CHAPTER 6. 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 adverse health effects (and techniques for developing methods to determine such health effects) of cyanide.

Data needs are defined as substance-specific informational needs that, if met, would reduce the uncertainties of human health risk 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 b**e proposed.**

6.1 EXISTING INFORMATION ON HEALTH EFFECTS

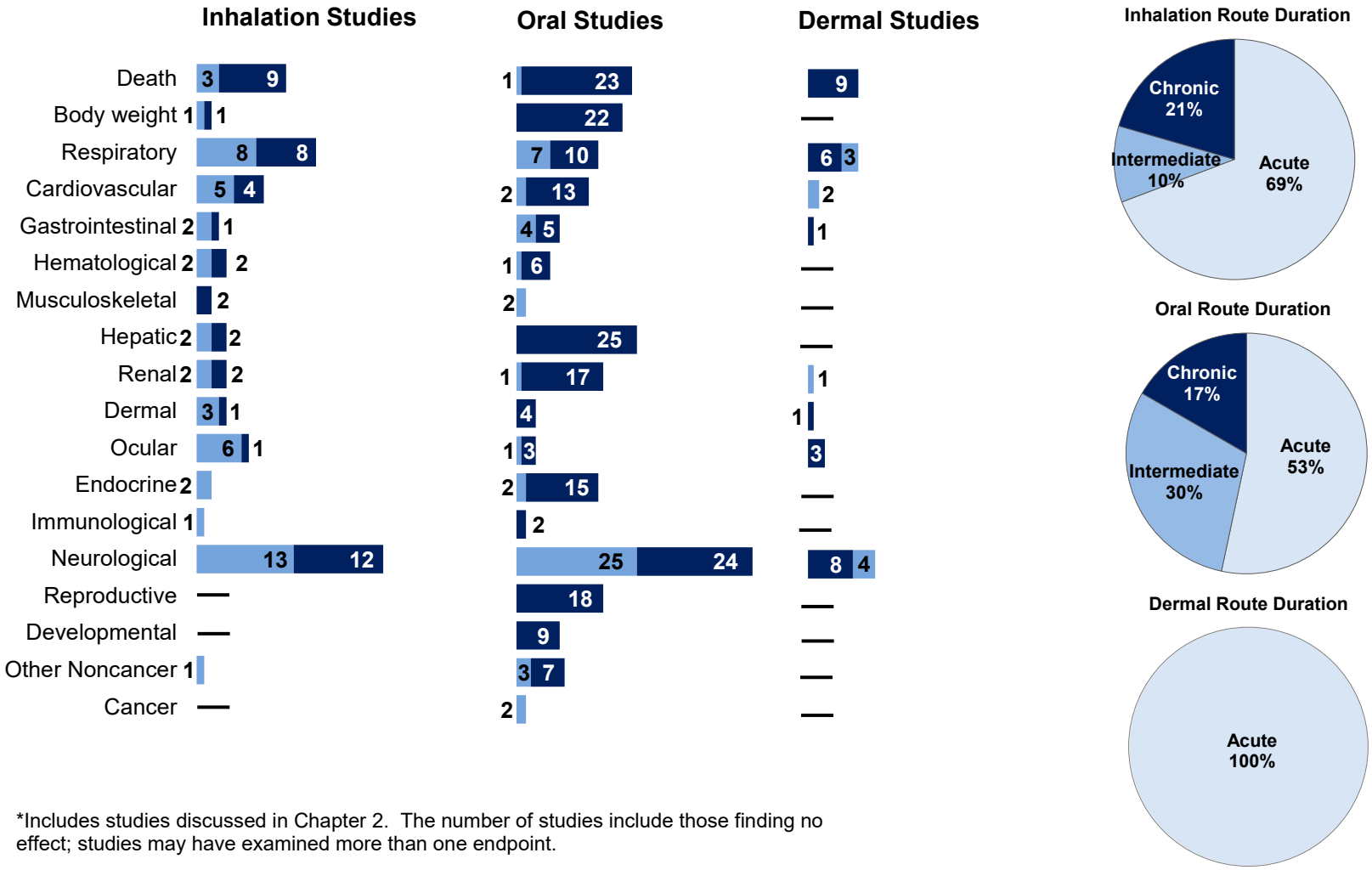
Studies evaluating the health effects of inhalation, oral, and dermal exposure of humans and animals to cyanide that are discussed in Chapter 2 are summarized in Figure 6-1. The purpose of this figure is to illustrate the information concerning the health effects of cyanide. The number of human and animal studies examining each endpoint is indicated regardless of whether an effect was found and the quality of the study or studie**s.**

6.2 IDENTIFICATION OF DATA NEEDS

Missing information in Figure 6-1 should not 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* (ATSDR 1989), is 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.

Figure 6-1. Summary of Existing Health Effects Studies on Cyanide by Route and Endpoint*

Potential neurological, lethal, and respiratory effects were the most studied endpoints
The majority of the studies examined inhalation and oral exposure in **animals** (versus **humans**)



*Includes studies discussed in Chapter 2. The number of studies include those finding no effect; studies may have examined more than one endpoint.

Acute-Duration MRLs. The database was inadequate to derive inhalation or oral acute-duration MRLs. Available acute-duration studies were largely limited to case reports in humans and acute lethality studies in animals. For inhalation, the only effect reported below concentrations associated with lethality was also a serious adverse effect (50% reduction in respiratory rate) and was therefore not suitable as the basis for an MRL. While there are numerous acute-duration oral studies, most of the studies administered cyanide compounds via bolus administration, which is considered less relevant to human exposure (due to saturation of detoxification pathways). The only acute-duration drinking water study had several limitations that made it unsuitable as the basis of the MRL. Additional acute-duration inhalation and drinking water studies using several sublethal dose levels and examining comprehensive endpoints would help to determine thresholds for known target organs and for any new target organs that might be identified. The information would be useful for populations living near hazardous waste sites that could be exposed to cyanide in contaminated water or soil for a short time.

Intermediate-Duration MRLs. The database was inadequate to derive an intermediate-duration inhalation MRL. Available intermediate-duration inhalation studies are limited to a study in rats evaluating a single exposure level and a limited set of cardiovascular endpoints and a series of poorly reported studies in dogs. Multi-dose, intermediate-duration studies examining a comprehensive set of endpoints would help to determine thresholds for known target organs and for any new target organs that might be identified. The database was adequate to derive an intermediate-duration oral MRL. Additional low-dose drinking water studies to identify a NOAEL and LOAEL values for sensitive neurobehavioral endpoints could reduce uncertainty in the MRL. The information would be useful for 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 MRLs. The database was inadequate to derive inhalation or oral chronic-duration MRLs. Inhalation data were limited to occupational exposure studies in humans with that were considered inadequate for deriving a chronic-duration inhalation MRL for one or more of the following reasons: limited or no exposure levels, small cohort size, probable concurrent dermal exposure, and concurrent exposure to other compounds that was not controlled for in the analysis. No chronic-duration animal inhalation studies with hydrogen cyanide were identified. For oral exposure, studies of populations that customarily eat cassava are not appropriate for MRL derivations because some effects may have resulted from other exposures associated with cassava, such as scopoletin or mycotoxin contamination (Obidoa and Obasi 1991; Olorunnado et al. 2024). Additionally, external exposure

estimates are not available, and biomarker exposure was often available only at (or after) diagnosis with thyroid or neurological abnormalities. Available chronic-duration oral studies in animals have major limitations. One is a study in rats with unstable cyanide levels in their feed, which was fumigated with hydrogen cyanide, due to evaporation of cyanide throughout the experiment (Howard and Hanzal 1955). Furthermore, no exposure-related effects were found in the study. The only other identified study is a foreign-language study in dogs; however, only one dog was used per dose and no concurrent control was included (Hertting et al. 1960). Therefore, data are not sufficient to derive MRL values for chronic-duration exposure. Additional chronic-duration studies in animals would be helpful to determine thresholds for target organs. The results of chronic toxicity would be useful for populations living near hazardous waste sites that could be repeatedly exposed to cyanide in contaminated water or soil for periods exceeding 1 year.

Health Effects.

Endocrine. Limited human data from occupational exposure studies and communities with high cassava intake suggest the thyroid may be a target of cyanide toxicity. These effects are attributable to competitive inhibition of the sodium-iodine symporter by thiocyanate. Oral studies in animals report decreased thyroid hormone levels, increased serum thyroid stimulating hormone, and thyroid enlargement. Additional drinking studies in the low-dose range for all durations that evaluate a comprehensive set of thyroid endpoints, including serum thyroid hormone levels, to best define the adverse effect level would be useful. No animal inhalation studies examining the thyroid were identified; these could be useful to confirm if the thyroid is a sensitive target via that route.

No data were located regarding other endocrine effects in humans or animals after inhalation or dermal exposure or oral studies in humans. However, a few oral cassava studies in animals reported effects in the pancreas and adrenal gland. Testing in animals under low-level exposure conditions would be useful to clarify whether other endocrine organs are targets of cyanide toxicity.

Male reproductive. No data were located regarding reproductive effects of cyanide in humans. 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); however, findings from this study were not

reproduced in a replicate study by Tyner and Greeley (2023). In contrast, a couple of gavage studies reported effects similar to those observed by NTP (1993), including Oyewopo et al. (2021a, 2021b) and Shivanoor and David (2015). Altered male gonadal weights were also reported following exposure to copper cyanide or potassium silver cyanide via gavage; however, the contribution of the metals cannot be ruled out (Gerhart 1986, 1987). Further investigation into potential male reproductive effects via relevant human exposure routes (inhalation, drinking water) may be helpful to determine the true nature of the relationship between cyanide exposure and testicular effects.

Developmental. 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 to cassava, and contradictory results were obtained. Teratogenic effects of cyanide exposure were observed in rats and hamsters fed a cassava diet (Frakes et al. 1986; Singh 1981), while no effects were found in rats fed cassava diets alone or supplemented with potassium cyanide (Tewe and Maner 1981a). However, the latter study is flawed in that it did not include a control group not exposed to cyanide. More data regarding developmental toxicity in experimental animals would be useful to identify the possible risk for humans. Studies on developmental neurotoxicology, 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 CNS is an important target for cyanide toxicity in humans and animals following exposure by all three routes. However, there are limited dose-response data at low, environmentally relevant levels. Animal studies designed to evaluate and define dose responses for sensitive neurobehavioral outcomes at low exposure levels for both inhalation and oral exposure would be beneficial for this critical endpoint. 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. A series of studies by de Sousa et al. (2007) reported severe CNS damage in rat dams exposed to potassium cyanide or potassium thiocyanide during gestation; however, similar findings were not observed in nonpregnant female rats or mice exposed to sodium cyanide at much higher concentrations (NTP 1993). Additional studies in pregnant rodents would be helpful to determine if pregnancy confers a unique susceptibility to cyanide neurotoxicity.

Epidemiological and Human Dosimetry Studies. Human exposure to low levels of cyanide is quite common. Cigarette and fire smoke contain cyanide (EPA 1981); cyanide is used as a postharvest pesticide fumigant (Jenks 1979) and can be detected at low levels in drinking water supplies (EPA 1981). 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. Additional studies examining exposure to cyanide via cassava consumption would be less useful, since cassava is not widely consumed in the United States, and it contains another substance such as scopoletin, which may contribute to neurotoxicity (Obidoa and Obasi 1991).

Biomarkers of Exposure and Effect. 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 background levels of cyanide can be found in the human tissues, urine, and expired air, this should be considered when interpreting laboratory findings, especially in scenarios of low-dose exposures. 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 (Blakley 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 and thiocyanate levels are only sustained for somewhat longer periods, other biomarkers of low-level exposure would be useful.

In acute poisoning scenarios, clinicians may not have time to wait for results of laboratory tests for cyanide or metabolite levels in the blood or urine; in these cases, the clinical presentation must be used for differential diagnosis and clinical management (Graham and Traylor 2023; Holstege and Kirk 2019). The target organs of cyanide toxicity are the CNS and the cardiovascular system, but exposure to other chemicals may have similar effects. Clinical signs classically associated with cyanide poisoning include detection of an almond-like odor on the breath of the patient (by the clinician) and "cherry-red skin" (due to impaired oxygen utilization); however, in practice, these clinical signs have shown low reliability (Parker-Cote et al. 2018). Funduscopic exam has been used to evaluate retinal veins for arterialization, which would also show evidence of impaired oxygen utilization (Holstege and Kirk 2019) Reductions in cytochrome c oxidase activity in specific organs, elevations in plasma lactate concentrations, and increased anion gap metabolic acidosis of unknown etiology (especially in the presence of altered mental state) have been used as measures of cyanide toxicity following acute-duration exposure (Baud et al. 1996, 2002; Holstege and Kirk 2019; Ikegaya et al. 2001). Imaging techniques, such as MRI and positron emission topography (PET) scan, have been used to follow the course of brain injury or monitor changes in glucose utilization by specific brain regions, respectively, following acute-duration 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 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-duration inhalation exposure. No data were found that dealt with saturation kinetics in cyanide metabolism; studies evaluating saturation kinetics would better inform relevance of bolus studies to environmental human exposures.

Comparative Toxicokinetics. Several studies on cyanide lethality and toxicity indicate that the CNS, reproductive system, and thyroid gland are potential target organs in both humans and animals. 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 (Blakley 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, other 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 enzymes compared to other species (Drawbaugh and Marrs 1987; Himwich and Saunders 1948; NIH/NINDS 2016a, 2016b; Rockwood et al. 2003), dogs do not appear to be the optimal model species for extrapolation to humans.

Children's Susceptibility. 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. 2002). 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.

Physical and Chemical Properties. 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. 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; Sittig 1980). 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, import and export data for individual cyanide

compounds are difficult to obtain (USDOC 2004). There are some less recent data regarding the release of cyanides in air (EPA 1981) but, except for hydrogen cyanide, 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 edible plants high in cyanogenic glycosides (EPA 1978, 1981; 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 consumer products. The two most likely sources of general population exposure to cyanide include people who inhale cigarette smoke (EPA 1981; Mahernia et al. 2015) or individuals who are exposed to a house or other type of building fire (Andrews et al. 1989; Ballantyne 1987; Bolstad-Johnson et al. 2000). There are EPA regulations regarding the disposal of cyanide wastes or Occupational Safety and Health Administration (OSHA) regulations and NIOSH recommendations regarding the levels of hydrogen cyanide in workplaces (see Chapter 7). Data are available on chemical and biological processes for degrading cyanide in leachate and wastewater generated during the extraction of gold and other precious metals from low-grade ore (Akcil and Mudder 2003; EPA 1994). 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 1981; 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 1978, 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 1978), 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 to 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 1978, 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 3.1.1 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); however, there is evidence suggesting the bioconcentration of cyanide metal complexes in fish (EPA 1979). Therefore, it would be useful to determine the bioconcentration potential for cyanide in fish exposed to less-toxic and water-soluble cyanide complexes. There is no indication of biomagnification of cyanides in aquatic and terrestrial food chains (EPA 1978). 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 (EPA 2010). 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 concentrations in drinking water from 35 U.S. water utilities were 0.45–0.8 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 1978, 1981; Honig et al. 1983; Pré 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 would 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 3.1.4, 3.3.1, and 5.6). 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 2004). These data are mainly limited to cyanide exposures that result from the consumption of cassava (Dufour 1988; Mlingi et al. 1992; Ojo and Deane 2002; Okafor et al. 2002; Onabolu et al. 2002; Tylleskar et al. 1992, 1994).

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. Studies in animals suggest that cyanide and thiocyanate can be transferred to infants via breast milk. Additional studies would be useful to characterize this potential source of exposure.

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.

6.3 ONGOING STUDIES

There are several ongoing studies evaluating potential adverse effects of cyanide in humans and laboratory animals as well as mechanisms of toxicity (Table 6-1).

Table 6-1. Ongoing Studies on Cyanide

Investigator	Affiliation	Research description	Sponsor
Tippets, Emily	University of Utah	Restoration of NAD+/NADH balance as treatment for cyanide poisoning and downstream mechanisms	NINDS
Patterson, Steven	University of Minnesota	Development of autoinjector with sulfanegen as a treatment for cyanide toxicity	NINDS
Bramble, Matthew	Children's Research Institute	Case control study with cyanide-induced disease konzo (motor neuron disease) examining differences in the microbiome	Other research-related
Rutter, Jared	Brigham and Women's hospital	Examine mechanisms of cyanide toxicity and investigate compounds that impact the citric acid cycle as potential therapeutics	NINDS
Peterson, Randall	Brigham and Women's hospital	Mechanism of glycoxylate (and derivatives) as an alternative or supplemental cyanide toxicity treatment (non-scavenging)	NINDS
Macrae, Calum	Brigham and Women's hospital	Mechanisms of cyanide induced lethality and evaluation of therapeutic compounds that manipulate metabolism	NINDS

NAD+/NADH = oxidized/reduced form of nicotinamide adenine dinucleotide; NINDS = National Institute of Neurological Disorders and Stroke

Source: NIH RePORTER 2023