figure 3-2) routes. Not all substances will have data on each route of exposure and will not, therefore, have all five of the tables and figures.

(2) Exposure Period. Three exposure periods—acute (less than 15 days), intermediate (15–364 days), and chronic (365 days or more)—are presented within each relevant route of exposure. In this example, an inhalation study of intermediate exposure duration is reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.

(3) Health Effect. The major categories of health effects included in LSE tables and figures are death, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the "System" column of the LSE table (see key number 18).

(4) Key to Figure. Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 18 has been used to derive a NOAEL and a Less Serious LOAEL (also see the two "18r" data points in sample Figure 3-1).

(5) Species. The test species, whether animal or human, are identified in this column. Chapter 2, "Relevance to Public Health," covers the relevance of animal data to human toxicity and Section 3.4, "Toxicokinetics," contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.

(6) Exposure Frequency/Duration. The duration of the study and the weekly and daily exposure regimens are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18), rats were exposed to “Chemical x” via inhalation for 6 hours/day, 5 days/week, for 13 weeks. For a more complete review of the dosing regimen, refer to the appropriate sections of the text or the original reference paper (i.e., Nitschke et al. 1981).

(7) System. This column further defines the systemic effects. These systems include respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. "Other" refers to any systemic effect (e.g., a decrease in body weight) not covered in these systems. In the example of key number 18, one systemic effect (respiratory) was investigated.

(8) NOAEL. A NOAEL is the highest exposure level at which no harmful effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system,

which was used to derive an intermediate exposure, inhalation MRL of 0.005 ppm (see footnote "b").

(9) LOAEL. A LOAEL is the lowest dose used in the study that caused a harmful health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific end point used to quantify the adverse effect accompanies the LOAEL. The respiratory effect reported in key number 18 (hyperplasia) is a Less Serious LOAEL of 10 ppm. MRLs are not derived from Serious LOAELs.

(10) Reference. The complete reference citation is given in Chapter 9 of the profile.

(11) CEL. A CEL is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases.

(12) Footnotes. Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. Footnote "b" indicates that the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

LEGEND

See Sample Figure 3-1 (page B-7)

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure concentrations for particular exposure periods.

(13) Exposure Period. The same exposure periods appear as in the LSE table. In this example, health effects observed within the acute and intermediate exposure periods are illustrated.

(14) Health Effect. These are the categories of health effects for which reliable quantitative data exists. The same health effects appear in the LSE table.

(15) Levels of Exposure. Concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m^3 or ppm and oral exposure is reported in mg/kg/day.

(16) NOAEL. In this example, the open circle designated 18r identifies a NOAEL critical end point in the rat upon which an intermediate inhalation exposure MRL is based. The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the table) to the MRL of 0.005 ppm (see footnote "b" in the LSE table).

(17) CEL. Key number 38m is one of three studies for which CELs were derived. The diamond symbol refers to a CEL for the test species-mouse. The number 38 corresponds to the entry in the LSE table.

(18) Estimated Upper-Bound Human Cancer Risk Levels. This is the range associated with the upper-bound for lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. These risk levels are derived from the EPA's Human Health Assessment Group's upper-bound estimates of the slope of the cancer dose response curve at low dose levels (q_1*).

(19) Key to LSE Figure. The Key explains the abbreviations and symbols used in the figure.

SAMPLE

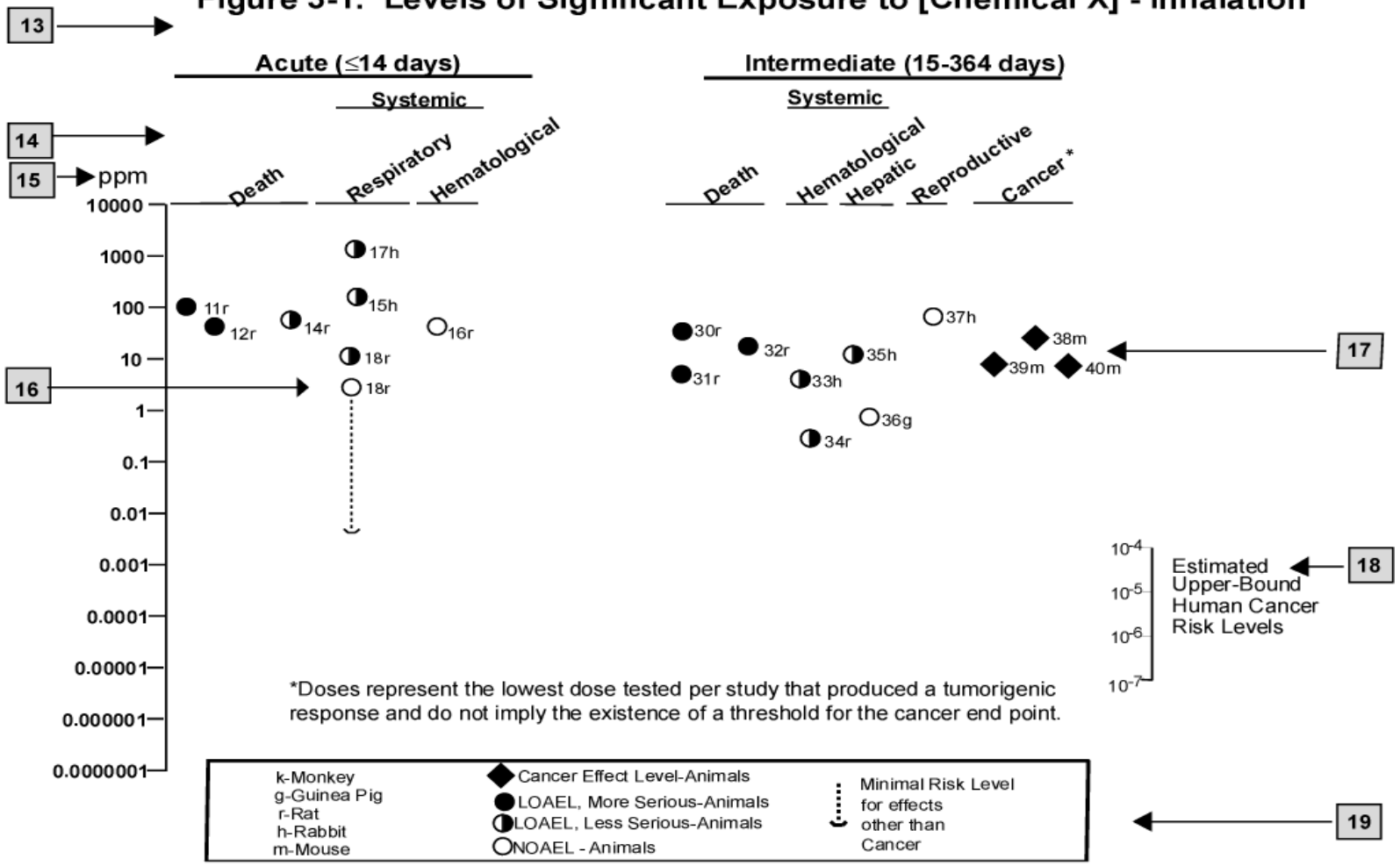
1 → **Table 3-1. Levels of Significant Exposure to [Chemical x] – Inhalation**

	Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	Serious (ppm)	Reference
2 →	INTERMEDIATE EXPOSURE							
		5	6	7	8	9		10
3 →	Systemic	↓	↓	↓	↓	↓		↓
4 →	18	Rat	13 wk 5 d/wk 6 hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
	CHRONIC EXPOSURE							
	Cancer					11		
						↓		
	38	Rat	18 mo 5 d/wk 7 hr/d			20	(CEL, multiple organs)	Wong et al. 1982
	39	Rat	89–104 wk 5 d/wk 6 hr/d			10	(CEL, lung tumors, nasal tumors)	NTP 1982
	40	Mouse	79–103 wk 5 d/wk 6 hr/d			10	(CEL, lung tumors, hemangiosarcomas)	NTP 1982

12 → [a] The number corresponds to entries in Figure 3-1.
[b] Used to derive an intermediate inhalation Minimal Risk Level (MRL) of $5x10^{-3}$ ppm; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

SAMPLE

Figure 3-1. Levels of Significant Exposure to [Chemical X] - Inhalation



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APPENDIX C. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ACOEM	American College of Occupational and Environmental Medicine
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AED	atomic emission detection
AFID	alkali flame ionization detector
AFOSH	Air Force Office of Safety and Health
ALT	alanine aminotransferase
AML	acute myeloid leukemia
AOAC	Association of Official Analytical Chemists
AOEC	Association of Occupational and Environmental Clinics
AP	alkaline phosphatase
APHA	American Public Health Association
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BAT	best available technology
BCF	bioconcentration factor
BEI	Biological Exposure Index
BMD	benchmark dose
BMR	benchmark response
BSC	Board of Scientific Counselors
C	centigrade
CAA	Clean Air Act
CAG	Cancer Assessment Group of the U.S. Environmental Protection Agency
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	cancer effect level
CELDS	Computer-Environmental Legislative Data System
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CI	confidence interval
CL	ceiling limit value
CLP	Contract Laboratory Program
cm	centimeter
CML	chronic myeloid leukemia
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
DOL	Department of Labor
DOT	Department of Transportation

DOT/UN/ NA/IMCO	Department of Transportation/United Nations/ North America/International Maritime Dangerous Goods Code
DWEL	drinking water exposure level
ECD	electron capture detection
ECG/EKG	electrocardiogram
EEG	electroencephalogram
EEGL	Emergency Exposure Guidance Level
EPA	Environmental Protection Agency
F	Fahrenheit
F_1	first-filial generation
FAO	Food and Agricultural Organization of the United Nations
FDA	Food and Drug Administration
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FPD	flame photometric detection
fpm	feet per minute
FR	Federal Register
FSH	follicle stimulating hormone
FT_3I	free triiodothyronine index
FT_4I	free thyroxine index
g	gram
GC	gas chromatography
gd	gestational day
GLC	gas liquid chromatography
GPC	gel permeation chromatography
HPLC	high-performance liquid chromatography
HRGC	high resolution gas chromatography
HSDB	Hazardous Substance Data Bank
IARC	International Agency for Research on Cancer
IDLH	immediately dangerous to life and health
ILO	International Labor Organization
IRIS	Integrated Risk Information System
Kd	adsorption ratio
kg	kilogram
kkg	metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{50}	lethal concentration, 50% kill
LCGU	local cerebral glucose utilization
LC_{Lo}	lethal concentration, low
LD_{50}	lethal dose, 50% kill
LD_{Lo}	lethal dose, low
LDH	lactic dehydrogenase
LH	luteinizing hormone
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
LT_{50}	lethal time, 50% kill
m	meter
MA	*trans,trans*-muconic acid

MAL	maximum allowable level
mCi	millicurie
MCL	maximum contaminant level
MCLG	maximum contaminant level goal
MF	modifying factor
MFO	mixed function oxidase
mg	milligram
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectrometry
NAAQS	National Ambient Air Quality Standard
NAS	National Academy of Science
NATICH	National Air Toxics Information Clearinghouse
NATO	North Atlantic Treaty Organization
NCE	normochromatic erythrocytes
NCEH	National Center for Environmental Health
NCI	National Cancer Institute
ND	not detected
NFPA	National Fire Protection Association
ng	nanogram
NHANES	National Health and Nutrition Examination Survey
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
NLM	National Library of Medicine
nm	nanometer
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPD	nitrogen phosphorus detection
NPDES	National Pollutant Discharge Elimination System
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NSPS	New Source Performance Standards
NTIS	National Technical Information Service
NTP	National Toxicology Program
ODW	Office of Drinking Water, EPA
OERR	Office of Emergency and Remedial Response, EPA
OHM/TADS	Oil and Hazardous Materials/Technical Assistance Data System
OPP	Office of Pesticide Programs, EPA
OPPT	Office of Pollution Prevention and Toxics, EPA
OPPTS	Office of Prevention, Pesticides and Toxic Substances, EPA
OR	odds ratio
OSHA	Occupational Safety and Health Administration

OSW	Office of Solid Waste, EPA
OTS	Office of Toxic Substances
OW	Office of Water
OWRS	Office of Water Regulations and Standards, EPA
PAH	polycyclic aromatic hydrocarbon
PBPD	physiologically based pharmacodynamic
PBPK	physiologically based pharmacokinetic
PCE	polychromatic erythrocytes
PEL	permissible exposure limit
pg	picogram
PHS	Public Health Service
PID	photo ionization detector
pmol	picomole
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
PSNS	pretreatment standards for new sources
RBC	red blood cell
REL	recommended exposure level/limit
RfC	reference concentration
RfD	reference dose
RNA	ribonucleic acid
RQ	reportable quantity
RTECS	Registry of Toxic Effects of Chemical Substances
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SIC	standard industrial classification
SIM	selected ion monitoring
SMCL	secondary maximum contaminant level
SMR	standardized mortality ratio
SNARL	suggested no adverse response level
SPEGL	Short-Term Public Emergency Guidance Level
STEL	short term exposure limit
STORET	Storage and Retrieval
T_3	triiodothyronine
T_4	thyroxine
TD_{50}	toxic dose, 50% specific toxic effect
TLV	threshold limit value
TOC	total organic carbon
TPQ	threshold planning quantity
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TSH	thyroid stimulating hormone
TWA	time-weighted average
UF	uncertainty factor
U.S.	United States
USDA	United States Department of Agriculture
USGS	United States Geological Survey

VOC	volatile organic compound
WBC	white blood cell
WHO	World Health Organization

>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
γ	gamma
δ	delta
μm	micrometer
μg	microgram
q_1^*	cancer slope factor
–	negative
+	positive
(+)	weakly positive result
(–)	weakly negative result

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APPENDIX D. INDEX