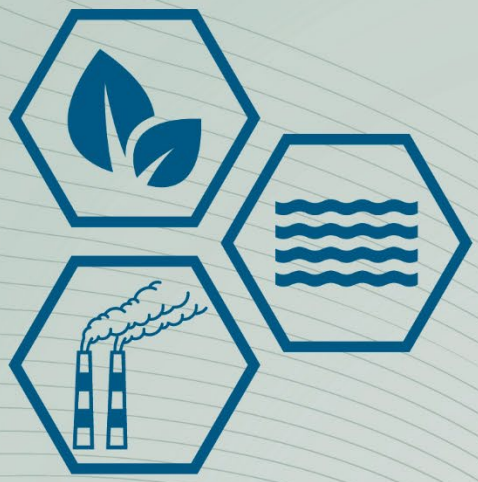

Toxicological Profile for Cyanide

Draft for Public Comment

October 2024

U.S. Department of Health and Human Services
Agency for Toxic Substances and Disease Registry

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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 these toxic substances described therein. Each peer-reviewed profile identifies and reviews the key literature that describes a 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 relevance to public health discussion which would allow a public health professional to make a real-time determination of whether the presence of a particular substance in the environment poses a potential threat to human health. 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 the protection of public health are identified by ATSDR.

Each profile includes the following:

(A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a toxic substance to ascertain the levels of significant human exposure for the substance and the associated acute, intermediate, 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 the levels of exposure that present a significant risk to human health due to acute-, intermediate-, and chronic-duration exposures; 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. ATSDR plans to revise these documents in response to public comments and as additional data become available. Therefore, we encourage comments that will make the toxicological profile series of the greatest use.

Electronic comments may be submitted via: www.regulations.gov. Follow the on-line instructions for submitting comments.

Written comments may also be sent to: Agency for Toxic Substances and Disease Registry
Office of Innovation and Analytics
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1600 Clifton Road, N.E.
Mail Stop S106-5
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The toxicological profiles are developed under the Comprehensive Environmental Response, Compensation, and Liability Act of 1980, as amended (CERCLA or Superfund). CERCLA Section 104(i)(1) directs the Administrator of ATSDR to "…effectuate and implement the health-related authorities" of the statute. This includes the preparation of toxicological profiles for hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL) and that pose the most significant potential threat to human health, as determined by ATSDR and the EPA. Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list. In addition, ATSDR has the authority to prepare toxicological profiles for substances not found at sites on the NPL, in an effort to "…establish and maintain inventory of literature, research, and studies on the health effects of toxic substances" under CERCLA Section 104(i)(1)(B), to respond to requests for consultation under Section 104(i)(4), and as otherwise necessary to support the site-specific response actions conducted by ATSDR.

This profile reflects ATSDR's assessment of all relevant toxicologic testing and information that has been peer-reviewed. Staffs 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 is being made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.

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Associate Director,
Agency for Toxic Substances and Disease Registry
Centers for Disease Control and Prevention

VERSION HISTORY

Date	Description
October 2024	Draft for public comment toxicological profile released
July 2006	Toxicological profile released
September 1997	Toxicological profile released
April 1993	Toxicological profile released
December 1989	Toxicological profile released

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These experts collectively have knowledge of toxicology, chemistry, and/or health effects. All reviewers were selected in conformity with Section 104(I)(13) of the Comprehensive Environmental Response, Compensation, and Liability Act, as amended.

ATSDR scientists review peer reviewers' comments and determine whether changes will be made to the profile based on comments. The peer reviewers' comments and responses to these comments are part of the administrative record for this compound.

The listing of peer reviewers should not be understood to imply their approval of the profile's final content. The responsibility for the content of this profile lies with ATSDR.

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CHAPTER 1. RELEVANCE TO PUBLIC HEALTH

1.1 OVERVIEW AND U.S. EXPOSURES

Cyanides, a diverse family of compounds containing the highly reactive cyanide anion (CN^-), are produced from both anthropogenic and natural sources. Chemicals that release cyanide are called cyanogenic compounds. 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 (StatPearls 2023). The use of the term 'cyanide' in this document 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 (Brandt-Rauf et al. 1988; Crutzen and Carmichael 1993; EPA 1981, 1994; Fields 2001; Gaffney et al. 1987; Huiatt 1985; Lobert and Warnatz 1993; Mudder and Botz 2000; Scott 1985). Numerous plant species contain cyanogenic glycosides that can release hydrogen cyanide upon biodegradation or ingestion (Cicerone and Zellner 1983; Crutzen and Carmichael 1993; EPA 1981; Jones 1998; Knowles 1988; Mudder and Botz 2000). 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 (EPA 1978; Honig et al. 1983; Lasch and El Shawa 1981; Swain et al. 1992). 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 (Mlingi et al. 1992, 1993; Olorunnado et al. 2024; O'Brien et al. 1992).

The general population is exposed to cyanides primarily by through inhalation of cigarette smoke and ingestion of certain foods. Reported levels of cyanide in outdoor air range from 0.33 to 0.76 ppbv (Jaszczak et al. 2017). 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 (Baker and Proctor 1990; Chepiga et al. 2000; EPA 1981; Guerin et al. 1987). Comprehensive water-quality data from the United States indicates that cyanide was detected in 22% of surface water samples collected between 1981 and 2023 (WQP 2024). Of these, <1% had cyanide concentrations >10 µg/L, three of which were drinking water samples with cyanide concentrations between 10 and 50 µg/L. Between 1992 and 1998, the cyanide content in 99.8% of public water systems using groundwater in the United States did not exceed the maximum concentration limit of 0.2 mg/L (EPA 1999). 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) (EPA 1978; Honig et al. 1983). 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.

1.2 SUMMARY OF HEALTH EFFECTS

Information on the toxicity of cyanide in humans primarily comes from numerous case-series and case reports following intentional exposure (e.g., suicidal or homicidal purposes) or accidental exposure. There are a limited number of occupational exposure studies and studies in populations with high dietary intake of natural cyanogenic glycosides (i.e., cassava) that also inform toxicity of cyanide. Further information on the noncancer toxicity of cyanide comes from several oral studies in animals, with far fewer inhalation studies in animals. Data following dermal exposure are very limited in humans and animals.

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 (Way 1984). The result is a reduction in oxygen sufficient to cause tissue damage (histotoxic 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 (Rieders 1971). 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 (Ardelt et al. 1989; Rieders 1971).

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 (Rieders 1971). 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 CN^-/kg. Within a few minutes after swallowing the toxicant, the victim collapses, frequently with a scream (Gettler and St. George 1934). Dyspnea, convulsions, and death from asphyxia follow. Dermal exposure to cyanide results in comparable effects, but at higher doses (Dodds and McKnight 1985; Trapp 1970). Based on case report studies, the following acute median lethal exposure levels for humans were estimated: an LC_{50} of 622 ppm for a 30-minute inhalation exposure to hydrogen cyanide (DOA 1976), an LD_{50} of 1.52 mg CN^-/kg for the oral route (EPA 1987), and an LD_{50} of 100 mg CN^-/kg for the dermal route (Rieders 1971), assuming that CN^- is readily released from the compound. Animal studies also reported dyspnea, convulsions, and asphyxiation as effects of high acute-duration exposure to cyanide by any route of exposure (Ballantyne 1983a, 1983b, 1988; Fairley et al. 1934; Ferguson 1962; Haymaker et al. 1952; Higgins et al. 1972; Matijak-Schaper and Alarie 1982; Smyth et al. 1969; Valade 1952; Walton and Witherspoon 1926).

As illustrated in Figures 1-1 and 1-2, sensitive targets in laboratory animals at nonlethal exposure levels include the respiratory system following inhalation exposure and the neurological and male reproductive system following oral exposure; body weight effects were also noted at low oral exposures. While reliable dose-response information is not available from human studies, potential sensitive targets of toxicity following repeated exposure to nonlethal exposure levels identified in occupational studies include respiratory, thyroid, and neurological effects. Studies in populations with high dietary cassava intake indicate that the thyroid and nervous system are potential targets of repeated, low-dose cyanide toxicity. Based on available data in humans and animals, a systematic review was conducted on thyroid, neurological, and male reproductive effects following oral exposure (see Appendix C for details). A formal systematic review was not conducted following inhalation exposure due to a limited database coupled with the lack of reliable dose-response data.

A systematic review of these endpoints resulted in the following hazard identification conclusions for oral exposure to cyanide:

- Thyroid effects are a presumed health effect for humans.

- Neurological effects are a known health effect for humans.
- Male reproductive effects a suspected health effect for humans.

Figure 1-1. Health Effects Found in Animals Following Inhalation Exposure to Cyanide

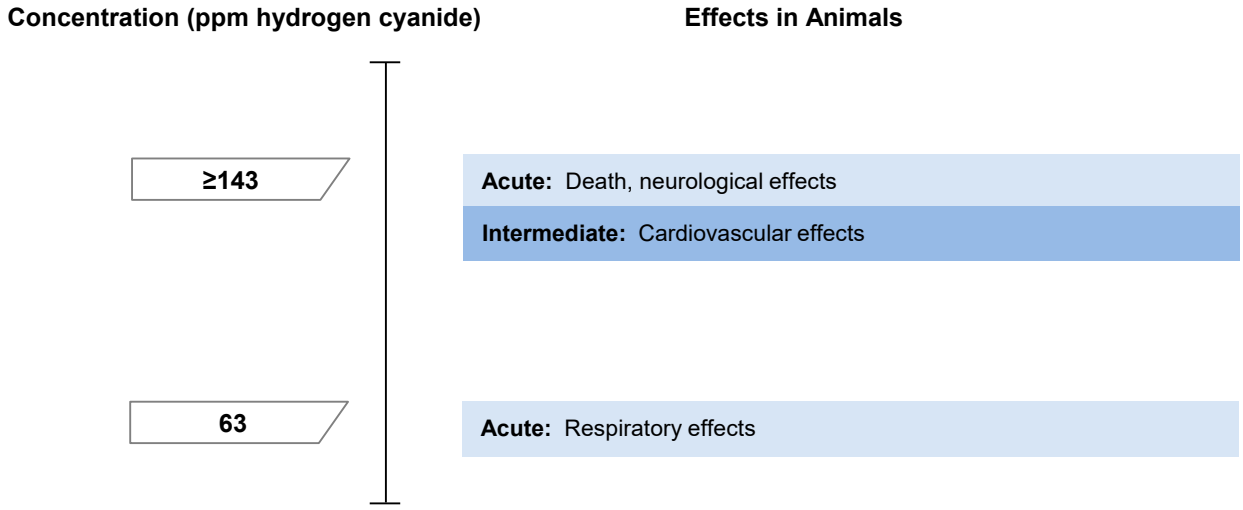
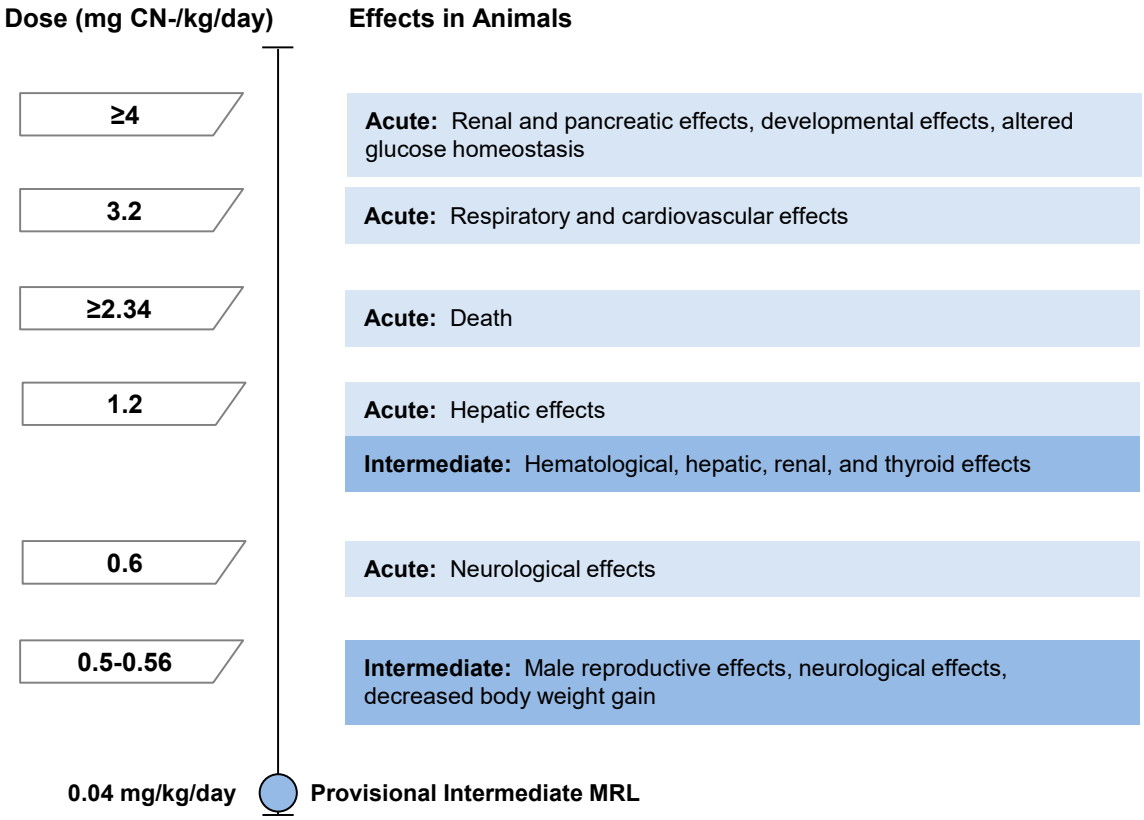


Figure 1-2. Health Effects Found in Animals Following Oral Exposure to Cyanide



Thyroid Effects. Thyroid effects are a presumed health effect following oral exposure based on a low level of evidence in humans, a moderate level of evidence in animals, and supporting mechanistic data. Thyroid effects following cyanide exposure can result from the interference of thiocyanate, a metabolite of cyanide, with iodine uptake and utilization in the thyroid gland (VanderLaan and Bissell 1946). Reduced serum thyroid hormone levels, increasingly elevated levels of thyroid stimulating hormone, and goiter are typical sequelae of chronic-duration cyanide exposure observed in tropical populations reliant on cassava as the main staple of the diet (Cliff et al. 1986; Delange and Ermans 1971; Ermans et al. 1980). 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. In animals, adverse thyroid effects (altered serum hormones, enlarged thyroid) have been reported in rats and rabbits following intermediate-duration oral exposure to cyanide compounds at ≥11.50 and 1.2 mg CN^-/kg/day, respectively (Avais et al. 2018; Philbrick et al. 1979; Tyner and Greeley 2023). At lower doses (≥0.12 mg CN^-/kg/day), evidence of induction of potential homeostatic mechanisms for thyroid function (dose-related increases in the number of resorption vacuoles in the thyroid gland) in the absence of clear evidence of altered thyroid function (i.e., altered serum hormone levels) has also been observed (Sousa et al. 2002; de Sousa et al. 2007).

While inhalation data are limited and do not provide reliable dose-response data, occupational studies provide additional support for the potential association between cyanide exposure and thyroid effects. Enlargement of the thyroid gland, altered iodine uptake, decreased thyroid hormone levels, and/or increased thyroid stimulating hormone were observed in workers occupationally exposed to cyanide at electroplating or silver-reclaiming factories (Banerjee et al. 1997; Blanc et al. 1985; El Ghawabi et al. 1975).

Neurological Effects. Neurological effects are a known health effect following oral exposure based on a high level of evidence from humans and animals. There is evidence of regional outbreaks of neurological disease in African communities reliant on a diet rich in cassava as a carbohydrate source (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). As noted for thyroid effects, these populations often suffered from nutritional deficiencies and these conditions may not apply to populations in the United States. Additionally, other compounds in cassava (e.g., scopoletin, a potent hypotensive and spasmolytic agent) may contribute to observed effects. However, the potential association is strengthened

by strong evidence of neurological effects from case reports and case-series reports that the central nervous system (CNS) is a primary target following high-level cyanide exposure (see Section 2.15 for references). Even single exposures have resulted in permanent neurological dysfunction; many case reports lack exposure data, but doses in the range of 4.5–8.57 mg CN^-/kg as potassium cyanide have been reported (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; Zaknun et al. 2005).

Studies evaluating sensitive neurobehavioral outcomes at nonlethal oral doses in animals is limited, particularly repeat-dose exposure via relevant exposure routes (drinking water or dietary exposures). However, bolus administration studies are consistent with human poisoning cases, showing neurobehavioral changes at low doses ≥0.56 mg CN^-/kg/day (Hawk et al. 2016; Ishaku et al. 2018; Mathangi et al. 2011; Ogundele et al. 2014b) and overt and severe clinical signs of neurotoxicity prior to death at lethal doses (Gerhart 1987; Rice et al. 2018; Sabourin et al. 2016). Damage to the tissues of the CNS has been observed in animal studies following acute- and intermediate-duration exposure to cyanide compounds at doses ≥0.6 and ≥0.24 mg CN^-/kg/day, respectively (de Sousa et al. 2007; Philbrick et al. 1979; Soto-Blanco et al. 2002).

While available inhalation data do not provide reliable dose-response data for neurological findings in humans and nearly all reported neurological effects in animals are in acute lethality studies, these data strongly support that the CNS is a primary target of cyanide toxicity via the general mechanism of toxicity (impaired cellular oxygen utilization), which is applicable to all routes. Acute-duration inhalation of high concentrations of cyanide provokes a brief CNS stimulation followed by depression, convulsions, coma, and death in humans (Bonsall 1984; Chen and Rose 1952; Lasch and El Shawa 1981; Peden et al. 1986; Potter 1950; Singh et al. 1989) and animals (Haymaker et al. 1952; McNerney and Schrenk 1960; Purser et al. 1984). 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 (Haymaker et al. 1952; Hirano et al. 1967; Levine 1969; Levine and Stypulkowski 1959).

Male Reproductive Effects. Male reproductive effects are a suspected health effect following oral exposure based on no human data and a moderate level of evidence in animals. No studies were located regarding male reproductive effects in humans after any route of exposure, but a few studies reported male reproductive effects in animals exposed via the oral route. Male reproductive effects were the only adverse effects observed in rats and mice ingesting 12.5 or 24.3 mg CN^-/kg/day, respectively, as sodium

cyanide in the drinking water for 13 weeks (NTP 1993). 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 (NTP 1993). The National Toxicology Program (NTP 1993) concluded that while findings were considered adverse, they were mild, and unlikely to adversely affect fertility in rodents. No studies evaluating male fertility were identified. However, a second study in the same strain of rats designed to replicate the NTP (1993) study design was unable to reproduce the testicular effects at the same water concentration (300 ppm; calculated daily intake of 11.50 mg CN^-/kg/day) (Tyner and Greeley 2023). Tyner and Greeley (2023) proposed that the reproductive effects noted in the NTP (1993) study may have been attributable to decreased water consumption in the highest dose group rather than due to direct toxic effects. To control for this, Tyner and Greeley (2023) included a water-restricted control group to match measured water consumption at the highest dose level. However, no clear exposure-related effects on male reproductive organ weights or sperm parameters were observed by Tyner and Greely (2023), compared to either the water-restricted controls or the *ad libitum* controls.

While drinking water studies are considered more relevant to human exposure, several gavage studies indicate that bolus administration of cyanide compounds (which may overwhelm detoxification mechanisms) can cause male reproductive damage. Adverse effects on the male reproductive system, including serum hormone changes, sperm effects, and mild histopathological effects, were noted following intermediate-duration exposure to doses ≥0.5 mg CN–/kg/day as sodium cyanide (Oyewopo et al. 2021a, 2021b; Shivanoor and David 2015), 14.5 mg CN–/kg/day as copper cyanide (Gerhart 1986), or 2.6 mg CN–/kg/day as potassium silver cyanide (Gerhart 1987). No adverse effects were noted at acute-duration doses up to 4.6 mg CN–/kg/day as potassium cyanide (Hawk et al. 2016; Sabourin et al. 2016).

Cancer Effects. There are no data in humans or animals regarding potential cancer effects after exposure to cyanide. The U.S. Environmental Protection Agency (EPA) determined that there is inadequate information to assess the carcinogenic potential of hydrogen cyanide and cyanide salts (IRIS 2010). The Department of Health and Human Services (NTP 2021) and the International Agency for Research on Cancer (IARC 2023) have not evaluated the potential for cyanide or cyanide compounds to cause carcinogenicity in humans.

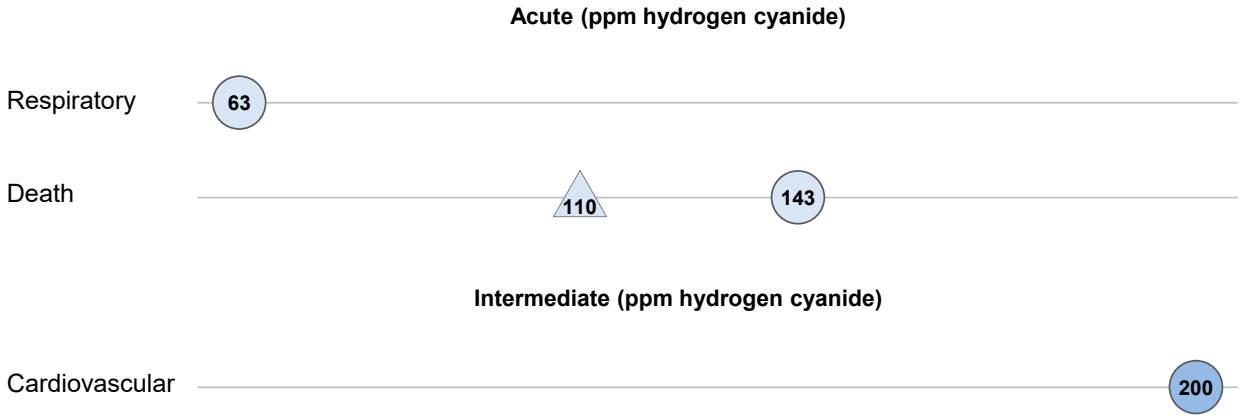
1.3 MINIMAL RISK LEVELS (MRLs)

The inhalation database was considered inadequate for derivation of inhalation MRLs for cyanide. As illustrated in Figure 1-3, no reliable dose-response data were available from human studies for nonlethal effects. The lethal concentration in humans shown in Figure 1-3 represents a concentration that may lead to death within 30–60 minutes, determined via review of case report data (WHO 2004). In laboratory animals, the respiratory system is the only system with a reported adverse effect below hydrogen cyanide concentrations associated with death. Effects observed in the respiratory system below the lethal level are also considered serious effects (50% reduction in respiratory rate), precluding derivation of inhalation MRLs.

Figure 1-3. Summary of Sensitive Targets of Cyanide – Inhalation

Available data indicate that the respiratory system is the most sensitive target of cyanide inhalation exposure.

Numbers in triangles and circles are the lowest LOAELs among health effects in humans and animals, respectively.



The oral database was considered adequate for derivation of a provisional intermediate-duration oral MRL for cyanide; the acute- and chronic-duration databases were inadequate to support MRL derivation. No reliable dose-response data were available for humans. The lethal dose in humans shown in Figure 1-4 represents the average fatal dose calculated from case reports (EPA 1987). In animals, while the entire oral database was considered for identification of sensitive targets, gavage studies were not considered for dose-response assessment during MRL derivation because bolus administration may overwhelm detoxification processes in a manner not typical of the gradual exposures from dietary sources or drinking water expected for the general population (see Appendix A for more details). Therefore, Figure 1-4 only includes data from dietary and drinking water studies in animals. As illustrated in Figure 1-4, the only available acute-duration drinking water study in laboratory animals identifies the

neurological system as the most sensitive system following acute-duration exposure. However, available intermediate-duration drinking water and dietary studies identify the endocrine system (thyroid) and male reproductive system as the most sensitive targets in laboratory animals.

The provisional MRL values are summarized in Table 1-1 and discussed in greater detail in Appendix A.

Figure 1-4. Summary of Sensitive Targets of Cyanide – Oral

Available data indicate that the neurological system is the most sensitive target following acute-duration oral exposure and the male reproductive and endocrine (thyroid) systems are the most sensitive targets following intermediate-duration oral exposure.

Numbers in triangles and circles are the lowest LOAELs among health effects in humans and animals, respectively.

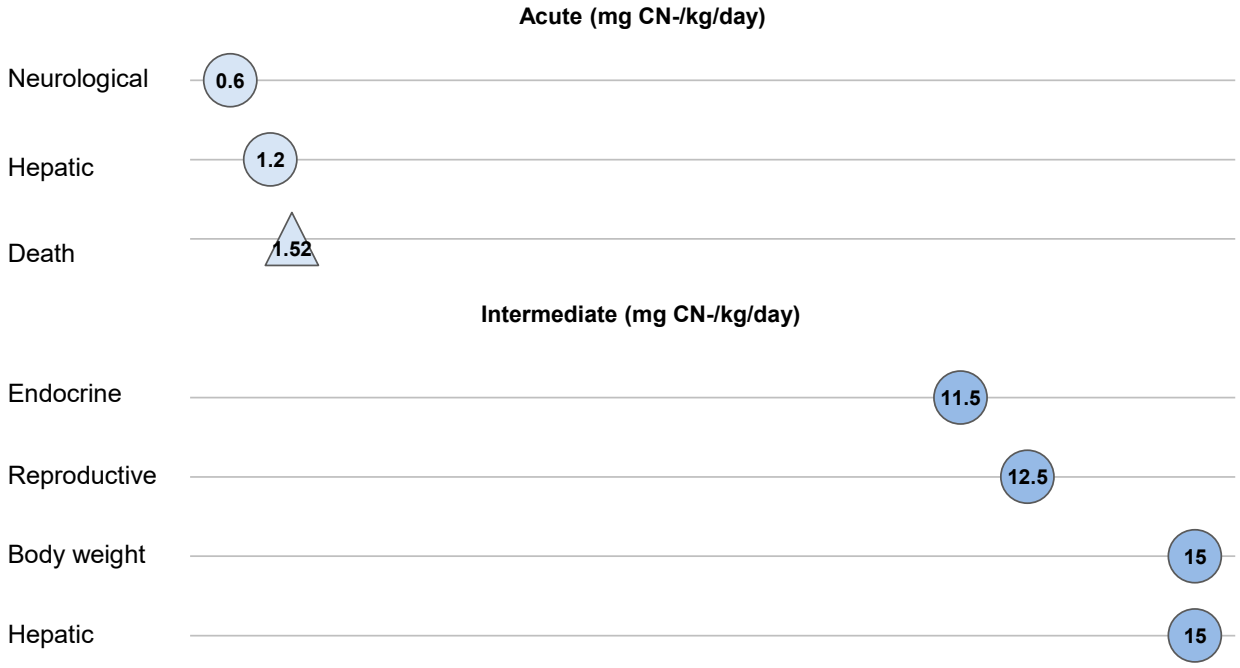


Table 1-1. Minimal Risk Levels (MRLs) for Cyanide[a]

Exposure route	Exposure duration	Provisional MRL	Critical effect	POD type	POD value	Uncertainty/ modifying factor	Reference
Inhalation	**No inhalation MRLs were derived for any duration.**						
Oral	Acute	None	–	–	–	–	–
	Intermediate	**0.04 mg CN^-/kg/day**	Increased absolute and relative thyroid weight, decreased serum T4	NOAEL	3.96 mg CN^-/kg/day	UF: 100	Tyner and Greeley 2023
	Chronic	None	–	–	–	–	–

[a]See Appendix A for additional information.

NOAEL = no-observed-adverse-effect level; POD = point of departure; T4 = thyroxine; UF = uncertainty factor

CHAPTER 2. HEALTH EFFECTS

2.1 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. When available, mechanisms of action relevant to specific target organs are discussed along with the health effects data; general mechanisms of action for cyanide (relevant to the entire organism) are discussed in Section 2.21. Toxicokinetic mechanistic data are discussed in Section 3.1.

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

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 by health effect. These data are discussed in terms of route of exposure (inhalation, oral, and dermal) and three exposure periods: acute (≤14 days), intermediate (15–364 days), and chronic (≥365 days).

As discussed in Appendix B, a literature search was conducted to identify relevant studies examining health effect endpoints. Figure 2-1 provides an overview of the database of studies in humans or experimental animals included in this chapter of the profile. These studies evaluate the potential health effects associated with inhalation, oral, or dermal exposure to cyanide, but may not be inclusive of the entire body of literature. A systematic review of the scientific evidence of the health effects associated with oral exposure to cyanide was also conducted; the results of this review are presented in Appendix C.

Human and animal inhalation studies are presented in Table 2-1 and Figure 2-2, animal oral studies are presented in Table 2-2 and Figure 2-3, and human and animal dermal data are presented in Table 2-3.

Levels of significant exposure (LSEs) 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. Effects have been classified into “less serious LOAELs” or “serious LOAELs (SLOAELs).” “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 endpoint 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 endpoints. 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.

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

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 1988). 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; however, health effects 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^-. Toxicological data for ferricyanide compounds are omitted from Chapter 2 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 natural cyanogenic glycosides (e.g., amygdalin) that can be broken down in the gastrointestinal tract to form cyanide (Lasch and El Shawa 1981; Mlingi et al. 1992, 1993; O'Brien et al. 1992; Swain et al. 1992; Voldrich and Kyzlink 1992). Cassava roots form the staple diet of some populations in Africa, Central and South America, and Asia (WHO 2004). 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 (Obidoa and Obasi 1991; WHO 2004). Mycotoxin contamination has also been documented in stored cassava and the most common cassava product in Africa, garri (Olorunnado et al. 2024). Therefore, while discussed in relevant sections of Chapter 2 (based on target organs evaluated) to aid in hazard identification, animal studies administering cassava and other natural cyanogenic glycosides are not useful for dose-response assessment; thus, they are omitted from the LSE tables and figures. Additionally, while discussed in relevant sections of Chapter 2 for hazard identification purposes, studies in dogs are omitted from the LSE tables and figures because they are not considered appropriate animal models for dose-response extrapolation to humans for cyanide toxicity. As discussed in Section 3.1.6, dogs have increased susceptibility to cyanide compared to other mammalian species due to known pharmacokinetic differences. When possible, all oral exposures are expressed as mg CN^-/kg/day throughout the profile.

The health effects of cyanide compounds have been evaluated in 58 human and 87 animal studies. As illustrated in Figure 2-1, most of the health effects data come from inhalation and oral exposure studies in animals and oral studies in humans. For the purposes of Figure 2-1, all occupational human studies were classified as inhalation studies, despite potential for multi-route exposure (e.g., dermal via direct vapor exposure).

For animal data, oral studies are available for all health effect and exposure duration categories and evaluate a complete set of endpoints, although chronic-duration data are limited. Animal inhalation studies include acute- and intermediate-duration studies only and evaluate a limited number of endpoints. The dermal animal database is limited to acute-duration studies evaluating a limited number of endpoints. The most examined endpoints in animal studies were neurological effects, lethality, and hepatic effects. The available human studies include some epidemiological data (including occupational studies and evaluations of populations with high dietary intake of naturally occurring cyanogenic compounds), but

available data are predominantly from case studies and case-series reports. Human studies that are included were predominantly focused on neurological and respiratory effects. As discussed in Section 2.2 and Appendix C, the extensive number of case studies reporting lethal cases of cyanide poisoning are not included in this profile; rather, included studies are lethal case reports focused on estimating lethal exposure levels following inhalation, oral, and dermal routes, relying on reviews when available. In a comprehensive database including all case reports and case-series studies, death is likely the most well-studied endpoint in the human database for cyanide.

As outlined in Chapter 1, the thyroid, neurological system, and male reproductive system appear to be sensitive targets of toxicity following oral exposure to cyanide. A systematic review was conducted on the available human and animal studies for these endpoints following oral exposure. The information in these oral studies indicate the following on the potential targets of cyanide toxicity:

- **Thyroid Endpoints.** Thyroid effects are a presumed health effect associated with cyanide exposure via oral exposure based on a low level of evidence in humans, a moderate level of evidence in animals, and supporting mechanistic data. Reduced serum thyroid hormone levels, increasingly elevated levels of thyroid stimulating hormone, and goiter have been reported in humans with high dietary intake of cassava containing natural sources of cyanide. In animals, adverse thyroid effects (altered serum hormones, enlarged thyroid) have been reported in rats and rabbits following intermediate-duration oral exposure to cyanide compounds. At lower doses, evidence of induction of potential homeostatic mechanisms for thyroid function (dose-related increases in the number of resorption vacuoles in the thyroid gland) in the absence of clear evidence of altered thyroid function has also been observed. Thyroid effects following cyanide exposure can result from the interference of thiocyanate, a metabolite of cyanide, with iodine uptake and utilization in the thyroid gland.

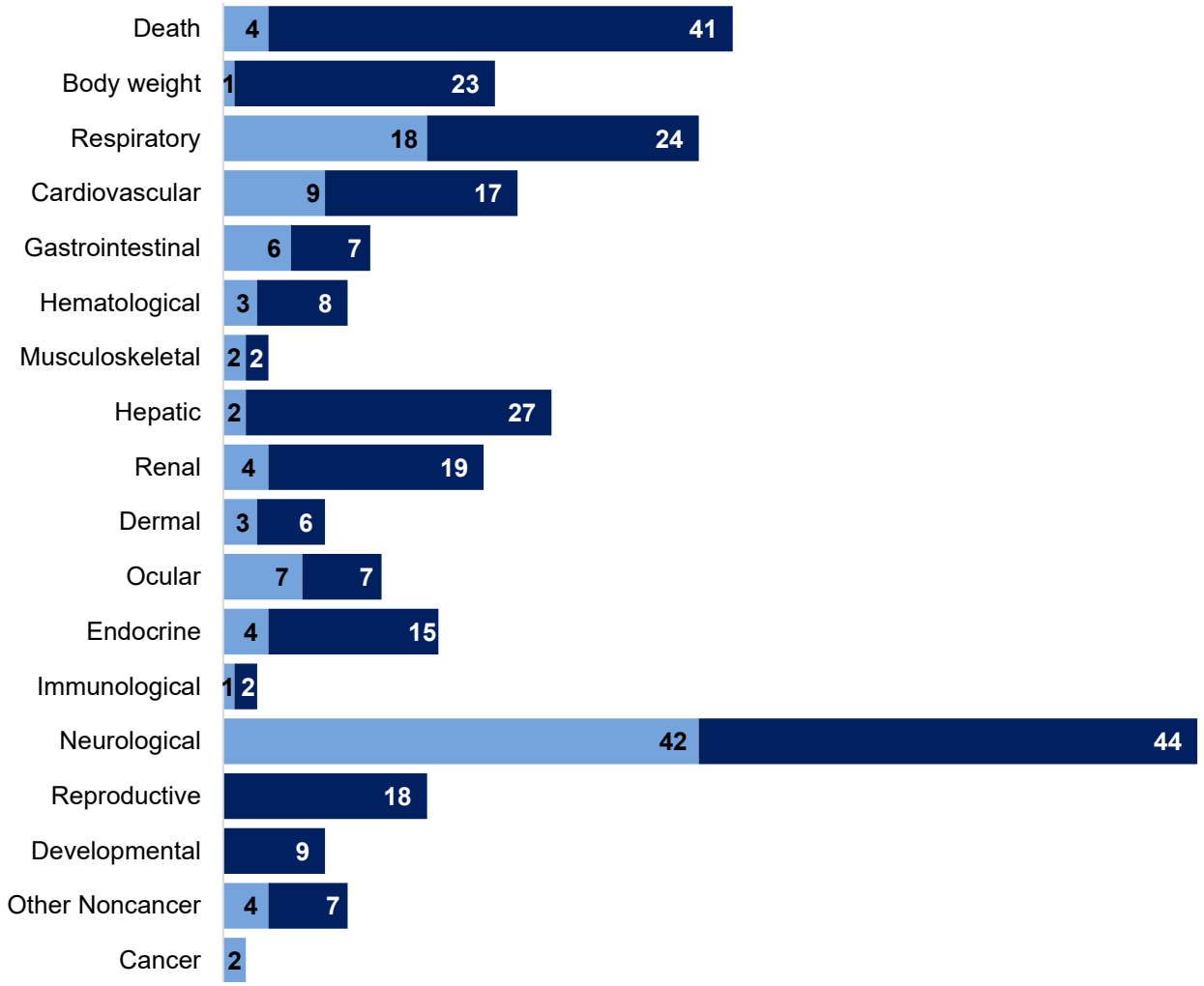
- **Neurological Endpoints.** Neurological effects are a known health effect for humans exposed to cyanide based on a high level of evidence in humans and animals. Regional outbreaks of neurological disease have occurred in African communities reliant on a diet rich in cassava as a carbohydrate source. Numerous case studies provide strong evidence that the CNS is a primary target of acute cyanide poisoning, with permanent and progressive neurological dysfunction occurring after single, high-dose exposures. In animal studies, neurobehavioral changes have been reported at low gavage doses, with overt and severe clinical signs of neurotoxicity prior to death at lethal doses. Damage to the tissues of the CNS have been observed in animal studies following acute- and intermediate-duration exposure to cyanide compounds. The CNS is a primary target of cyanide toxicity via the general mechanism of toxicity (impaired cellular oxygen utilization), which can lead to rapid biochemical changes in the brain.

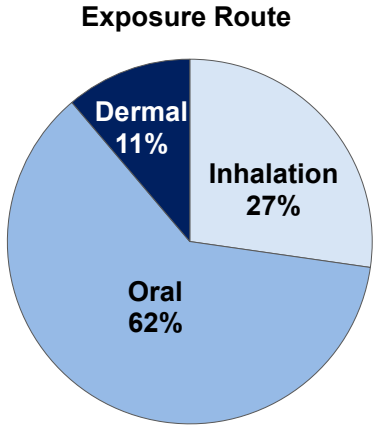
- **Male Reproductive Endpoints.** Male reproductive effects are a suspected health effect associated with cyanide exposure via oral exposure based on no human data and a moderate level of evidence in animals. Data from studies utilizing the most relevant route of exposure (drinking water) are conflicting. In the first study by NTP (1993), adverse effects were reported in male rats (decreases in the caudal epididymal weight, epididymis weight, testis weight, spermatid heads, and spermatid counts) and mice (decreases in the epididymal and caudal epididymal weights); however, a replicate rat study using the same protocol by Tyner and Greeley (2023)

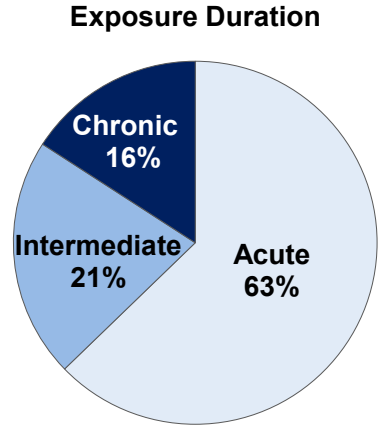
could not reproduce the male reproductive findings. Tyner and Greeley (2023) proposed that male reproductive effects noted in the NTP (1993) study may have been attributable to decreased water consumption in the highest dose group rather than due to direct toxic effects. To control for this, Tyner and Greeley (2023) included a water-restricted control group to match measured water consumption at the highest dose level. No adverse male reproductive effects were observed in exposed rats in the study by Tyner and Greeley (2023), compared to either the water-restricted or the *ad libitum* control group. While drinking water studies are considered more relevant to human exposure, several intermediate-duration gavage studies indicate that bolus administration of cyanide compounds (which may overwhelm detoxification mechanisms) can cause mild adverse effects on the male reproductive system (serum hormone changes, sperm effects, and mild histopathological effects). No studies evaluating male fertility were identified, but NTP (1993) concluded that observed effects in their study were unlikely to impair fertility in rodents.

Figure 2-1. Overview of the Number of Studies Examining Cyanide Health Effects*

Most studies examined the potential neurological, lethal, and respiratory effects of cyanide
Fewer studies evaluated health effects in humans than animals (counts represent studies examining endpoint)







*Includes studies discussed in Chapter 2. A total of 145 studies (including those finding no effect) have examined toxicity; most studies examined multiple endpoints.

Table 2-1. Levels of Significant Exposure to Hydrogen Cyanide – Inhalation (ppm)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
ACUTE EXPOSURE									
Ballantyne 1983a									**HCN**
1	Rat (NS) 6–10 NS	60 minutes	Not reported	LE	Death			143	60-minute LC_{50}
Fechter et al. 2002									**HCN**
2	Rat (Long-Evans) 6–16 M	3.5 hours	0, 10, 30, 50	HP, NX	Neuro	50			
Higgins et al. 1972									**HCN**
3	Rat (Wistar) 10 NS	5 minutes	283, 657, 368, 497, 583, 690	CS, LE	Death			503	5-minute LC_{50}
Higgins et al. 1972									**HCN**
4	Mouse (ICR) 15 NS	5 minutes	200, 283, 357, 368, 414, 427	CS, LE	Death			323	5-minute LC_{50}
Hume et al. 1995									**HCN**
5	Mouse (ICR) 10 M	3 minutes	400	LE	Death			400	90% lethality
Ma et al. 2021									**HCN**
6	Mouse (CD-1) 16–24 M	40 minutes (N)	0, 327	LE, CS, NX	Death			327	8/24 died
					Resp			327	Gasping, labored breathing
					Neuro			327	Lethargy, loss of righting reflex, convulsions, tremors

Table 2-1. Levels of Significant Exposure to Hydrogen Cyanide – Inhalation (ppm)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Matijak-Schaper and Alarie 1982									**HCN**
7	Mouse (Swiss-Webster) 4 M	30 minutes	15, 25, 35, 65, 70, 100, 150, 220, 330, 500, 760, 1,000, 1,150	CS, LE	Death			166	30-minute LC_{50}
					Resp			63	Calculated DC_{50} (50% decrease in respiratory rate)
Ballantyne 1983a									**HCN**
8	Rabbit (NS) 6–10 NS	35 minutes	Not reported	LE	Death			188	35-minute LC_{50}
INTERMEDIATE EXPOSURE									
O'Flaherty and Thomas 1982									**HCN**
9	Rat (Long-Evans) 4 M	20 days 4-day intervals between exposures (5 total exposures) 12.5 minutes/day	0, 200	CS, BC, HP	Cardio		200		Increased creatine phosphokinase activity

[a]The number corresponds to entries in 2-2; differences in levels of health effects between male and females are not indicated in Figure 2-2. Where such differences exist, only the levels of effect for the most sensitive sex are presented.

BC = serum (blood) chemistry; Cardio = cardiovascular; CS = clinical signs; DC_{50} = concentration associated with 50% depression in respiratory rate; HCN = hydrogen cyanide; HP = histopathology; LC_{50} = concentration associated with 50% lethality; LE = lethality; LOAEL = lowest-observed-adverse-effect level; M = male(s); Neuro = neurological; NOAEL = no-observed-adverse-effect-level; NS = not specified; NX = neurological function; Resp = respiratory

Figure 2-2. Levels of Significant Exposure to Hydrogen Cyanide – Inhalation
Acute (≤14 days)

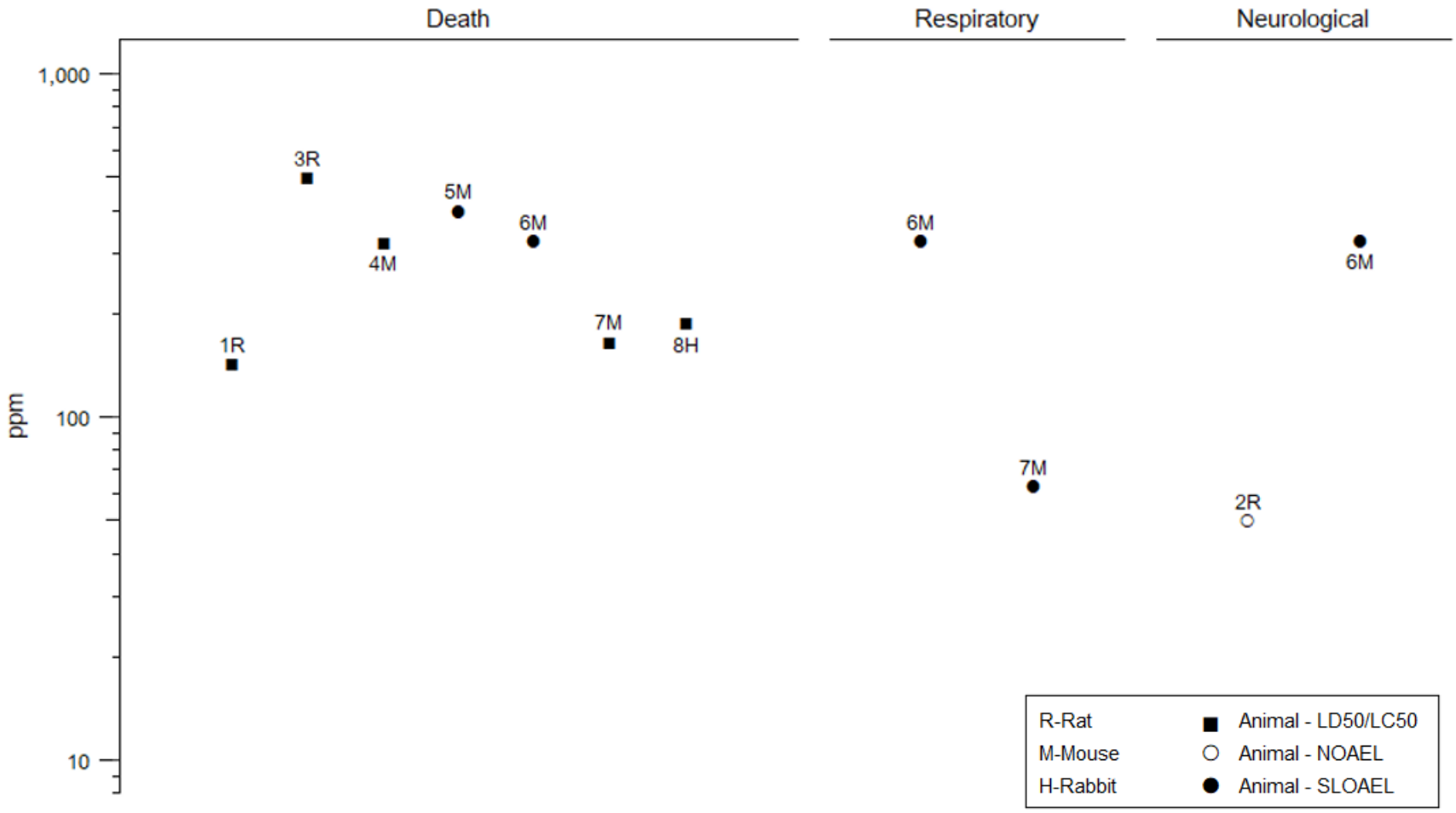


Figure 2-2. Levels of Significant Exposure to Hydrogen Cyanide – Inhalation
Intermediate (15–364 days)

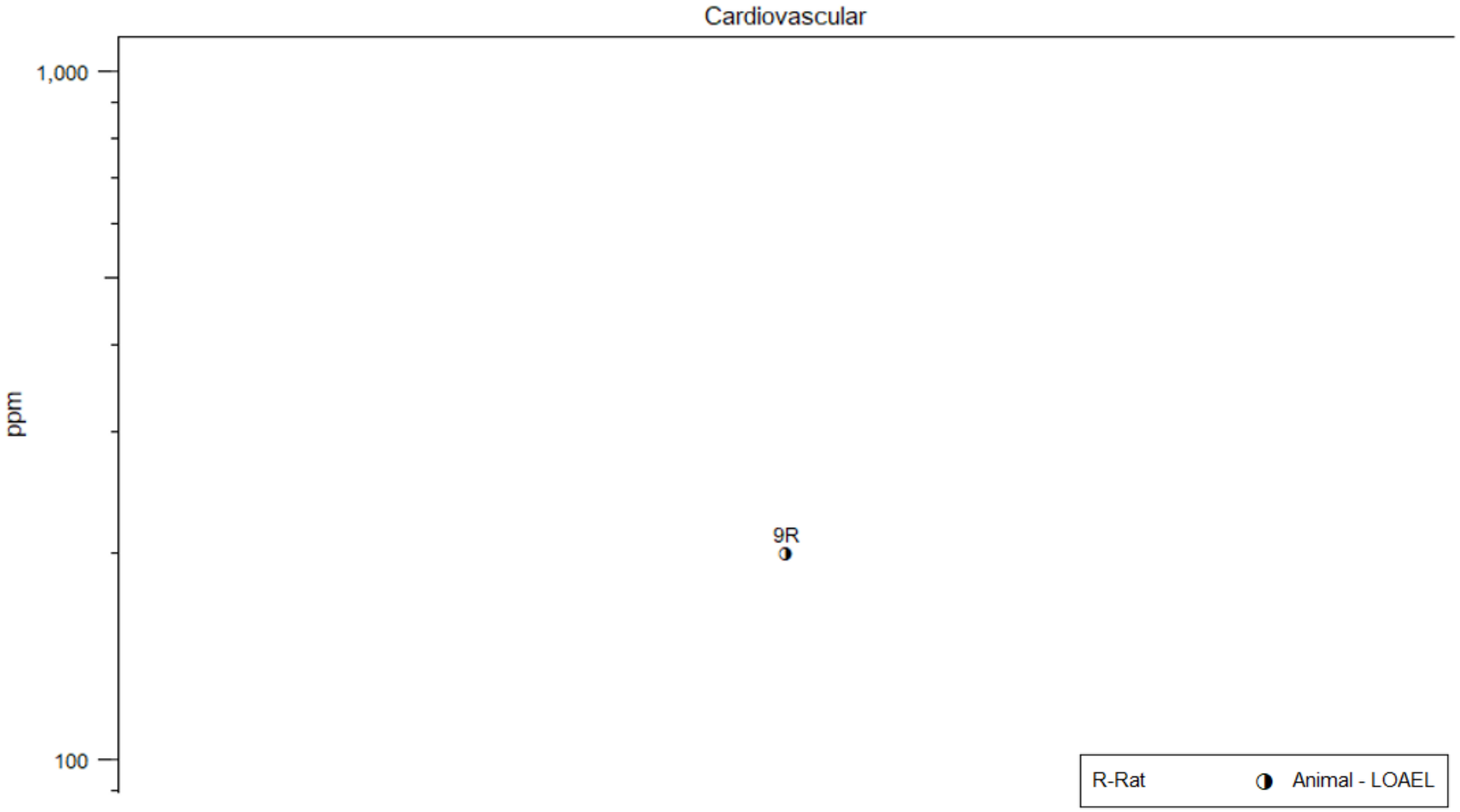


Table 2-2. Levels of Significant Exposure to Cyanide – Oral (mg CN^-/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
ACUTE EXPOSURE									
Ballantyne 1988									**NaCN**
1	Rat (Porton) 10 F	Once (GW)	2.39–3.34	CS, LE	Death			3	LD_{50} in unfasted rats
Ballantyne 1988									**NaCN**
2	Rat (Porton) 10 F	Once (GW)	2.09–4.19	CS, LE	Death			2.7	LD_{50} in fasted rats
de Sousa et al. 2007									**KCN**
3	Rat (Wistar) 10 F	14 days GDs 6–20 (W)	0, 0.4, 1.2, 12	LE, CS, BW, BC, DX, HP	Bd wt	12			
					Resp	12			
					Hepatic		1.2		Mild to moderate hepatocyte vacuolation and congestion
					Renal	12			
					Endocr		12		Moderate pancreas islet cell vacuolation
					Immuno	12			
					Neuro			12	Hemorrhagic areas in the brain and gliosis; mild-to-moderate necrosis, neuronophagia, and CNS congestion
					Develop	12			
					Other noncancer	1.2	12		Elevated serum glucose

Dams were sacrificed on GD 20; NOAELs for histological findings could not be determined

Table 2-2. Levels of Significant Exposure to Cyanide – Oral (mg CN^-/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
de Sousa et al. 2007									**KCN**
4	Rat (Wistar) 10 F	14 days GDs 6–20 (W)	0, 0.4, 1.2, 12	LE, CS, BW, BC, DX, HP	Hepatic		1.2		Mild to moderate hepatic congestion and vacuolation
					Neuro			12	Hemorrhagic areas in the brain and gliosis; mild-to-moderate necrosis, neuronophagia, and CNS congestion
					Develop			12	Effects in PND 22 pups: CNS gliosis, mild-to-moderate neuronophagia, and congestion; mild-to-moderate hepatic congestion and vacuolation; mild bile duct proliferation
Dams and pups sacrificed on PND 22; NOAELs for histological findings could not be determined									
de Sousa et al. 2007									**KSCN**
5	Rat (Wistar) 10 F	14 days GDs 6–20 (W)	0, 0.2, 0.6, 6.4	LE, CS, BW, BC, RX, DX, HP	Bd wt	6.4			
					Resp	6.4			
					Hepatic		6.4		Mild vacuolation of hepatocytes and bile duct proliferation
					Renal	6.4			
					Immuno	6.4			
					Neuro			0.6	Brain gliosis
					Develop	6.4			
					Other noncancer	6.4			
Dams were sacrificed on GD 20; NOAELs for histological findings could not be determined									

Table 2-2. Levels of Significant Exposure to Cyanide – Oral (mg CN^-/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
de Sousa et al. 2007									**KSCN**
6	Rat (Wistar) 10 F	14 days GDs 6–20 (W)	0, 0.2, 0.6, 6.4	LE, CS, BW, BC, DX, HP	Hepatic		6.4		Mild vacuolation of hepatocytes and bile duct proliferation
					Neuro			0.6	Brain gliosis
					Develop			6.4	Effects in PND 22 pups: CNS gliosis, mild-to-moderate neuronophagia, and congestion; mild-to-moderate hepatic congestion and vacuolation; mild bile duct proliferation
Dams and pups sacrificed on PND 22; NOAELs for histological findings could not be determined									
Ferguson 1962									**KCN**
7	Rat (Sprague-Dawley) 20 NS	Once (GW)	4	CS, LE	Death			4	19/20 died
Ogundele et al. 2014a									**KCN**
8	Rat (Wistar) 6–12 M	10 days (G)	0, 12	OF	Cardio		12		Arterial wall degeneration (reduction in cell number) and decreased lumen width in middle cerebral artery; increased diameter of common carotid artery
Ogundele et al. 2014b									**KCN**
9	Rat (Wistar) 6–12 M	10 days (G)	0, 12	NX	Neuro			12	Decreased locomotor activity, impaired memory (spatial, object recognition)
Rice et al. 2018									**NaCN**
10	Rat (Sprague-Dawley) 2–7 M	Once (IN)	2, 4, 8.5, 17, 34, 43, 51, 68	LE, CS, BW, FI	Death			34	LD_{50}
					Neuro	4	8.5	17	LOAEL: Lethargy SLOAEL: Convulsions

Table 2-2. Levels of Significant Exposure to Cyanide – Oral (mg CN^-/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Smyth et al. 1969									**Ca(CN)2**
11	Rat (NS) NS	Once (GW)	Not reported	CS, LE	Death			22	LD_{50}
Smyth et al. 1969									**NaCN**
12	Rat (NS) NS	Once (GW)	Not reported	CS, LE	Death			8	LD_{50}
Ferguson 1962									**KCN**
13	Mouse (Swiss-Webster) 20 NS	Once (GW)	6	CS, LE	Death			6	19/20 died
Hawk et al. 2016									**KCN**
14	Mouse (CD-1) 70 M, 70 F	Once (NS)	0, 3.2	LE, BW, OW, HP, NX	Bd wt	3.2			
					Cardio	3.2			
					Hepatic	3.2			
					Renal	3.2			
					Endocr	3.2			
					Neuro			3.2	Findings at 0.5 hours post-exposure: Reduced motor activity and altered gait, decreased sensorimotor reflexes, tremor, and clinical signs of CNS depression
					Repro	3.2 M			
Juvenile rats (10/sex/timepoint) were assessed prior to exposure and 0.5 and 24 hours and 6, 13, 27, and 41 days post-exposure									
Hawk et al. 2016									**KCN**
15	Mouse (CD-1) 70 M, 70 F	Once (NS)	0, 3.2	LE, BW, OW, HP, NX, OF	Bd wt	3.2			
					Cardio		3.2		Decreased systolic, diastolic, and mean arterial blood pressure; reduced heart rate
					Hepatic	3.2			
					Renal	3.2			

Table 2-2. Levels of Significant Exposure to Cyanide – Oral (mg CN^-/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
					Endocr	3.2			
					Neuro			3.2	Findings at 0.5 hours post-exposure: Reduced motor activity and altered gait, decreased sensorimotor reflexes, tremor, clinical signs of CNS depression
					Repro	3.2 M			
Adult rats (10/sex/timepoint) were assessed prior to exposure and 0.5 and 24 hours and 6, 13, 27, and 41 days post-exposure									
Ishaku et al. 2018									**KCN**
16	Mouse (Swiss) 7 M	14 days (NS)	0, 0.6	LE, CS, NX	Neuro		0.6		Decreased motor strength and activity
Sabourin et al. 2016									**KCN**
17	Mouse (CD-1) 18 M, 18 F	Once (GW)	0, 2.4, 3.2, 4.16	BW, BC, OW, HP	Bd wt	4.16			
					Cardio	4.16			
					Hepatic	4.16			
					Renal	4.16			
					Endocr	4.16			
					Neuro	4.16			
					Repro	4.16 M			
Juvenile mice were assessed at various timepoints post-exposure for serum biomarkers (8/sex/timepoint) and histopathology (4/sex/timepoint)									
Sabourin et al. 2016									**KCN**
18	Mouse (CD-1) 6–18 M, 6–18 F	Once (GW)	0, 0.8, 1.2, 1.6, 2.4, 3.2, 4.0, 4.4, 4.8, 5.2, 5.6	LE, CS	Death			4.40 F	LD_{50} in adult female mice
								4.75 M	LD_{50} in adult male mice
					Resp	2.4		3.2	Labored and difficult breathing
					Neuro	1.2	1.6	3.2	LOAEL: Decreased activity SLOAEL: Convulsions and tremors

Table 2-2. Levels of Significant Exposure to Cyanide – Oral (mg CN^-/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Sabourin et al. 2016									**KCN**
19	Mouse (CD-1) 6–18 M, 6–18 F	Once (GW)	0, 0.8, 1.6, 2.4, 3.2, 4.0, 4.4, 4.8, 5.2, 5.6	LE, CS	Death			4.0 F	LD_{50} in juvenile female mice
								4.36 M	LD_{50} in juvenile male mice
					Resp	2.4		3.2	Labored and difficult breathing
					Neuro	0.8	1.6	3.2	LOAEL: Decreased activity SLOAEL: Convulsions and tremors
Sabourin et al. 2016									**KCN**
20	Mouse (CD-1) 18 M, 18 F	Once (GW)	0, 2.4, 3.2, 4.60	BW, BC, OW, HP	Bd wt	4.6			
					Cardio	4.6			
					Hepatic	4.6			
					Renal	4.6 F	4.6 M		Minimal-to-mild acute tubular necrosis
					Endocr	4.6			
					Neuro	4.6			
					Repro	4.6 M			
Adult mice were assessed at various timepoints post-exposure for serum biomarkers (8/sex/timepoint) and histopathology (4/sex/timepoint)									
Ballantyne 1983a									**HCN**
21	Rabbit (NS) 6–10 F	Once (GW)	Not reported	LE	Death			2.39	LD_{50}
Ballantyne 1983a									**KCN**
22	Rabbit (NS) 6–10 F	Once (GW)	Not reported	LE	Death			2.34	LD_{50}
Ballantyne 1983a									**NaCN**
23	Rabbit (NS) 6–10 F	Once (GW)	Not reported	LE	Death			2.7	LD_{50}
Ballantyne 1988									**NaCN**
24	Rabbit (New Zealand) 10 F	Once (G)	2.12–3.37	CS, LE	Death			2.7	LD_{50}

Table 2-2. Levels of Significant Exposure to Cyanide – Oral (mg CN^-/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
INTERMEDIATE EXPOSURE									
Mathangi et al. 2011									**KCN**
25	Rat (Wistar) 10 NS	90 days (GW)	0, 0.56	BW, NX, OW, HP	Bd wt	0.56			
					Renal	0.56			
					Neuro		0.56		Decreased motor coordination; increased dopamine in corpus striatum and cerebral cortex
NTP 1993									**NaCN**
26	Rat (Fischer-344) 10 M, 10 F	13 weeks (W)	M: 0, 0.2, 0.5, 1.4, 4.5, 12.5; F: 0, 0.2, 0.5, 1.7, 4.9, 12.5	LE, BW, OW, GN, HP, BC, WI, UR	Bd wt	12.5			
					Resp	12.5			
					Cardio	12.5			
					Gastro	12.5			
					Hemato	12.5			
					Hepatic	12.5			
					Renal	12.5			
					Dermal	12.5			
					Endocr	12.5			
					Immuno	12.5			
					Neuro	12.5			
					Repro	12.5 F			
						4.5 M	12.5 M		Decreased absolute left testes, epididymal, and caudal epididymal weights; decreased number of spermatid heads per testis and total spermatid count
Oyewopo et al. 2021a									**NaCN**
27	Rat (Wistar) 8 M	56 days (G)	0, 0.5, 1	BW, BC, OW	Bd wt			0.5	25% decrease in body weight gain
					Repro		0.5		Decreased serum testosterone, FSH, and LH; increased serum prolactin

Table 2-2. Levels of Significant Exposure to Cyanide – Oral (mg CN^-/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Oyewopo et al. 2021a									**NaCN**
28	Rat (Wistar) 8 M	30 days (NS)	0, 0.5, 1	BW, BC, OW	Bd wt		0.5		15% decrease in body weight gain
					Repro		0.5		Decreased serum testosterone, FSH, and LH; increased serum prolactin
Oyewopo et al. 2021b									**NaCN**
29	Rat (Wistar) 8 M	30 or 56 days (G)	0, 0.5, 1	BW, HP, RX	Repro		0.5		Decreased total sperm count, percent motility, and percent normal sperm; morphological changes in testes (decreased diameter of seminiferous tubules, decreased epithelial cell height; increased Leydig cell area, and decreased nuclear volume of Sertoli cells)
Philbrick et al. 1979									**KCN**
30	Rat (NS) 10 M	11.5 months (F)	0, 53	LE, CS, BW, BC, OW, HP	Bd wt			53	32% decreased weight gain
					Endocr		53		Decreased plasma T4 at 4 months; decreased T4 secretion rate at 4 and 11 months
					Neuro			53	Modest myelin degeneration in spinal cord
Philbrick et al. 1979									**KSCN**
31	Rat (NS) 10 M	11.5 months (F)	0, 47	LE, CS, BW, BC, OW, HP	Bd wt	47			
					Endocr		47		Decreased plasma T4 at 4 and 11 months; decreased T4 secretion rate at 4 months
					Neuro			47	Modest myelin degeneration in spinal cord

Table 2-2. Levels of Significant Exposure to Cyanide – Oral (mg CN^-/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Shivanoor and David 2015									**NaCN**
32	Rat (Wistar) NS M	90 days (GW)	0, 0.34, 0.64, 1.70	LE, BW, RX, HP	Bd wt	1.7			
					Repro	0.34	0.64		Decreased sperm count and motility; decreased serum testosterone and LH; decreased prostate and testes weights; mild atrophy and degeneration of seminiferous tubules; mild vacuolation in the epididymis
Soto-Blanco et al. 2002									**KCN**
33	Rat (Wistar) 6–7 M	3 months 1 time/day (GW)	0, 0.02, 0.12, 0.24	BW, BC, HP	Bd wt	0.24			
					Endocr	0.24			
Tyner and Greeley 2023									**NaCN**
34	Rat (Fischer-344) 20 M	13 weeks (W)	0, 0.12, 0.43, 1.28, 3.96, 11.50	LE, BW, BC, HE, UR, OW, OP, GN, HP, RX	Bd wt	11.5			
					Hemato	11.5			
					Hepatic	11.5			
					Renal	11.5			
					Ocular	11.5			
					Endocr	3.96[b]	11.5		Increased absolute and relative thyroid weights; reduced serum T4
					Repro	11.5			
Ishaku et al. 2018									**KCN**
35	Mouse (Swiss) 7 M	28 days (NS)	0, 0.6	LE, CS, NX	Neuro		0.6		Decreased motor strength and activity

Table 2-2. Levels of Significant Exposure to Cyanide – Oral (mg CN^-/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
NTP 1993									**NaCN**
36	Mouse (B6C3F1) 10 M, 10 F	13 weeks (W)	M: 0, 0.3, 1.0, 2.7, 8.6, 24.3, F: 0, 0.3, 1.1, 3.3, 10.1, 28.8	LE, BW, OW, GN, HP, BC, WI	Bd wt	28.8 F			
						24.3 M			
					Resp	28.8 F			
						24.3 M			
					Cardio	28.8 F			
						24.3 M			
					Gastro	28.8 F			
						24.3 M			
					Hemato	28.8 F			
						24.3 M			
					Hepatic	28.8 F			
						24.3 M			
					Renal	28.8 F			
						24.3 M			
					Dermal	28.8 F			
						24.3 M			
					Endocr	28.8 F			
						24.3 M			
					Immuno	28.8 F			
						24.3 M			
					Neuro	28.8 F			
						24.3 M			
					Repro	28.8 F			
						8.6 M	24.3 M		Decreased epididymal weights

Table 2-2. Levels of Significant Exposure to Cyanide – Oral (mg CN^-/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Avais et al. 2014									**KCN**
37	Rabbit (NS) 6 M	40 days (G)	0, 1.2	BW, FI, HE	Bd wt			1.2	39% decrease in body weight gain
					Hemato		1.2		Decreased RBC count, hemoglobin levels, PCV, and MCV; increased MCHC
Avais et al. 2018									**KCN**
38	Rabbit (NS) 6 M	40 days (G)	0, 1.2	BW, FI, BC, GN	Hepatic		1.2		Increased serum bilirubin, ALT, AST, ALP, and LDH; decreased total serum albumin and protein
					Renal		1.2		Increased serum creatinine, urea, uric acid; decreased albumin and total protein
					Endocr		1.2		Increased serum levels of T3 and T4
Okolie and Iroanya 2003									**NaCN**
39	Rabbit (New Zealand) 6 NS	4 weeks (F)	0, 15	BW, BC, BI, FI	Bd wt			15	22% decrease in body weight gain
					Hepatic		15		Increased serum ALT, ALP, and LDH
Okolie and Osagie 1999, 2000									**KCN**
40	Rabbit (New Zealand) 6 M	40 weeks (F)	0, 20	BC, BW, BI, FI	Bd wt			20	33% decrease in body weight gain
					Cardio	20			
					Hepatic		20		Increased serum SDH, ALT, ALP, and LDH
					Renal		20		Increased serum creatinine and urea
					Endocr	20			
					Other noncancer	20			

Table 2-2. Levels of Significant Exposure to Cyanide – Oral (mg CN^-/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Ozolua et al. 2007									**KCN**
41	Rabbit NS 4–7 NS	25 days (G)	0, 0.15	LE, BW, HE, BC	Bd wt	0.15			
					Cardio	0.15			
					Hemato	0.15			
					Hepatic	0.15			

[a]The number corresponds to entries in Figure 2-3; differences in levels of health effects between male and females are not indicated in Figure 2-3. Where such differences exist, only the levels of effect for the most sensitive sex are presented.
[b]Used to derive an intermediate-duration oral MRL of 0.04 mg CN^-/kg/day; dose was divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BC = serum (blood) chemistry; Bd wt or BW = body weight; BI = biochemical changes; Ca(CN)2 = calcium cyanide; Cardio = cardiovascular; CN = cyanide; CNS = central nervous system; CS = clinical signs; DX = developmental toxicity; Endocr = endocrine; F = female(s); (F) = feed; FI = food intake; FSH = follicle-stimulating hormone; (G) = gavage, not specified; Gastro = gastrointestinal; GD = gestational day; GN = gross necropsy; (GW) = gavage, water; HCN = hydrogen cyanide; HE = hematology; Hemato = hematological; HP = histopathology; Immuno = immunological; (IN) = ingestion; KCN = potassium cyanide; KSCN = potassium thiocyanate; LD_{50} = dose associated with 50% lethality; LDH = lactate dehydrogenase; LE = lethality; LH = luteinizing hormone; LOAEL = lowest-observed-adverse-effect level; M = male(s); MCHC = Mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; MRL = Minimal Risk Level; NaCN = sodium cyanide; Neuro = neurological; NOAEL = no-observed-adverse-effect-level; NS = not specified; NX = neurological function; OF = organ function; OP = ophthalmology; OW = organ weight; PND = postnatal day; PCV = packed cell volume; RBC = red blood cell; Repro = reproductive; Resp = respiratory; RX = reproductive function; SDH = sorbitol dehydrogenase; SLOAEL = serious LOAEL; T3 = triiodothyronine; T4 = thyroxine; UR = urinalysis; (W) = water; WI = water intake

Figure 2-3. Levels of Significant Exposure to Cyanide – Oral
Acute (≤14 days)

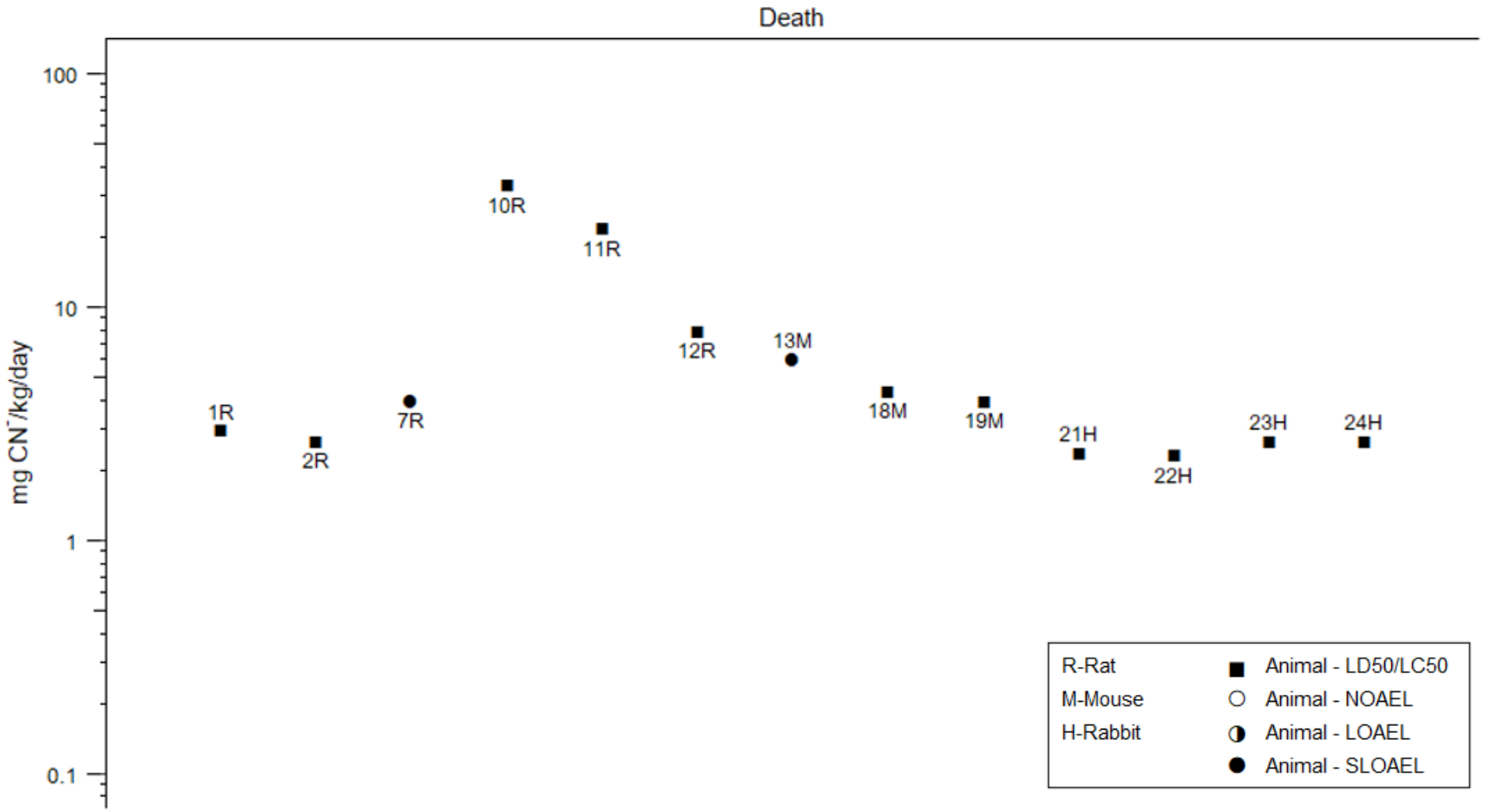


Figure 2-3. Levels of Significant Exposure to Cyanide – Oral
Acute (≤14 days)

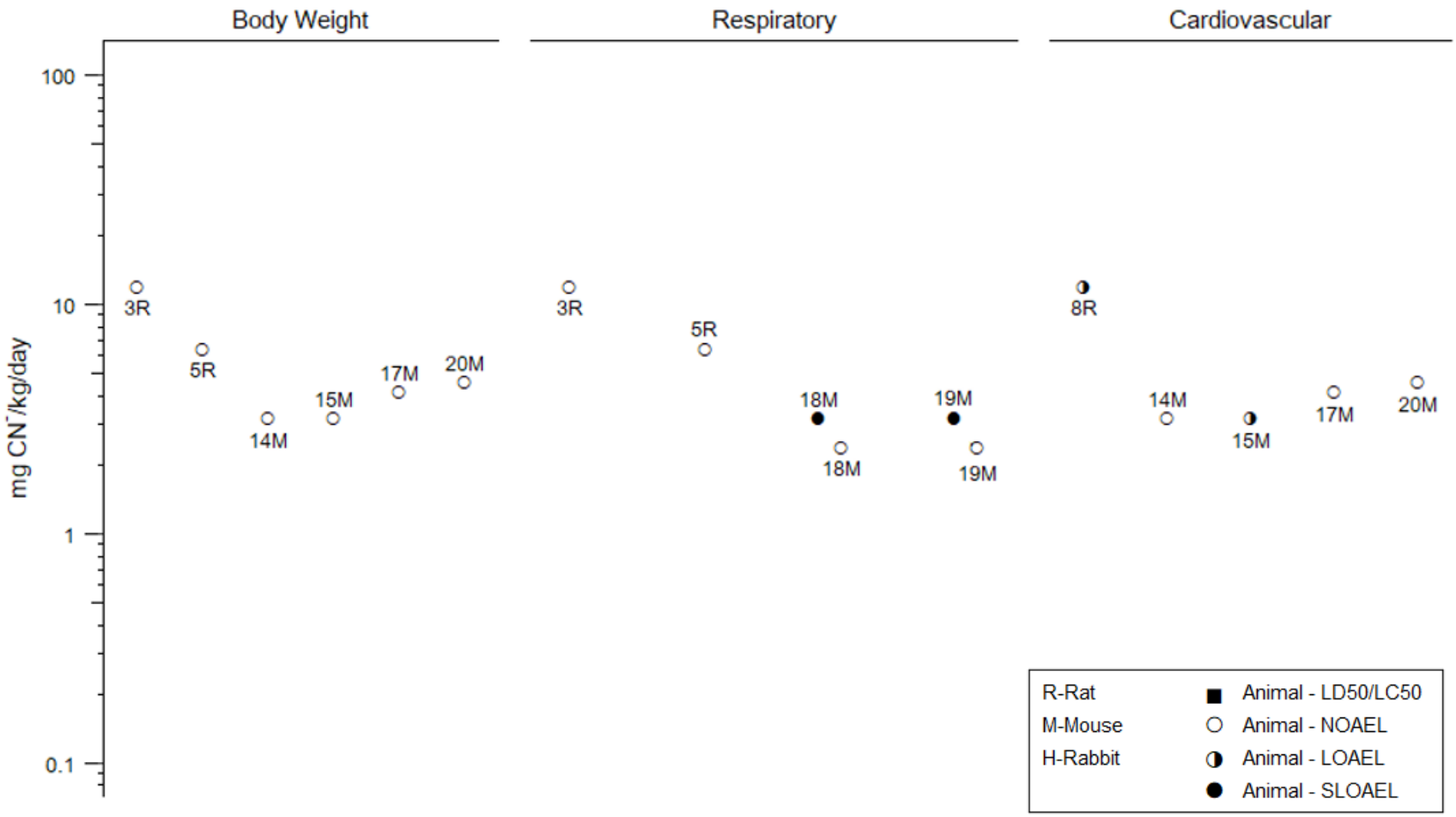


Figure 2-3. Levels of Significant Exposure to Cyanide – Oral
Acute (≤14 days)

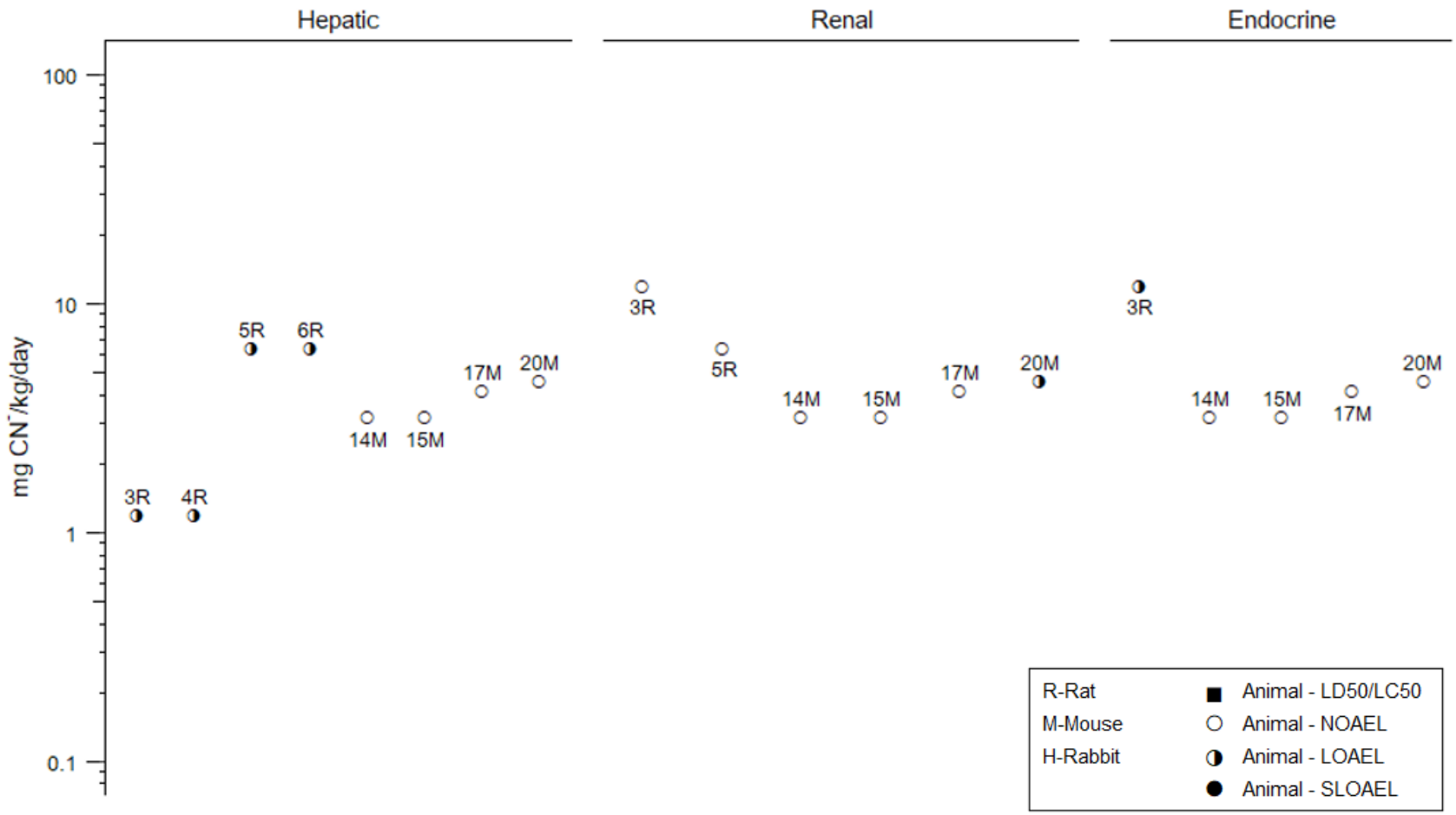


Figure 2-3. Levels of Significant Exposure to Cyanide – Oral
Acute (≤14 days)

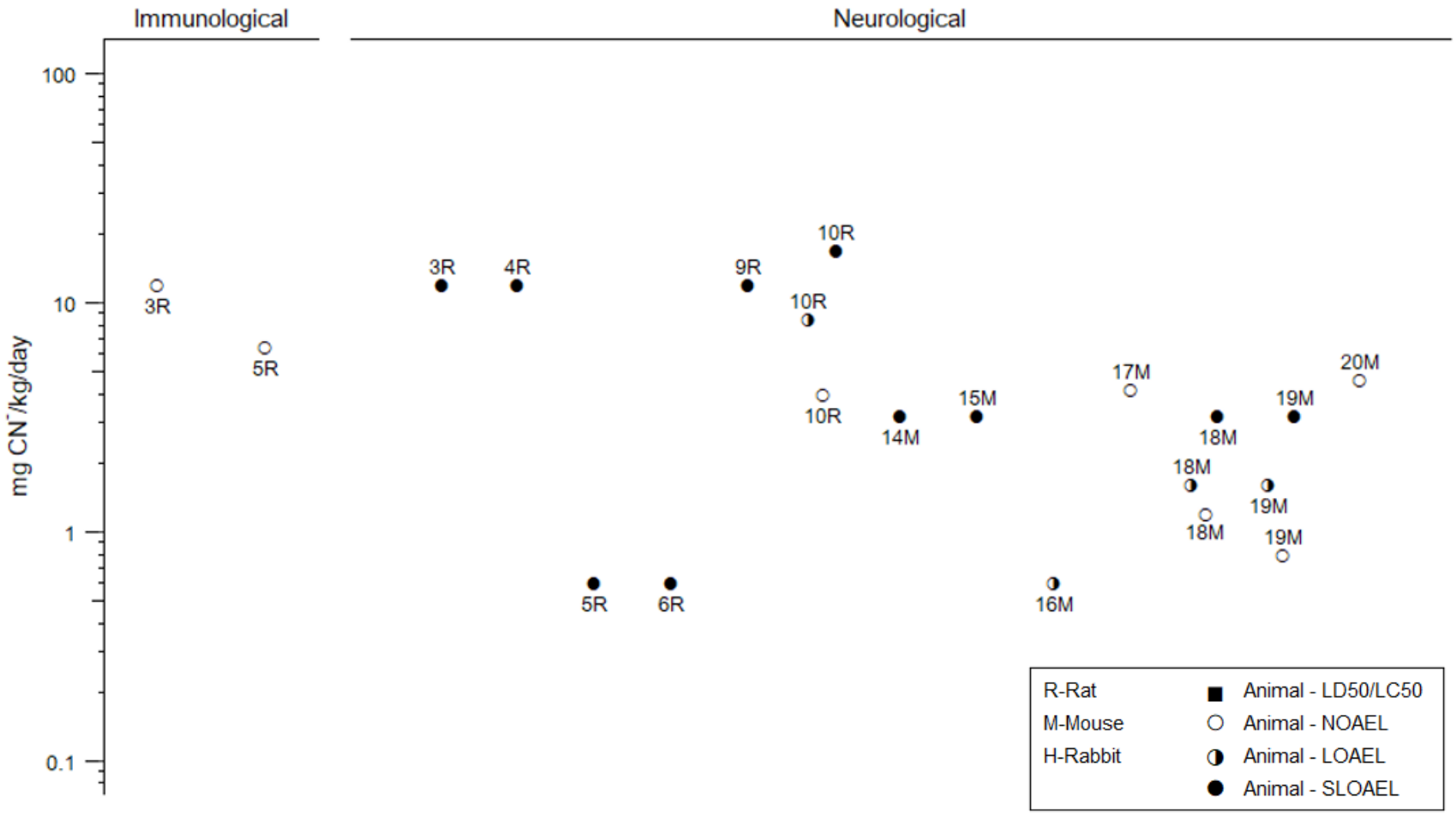


Figure 2-3. Levels of Significant Exposure to Cyanide – Oral
Acute (≤14 days)

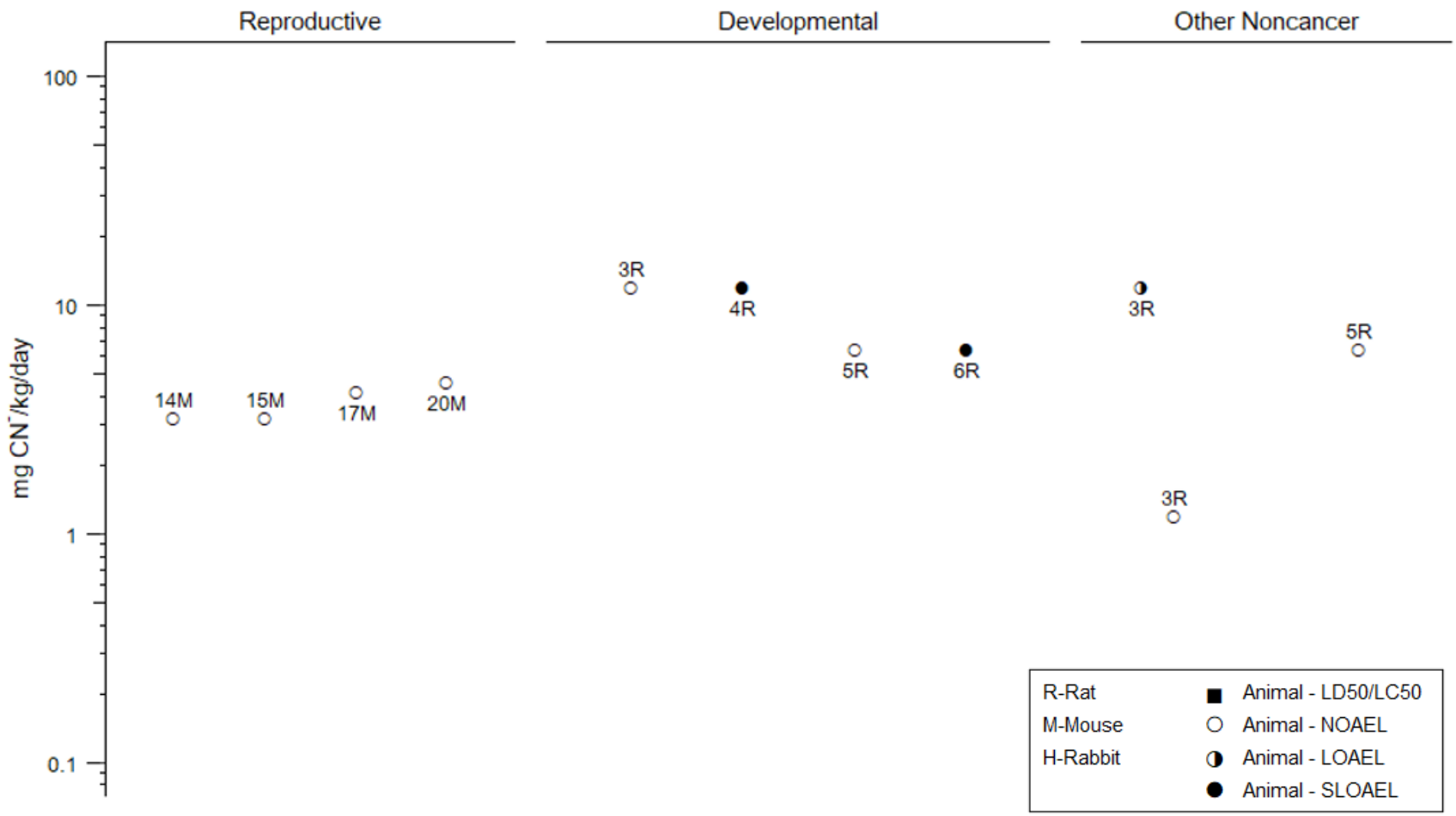


Figure 2-3. Levels of Significant Exposure to Cyanide – Oral
Intermediate (15–364 days)

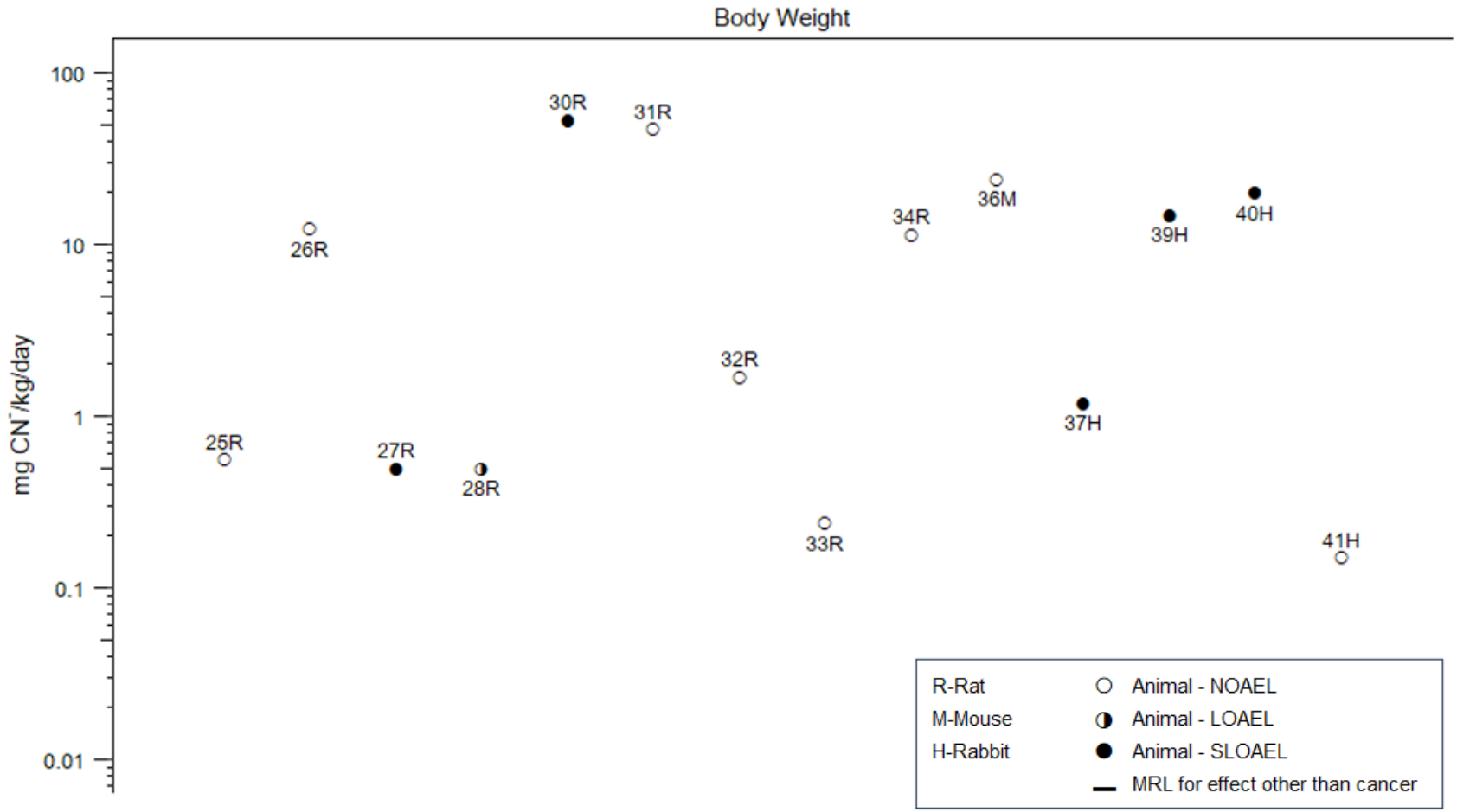


Figure 2-3. Levels of Significant Exposure to Cyanide – Oral
Intermediate (15–364 days)

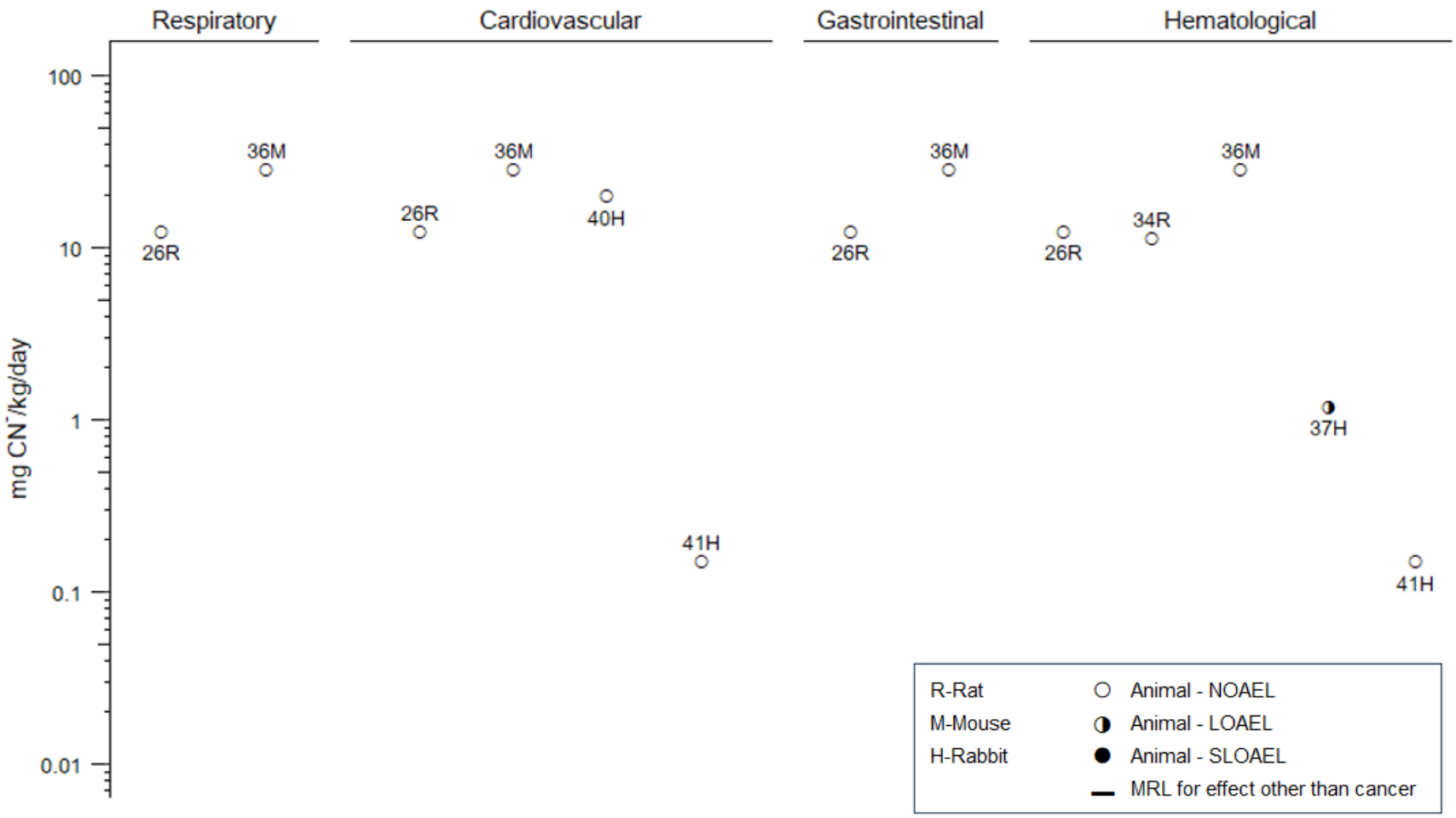


Figure 2-3. Levels of Significant Exposure to Cyanide – Oral
Intermediate (15–364 days)

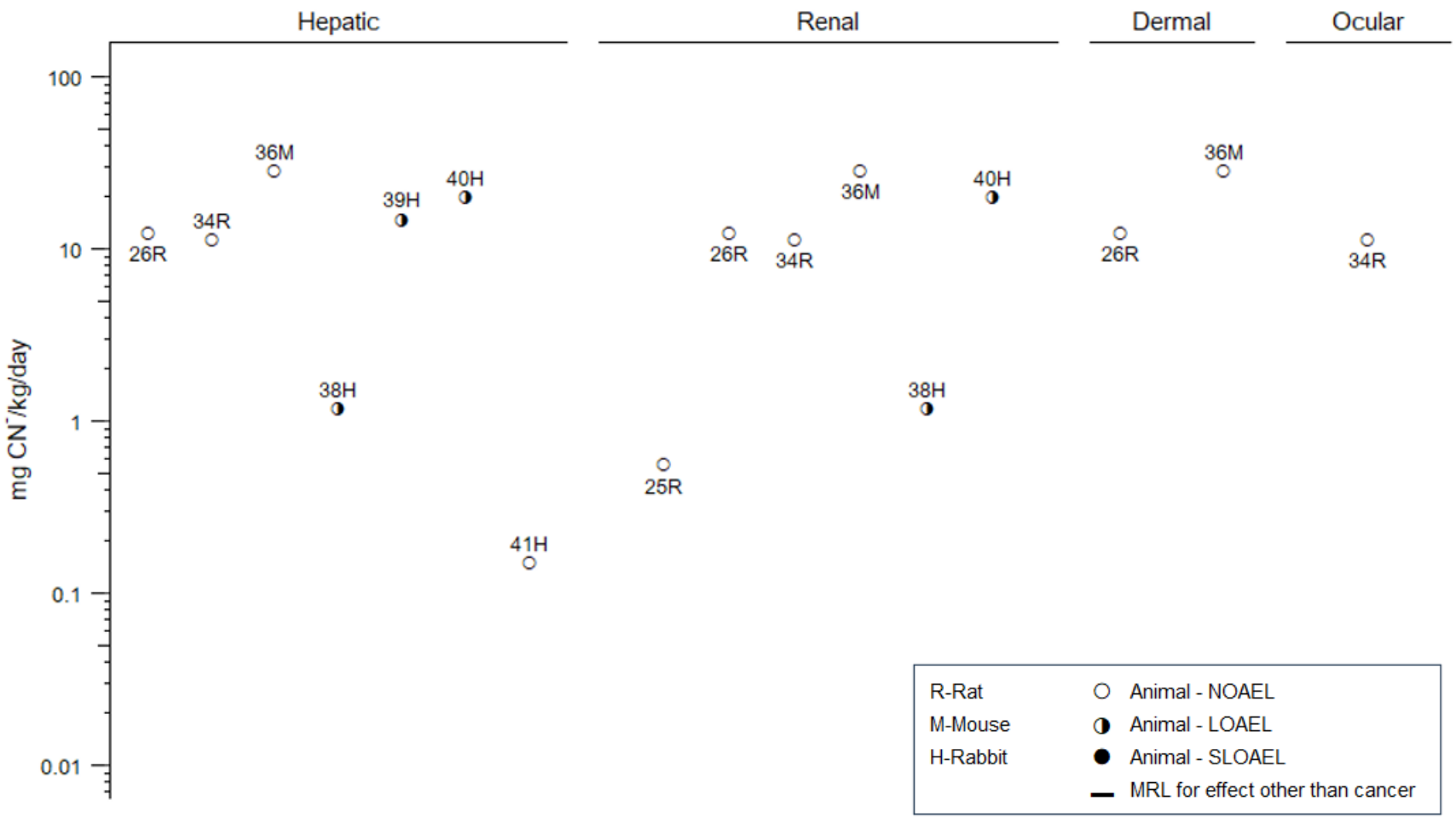


Figure 2-3. Levels of Significant Exposure to Cyanide – Oral
Intermediate (15–364 days)

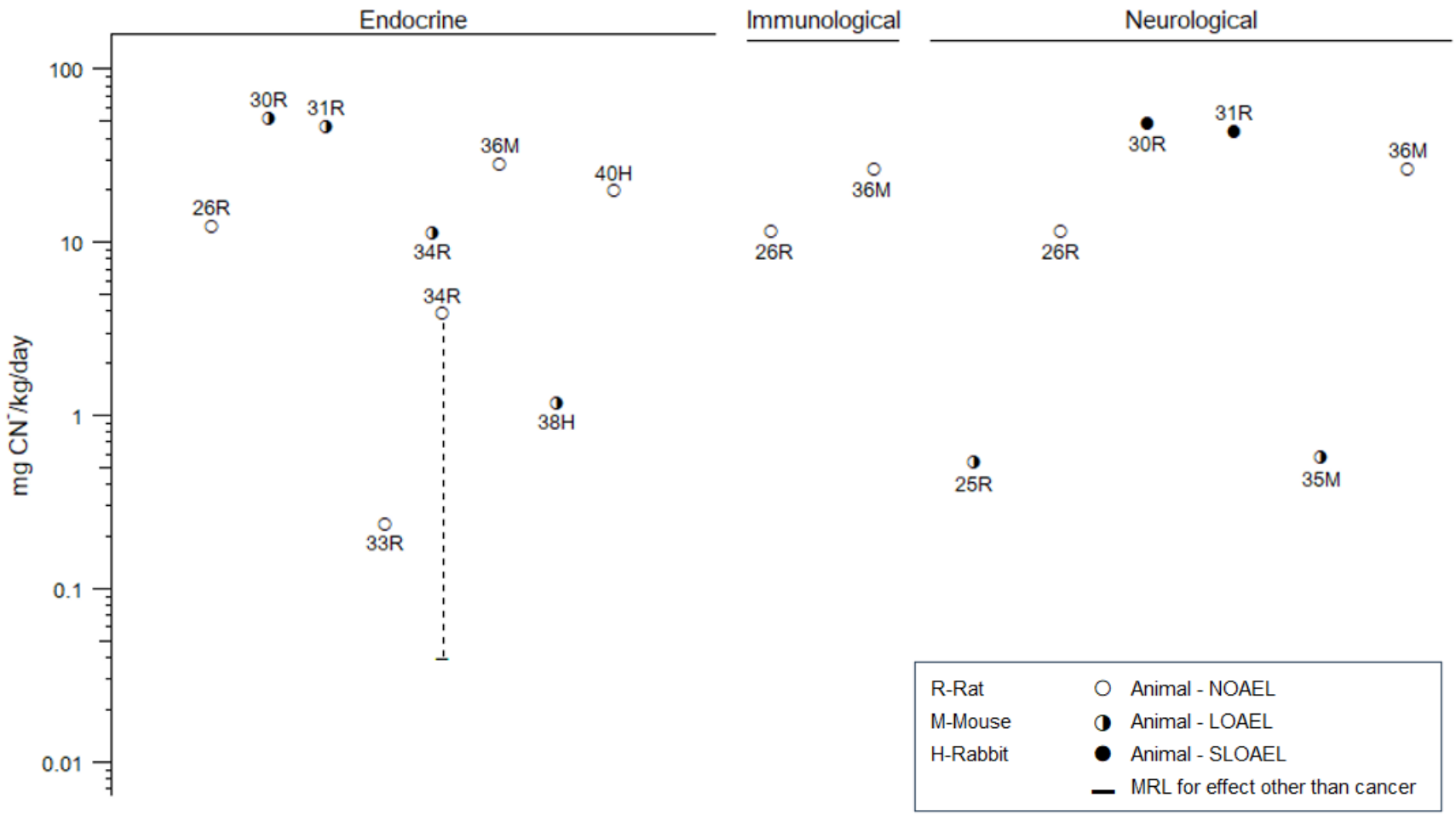


Figure 2-3. Levels of Significant Exposure to Cyanide – Oral
Intermediate (15–364 days)

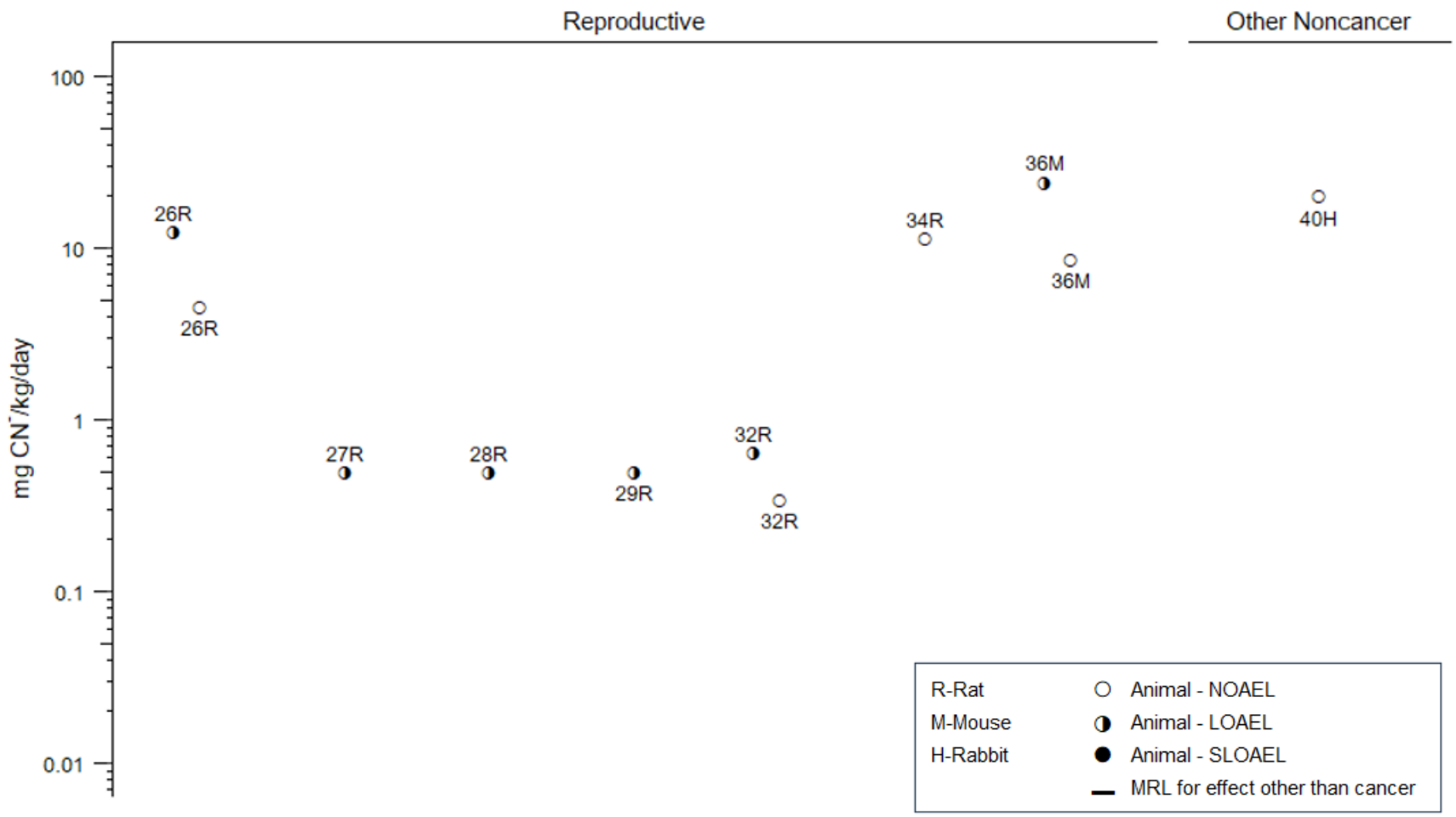


Table 2-3. Levels of Significant Exposure to Cyanide – Dermal

Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
ACUTE EXPOSURE								
Drinker 1932								**HCN**
Human 3 M	8–10 minutes Occupational	20,000 ppm in air	CS	Cardio			20,000	Palpitations
				Neuro			20,000	Dizziness, weakness, headache
Due to use of PPE (respiratory masks), dermal absorption of cyanide was suspected								
Ballantyne 1983a, 1983b								**HCN**
Rabbit (albino) 10 F	Once	0.90–1.14 mg CN^-/kg	LE, CS	Death			1	Transocular LD_{50}
Ballantyne 1983a, 1983b								**KCN**
Rabbit (albino) 10 F	Once	2.5–6.4 mg CN^-/kg	LE, CS	Death			3.2	Transocular LD_{50}
Ballantyne 1983a, 1983b								**NaCN**
Rabbit (albino) 10 F	Once	1.67–3.34 mg CN^-/kg	LE, CS	Death			2.68	Transocular LD_{50}
Ballantyne 1983b								**HCN**
Rabbit (albino) 10 F	Once	0.9–1.14 mg CN^-/kg	LE, CS	Resp		0.9		Rapid breathing
				Ocular			0.9	Corneal opacity, keratitis
				Neuro			0.9	Convulsions and loss of consciousness
Ballantyne 1983b								**KCN**
Rabbit (New Zealand) 4–6 F	Once	2.5–6.4 mg CN^-/kg	LE, CS	Neuro			2.5	Convulsions and loss of consciousness
Ballantyne 1983b								**KCN**
Rabbit (albino) 10 F	Once	2.5–6.4 mg CN^-/kg	LE, CS	Resp		2.5		Rapid breathing
				Ocular			2.5	Corneal opacity, keratitis
Ballantyne 1983b								**NaCN**
Rabbit (albino) 4–6 F	Once	1.7–3.34 mg CN^-/kg	LE, CS	Neuro	1.7		2.1	Convulsions and loss of consciousness

Table 2-3. Levels of Significant Exposure to Cyanide – Dermal

Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Ballantyne 1983b								**NaCN**
Rabbit (albino) 10 F	Once	1.69–3.34 mg CN^-/kg	LE, CS	Resp	1.69	2.1		Rapid breathing
				Ocular	1.69		2.1	Corneal opacity, keratitis
Ballantyne 1988								**NaCN**
Rabbit (New Zealand) 10 F	Once	1.69–5.28 mg CN^-/kg	LE, CS	Death			2.4	Transocular LD_{50}
Ballantyne 1994								**HCN**
Rabbit (albino) 9–10 F	Once	2.0–3.2 mg CN^-/kg	LE, CS	Death			2.3	Dermal LD_{50}, abraded skin
Ballantyne 1994								**KCN**
Rabbit (albino) 6–10 F	Once	4.0–16.0 mg CN^-/kg	LE, CS	Death			8.9	Dermal LD_{50}, intact skin
Ballantyne 1994								**NaCN**
Rabbit (albino) 9–19 F	Once	6.7–8.4 mg CN^-/kg	LE, CS	Death			7.7	Dermal LD_{50}, intact skin (NaCN solution)
Ballantyne 1994								**KCN**
Rabbit (albino) 9–10 F	Once	5.0–6.4 mg CN^-/kg	LE, CS	Death			5.7	Dermal LD_{50}, abraded skin
Ballantyne 1994								**HCN**
Rabbit (albino) 10 F	Once	5.4–7.6 mg CN^-/kg	LE, CS	Death			6.6	Dermal LD_{50}, intact skin
Ballantyne 1994								**NaCN**
Rabbit (albino) 9–10 F	Once	5.3–8.4 mg CN^-/kg	LE, CS	Death			5.9	Dermal LD_{50}, abraded skin (NaCN solution)
Ballantyne 1994								**NaCN**
Rabbit (albino) 6 F	Once	3.7–10.6 mg CN^-/kg	LE, CS	Death			6.3	Dermal LD_{50}, moist skin (NaCN powder)

Table 2-3. Levels of Significant Exposure to Cyanide – Dermal

Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Ballantyne 1994								**NaCN**
Rabbit (albino) 6–12 F	Once	2.6–5.3 mg CN^-/kg	LE, CS	Death			3.9	Dermal LD_{50}, abraded skin (NaCN powder)

Cardio = cardiovascular; CN = cyanide; CS = clinical signs; F = female(s); HCN = hydrogen cyanide; KCN = potassium cyanide; LD_{50} = dose associated with 50% lethality; LE = lethality; LOAEL = lowest-observed-adverse-effect level; M = male(s); NaCN = sodium cyanide; Neuro = neurological; NOAEL = no-observed-adverse-effect-level; PPE = personal protective equipment; Resp = respiratory

2.2 DEATH

It is well-established that death can occur following intentional or accidental cyanide poisoning, as documented in several reviews and regulatory documents (Asiah et al. 2014; Bhattacharya and Flora 2009; EPA 2006a, 2010; Geller et al. 2006; NIH/NINDS 2016a, 2016b; WHO 2004). Information contained in these sources is briefly reviewed below. Cyanide and cyanide compounds have been weaponized throughout history due to their lethality, with documented use during the Roman Empire, Franco-Prussian War, and both World Wars. Inhalation of cyanide fumes is often a contributing factor to fatalities related to fire smoke inhalation. Cyanide causes death by widespread inhibition of cellular oxygen utilization (see Section 2.21 for details). While cardiac abnormalities are common, death is almost always due to respiratory arrest due to CNS depression. Clinical signs that precede death include rapid breathing followed by slowed irregular breathing, light-headedness and giddiness, nausea and vomiting, confusion, restlessness and anxiety, hypotension, bradycardia, cyanosis, syncope, cardiac arrhythmia, stupor, spasms, convulsions, or coma. Metabolic acidosis precedes death in poisonings that are not immediately lethal. A comprehensive review of available case-reports or case-series reports that reviewed cyanide-related deaths is not included in this profile. Rather, this section is focused on available studies in humans and animals that estimated lethal exposure levels via the inhalation, oral, and/or dermal routes.

Based on analysis of available human and animal data, DOA (1976) estimated an average hydrogen cyanide concentration that would be fatal for humans within 30 minutes would be 622 ppm, with estimated total absorbed doses in fatal cases as low as 0.7 mg CN^-/kg (Rieders 1971). In one case, a worker exposed to 200 ppm hydrogen cyanide in a silverplating tank became unconscious and eventually died even though he had received antidotal therapy in a hospital (Singh et al. 1989). 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. Cyanide exposure was confirmed in one of the men based on a cyanide concentration of 0.05 mg/L in a postmortem blood sample. In other cases, exposure to 270 ppm hydrogen cyanide led to immediate 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). WHO (2004) determined that hydrogen cyanide concentrations of ≥110 ppm may lead to death within 30–60 minutes, and that 270 ppm hydrogen cyanide could be immediately fatal. Due to the detoxification rate of hydrogen cyanide (17 µg/kg/minute), the concentration that is lethal for 50% of the population

(LC_{50}) is higher for a longer exposure duration (e.g., 60 minutes) than for a shorter duration (e.g., 2 minutes) (NIH/NINDS 2016a, 2016b).

Levels of acute-duration exposure resulting in animal deaths were reported in multiple studies and LC_{50} values were determined 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 rats and 323 ppm for mice were reported by Higgins et al. (1972). At lethal concentrations, rodents exhibited hyperactivity and asphyxia convulsions with death occurring within 20 minutes of exposure; gross pathology findings included pulmonary hemorrhage and congestion of the liver and kidney. The 30-minute LC_{50} value in mice for hydrogen cyanide was 166 ppm (Matijak-Schaper and Alarie 1982). Hume et al. (1995) reported 90% lethality in mice after exposure to 400 ppm hydrogen cyanide for 3 minutes, and Ma et al. (2021) reported 33% lethality in mice after exposure to 327 ppm hydrogen cyanide for 40 minutes. LC_{50} values for hydrogen cyanide in rabbits ranged from 188 ppm for 30 minutes to 2,200 ppm for 45 seconds (Ballantyne 1983a). Mortality was 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 the different exposure regimens, so statistical significance could not be evaluated.

An average fatal oral dose of 1.52 mg CN^-/kg for humans has been calculated from case report studies of intentional or accidental poisonings (EPA 1987). Assuming a 70-kg individual, estimated lethal doses for specific cyanide compounds are 0.67–3.37 mg CN^-/kg as hydrogen cyanide and 0.86–1.43 mg CN^-/kg as potassium cyanide (Bhattacharya and Flora 2009). Suicide cases have involved ingestion of 100–600 g of potassium or sodium cyanide, absorbing up to about 3.5 mg CN^-/kg prior to death (Rieders 1971). The lowest fatal oral dose reported in humans was estimated as 0.56 mg CN^-/kg (form not specified), based on data obtained from the case history in a report by Gettler and Baine (1938). However, analytical measurements at the time of this study lacked the precision of current technology.

Several studies have calculated oral doses associated with 50% lethality (LD_{50} values) for animals following a single oral exposure to cyanide compounds. The LD_{50} values for sodium cyanide in rats ranged widely from 2.7 to 34 mg CN^-/kg; findings may be sex- and/or species-related but data are too limited to make a clear determination (Ballantyne 1988; Rice et al. 2018; Smyth et al. 1969). The highest LD_{50} value of 34 mg CN^-/kg was reported in male Sprague-Dawley rats (Rice et al. 2018), while the lowest value of 2.7 mg CN^-/kg was reported in female Porton rats (Ballantyne 1988). Ballantyne (1988) showed that values were similar in fasted (2.7 mg CN^-/kg) and unfasted (3 mg CN^-/kg) female Porton

rats; however, death occurred sooner in unfasted animals (17 minutes compared to 22 minutes). An intermediate value of 34 mg CN^-/kg was reported in rats of unspecified strain and sex (Rice et al. 2018). For calcium cyanide, the reported LD_{50} value in rats was 22 mg CN^-/kg (Smyth et al. 1969). Mortality was 95% in rats and mice that received a single gavage 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. In mice, LD_{50} values for potassium cyanide were similar in adults and juveniles, with values of 4.4 and 4.75 CN^-/kg in adult females and males, respectively, and values of 4.0 and 4.36 mg CN^-/kg in juvenile females and males, respectively (Sabourin et al. 2016). Acute LD_{50} values in rabbits were similar (2.34–2.7 mg CN^-/kg) regardless of whether the source was hydrocyanic acid, sodium cyanide, or potassium cyanide (Ballantyne 1983a, 1988).

Intermediate-duration drinking water and dietary studies did not report increased mortality in rats or mice, even at doses higher than those associated with mortality in acute-duration gavage studies. No exposure-related deaths were reported in rat or mice exposed to doses up to 12.5 or 28.8 mg CN^-/kg/day, respectively, in the drinking water for 13 weeks (NTP 1993; Tyner and Greeley 2023). Similarly, mortality was not increased in rats following dietary exposure to doses up to 47 mg CN^-/kg/day as potassium thiocyanate or 53 mg CN^-/kg/day as potassium cyanide for 11.5 months (Philbrick et al. 1979). Increased mortality was observed in rats exposed to 14.5 mg CN^-/kg/day as copper cyanide for 90 days (Gerhart 1986) and 2.6 mg CN^-/kg/day as potassium silver cyanide for 90 days (Gerhart 1987); these data are omitted from the LSE table because of the possible confounding effect of the metals. Hemolytic anemia, which was probably related to copper toxicity, was most likely responsible for observed deaths in rats exposed to copper cyanide (Gerhart 1986).

Since absorption of hydrogen cyanide through the skin is much slower than the lungs, the estimated LD_{50} value of 100 mg CN^-/kg for dermal exposure to hydrogen cyanide in humans is higher than estimated LC_{50} values via inhalation (Rieders 1971). In individuals wearing proper respiratory protection but lacking dermal protective gear, extremely high air concentrations of hydrogen cyanide (6,300–10,000 ppm) can be fatal through the dermal route (EPA 2006a).

Based on a series of LD_{50} studies in rabbits (Ballantyne 1994), dermal absorption (and the resulting toxicity) is increased through moist or abraded skin. Reported LD_{50} values for dermal exposure to cyanides in rabbits on dry skin include 6.6 mg CN^-/kg as hydrogen cyanide solution, 7.7 mg CN^-/kg as sodium cyanide solution, and 8.9 mg CN^-/kg as potassium cyanide solution; no lethality was observed

when sodium cyanide powder was applied to dry rabbit skin at doses up to 106 mg CN^-/kg (Ballantyne 1994). For moist skin, the dermal LD_{50} value for sodium cyanide powder was 6.3 mg CN^-/kg in rabbits. In abraded skin, dermal LD_{50} values in rabbits included 2.3 mg CN^-/kg for hydrogen cyanide solution, 5.9 mg CN^-/kg for sodium cyanide solution, 3.9 mg CN^-/kg for sodium cyanide powder, and 5.7 mg CN^-/kg for potassium cyanide solution (Ballantyne 1994). 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. Overt signs of toxicity in rabbits prior to death for both dermal or intraocular exposure included dyspnea, gasping, weakness, spasms, unsteadiness, convulsions, and coma. Deaths occurred also in guinea pigs when their skin was exposed to hydrogen cyanide; however, doses were not quantified (Fairley et al. 1934; Walton and Witherspoon 1926). It should be noted that none of the dermal studies reported the surface area to which the cyanide was applied. Similar to overt toxicity observed in rabbits, convulsions and coma preceded death in guinea pigs.

2.3 BODY WEIGHT

Body weight data in humans are limited to a single occupational exposure study. In an occupational setting, weight loss (mean of 5.6 kg) during employment was self-reported in 50% of workers formerly exposed to 15 ppm hydrogen cyanide for a mean duration of 11 months in a silver-reclaiming facility (Blanc et al. 1985). When workers were qualitatively stratified into low-, moderate-, and high-exposure levels based on job title, a dose-relationship between exposure and reported body weight loss was observed. This finding was associated with a reported loss of appetite in 58% of workers. Limitations of this study include lack of quantitative exposure levels for the low-, moderate-, and high-exposure groups, reliance on self-reporting of symptoms that occurred during employment that ceased 7–30 months prior to the assessment, and co-exposure to other chemicals during the silver-reclaiming process. Appetite loss was also reported in 25% of workers exposed to an unknown level of hydrogen cyanide vapor during heat treatment (case hardening) and electroplating for an unreported duration (Kumar et al. 1992). Body weight loss was not examined in this cohort.

No studies were located regarding body weight effects in animals after inhalation exposure to hydrogen cyanide. Decreased body weight (13%) was reported in rats intermittently exposed to 25 ppm cyanogen via inhalation for 6 months (Lewis et al. 1984). As discussed in Section 2.1, this study is not included in the LSE table due to difficulty in estimation of cyanide levels in body tissues after cyanogen exposure.

Reports of body weight effects in animals exposed to cyanide compounds via drinking water are inconsistent. One study reported a 70% reduction body weight gain in male rats that ingested 3.6 mg CN^-/kg/day as potassium cyanide in drinking water for 15 days, noting that the effect was significant as early as the first week of treatment (Sousa et al. 2002). However, several other drinking water studies have not observed adverse effects on body weight in rats after exposure to doses up to 6.4 mg CN^-/kg/day as potassium thiocyanide or 12 mg CN^-/kg/day as potassium cyanide for 14 days (de Sousa et al. 2007) or up to 12.5 mg CN^-/kg/day as sodium cyanide in drinking water for 13 weeks (NTP 1993; Tyner and Greeley 2023). Additionally, no body weight effects were observed in mice exposed to doses up to 28.8 mg CN^-/kg/day as sodium cyanide in drinking water for 13 weeks (NTP 1993). It is difficult to interpret the adversity of the findings reported by Sousa et al. (2002) in the absence of absolute body weight and water intake data and lack of support from other available drinking water studies.

In intermediate-duration dietary studies, decreased body weight gains of 22–33% were reported in rabbits exposed to 15 mg CN^-/kg/day as sodium cyanide (Okolie and Iroanya 2003) and in rats and rabbits exposed to 53 or 20 mg CN^-/kg/day as potassium cyanide, respectively (Okolie and Osagie 1999, 2000; Philbrick et al. 1979). However, no adverse effects on body weight were observed in rats exposed to dietary potassium thiocyanate at doses up to 47 mg CN^-/kg/day for 11.5 months (Philbrick et al. 1979).

Findings from studies that employed bolus dosing (i.e., gavage, buccal bolus) also reported inconsistent findings for body weight effects following exposure to cyanide. When effects were observed, they were generally associated with doses below those associated with effects in dietary studies. This observation is likely because bolus administration may overwhelm detoxification processes.

Acute-duration bolus administration studies in animals do not report adverse effects on body weight following exposure to cyanide compounds, with no body weight effects in mice exposed once to doses up to 4.6 mg CN^-/kg as potassium cyanide (Hawk et al. 2016; Sabourin et al. 2016). Decreased body weight gains of 25–39% were reported in some intermediate-duration oral bolus administration studies, including rats exposed to ≥0.5 mg CN^-/kg/day as sodium cyanide (Oyewopo et al. 2021a) and in rabbits exposed to 1.2 mg CN^-/kg/day as potassium cyanide (Avais et al. 2014). In contrast, no adverse effects on body weight were observed in rats at oral bolus doses up to 0.56 mg CN^-/kg/day as potassium cyanide (Mathangi et al. 2011; Soto-Blanco et al. 2002) or 1.7 mg CN^-/kg/day as sodium cyanide (Shivanoor and David 2015). No effect on body weight gain was observed in rabbits exposed to 0.15 mg CN^-/kg/day via gavage as potassium cyanide for up to 3 months (Ozolua et al. 2007).

In a 90-day gavage study, reduced body weight gain was reported in male rats exposed to ≥4.35 mg CN^-/kg/day as copper cyanide, but not in those exposed to 1.45 mg CN^-/kg/day (Gerhart 1986). Additionally, decreased weight gain was found in male rats exposed to ≥2.6 mg CN^-/kg/day via gavage as potassium silver cyanide for 90 days (Gerhart 1987). Since the presence of the copper or silver may have contributed to the observed decreases in body weight, these data are omitted from the LSE table.

As discussed in Section 2.1, animal studies on cassava are discussed in this profile, but are not included in the LSE table due to concurrent exposure to additional compounds found in cassava root. Pregnant hamsters fed 1.0 mg CN^-/kg/day in cassava for 10 days during gestation had decreased body weight gain (Frakes et al. 1986). Body weights were decreased by 24% in rats exposed to 5.50 mg CN^-/kg/day as cassava in the diet for 28 days, compared to control, and exposed animals lost body weight during the exposure period (Udeme et al. 2015). However, Udeme et al. (2015) did not report food intake data.

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

2.4 RESPIRATORY

Respiratory effects, primarily respiratory irritation and breathing difficulties, have been reported following exposure to cyanide compounds via all routes examined in both humans and animals. With the exception of local irritation, effects are attributed to general toxic actions of cyanide (impaired cellular oxygen utilization; see Section 2.21) and/or cyanide-related CNS depression rather than direct toxic action on the respiratory tract.

In case reports of humans acutely exposed to high levels of hydrogen cyanide requiring hospitalization, the rate of respiration is initially increased followed by subsequent dyspnea (Chen and Rose 1952; Peden et al. 1986; Potter 1950). The levels of exposure in these accidental poisonings were not provided.

Subjective complaints of respiratory effects were reported in a cohort of 56 workers exposed to hydrogen cyanide vapor during heat treatment (case hardening) and electroplating, including throat irritation (16.1%), breathlessness (8.9%), and cough (12.5%); physical exam revealed throat congestion in 25% of workers (Kumar et al. 1992). Breathing difficulties were self-reported in some workers exposed to unspecified levels of hydrogen cyanide in the cassava processing industry (Janagam et al. 2008).

Reporting in these studies was inadequate to determine if reported findings were increased over unexposed individuals and/or attributable to exposure.

Results of other occupational studies evaluating potential associations between cyanide exposure and adverse respiratory effects are reported in Table 2-4. Cough and throat congestion were more prevalent in workers employed for >10 years, compared to those employed <10 years; other symptoms were not associated with duration of employment. Exposure levels were not reported in this study. In an occupational study of three electroplating factories, an increased incidence of subjective respiratory complaints, including dyspnea and throat irritation, was observed in 36 male workers exposed to sodium cyanide and copper cyanide for 5–15 years, compared to 20 unexposed referents (El Ghawabi et al. 1975). Measured mean concentrations of "cyanides" (not further characterized) in the three factories were 6.416–10.375 ppm. Dyspnea, cough, wheezing, sore throat, hemoptysis, epistaxis, nasal congestion, and altered sense of smell were also self-reported in 19–47% workers formerly exposed to 15 ppm hydrogen cyanide for a mean duration of 11 months in a silver-reclaiming facility (Blanc et al. 1985). When the 36 workers were qualitatively stratified into low-, moderate-, and high-exposure levels based on job title, a positive association between exposure and self-reported incidence of nasal congestion was observed; no association was observed for dyspnea (other respiratory complaints were not evaluated for exposure-response). Limitations of this study include lack of quantitative exposure levels for the low-, moderate-, and high-exposure groups and reliance on self-reporting of symptoms that occurred during employment that ceased 7–30 months prior to the assessment. In general, findings in these occupational studies were confounded by other known chemical co-exposures, including as metals, cleaners, and cutting oils.

Table 2-4. Results of Select Epidemiological Studies Evaluating Occupational Exposure to Cyanide and Respiratory Effects

Reference, study type, and population	Measure of exposure	Outcome evaluated	Result
Blanc et al. 1985 Cohort; 36 former workers from a silver-reclaiming facility; mean duration of employment was 11 months and mean duration elapsed since employment was 10.5 months (United States, Illinois)	Time-weighted average concentration of hydrogen cyanide (measured after plant ceased operations): 15 ppm REI estimated based on job title; no quantitative exposure levels: Low (n=7) Moderate (n=13) High (n=16)	Dyspnea	↔ (REI)
		Nasal congestion	↑ (REI)

Table 2-4. Results of Select Epidemiological Studies Evaluating Occupational Exposure to Cyanide and Respiratory Effects

Reference, study type, and population	Measure of exposure	Outcome evaluated	Result
Chatgtopadhyay et al. 2000 Prospective cohort; 24 workers exposed to cyanide fumes from a metal tempering plant (at initial investigation; mean exposure of 21.00 years), 17 workers at 2-year follow-up (mean exposure of 22.96 years), and 14 unexposed referents (India)	Not reported	Pulmonary function (when categorized by smoking status)	
		FEV_1	↔ (initial) ↔ (follow-up) ↔ (duration of exposure)
		$FEV_{1\%}$	↓ (initial, smokers) ↔ (follow-up) ↔ (duration of exposure)
		FEF	↓ (initial, smokers) ↔ (follow-up) ↔ (duration of exposure)
		$FEF_{25–75\%}$	↔ (initial) ↔ (follow-up) ↔ (duration of exposure)
		FVC	↔ (initial) ↔ (follow-up) ↔ (duration of exposure)
		VC	↔ (initial) ↔ (follow-up) ↔ (duration of exposure)
		PEFR	↔ (initial) ↓ (follow-up, smokers) ↔ (duration of exposure)
El Ghawabi et al. 1975 Cross-sectional; 36 male workers from three electroplating factories (9 from Factory A, 12 from Factory B, 15 from Factory C; employed 5–15 years) and 20 unexposed male referents (Egypt)	Mean (range) "cyanides" concentrations, ppm: Factory A: 10.375 (8.2–12.4) Factory B: 6.416 (4.2–8.8) Factory C: 8.083 (5.9–9.6) "Cyanides" measured were not further described; cyanide exposure evolved from plating bath containing sodium cyanide and copper cyanide.	Self-reported respiratory complaints (dyspnea, throat irritation)	↑ (workers versus referents)

↑ = association; ↓ = inverse association; ↔ = no association; FEF = forced expiratory flow; $FEF_{25–75\%}$ = forced mid expiratory flow; FEV_1 = forced expiratory volume in 1 second; $FEV_{1\%}$ = forced expiratory volume in 1 second expressed as a percentage of forced vital capacity; FVC = forced vital capacity; PEFR = peak expiratory flow rate; REI = relative exposure index; VC = vital capacity

Chatgtopadhyay et al. (2000) reported decreases in several measures of pulmonary function in 24 workers exposed to an unreported level of cyanide fumes for an average of 21 years in a metal tempering plant,

compared to 14 unexposed referents. Pulmonary function worsened over the next 2 years in 17 workers with follow-up data. However, once workers and referents were divided by smoking status, the only differences that remained included the following parameters in smoking workers, compared to smoking referents: (1) decreased forced expiratory volume in 1 second as the percentage of forced vital capacity ($FEV_{1\%}$) at the initial examination (but not follow-up); (2) decreased forced expiratory flow (FEF) at the initial examination; (but not follow-up); and (3) decreased peak expiratory flow rate (PEFR) at the follow-up examination. No differences were noted between nonsmoking workers and nonsmoking referents.

Data for respiratory effects in animals following inhalation exposure to hydrogen cyanide are limited; most studies had major limitations. Following exposure to a series of hydrogen cyanide concentrations for 30 minutes, the concentration associated with a 50% reduction in the respiratory rate of mice was calculated at 63 ppm hydrogen cyanide (Matijak-Schaper and Alarie 1982). Decreased respiratory rate was attributed to depression of the respiratory center. Exposure to 327 ppm hydrogen cyanide for 40 minutes resulted in gasping and labored breathing in mice that survived that persisted for up to 60 minutes post-exposure (Ma et al. 2021). Other identified studies in dogs and monkeys reported severe respiratory effects but are not included in the LSE table due to inadequate study design (low animal number and/or lack of concurrent control) and/or poor reporting of study design and results. Acute-duration studies reported asphyxia and pulmonary edema in dogs at concentrations of 149–633 ppm hydrogen cyanide for 2–10 minutes (Haymaker et al. 1952) and severe dyspnea in monkeys exposed to ≥100 ppm hydrogen cyanide for 30 minutes (Purser et al. 1984). In an intermediate-duration study in dogs, dyspnea was reported following exposure to 45 ppm hydrogen cyanide for 30 minutes a day at 2–8-day intervals for 28–96 days (Valade 1952).

Nasal irritation was reported in volunteers exposed to 16 ppm cyanogen for 6–8 minutes (McNerney and Schrenk 1960). No effects were reported at 8 ppm cyanogen. In laboratory animals, asphyxia was observed in rats exposed to 250 ppm cyanogen for 7.5–120 minutes (McNerney and Schrenk 1960). In intermediate-duration studies, no respiratory effects were reported in rats exposed to 25 ppm cyanogen for 6 months, and a decrease in total lung moisture content was the only finding in monkeys exposed to 11 ppm cyanogen, also for 6 months (Lewis et al. 1984). As discussed in Section 2.1, these studies are not included in the LSE table due to difficulty in estimation of cyanide levels in body tissues after cyanogen exposure.

Breathing irregularities have also been reported in humans after oral cyanide poisoning. Stertorous, deep, and rapid breathing was reported in a man who ingested approximately 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 with potassium cyanide; one man ingested 7.6 mg CN^-/kg (Goodhart 1994) and the other man ingested 0.57 mg CN^-/kg (Saincher et al. 1994). 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).

Respiratory effects in animals exposed via drinking water or dietary ingestion were limited, and studies with reliable study designs and data reporting did not report adverse effects. No effects on lung weights or histology were observed in rat dams given up to 12 mg CN^-/kg/day as potassium cyanide or 6.43 mg CN^-/kg/day as potassium thiocyanide in drinking water on gestation days (GDs) 6–20 (De Sousa et al. 2007). Similarly, no exposure-related effects on lung weight or histology were observed in rats or mice exposed to doses up to 12.5 or 28.8 mg CN^-/kg/day as sodium cyanide, respectively, in drinking water for 13 weeks (NTP 1993).

In contrast, Okolie and Iroanya (2003) qualitatively reported evidence of pulmonary edema (thickened alveolar walls and congestion) and evidence of tissue damage (increased lactate dehydrogenase [LDH] in the lung tissue) in rabbits that ingested 15 mg CN^-/kg/day as sodium cyanide in feed for 4 weeks. However, due to lack of quantitative histopathology data reporting, statistical significance of the findings could not be determined. Therefore, these findings are omitted from the LSE table. In a 2-year study in rats, no respiratory effects were reported at a target dietary dose of 10.4 mg CN^-/kg/day as hydrogen cyanide (Howard and Hanzal 1955). However, there is uncertainty in the dose because evaporation of the cyanide from the feed resulted in unstable cyanide levels throughout the experiment. Due to uncertainty in dose estimates for Howard and Hanzal (1955), this study is not included in the LSE table.

A limited number of gavage studies in animals reported respiratory effects at doses below those associated with effects in dietary studies. This observation is likely because bolus administration may overwhelm detoxification processes. In an acute-duration study, labored respiration was observed in

adult and juvenile mice given single gavage doses ≥3.2 mg CN^-/kg/day as potassium cyanide (Sabourin et al. 2016). Labored respiration was reported in rats treated by gavage with 4.35 mg CN^-/kg/day as copper cyanide or 0.8 mg CN^-/kg/day as a form of potassium silver cyanide for 90 days (Gerhart 1986, 1987). Due to the unknown contribution of copper and silver to observed respiratory effects in the Gerhart (1986, 1987) studies, these data are omitted from the LSE table.

In dermal exposure studies in humans, breathing irregularities, including Cheyne-Stokes respiration (atypical breathing pattern defined by cycles of slow, deep breathing or apnea followed by rapid, short breaths/hyperventilation) (Rudrappa et al. 2023), 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).

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).

Mechanisms of Respiratory Toxicity. Clinical signs of labored or difficult breathing are most likely due to general mechanisms of cyanide toxicity (histotoxic anoxia), in which cells are unable to utilize oxygen (see Section 2.21 for details), rather than a direct effect of the respiratory system. However, 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.

Respiratory system effects may also be secondary to neurotoxic effects of cyanide, such as CNS depression (see Section 2.15). 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 adenosine triphosphate (ATP)-sensitive potassium currents, an effect that was antagonized by diazoxide, an opener of ATP-sensitive K^+ channels. The study authors suggested 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 study 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 CNS.

2.5 CARDIOVASCULAR

There is limited evidence of cardiovascular effects, primarily bradycardia and irregular heartbeat, following exposure to cyanide compounds in both humans and animals. Some of these findings are attributed to general toxic actions of cyanide (impaired cellular oxygen utilization; see Section 2.21) and/or cyanide-related CNS depression rather than direct toxic action on the cardiovascular system.

Wexler et al. (1947) reported that four men who were executed via inhalation of hydrogen cyanide gas (concentration not reported) had 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).

Subjective complaints of chest pain have been reported in some workers occupationally exposed to cyanide; it is unclear if this nonspecific complaint is directly related to potential cardiovascular effects. Subjective complaints of chest pain were reported in a 13/56 workers exposed to an unknown concentration of hydrogen cyanide vapor during heat treatment (case hardening) and electroplating (Kumar et al. 1992). In another occupational study, 7/36 workers exposed to an unspecified form of cyanide at mean concentrations of 6.416–10.375 ppm for 5–15 years from Egyptian electroplating factories complained of precordial pain, compared to 1/20 unexposed referents (El Ghawabi et al. 1975). The source of cyanide exposure was an electroplating bath containing sodium cyanide and copper cyanide. In 36 workers formerly exposed to 15 ppm hydrogen cyanide for a mean duration of 11 months in a silver-reclaiming facility, 31% of workers recalled chest pain and 14% of workers recalled palpitations during employment (Blanc et al. 1985). When workers were qualitatively stratified into low-, moderate-, and high-exposure levels based on job title, a dose-relationship between exposure and self-

reported incidence of chest pain was observed (incidence of palpitations was not evaluated for exposure-response). Limitations of this study include lack of quantitative exposure levels for the low-, moderate-, and high-exposure groups and reliance on self-reporting of symptoms that occurred during employment that ceased 7–30 months prior to the assessment. Additionally, findings in both studies are confounded by other known chemical co-exposures, including metals, cleaners, and cutting oils.

A limited number of studies evaluated cardiovascular endpoints in animals following inhalation exposure to cyanide compounds. Bradycardia, arrhythmias, and T-wave abnormalities were observed in monkeys exposed to 100 ppm hydrogen cyanide for 30 minutes (Purser et al. 1984). While these data suggest cyanide-related changes in cardiac function, use of a single animal per exposure level and lack of a concurrent control preclude inclusion in the LSE table. Increased cardiac-specific creatine 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 between exposures (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 intermittently exposed to 25 ppm cyanogen for 6 months (Lewis et al. 1984). As discussed in Section 2.1, cyanogen studies are not included in the LSE table due to difficulty in estimation of cyanide levels in body tissues after cyanogen exposure.

Several case studies also 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).

Cardiovascular function was not evaluated in animal studies following drinking water or dietary exposure. No treatment-related changes in heart weight or histology were seen in rats or mice exposed to doses up to 12.5 or 28.8 mg CN^-/kg/day, respectively, as sodium cyanide in the drinking water for 13 weeks (NTP 1993). No treatment-related effects on heart histopathology and no change in cardiac tissue levels of aspartate aminotransferase (AST) or alkaline phosphatase (ALP) were observed in male rabbits that ingested 20 mg CN^-/kg/day as potassium cyanide via the diet for 40 weeks (Okolie and Osagie 2000). While no changes in heart weight or histology 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, the reliability of the dose 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 (Howard and Hanzal 1955). Due to low confidence in dose estimates, the 2-year dietary study is omitted from the LSE table.

Cardiovascular function was assessed in animal studies that employed bolus dosing (i.e., gavage, buccal bolus). It is noted that histopathological changes in the cardiovascular system were observed at doses below those eliciting no effects following drinking water or dietary exposure. This observation is likely because bolus administration may overwhelm detoxification processes. These studies are discussed below.

An acute, single gavage dose of 3.2 mg CN^-/kg/day as potassium cyanide to adult mice resulted in decreased systolic, diastolic, and mean arterial blood pressure and decreased heart rate that were observed beginning immediately upon dosing through 1 hour post dosing (Hawk et al. 2016). Following dose administration, four mice (two mice per sex) experienced cardiovascular events on the electrocardiogram (ECG); however, it was unclear whether these were treatment-related as the incidence was low and the events were varied. There were no effects noted on heart weight or histopathology in either adult or juvenile mice exposed once to 3.2 mg CN^-/kg/day as potassium cyanide; cardiovascular function was not assessed in juvenile mice (Hawk et al. 2016). In another study, a single gavage dose of up to 4.6 mg CN^-/kg/day as potassium cyanide did not result in any weight or histological changes to the heart nor any significant effects on serum levels of biomarkers of cardiac damage (Sabourin et al. 2016). In a 10-day gavage study, rats given 12 mg CN–/kg/day had increased vascular resistance in the brain characterized by decreased lumen size and arterial wall cellular degeneration in the middle cerebral artery. This resulted in responsive dilation of the common carotid artery (increased diameter) (Ogundele et al. 2014a). Following a 10-day recovery period, attenuation of cyanide-related vascular effects was observed. There were no treatment-related effects on contractile strength or electrophysiology of the aortic ring in rabbits following gavage of 0.15 mg CN^-/kg/day as potassium cyanide for 25 days (Ozolua et al. 2007). 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).

As discussed in Section 2.1, animal studies on cassava are discussed in this profile, but are not included in the LSE table due to concurrent exposure to additional compounds found in cassava root. 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 (Kamalu 1993). Dogs similarly fed rice to which 1.04 mg CN^-/kg food was added (sodium cyanide was added to release hydrogen cyanide during the

cooking process) did not show any apparent cardiovascular effects (Kamalu 1993), suggesting that observed cardiovascular effects in cassava-fed dogs were attributable to other compounds found in cassava root and/or interactions between cyanide and other compounds. However, findings in this study were confounded by concurrent diseases in study animals requiring pharmaceutical intervention (Kamalu 1991, 1993); therefore, the sodium cyanide study is omitted from the LSE table.

In a dermal exposure study, 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.

Mechanisms of cardiovascular toxicity. While some of the reported cardiovascular effects associated with cyanide exposure may be attributable to general cyanide histotoxic anoxia (see Section 2.21) or secondary to CNS depression (see Section 2.15), 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 resulted in elevated intracellular calcium levels, but only after a substantial contracture develops (Allen and Smith 1985). The study authors proposed that intracellular calcium may precipitate cell damage and arrhythmias. Cheung et al. (2019) demonstrated that, *in vitro*, cyanide induces calcium influx by activating protein kinase C epsilon, which phosphorylates the L-type calcium channel on myocytes (Cheung et al. 2019). Additionally, a number of gene expression changes in the transcriptome from pathways associated with cardiac injury, such as angiogenesis, cardiac contractility, and fibrogenesis, were observed in mice following exposure to 327 ppm hydrogen cyanide for 40 minutes, a concentration that was lethal to 8/24 mice (Ma et al. 2021).

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).

2.6 GASTROINTESTINAL

Gastrointestinal effects reported in occupational studies of cyanide exposure are probably provoked by CNS effects and/or by irritation of the gastric mucosa in cases in which the gas is swallowed during breathing. In an occupational hygiene study in three electroplating factories, an increased incidence of self-reported vomiting was observed in 36 male workers exposed to sodium cyanide and copper cyanide for 5–15 years, compared to 20 unexposed referents (El Ghawabi et al. 1975). Measured mean concentrations of "cyanides" (not further characterized) were 6.416–10.375 ppm. Nausea or vomiting was also reported in 69% of workers formerly exposed to 15 ppm hydrogen cyanide for a mean duration of 11 months in a silver reclaiming facility (Blanc et al. 1985). When the 36 workers were qualitatively stratified into low-, moderate-, and high-exposure levels based on job title, a dose-relationship between exposure and reported incidence of nausea and vomiting was observed. Limitations of this study include lack of quantitative exposure levels for the low-, moderate-, and high-exposure groups and reliance on self-reporting of symptoms that occurred during employment that ceased 7–30 months prior to the assessment. Additionally, findings in both studies are confounded by other known chemical co-exposures, including metals, cleaners, and cutting oils.

Information regarding gastrointestinal effects in animals exposed via inhalation is limited to a report of vomiting in dogs exposed to 45 ppm hydrogen cyanide for 28–96 days (Valade 1952). This study is omitted from the LSE table due to poor reporting of study design and results and lack of a concurrent control group.

Gastrointestinal effects observed in acute oral cyanide poisoning cases in humans are attributed to alkaline properties of cyanide compounds, resulting in corrosive effects in the gastrointestinal tract. 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).

Data pertaining to potential gastrointestinal effects in animals following oral exposure to cyanide are limited, but do not suggest that the gastrointestinal tract is a primary target of cyanide toxicity. No histopathological changes were observed in the gastrointestinal tract in rats or mice exposed to doses up to 12.5 or 28.8 mg CN^-/kg/day as sodium cyanide, respectively, in drinking water for 13 weeks (NTP

1993). Diarrhea was observed in rats treated orally with 14.5 mg CN^-/kg/day copper cyanide for 90 days (Gerhart 1986). However, since diarrhea has been observed in both humans and animals following oral exposure (ATSDR 2024), the diarrhea was probably due to the toxicity of copper. Therefore, gastrointestinal data from Gerhart (1986) are omitted from the LSE table. No gastrointestinal effects were found in rats exposed to 7.8 mg CN^-/kg/day as potassium silver cyanide for 90 days (Gerhart 1987). Chronic intestinal inflammation occurred in dogs exposed to ≥0.27 mg CN^-/kg/day as sodium cyanide via capsules for 14.5 months (Hertting et al. 1960). However, this study is omitted from the LSE table due to lack of concurrent control and use of only one animal per dose group.

Reduced height of the stratum corneum of the oral mucosa was observed in hamsters administered 14.7 mg CN^-/kg/day as potassium cyanide directly to the cheek pouch mucosa for 90 days (Salum et al. 2006). No other histological changes (e.g., epithelial changes, inflammation) were evident. The biological relevance of this portal-of-entry effect is unclear.

No studies were located regarding gastrointestinal effects in humans after dermal exposure to cyanide. Acute-duration 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).

2.7 HEMATOLOGICAL

There is limited evidence of altered hematological endpoints following occupational exposure to cyanide in electroplating plants; however, findings are confounded by co-exposure to copper, a known hematotoxic agent. In an occupational hygiene study in three electroplating factories, increases in hemoglobin levels and percent lymphocytes were observed in 36 male workers exposed to sodium cyanide and copper cyanide for 5–15 years, compared to 20 unexposed referents (El Ghawabi et al. 1975). Additionally, punctate basophilia of erythrocytes, which indicated toxic poisoning, was present in 28 of 36 subjects. Measured mean concentrations of "cyanides" (not further characterized) were 6.416–10.375 ppm. 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 (compared to normal clinical ranges) were noted in 34 male workers exposed to unspecified concentrations of hydrogen cyanide for an unspecified duration during case hardening and electroplating.

No studies were located regarding hematological effects in animals after inhalation exposure to hydrogen cyanide. No hematological effects were found in rats or monkeys intermittently exposed to 25 ppm cyanogen for 6 months (Lewis et al. 1984). As discussed in Section 2.1, this study is not included in the LSE table due to difficulty in estimation of cyanide levels in body tissues after cyanogen exposure.

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

A limited number of studies evaluated hematological effects in animals following oral exposure. As discussed below, no adverse effects were observed in drinking water studies. Effects observed at lower doses in gavage studies may be attributable to overwhelming detoxification processes and/or other cations in the administered compound (e.g., copper).

No treatment-related hematological effects were observed in rats or mice exposed to doses of up to 12.5 or 28.8 mg CN^-/kg/day, respectively, as sodium cyanide in drinking water for 13 weeks (NTP 1993; Tyner and Greeley 2023). Decreased erythrocyte counts, hemoglobin levels, packed cell volume, and mean corpuscular volume were observed in rabbits exposed to 1.2 mg CN^-/kg/day as potassium cyanide via gavage for 40 days (Avais et al. 2014).

Hemolytic anemia, characterized by decreased erythrocytes, hemoglobin concentrations, and hematocrit, was observed in rats given a gavage dose of 14.5 mg CN^-/kg/day as copper cyanide for 90 days (Gerhart 1986). 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 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; it is unclear whether the hematological effects can be partially attributed to copper toxicity rather than to cyanide toxicity; thus, the data are omitted from the LSE table. Increased mean corpuscular volume, mean corpuscular hemoglobin concentration, and spleen weights were indicative of hematological effects in rats exposed to 7.8 mg CN^-/kg/day as potassium silver cyanide for 90 days by gavage (Gerhart 1987). No effects were found at 2.6 mg CN^-/kg/day. Due to unknown contribution of silver to the hematological effects, these data are omitted from the LSE table.

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

2.8 MUSCULOSKELETAL

Data regarding potential musculoskeletal effects in humans or animals after exposure to cyanide or cyanide compounds are extremely limited.

Muscular rigidity was observed in humans after acute oral 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). Clinical laboratory findings of increased serum creatinine and serum creatine kinase in this case are evidence of the observed breakdown of muscle fibers.

No musculoskeletal effects were observed at necropsy in rats or monkeys intermittently exposed to 25 ppm cyanogen for 6 months (Lewis et al. 1984). As discussed in Section 2.1, this study is not included in the LSE table due to difficulty in estimation of cyanide levels in body tissues after cyanogen exposure.

2.9 HEPATIC

Data pertaining to potential hepatotoxicity in humans are limited to two occupational studies. An increase in serum ALP was noted in 10 of the 15 electroplating and case hardening workers exposed to an unspecified concentration of hydrogen cyanide for an unspecified duration, compared to normal clinical ranges (Kumar et al. 1992). Serum bilirubin was found to be within the normal range in all 15 workers. Serum AST was marginally elevated in 20 workers exposed to unspecified levels of hydrogen cyanide in the cassava processing industry, compared to 20 age-matched referents; however, AST levels in workers were within the normal clinical range (Janagam et al. 2008). Serum alanine aminotransferase (ALT) and total protein levels were comparable between workers and unexposed referents. Cassava workers showed an altered lipid profile, compared with unexposed referents, with elevated total serum cholesterol, triglycerides, high-density lipoproteins (HDL), and very low-density lipoproteins (VLDL); levels of low-density lipoproteins (LDL) were comparable between groups (Janagam et al. 2008). Of these findings, the study authors proposed that the elevated triglycerides show the most clinical relevance and are likely due to altered energy metabolism (decreased glycolysis) associated with cyanide exposure.

No studies were located regarding hepatic effects in animals after inhalation exposure to hydrogen cyanide. No changes in clinical chemistry or liver histology were observed in rats or monkeys exposed to 25 ppm cyanogen for 6 months (Lewis et al. 1984). As discussed in Section 2.1, these studies are not included in the LSE table due to difficulty in estimation of cyanide levels in body tissues after cyanogen exposure.

There is inconsistent evidence of hepatotoxicity in animals following exposure to cyanide via drinking water, with findings in short-duration studies not confirmed in longer-duration studies. Acute-duration oral exposure to potassium cyanide at doses ≥1.2 mg CN^-/kg/day in drinking water on GDs 6–20 resulted in mild hepatic vacuolation and mild-to-moderate hepatic congestion in 100% of examined dams (de Sousa et al. 2007). These effects persisted in dams similarly treated on GDs 6–20 but sacrificed on postnatal day (PND) 22 after a 3-week recovery period. Although incidences were not reported in this study, the study authors only reported severity scores when all animals analyzed showed the same alteration. Therefore, it is unclear if hepatic lesions were observed in some animals (but not all) at the lowest dose tested (0.4 mg CN^-/kg/day); thus, a NOAEL for hepatic effects could not be established for this study. All dams similarly exposed to 6.4 mg CN^-/kg/day as potassium thiocyanate also exhibited mild hepatocyte vacuolation and bile duct proliferation at GD 20 and PND 22; again, it is unclear if hepatic lesions were observed in some (but not all) of the dams exposed to lower potassium thiocyanate doses (0.2 or 0.6 mg CN^-/kg/day). In a 15-day study, severe cytoplasmic vacuolization of hepatocytes was observed in male rats that ingested 3.6 mg CN^-/kg/day as potassium cyanide in drinking water (Sousa et al. 2002); hepatic effects were reportedly minimal at 0.36–1.2 mg CN^-/kg/day and absent at 0.12 mg CN^-/kg/day. However, since incidence data for histopathological lesions were not provided, significance of the findings cannot be determined; therefore, these data are omitted from the LSE table. In contrast to the 14- to 15-day studies, no adverse effects on liver weight or histology were observed in rats or mice exposed to up to 12.5 or 28.8 mg CN^-/kg/day, respectively, as sodium cyanide in the drinking water for 13 weeks (NTP 1993; Tyner and Greeley 2023). Drinking water studies did not find any exposure-related changes in hepatic clinical chemistry values (Sousa et al. 2002; NTP 1993; Tyner and Greeley 2023).

Liver damage was reported in rabbits exposed to dietary sodium or potassium cyanide. Based on the limited database, it is unknown if these findings represent a species (rabbit versus rodent) or route (dietary versus drinking water) susceptibility. Liver damage was observed in rabbits that ingested 15 mg CN^-/kg/day from sodium cyanide in feed for 4 weeks, as indicated by increased serum enzyme activities (ALP, ALT, LDH), histopathological lesions (necrosis, fatty degeneration, and congestion), and decreased hepatic enzyme ALP activities (Okolie and Iroanya 2003). Increased serum levels of ALT,

ALP, LDH, and sorbitol dehydrogenase (SDH) and focal hepatocellular congestion and necrosis were also observed in male rabbits that ingested 20 mg CN^-/kg/day as potassium cyanide via the diet for 10 months (Okolie and Osagie 1999). For both studies, quantitative data were only provided for serum enzyme data. Since incidence data were not reported for liver lesions, the significance of the findings could not be determined. Therefore, histological findings from the rabbit studies are omitted from the LSE table.

In rodents, dietary cyanide exposure is limited to a single chronic-duration study in which no hepatic effects were observed in rats following exposure 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, the reliability of the dose 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. Due to low confidence in dose estimates, this study in rats is omitted from the LSE table.

A gavage study in rabbits supports that this species may be susceptible to hepatotoxicity following exposure to cyanide; however, susceptibility may be attributable to overwhelming the detoxification processes. Increased serum levels of ALT, AST, ALP, bilirubin, and LDH, along with decreased serum levels of total serum albumin and protein, were observed in rabbits given 1.2 mg CN^-/kg/day as potassium cyanide via gavage for 40 days (Avais et al. 2018). Liver histology was not assessed in this study. No effects were observed on serum levels of ALT or AST in rabbits gavaged with very low doses of 0.15 mg CN^-/kg/day as potassium cyanide for 25 days (Ozulu et al. 2007).

In bolus studies in rodents, no changes in liver weight or histology were observed in mice at single oral doses up to 4.6 mg CN^-/kg/day as potassium cyanide (Hawk et al. 2016; Sabourin et al. 2016). In rats exposed 0.56 mg CN^-/kg/day as potassium cyanide for 90 days via gavage, increases in hepatic microgranuloma, spotty necrosis, and portal inflammation were qualitatively described (Mathangi et al. 2011). However, due to lack of quantitative histopathology data reporting, statistical significance of the findings could not be determined. Therefore, these findings are omitted from the LSE table. There were no reported changes in liver weights in this study. Rats treated for 90 days by gavage with 14.5 mg CN^-/kg/day as copper cyanide had increased serum levels of ALT, AST, bilirubin, and ALP, and decreased globulin levels in the blood (Gerhart 1986). Liver necrosis was observed in low incidences (not quantified) in both sexes at 14.5 mg CN^-/kg/day and in females at 4.35 mg CN^-/kg/day. The hepatic effects of copper cyanide could possibly be due to the toxicity of copper rather than of cyanide and are

therefore omitted from the LSE table. 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).

As discussed in Section 2.1, animal studies on cassava are discussed in this profile, but are not included in the LSE table due to concurrent exposure to additional compounds found in cassava root. Serum levels of ALT, AST, and ALP were elevated in rats exposed to ≥5.50 mg CN^-/kg/day as cassava in the diet for 28 days (Okafor et al. 2006; Udeme et al. 2015). No adverse changes in serum hepatic enzymes were noted in rats similarly exposed to 6.27 mg CN^-/kg/day for 7 days (Okafor et al. 2006). Periportal vacuolation and congestion were observed in the livers of dogs fed 1.04 mg CN^-/kg/day in rice as cassava for 14 weeks (Kamalu 1993). Dogs similarly fed rice to which 1.04 mg CN^-/kg food was added (sodium cyanide was added to release hydrogen cyanide during the cooking process) did not show any apparent hepatic effects (Kamalu 1993), suggesting that observed hepatic effects in cassava-fed dogs were attributable to other compounds found in cassava root and/or interactions between cyanide and other compounds. However, findings in this study were confounded by concurrent diseases in study animals requiring pharmaceutical intervention (Kamalu 1991, 1993); therefore, the sodium cyanide study is omitted from the LSE table.

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

2.10 RENAL

Data pertaining to potential renal toxicity in humans following inhalation exposure are limited. Serum creatinine was elevated in 20 workers exposed to unspecified levels of hydrogen cyanide in the cassava processing industry, compared to 20 age-matched referents; however, levels in workers were within the normal clinical range (Janagam et al. 2008). In a case report, anuria followed by polyuria was observed in a man who was occupationally exposed to 200 ppm hydrogen cyanide for an unspecified length of time (Singh et al. 1989).

No studies were located regarding renal effects in animals after inhalation exposure to hydrogen cyanide. No histopathological changes were observed in kidneys of rats or monkeys intermittently exposed to 25 ppm cyanogen for 6 months (Lewis et al. 1984). As discussed in Section 2.1, these studies are not included in the LSE table due to difficulty in estimation of cyanide levels in body tissues after cyanogen exposure.

Data pertaining to potential renal toxicity in humans following oral exposure are limited to a single case report of albuminuria 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).

Studies reporting renal effects in animals exposed to cyanide via drinking water and the diet are mixed. Multiple studies reported histological lesions in the kidney, but few reported incidence data, precluding independent assessment of the significance of the findings. Therefore, histopathology data from drinking water and dietary studies discussed below that lack quantitative data are omitted from the LSE table.

No renal lesions were observed in rat dams exposed to doses up to 12 mg CN^-/kg/day as potassium cyanide or up to 6.4 mg CN^-/kg/day as potassium thiocyanide in drinking water on GDs 6–20 (de Sousa et al. 2007). In a 15-day study, renal congestion and cytoplasmic vacuolization of the proximal tubular epithelium (moderate-to-severe) were qualitatively reported in male rats exposed to 1.2–3.6 mg CN^-/kg/day as potassium cyanide in drinking water (Sousa et al. 2002); lesions were reportedly minimal in severity at 0.3 mg CN^-/kg/day and absent at 0.12 mg CN^-/kg/day. In contrast, there were no treatment-related changes in kidney weights or histology in rats or mice exposed to up to 12.5 or 28.8 mg CN^-/kg/day as sodium cyanide in the drinking water for 13 weeks (NTP 1993; Tyner and Greeley 2023). Drinking water studies did not find any exposure-related changes in renal clinical chemistry values in rodents (NTP 1993; Sousa et al. 2002; Tyner and Greeley 2023).

Renal damage was reported in rabbits exposed to dietary sodium or potassium cyanide. Based on the limited database, it is unknown if these findings represent a species (rabbit versus rodent) or route (dietary versus drinking water) susceptibility. In rabbits, evidence of tissue damage (increased LDH in kidney tissue) was observed, and renal tubular and glomerular necrosis were qualitatively reported following dietary exposure to 15 mg CN–/kg/day as sodium cyanide for 4 weeks (Okolie and Iroanya 2003) or 20 mg CN^-/kg/day as potassium cyanide for 40 weeks (Okolie and Osagie 1999). In the 40-week study, increased serum levels of creatinine and urea were also observed.

In rodents, dietary cyanide exposure is limited to a single chronic-duration study in which no renal effects were observed in rats following exposure 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, the reliability of the dose 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. Due to low confidence in dose estimates, this study is omitted from the LSE table. Cloudy swelling of epithelial cells of renal tubules

was reported in three dogs exposed to cyanide via capsule for 14.5 months; each dog was exposed to a different dose of sodium cyanide (ranging from 0.27 to 1.68 mg CN^-/kg/day) (Hertting et al. 1960). However, this study is omitted from the LSE table due to lack of concurrent control and use of only one animal per dose group.

Consistent with drinking water and dietary studies, renal findings following exposure to cyanide compounds via bolus dosing (i.e., gavage, buccal bolus) are inconsistent between studies and species. Any observed increases in susceptibility via this route may be attributable to overwhelming detoxification processes and/or other cations in the administered compound (e.g., copper). These studies are discussed below.

A single gavage dose of up to 4.6 mg CN^-/kg/day as potassium cyanide resulted in minimal-to-mild acute tubular necrosis in adult male mice sacrificed 24 hours post-exposure (1/4) or 7 days post-exposure (2/4); lesions were not observed 28 days post-exposure (Sabourin et al. 2016). However, in the same study, Sabourin et al. (2016) found no treatment-related renal effects changes in adult female mice. In similarly exposed juvenile mice, single gavage doses up to 4.16 mg CN^-/kg/day as potassium cyanide did not induce changes in kidney weight or histology (Sabourin et al. 2016). Hawk et al. (2016) found no treatment related renal effects in adult or juvenile mice exposed to a single oral dose of 3.2 mg CN^-/kg/day as potassium cyanide. Rabbits administered 1.2 mg CN^-/kg/day as potassium cyanide via gavage for 40 days exhibited increased serum levels of creatinine, urea, and uric acid, and decreased serum levels of albumin and total protein; renal histology was not assessed in this study (Avais et al. 2018). No effects on kidney weights or histology were observed in rats given gavage doses of 0.56 mg CN^-/kg/day as potassium cyanide for 90 days (Mathangi et al. 2011). Decreased kidney weights were 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. However, as copper toxicity may have contributed to observed kidney effects, these data are omitted from the LSE table. Increased blood urea nitrogen was found in rats exposed to 7.8 mg CN^-/kg/day as potassium silver cyanide, but not at 2.6 mg CN^-/kg/day (Gerhart 1987). The contribution of silver to this effect is not known; therefore, these data are omitted from the LSE table.

Data pertaining to potential renal toxicity in humans following dermal exposure are limited to a single case report of transitory oliguria (scanty urination) 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.

2.11 DERMAL

Data pertaining to potential dermal effects of cyanide exposure in humans are limited to occupational exposure studies. Reported dermal effects in these studies may be due to direct dermal exposure to vapors, rather than due to systemic effects of cyanide. 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). Skin rash was reported in 42% of workers exposed to 15 ppm hydrogen cyanide for an average of 11 months in a silver-reclaiming facility, with 25% of workers reporting persistent rash at a mean duration of 10.5 months post-employment (Blanc et al. 1985). When the 36 workers were qualitatively stratified into low-, moderate-, and high-exposure levels based on job title, a dose-relationship was observed between exposure and self-reported incidence of persistent skin rash. In contrast, dermatitis was not reported in 36 male workers exposed to mean concentrations of an unspecified form of cyanide of 6.416–10.375 ppm for 5–15 years (El Ghawabi et al. 1975). The source of cyanide exposure was electroplating bath fluid containing sodium cyanide and copper cyanide.

No studies were located regarding dermal effects in animals after inhalation exposure to hydrogen cyanide. No dermal lesions were found in rabbits exposed to 5,000 ppm cyanogen for 8 hours (McNerney and Schrenk 1960). As discussed in Section 2.1, these studies are not included in the LSE table due to difficulty in estimation of cyanide levels in body tissues after cyanogen exposure.

Data pertaining to dermal effects in animals following oral exposure are limited. No histopathological changes of the skin were observed in rats or mice following exposure to doses up to 12.5 or 28.8 mg CN^-/kg/day as sodium cyanide, respectively, in drinking water for 13 weeks (NTP 1993). 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). However, as these findings were likely due to the metal components of the administered compounds, these data are omitted from the LSE table.

No standard dermal irritation studies in animals with exposure level data were identified for cyanide compounds. 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).

2.12 OCULAR

Evidence from humans and animals indicate that direct ocular exposure to cyanide (or cyanide compounds, including vaporized forms) is irritating to the eyes. Evidence for ocular effects from systemic exposure to cyanide (e.g., via oral exposure) are extremely limited.

In occupational studies, eye irritation was reported by 58% of workers exposed to 15 ppm hydrogen cyanide (Blanc et al. 1985) and 25% of workers exposed to mean concentrations of an unspecified form of cyanide of 6.416–10.375 ppm (El Ghawabi et al. 1975). The source of cyanide exposure in the study by El Ghawabi et al. (1975) was electroplating bath fluid containing sodium cyanide and copper cyanide. Subjective complaints of eye irritation were also reported in a cohort of 56 workers exposed to hydrogen cyanide vapor during heat treatment (case hardening) and electroplating, including lacrimation (17.8%) and congestion of the eyes (14.3%); physical exam revealed conjunctivitis (8.9%) and exophthalmos (3.6%) in some workers (Kumar et al. 1992). Exposure levels were not reported in this study. Eye irritation was also reported in 15/20 (75%) of workers exposed to an unspecified concentration of hydrogen cyanide in the cassava processing industry (Janagam et al. 2008). The ocular effects reported in occupational studies may not be due solely to cyanide exposure, as workers may be exposed to a variety of chemicals that are irritating to the eyes.

Cyanogen caused eye irritation in volunteers during acute-duration 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). 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). As discussed in Section 2.1, this study is not included in the LSE table due to difficulty in estimation of cyanide levels in body tissues after cyanogen exposure.

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 study authors indicated that nutritional deficiencies in the study population contributed to neuropathy. See Section 2.15 for more details on neurological effects associated with cassava ingestion.

Data on ocular effects following oral exposure in animals are limited. No exposure-related ophthalmological effects or histopathological lesions in the eye or optic nerve were reported in male rats exposed to doses up to 11.50 mg CN^-/kg/day as sodium cyanide in the drinking water for 13 weeks (Tyner and Greeley 2023). In gavage studies, ocular opacity was noted in rats exposed to 2.6 mg CN^-/kg/day as potassium silver cyanide for 90 days (Gerhart 1987). However, since it is likely that opacity resulted from deposition of silver, these data are omitted from the LSE table. 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).

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, or 2.5 mg CN^-/kg as potassium cyanide.

2.13 ENDOCRINE

The endocrine system, specifically the thyroid gland, has been identified as a potential target of toxicity in workers with occupational exposure to cyanide and populations with elevated cyanide exposure associated with dietary cassava intake. In animal studies, the thyroid is one of the most sensitive targets of oral toxicity; thyroid toxicity has not been evaluated following inhalation or dermal exposure in animals. Mechanistic data indicate that observed thyroid toxicity is attributable to the metabolite, thiocyanate, which competes with iodine for binding to the sodium-iodine symporter. Based on systematic review, the thyroid is a presumed target of toxicity following oral exposure based on a low level of evidence in humans, a moderate level of evidence in animals, and supporting mechanistic data (see Appendix C). Systematic review was not conducted for inhalation exposure due to inadequate dose-response data for that exposure route.

Epidemiological data pertaining to thyroid effects in occupationally exposed workers are presented in Table 2-5. Mean thyroid stimulating hormone (TSH) levels were 29% higher in a group of 36 male workers formerly exposed to 15 ppm hydrogen cyanide for a mean duration of 11 months in a silver-reclaiming facility, compared to 100 laboratory reference values (Blanc et al. 1985). Serum triiodothyronine (T3) levels were comparable to reference values in the entire cohort. However, a different pattern was observed in a subgroup of the 16 highest exposed workers (determined by job title).

This subgroup had mildly elevated serum T3 levels (8%) relative to laboratory reference values; however, serum TSH levels were comparable to laboratory reference values. No exposure-related changes were observed for serum thyroxine (T4). The study investigators indicated that the absence of T4 abnormalities could be accounted for by the time lapse between exposure and examination (median 10.5 months) (Blanc et al. 1985). No evidence of thyroid enlargement was observed in the 36 formerly exposed workers. Limitations of this study include lack of quantitative exposure levels for the low-, moderate-, and high-exposure groups, reliance on self-reporting of symptoms that occurred during employment that ceased 7–30 months prior to the assessment, and co-exposure to other chemicals during the silver-reclaiming process.

Table 2-5. Results of Epidemiological Studies Evaluating Occupational Exposure to Cyanide and Thyroid Effects

Reference, study type, and population	Measure of exposure	Outcome evaluated	Result
Banerjee et al. 1997 Cross-sectional study; 35 male workers exposed to cyanide in electroplating factory for >5 years and 35 unexposed referents (India)	Mean±standard deviation serum thiocyanate concentrations: Exposed: 316±15 µmol/L Referents: 90.8±9.02 µmol/L	Serum T3	↓ (exposed versus referent)
		Serum TSH	↑ (exposed versus referent)
		Serum T4	↓ (exposed versus referent)
Blanc et al. 1985 Retrospective cohort; 36 former workers from a silver-reclaiming facility (mean duration of employment was 11 months; mean duration elapsed since employment was 10.5 months) and 100 laboratory control referents (United States, Illinois)	Time-weighted average concentration of hydrogen cyanide (measured after plant ceased operations): 15 ppm Relative exposure index (REI) estimated based on job title; no quantitative exposure levels: Low (n=7) Moderate (n=13) High (n=16)	Serum T3	↔ (exposed versus referent) ↑ (high versus referent)
		Serum TSH	↑ (exposed versus referent) ↔ (high versus referent)
		Serum T4	↔ (exposed versus referent)
		Enlarged thyroid	↔

Table 2-5. Results of Epidemiological Studies Evaluating Occupational Exposure to Cyanide and Thyroid Effects

Reference, study type, and population	Measure of exposure	Outcome evaluated	Result
El Ghawabi et al. 1975 Cross-sectional; 36 male workers from three electroplating factories (9 from Factory A, 12 from Factory B, 15 from Factory C; employed 5–15 years) and 20 unexposed male referents (Egypt)	Mean (range) "cyanides" concentrations, ppm: Factory A: 10.375 (8.2–12.4) Factory B: 6.416 (4.2–8.8) Factory C: 8.083 (5.9–9.6) "Cyanides" measured were not further described; cyanide exposure evolved from plating bath containing sodium cyanide and copper cyanide.	Thyroid enlargement	↑ (workers versus referents)
		Thyroid iodine uptake	↑ (workers versus referents)

↑ = association; ↓ = inverse association; ↔ = no association; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid stimulating hormone

Thyroid effects were also noted in cross-sectional studies of electroplating workers; however, exposure to other chemicals such as cleaners and cutting oils also occurs during electroplating operations. Thyroid enlargement was present in 20 of 36 male workers exposed to mean concentrations of an unspecified form of cyanide of 6.416–10.375 ppm (El Ghawabi et al. 1975). The source of cyanide exposure was electroplating bath fluid containing sodium cyanide and copper cyanide. Additionally, thyroid ^{131}I uptake was significantly higher in the 36 male workers, compared to 20 unexposed male referents. The study authors proposed that this finding 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). In another study, serum T3 and T4 levels were decreased and serum TSH levels were elevated in 35 nonsmoking male workers exposed to cyanide in an electroplating factory for >5 years, compared to 35 unexposed referents (Banerjee et al. 1997). External exposure concentrations were not reported, but mean serum thiocyanate concentrations were 316 and 90.8 µmol/L in workers and referents, respectively.

No inhalation studies in animals evaluating potential effects on the thyroid gland or other endocrine organs were identified.

Chronic-duration oral exposure to cyanide in humans who eat cassava as a main carbohydrate source of their diet has been associated with thyroid toxicity. 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 T3 to T4 were detected in serum; consistent with these measurements, the study authors calculated a decrease in the index of free thyroxine (FT4I) and an increase in free triiodothyronine (FT3I). 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). Congenital hypothyroidism has been observed in some children who were exposed to increased thiocyanate levels because of the maternal cassava diet during pregnancy, as reviewed by Ermans et al. (1980). While observed effects may be associated with cyanide exposure, findings are confounded by exposures to several other known compounds that occur with cassava consumption. Additionally, individuals who rely heavily on cassava as a main source of carbohydrates in their diet may suffer from nutritional deficiencies (Makene and Wilson 1972; Osuntokun 1972; Osuntokun et al. 1969), which may further confound findings.

Thyroid effects were also found in some animals following oral exposure to cyanide via drinking water. Dose-related increases in the number of resorption vacuoles in the thyroid gland 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). This finding is generally associated with increased activity of the thyroid; however, since plasma levels of T3 and T4 were unaffected by treatment, the findings are of unclear biological significance. Similarly, de Sousa et al. (2007) reported dose-related increases in the number of resorption vacuoles in female rat dams exposed to potassium thiocyanate or potassium cyanide in drinking water at doses ≥0.21 or 0.4 mg CN^-/kg/day, respectively, on GDs 6–20. However, the biological significance of the findings could not be determined in the absence of additional thyroid lesions or evaluation of serum thyroid hormone levels in rat dams. Therefore, NOAEL/LOAEL determinations could not be made for thyroid effects reported by Sousa et al. (2002) or de Sousa et al. (2007). In contrast to these studies, no histopathological lesions to the thyroid were observed in rats or mice exposed to dose up to 12.5 or 28.8 mg CN^-/kg/day, respectively, as sodium cyanide in drinking water for 13 weeks (NTP 1993; Tyner and Greeley 2023). However, elevated absolute and relative thyroid weights and decreased serum T4 levels were reported in rats at 11.50 mg CN^-/kg/day, but not at doses ≤3.96 mg CN^-/kg/day (Tyner and

Greeley 2023). These effects were no longer observed after a 70-day recovery period. The 13-week study by NTP (1993) did not assess thyroid weight or serum thyroid hormone levels.

Dietary studies in rats support altered thyroid function following intermediate-duration exposure to cyanide. Rats fed a diet containing 53 mg CN^-/kg/day as potassium cyanide for 4 months had a significant decrease in plasma T4 levels and thyroid T4 secretion rates; at 11 months, treated rats showed no significant decreases in plasma T4 concentrations, but T4 secretion rates remained depressed (Philbrick et al. 1979). Relative thyroid weights were also elevated at necropsy at 11.5 months; however, this finding is confounded by a concurrent decrease in body weight gain and lack of absolute thyroid weight data reporting. In rats similarly exposed to diets containing 47 mg CN^-/kg/day as potassium thiocyanate, decreased serum T4 was observed at both 4 and 11 months, with decreased thyroid T4 secretion rates at 4 months only (Philbrick et al. 1979).

Data from animal studies that employed bolus dosing (i.e., gavage, buccal bolus) are limited. Findings reported at doses below those associated with effects in drinking water and dietary studies may be attributable to overwhelming detoxification processes by bolus dosing.

No exposure-related changes in thyroid weight or histology were observed in mice exposed once to potassium cyanide at bolus doses up to 4.6 mg CN^-/kg as potassium cyanide; serum thyroid hormone levels were not assessed in these studies (Hawk et al. 2016; Sabourin et al. 2016). Additionally, no exposure-related changes in plasma levels of T3 and T4 or thyroid histology were observed in rats exposed to gavage doses up to 0.24 mg CN^-/kg/day as potassium cyanide for 3 months (Soto-Blanco et al. 2002). However, increased serum T3 and T4 levels were reported in rabbits exposed to 1.2 mg CN^-/kg/day as potassium cyanide for 40 days via gavage (Avais et al. 2018). Thyroid histology was not evaluated in the rabbit study.

There is limited evidence of toxicity in other endocrine organs following oral exposure to cyanide. Acute-duration oral exposure to potassium cyanide at 12 mg CN^-/kg/day in drinking water on GDs 6–20 resulted in moderate pancreas islet cell vacuolation in 100% of examined dams (de Sousa et al. 2007). These effects were transient and were no longer apparent in dams similarly treated on GDs 6–20, but sacrificed on PND 22 after a 3-week recovery period. Although incidences were not reported in this study, the study authors only reported severity scores when all animals analyzed showed the same alteration. Therefore, it is unclear if pancreatic lesions were observed in some animals (but not all) at the lower doses (≤1.2 mg CN^-/kg/day); thus, a NOAEL for pancreatic effects could not be established for this

study. However, elevated serum glucose levels were observed at 12 mg CN^-/kg/day only; glucose levels at ≤1.2 mg CN^-/kg/day were comparable to control. Pancreatic lesions and alterations in serum glucose levels were not observed in dams similarly exposed to 6.4 mg CN^-/kg/day as potassium thiocyanate (de Sousa et al. 2007). In longer-duration studies, no exposure-related lesions were observed in the pancreas, adrenal gland, or pituitary glands of rats or mice exposed to doses up to 12.5 or 28.8 mg CN^-/kg/day as sodium cyanide for 13 weeks (NTP 1993). The histology of the pancreas was unaffected in male rabbits that ingested 20 mg CN^-/kg/day as potassium cyanide via the diet for 40 weeks (Okolie and Osagie 2000).

As discussed in Section 2.1, animal studies on cassava are discussed in this profile, but are not included in the LSE table due to concurrent exposure to additional compounds found in cassava root. Lesions in the adrenal gland (swelling of the adrenal cortex, hemorrhage, and fibrosis) and pancreas (hemorrhage, necrosis, fibrosis, and atrophy of the acinar tissue; fibrosis of islets of Langerhans) were observed in the dogs fed 1.04 mg CN^-/kg/day in rice as cassava for 14 weeks (Kamalu 1991, 1993). Similar effects were observed in dogs fed rice containing the same concentration of cyanide (sodium cyanide was added to release hydrogen cyanide during the cooking process), although hemorrhage was not observed in the pancreas and fibrosis was more prominent (Kamalu 1991, 1993). Dogs fed rice plus cyanide, but not dogs fed cassava diet, also showed decreased serum T3 levels and thyroid enlargement (Kamalu and Agharanya 1991). However, findings in this study were confounded by concurrent diseases in study animals requiring pharmaceutical intervention (Kamalu 1991, 1993); therefore, the sodium cyanide study is also omitted from the LSE table.

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

Mechanisms of Thyroid Toxicity. Thyroid effects following cyanide exposure can result from the interference of thiocyanate, a metabolite of cyanide, with iodine uptake and utilization in the thyroid gland (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). This mechanism of action (competitive inhibition of the sodium-iodine symporter) has been proposed for other thyroid disrupting compounds, such as perchlorate, nitrate, chlorate, and fluoroborate (EPA 2010). Thiocyanate has a higher binding affinity for the sodium iodine symporter than the physiological ligand, iodine; however, it has a lower affinity than some other compounds (e.g., perchlorate) (De Groef et al. 2006; Tonacchera et al. 2004). This mode of action indicates that thyroid disruption will only be clinically relevant when thiocyanate levels are such that homeostatic processes

(e.g., stimulation of thyroid hormone production) are overwhelmed and clinical evidence of hypothyroidism is detected, such as thyroid gland enlargement, decreased thyroid hormones, and increased TSH (EPA 2010).

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).

2.14 IMMUNOLOGICAL

Data pertaining to immunological effects in humans after exposure to cyanide are limited to a single cross-sectional study evaluating lymphocyte subpopulations in 17 male automotive painting workers exposed to inorganic cyanide compounds for 5–20 years, compared to 5 unexposed male referents (Haleem and Hussein 2024). Details on the referents were limited to the information on sex and age; mean ages were 33.11 years for exposed workers and 33.4 years for referents. The mean hydrogen cyanide level in workplace air was 2.8 ppm and mean plasma thiocyanate levels were 0.54 µM in referents, 1.78 µM in workers aged 22–33 years, and 1.99 µM in workers aged 33–44 years. Compared to unexposed referents, the percentage of CD3+ and CD4+ lymphocytes was decreased and the percentage of CD8+ lymphocytes and natural killer cells was increased. No difference was observed in the CD4+:CD8+ ratio. It is noted that automotive painting workers are exposed to numerous chemicals that were not accounted for in this analysis, and no analysis was conducted to determine if lymphocyte levels were associated with plasma thiocyanate levels.

No animal studies evaluating the function of the immune system in animals following exposure to cyanide via any route were identified.

A limited number of drinking water studies in animals evaluated potential effects of cyanide exposure on weight and/or histology of immune organs; no adverse effects were observed. No histological lesions were observed in the spleen of rat dams exposed to drinking water doses up to 12 mg CN^-/kg/day as potassium cyanide or 6.4 mg CN^-/kg/day as potassium thiocyanate on GDs 6–20 (de Sousa et al. 2007). No exposure-related changes in immune organ weight and/or histology (thymus, spleen, lymph nodes,

bone marrow) were noted in rats or mice exposed to doses up to 12.5 or 28.8 mg CN^-/kg/day as sodium cyanide, respectively, in drinking water for 13 weeks (NTP 1993).

2.15 NEUROLOGICAL

Data from both human and animal studies indicate that the CNS is a primary target for cyanide toxicity. Numerous plausible mechanisms for CNS toxicity have been proposed. Based on systematic review, the neurological system is a known target of cyanide toxicity in humans following oral exposure based on a high level of evidence from humans and animals. Systematic review was not conducted for inhalation exposure due to inadequate dose-response data for that exposure route.

Acute-duration inhalation exposure of humans to fatal levels of hydrogen cyanide causes a brief stage of CNS 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). Although clinical symptoms of cyanide poisoning are well recognized, specific dose-response data are generally not known. Acute-duration 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-duration exposure to cyanide gas (Lam and Lau 2000). 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).

Severe neurological effects such as hemiparesis and hemianopia have been reported in case reports of chronic-duration occupational exposure to potassium cyanide and other chemicals (Sandberg 1967). Milder effects (headache, dizziness) were self-reported in some workers exposed to unspecified levels of hydrogen cyanide in the cassava processing industry (Janagam et al. 2008).

Epidemiological data pertaining to neurological effects in occupationally exposed workers are presented in Table 2-6. In an occupational hygiene study in three electroplating factories from Egypt, an increased incidence of subjective neurological complaints, including headache, weakness, changes in taste and smell, and dizziness, was observed in 36 male workers exposed to sodium cyanide and copper cyanide for 5–15 years, compared to 20 unexposed referents (El Ghawabi et al. 1975). Measured mean concentrations of “cyanides” (not further characterized) were 6.416–10.375 ppm. Two to three workers also reported salivation, disturbances of accommodation, and psychotic episodes, none of which were

reported in the referent group (El Ghawabi et al. 1975). A high percentage of 36 workers formerly exposed to 15 ppm hydrogen cyanide for a mean duration of 11 months in a silver-reclaiming facility also recalled adverse neurological symptoms during employment, including headache (72%), dizziness (72%), and easy fatigue (47%) (Blanc et al. 1985). Other effects reported at lower incidence (14–26%) included disturbed sleep, ringing in ears, paresthesia in extremities, and syncope. When the 36 workers were qualitatively stratified into low-, moderate-, and high-exposure levels based on job title, a dose-relationship between exposure and self-reported incidence a "neurological symptom complex" (headache, dizziness, dyspnea, nausea or vomiting, syncope) was found, as well as the following individual neurological symptoms: syncope, disturbed sleep, paresthesia in extremities, and syncope. When current symptoms were assessed in former workers, who on averaged ceased working 10.5 months prior to assessment, 33% still reported frequent headache (at least 10 times/month) and a dose-relationship between prior exposure and persistent headache was observed.

Table 2-6. Results of Epidemiological Studies Evaluating Occupational Exposure to Cyanide and Neurological Effects

Reference, study type, and population	Measure of exposure	Outcome evaluated	Result
Blanc et al. 1985 Retrospective cohort; 36 former workers from a silver-reclaiming facility; mean duration of employment was 11 months and mean duration elapsed since employment was 10.5 months (United States, Illinois)	Time-weighted average concentration of hydrogen cyanide (measured after plant ceased operations): 15 ppm REI estimated based on job title; no quantitative exposure levels: Low (n=7) Moderate (n=13) High (n=16)	Neurological symptom complex (headache, dizziness, dyspnea, nausea or vomiting, syncope)	↑ (REI)
		Headache	↔ (REI, during employment) ↑ (REI, residual, post-employment)
		Dizziness	↔ (REI)
		Syncope	↑ (REI)
		Disturbed sleep	↑ (REI)
		Paresthesia of extremities	↑ (REI)
		Easy fatigue	↑ (REI)
Chandra et al. 1988 Retrospective cohort; 111 workers from two electroplating and heat treatment plants (40 from Factory A, 71 from Factory B; exposed 5–19 years) and 30 unexposed referents (India)	Range of thiocyanate in urine, mg/100 mL: Factory A: 0.10–8.10 Factory B: 0.22–5.23 Control: 0.3–3.8	Presence of cyanide "disease"[a]	↑ (concentration × duration)

Table 2-6. Results of Epidemiological Studies Evaluating Occupational Exposure to Cyanide and Neurological Effects

Reference, study type, and population	Measure of exposure	Outcome evaluated	Result
El Ghawabi et al. 1975 Cross-sectional; 36 male workers from three electroplating factories (9 from Factory A, 12 from Factory B, 15 from Factory C; employed 5–15 years) and 20 unexposed male referents (Egypt)	Mean (range) "cyanides" concentrations, ppm: Factory A: 10.375 (8.2–12.4) Factory B: 6.416 (4.2–8.8) Factory C: 8.083 (5.9–9.6) "Cyanides" measured were not further described; cyanide exposure evolved from plating bath containing sodium cyanide and copper cyanide	Self-reported neurological complaints (headaches, weakness, changes in taste and smell, dizziness)	↑ (workers versus referents)
		Self-reported neurological complaints (salivation disturbances of accommodation, psychosis)	↔ (workers versus referents)
Knoblauch et al. 2020 Cross-sectional; 189 artisanal and small-scale gold miners (99 that utilized cyanide leaching, 90 that did not use cyanide) and 90 non-miners from the nearby community (Burkina Faso)	Mean blood lactate levels, mmol/L[b]: Cyanide miners: 4.7 Non-cyanide miners: 3.4 Non-miners: 2.8	Self-reported symptoms in past 2 weeks: Bizarre behavior	↑ (lactate levels)
		Changes in taste	↑ (lactate levels)
		Memory loss	↑ (lactate levels)
Kumar et al. 1992 Cross-sectional; 56 male workers exposed to hydrogen cyanide in copper electroplating and case hardening and 26 unexposed referents (India)	Hydrogen cyanide (unspecified concentration)	Impaired immediate memory (Benton visual retention test)	↑ (workers versus referents)
		Impaired short-term memory (Benton visual retention test)	↑ (workers versus referents)
		Impaired visual ability (Koh's block test)	↑ (workers versus referents)
		Impaired visual learning (Digit symbol test)	↑ (workers versus referents)
		Impaired psychomotor ability (Mirror drawing test)	↑ (workers versus referents)

[a]Cyanide disease was defined by three categorization schemes: biochemical categorization (urinary thiocyanate levels), clinical categorization (self-reporting of headache, giddiness, lacrimation, itching of the eyes, congestion of eyes, and coated tongue), and behavioral categorization (based on functional testing of delayed memory, visual ability, visual learning, and psychomotor ability). Results were reported only in terms of "healthy," "moderate," or "diseased," with no further information regarding specific neurological findings.
[b]Serum lactate levels were used as a biomarker of cyanide exposure. Normal levels are 0.5–1.5 mmol/L.

↑ = association; ↓ = inverse association; ↔ = no association; REI = relative exposure index

An association between both the concentration and duration of exposure to hydrogen cyanide and "cyanide disease" was reported in workers from two electroplating factories from India (Chandra et al.

1988). Cyanide disease was defined by three categorization schemes: biochemical categorization (urinary thiocyanate levels), clinical categorization (self-reporting of headache, giddiness, lacrimation, itching of the eyes, congestion of eyes, and coated tongue), and behavioral categorization (based on functional testing of delayed memory, visual ability, visual learning, and psychomotor ability). Results were reported only in terms of "healthy," "moderate," or "diseased," with no further information regarding neurological findings. In both factories, "cyanide-hours" were positively associated with diagnosis of "cyanide disease;" however, due to lack of detailed reporting on clinical signs or results of behavioral testing, specific details regarding observed neurological effects cannot be ascertained. Subjective complaints of neurological effects were also reported in another study of 56 Indian workers exposed to an unspecified concentration of hydrogen cyanide during heat treatment (case hardening) and electroplating, including headache (26.6%), tiredness (8.9), and giddiness or dizziness (8.9%) (Kumar et al. 1992). Giddiness and dizziness were more prevalent in workers employed for >10 years, compared to those employed <10 years; other symptoms were not associated with duration of employment. Neurobehavioral examinations showed impaired performance on measures of immediate and short-term memory (Benton visual retention test), visual ability (Koh's block test), visual learning (Digit symbol test), and psychomotor ability (Mirror drawing test) in the workers, compared with 26 unexposed referents (Kumar et al. 1992).

Self-reported neurological complaints (bizarre behavior, changes in taste, and memory loss) were also associated with cyanide exposure in a cross-sectional study in artisanal and small-scale gold miners from Burkina Faso in West Africa who utilized potassium cyanide during vat leaching (Knoblauch et al. 2020). These complaints were positively associated with blood lactate levels, which were used as a biomarker of cyanide exposure. The study subjects included 99 miners who used cyanide in the leaching process, 90 who did not use cyanide in the leaching process, and nearby community members who were not miners. While blood lactate levels were (as expected) highest in miners using cyanide, followed by miners not utilizing cyanide, then community members; lactate levels in the community were still above normal clinical ranges for blood lactate levels. The study authors indicated that this is a limitation of the study, as the community members are not true unexposed referents and likely had elevated levels due to direct or indirect exposure to cyanide due to the proximity to the mines. However, there are other possible explanations for elevated blood lactate levels in the groups without direct cyanide exposure (disease or injury, pharmaceutical agents, substance abuse), none of which were controlled for in this study.

The CNS is also a primary target for toxicity in animals following acute-duration inhalation exposure to hydrogen cyanide. While these studies are useful for hazard identification, due to various limitations (unreported exposure levels, lack of concurrent control, inadequate study reporting, and/or inadequate animal number), all but one of these acute-duration inhalation studies are omitted from the LSE table. The only study with adequate design and data reporting showed overt clinical signs of neurotoxicity in mice that survived exposure to 327 ppm hydrogen cyanide for 40 minutes that persisted for up to 60 minutes post exposure (Ma et al. 2021). Observed effects included lethargy, loss of righting reflex, convulsions, and tremors; lower concentrations were not evaluated in this study. In other studies, rats exposed to unspecified concentrations of hydrogen cyanide and kept unconscious for 20–60 minutes developed lesions of various degrees in the brain (Hirano et al. 1967; Levine 1969; Levine and Stypulkowski 1959). 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-duration 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-duration 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. Exposure of dogs to 45 ppm hydrogen cyanide for 28–96 days also caused tremors, convulsions, and coma (Valade 1952). Vascular and cellular lesions were found in the CNS.

CNS effects were also noted in animals following exposure to cyanogen. Following acute-duration inhalation exposure, neurological effects before death included restless and panic movements, poor coordination, tremor, and lethargy in rats exposed to 250 ppm cyanogen for 1.5–120 minutes (McNerney and Schrenk 1960). Only transitory behavioral changes were reported in monkeys intermittently exposed to 25 ppm cyanogen for 6 months (Lewis et al. 1984). No effects were found at 11 ppm cyanogen. As discussed in Section 2.1, these studies are not included in the LSE table due to difficulty in estimation of cyanide levels in body tissues after cyanogen exposure.

One study evaluated potential auditory effects in rats following inhalation exposure to hydrogen cyanide. In rats exposed to 10–50 ppm hydrogen cyanide for 3.5 hours, there was no adverse effect on hearing or the histology of cochlear hair cells when evaluated 4 weeks post exposure (Fechter et al. 2002).

However, co-administration for 2 hours to a single 100 dB broadband noise (13.6 kHz) treatment after and during exposures to hydrogen cyanide at concentrations ≥30 ppm caused exacerbation of noise-induced hearing deficits as measured by increases in auditory compound action potential thresholds, compared to noise-only controls. In rats exposed to hydrogen cyanide with noise, this finding was associated with a loss of outer hair cells in the base of the cochlea. Findings from a 3-day intraperitoneal injection study of potassium cyanide in rats support that the cochlea is a target of cyanide toxicity (Tawackoli et al. 2001). Rats specifically showed hearing deficits in high-frequency tones due to dysfunction of the stria vascularis region of the cochlea.

In humans, neurologic toxicity following cyanide ingestion 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 unknown. 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 number of ingested pits. Comatose patients were admitted to a hospital after ingesting potassium cyanide doses of 5.7–229 mg CN^-/kg (Goodhart 1994; Kasamo et al. 1993; Liebowitz and Schwartz 1948; Valenzuela et al. 1992). 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 an unknown dose of 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 case studies report development of Parkinsonism-like signs in patients that survived acute cyanide poisoning (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; Zaknun et al. 2005). The dose (and sometime form) of cyanide was unknown in several cases, but when known doses ranged from 4.5 to 8.57 mg CN^-/kg as potassium cyanide (assuming 70 kg weight in some cases). Common

clinical signs in these patients developing weeks after exposure included drooling, marked micrographia, masked faces, mild intention tremor, bradykinesia, and cogwheel rigidity or stiffness. In some cases, symptoms continued to progress over the next several years, with progressive Parkinsonism, speech and balance impairments, dystonia, and apraxia of eye opening (Carella et al. 1988; Grandas et al. 1989). Numerous abnormalities were observed in the brain using computed tomography and magnetic resonance image in these cases, most often in the basal ganglia (putamen and globus pallidus) and substantia nigra, but also throughout the cerebral and cerebellar hemispheres. 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 a patient that ingested 7.4 mg CN^-/kg as potassium cyanide (Rosenow et al. 1995). 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).

Outbreaks of adverse neurological effects have been reported 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; Tylleskar et al. 1994). Due to this, a limited number of population-based studies of adverse neurological effects were conducted in these regions; however, dietary cyanide intake was not quantified and biomarkers of exposure (urinary thiocyanate levels) were measured at the time of (or after) diagnosis of neurological disease (Money 1958; Osuntokun 1968, 1972; Osuntokun et al. 1969). 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,” as reviewed by 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.

A case-series reported optic atrophy associated with macular degeneration in 20 West Africans who were presumably exposed to elevated cyanide levels over an unspecified period during a drought in which the only food available was bitter cassava (van Heijst et al. 1994). Of these patients, 14 were evaluated for neurological deficits. Six of the 14 cases demonstrated neurological signs and symptoms (e.g., including tinnitus, hearing loss, paresthesia, and impaired sensory discrimination). Of the nine individuals with self-reported hearing loss, three showed severe deafness in a pure-tone audiogram (30–100 dB loss in the low tones of 250–1,000 Hz). It is noted that mean levels of thiocyanate and cyanide in these patients were elevated but were not statistically different from controls (hospital staff). However, two of the three patients with severe hearing loss did have markedly higher thiocyanate levels (45.6 and 54.9 µmol/L) compared to controls (18.85 µmol/L); the sample of the third patient with hearing loss was not tested. Controls were used for blood level comparisons only; neurological testing was not conducted in controls.

The CNS is also a primary target of orally administered cyanide in animals. As observed in human studies, neurologic toxicity following cyanide ingestion differs depending on the rate at which treatment is administered, with toxicity occurring at lower doses following bolus administration. This observation is likely because bolus administration may overwhelm detoxification processes.

Evidence for damage to the CNS was reported in some drinking water and dietary studies in animals; however, there were some inconsistencies between studies. Neurobehavioral assays were not conducted in any of the drinking water or dietary studies. Acute-duration oral exposure to potassium thiocyanate at doses ≥0.6 mg CN^-/kg/day in drinking water on GDs 6–20 resulted in mild-to-moderate brain gliosis in 100% of examined dams; mild CNS congestion and neuronophagia (phagocytosis of dead neurons) was

observed at 6.4 mg CN^-/kg/day (de Sousa et al. 2007). These effects persisted in dams similarly treated on GDs 6–20 but sacrificed on PND 22 after a 3-week recovery period. Although incidences were not reported in this study, the study authors only reported severity scores when all animals analyzed showed the same alteration. Therefore, it is unclear if neurological lesions were observed in some animals (but not all) at the lowest dose tested (0.2 mg CN^-/kg/day); thus, a NOAEL for neurological effects could not be established for this study. All dams similarly exposed to 12 mg CN^-/kg/day as potassium cyanide also exhibited mild-to-moderate congestion, gliosis, necrosis, and neuronophagia along with hemorrhagic areas in the brain at GD 20 and PND 22; again, it is unclear if brain lesions were observed in some (but not all) of the dams exposed to lower potassium cyanide doses (0.4 or 1.2 mg CN^-/kg/day). In contrast to findings from this acute-duration drinking water study, intermediate-duration studies did not report exposure-related changes in brain weight or histology in rats or mice following exposure to sodium cyanide at drinking water concentrations up to 12.5 or 28.8 mg CN^-/kg/day for 13 weeks (NTP 1993).

Dietary studies reported modest myelin degeneration in the spinal cord of rats exposed to 47 mg CN^-/kg/day as potassium thiocyanate or 53 mg CN^-/kg/day as potassium cyanide for 11.5 months (Philbrick et al. 1979). The study 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; however, vitamin B12 deficiency was ruled out as an etiological factor in this study. 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. Due to uncertainty in dose estimation, this study is not included in the LSE table. 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). However, this study is omitted from the LSE table due to lack of concurrent control and use of only one animal per dose group.

Several gavage or other oral administration (e.g., cheek bolus) studies evaluated neurobehavioral endpoints after cyanide exposure, reporting a variety of neurocognitive and sensorimotor deficits in rodents following acute- and intermediate-duration exposure.

In acute-duration studies, reduced motor activity along with altered gait, decreased sensorimotor reflexes, tremor, and clinical signs of CNS depression were observed in adult and juvenile mice 30 minutes after a single exposure to 3.2 mg CN^-/kg as potassium cyanide (Hawk et al. 2016). These neurobehavioral findings in mice did not persist 24 hours post-exposure. Decreased motor strength and activity were also

observed following a 14-day oral exposure to 0.6 mg CN^-/kg/day as potassium cyanide (Ishaku et al. 2018). In rats, decreased locomotor activity and impaired spatial memory and object recognition were observed in rats after exposure to 12 mg CN^-/kg/day (the only dose tested) as potassium cyanide for 10 days (Ogundele et al. 2014b). Neurobehavioral impairments were no longer observed following a 10-day recovery period. Clinical signs of neurotoxicity were reported in a dose-range finding study in adult and juvenile mice exposed to potassium cyanide via gavage, including decreased activity at ≥1.6 mg CN^-/kg and convulsions and tremors at ≥3.2 mg CN^-/kg (Sabourin et al. 2016). Overt clinical signs of neurotoxicity, including lethargy and convulsions, were also observed in rats following a single exposure to doses ≥8.5 and ≥17 mg CN^-/kg as sodium cyanide (Rice et al. 2018). This study also reported impaired operant conditioning in exposed animals; however, due to a lack of a concurrent unexposed control group, findings from the operant conditioning assay cannot be adequately interpreted.

In intermediate-duration studies, decreased motor strength and activity were observed in mice orally exposed to 0.6 mg CN^-/kg/day as potassium cyanide for 28 days and decreased motor coordination was observed in rats exposed to 0.56 mg CN^-/kg/day as potassium cyanide for 90 days (Ishaku et al. 2018; Mathangi et al. 2011). Motor impairments were associated with elevated dopamine levels in the corpus striatum and cerebral cortex (Mathangi et al. 2011).

Histopathological lesions of the spinal cord (axonal "spheroids" or swellings), hippocampus (neuronal loss), and cerebellum (damage to Purkinje cells and loss of white matter) were qualitatively reported in male rats receiving 0.24 mg CN^-/kg/day as potassium cyanide by gavage for 3 months (Soto-Blanco et al. 2002). However, since incidence data were not reported, the significance of these findings cannot be determined; therefore, these data are omitted from the LSE table. In contrast, no exposure-related changes in brain weight or histology were observed in mice exposed once to gavage doses up to 4.6 mg CN^-/kg as potassium cyanide (Hawk et al. 2016; Sabourin et al. 2016) or in rats exposed to 0.56 mg CN^-/kg/day as potassium cyanide via gavage for 90 days (Mathangi et al. 2011).

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. Due to potential confounding effects of silver and copper on observe dose-response; these studies are not included in the LSE table.

Deep coma developed in two persons who accidentally fell into cisterns containing copper cyanide (Dodds and McKnight 1985) and potassium cyanide (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). In dermal acute lethality studies, overt signs of neurotoxicity preceded death in rabbits exposed to lethal concentrations of hydrogen cyanide, potassium cyanide, or sodium cyanide (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).

Mechanisms of Neurotoxicity. Acute effects of cyanide on the CNS 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. Tawackoli et al. (2001) proposed that observed ototoxicity in some studies is attributable to disruption of the electron transport chain in the metabolically active cochlea, specifically the stria vascularis.

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 Erecinska 1971; Gibson and Greenwood 1963), the key molecular target in cyanide poisoning. Real-time measurements during sublethal cyanide exposure showed decreased cerebral metabolic activity in rats exposed to 2 mg/kg/hour for 90 minutes via a femoral line, compared to saline-exposed controls (Alomaja et al. 2023). Metabolic activity was measured via lactate, pyruvate, glycerol, and glucose levels measured in cerebral microdialysis samples taken at 30-minute intervals. The lactate-to-pyruvate ratio was decreased in exposed rats at each timepoint, compared to controls. Consistent with these findings, isolated cerebellar mitochondria obtained post-exposure showed decreased *ex vivo* mitochondrial respiration and ATP concentrations (Alomaja et al. 2023).

Inhalation and oral studies in animals have shown that acute- or chronic-duration 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, pallidum, 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 1959) and chronic-duration exposures (Hertting et al. 1960). Necrosis is a prevalent CNS 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). 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 study 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-duration 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 study 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. Increases in cellular NADH, therefore, are important events 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 the 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 tissues, 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 the 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 monoamine 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 deoxyribonucleic acid (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). A series of RNAi knock-down studies in cultured rat N27 dopaminergic mesencephalic cells confirmed that down regulation of Bcl-2 expression following cyanide exposure mediates cyanide-associated neuronal cell death (Zhang et al. 2009).

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 magnetic resonance imaging (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). Osmotic imbalance and generation of reactive oxygen species with lipid peroxidation was associated with cellular degeneration in the cortex and cerebellum of rats exposed to ≥4 mg CN^-/kg/day as potassium cyanide for 15 days (Ogundele et al. 2013). Jones et al. (2000, 2003) 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 study authors suggested 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).

2.16 REPRODUCTIVE

No studies were located regarding reproductive effects in humans following exposure to cyanide via any route. Studies evaluating reproductive effects in animals are limited to the oral route and are primarily focused on potential adverse effects on the male reproductive system. Animal studies identify the male reproductive system as a potentially sensitive target of cyanide toxicity following gavage exposure; however, findings from drinking water studies are mixed. Based on systematic review, male reproductive effects are suspected human health effects following oral exposure based on no human data and a moderate level of evidence in animals (see Appendix C).

A number of exposure-related changes in the male reproductive system were reported following exposure of rats and mice to sodium cyanide in the drinking water for 13 weeks (NTP 1993). In male rats, exposure-related effects on male reproductive organs observed included decreased absolute left epididymis weight, decreased absolute left cauda epididymis weight, and decreased absolute left testis weight at the highest administered dose (12.5 mg CN^-/kg/day); mild decreases in decreased absolute left cauda epididymis weight were also observed at 1.7 and 4.9 mg CN^-/kg/day. Relative organ weights were not reported for the left testis or epididymis weights, and no changes in the absolute or relative right testis weights were observed at any dose. Sperm analysis showed a decreased number of spermatid heads per testis (but not number of spermatid heads per gram testis) and decreased total spermatid counts at 12.5 mg CN^-/kg/day. Sperm motility was slightly decreased at ≥1.7 mg CN^-/kg/day but findings were not dose related; no changes in spermatozoa concentration were observed. In similarly exposed and evaluated male mice, findings were limited to a significant decrease in the absolute left epididymal and caudal epididymal weights at the highest dose of 24.3 mg CN^-/kg/day (NTP 1993). No histopathological changes in male reproductive organs were found in male rats or mice at doses up to 12.5 or 24.3 mg CN^-/kg/day, respectively (NTP 1993).

The male rat reproductive findings from the NTP (1993) study have been questioned due to decreased water intake observed in the highest dose group. To re-evaluate findings controlling for this potential confounding factor, Tyner and Greeley (2023) repeated the NTP (1993) study in male F344 rats utilizing a water-intake-matched control for the highest dose group (300 ppm; calculated at 11.50 mg CN^-/kg/day based on measured body weight and water intake for this study). In contrast to the NTP (1993) study, no exposure-related changes in absolute or relative testes, epididymis, or cauda epididymis weights were observed compared to either the standard or water-restricted controls. While some dose-related trends were observed for decreased sperm motility compared to standard control, this trend disappeared when

compared to the water-intake-matched control. Consistent with the NTP (1993) study, no histopathological changes in male reproductive organs were found in male rats at doses up to 11.50 mg CN^-/kg/day.

In general, animal studies that employed bolus dosing (i.e., gavage, buccal bolus) reported male reproductive effects at doses below those associated with effects in the drinking water study by NTP (1993). This observation is likely because bolus administration may overwhelm detoxification processes.

Acute-duration bolus administration studies in animals do not report exposure-related changes in the weight or histology of the cauda epididymis in mice exposed once to doses up to 4.6 mg CN^-/kg as potassium cyanide (Hawk et al. 2016; Sabourin et al. 2016). In a series of intermediate-duration studies in rats, exposure to sodium cyanide at gavage doses ≥0.5 mg CN^-/kg/day for 30 or 56 days resulted in alterations in serum reproductive hormones (decreased serum testosterone, follicle stimulating hormone, and luteinizing hormone; increase serum prolactin), sperm alterations (decreased total sperm count, percent motility, and percent normal sperm), and morphological changes in the testes (decreased diameter of seminiferous tubules, decreased epithelial cell height; increased Leydig cell area, and decreased nuclear volume of Sertoli cells) (Oyewopo et al. 2021a, 2021b). Absolute testicular weights were also decreased; however, findings were confounded by concurrent decreases in body weight gain and lack of reported relative organ weights (Oyewopo et al. 2021a). Altered serum hormones (decreased serum testosterone and luteinizing hormone), sperm alterations (decreased sperm count and motility), decreased prostate and testes weights, and histopathological changes (mild atrophy and degeneration of seminiferous tubules; mild vacuolation in the epididymis) were also reported in rats exposed to sodium cyanide via gavage at doses ≥0.64 mg CN^-/kg/day for 90 days (Shivanoor and David 2015). Additional effects noted at 1.70 mg CN^-/kg/day include decreased epididymal weights, increased sperm abnormalities, and desquamation of the glandular epithelium in the prostate.

Increased gonadal weight was observed in male rats exposed for 90 days by gavage to 14.5 mg CN^-/kg/day as copper cyanide (Gerhart 1986) or 2.6 mg CN^-/kg/day as potassium silver cyanide (Gerhart 1987). The NOAEL values were 4.35 mg CN^-/kg/day (Gerhart 1986) and 0.8 mg CN^-/kg/day (Gerhart 1987), respectively. Due to potential confounding effects of silver and copper on the observed dose-response, these studies are not included in the LSE table.

As discussed in Section 2.1, animal studies on cassava are discussed in this profile, but are not included in the LSE table due to concurrent exposure to additional compounds found in cassava root. Dogs fed a diet

of cassava ingested an estimated 1.04 mg CN^-/kg/day for 14 weeks showed a reduction in the spermatogenic cycle, testicular germ cell sloughing and degeneration, and occasional abnormal cells (Kamalu 1993). Dogs similarly fed rice to which 1.04 mg CN^-/kg food was added (sodium cyanide was added to release hydrogen cyanide during the cooking process) showed similar effects (Kamalu 1993). However, findings in this study were potentially confounded by concurrent diseases in study animals requiring pharmaceutical intervention (Kamalu 1991, 1993); therefore, the sodium cyanide study is also omitted from the LSE table.

Data pertaining to potential adverse effects in the female reproductive system are limited. In female rats exposed to sodium cyanide in drinking water for 13 weeks, 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; however, these effects were not considered to be adverse since overall length of estrus was unaffected (NTP 1993). No changes were noted on the estrus cycle in female mice similarly exposed to doses up to 28.8 mg CN^-/kg/day (NTP 1993). No exposure-related changes in female reproductive organ weight or histology were observed in rats or mice at doses up to 12.5 or 28.8 mg CN^-/kg/day, respectively (NTP 1993). No exposure-related changes in female reproductive organs were observed in rats in 90-day gavage studies at doses up to 14.5 mg CN^-/kg/day as copper cyanide (Gerhart 1986) or 15.6 mg CN^-/kg/day as potassium silver cyanide (Gerhart 1986).

Mechanisms of Male Reproductive Toxicity. No studies specifically evaluating mechanisms of male reproductive toxicity were identified. EPA (2010) proposed that cyanide-associated hypothyroidism could potentially underlie male reproductive effects observed in some studies. In support, male infertility, altered sperm parameters, and/or altered reproductive hormone levels have been associated with thyroid disease in humans, either hypo- or hyperthyroidism (Krajewska-Kulak and Sengupta 2013; Krassas and Pontikides 2004; Trokoudes et al. 2006). However, a review by Williams and DeSesso (2023) challenged this proposal, pointing out that the perchlorate anion has a much higher affinity for the sodium iodide symporter compared to thiocyanide (see *Mechanisms of Thyroid Toxicity* in Section 2.13 for details), but shows no evidence of adverse effects on the male reproductive system.

2.17 DEVELOPMENTAL

No studies were located regarding developmental effects in humans following exposure to cyanide via any route. Studies evaluating developmental effects in animals are very limited and are restricted to the oral route.

The overall number of fetuses with any visceral abnormality was increased when rat dams were exposed to 12 mg CN^-/kg/day as potassium cyanide in the drinking water on GDs 6–20, compared to control (de Sousa et al. 2007). However, no single abnormality was increased compared with the control, and the overall number of affected litters was comparable to control (de Sousa et al. 2007). No exposure-related external or skeletal malformations were observed at maternal doses up to 12 mg CN^-/kg/day potassium cyanide. No exposure-related external, visceral, or skeletal malformations were observed in the fetuses of rat dams similarly exposed to 6.4 mg CN^-/kg/day as potassium thiocyanate in the drinking water on GDs 6–20 (de Sousa et al. 2007). In the same study, additional groups of dams were similarly exposed on GDs 6–20 and allowed to deliver, and pups were examined on PND 22. Effects observed in pups born to dams exposed to 12 mg CN^-/kg/day as potassium cyanide or 6.4 mg CN^-/kg/day as potassium thiocyanate during gestation included brain lesions (CNS gliosis, mild-to-moderate necrosis, mild-to-moderate neuronophagia, congestion) and hepatic lesions (mild-to-moderate vacuolation and congestion, mild bile duct proliferation). Although incidences were not reported in this study, the study authors only reported severity scores when all pups analyzed showed the same alteration. Therefore, it is unclear if brain and/or hepatic lesions were observed in some pups (but not all) at the lower maternal doses; thus, a NOAEL for developmental effects in PND 22 pups could not be established for this study.

As discussed in Section 2.1, animal studies on cassava and natural cyanogenic glycosides are discussed in this profile but are not included in the LSE table due to concurrent exposure to additional compounds found in cassava root. Increased early embryonic deaths and increased developmental abnormalities (microcephaly with open eyes, limb defects, and growth retardation) were observed in fetuses of rats fed a diet containing 80% cassava powder during gestation, but no developmental effects were found in a group fed with 50% cassava powder (Singh 1981). 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. 1986) or to the cyanogenic glucoside, linamarin, at 120 or 140 mg/kg (Frakes et al. 1985). Teratogenic effects (encephalocele and rib abnormalities) were also reported in hamsters exposed to a single oral dose of the cyanogenic glucoside, amygdalin, during gestation, but these changes were found only at maternally toxic doses (Willhite 1982). 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 GDs 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*.

2.18 OTHER NONCANCER

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). Metabolic acidosis also developed in six of eight individuals who entered a 27-m^3 well that contained pickled bamboo shoots; four recovered with supportive care (Sang-a-Gad et al. 2011). Model simulations estimated air levels of 10 ppm hydrogen cyanide (as well as 7.5 ppm sulphur dioxide).

Cyanide exposure may alter glucose homeostasis. In an acute-duration oral study, rat dams exposed to 12 mg CN^-/kg/day as potassium cyanide in drinking water on GDs 6–20 had a 38% increase in serum glucose levels (de Sousa et al. 2007). This is consistent with pancreatic islet cell vacuolation observed at the same dose (see Section 2.13 for more details). Findings did not persist after a 3-week recovery period. In contrast, no effects on serum glucose were observed in rat dams similarly exposed to drinking water doses up to 6.4 mg CN^-/kg/day as potassium thiocyanate on GDs 6–20 (de Sousa et al. 2007) and there were no changes in serum levels of glucose in rabbits fed 20 mg CN^-/kg/day as potassium cyanide for 40 weeks (Okolie and Osagie 2000). In humans, blood glucose levels were comparable between 20 workers exposed to unspecified levels of hydrogen cyanide in the cassava processing industry and 20 age-matched referents (Janagam et al. 2008).

As discussed in Section 2.1, animal studies on cassava are discussed in this profile, but are not included in the LSE table due to concurrent exposure to additional compounds found in cassava root. Serum levels of glucose were elevated in rats exposed to ≥5.50 mg CN^-/kg/day as cassava in the diet for 28 days (Okafor et al. 2006; Udeme et al. 2015). No exposure-related changes in serum glucose were noted in rats exposed to 6.27 mg CN^-/kg/day as cassava in the diet for 7 days (Okafor et al. 2006). Yessoufou et al. (2006) examined the potential role of cassava (in general) versus cyanide in glucose homeostasis in a diabetic rat model (streptozotocin-induced model of diabetes, or STZ-rats). In this study, healthy and STZ-rats were fed standard diets, diets containing cassava flour that was certified as cyanide-free (CFC diets), or CFC diets supplemented with 1.9 g/kg of potassium cyanide (delivering a cyanide dose of

72 CN^-/mg /kg/day) for 28 days. CFC diets did not induce hyperglycemia in healthy rats; however, CFC diets (with or without potassium cyanide) exacerbated measures of hyperglycemia (elevated blood glucose, decreased serum insulin) in STZ-rats, compared to STZ-rats fed standard diets.

2.19 CANCER

The EPA (IRIS 2010) determined that there is inadequate information to assess the carcinogenic potential of hydrogen cyanide and cyanide salts. IARC (2023) and NTP (2021) have not evaluated the potential for cyanide or cyanide compounds to cause carcinogenicity in humans.

No studies were located regarding cancer effects in humans or animals after exposure to cyanide. Some populations with high intake of cassava have shown decreased risk for thyroid cancer (Cléro et al. 2012) or breast cancer (Jayalekshmi et al. 2009).

2.20 GENOTOXICITY

A limited number of studies evaluating *in vivo* genotoxicity studies were identified (Table 2-7).

One cross-sectional study evaluated clastogenicity in 17 male automotive painting workers exposed to inorganic cyanide compounds for 5–20 years, compared to 5 unexposed male referents (Haleem and Hussein 2024). Details on the referents were limited to the information on sex and age; mean ages were 33.11 years for exposed workers and 33.4 years for referents. The mean hydrogen cyanide level in workplace air was 2.8 ppm and mean plasma thiocyanate levels were 0.54 µM in referents, 1.78 µM in workers aged 22–33 years, and 1.99 µM in workers aged 33–44 years. Both total chromosomal aberrations and micronuclei were increased in exposed workers, compared to referents. However, it is noted that automotive painting workers are exposed to numerous chemicals and no analysis was conducted to determine if the observed effects were associated with plasma thiocyanate levels.

A single oral dose of 1 mg CN^-/kg as potassium cyanide did not inhibit testicular DNA synthesis in mice (Friedman and Staub 1976). Increased DNA fragmentation was observed in mice in two studies. Increased DNA fragmentation was observed by electrophoresis in isolated brain mitochondria of male ddy mice that had received a single subcutaneous injection of 2.8 mg CN^-/kg/day as potassium cyanide (Yamamoto and Mohanan 2002). DNA fragmentation was also detected by *in situ* terminal deoxynucleotide transferase nick-end labeling (TUNEL) in the parietal and suprarhinal regions of the

motor cortex in mice injected with 2.4 mg CN/kg/day as potassium cyanide for 1–12 days (Mills et al. 1999).

Table 2-7. Genotoxicity of Cyanide *In Vivo*

Species (exposure route)	Endpoint	Results	Reference	Form
Human (inhalation)	Chromosomal aberrations	+	Haleem and Hussein 2024	HCN
Human (inhalation)	Micronuclei	+	Haleem and Hussein 2024	HCN
Mouse (oral)	DNA damage	-	Friedman and Staub 1976	KCN
Mouse (i.p.)	DNA damage	+	Yamamoto and Mohanan 2002	KCN
Mouse (i.p.)	DNA damage	+	Mills et al. 1999	KCN

– = negative result; + = positive result; i.p. = intraperitoneal; DNA = deoxyribonucleic acid; HCN = hydrogen cyanide; KCN = potassium cyanide

The *in vitro* genotoxicity of cyanide has been examined in prokaryotic organisms and mammalian cell systems, and studies are summarized in Table 2-8. In prokaryotic cells, the overall evidence indicates that cyanide is not mutagenic. 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). 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). 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). A positive mutagenic response was reported for hydrogen cyanide in strain TA100 without metabolic activation (Kushi et al. 1983). Adding S9 mix to the culture decreased the induction of reverse mutations by cyanide to 40% of the nonactivated reaction. *S. typhimurium* strain TA98 was negative for mutagenicity (Kushi et al. 1983). 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). Sodium cyanide tested at concentrations up to 0.8 mM without metabolic activation yielded negative results for DNA damage in a screening assay (vitotox test) (Meriläinen and Lampinen 2004)

Table 2-8. Genotoxicity of Cyanide *In Vitro*

Species (test system)	Endpoint	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
S. typhimurium TA100	Reverse mutation	(+)	+	Kushi et al. 1983	HCN
S. typhimurium TA98, TA100	Reverse mutation	–	–	Kubo et al. 2002	KCN
S. typhimurium TA97, TA98, TA 100, TA 1535	Reverse mutation	–	–	NTP 1993	NaCN
Escherichia coli WP67, CM871, WP2	DNA repair test	–	–	De Flora et al. 1984	KCN
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 Laskshmana Rao 1997	KCN
Hamster BHK-21 cells	DNA breakage		$+^{cyt}$	Bhattacharya and Laskshmana Rao 1997	KCN
Rat hepatocytes (primary)	DNA breakage		$+^{cyt}$	Storer et al. 1996	KCN
Primary brain cells, mitochondrial fraction (male ddy mice)	DNA breakage (mitochondria)		+	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

In mammalian cell systems, DNA fragmentation was observed with cytotoxicity in numerous studies. In cultured A549 human epithelial-like lung carcinoma cells, potassium cyanide induced dose-related

reductions in cell viability by 8 hours and increases in double-strand DNA breaks by 24 hours (Vock et al. 1998). Based on the temporal relationship and the small size of DNA fragments (<0.5 Mbp), the study authors concluded that the effect of cyanide on DNA was indirect and a result of the activation of endonucleases by calcium entering the damaged cells. Dose-related increases in DNA breaks were induced in rat thymocytes and baby hamster kidney (BHK-21) cells exposed to potassium cyanide (Bhattacharya and Laskshmana 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 including potassium cyanide for DNA strand breaks in an alkaline elution assay in primary cultures of rat hepatocytes. The study included a battery of assays for cytotoxicity including tetrazolium dye reduction, trypan blue dye exclusion, 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. Following treatment with potassium cyanide, DNA strand breakage 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) detected significant DNA breakage, characterized by DNA migration, in TK6 human lymphoblastoma cells treated with potassium cyanide at concentrations that also reduced cell survival (as measured by trypan blue exclusion). Exposure to potassium cyanide resulted in dose-related increases in DNA breaks in the mitochondrial fraction of primary cultures of brain cells from male ddy mice (Yamamoto and Mohanan 2002).

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

In conclusion, the overall evidence indicates that cyanide is probably not a direct genotoxic agent, as cyanide-induced DNA fragmentation is secondary to cytotoxicity. *In vivo* studies on the genotoxicity of cyanide were limited. Available human data are limited by small sample size, lack of appropriate statistical analysis, and lack of control for known co-exposures. No DNA damage was found in mice exposed orally to potassium cyanide; however, DNA fragmentation has been detected in the brains of mice injected with potassium cyanide. A number of *in vitro* studies on mammalian cells reported DNA fragmentation following exposure to potassium cyanide. These studies indicate that the DNA fragmentation is secondary to the cytotoxicity of cyanide, which results in the release of endonucleases by the dying cells. *In vitro* studies in prokaryotes with cyanide in the form of potassium or sodium cyanide did not show any mutagenic activity in *S. typhimurium* or *E. coli*. One study in *S. typhimurium* TA100 suggested that hydrogen cyanide may be mutagenic in the absence of metabolic activation; however, no

additional studies were available to support this result, possibly due to the volatility of hydrogen cyanide. Additionally, there are no structural reasons to suggest that cyanide may be genotoxic.

2.21 MECHANISMS OF ACTION

This section discusses the general toxic mechanism of cyanide that can occur throughout the body following exposure. Specific information on target organ toxicity is discussed in the preceding sections.

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 ATP/adenosine diphosphate (ADP) ratio (Rieders 1971; Way 1984). Wilson et al. (1994) suggested 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. As reviewed by Zuhran and Szabo (2022), studies *in vitro* have described that cyanide-mediated inhibition of complex IV of the mitochondrial electron transport chain via cytochrome c oxidase results in impaired ATP generation. This has been confirmed in *ex vivo* studies in numerous tissues, especially those with high energy needs. Energy deficiency in tissues with high pools of phosphocreatine present with phosphocreatine depletion, rather than decreased ATP.

The inhibition of oxygen use by cells (termed histotoxic 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).

CHAPTER 3. TOXICOKINETICS, SUSCEPTIBLE POPULATIONS, BIOMARKERS, CHEMICAL INTERACTIONS

3.1 TOXICOKINETICS

- Absorption of cyanide gas and salts such as sodium or potassium cyanide is rapid through the lungs and gastrointestinal tract. Absorption of cyanide gas and salts through the skin is slower.
- Following inhalation, cyanide is rapidly distributed throughout the body, with measurable levels detected in all organs studied to date. 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-duration oral exposure.
- The predominant metabolic pathway for cyanide is conversion to thiocyanate by a sulfur donor (e.g., rhodanese). Minor metabolic pathways include conversion to 2-amino-2-thiazoline-4-carboxylic acid (ATCA) via reaction with cysteine, incorporation into the 1 carbon metabolic pool, and formation of cyanocobalamin via reaction with hydroxocobalamin. Cyanide has a plasma half-life of 20 minutes to 1 hour.
- Cyanide metabolites are excreted primarily in the urine (approximately 80% as thiocyanate), with small amounts excreted through the lungs.
- Two types of physiologically based pharmacokinetic (PBPK) models are currently available. The first extrapolates internal cyanide doses from oral or inhalation exposure levels. The second extrapolates inhaled cyanide levels based on biomarker levels. PBPK models for interspecies and route-to-route dosimetry extrapolation have not been developed.

3.1.1 Absorption

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.

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. As discussed in Section 2.1, since free cyanide absorption and toxicity is unusually low for these iron compounds, the data are not discussed in Chapter 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.

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.

Oral bioavailability of cyanide from foods containing naturally occurring cyanogenic glycosides such as cassava, linseed, and bitter apricot kernels, is lower than ingestion of the same administered dose as free cyanide due to a variety of factors including delayed and/or incomplete release of cyanide from the cyanogenic glycosides, (Abraham et al. 2016). Cyanide release is greatly reduced in processed food sources (e.g., cassava flour) compared to unprocessed or raw sources containing intact ß-glucosidase. In volunteers given foods containing the same "dose" of naturally occurring cyanide (6.8 mg), blood cyanide levels were highest after consumption of cassava, followed by bitter apricot kernels, then linseed, with very low levels detected after ingestion of persipan paste (Abraham et al. 2016). Peak blood cyanide levels occurred after 37.5 minutes for cyanide (15.4 µM), 20 minutes for bitter apricot kernels (14.3 µM), 40 minutes for linseed (5.7 µM) and 105 minutes for persipan paste (1.3 µM).

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 (Drinker 1932; Rieders 1971). Hydrogen cyanide is moderately lipid-soluble, which, along with its small size, allows it to rapidly cross mucous membranes; however, penetration across the epidermis is less rapid (Ballantyne 1983a, 1983b, 1988; Walton and Witherspoon 1926). 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). *In vitro* studies indicate minimal penetration of hydrogen cyanide vapor through human skin samples at concentrations up to 800 ppm; absorption was not significantly impacted by clothing or presence of sunscreen (Gaskin et al. 2013).

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.

3.1.2 Distribution

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 (Gettler and Baine 1938). In one 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 (Finck 1969). Following chronic-duration 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 a case of death due to oral cyanide 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). 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). In a review of 21 oral cyanide-related fatalities, distribution of cyanide in the heart blood, peripheral blood, and gastric contents were 0.1–248.6 mg/L, 0.3–212.4 mg/L, and 2.0–6398.0 mg/kg, respectively (Rhee et al. 2011). 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 sample/blood coefficients ranging from 0.24 to 0.35.

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 µg /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).

Small but significant levels of cyanide are present in normal blood plasma at concentrations of 0–14 µg % in humans (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 were 0.06–1.37 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 were 0.22–0.91 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). The pattern of distribution did not vary with administered concentration. When six rats were treated with 4 mg CN^-/kg as potassium cyanide, signs of CNS 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-duration 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.

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). Rabbits were administered 5.25 mg CN^-/kg as hydrogen cyanide, sodium cyanide, or potassium cyanide to their conjunctival sac (Ballantyne 1983b). Cyanide concentrations in the tissues were measured immediately after death, which occurred 3–12 minutes after administration. 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.

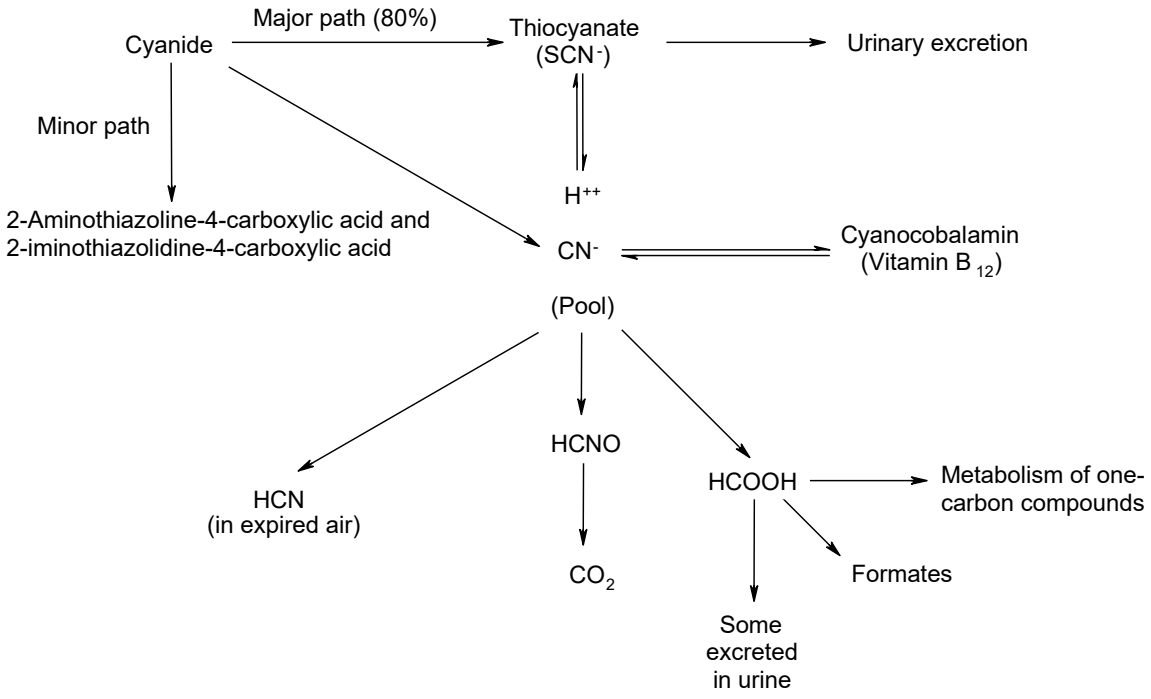
3.1.3 Metabolism

Reports of ingestion of cyanides by humans and reports of occupational exposure 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). In rats and pigs, peak plasma thiocyanate concentrations were reached within 6 hours following gavage exposure to a single dose of 1.2 mg CN^-/kg as potassium cyanide (Sousa et al. 2003).

The metabolism of cyanide has been well-studied in animals and major metabolic pathway (conversion of cyanide to thiocyanate) was first demonstrated in 1894. All proposed metabolic pathways are shown in Figure 3-1, including (1) the major pathway, conversion to thiocyanate by either rhodanese or

3-mercaptopyruvate sulfur transferase; (2) conversion to ACTA (or its tautomeric form 2-iminothiazolidine-4-carboxylic acid, ICTA) (Logue et al. 2010; Wood and Cooley 1956); (3) incorporation into a 1-carbon metabolic pool (Boxer and Rickards 1952); and (4) combining with hydroxocobalamin to form cyanocobalamin (vitamin B_{12}) (Ansell and Lewis 1970). Thiocyanate has been shown to account for up to 80% of an administered cyanide dose (Blakley and Coop 1949; Wood and Cooley 1956) while ACTA acid accounts for about 15% of the dose (Wood and Cooley 1956). It is possible that the formation of ACTA could occur over thiocyanate in conditions in which sulfur donors such as rhodanese become depleted or have low initial levels (Logue et al. 2010). Under acidic conditions, thiocyanate can be converted back into cyanide (Seto 1995).

Figure 3-1. Basic Processes Involved in the Metabolism of Cyanide



Source: Ansell and Lewis 1970

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 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.

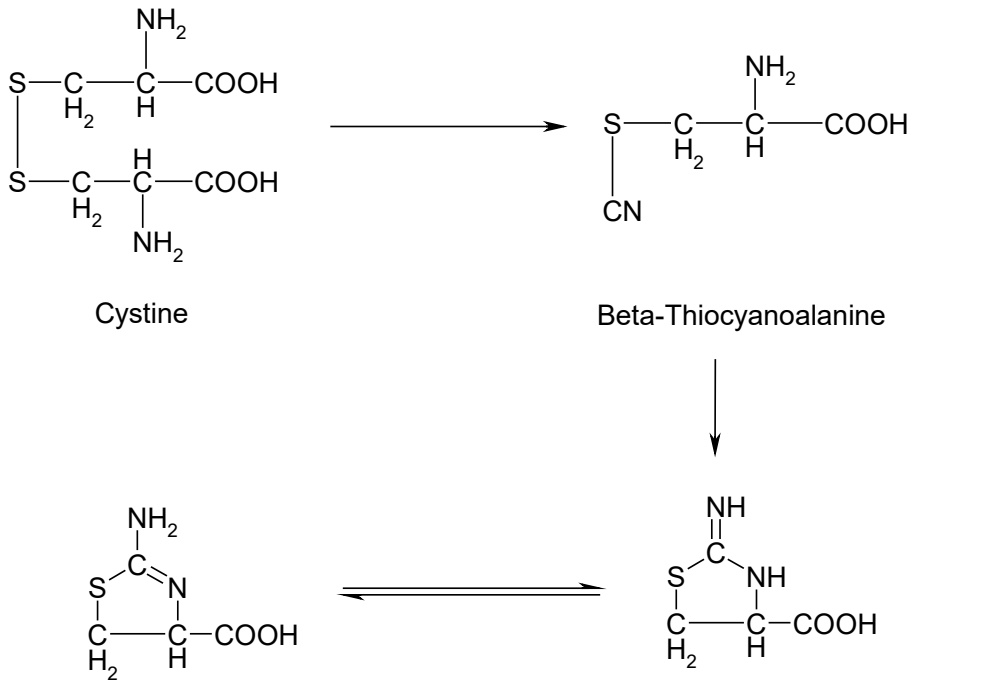
Radioisotopic studies showed that albumin interacts with the sulfane pool and that the serum albumin-sulfane sulfur carrier complex can react with cyanide (Schneider and Westley 1969). Higher hepatic rhodanese and lower serum albumin levels were found in mice fed a protein-free diet for 14 days compared 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. Low levels of rhodanese activity were found for the brain, testes, lungs, spleen, and muscle among various species. It should be noted that 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 (Drawbaugh and Marrs 1987). Rhodanese activities in the liver, expressed as units per g wet organ weight, were as follows: 1,310–1,313 units in rats, 1,104–1,103 units in hamsters, 917–928 units in guinea pigs, 540–722 units in rabbits, 478–502 units in pigeons, 476–516 units in marmoset monkeys, and 453 units in Beagle dogs (Drawbaugh and Marrs 1987). In the kidney, rhodanese activities were as follows: 802–823 units in rats, 734–748 units in guinea pigs, 590–680 units in rabbits, 555–591 units in hamsters, 424–434 units in pigeons, 292–318 units in marmoset monkeys, and 301 units in Beagle dogs (Drawbaugh and Marrs 1987). Dogs also showed the lowest activity levels for 3-mercaptopyruvate sulfur transferase (NIH/NINDS 2016a, 2016b). Mean 3-mercaptopyruvate sulfur transferase activity in human blood was 113.3 and 114.8 units, defined as μmoles of pyruvate generated per minute per 10^{10} red blood cells. In other species, activities were as follows: 15.1–18.2 units in Beagle dogs, 40.8 units in cynomolgus monkeys, 62.5 units in rabbits, 121.8 units in Swiss mice, and 532.2–639.7 in Wistar rats (NIH/NINDS 2016a, 2016b).

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 3-2 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 ACTA and its tautomer, ITCA (Wood and Cooley 1956). Zottola et al. (2009) propose an alternate oxidative pathway for ACTA formation in which cyanide interacts with an oxidized disulfide to form methyl thiocyanate, which interacts with a sulfur nucleophile from glutathione to form ACTA. However, this theoretical pathway has not been demonstrated *in vitro or in vivo*.

Figure 3-2. Minor Path for the Removal of Cyanide from the Body



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 (Bhattacharya and Flora 2009).

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 (Bhattacharya and Flora 2009). Cyanocobalamin (vitamin B_{12}), which contains cyanide and cobalt, is essential for the health of mammalian organisms.

3.1.4 Excretion

Following chronic-duration 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.

Cyanide metabolites are normally excreted in urine, with small amounts eliminated through the lungs (Asiah et al. 2014; Logue et al. 2010; Stamyr et al. 2008, 2015). 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 (a cyanide-related neurological disease in which upper motor neuron damage results in paralysis) and 350 µmol/L in an unaffected village, with the villages being comparable in all other respects.

When male Sprague-Dawley rats were given an oral dose of 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.

Following oral administration of potassium cyanide during gestation and lactation, thiocyanate was detected in amniotic fluid and milk of lactating rats, indicating it can cross the placenta and be excreted via breast milk (Soto-Blanco and Gorniak 2004). Orally administered cyanide and its metabolite thiocyanate were also eliminated in the breast milk of lactating goats (Soto-Blanco and Gorniak 2003). The relevance of the goat data to humans is not established.

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

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

Models are simplified representations of a system with the intent of reproducing or simulating its structure, function, and behavior. PBPK models are more firmly grounded in principles of biology and biochemistry. They use mathematical descriptions of the processes determining uptake and disposition of chemical substances as a function of their physicochemical, biochemical, and physiological characteristics (Andersen and Krishnan 1994; Clewell 1995; Mumtaz et al. 2012a; Sweeney and Gearhart 2020). PBPK models have been developed for both organic and inorganic pollutants (Ruiz et al. 2011) and 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 (Mumtaz et al. 2012b; Ruiz et al. 2011; Sweeney and Gearhart 2020; Tan et al. 2020). PBPK models can also be used to more accurately extrapolate from animal to human, high dose to low dose, route to route, and various exposure scenarios and to study pollutant mixtures (El-Masri et al. 2004). Physiologically based pharmacodynamic (PBPD) models use mathematical descriptions of the dose-response function to quantitatively describe the relationship between target tissue dose and toxic endpoints (Clewell 1995).

Tran et al. (2020a, 2020b) developed PBPK models for oral and inhalation exposure to hydrogen cyanide in humans. Due to limited toxicokinetic data for inhalation exposure, the inhalation model relies heavily on parameters from the oral PBPK model (which was developed first). These models are described in detail below. Stamyr et al. (2015) also developed a preliminary PBPK model to estimate hydrogen cyanide exposure levels and concentration time-course using a four-compartment model (blood, muscle, liver, and other tissue) based on hydrogen cyanide levels in exhaled breath. However, due to critical limitations of this preliminary model, namely validation against only two datasets, this model is not further described.

Tran et al. (2020b) created a model to predict kinetics of hydrogen cyanide in human tissues following oral exposure to either potassium cyanide or cyanogenic glycosides from food. The body was divided into four main compartments: the lungs, kidney, liver, and slowly perfused tissues. Each compartment is connected via the blood circulation, with distinct blood flood rates (Q) for each compartment. Absorption into the circulatory system through the gut lumen was estimated. Metabolism is modeled in the liver compartment, with 80% of absorbed dose metabolized to thiocyanate and 20% metabolized via other pathways (Ansell and Lewis 1970). Model parameters were optimized using data from a studies in which cyanide concentrations were determined in 12 volunteers following ingestion of potassium cyanide or various food sources of cyanogenic glycosides containing the same dose of total cyanide (Abraham et al. 2016) or a single volunteer that ingested various doses of potassium cyanide (Schulz 1984). Unknown parameters (maximum velocity of rhodanese, absorption rate constant, bioavailability) were estimated via parameter optimization using Berkely Madonna software. Model simulations were validated against clinical results from exposure to potassium cyanide or linseed at three doses that differed from the doses used in model optimization. PBPK model estimates of accumulation and elimination of hydrogen cyanide from the blood showed good agreement with experimental data, validating the model.

Tran et al. (2020a) developed a Human Continuous Cyanide Inhalation Predictor (HCCIP) model to predict concentration-time courses of cyanide in inhaled air (based on cyanide levels in the blood) or in the blood and exhaled air (based on cyanide levels in the inhaled air). Due to the paucity of pharmacokinetic data for hydrogen cyanide following inhalation exposure, this model was developed using the data curated for the oral PBPK model described above (Tran et al. 2020b) with the addition of inhalation parameters (inhalation and exhalation concentrations). Similar to that model, the body was divided into four main compartments: the lungs, kidney, liver, and slowly perfused tissues. HCCIP model

estimates of cyanide levels in inhaled air and the blood showed good agreement with experimental data, validating the model.

3.1.6 Animal-to-Human Extrapolations

Biological effects of cyanide in humans have been demonstrated (Smith 1996; Wexler et al. 1947). While there are no studies directly comparing the cytotoxicity between animal and human cells, 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 activity of the sulfur donors, rhodanese and 3-mercaptopyruvate sulfur transferase, is much lower in dogs compared to other mammalian species (Drawbaugh and Marrs 1987; NIH/NINDS 2016a, 2016b), which is consistent with the greater susceptibility of dogs to the acute effects of cyanide. Thus, dogs may be an inappropriate model from which to extrapolate the toxicity of cyanide to humans. For example, measured rhodanese activities are 1,310–1,313 units/g liver and 802–823 units/g kidney in rats compared to 453 units/g liver and 301 units/g kidney in Beagle dogs (Drawbaugh and Marrs 1987). Details on additional species can be found in Section 3.1.3. For 3-mercaptopyruvate sulfur transferase, mean blood activity in humans was 113.3 and 114.8 units, defined as μmoles of pyruvate generated per minute per 10^{10} red blood (NIH/NINDS 2016a, 2016b). In other species, activities were as follows: 15.1–18.2 units in Beagle dogs, 40.8 units in cynomolgus monkeys, 62.5 units in rabbits, 121.8 units in Swiss mice, and 532.2–639.7 in Wistar rats (NIH/NINDS 2016a, 2016b).

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, further suggesting that dogs may not be a suitable animal model from which to extrapolate the toxicity of cyanide to humans. 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.

3.2 CHILDREN AND OTHER POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans. 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. Children may be more or less susceptible than adults to health effects from exposure to hazardous substances and the relationship may change with developmental age.

This section also discusses unusually susceptible populations. A susceptible population may exhibit different or enhanced responses to certain chemicals than most persons exposed to the same level of these chemicals in the environment. Factors involved with increased susceptibility may include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters can reduce detoxification or excretion or compromise organ function.

Populations at greater exposure risk to unusually high exposure levels to cyanide are discussed in Section 5.7, Populations with Potentially High Exposures.

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 (Bhattacharya and Flora 2009). 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. 1986; 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 studies in lactating rats and goats indicate that cyanide and thiocyanate can be transferred through milk to nursing offspring (Soto-Blanco and Gorniak 2003, 2004).

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; Randell 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 thiosulfate 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 thiosulfate to gravid ewes prevented the elevation in erythrocyte cyanide levels in ewes and fetuses. Curry et al. (1997) concluded that sodium thiosulfate, like cyanide and sodium nitroprusside, cross the placenta in goats. The relevance of the goat study to humans is not known.

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). 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 like those noted for the general population in Section 5.6 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 5.6 for the general population, it is likely to exceed cyanide intake from inhalation of air and ingestion of drinking water (EPA 1981). 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 1981; 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 of 0.45–0.8 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 2004).

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).

3.3 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as biomarkers of exposure, biomarkers of effect, and biomarkers of susceptibility (NAS/NRC 2006).

The National Report on Human Exposure to Environmental Chemicals provides an ongoing assessment of the exposure of a generalizable sample of the U.S. population to environmental chemicals using biomonitoring (see http://www.cdc.gov/exposurereport/). If available, biomonitoring data for cyanide from this report are discussed in Section 5.6, General Population Exposure.

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 2006). The preferred biomarkers of exposure are generally the substance itself, substance-specific metabolites in readily obtainable body fluid(s), or excreta. Biomarkers of exposure to cyanide are discussed in Section 3.3.1.

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 2006). 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 effect caused by cyanide are discussed in Section 3.3.2.

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 3.2, Children and Other Populations that are Unusually Susceptible.

3.3.1 Biomarkers of Exposure

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 (Holstege and Kirk 2019; 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. Following acute exposures, blood cyanide levels and urinary thiocyanate levels are useful for confirming cyanide exposure but may have limited value in the initial treatment of the poisoning (Holstege and Kirk 2019).

Several studies showed increased cyanide and thiocyanate levels in body fluids of smokers. 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 (Maliszewski and Bass 1955). Another study reported that mean thiocyanate levels 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 in smokers and nonsmokers, respectively (Jarvis 1989). The number of cigarettes smoked per day is positively correlated with the thiocyanate levels in plasma and in saliva (Yamanaka et al. 1991). Based on changes in salivary thiocyanate in six former smokers, 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 of those found in whole blood, depending on the species (Ballantyne 1983a). However, plasma levels 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). While cyanide binds to hemoglobin, hemoglobin does not play any role in the metabolism, though some authors argue that cyanide in red blood cells may be biologically active (Way 1984). Cyanide also rapidly leaves serum and plasma, especially in the first 20 minutes. Therefore, 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 addition to thiocyanate, another cyanide metabolite, ATCA, has been shown to be a stable biomarker of cyanide exposure. ATCA 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. Logue et al (2005) report that ATCA is readily recovered from plasma or urine and analyzed 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). ATCA can also be detected in urine via liquid chromatography/mass spectrometry (LC/MS), with a detection limit of 15 ng/mL and a recovery rate ≥94% (Alwis et al. 2012). However, ATCA is produced via a minor metabolic pathway and may not be a sensitive biomarker. In rats exposed to potassium cyanide via subcutaneous injection, ATCA levels did not change in blood plasma, though elevated levels of ATCA were observed in the liver (Petrikovics et al. 2011). If human distribution of ATCA metabolism is similar, ATCA may not be a promising diagnostic biomarker in sublethal cases, but it may be useful for postmortem examinations.

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.

While blood or urinary levels of cyanide or its metabolites are useful for confirming exposure, they may not be clinically useful in acute poisoning scenarios as results will likely not be available in time for clinical management (Graham and Traylor 2023; Holstege and Kirk 2019). In these cases, clinical presentation may be used initially for differential diagnosis in cases of suspected poisoning. Classical signs associated with cyanide exposure include an almond-like smell detected on the breath of the patient by the clinician and "cherry-red skin" (due to increased venous oxygen saturation). However, the reliability of these signs as biomarkers, on their own, has been questioned (Holstege and Kirk 2019; Parker-Cote et al. 2018). First, the ability to smell the bitter almond odor of hydrogen cyanide is genetically linked and approximately 60–70% of the population can detect it (Graham and Traylor 2023). The odor threshold for detection is estimated at concentrations of 1–5 ppm in the air. In a systematic review of 102 cases of cyanide poisoning, a detection of a bitter almond odor by the clinician was only reported in approximately 7% of cases, and a different odor was reported in about 8% of cases (Parker-Cote et al. 2018). However, it should be noted that most cases did not comment on the presence or absence of an odor. Similarly, "cherry red skin" was only present in 11% of cases reviewed by Parker-Cote et al. (2018). Arterialization of retinal veins (red presentation of retinal veins similar in color to retinal arteries) detected by funduscopic examination has also been proposed as a method to check for increased venous oxygen saturation in patients with suspected cyanide poisoning (Holstege and Kirk 2019). Other clinical abnormalities that may be observed in patients with cyanide poisoning include elevated plasma lactate, increased anion gap metabolic acidosis, increased venous oxygen saturation level, and dilated pupils (Graham and Traylor 2023; Holstege and Kirk 2019). While none of these findings alone are definitive biomarkers of exposure to cyanide, collectively, this clinical picture (particularly the known metabolic abnormalities including increased anion gap metabolic acidosis of unknown etiology), along with an altered mental status, is suggestive of potential cyanide poisoning (Holstege and Kirk 2019). Clinical signs associated with cyanide toxicity are further discussed in Section 3.3.2 (Biomarkers of Effect).

For inhalation exposures, particularly in fire victims, exhaled levels of hydrogen cyanide in the breath have been proposed as biomarker of systemic exposure (Stamyr et al. 2008). While there is concern that exhaled breath may contain unabsorbed hydrogen cyanide (from very recent exposure), Stamyr et al. (2008) determined that washin-washout kinetics from the airways would have a negligible effect on measured hydrogen cyanide levels due to the rapid half-life of hydrogen cyanide in breath (16 seconds).

Some effects of cyanide that can also be used to monitor exposure are discussed in Section 3.3.2.

3.3.2 Biomarkers of Effect

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. Lack of oxygen usage results in increased venous oxygen saturation, but this is not a useful biomarker for cyanide as several other chemical exposures (e.g., carbon monoxide) and medical conditions can cause this phenomenon (Holstege and Kirk 2019). The shift to anaerobic metabolism results in the reduction of pyruvate to lactate leading to lactate acidosis (Bhattacharya and Flora 2009). Plasma lactate concentrations have been found to be correlated to blood cyanide concentrations (Baud et al. 2002) and have been used to assess the severity of cyanide poisoning in humans (Baud et al. 1996, 2002; Haden et al. 2022). However, lactate acidosis is not specific to cyanide toxicity. Elevated anion gap metabolic acidosis is also suggestive of cyanide poisoning, but like lactate acidosis, this finding is not specific to cyanide toxicity (Holstege and Kirk 2019).

Dyspnea, palpitations, hypotension, convulsions, and vomiting are among the first effects of acute cyanide poisoning resulting in death. Death is caused by respiratory failure secondary to histotoxic hypoxia. 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-duration exposure, cyanide has been associated with the development of tropical neuropathy, tobacco amblyopia, and Leber's hereditary optic atrophy (Wilson 1965). Chronic-duration 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 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 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. In an *in vitro* study in endothelial cells, changes in mitochondrial reactive oxygen species, an increase in the mitochondria:cytosol ratio of the apoptosis regulator Bcl-2 associated X (BAX), and an increase in the expression of hypoxia inducible factor (HIF-1α) were observed (Zuhra and Szabo 2022). 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*.

3.4 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 CNS 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 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, as reflected by a decrease of the hydrogen cyanide LC_{50} value from 110 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 co-exposed to potassium cyanide via injection and carbon monoxide via inhalation.

Potentiation has been observed between cyanide and ascorbic acid (vitamin C). 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 those pre-treated with 1.3 g/kg ascorbic acid for 3 consecutive days, 100% exhibited severe tremors, ataxia, muscle twitches, paralysis, and convulsions. It has been suggested that this potentiation 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: sulfane sulfur donors for rhodanese-catalyzed cyanide detoxification and chemicals that bind cyanide (methemoglobin inducers and cobalt compounds). Sulfur donors are used to enhance cyanide conversion to thiocyanate and include sodium thiosulfate, polythionates, and thiosulfates (Bhattacharya and Flora 2009). 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 methemoglobinemia inducers which provide a large pool of ferric (3+) iron to which cyanide preferentially binds when compared to cytochrome c oxidase (Bhattacharya and Flora 2009). These compounds include sodium nitrite, amyl nitrite, and 4-dimethylaminophenol (Way 1984, Bhattacharya and Flora 2009). 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, offered 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 as the cobalt ion forms a stable complex with cyanide (Bhattacharya and Flora 2009). Examples include hydroxocobalamin and dicobalt ethylenediamine tetra-acetate acid (Co_2EDTA). 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 study 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 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 3.1.3) 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 (i.p.) injection of potassium cyanide prevented lethality and decreased cyanide-induced toxic effects in mice (Mushett et al. 1952).

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.

Oxygen supplementation is often a first line of supportive therapy in cyanide toxicity (Bhattacharya and Flora 2009). Enhancement of the glucose oxidation to carbon dioxide was observed when oxygen, sodium nitrite, and sodium thiosulfate were given to mice dosed with 18 mg CN^-/kg as potassium cyanide; no enhancement was observed at 4 or 6 mg CN^-/kg as potassium cyanide (Isom and Way 1974). These studies indicate that oxygen can be used in support with cyanide antagonists, but not alone as even hyperbaric oxygen alone had no effect on cyanide poisoning in mice (Way et al. 1972). The mechanism of the action of oxygen as an adjunct is not known, however, since cyanide inhibits the cellular utilization of oxygen through inhibiting cytochrome c oxidase, theoretically, the administration of oxygen should have no effect (Smith 1996).

Co administration of additional compounds with afore discussed antidotes have been examined for augmentation of the efficacy of antidotal therapy. The nucleophilic activity of cyanide to combine with carbonyl groups of ketone or aldehyde intermediary metabolites (e.g., sodium pyruvate, α-ketoglutarate) to form cyanohydrin has also been used for sequestration. Pretreatment of mice with sodium pyruvate (1 g/kg i.p.) prior to subcutaneous injection of potassium cyanide caused a statistically significant increase in the LD_{50} value from 3.1 to 5 mg CN^-/kg and prevention of convulsions (Schwartz et al. 1979). Similarly, pretreatment of mice with α-ketoglutarate (2 g/kg, i.p.) before exposure to potassium cyanide (i.p.) 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).

Chlorpromazine, in conjunction with a sulfur donor, significantly attenuates effects of cyanide toxicity. Adjunctive compounds include α-adrenergic blockers and calcium channel blockers (Bhattacharya and

Flora 2009). Pretreatment of rats with chlorpromazine (10 mg/kg intramuscularly) and sodium thiosulfate (1,000 mg/kg intraperitoneally) abolished or greatly diminished 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 via reduction of lipid peroxidation of membranes (Maduh et al. 1988).

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

An inhibitor of the enzyme cystathionine gamma-lyase, propargylglycine, significantly lowered the LD_{50} for sodium cyanide (i.p.) in rats (Porter et al. 1996). The study authors suggested that the enzyme contributes to cyanide detoxification, possibly through a pathway that provides sulfur donors.

CHAPTER 4. CHEMICAL AND PHYSICAL INFORMATION

4.1 CHEMICAL IDENTITY

Information regarding the chemical identities of the most common compounds containing cyanide is presented 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.

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

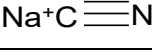
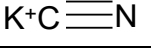
Characteristic	Information		
Chemical name	Hydrogen cyanide	Sodium cyanide	Potassium cyanide
Synonym(s) and registered trade name(s)	Formonitrile; hydrocyanic acid; prussic acid; Cyclone B; Cyclon[b]	Cyanide of sodium; hydrocyanic acid; sodium salt; Cyanogran[c]	Cyanide of potassium; hydrocyanic acid; potassium salt
Chemical formula	HCN	NaCN	KCN
SMILES	C#N	[C-]#N.[Na+]	[C-]#N.[K+]
Chemical structure			
CAS Registry Number	74-90-8	143-33-9	151-50-8
Chemical name	Calcium cyanide	Copper(I) cyanide	Potassium silver cyanide
Synonym(s) and registered trade name(s)	Calcid; calcyan; cyanide of calcium; Caswell No. 142; Cyanogas[c]	Cuprous cyanide[c]; cupricin[c]; AI3–28745	Potassium argentocyanide; potassium dicyanoargentate
Chemical formula	$Ca(CN)_2$	CuCN	$KAg(CN)_2$
SMILES	[Ca+2].[C-]#N.[C-]#N	[C-]#N.[Cu+]	[C-]#N.[C-]#N.[K+].[Ag+].

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

Characteristic	Information		
Chemical structure	$^{-}N\equiv C\ Ca^{+2}C\equiv N^{-}$	$Cu^{+}C\equiv N^{-}$	$K^{+}[Ag(CN)_2]^{-}$
CAS Registry Number	592-01-8	544-92-3	506-61-6
Chemical name	Cyanogen	Cyanogen chloride	Ammonium thiocyanate
Synonym(s) and registered trade name(s)	Carbon nitride; dicyanogen; ethanedinitrile	Chlorine cyanide; chlorocyan; Caswell No. 267	Thiocyanic acid, ammonium salt; ammonium rhodanide; ammonium sulfocyanate[c]; Trans-Aid[b]
Chemical formula	$(CN)_2$	CNCl	NH_4SCN
SMILES	N#CC#N	ClC#N	[S-]C#N.[NH4+]
Chemical structure	$N\equiv C-C\equiv N$	$Cl-C\equiv N$	$NH_4{}^{+}S-C\equiv N^{-}$
CAS Registry Number	460-19-5	506-77-4	1762-95-4

[a]All data are from HSDB 2004 unless otherwise noted.
[b]NLM 2024a, 2024b.
[c]Budavari 1989.

CAS = Chemical Abstracts Service; SMILES = simplified molecular-input line-entry system

4.2 PHYSICAL AND CHEMICAL PROPERTIES

Information regarding physical and chemical properties of cyanide is presented 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 1978) or digested (Ellenhorn and Barceloux 1997; WHO 2004). 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-glucopyranosyl groups from amygdalin through the action of beta-glucosidase to form the cyanogenic glycoside, prunasin. The enzyme then hydrolyzes prunasin to form hydrogen cyanide, glucose, and benzaldehyde.

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

Property	Information	
Chemical name	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
Taste threshold	No data	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 (calculated)[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	Information	
Chemical name	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
Taste threshold	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	Information	
Chemical name	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]
Taste threshold	No data	No data
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	Information	
Chemical name	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
Taste threshold	No data	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	Information
Chemical name	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
Taste threshold	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

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

Property	Information
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 1984.
[h]Verschueren 1983.
[i]Yoo et al. 1986; value at 25°C and saturation pressure.
[j]NLM 2024a, 2024c, 2024d, 2024e, 2024f.
[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 1985b.
[n]Hansch et al. 1995.
[o]EPA 1978.
[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 1976); therefore, solutions of cyanide compounds in water (such as from sodium cyanide and potassium cyanide) can form hydrogen cyanide and acid at slightly lower than neutral pHs. Alkaline solutions with pH >12 are practical for preventing significant outgassing of hydrogen cyanide.

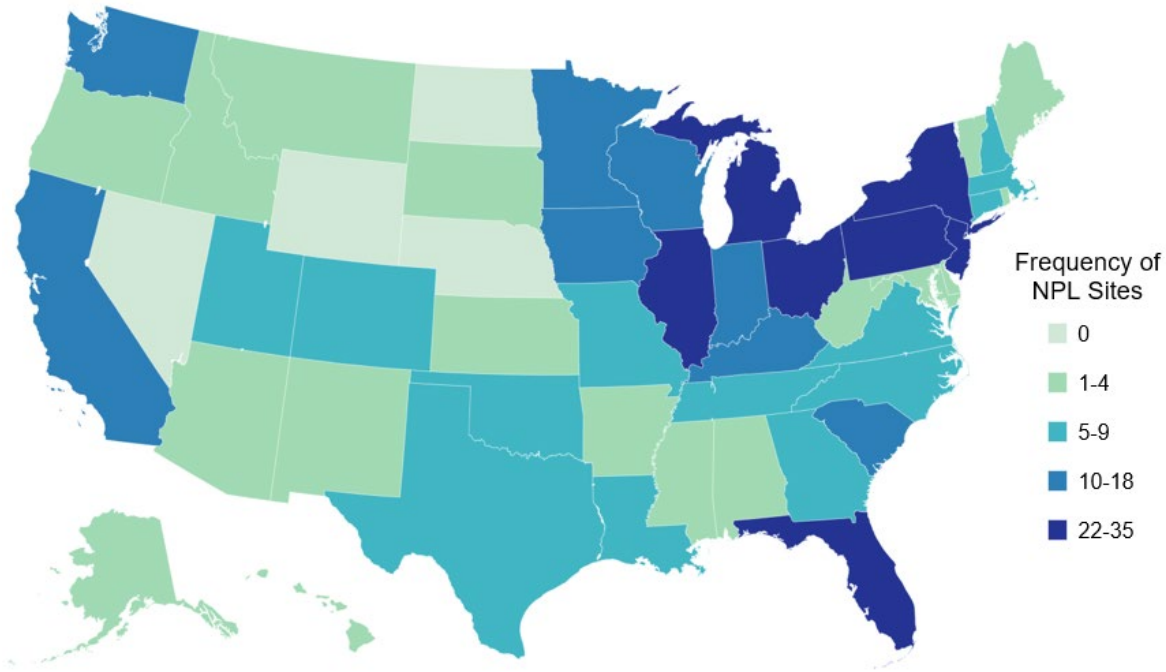
Hydrogen cyanide is a fire hazard and may be explosive when an excess of a strong acid is added to confined hydrogen cyanide. Solutions of some cyanide compounds are not stable and may decompose upon exposure to air or light.

CHAPTER 5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

Cyanide (reported as cyanide, hydrogen cyanide, sodium cyanide, potassium cyanide, or copper (I) cyanide) has been identified in at least 459 of the 1,868 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (ATSDR 2022a). However, the number of sites in which cyanide has been evaluated is not known. The number of sites in each state is shown in Figure 5-1.

Figure 5-1. Number of NPL Sites with Cyanide Contamination



Source: ATSDR 2022a

- The primary route of exposure for the general population to hydrogen cyanide is via inhalation of cigarette smoke and the consumption of certain foods.
- Occupational exposure may occur in facilities that use hydrogen cyanide.
- Since hydrogen cyanide has a very high vapor pressure and Henry's law constant, it is expected to volatize rapidly and exist primarily in the vapor phase.
- In the atmosphere, the main degradation pathway of hydrogen cyanide will be through its reaction with photochemically generated hydroxyl radicals.

- Unless microorganisms are acclimated to hydrogen cyanide, biodegradation is not likely to play a large role at high concentrations due to the toxicity of cyanide compounds.

The descriptor cyanogenic in this Toxicological Profile refers to a compound that releases the cyanogen radical or the cyanide anion. 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 anion (CN^-) (EPA 1981; Oudjehani et al. 2002; Shifrin et al. 1996; WHO 2004).

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 1981; Jones 1998; Knowles 1988; Mudder and Botz 2000). Certain species of millipedes contain cyanogenic compounds (e.g., benzoyl cyanide) in their chemical defense glands that release hydrogen cyanide once secreted (Shear 2015). 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 (WHO 2009). Effluents from the cyanidation process used in precious metal extraction contain high amounts of cyanide (WHO 2009). The contribution of this source to the total cyanide discharge in water is insignificant on average (EPA 1981). 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 (Baum et al. 2007) and biomass burning (Le Breton 2017) 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 (Pandolfo et al. 2012; Jaszczak et al. 2017). Cyanogen chloride is formed in drinking water from reaction of humic substances with chloramine produced during chlorination (WHO 2009). Thiocyanate is released to water primarily from discharges of industrial wastewaters 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 wastewaters 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, 1994). 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, recent monitoring data are limited. Cyanide levels in outdoor air range from 0.33 to 0.76 ppbv, with the highest levels measured near a gold heap leach field (Jaszczak et al. 2017). Compiled water-quality data from 1981–2023 in the Water Quality Portal (WQP) from the U.S. Geological Survey (USGS), EPA, and over 400 state, federal, tribal, and local agencies indicate that cyanide is a relatively common water pollutant and was detected in 37% of samples (WQP 2024). Less than 1% had values that were >10 µg/L, with 91 drinking/potable water samples with values between 10 and 50 µg/L.

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 compounds (based on total glucosinolate concentrations) with concentrations ranging up to 1,172 μmol/100 g fresh weight (Felker et al. 2016). No data were found in the available literature on thiocyanate concentrations in surface water, groundwater, or drinking water.

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. 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 1981; Mahernia et al. 2015) and individuals who are exposed to house fires or other types of building fires (Andrews et al. 1989; Bolstad-Johnson et al. 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. The amount of cyanide in emissions from commonly sold tobacco products has not decreased significantly; therefore, older data regarding exposure may still be relevant (Mahernia et al. 2015). 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 1992; 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. Workers may be exposed to cyanides in various occupations, including electroplating, metallurgy, pesticide application, firefighting, steel manufacturing, gas works operations, and metal cleaning (EPA 1981; NRC 2002; WHO 2004). The manufacture of industrial inorganic chemicals may be a potential source of occupational exposure to cyanogen chloride (NIOSH 1989; NRC 2002). 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 1989). 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).

5.2 PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

5.2.1 Production

Table 5-1 summarizes information on companies that reported the production, import, or use of cyanide for the Toxics Release Inventory (TRI) in 2022 (TRI22 2024). TRI data should be used with caution since only certain types of industrial facilities are required to report. This is not an exhaustive list.

Table 5-1. 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	3	100,000	999,999	1, 3, 5, 6, 10
AL	3	100	999,999	1, 3, 4, 5, 6, 12
AR	3	1,000	99,999	2, 3, 9, 12
AZ	2	1,000	999,999	1, 3, 10, 14
CA	5	0	999,999	1, 3, 5, 6, 10, 12
CO	1	100,000	999,999	1, 3, 5, 6, 10
GA	4	1,000	9,999	7, 10, 11, 12
IA	1	1,000	9,999	10
ID	2	1,000	99,999	1, 3, 7, 12
IL	17	100	99,999	1, 3, 5, 6, 7, 10, 12
IN	9	0	999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14
KY	4	0	99,999	1, 5, 6, 11, 14
LA	4	100	99,999	1, 5, 6, 12
MA	3	1,000	99,999	1, 2, 4, 6, 10, 12
ME	1	1,000	9,999	10
MI	9	0	999,999	1, 2, 3, 5, 6, 7, 10, 11, 12
MN	3	1,000	999,999	1, 3, 5, 6, 10
MO	6	1,000	99,999	1, 5, 6, 10, 11, 12, 14
MS	1	10,000	99,999	1, 5
NC	2	100	9,999	6, 7, 8, 10
NE	1	10,000	99,999	9, 12
NV	25	1,000	9,999,999	1, 3, 4, 5, 6, 9, 10, 11, 12, 13, 14
NY	2	1,000	9,999	6, 10, 14
OH	17	100	999,999	1, 3, 5, 6, 7, 8, 10, 11, 12, 13

Table 5-1. 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]
PA	4	0	999,999	1, 5, 10, 12, 13
PR	1	1,000	9,999	12
RI	4	100	9,999	1, 3, 4, 6, 7, 8, 10, 14
SC	5	100	999,999	1, 2, 3, 5, 8, 10, 11, 12, 13
SD	1	100,000	999,999	10
TN	3	10,000	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 10
TX	16	0	9,999,999	1, 2, 3, 4, 5, 6, 8, 9, 10, 11, 12, 13
UT	3	1,000	99,999	1, 5, 7, 9, 11, 12
WI	5	100	999,999	1, 3, 5, 7, 10
WV	2	1,000	99,999	1, 5, 11, 14

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

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

Source: TRI22 2024 (Data are from 2022)

The Chemical Data Reporting (CDR) rule, under the Toxic Substances Control Act (TSCA), requires manufacturers (including importers) to provide EPA with information on the production and use of chemicals in commerce (EPA 2023a). Table 5-2 shows data for cyanide compounds from the 2020 national review.

Table 5-2. Nationally Aggregated Production Volume for Cyanide Compounds

Chemical name	2019	2018	2017	2016
Copper cyanide (CuCN)	100,000–<500,000	100,000–<500,000	100,000–<500,000	100,000–<500,000
Gold cyanide (AuCN)	145,715	139,809	145,226	159,878
Hydrocyanic acid	1,000,000,000–<5,000,000,000	1,000,000,000–<5,000,000,000	1,000,000,000–<5,000,000,000	1,000,000,000–<5,000,000,000
Potassium cyanide (KCN)	1,000,000–<20,000,000	1,000,000–<20,000,000	<1,000,000	1,000,000–<20,000,000

Table 5-2. Nationally Aggregated Production Volume for Cyanide Compounds

Chemical name	2019	2018	2017	2016
Sodium cyanide (NaCN)	250,000,000–<500,000,000	250,000,000–<500,000,000	250,000,000–<500,000,000	250,000,000–<500,000,000

Source: EPA 2023a

There are two common methods of manufacturing hydrogen cyanide. The first method 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, has been applied in Spain and Australia and 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 predominant method of manufacture is the Andrussow process, which is used to make over 70% of the hydrogen cyanide; the remaining 30% is as a byproduct of acrylonitrile production (Maxwell et al. 2020).

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 (Maxwell et al. 2020). 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 (Maxwell et al. 2020). 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). As of 2009, no on-purpose calcium cyanide production facilities are operating (Maxwell et al. 2020).

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

5.2.2 Import/Export

The imports and exports of hydrogen cyanide through principal U.S. customs districts are negligible (CMR 2001). 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 million 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.

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

Cyanides and cyanide oxides of sodium comprise most 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. Export data could not be found in the available literature for calcium cyanide, potassium silver cyanide, cyanogen, or cyanogen chloride.

5.2.3 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 1993). 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 1978, 1993; Maxwell et al. 2020). 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 5.5 and 5.6). 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 1978; Maxwell et al. 2020). 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, 2004).

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 (Maxwell et al. 2020). Estimates of worldwide uses for hydrogen cyanide in 2020 are as follows: adiponitrile for nylon (~28%); acetone cyanohydrin for acrylic plastics (~27%); sodium cyanide for gold, silver, and other metal recovery processes (~24%); methionine (Chemical Abstracts Service Registry Number [CASRN] 63-68-3) for animal feed (~10%); cyanuric chloride for pesticides and other agricultural products (~7%); and chelating agents such as ethylenediaminetetraacetic acid (EDTA) (~1%) (Maxwell et al. 2020).

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 1978; 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 (Maxwell et al. 2020).

The principal use of sodium cyanide is for the recovery of precious metals. Recovery of gold by cyanidation is the largest single mining use for sodium cyanide and has been growing owing to high gold prices (Maxwell et al. 2020).

Potassium cyanide is used for electrolytic refining of platinum; fine silver plating, as an electrolyte for the separation of gold, silver, and copper from platinum; and for metal coloring (Maxwell et al. 2020). 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 (Maxwell et al. 2020).

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). 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; 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 et al. 2006; Windholz 1983).

5.2.4 Disposal

Regulations governing the treatment and disposal of cyanide-containing wastes are detailed in Chapter 7. 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 (EPA 2023c). 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 1980). Eleven solid waste streams in the United States are classified as hazardous wastes under RCRA based on presence of cyanide salts and complexes (EPA 2023b). 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 2023b). 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-wastewater) should not exceed 590 mg/kg for total cyanides and 30 mg/kg for cyanides amenable to chlorination (EPA 1988). While liquids are prohibited from land disposal, the maximum concentrations allowable in most treated wastewaters, with the exception of the bottom streams from the acetonitrile column and the wastewater 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 1988).

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 wastewaters and slurries generated as a consequence of cyanide heap leaching gold and other precious metals from low grade ores (EPA 1994). However, few mining sites currently use this technology. Instead, cyanide in wastewater 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 1994). 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 wastewater 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 1994). 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 1994). Biodegradation of cyanide in wastewater and leachate is effective on soluble forms of cyanide, but may not be effective on degrading cyanide bound in metal complexes (EPA 1994).

Cyanide salts should not be treated with acid in preparation for disposal or flushed into drains that may contain, or subsequently receive, acid waste (IRPTC 1985). 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).

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 wastewaters demonstrate effective removal of cyanide, metal complexed cyanide, and thiocyanate (Boucabeille et al. 1994b; EPA 1994), 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 wastewaters by alkaline chlorination, electrolysis, or ozonation processes (Grosse 1986). 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). The injection of wastewater containing hydrogen cyanide and cyanide compounds through underground injection is a major method for disposal of these wastes.

5.3 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 2022a). This is not an exhaustive list. Manufacturing and processing facilities are required to report information to the TRI only if they employ ≥10 full-time employees; if their facility's North American Industry Classification System (NAICS) codes is covered under EPCRA Section 313 or is a federal facility; and if their facility manufactures (defined to include importing) or processes any TRI chemical in excess of 25,000 pounds, or otherwise uses any TRI chemical in excess of 10,000 pounds, in a calendar year (EPA 2022a).

5.3.1 Air

Estimated releases of 137,365 pounds (~6.31 metric tons) of cyanide to the atmosphere from 17 domestic manufacturing and processing facilities in 2022, accounted for about 1.55% of the estimated total environmental releases from facilities required to report to the TRI (TRI22 2024). These releases are summarized in Table 5-4.

Table 5-4. 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
AL	3	3,060	429	0	437,000	2,213	440,489	2,213	442,702
AK	3	0	45	0	160,042	0	160,086	0	160,086
AZ	2	384	0	0	263	0	647	0	647
AR	3	7	0	0	417,836	0	417,813	30	417,843
CA	5	0	1,525	0	1,392	0	200	2,717	2,917
CO	1	0	0	0	0	0	0	0	0
GA	4	30	5	0	0	0	35	0	35
ID	2	193	104	0	44	21	193	169	362

Table 5-4. 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
IL	17	806	391	0	86	17,422	807	17,900	18,706
IN	9	14	4,490	53,754	1,727	0	58,152	1,833	59,985
IA	1	2	21	0	0	0	2	21	23
KY	4	74,392	14	0	0	11	74,392	25	74,417
LA	4	2	34	667,739	0	0	667,775	0	667,775
ME	1	4	1	0	0	10,055	4	10,056	10,060
MA	3	13	261	0	0	16,877	13	17,138	17,151
MI	9	340	91	0	5	1	341	95	436
MN	3	829	85	0	0	333	829	418	1,247
MS	1	0	0	0	3	0	0	3	3
MO	6	34	5	0	0	0	39	0	39
NE	1	2	0	0	0	0	2	0	2
NV	24	23,183	0	0	2,434,949	69	2,458,106	95	2,458,201
NY	2	0	31	0	302	166	333	166	499
NC	2	0	0	0	45	250	0	295	295
OH	17	9,999	139	63,334	587	3,935	73,360	4,633	77,994
PA	4	10,463	9,106	0	60	677,538	19,569	677,598	697,167
RI	4	10	6	0	0	1,897	15	1,898	1,913
SC	5	25	273	0	36,561	0	2,843	34,017	36,860
SD	1	1,830	0	0	42	0	1,872	0	1,872
TN	3	3,440	11,778	0	137	673	5,691	10,337	16,028
TX	16	5,043	4,572	3,637,312	5,609	8,908	3,646,881	14,562	3,661,444
UT	3	2,679	1,845	0	589	0	5,091	22	5,113
WV	2	447	2,729	0	4,600	0	3,176	4,600	7,776
WI	5	133	8	0	21,606	72	133	21,686	21,819

Table 5-4. 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
PR	1	0	0	0	0	0	0	0	0
Total	171	137,365	37,987	4,422,139	3,523,484	740,441	8,038,889	822,527	8,861,417

[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, wastewater 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 onsite 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: TRI22 2024 (Data are from 2022)

Vehicular emissions are the dominant source of urban ambient hydrogen cyanide. A 2016 report conservatively estimated that 654 tons of hydrogen cyanide were emitted in Canada in 2012 from light-duty vehicles (Moussa et al. 2016). In a 2007 study that estimated hydrogen cyanide emissions from motor vehicles in the South Coast Air Basin of California, hydrogen cyanide emissions from idling light-duty motor vehicles were estimated to be 4.9×10^{-3} tons/day (cold-start) (Baum et al. 2007).

EPA's National Emission Inventory (NEI) database contains information regarding sources that emit criteria air pollutants (CAPs) and their precursors, and hazardous air pollutants (HAPs) for the 50 United States, Washington DC, Puerto Rico, and the U.S. Virgin Islands. Emissions are estimated from multiple sources, including state and local environmental agencies; the TRI database; computer models for on- and off-road emissions; and databases related to EPA's Maximum Achievable Control Technology (MACT) programs to reduce emissions of HAPs. Cyanide emissions estimated from the 2017 inventory are summarized in Table 5-5.

Table 5-5. Pounds of Cyanide Emitted by Sector

Emission sector	Pounds of cyanide emitted
Fuel combustion, commercial/institutional, coal	3,500
Fuel combustion, commercial/institutional, natural gas	7
Fuel combustion, commercial/institutional, oil	809
Fuel combustion, electric generation, coal	678,044
Fuel combustion, electric generation, natural gas	1,716
Fuel combustion, electric generation, oil	1
Fuel combustion, electric generation, other	740
Fuel combustion, industrial boilers, internal combustion engines, biomass	74
Fuel combustion, industrial boilers, internal combustion engines, coal	41,685
Fuel combustion, industrial boilers, internal combustion engines, natural gas	960
Fuel combustion, industrial boilers, internal combustion engines, other	94,047
Industrial processes, ferrous metals	7,947
Industrial processes, mining	98,805
Industrial processes, not elsewhere classified	82,089
Industrial processes, non-ferrous metals	42,673
Industrial processes, petroleum refineries	1,464,585
Industrial processes, pulp and paper	4,416
Industrial processes, storage and transfer	22,849
Miscellaneous non-industrial, not elsewhere classified	181,865
Solvent, degreasing	674
Solvent, dry cleaning	580
Solvent, graphic arts	581
Solvent, industrial surface coating and solvent use	3,646
Waste disposal	48,433

Source: EPA 2022b

5.3.2 Water

Estimated releases of 37,987 pounds (~17.23 metric tons) of cyanide to surface water from 17 domestic manufacturing and processing facilities in 2022, accounted for about 0.43% of the estimated total environmental releases from facilities required to report to the TRI (TRI22 2024). This estimate includes releases to wastewater treatment and publicly owned treatment works (POTWs) (TRI22 2024). These releases are summarized in Table 5-4.

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 POTWs, iron and steel production, and organic chemical industries (EPA 1981). 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 1981). 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 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 1994; 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 1981), 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 method 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). Sodium ferrocyanide, which is used as an anticaking agent in road salts during the winter in the northeastern United States as well as Canada (AWI 2010; Exall et al. 2011), can potentially be washed off from roads into streams and storm sewers.

Thiocyanate is released to water primarily from discharges of industrial wastewaters from coal processing and extraction of gold and silver (Boucabeille et al. 1994a). Thiocyanate is also found in mining

wastewaters where it results from the reaction of the cyanide anion (CN^-) with sulphur (Boucabeille et al. 1994b).

5.3.3 Soil

Estimated releases of 3,523,484 pounds (~1,598.23 metric tons) of cyanide to soil from 17 domestic manufacturing and processing facilities in 2022, accounted for about 39.76% of the estimated total environmental releases from facilities required to report to the TRI (TRI22 2024). An additional 4,422,139 pounds (~2,005.85 metric tons), constituting about 49.90% of the total environmental emissions, were released via underground injection (TRI22 2024). These releases are summarized in Table 5-4.

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 1981; 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 (WHO 2004). 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 were <2,000 mg/kg (Shifrin et al. 1996; WHO 2004). The cyanides in these soils were predominantly (97%) in the form of ferrocyanides.

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

5.4 ENVIRONMENTAL FATE

5.4.1 Transport and Partitioning

Air. Because hydrogen cyanide is a gas and has a relatively slow degradation rate in air (see Section 5.4.2), 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.

Water. 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 1978). 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 1992). 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 5.4.2) (EPA 1992). 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 (EPA 1979). 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 5.4.2)

(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.

Sediment and Soil. 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, 1992).

Other Media. There are no data available to indicate that simple metal cyanides and hydrogen cyanide bioconcentrate in aquatic organisms (EPA 1979, 1980, 1985a, 1992). 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 1992). There is no evidence of biomagnification of cyanides in the food chain (EPA 1978). 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 1978).

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 5.4.2) (EPA 1978). In soils where cyanide levels are high enough to be toxic to microorganisms (i.e., landfills, spills), this compound may leach into groundwater (EPA 1984). 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 5.4.2) (Brown and Morra 1993).

5.4.2 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 5-6.

Table 5-6. 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, NCOH, and other compounds	In the presence of water; slow reaction	EPA 1979

Table 5-6. Environmental Transformation Products of Cyanide Compounds by Medium

Parent compound	Product(s)	Comments	Reference
Water			
HCN	NH_4^+ + $HCOO^-$ in equilibrium with H_2NCHO + H_2	pH dependent (pH <1, half-life: 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, 1992
	Complex metallocyanides	Excess CN^- in the presence of metals; solubilities of metallocyanides vary	EPA 1979, 1992
	>99% HCN	pH <7	EPA 1978
	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	SCN^-, NH_3 + CO_2, $CHOO^-$	Biotransformation	EPA 1978
Cyanogen	HCN, 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
	OCN^-	Oxidation	EPA 1992
	CO_2 + N_2	In the presence of strong oxidizing agents	EPA 1992
SCN^-	HCN	In acidic media	EPA 1979
Sediment and soil			
CN^-	Metallocomplexes	Abiotic transformation in the presence of metals	EPA 1978
	NH_3 + CO_2 (NH_3 converted to nitrite and nitrate in presence of nitrifying bacteria)	Aerobic biotransformation (predicted from fate in wastewater)	Richards and Shieh 1989
	N_2 + CO_2	Aerobic biotransformation under denitrification conditions (predicted from fate in wastewater)	Richards and Shieh 1989
SCN^-	COS (possibly; microbial degradation pathway not known)	Microbial degradation	Brown and Morra 1993

Table 5-6. Environmental Transformation Products of Cyanide Compounds by Medium

Parent compound	Product(s)	Comments	Reference
Wastewater/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^-/metallocyanides (including cuprocyanide)	$NH_3 + CO_2$	Microbial degradation in mining wastewaters	Boucabeille et al. 1994b
SCN^-	$NH_3 + CO_2 + SO_4$	Microbial degradation in mining wastewaters	Boucabeille et al. 1994a
	$COS + NH_3$	Microbial degradation in activated sludge	Katayama et al. 1993

CHO^- = carbonyl ion; $CHOO^-$ = formate ion; CN^- = cyanide anion; CO_2 = carbon dioxide; COS = carbonyl sulfide; H_2 = hydrogen gas; H_2NCHO = formamide; HO_2 = hydroperoxyl radical; HCN = hydrogen cyanide; HNC = hydrogen isocyanide; HOCN = cyanic acid; N_2 = nitrogen gas; NCOH = cyanic acid; NH_3 = ammonia; NO = nitric oxide; OCN^- = isocyanate; OH = hydroxide; SCN^- = thiocyanate; SO_4 = sulfate

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 1984). 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-second) 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 1978). 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-second) 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 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 $6.45x10^{-5}$ $molecules^{-1}second^{-1}$) (U.S. Army 1989). Therefore, hydrolysis of this compound may be a possible atmospheric degradation pathway in air.

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 1978). 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 1992).

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 1978). 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 1978). 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 1992). 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. 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 1978, 1979, 1992). 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 detoxifying cyanide-containing wastes (Akcil and Mudder 2003; EPA 1994; Raybuck 1992). It is known that there is a natural attenuation of the cyanide ion and thiocyanide concentrations in wastewaters (e.g., gold mill tails) due to 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 (e.g., *Pseudomonas*) are capable of using the cyanide ion and thiocyanate as the sole source of carbon and nitrogen and are therefore particularly effective at cyanide degradation. In fact, *Pseudomonas* is the basis of commercial applications for degrading the cyanide ion to ammonia and carbonate in wastewaters 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) reviewed the role of microbes in cyanide degradation and 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 wastewaters (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 wastewaters (e.g., Akcil and Mudder 2003; Boucabeille et al. 1994b; EPA 1994; 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 wastewaters by various bacteria belonging to the families *Pseudomonadaceae*, *Vibrioniaceae,* and *Enterobacteriaceae* has 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) 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} molecules^{-1}second^{-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 6–8×10^{2} molecules^{-1}second^{-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.

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 (Fuller 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 1978).

No information was 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 (Minami 1982; Minami and Fukushi 1981). Katayama et al. (1992, 1993) 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 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 ≤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.

5.5 LEVELS 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. 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.

Table 5-7 shows the lowest limit of detections that are achieved by analytical analysis in environmental media. An overview summary of the range of concentrations detected in environmental media is presented in Table 5-8.

Table 5-7. Lowest Limit of Detection for Cyanide Anion based on Standards[a]

Media	Detection limit	Reference
Air	0.16 ppbv	Zain et al. 2017
Drinking water	0–0.5 ppb	EPA 2020
Surface water and groundwater	0.5 ppb	EPA 2020
Soil	0.2 ppm	EPA 2014
Sediment	0.2 ppm	EPA 2014

[a]Detection limits based on using appropriate preparation and analytics. These limits may not be possible in all situations.

Table 5-8. Summary of Environmental Levels of Cyanide

Media	Low	High	For more information
Outdoor air (ppbv)	0.16	0.76	Section 5.5.1
Indoor air (ppmv)	1.8	320	Section 5.5.1
Surface water (ppb)	<1	444	Section 5.5.2
Groundwater (ppb)	No data	>200	Section 5.5.2
Drinking water (ppm)	<1	50	Section 5.5.2
Food (ppm)	0.001	1,515	Section 5.5.5
Soil (ppm)	0.32	70.55	Section 5.5.3

Detections of cyanide in air, water, and soil at NPL sites are summarized in Table 5-9.

Table 5-9. Cyanide Levels in Water, Soil, and Air of National Priorities List (NPL) Sites

Medium	Median[a]	Geometric mean[a]	Geometric standard deviation[a]	Number of quantitative measurements	NPL sites
Cyanide					
Water (ppb)	123	236	24.1	138	86
Soil (ppb)	24,100	26,500	26.8	140	84

Table 5-9. Cyanide Levels in Water, Soil, and Air of National Priorities List (NPL) Sites

Medium	Median[a]	Geometric mean[a]	Geometric standard deviation[a]	Number of quantitative measurements	NPL sites
Air (ppbv)	26.2	64.2	6.5	4	2
Hydrogen cyanide					
Water (ppb)			No data		
Soil (ppb)			No data		
Air (ppbv)	990	1,250	1.5	3	2

[a]Concentrations found in ATSDR site documents from 1981 to 2022 for 1,868 NPL sites (ATSDR 2022a). Maximum concentrations were abstracted for types of environmental media for which exposure is likely. Pathways do not necessarily involve exposure or levels of concern.

5.5.1 Air

Recently reported concentrations of cyanide in outdoor range from 0.33 to 0.76 ppbv (Jaszczak et al. 2017). The high value of 0.76 ppbv was found near a gold heap leach field. For indoor air, levels of 320 ppmv (vehicular exposure in a garage), 14–20 ppmv (air in a car), and 1.8 ppmv (after a fire) were reported (Jaszczak et al. 2017).

Historical air concentrations of hydrogen cyanide in the northern hemisphere's non-urban troposphere ranged from 0.16 to 0.166 ppbv (Cicerone and Zellner 1983; Jaramillo et al. 1989). Semi-quantitatively measured hydrogen cyanide concentrations in the offgas from shale oil retorting processes measured from 1977 and 1980 were 6–39 ppmv in one retort at one site; however, hydrogen cyanide was not detected in retorts at another site (Sklarew and Hayes 1984).

5.5.2 Water

The WQP is a source of discrete water-quality data in the United States and beyond (WQP 2024). This cooperative service integrates publicly available water-quality data from the USGS, EPA, and over 400 state, federal, tribal, and local agencies. Analysis of compiled data from the WQP that spans 4 decades (1981–2023) indicates that cyanide is a common water pollutant. Of 1178,204 samples analyzed, cyanide was detected in 67,266 (37.8% of samples). Of those 67,266 samples, only 688 had values >10 µg/L. There were 91 drinking/potable water samples found, with values between 10 and 50 µg/L. Cyanide levels were below the level of detection (1.0 µg/L) in drinking water samples from

Sunnyvale, San Jose, and Twain Harte Valley, California in the early 2000s (Christison and Rohrer 2007). Surface water samples in nearby mining areas (Twain Harte Valley and Alamitos Creek) also showed cyanide levels below the level of detection. Data from 1993–1998 indicated that only 0.2% of public water systems using groundwater exceeded the maximum contaminant level (MCL) of 0.2 mg/L (EPA 1999).

In a study that measured cyanide in urban snowmelt and runoff from deicer (which contains ferricyanide) in Canada, values were detected between 1 and 444 µg/L for weakly dissociable cyanide (Exall et al. 2011). 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.

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; WHO 2007). No recent data on levels of cyanogen chloride in drinking water were found in the available literature. In a mid-1970s EPA survey, cyanogen chloride was detected in drinking water from 8 of 10 U.S. cities (Fielding and Packham 1977). 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 were provided) (Bedding et al. 1982). In a 1988 survey of 35 water utilities, the quarterly median cyanogen chloride concentrations in drinking water were 0.45–0.80 µg/L (Krasner et al. 1989).

No recent information could be found in the available literature on the levels of thiocyanate in groundwater, surface water, or drinking water. Thiocyanate is found at concentrations of 100–4,000 mg/L in coal and coke plant wastewaters (Ganczarczyk 1979; Jensen and Tuan 1993; Xiao et al. 2023) and 300–450 mg/L in mining (gold extraction) wastewaters (Boucabeille et al. 1994b).

5.5.3 Sediment and Soil

Limited information was found in the available literature on concentrations of cyanides in soil or sediments at several hazardous waste sites. Cyanide concentrations were between 0.32 and 0.95 mg/kg near the Techatticup mining site in Nelson, Nevada (Sims and Francis 2008). In a review, Jaszczak et al. (2017) reported the following ranges of concentrations for various locations: soil near coking plant sites in France and Germany, 0.14–46.5 mg/L; soil near a Brazilian goldmine, 0.83–1.44 mg/kg; and soil near a Chinese goldmine, 70.55 mg/kg.

In general, 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).

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).

5.5.4 Other 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 1980, 1981; 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 1981). 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 1978; 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, while hydrogen cyanide is detected in nearly all (98.3%) samples of garri (a flour product of grated, pressed, and fermented cassava root pulp) from five agroecological zones in Nigeria, levels were much lower than in raw cassava root (0.056–2.463 mg/kg hydrogen cyanide; 0.054–2.364 μg/g CN^-) (Olorunnado et al. 2024). A somewhat wider distribution of results was obtained in an older 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 >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. Voldrich and Kyzlink (1992) reported cyanide concentrations in canned unpitted fruits (peaches, apricots, plums, and cherries) of 0–4 mg/kg (µg/g) w/w, depending on the glycoside content of the raw fruits and the conditions of heat processing. The study 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 g (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 homemade 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 1981). 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 1981).

Edible plants such as kale, cabbage, radishes, broccoli, brussels sprouts, cauliflower, collards, mustard greens, turnips, and kohlrabi contain glucosinolates and are hydrolyzed 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 of ~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 of 0.10–16.20 µg/g, whereas concentrations in meat products have been reported as 0.5–0.7 µg/g (Weuffen et al. 1984; Yong et al. 2017).

A 2018 study that looked at cyanide toxicity for frequently consumed smoothies and juices reported that the highest CN^- content was in drinks containing raw almond milk and fresh whole apple juice (Baker et al. 2018). Concentrations were detected as high as 341 µg/L in commercially available smoothies containing vegetables, raw flax seeds, almond milk, and fruits. Smoothies with vegetables, fruits, unpasteurized almond milk, and no flax seeds contained 41 µg/L, while similar smoothies containing pasteurized almond milk contained up to 9.6 µg/L.

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 1981). In studies that included non-U.S. commercial cigarettes, hydrogen cyanide concentrations in mainstream and sidestream smoke were 280–550 and 53–111 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). In a 2017 review (Jaszczak et al. 2017), the levels of hydrogen cyanide in mainstream smoke were 6.6–184 µg per cigarette. In another study that looked at the levels of hydrogen cyanide in a wide range of cigarette and cigar products, a range of 17.56–1553 µg/stick was found (Mahernia et al. 2015).

5.6 GENERAL POPULATION 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 5.4.2), 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 5.5.1). 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.

Vapor intrusion may be a potential source of hydrogen cyanide exposure, although indoor and ambient sources may also contribute to indoor air levels. The EPA (2016) includes hydrogen cyanide in its Vapor Intrusion Screening Levels (VISL) Calculator, indicating that it is sufficiently volatile and sufficiently toxic to be considered a concern for vapor intrusion from soil water and groundwater. Accordingly, ATSDR (2016) recommends that health assessors should evaluate potential health implications of vapor intrusion for hydrogen cyanide during site risk assessments. Tran et al. (2022) assessed risk of vapor intrusion of cyanide in villages near the largest gold mine in Thailand (Phichit's Gold Mine) due to several incidents of leakage or illegal discharge of cyanide-contaminated gold mine wastewater in Asia. The specific incident investigated was the "black water incident" of February 2015, in which the mining tailing storage facility leaked "black water" containing 2.13 mg/L cyanide into a nearby rice paddy, lotus pond, and creek. Speciation of the cyanide (11.30% free cyanide, 80.43% weak metal complex, and 8.26% strong acid dissociable) along with atmospheric modeling determined that up to 23 nearby villages were at elevated risk of acute health effects due to vapor intrusion from this and future incidents if seepages contain cyanide levels >0.65 mg/L.

Hydrogen cyanide in water is expected to rapidly volatilize; thus, there is potential for inhalation exposure during domestic water use activities, primarily showering and bathing. ATSDR's three-compartment Shower and Household-Use Exposure (SHOWER) model predicts air concentrations in the shower stall, bathroom, and main house throughout the day by estimating the contribution from showering or bathing and the contribution from other water sources in the house, such as the dishwasher, clothes washer, and faucets (ATSDR 2022b). This information, along with human activity patterns, is used to calculate a daily time-weighted average (TWA) exposure concentration via inhalation exposure and from dermal uptake from skin contact. ATSDR's SHOWER model is available by sending a request to showermodel@cdc.gov. Using a median value of 0.3 μg/L from the typical range for cyanide in treated water levels as discussed in Section 5.5.2 (based on WQP 2024) and a conservative representative outdoor air level of 0.33 μg/L as discussed in Section 5.5.1 (based on Jaszczak et al. 2017), reasonable maximum exposure (RME) levels were calculated for hydrogen cyanide (ATSDR 2022b). RME levels for different exposure groups are shown in Table 5-10.

Table 5-10. Reasonable Maximum Exposure Daily Inhalation Concentration and Administered Dermal Dose of Hydrogen Cyanide for the Target Person

Exposure group	Inhalation (µg/m³)	Dermal (µg/kg/day)
Birth–<1 year	NC	$4.2x10^{-5}$
1–<2 years	NC	$3.8x10^{-5}$
2–<6 years	NC	$3.4x10^{-5}$
6–<11 years	NC	$2.8x10^{-5}$
11–<16 years	NC	$2.3x10^{-5}$
16–<21 years	NC	$2.1x10^{-5}$
Adult	NC	$2.0x10^{-5}$
Pregnant and breastfeeding women	NC	$2.0x10^{-5}$

NC = not calculated

Source: ATSDR 2022b

Water quality data from the United States spanning 4 decades (1981–2023) indicates that 99% of water samples contained cyanide at concentrations <10 µg/L (WQP 2024). Using the upper cut-off (10 µg/L) and assuming a daily water consumption of 2 L for a 70-kg adult, the daily intake of cyanide for the general population is estimated at <0.02 mg. EPA has established an MCL of 0.2 mg/L for cyanide in drinking water (EPA 2009; see Chapter 7), 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 1991). In chlorinated drinking water, cyanide may be present as cyanogen chloride (see Section 5.4.2), which is less volatile than hydrogen cyanide.

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 it is likely to exceed cyanide intake from inhalation of air and ingestion of drinking water (CEPA 1997; EPA 1981). EPA has established tolerances in various foods ranging from 25 to 250 ppm for hydrogen cyanide and from 5 to 25 ppm for calcium cyanide (EPA 1981). Poitrast et al. (1988) 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 breastmilk is quite low.

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.

Urinary thiocyanate levels are available from the National Health and Nutrition Examination Survey (NHANES) for 2011–2016. The geometric means and selected percentiles of urinary levels of cyanide for smokers and nonsmokers are shown in Tables 5-11 and 5-12, respectively; creatinine-corrected urinary levels are shown in Tables 5-13 and 5-14, respectively (CDC 2024).

5.7 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 1981) and people who are exposed to house or other building fires (Andrews et al. 1989; Ballantyne 1987; 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 and the children of smokers may be subjected to potentially high exposures of cyanide and thiocyanate (Bottoms et al. 1982; EPA 1992; Hauth et al. 1984).

NHANES data from 2011–2016 (Tables 5-11 through 5-14) show elevated urinary cyanide and thiocyanate concentrations in smokers, compared to nonsmokers (CDC 2024). The results of several additional studies that have shown similar elevations in cyanide or thiocyanate concentrations in body fluids of smokers, compared to nonsmokers; these studies are summarized in Table 5-15. 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; Pré 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. Pré 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 study authors concluded that a plasma thiocyanate concentration <20 μmol/L (1,200 μg/L) indicated that passive smoking was very unlikely, whereas concentrations >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

Table 5-11. Urinary Thiocyanate Concentrations (mg/L) in the Cigarette Smoking[a] U.S. General Population

Survey years	Geometric mean (95% confidence interval)[b]	Percentiles (95% confidence interval)[b]				Sample size
		50th	75th	90th	95th	
Total						
2011–2012	4.10 (3.58–4.69)	4.60 (3.98–5.37)	7.16 (6.43–8.09)	11.2 (9.43–12.7)	14.6 (12.7–16.2)	869
2013–2014	3.93 (3.56–4.33)	4.48 (3.93–4.78)	7.45 (6.70–8.23)	12.5 (10.2–14.0)	15.2 (13.9–17.7)	944
2015–2016	3.88 (3.47–4.33)	4.65 (3.91–5.51)	8.28 (7.72–8.57)	11.8 (11.1–13.0)	15.0 (13.7–16.5)	824
Age group						
20–49 years						
2011–2012	4.18 (3.72–4.69)	4.67 (4.15–5.05)	7.38 (6.43–8.20)	11.7 (10.2–13.3)	15.9 (12.7–17.8)	518
18–49 years						
2013–2014	3.99 (3.46–4.61)	4.72 (3.90–5.32)	7.90 (6.96–8.89)	13.5 (10.8–14.5)	16.0 (14.1–18.0)	575
2015–2016	3.52 (2.96–4.18)	4.16 (3.53–5.07)	8.33 (7.10–9.77)	12.9 (11.3–14.5)	16.3 (14.3–19.8)	448
≥50 years						
2011–2012	3.98 (3.24–4.90)	4.38 (3.37–5.94)	6.90 (5.48–8.14)	9.94 (7.67–13.5)	12.8 (9.50–15.3)	351
2013–2014	3.79 (3.40–4.23)	3.87 (3.41–4.63)	6.53 (5.45–7.58)	9.98 (9.02–12.6)	14.4 (11.5–18.3)	369
2015–2016	4.51 (3.73–5.45)	5.36 (3.91–6.41)	7.88 (6.89–9.02)	10.5 (9.39–12.1)	12.8 (11.1–15.5)	376
Gender						
Males						
2011–2012	4.03 (3.26–4.98)	4.51 (3.30–6.14)	7.23 (6.43–8.59)	11.1 (8.99–13.4)	14.5 (11.8–17.8)	525
2013–2014	3.81 (3.31–4.39)	4.63 (3.73–5.19)	7.59 (6.60–8.92)	13.5 (10.7–14.5)	15.6 (14.1–18.5)	508
2015–2016	3.64 (2.99–4.44)	4.22 (3.40–5.65)	8.64 (7.69–9.70)	12.4 (11.1–14.8)	15.5 (13.7–19.5)	485
Females						
2011–2012	4.19 (3.81–4.61)	4.71 (4.31–5.37)	6.83 (6.12–7.95)	11.3 (8.53–13.1)	15.3 (11.9–18.2)	344
2013–2014	4.05 (3.61–4.54)	4.30 (3.88–4.78)	7.15 (6.16–8.24)	11.3 (9.40–14.1)	14.5 (11.3–17.7)	436
2015–2016	4.19 (3.73–4.70)	5.03 (4.06–5.92)	7.93 (7.35–8.33)	10.8 (9.58–12.7)	13.9 (11.7–18.8)	339

[a]Cigarette smokers were defined by an affirmative response to the question, 'Have you smoked at least 100 cigarettes in your life?' and confirmation that they smoke either every day or some days.
[b]Limits of detection for survey years 2011–2012, 2013–2014, and 2015–2016 were 0.020, 0.020, and 0.020 mg/L, respectively.

Source: CDC 2024

Table 5-12. Urinary Thiocyanate Concentrations (mg/L) in the Nonsmoking[a] U.S. General Population

Survey years	Geometric mean (95% confidence interval)[b]	Percentiles (95% confidence interval)[b]				Sample size
		50th	75th	90th	95th	
Total						
2011–2012	0.795 (0.737–0.858)	0.875 (0.819–0.929)	1.56 (1.41–1.74)	2.54 (2.23–2.92)	3.23 (2.97–3.57)	1,319
2013–2014	0.791 (0.745–0.841)	0.799 (0.737–0.861)	1.48 (1.37–1.55)	2.55 (2.31–2.89)	3.67 (2.96–4.47)	1,476
2015–2016	0.817 (0.740–0.901)	0.875 (0.762–0.979)	1.57 (1.39–1.81)	2.69 (2.48–3.12)	3.78 (3.13–4.54)	1,455
Age group						
20–49 years						
2011–2012	0.855 (0.777–0.940)	0.927 (0.854–1.00)	1.71 (1.50–1.92)	2.67 (2.29–3.17)	3.43 (3.01–4.36)	659
18–49 years						
2013–2014	0.838 (0.774–0.907)	0.862 (0.766–0.988)	1.54 (1.43–1.73)	2.54 (2.31–2.96)	3.75 (2.96–5.03)	774
2015–2016	0.894 (0.816–0.981)	0.904 (0.821–1.02)	1.74 (1.40–1.96)	3.02 (2.30–3.72)	3.92 (3.16–4.66)	741
≥50 years						
2011–2012	0.736 (0.666–0.814)	0.833 (0.726–0.897)	1.44 (1.21–1.68)	2.39 (1.94–2.90)	2.92 (2.39–3.86)	660
2013–2014	0.742 (0.668–0.824)	0.751 (0.668–0.843)	1.36 (1.19–1.57)	2.66 (1.96–3.26)	3.67 (2.70–4.81)	702
2015–2016	0.739 (0.630–0.868)	0.814 (0.687–1.01)	1.47 (1.23–1.76)	2.59 (2.18–3.03)	3.29 (2.60–4.28)	714
Gender						
Males						
2011–2012	0.968 (0.865–1.08)	1.01 (0.913–1.20)	1.90 (1.57–2.20)	2.79 (2.31–3.25)	3.43 (2.94–4.10)	628
2013–2014	0.938 (0.853–1.03)	0.911 (0.830–1.05)	1.79 (1.55–2.07)	2.96 (2.44–3.81)	4.33 (3.10–5.93)	661
2015–2016	1.00 (0.873–1.16)	1.06 (0.923–1.23)	1.86 (1.64–2.23)	3.25 (2.62–4.28)	4.58 (3.54–6.37)	658
Females						
2011–2012	0.681 (0.600–0.773)	0.727 (0.603–0.843)	1.36 (1.21–1.50)	2.27 (1.97–2.54)	3.17 (2.52–3.32)	691
2013–2014	0.687 (0.634–0.744)	0.694 (0.621–0.779)	1.29 (1.14–1.39)	2.20 (1.91–2.36)	3.10 (2.67–3.75)	815
2015–2016	0.690 (0.624–0.763)	0.723 (0.624–0.798)	1.31 (1.12–1.52)	2.35 (2.00–2.64)	3.02 (2.48–3.84)	797

[a]Cigarette nonsmokers who used other tobacco products were excluded.
[b]Limits of detection for Survey years 2011–2012, 2013–2014, and 2015–2016 were 0.020, 0.020, and 0.020 mg/L, respectively.

Source: CDC 2024

Table 5-13. Urinary Thiocyanate Concentrations (Creatinine Corrected) (µg/g Creatinine) in the Cigarette Smoking[a] U.S. General Population

Survey years	Geometric mean (95% confidence interval)[b]	Percentiles (95% confidence interval)[b]				Sample size
		50th	75th	90th	95th	
Total						
2011–2012	4.53 (4.02–5.10)	5.04 (4.38–5.47)	8.28 (7.42–10.0)	14.4 (11.6–15.7)	16.7 (15.3–18.9)	869
2013–2014	3.99 (3.57–4.47)	4.37 (3.99–5.00)	7.81 (7.12–8.51)	11.9 (10.4–14.3)	15.6 (13.5–18.6)	944
2015–2016	3.91 (3.51–4.36)	4.41 (3.74–5.21)	7.88 (6.97–8.75)	11.8 (10.8–12.8)	15.4 (13.4–16.4)	824
Age group						
20–49 years						
2011–2012	4.35 (3.87–4.89)	4.84 (3.82–5.47)	7.98 (7.54–8.91)	14.0 (11.1–16.1)	16.7 (14.2–19.9)	518
18–49 years						
2013–2014	3.69 (3.25–4.19)	4.17 (3.75–4.68)	7.40 (6.33–8.43)	11.7 (10.4–13.8)	14.4 (12.9–15.9)	575
2015–2016	3.30 (2.80–3.90)	3.96 (2.97–4.83)	6.99 (5.55–8.68)	10.4 (8.86–11.7)	11.8 (10.6–15.1)	448
≥50 years						
2011–2012	4.81 (4.06–5.71)	5.28 (4.43–6.84)	8.84 (7.11–12.1)	15.3 (10.5–17.2)	16.6 (15.3–18.3)	351
2013–2014	4.71 (4.16–5.34)	4.68 (4.42–5.62)	8.12 (7.37–9.45)	12.9 (10.3–18.4)	18.6 (11.0–22.8)	369
2015–2016	5.05 (4.28–5.96)	5.70 (4.25–6.77)	8.63 (7.78–11.0)	14.8 (11.5–16.2)	17.0 (14.8–24.8)	376
Gender						
Males						
2011–2012	3.81 (3.28–4.43)	4.20 (3.64–5.06)	7.30 (6.54–7.77)	11.1 (9.41–12.5)	14.3 (12.3–15.6)	525
2013–2014	3.38 (2.96–3.86)	4.14 (3.13–4.49)	7.12 (6.14–7.87)	11.0 (9.50–11.7)	13.2 (11.7–14.9)	508
2015–2016	3.17 (2.70–3.72)	3.34 (2.52–4.40)	6.85 (5.39–7.42)	10.2 (8.75–10.9)	12.2 (10.8–16.0)	485
Females						
2011–2012	5.62 (4.64–6.81)	5.82 (4.69–8.05)	11.1 (8.53–14.6)	16.7 (14.0–18.9)	19.2 (16.7–24.0)	344
2013–2014	4.73 (4.12–5.42)	4.87 (4.08–5.92)	8.19 (7.52–9.75)	13.8 (10.7–17.1)	17.9 (14.2–21.2)	436
2015–2016	5.03 (4.39–5.76)	5.86 (5.14–6.61)	8.83 (8.26–10.6)	13.9 (11.8–15.4)	15.8 (14.8–17.8)	339

[a]Cigarette smokers were defined by an affirmative response to the question, 'Have you smoked at least 100 cigarettes in your life?' and confirmation that they smoke either every day or some days.
[b]Limits of detection for Survey years 2011–2012, 2013–2014, and 2015–2016 were 0.020, 0.020, and 0.020 mg/L, respectively.

Source: CDC 2024

Table 5-14. Urinary Thiocyanate Concentrations (Creatinine Corrected) (µg/g Creatinine) in the Nonsmoking[a] U.S. General Population

Survey years	Geometric mean (95% confidence interval)[b]	Percentiles (95% confidence interval)[b]				Sample size
		50th	75th	90th	95th	
Total						
2011–2012	0.933 (0.881–0.988)	0.976 (0.905–1.10)	1.69 (1.54–1.84)	2.70 (2.34–2.99)	3.29 (3.02–3.89)	1,318
2013–2014	0.948 (0.882–1.02)	0.994 (0.908–1.06)	1.68 (1.54–1.80)	2.71 (2.28–3.00)	3.74 (3.13–4.47)	1,475
2015–2016	0.922 (0.844–1.01)	0.953 (0.874–1.08)	1.74 (1.56–1.87)	2.68 (2.40–2.88)	3.60 (3.11–4.10)	1,453
Age group						
20–49 years						
2011–2012	0.938 (0.864–1.02)	1.01 (0.902–1.10)	1.67 (1.46–1.84)	2.51 (2.18–2.91)	3.02 (2.91–3.18)	658
18–49 years						
2013–2014	0.922 (0.843–1.01)	0.950 (0.860–1.04)	1.52 (1.37–1.66)	2.33 (2.09–2.57)	3.37 (2.60–4.40)	774
2015–2016	0.934 (0.865–1.01)	0.898 (0.815–1.04)	1.66 (1.50–1.81)	2.54 (2.23–3.15)	3.74 (3.13–4.59)	739
≥50 years						
2011–2012	0.927 (0.852–1.01)	0.965 (0.830–1.18)	1.72 (1.46–1.99)	2.91 (2.16–3.37)	3.76 (3.16–4.33)	660
2013–2014	0.979 (0.880–1.09)	1.05 (0.890–1.24)	1.85 (1.55–2.08)	2.92 (2.41–3.56)	4.13 (3.14–5.08)	701
2015–2016	0.910 (0.780–1.06)	1.03 (0.881–1.22)	1.85 (1.47–2.14)	2.68 (2.22–3.14)	3.60 (2.78–4.39)	714
Gender						
Males						
2011–2012	0.865 (0.782–0.956)	0.941 (0.743–1.09)	1.56 (1.28–1.87)	2.66 (2.09–2.96)	3.37 (2.67–4.05)	627
2013–2014	0.912 (0.832–0.999)	0.983 (0.854–1.12)	1.62 (1.47–1.82)	2.75 (2.17–3.19)	4.13 (2.88–5.08)	660
2015–2016	0.923 (0.812–1.05)	0.944 (0.814–1.18)	1.77 (1.50–1.98)	2.81 (2.30–3.27)	3.87 (2.89–5.02)	658
Females						
2011–2012	0.990 (0.910–1.08)	1.05 (0.936–1.17)	1.75 (1.59–1.91)	2.86 (2.41–3.03)	3.29 (2.97–3.96)	691
2013–2014	0.980 (0.910–1.05)	1.01 (0.923–1.06)	1.71 (1.55–1.81)	2.69 (2.26–3.13)	3.53 (2.94–4.15)	815
2015–2016	0.921 (0.836–1.02)	0.955 (0.874–1.05)	1.73 (1.56–1.86)	2.52 (2.38–2.88)	3.58 (2.88–4.14)	795

[a]Cigarette nonsmokers who used other tobacco products were excluded.
[b]Limits of detection for Survey years 2011–2012, 2013–2014, and 2015–2016 were 0.020, 0.020, and 0.020 mg/L, respectively.

Source: CDC 2024

Table 5-15. Cyanide and Thiocyanate Concentrations (µg/mL)[a] in Smokers and Nonsmokers

	Plasma/blood		Serum		Saliva		Urine		
Compound	Smoker	Nonsmoker	Smoker	Nonsmoker	Smoker	Nonsmoker	Smoker	Nonsmoker	Reference
Cyanide			2.11 (1.42–3.67)	0.78 (0.44–1.15)					Cardeal et al. 1993[b]
			6.8 (1.3–19.4)	2.9 (0.0–11.7)					Symington et al. 1987[b,c]
	0.27 (0.14–0.41)[d]	0.17 (0.11–0.25)[d]			0.66 (0.13–2.07)[d]	0.38 (0.05–1.20)[d]			Tsuge et al. 2000
Thiocyanate			232 (10)	92 (9)					Banerjee and Muthu 1994[e]
	7.1	2.9			142	76	9.0	5.8	Jarvis 1989[f]
	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[b]
	8.7[g] (4.4–21.5)	1.8[h] (0.5–4.4)							Pré and Vassy 1992[e]
	3.3[i] (1.0–4.6)								
			6.6 (1.5)	1.2 (0.3)					Pré and Vassy 1993[e]
	111.2 (1.7–290)[d]	33.5 (6.3–94)[d]			1,655 (270–2,940)[d]	542 (13–1,630)[d]			Tsuge et al. 2000

Table 5-15. Cyanide and Thiocyanate Concentrations (µg/mL)[a] in Smokers and Nonsmokers

	Plasma/blood		Serum		Saliva		Urine		
Compound	Smoker	Nonsmoker	Smoker	Nonsmoker	Smoker	Nonsmoker	Smoker	Nonsmoker	Reference
			(<0.05–0.35)	(<0.05–0.08)					Waage et al. 1992[e,j]
	2.1	3.7			88	33	18	19	Yamanaka et al. 1991[j,k]

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

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.

No data were found related to the levels of cyanide or thiocyanate exposure in cassava eaters in the United States. However, elevated levels of thiocyanate in body fluids resulting from consumption of cyanide-containing foods have been reported in populations from tropical regions that may consume large quantities of improperly processed cyanogenic plants such as cassava (WHO 2004). 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±standard error) 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 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.

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). High serum thiocyanate concentrations (>180 µmol/L) were also reported in this population. 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 Deane 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 (Panghal et al. 2019). When outbreaks of acute cyanide intoxications from incomplete processing of cassava occur in African populations, highly elevated cyanide levels were observed in combination with chronic dietary protein malnutrition (WHO 2004). 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).

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 1981; NIOSH 1989). 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 1989; WHO 2004). 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 1987) and patients with motor neuron disease (Kato et al. 1985).

Occupational exposures to cyanide are expected to occur primarily through inhalation and, less frequently, through skin absorption. Preliminary data from the NOES conducted by the National Institute for Occupational Safety and Health (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 1989): 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 1989). These numbers do not include workers potentially exposed to tradename 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 1981; Lucas 1992; WHO 2004; 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 5.3.1). 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 1989). 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 1989).

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 were 0.001–0.004 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 short-term exposure limit of 4.7 ppm (NIOSH 1992).

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

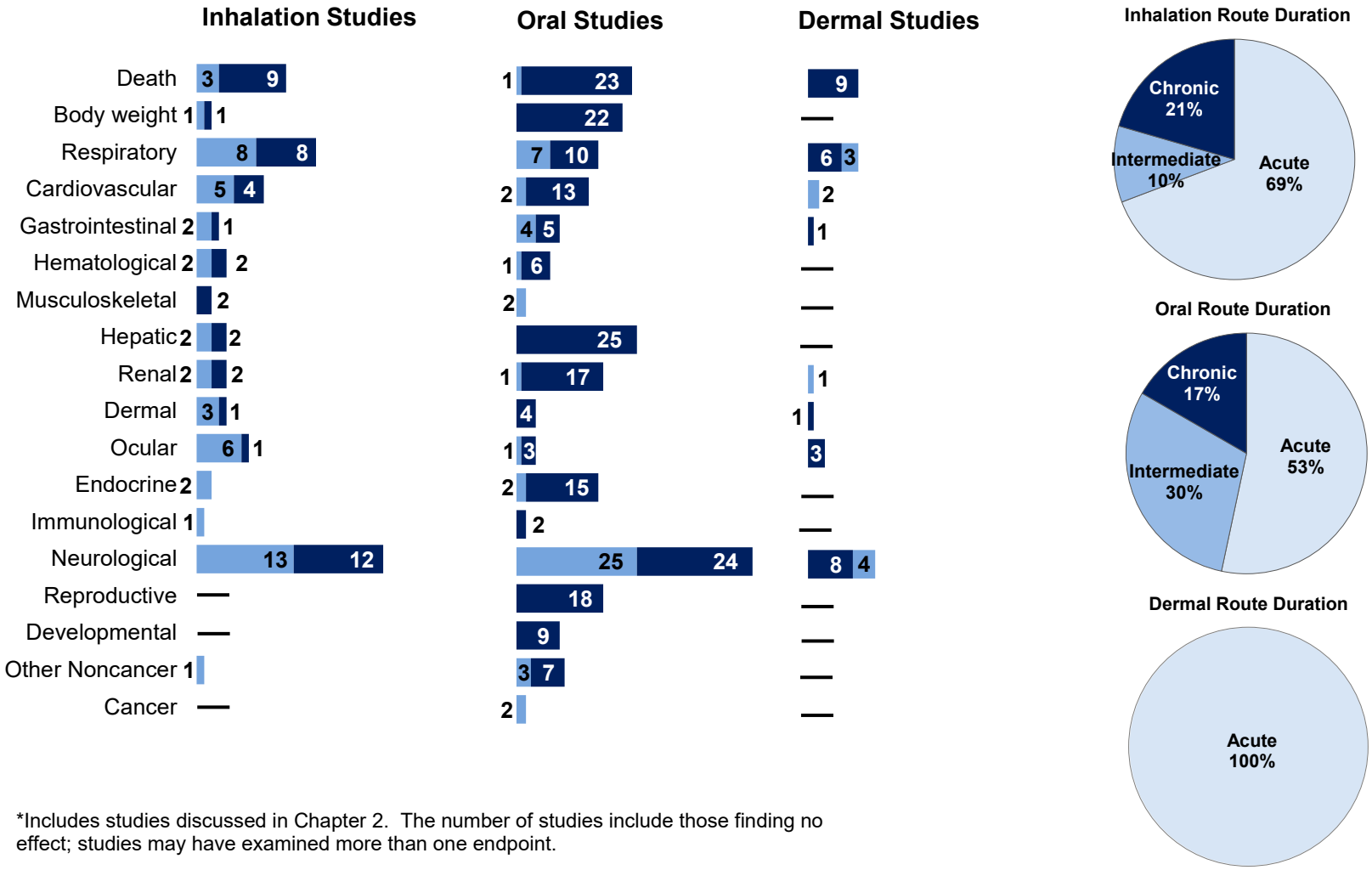
Studies evaluating the health effects of inhalation, oral, and dermal exposure of humans and animals to cyanide that are discussed in Chapter 2 are summarized in Figure 6-1. The purpose of this figure is to illustrate the information concerning the health effects of cyanide. The number of human and animal 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

CHAPTER 7. REGULATIONS AND GUIDELINES

Pertinent international and national regulations, advisories, and guidelines regarding cyanide in air, water, and other media are summarized in Table 7-1. This table is not an exhaustive list, and current regulations should be verified by the appropriate regulatory agency.

ATSDR develops MRLs, which are substance-specific guidelines intended to serve as screening levels by ATSDR health assessors and other responders to identify contaminants and potential health effects that may be of concern at hazardous waste sites. See Section 1.3 and Appendix A for detailed information on the MRLs for cyanide.

Table 7-1. Regulations and Guidelines Applicable to Cyanide

Agency	Description	Information	Reference
	Air		
EPA	RfC		
	Hydrogen cyanide	0.0008 mg/m^3 (0.0007 ppm)	IRIS 2010
WHO	Air quality guidelines	Not listed	WHO 2010
	Water & Food		
EPA	Drinking water standards and health advisories		EPA 2018a
	Cyanide		
	1-Day health advisory (10-kg child)	0.2 mg/L	
	10-Day health advisory (10-kg child)	0.2 mg/L	
	Cyanogen chloride		
	1-Day health advisory (10-kg child)	0.05 mg/L	
	10-Day health advisory (10-kg child)	0.05 mg/L	
	DWEL	2 mg/L	
	National primary drinking water regulations		EPA 2009
	Cyanide (as free cyanide)		
	MCL	0.2 mg/L	
	MCLG	0.2 mg/L	
	RfD		
	Cyanide (as free cyanide)	0.0006 mg/kg/day	IRIS 2010
	Calcium cyanide	0.001 mg/kg/day	
	Hydrogen cyanide, aqueous	0.0007 mg/kg/day	
	Potassium cyanide	0.002 mg/kg/day	
	Potassium silver cyanide	0.005 mg/kg/day	
	Sodium cyanide	0.001 mg/kg/day	
	Cyanogen	0.001 mg/kg/day	

Table 7-1. Regulations and Guidelines Applicable to Cyanide

Agency	Description	Information	Reference
	Cyanogen chloride	0.05 mg/kg/day	IRIS 2005a
	Copper cyanide	0.005 mg/kg/day	IRIS 2005b
	Provisional peer reviewed toxicity values		
	Thiocyanates		EPA 2006b
	Provisional chronic RfD	0.0002 mg/kg/day	
	Provisional subchronic RfD	0.0006 mg/kg/day	
WHO	Drinking water quality guidelines		WHO 2022
	Cyanide	Guideline not established[a]	
	Cyanogen chloride	Guideline not established[b]	
FDA	Substances added to food (formerly EAFUS)	Not listed	FDA 2023b
	Allowable level in bottled water	0.2 mg/L	FDA 2023a
	Cancer		
HHS	Carcinogenicity classification	Not evaluated	NTP 2021
EPA	Carcinogenicity classification	Inadequate information to assess the carcinogenic potential	IRIS 2010
IARC	Carcinogenicity classification	Not evaluated	IARC 2023
	Occupational		
OSHA	PEL (8-hour TWA) for general industry, shipyards, and construction		OSHA 2021a, 2021b, 2021c
	Cyanides (as CN)	5 mg/m³ [c]	
	Hydrogen cyanide	10 ppm (11 mg/m³)[d]	
	PEL (8-hour TWA) for shipyards and construction		
	Cyanogen	10 ppm	
NIOSH	Ceiling REL		
	Cyanides (as CN), except hydrogen cyanide; 10-minute ceiling	5 mg/m³ (4.7 ppm)	NIOSH 2019d
	Cyanogen chloride	0.3 ppm (0.6 mg/m^3)	NIOSH 2019b
	STEL		
	Hydrogen cyanide	4.7 ppm (5 mg/m^3)[e]	NIOSH 2019c
	REL (up to 10-hour TWA)		
	Cyanogen	10 ppm (20 mg/m^3)	NIOSH 2019a
	Emergency Criteria		
NIOSH	IDLH		
	Cyanides (as CN)	25 mg/m³	NIOSH 1994a
	Hydrogen cyanide	50 ppm	NIOSH 1994b

Table 7-1. Regulations and Guidelines Applicable to Cyanide

Agency	Description	Information	Reference
EPA	AEGLs-air		EPA 2018b
	Hydrogen cyanide		
	AEGL 1[f]		
	10-minute	2.5 ppm	
	30-minute	2.5 ppm	
	60-minute	2.0 ppm	
	4-hour	1.3 ppm	
	8-hour	1.0 ppm	
	AEGL 2[f]		
	10-minute	17 ppm	
	30-minute	10 ppm	
	60-minute	7.1 ppm	
	4-hour	3.5 ppm	
	8-hour	2.5 ppm	
	AEGL 3[f]		
	10-minute	27 ppm	
	30-minute	21 ppm	
	60-minute	15 ppm	
	4-hour	8.6 ppm	
	8-hour	6.6 ppm	
	Calcium cyanide		
	AEGL 1[f]		
	10-minute	4.7 mg/m^3	
	30-minute	4.7 mg/m^3	
	60-minute	3.8 mg/m^3	
	4-hour	2.4 mg/m^3	
	8-hour	1.9 mg/m^3	
	AEGL 2[f]		
	10-minute	32 mg/m^3	
	30-minute	19 mg/m^3	
	60-minute	13 mg/m^3	
	4-hour	6.6 mg/m^3	
	8-hour	4.7 mg/m^3	
	AEGL 3[f]		
	10-minute	51 mg/m^3	
	30-minute	39 mg/m^3	
	60-minute	28 mg/m^3	
	4-hour	16 mg/m^3	
	8-hour	12 mg/m^3	
	Potassium cyanide		
	AEGL 1[f]		
	10-minute	6.6 mg/m^3	
	30-minute	6.6 mg/m^3	
	60-minute	5.3 mg/m^3	
	4-hour	3.5 mg/m^3	
	8-hour	2.7 mg/m^3	

Table 7-1. Regulations and Guidelines Applicable to Cyanide

Agency	Description	Information	Reference
	AEGL 2[f]		
	10-minute	45 mg/m^3	
	30-minute	27 mg/m^3	
	60-minute	19 mg/m^3	
	4-hour	9.3 mg/m^3	
	8-hour	6.6 mg/m^3	
	AEGL 3[f]		
	10-minute	72 mg/m^3	
	30-minute	56 mg/m^3	
	60-minute	40 mg/m^3	
	4-hour	23 mg/m^3	
	8-hour	18 mg/m^3	
	Sodium cyanide		
	AEGL 1[f]		
	10-minute	5.0 mg/m^3	
	30-minute	5.0 mg/m^3	
	60-minute	4.0 mg/m^3	
	4-hour	2.6 mg/m^3	
	8-hour	2.0 mg/m^3	
	AEGL 2[f]		
	10-minute	34 mg/m^3	
	30-minute	20 mg/m^3	
	60-minute	14 mg/m^3	
	4-hour	7.0 mg/m^3	
	8-hour	5.0 mg/m^3	
	AEGL 3[f]		
	10-minute	54 mg/m^3	
	30-minute	42 mg/m^3	
	60-minute	30 mg/m^3	
	4-hour	17 mg/m^3	
	8-hour	13 mg/m^3	
	Cyanogen		
	AEGL 1[f]		
	10-minute	2.5 ppm	
	30-minute	2.5 ppm	
	60-minute	2.0 ppm	
	4-hour	1.3 ppm	
	8-hour	1.0 ppm	
	AEGL 2[f]		
	10-minute	50 ppm	
	30-minute	17 ppm	
	60-minute	8.3 ppm	
	4-hour	4.3 ppm	
	8-hour	4.3 ppm	

Table 7-1. Regulations and Guidelines Applicable to Cyanide

Agency	Description	Information	Reference
	AEGL 3[f]		
	10-minute	150 ppm	
	30-minute	50 ppm	
	60-minute	25 ppm	
	4-hour	13 ppm	
	8-hour	13 ppm	
DOE	PACs-air		DOE 2018a
	Cyanide		
	PAC-1[g]	6 mg/m^3	
	PAC-2[g]	8.3 mg/m^3	
	PAC-3[g]	50 mg/m^3	
	Hydrogen cyanide		
	PAC-1[g]	2 ppm	
	PAC-2[g]	7.1 ppm	
	PAC-3[g]	15 ppm	
	Calcium cyanide		
	PAC-1[g]	3.8 mg/m^3	
	PAC-2[g]	13 mg/m^3	
	PAC-3[g]	28 mg/m^3	
	Copper cyanide		
	PAC-1[g]	21 mg/m^3	
	PAC-2[g]	29 mg/m^3	
	PAC-3[g]	170 mg/m^3	
	Potassium cyanide		
	PAC-1[g]	5.3 mg/m^3	
	PAC-2[g]	19 mg/m^3	
	PAC-3[g]	40 mg/m^3	
	Potassium silver cyanide		
	PAC-1[g]	2.9 mg/m^3	
	PAC-2[g]	32 mg/m^3	
	PAC-3[g]	190 mg/m^3	
	Sodium cyanide		
	PAC-1[g]	4.0 mg/m^3	
	PAC-2[g]	14 mg/m^3	
	PAC-3[g]	30 mg/m^3	
	Cyanogen		
	PAC-1[g]	2.0 ppm	
	PAC-2[g]	8.3 ppm	
	PAC-3[g]	25 ppm	
	Cyanogen chloride		
	PAC-1[g]	0.0045 ppm	
	PAC-2[g]	0.05 ppm	
	PAC-3[g]	4 ppm	

Table 7-1. Regulations and Guidelines Applicable to Cyanide

Agency	Description	Information	Reference
	Ammonium thiocyanate		
	PAC-1[g]	2.3 mg/m^3	
	PAC-2[g]	25 mg/m^3	
	PAC-3[g]	150 mg/m^3	
	Potassium thiocyanate		
	PAC-1[g]	2.6 mg/m^3	
	PAC-2[g]	28 mg/m^3	
	PAC-3[g]	170 mg/m^3	

[a]Reason: occurs in drinking-water at concentrations well below those of health concern, except in emergency situations following a spill to a water source.
[b]Reason: occurs in drinking-water at concentrations well below those of health concern.
[c]Skin designation for general industry and construction.
[d]Skin designation for general industry, shipyards, and construction.
[e]Skin designation.
[f]Definitions of AEGL terminology are available from EPA (2018c).
[g]Definitions of PAC terminology are available from DOE (2018b).

AEGL = acute exposure guideline levels; DOE = Department of Energy; DWEL = drinking water equivalent level; EAFUS = Everything Added to Food in the United States; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; HHS = Department of Health and Human Services; IARC = International Agency for Research on Cancer; IDLH = immediately dangerous to life or health; IRIS = Integrated Risk Information System; MCL = maximum contaminant level; MCLG = maximum contaminant level goal; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; PAC = protective action criteria; PEL = permissible exposure limit; REL = recommended exposure limit; RfC = inhalation reference concentration; RfD = oral reference dose; STEL = short-term exposure limit; TWA = time-weighted average; WHO = World Health Organization

CHAPTER 8. REFERENCES

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APPENDIX A. ATSDR MINIMAL RISK LEVEL WORKSHEETS

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 route and duration of exposure. MRLs are based on noncancer health effects only; cancer effects are not considered. 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 NOAEL/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) 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 substance-induced endpoint considered to be of relevance to humans. LOAELs for serious health effects (such as irreparable damage to the liver or kidneys, or serious 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 substances 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 Office of Innovation and Analytics, Toxicology Section, 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 MRLs. For additional information regarding MRLs, please contact the Office of Innovation and Analytics, Toxicology Section, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop S106-5, Atlanta, Georgia 30329-4027.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Cyanide and compounds
CAS Numbers: Various
Date: October 2024
Profile Status: Draft for Public Comment
Route: Inhalation
Duration: Acute

MRL Summary: There are insufficient data to support derivation of an acute-duration inhalation MRL. Available data for hydrogen cyanide indicate serious adverse effects occurring at the lowest reported adverse effect levels in both humans and animals.

Rationale for Not Deriving an MRL: Available human data are limited to case reports of exposure to hydrogen cyanide, most of which do not have exposure data. Studies with exposure data indicate brief exposures to 200–452 ppm are associated with serious neurological effects (coma with slight loss of peripheral vision after recovery, brain damage), metabolic effects (lactic acidosis indicative of impaired respiration), and death (Bonsall 1984; Singh et al. 1989). These studies are not considered suitable for MRL derivation.

Reliable NOAELs and LOAELs identified for hydrogen cyanide in acute-duration inhalation studies in animals are shown in Table A-1. The only effect noted below the lowest reported LC_{50} value of 143 ppm (Ballantyne 1983a) was depressed respiration; the calculated DC_{50} (estimated concentration associated with a 50% decrease in the respiratory rate) in mice was 63 ppm (Matijak-Schaper and Alarie 1982). This effect was considered a serious LOAEL; therefore, it is not considered suitable as the basis for the acute-duration inhalation MRL. A study of auditory function and histology in rats by Fechter et al. (2002) reported a no-observed-adverse-effect level (NOAEL) of 50 ppm hydrogen cyanide for a 3.5-hour exposure (some deficits were observed when hydrogen cyanide exposure was concurrent with noise exposure). However, the study by Fechter et al. (2002) is not suitable for derivation of an MRL because the ear was the only organ evaluated in this study; therefore, the identified NOAEL may not be protective of more sensitive effects of hydrogen cyanide exposure.

In addition to the reliable studies reported in Table A-1, a study in monkeys reported neurological impairments, cardiological effects, and respiratory distress following exposure to ≥100 ppm for 30 minutes (Purser et al. 1984). However, due to critical study design deficiencies (one monkey/group; no control group), NOAEL and LOAEL values were not established. Therefore, this study is not suitable for MRL derivation.

Table A-1. NOAEL and LOAEL Values in Animals Following Acute-Duration Inhalation Exposure to Hydrogen Cyanide

		Effect level (ppm hydrogen cyanide)			
Species	Duration	NOAEL	SLOAEL	Effect	Reference
Rat	3.5 hours	50			Fechter et al. 2002
Mouse	30 minutes		63	Calculated DC_{50} (estimated 50% decrease in respiratory rate)	Matijak-Schaper and Alarie 1982

Table A-1. NOAEL and LOAEL Values in Animals Following Acute-Duration Inhalation Exposure to Hydrogen Cyanide

Species	Duration	Effect level (ppm hydrogen cyanide) NOAEL	SLOAEL	Effect	Reference
Mouse	40 minutes		327	33% lethality; clinical signs of toxicity in survivors (gasping, labored breathing, lethargy, loss of righting reflex, convulsions, tremors)	Ma et al. 2021
Mouse	3 minutes		400	90% lethality	Hume et al. 1995

DC_{50} = concentration associated with 50% depression in respiratory rate; NOAEL = no-observed-adverse-effect level; SLOAEL = serious lowest-observed-adverse-effect level

Agency Contacts (Chemical Managers): Malcolm Williams, D.V.M., Ph.D.

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Cyanide and compounds
CAS Numbers: Various
Date: October 2024
Profile Status: Draft for Public Comment
Route: Inhalation
Duration: Intermediate

MRL Summary: There are insufficient data to support derivation of an intermediate-duration inhalation MRL. The database for hydrogen cyanide is limited to one occupational study in humans (Blanc et al. 1985), a single-exposure level study in rats with a very limited scope (O'Flaherty and Thomas 1982), and a series of a poorly-reported studies in dogs (Valade 1952).

Rationale for Not Deriving an MRL: The intermediate-duration inhalation database for hydrogen cyanide is very limited. The only identified human study, a human occupational study by Blanc et al. (1985), is not considered adequate for MRL derivation. This study evaluated former workers from a silver reclaiming factory reporting an average employment of an intermediate-duration (11 months). Based on worker-recall 7–30 months post-employment, subjective symptoms experienced during employment included decreased weight, loss of appetite, respiratory irritation, chest pain, nausea or vomiting, skin rash (which persisted in some post-employment), eye irritation, headache, dizziness, and fatigue; skin rash and headache persisted in some post-employment. When evaluated 7–30 months after exposure ceased, serum thyroid-stimulating hormone (TSH) levels were elevated compared to laboratory reference values. Major limitations of this study include exposure levels measured only at one point in time after the factory shut down (15 ppm) and either reliance on self-reporting of symptoms that occurred during employment that ceased 7–30 months prior to the assessment or assessment of endpoints only 7–30 months after exposure ceased.

Only one intermediate-duration animal study evaluating hydrogen cyanide was considered adequate to make a NOAEL/LOAEL determination. This study in rats evaluated potential cardiovascular effects of brief, intermittent exposure to hydrogen cyanide (12.5 minutes/day at 4-day intervals) over a 20-day period (O'Flaherty and Thomas 1982). The study reported evidence of potential cardiovascular damage (increased serum creatine phosphokinase [CPK] activity 2-hours post exposure) at the only exposure concentration of 200 ppm. However, CPK levels did not show any time-dependence (findings were not dependent upon the number of previous exposures), suggesting that observations may reflect acute exposures rather than cumulative exposure over the 20-day experimental duration. Changes in CPK activity were not associated with any histopathological changes in the heart at the end of the exposure period. Due to the limited scope of this study, it is not considered adequate for the derivation of an intermediate-duration MRL for cyanide in the absence of support from additional studies.

Other intermediate-duration inhalation data for hydrogen cyanide are restricted to a series of a poorly-reported studies in dogs intermittently exposed to 50 ppm for 28–96 days (Valade 1952). Effects noted by the study authors included lethality, serious neurological effects (tremors, ataxia, brain atrophy), gastrointestinal effects, and dyspnea. However, due to poor reporting of study design and results and lack of a control group, interpretation of the study results (e.g., number of affected animals at different timepoints) was not possible. Most notably, it is unclear if reported deaths were attributable to exposure, as some appeared to occur long after the exposure period ceased. Thus, due to poor data reporting, this study was considered inadequate for NOAEL/LOAEL determination or the derivation of an intermediate-duration MRL for cyanide.

Agency Contacts (Chemical Managers): Malcolm Williams, D.V.M., Ph.D.

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Cyanide and compounds
CAS Numbers: Various
Date: October 2024
Profile Status: Draft for Public Comment
Route: Inhalation
Duration: Chronic

MRL Summary: There are insufficient data to support derivation of a chronic-duration inhalation MRL.

Rationale for Not Deriving an MRL: A chronic-duration inhalation MRL was not derived for cyanide because of the lack of suitable data in humans; no animal data were identified. The human chronic-duration inhalation database for cyanide is limited to occupational studies in workers in electroplating and metal processing jobs (Banerjee et al. 1997; Chandra et al. 1988; El Ghawabi et al. 1975; Janagam et al. 2008; Knoblauch et al. 2020; Kumar et al. 1992). Collectively, these studies have reported associations between some adverse effects and occupational exposure to cyanide, primarily neurological, respiratory, and thyroid effects with limited evidence for hematological and hepatic effects. However, the available occupational studies were not considered adequate for deriving a chronic-duration inhalation MRL for one or more of the following reasons:

- Limited or lack of information on exposure levels
- Small size of cohort
- Probable concurrent dermal exposure with liquid cyanide
- Concurrent exposure to other compounds (e.g., gasoline, hydrochloric acid, copper cyanide)

Agency Contacts (Chemical Managers): Malcolm Williams, D.V.M., Ph.D.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Cyanide and compounds
CAS Numbers: Various
Date: October 2024
Profile Status: Draft for Public Comment
Route: Oral
Duration: Acute

MRL Summary: There are insufficient data to support derivation of an acute-duration oral MRL. Human studies are limited to case reports. Most acute-duration oral studies in animals administered cyanide via oral bolus administration, which is considered less relevant to human exposure (due to saturation of detoxification pathways). Only one acute-duration drinking water study in animals was identified (de Sousa et al. 2007); however, this study was not considered suitable for MRL derivation due to study limitations precluding reliable NOAEL/LOAEL determinations.

Rationale for Not Deriving an MRL: Endpoints identified as potential sensitive effects of cyanide following oral exposure based on human and animal studies (thyroid, neurological, male reproductive effects) were considered as candidate critical effects for the acute-duration oral MRL for cyanide.

No adequate acute-duration human data were available; human studies are limited to case reports following intentional (homicide/suicide) or accidental exposure. For animal data, studies that employed bolus (e.g., gavage) dosing are omitted from MRL consideration because bolus administration may overwhelm detoxification processes in a manner not typical of gradual exposures from dietary sources or drinking water for the general population. The only acute-duration oral toxicity data for cyanide following drinking water exposure in animals are provided by a series of studies by de Sousa et al. (2007). In these studies, rat dams were exposed to 0.2–6.4 mg CN^-/kg/day as potassium thiocyanate or 0.4–12 mg CN^-/kg/day as potassium cyanide on GDs 6–20. Relevant to the candidate critical endpoints discussed above, brains and thyroid glands were evaluated for histopathological changes in dams and their offspring on GD 20 (dams only) or PND 22. As discussed in Section 2.13, thyroid effects noted in this study (increased resorption vacuoles) are of uncertain biological relevance, and are therefore not suitable as the basis for an MRL. Neurological findings following exposure to potassium thiocyanate included brain gliosis in dams on GD 20 or PND 22 at ≥0.6 mg CN^-/kg/day, CNS congestion and neuronophagia in dams on GD 20 or PND 22 at 6.4 mg CN^-/kg/day, and brain gliosis, neuronophagia, and CNS congestion in PND 22 offspring at 6.4 mg CN^-/kg/day. Neurological findings following exposure to potassium cyanide at 12 mg CN^-/kg/day included hemorrhagic areas, gliosis, necrosis, neuronophagia, and CNS congestion in dams at GD 20 and PND 22 and gliosis, neuronophagia, and CNS congestion in PND 22 pups. However, neurological findings from this study were not considered suitable for MRL derivation for the following reasons:

- Study limitations of de Sousa et al. (2007): Incidence data were not reported. Rather, lesion intensity was reported only when all animals in a dose group showed the same alteration. This method of reporting allowed identification of adverse effects; however, it did not allow for reliable NOAEL/LOAEL identification. Additionally, only a small number of animals (four per group) underwent histological evaluation.

- Acute-duration oral database limitations: Only a single acute-duration drinking water study was identified.

- Oral database inconsistencies: Findings of brain lesions were not confirmed in longer-duration studies. No histopathological brain lesions were observed in adult rats or mice following exposure to sodium cyanide in drinking water for 13 weeks at doses up to 12.5 or 28.8 mg CN^-/kg/day, respectively (NTP 1993).

Agency Contacts (Chemical Managers): Malcolm Williams, D.V.M., Ph.D.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name:	Cyanide and compounds
CAS Numbers:	Various
Date:	October 2024
Profile Status:	Draft for Public Comment
Route:	Oral
Duration:	Intermediate
Provisional MRL:	0.04 mg/kg/day
Critical Effect:	Thyroid effects (elevated thyroid weight, decreased serum T4)
Reference:	Tyner and Greeley 2023
Point of Departure:	3.96 mg CN^-/kg/day
Uncertainty Factor:	100
LSE Graph Key:	34
Species:	Rat

MRL Summary: A provisional intermediate-duration oral MRL of 0.04 mg CN^-/kg/day was derived for cyanide based on elevated absolute and relative thyroid weight and decreased serum T4 levels in rats exposed to sodium cyanide in drinking water at a LOAEL of 11.50 mg CN^-/kg/day for 13 weeks; a NOAEL of 3.96 mg CN^-/kg/day (Tyner and Greeley 2023). The MRL is based on the NOAEL of 3.96 mg CN^-/kg/day and divided by a total uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

Selection of the Critical Effect: Endpoints identified as potential sensitive effects of cyanide toxicity (thyroid, neurological, male reproductive effects) based on human and animal studies were considered as candidate critical effects for the intermediate-duration oral MRL for cyanide. No adequate intermediate-duration human data were available. For animal data, studies that employed bolus (e.g., gavage) dosing are omitted from MRL consideration because bolus administration may overwhelm detoxification processes in a manner not typical of gradual exposures from dietary sources or drinking water for the general population. In addition, oral studies in dogs are omitted from consideration. As discussed in Section 3.1.6, dogs are not considered suitable animal models from which to extrapolate the toxicity of cyanide to humans because dogs have a relatively low amount of the detoxifying enzymes (Drawbaugh and Marrs 1987; Himwich and Saunders 1948; NIH/NINDS 2016a, 2016b; Rockwood et al. 2003), making them unusually susceptible to cyanide toxicity compared to humans or other mammals. Additionally, interpretation of findings from intermediate-duration studies identified in dogs (Kamalu 1991, 1993; Kamalu and Agharanya 1991) were further confounded due to concurrent disease in study animals.

Table A-2 shows available NOAELs and LOAELs in rodents for candidate critical effects identified in intermediate-duration animal drinking water and dietary studies. The lowest LOAELs were identified in rats exposed to 300 ppm sodium cyanide in drinking water 13 weeks in studies by NTP (1993) and Tyner and Greeley (2023). Since calculated intakes in these studies were comparable (12.5 and 11.50 mg CN^-/kg/day, respectively), both endpoints were further examined as potential critical effects.

Table A-2. NOAEL and LOAEL Values for Candidate Critical Effects in Animals Following Intermediate-Duration Oral Exposure to Cyanide Compounds via Drinking Water or Diet

Species	Duration (subroute)	Effect level (mg CN^-/kg/day) NOAEL	LOAEL	Effect	Compound	Reference
Thyroid effects						
Fischer-344 rat	13 weeks (W)	12.5[a]			NaCN	NTP 1993
Fischer-344 rat	13 weeks (W)	3.96	11.50	Increased absolute (35%) and relative (40%) thyroid weights; decreased serum T4 (14%)	NaCN	Tyner and Greeley 2023
B6C3F1 mouse	13 weeks (W)	28.8[a]			NaCN	NTP 1993
Rat (NS)	11.5 months (F)	ND	47	Decreased plasma T4 at 4 months (55%) and 11 months (26%); decreased T4 secretion rate at 4 months (63%)	KSCN	Philbrick et al. 1979
Rat (NS)	11.5 months (F)	ND	53	Decreased plasma T4 at 4 months (52%); decreased T4 secretion rate at 4 months (68%) and 11 months (27%)	KCN	Philbrick et al. 1979
Neurological effects						
Fischer-344 rat	13 weeks (W)	12.5			NaCN	NTP 1993
B6C3F1 mouse	13 weeks (W)	28.8			NaCN	NTP 1993
Rat (NS)	11.5 months (F)	ND	47	Modest myelin degeneration in spinal cord	KSCN	Philbrick et al. 1979
Rat (NS)	11.5 months (F)	ND	53	Modest myelin degeneration in spinal cord	KCN	Philbrick et al. 1979
Male reproductive effects						
Fischer-344 rat	13 weeks (W)	4.5	12.5	Decreased absolute left epididymal (7%), cauda epididymal (13%), and testes weights (8%); decreased number of spermatid heads per testis (14%) and total spermatid count (14%)	NaCN	NTP 1993
Fischer-344 rat	13 weeks (W)	11.50			NaCN	Tyner and Greeley 2023

Table A-2. NOAEL and LOAEL Values for Candidate Critical Effects in Animals Following Intermediate-Duration Oral Exposure to Cyanide Compounds via Drinking Water or Diet

Species	Duration (subroute)	Effect level (mg CN^-/kg/day) NOAEL	LOAEL	Effect	Compound	Reference
B6C3F1 mouse	13 weeks (W)	8.6	24.3	Decreased weight of left epididymis (10%) and cauda epididymis (18%)	NaCN	NTP 1993

[a]Thyroid NOAEL based on lack of histopathological changes; thyroid weight and serum thyroid hormone levels were not assessed by NTP (1993).

Selected study for the intermediate-duration inhalation MRL derivation.

CN^- = cyanide; (F) = feed; KCN = potassium cyanide; KSCN = potassium thiocyanide; LOAEL = lowest-observed-adverse-effect level; NaCN = sodium cyanide; ND = not determined; NOAEL = no-observed-adverse-effect level; NS = not specified; T4 = thyroxine; (W) = drinking water

In the NTP (1993) study, the adverse effect identified at 12.5 mg CN^-/kg/day was male reproductive effects in rats. Reported effects include decreased absolute weight of the left (but not right) testes, along with decreased absolute weight of the left epididymis and cauda epididymis; decreased number of spermatid heads per testis (but not spermatid heads per gram testis); and decreased total spermatid count. However, these findings were not reproduced in the repeat study by Tyner and Greeley (2023) at calculated intakes up to 11.50 mg CN^-/kg/day. Tyner and Greeley (2023) proposed that male reproductive effects noted in the NTP (1993) study may have been attributable to decreased water consumption in the highest dose group rather than due to direct toxic effects. To control for this, Tyner and Greeley (2023) included a water-restricted control group to match measured water consumption at the highest dose level. While a nonsignificant trend toward lower sperm motility was observed in rats exposed to 11.50 mg CN^-/kg/day compared to standard controls, this trend was not apparent when compared to the water-restricted control. Similarly, findings of decreased sperm concentration were non-dose-related and not significant compared to the water-restricted control. No adverse changes in male reproductive organ weights were observed compared to either the water-restricted or the *ad libitum* control groups. However, it is noted that decreased water intake at the highest concentration (300 ppm) was greater in the study by NTP (1993; 18%) than the study by Tyner and Greeley (2023; 11%). Therefore, it is still unclear if the greater decrease in water intake observed in the NTP study confounded the observed male reproductive findings. Based on concerns raised by the Tyner and Greeley (2023) study, there are too many uncertainties surrounding the findings from the NTP (1993) study to use these findings to support selection of male reproductive effects as the critical effect.

In the Tyner and Greeley (2023) study, the adverse effect identified in rats at 11.50 mg CN^-/kg/day was increased absolute and relative thyroid weights and reduced serum T4. These findings are statistically significant compared to both standard and water-restricted controls. While no changes in thyroid histology were observed at doses up to 12.5 mg CN^-/kg/day in the NTP (1993) study, thyroid weights and serum thyroid hormone levels were not assessed. Since thyroid effects have been reported in dietary studies in rats at higher doses (Philbrick et al. 1979), as well as human populations with high dietary cassava intake (Cliff et al. 1986; Delange and Ermans 1971), adverse effects on the thyroid are selected as the critical effects for intermediate-duration oral exposure to cyanide.

Systematic review conclusions support selection of thyroid effects over male reproductive effects as the critical effect, as there is stronger evidence for thyroid effects compared to male reproductive effects following oral exposure (see Appendix C). Thyroid effects following oral exposure are presumed health effects based on low evidence in humans, moderate evidence in animals, and supporting mechanistic data, while male reproductive effects are suspected health effects based on no human data and moderate evidence in animals. Furthermore, the NOAEL of 3.96 mg CN^-/kg/day associated with the lowest LOAEL for thyroid effects is comparable to the NOAEL of 4.5 mg CN^-/kg/day associated with the lowest LOAEL for male reproductive effects. Thus, selection of thyroid effects as the critical effect should be protective of potential male reproductive effects.

Selection of the Principal Study: Tyner and Greeley (2023) was selected as the principal study because it provided the lowest candidate point of departure (POD) (3.96 ppm) for the critical effect (thyroid effects).

Summary of the Principal Study:

Tyner MC, Greeley MA. (2023). A new 90-day drinking water study of sodium cyanide in rats to further evaluate National Toxicology Program findings and inform risk assessment. Birth Defects Res 115(7):722-752. https://doi.org/10.1002/bdr2.2163.

Groups of 20 male Fischer-344 rats were administered sodium cyanide at doses of 0, 3, 10, 30, 100, or 300 ppm in drinking water for 13 weeks. The study authors calculated daily intake levels of 0, 0.23, 0.81, 2.41, 7.46, or 21.66 mg NaCN/kg/day, respectively. Doses in cyanide were calculated to be 0, 0.12, 0.43, 1.28, 3.96, and 11.50 mg CN^-/kg/day, respectively. Additional details on dose conversions can be found in Table A-3.

Table A-3. Dose Conversions for Tyner and Greely (2023)

Dose (ppm)	Dose (mg NaCN/kg/day)[a]	Dose (mg CN^-/kg/day)[b]
3	0.23	0.12
10	0.81	0.43
30	2.41	1.28
100	7.46	3.96
300	21.66	11.50

[a]Reported by the study authors. Due to ambiguity in dose reporting (reported as doses in terms of the anion in text but as administered compound in Table 1 of the study report), the study authors were contacted for clarification. It was confirmed via personal communication (Tyner 2024) that the reported doses were in terms of the administered compound (NaCN).
[b]Calculated based on the ratio of molecular weights for sodium cyanide (49.01 g/mol) and cyanide (26.02 g/mol). Conversions were calculated as follows: dose in mg NaCN × (26.02/49.01) = dose in CN^-.

CN = cyanide; NaCN = sodium cyanide

An additional control group was included, and water consumption was restricted based on levels consumed at the high-dose group. Animals were observed twice daily for clinical signs. Body weights and food consumption were monitored weekly and water consumption was recorded twice weekly. Ophthalmological examinations occurred prior to dosing and after the dosing and recovery periods. Urinalysis and blood collection for hematology and clinical chemistry were done after dosing and recovery periods. Blood was also collected for thyroid hormone analysis (TSH, T3, and T4) on days 28, 56, 90, 118, and 160. Prior to sacrifice, animals were fasted and placed in metabolic cages. Ten animals

were sacrificed following the final dose and 10 animals were sacrificed following a 10-week untreated recovery period. Following sacrifice, a necropsy was performed including all external surfaces of the brain and thoracic, abdominal, and pelvic cavities and organs. Weights of organs were recorded (adrenal glands, epididymides [total and cauda], heart, kidneys, liver, pituitary, prostate with seminal vesicles and coagulating glands, spleen, testes, thymus, and thyroid with parathyroids [weighed after fixation]). Tissues were fixed for histopathology (testes, epididymides, prostate gland, seminal vesicles, eyes with optic nerve, brain, pituitary, parathyroid, thyroid, any macroscopic lesion). Sperm parameters were measured and graded in a semi-quantitative manner (according to Stump et al. 2008 and 2014).

No dose-related mortality occurred. One death in the water-restricted control group showed no effects on necropsy. No clinical signs or effects on body weights or food consumption were observed. Water consumption was decreased in the 100 and 300 ppm groups by 11% compared to the *ad libitum* control but by the end of recovery, water consumption was comparable across all groups. No effects were noted in ophthalmology, hematology, serum chemistry, or urinalysis. Serum T4 was significantly decreased at 300 ppm after 90 days compared to both *ad libitum* control (14%) and water-restricted control (13%); these effects were no longer evident after a 28-day recovery period. Other thyroid hormones did not differ from control at the end of the exposure period; however, serum TSH was significantly decreased at 300 ppm at the end of the 28-day recovery period (compared to water-restricted controls only). The biological significance of this finding is unclear, particularly because serum TSH was significantly higher in water-restricted controls compared to *ad libitum* controls and because similar findings were not observed during the exposure period. Dose-related increases in absolute and relative thyroid (with parathyroid) weights were observed at ≥30 ppm, with elevations reaching statistical significance compared to both *ad libitum* and water-restricted controls at 300 ppm (35–40%). Organ weights were comparable to controls following the recovery period. There were no other treatment-related effects in measured organ weights. There were no treatment-related histological findings in the thyroid, liver, or male reproductive organs; findings in other organs (including the brain) were not specifically discussed. No statistically significant, exposure-related changes were observed in sperm concentration, production, or motility were observed.

Selection of the Point of Departure for the MRL: The NOAEL of 3.96 mg CN^-/kg/day for increased absolute and relative thyroid weight and decreased serum T4 in rats reported by Tyner and Greeley (2023) was selected as the POD for the intermediate-duration oral MRL.

In order to identify the most sensitive POD, benchmark dose (BMD) modeling was attempted for all thyroid endpoints reported by Tyner and Greeley (2023) when data were amenable to modeling. The data were fit to all available continuous models in EPA's Benchmark Dose Software (BMDS; version 3.3) using a benchmark response (BMR) of 1 standard deviation (SD). Adequate model fit was judged by four criteria: goodness-of-fit statistics (p-value >0.1), visual inspection of the dose-response curve, a 95% lower confidence limit on the BMD (BMCL) that is not 10 times lower than the lowest non-zero dose, and scaled residual within ±2 units at the data point (except the control) closest to the predefined BMR. Among all of the models providing adequate fit to the data, the lowest BMCL was selected as the POD when the difference between the BMCLs estimated from these models was >3-fold; otherwise, the BMCL from the model with the lowest Akaike information criterion (AIC) was chosen.

The datasets used for BMD modeling are presented in Table A-4 (absolute thyroid weight, serum T4 levels); relative thyroid weight data were reported without variance data and were therefore not amenable for modeling. For absolute thyroid weight and serum T4 levels, inclusion of two control groups by Tyner and Greeley (2023) presented a challenge for modeling, as the *ad libitum* control was the appropriate control for the first three doses while the water-restricted control was the appropriate control for the two highest doses. To evaluate both options, models were run using two datasets for each endpoint, one with

all exposure groups and the *ad libitum* control and one with all exposure groups and the water-restricted control.

Table A-4. Thyroid Endpoints in Male Rats Following Drinking Water Exposure to Sodium Cyanide for 13 Weeks

	Dose (CN^-/kg/day)						
Endpoint[a]	0 (ad lib)	0 (restrict)	0.12	0.43	1.28	3.96	11.50
Absolute thyroid weights (g)	0.0104± 0.0015 (10)	0.0105± 0.0012 (9)	0.0096± 0.0018 (10)	0.0106± 0.0019 (10)	0.0122± 0.0024 (10)	0.0122± 0.0032 (10)	0.0140± 0.0029[b] (10)
Serum T4 (pg/mL)	51,120± 4,313.8 (10)	50,530± 7,154.8 (9)	45,870± 8,903.4 (10)	47,450± 4,468.7 (10)	47,300± 8,065.2 (10)	48,340± 3,022.2 (10)	44,200± 3919.5[b] (10)

[a]Mean±SD (number of animals).
[b]p<0.05.

ad lib = *ad libitum*; restrict = water-restricted; SD = standard deviation

Source: Tyner and Greeley (2023)

No adequate model fits were achieved for serum T4 data using either constant or nonconstant variance with either control group. While model fits were achieved using constant variance for absolute thyroid weight using either the *ad libitum* or water-restricted control data, the model control response SD values were >1.5-fold different than the actual response SD, lending considerable uncertainty to the standard BMR (1 SD). The large SDs of the data result in model estimates having large SDs. Consequently, this leads to increased uncertainty in BMD estimates. The BMDL is described as the lower confidence interval of the BMD. With large SDs in BMD estimates, in some extreme cases, the BMDL estimates could be much lower than the NOAEL, which is questionable. Using nonconstant variance, a limited number of models provided statistical fits to the data for the *ad libitum* control (Exponential 5 model) and the water-restricted control (Exponential 5, Hill). While modeled SD values did not differ as widely as seen with the constant variance model, the BMDL estimates (0.74 mg CN^-/kg/day for *ad libitum* control; 0.79 CN^-/kg/day for water-restricted control) were markedly lower than the empirical NOAEL of 3.96 CN^-/kg/day (as well as the dose below the NOAEL, 1.28 CN^-/kg/day). Therefore, the nonconstant model results were also considered questionable for this dataset. BMD model outputs for *ad libitum* and water-restricted controls are shown in Tables A-5 and A-6, respectively.

Table A-5. Model Predictions for Absolute Thyroid Weight in Male Rats Exposed to Sodium Cyanide for 13 Weeks: *Ad Libitum* Control (Tyner and Greeley 2023)

	BMD_{1SD}[a] (mg CN^-/kg/day)	$BMDL_{1SD}$[a] (mg CN^-/kg/day)			Scaled residuals	
Model			Test 4 p-value[b]	AIC	Dose near BMD	Control dose group
Constant variance						
Exponential 3[c,d]			–	–	–	–
Exponential 5[c]	3.07	1.89	0.37	-550.65	-0.82	0.36
Hill[c]			0.01	-541.96	0.00	-0.78
Polynomial Degree 2[c]	7.36	5.21	0.27	-550.56	0.48	-0.25

Table A-5. Model Predictions for Absolute Thyroid Weight in Male Rats Exposed to Sodium Cyanide for 13 Weeks: *Ad Libitum* Control (Tyner and Greeley 2023)

Model	BMD_{1SD}[a] (mg CN^-/kg/day)	$BMDL_{1SD}$[a] (mg CN^-/kg/day)	Test 4 p-value[b]	AIC	Scaled residuals: Dose near BMD	Scaled residuals: Control dose group
Polynomial Degree 3[c]	7.36	5.21	0.27	-550.56	0.48	-0.25
Power[c]	7.36	5.21	0.27	-550.56	0.48	-0.25
Linear	7.36	5.19	0.27	-550.56	0.48	-0.25
Nonconstant variance						
Exponential 3[c,d]			0.06	-550.87	0.56	-0.27
Exponential 5[c]	1.02	0.75	0.43	-554.35	0.15	0.74
Hill[c]			0.06	-550.70	0.18	-0.06
Polynomial Degree 2[c]			0.08	-551.61	0.40	-0.17
Polynomial Degree 3[c]			0.08	-551.61	0.40	-0.17
Power[c]			0.08	-551.61	0.40	-0.17
Linear			0.08	-551.61	0.40	-0.17

[a]BMD and BMDL values for models that do not provide adequate fit are not included in this table.
[b]Values <0.1 fail to meet adequate fit.
[c]Restricted model.
[d]BMD computation failed.

AIC = Akaike Information Criterion; BMD = maximum likelihood estimate of the exposure dose associated with the selected benchmark response; BMDL = 95% lower confidence limit on the BMD (subscripts denote benchmark response: i.e., $_{1SD}$ = exposure dose associated with a 1 standard deviation change from the control)

Table A-6. Model Predictions for Absolute Thyroid Weight in Male Rats Exposed to Sodium Cyanide for 13 Weeks: Water-Restricted Control (Tyner and Greeley 2023)

Model	BMD_{1SD}[a] (mg CN^-/kg/day)	$BMDL_{1SD}$[a] (mg CN^-/kg/day)	Test 4 p-value[b]	AIC	Scaled residuals: Dose near BMD	Scaled residuals: Control dose group
Constant variance						
Exponential 3[c,d]			–	–	–	–
Exponential 5[c]	1.37	1.00	0.14	-539.15	-0.03	0.58
Hill[c]	6.77	4.64	0.19	-540.37	0.31	-0.07
Polynomial Degree 2[c]	7.40	5.22	0.27	-541.93	0.46	-0.14
Polynomial Degree 3[c]	7.39	5.22	0.27	-541.93	0.46	-0.14
Power[c]	7.39	5.22	0.27	-541.93	0.46	-0.14
Linear	7.39	5.21	0.27	-541.93	0.46	-0.14

Table A-6. Model Predictions for Absolute Thyroid Weight in Male Rats Exposed to Sodium Cyanide for 13 Weeks: Water-Restricted Control (Tyner and Greeley 2023)

Model	BMD_{1SD}[a] (mg CN^-/kg/day)	$BMDL_{1SD}$[a] (mg CN^-/kg/day)	Test 4 p-value[b]	AIC	Scaled residuals: Dose near BMD	Scaled residuals: Control dose group
Nonconstant variance						
Exponential 3[c,d]			0.05	-542.50	0.54	-0.15
Exponential 5[c]	0.96	0.71	0.47	-546.56	0.14	0.92
Hill[c]	0.94	0.79	0.56	-546.89	0.28	0.96
Polynomial Degree 2[c]			0.07	-543.25	0.38	-0.05
Polynomial Degree 3[c]			0.07	-543.25	0.38	-0.05
Power[c]			0.07	-543.25	0.38	-0.05
Linear			0.07	-543.25	0.38	-0.05

[a]BMD and BMDL values for models that do not provide adequate fit are not included in this table.
[b]Values <0.1 fail to meet adequate fit.
[c]Restricted model.
[d]BMD computation failed.

AIC = Akaike Information Criterion; BMD = maximum likelihood estimate of the exposure dose associated with the selected benchmark response; BMDL = 95% lower confidence limit on the BMD (subscripts denote benchmark response: i.e., $_{1SD}$ = exposure dose associated with a 1 standard deviation change from the control)

Alternative datasets were also attempted where the water-restricted control data were modeled with only the two highest doses (groups in which animals demonstrated decreased water intake). For these datasets, no models adequately fit the serum T4 data or absolute thyroid weights assuming constant or nonconstant variance, confirming the difficulty of the control group variability.

Due to model uncertainties discussed above and challenges regarding which control group was the most appropriate to use for BMD modeling, the NOAEL of 3.96 mg CN^-/kg/day was selected as the POD.

Calculations: None. Available PBPK models (Stamyr et al. 2015; Tran et al. 2020a, 2020b) are specific to human external-to-internal dose extrapolation. These models are not suitable for oral dose extrapolation between species.

Uncertainty Factors: The following uncertainty factors were applied to the NOAEL to derive the MRL:

- Uncertainty factor of 10 for extrapolation from animals to humans
- Uncertainty factor of 10 for human variability

Subsequently, the provisional oral MRL for intermediate-duration exposure to cyanide is:

$$Provisional\ MRL = \frac{NOAEL}{(UF)} = \frac{3.96\ mg\ CN^-/kg/day}{10 \times 10}$$

$$= 0.00396\ mg\ CN^-/kg/day \approx 0.04\ mg\ CN^-/kg/day$$

Other Additional Studies or Pertinent Information that Lend Support to this MRL: Systematic review concluded that thyroid effects are a presumed health effect following exposure to cyanide based on a low level of evidence in humans, a moderate level of evidence in animals, and supporting mechanistic data (see Appendix C).

Thyroid effects following cyanide exposure can result from the interference of thiocyanate, a metabolite of cyanide, with iodine uptake and utilization in the thyroid gland (VanderLaan and Bissell 1946). Thiocyanate competes with iodine to bind the sodium-iodine symporter and has a higher binding affinity than the endogenous ligand (De Groef et al. 2006; EPA 2010; Tonacchera et al. 2004). Reduced serum thyroid hormone levels, increasingly elevated levels of TSH, and goiter are typical sequelae of chronic-duration cyanide exposure observed in tropical populations reliant on cassava as the main staple of the diet (Cliff et al. 1986; Delange and Ermans 1971; Ermans et al. 1980). While inhalation data are limited and do not provide reliable dose-response data, occupational studies provide additional support for the potential association between cyanide exposure and thyroid effects. Enlargement of the thyroid gland, altered iodine uptake, decreased thyroid hormone levels, and/or increased TSH were observed in workers occupationally exposed to cyanide at electroplating or silver-reclaiming factories (Banerjee et al. 1997; Blanc et al. 1985; El Ghawabi et al. 1975).

Agency Contact (Chemical Manager): Malcolm Williams, D.V.M., Ph.D.

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Cyanide and compounds
CAS Numbers: Various
Date: October 2024
Profile Status: Draft for Public Comment
Route: Oral
Duration: Chronic

MRL Summary: There are insufficient data to support derivation of a chronic-duration oral MRL.

Rationale for Not Deriving an MRL: A chronic-duration oral MRL was not derived for cyanide because of the lack of suitable data in humans and animals.

Available human data are limited to populations that have high intake of cassava root; however, studies of these populations are not appropriate for MRL derivations because findings are confounded by co-exposure to other compounds (e.g., scopoletin) as well as concurrent nutritional deficiencies (Makene and Wilson 1972; Obidoa and Obasi 1991; Osuntokun 1972; Osuntokun et al. 1969). Additionally, external exposure estimates are not available, and biomarker exposure was often available only at (or after) diagnosis with thyroid or neurological abnormalities.

Two inadequate chronic-duration oral studies in animal studies were identified. One 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 CN^-/kg/day for males or 10.4 mg CN^-/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. The other is a foreign-language study in dogs that only used one dog per dose and lacked a concurrent control (Hertting et al. 1960).

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APPENDIX B. LITERATURE SEARCH FRAMEWORK FOR CYANIDE

The objective of the toxicological profile is to evaluate the potential for human exposure and the potential health hazards associated with inhalation, oral, or dermal/ocular exposure to cyanide.

B.1 LITERATURE SEARCH AND SCREEN

A literature search and screen were conducted to identify studies examining health effects, toxicokinetics, mechanisms of action, susceptible populations, biomarkers, chemical interactions, physical and chemical properties, production, use, environmental fate, environmental releases, and environmental and biological monitoring data for cyanide. ATSDR primarily focused on peer-reviewed articles without publication date or language restrictions. Foreign language studies are reviewed based on available English-language abstracts and/or tables (or summaries in regulatory assessments, such as International Agency for Research on Cancer [IARC] documents). If the study appears critical for hazard identification or MRL derivation, translation into English is requested. Non-peer-reviewed studies that were considered relevant to the assessment of the health effects of cyanide have undergone peer review by at least three ATSDR-selected experts who have been screened for conflict of interest. The inclusion criteria used to identify relevant studies examining the health effects of cyanide are presented in Table B-1.

Table B-1. Inclusion Criteria for the Literature Search and Screen[a]

Health Effects
Species
Human
Laboratory mammals
Route of exposure
Inhalation
Oral
Dermal (or ocular)
Parenteral (these studies will be considered supporting data)
In vitro (these studies will be considered supporting data)
Health outcome
Death
Systemic effects
Body weight effects
Respiratory effects
Cardiovascular effects
Gastrointestinal effects
Hematological effects
Musculoskeletal effects
Hepatic effects
Renal effects
Dermal effects
Ocular effects
Endocrine effects
Immunological effects
Neurological effects

Table B-1. Inclusion Criteria for the Literature Search and Screen[a]

Reproductive effects
Developmental effects
Other noncancer effects
Cancer
Toxicokinetics
Absorption
Distribution
Metabolism
Excretion
PBPK models
Biomarkers
Biomarkers of exposure
Biomarkers of effect
Interactions with other chemicals
Potential for human exposure
Releases to the environment
Air
Water
Soil
Environmental fate
Transport and partitioning
Transformation and degradation
Environmental monitoring
Air
Water
Sediment and soil
Other media
Biomonitoring
General populations
Occupation populations

[a]Physical-chemical properties are not generally obtained from literature searches, but rather from curated governmental databases such as PubChem.

B.1.1 Literature Search

The current literature search was intended to update the Toxicological Profile for Cyanide released in 2006. All literature cited in the previous (2006) toxicological profile was considered for inclusion in the updated profile; thus, the literature search was restricted to studies published between January 2004 and August 2023. The following main databases were searched in July and August 2023:

- PubMed
- National Technical Reports Library (NTRL)
- Scientific and Technical Information Network's TOXCENTER

The search strategy used the chemical names, Chemical Abstracts Service (CAS) numbers, synonyms, Medical Subject Headings (MeSH) headings, and keywords for cyanide. The query strings used for the literature search are presented in Table B-2.

The search was augmented by searching the Toxic Substances Control Act Test Submissions (TSCATS), NTP website, and National Institute of Health Research Portfolio Online Reporting Tools Expenditures and Results (NIH RePORTER) databases using the queries presented in Table B-3. Additional databases were searched in the creation of various tables and figures, such as the TRI Explorer, the Substance Priority List (SPL) resource page, and other items as needed. Regulations applicable to cyanide were identified by searching international and U.S. agency websites and documents.

Review articles were identified and used for the purpose of providing background information and identifying additional references. ATSDR also identified reports from the grey literature, which included unpublished research reports, technical reports from government agencies, conference proceedings and abstracts, and theses and dissertations.

Table B-2. Database Query Strings

Database search date	Query string
PubMed	
08/2023	(("Hydrogen Cyanide"[mh:noexp] AND ("Hydrogen Cyanide/toxicity"[mh] OR "Hydrogen Cyanide/adverse effects"[mh] OR "Hydrogen Cyanide/poisoning"[mh] OR "Hydrogen Cyanide/pharmacokinetics"[mh] OR "Hydrogen Cyanide/blood"[mh] OR "Hydrogen Cyanide/cerebrospinal fluid"[mh] OR "Hydrogen Cyanide/urine"[mh] OR "Hydrogen Cyanide/antagonists and inhibitors"[mh] OR ("Hydrogen Cyanide/metabolism"[mh] AND ("humans"[mh] OR "animals"[mh])) OR "Hydrogen Cyanide/pharmacology"[majr] OR ("Hydrogen Cyanide"[mh] AND ("environmental exposure"[mh] OR "chemically induced"[sh] OR toxicokinetics[mh:noexp] OR "endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh] OR "computational biology"[mh] OR "medical informatics"[mh] OR genomics[mh] OR genome[mh] OR proteomics[mh] OR proteome[mh] OR metabolomics[mh] OR metabolome[mh] OR genes[mh] OR "gene expression"[mh] OR phenotype[mh] OR genetics[mh] OR genotype[mh] OR transcriptome[mh] OR ("systems biology"[mh] AND ("environmental exposure"[mh] OR "epidemiological monitoring"[mh] OR analysis[sh])) OR "transcription, genetic "[mh] OR "reverse transcription"[mh] OR "transcriptional activation"[mh] OR "transcription factors"[mh] OR ("biosynthesis"[sh] AND (RNA[mh] OR DNA[mh])) OR "RNA, messenger"[mh] OR "RNA, transfer"[mh] OR "peptide biosynthesis"[mh] OR "protein biosynthesis"[mh] OR "reverse transcriptase polymerase chain reaction"[mh] OR "base sequence"[mh] OR "trans-activators"[mh] OR "gene expression profiling"[mh])) OR ("Hydrogen Cyanide"[mh] AND ((indexingmethod_automated OR indexingmethod_curated) AND ("RNA"[mh] OR "DNA"[mh] OR "DNA Replication"[mh] OR "Salmonella typhimurium"[mh] OR antagonist*[tw] OR inhibitor*[tw] OR "blood"[tw] OR "serum"[tw] OR "plasma"[tw] OR pharmacokinetic*[tw] OR toxicokinetic*[tw] OR "pbpk"[tw] OR "poisoned"[tw] OR "poisoning"[tw] OR "urine"[tw] OR "urinary"[tw] OR "toxicity"[sh] OR "occupational diseases"[mh] OR "hazardous substances"[mh] OR "epidemiology"[sh] OR "epidemiologic studies"[mh]))) OR ("Hydrogen Cyanide"[mh] AND (("Neoplasms"[mh] OR

Table B-2. Database Query Strings

Database search date	Query string
	"Carcinogens"[mh] OR "Lymphoproliferative disorders"[mh] OR "Myeloproliferative disorders"[mh] OR "Toxicity Tests"[mh] OR ((cancer*[tiab] OR carcinogen*[tiab]) AND (risk*[tiab] OR health[tiab]) AND assessment*[tiab]) OR "Mutagens"[mh] OR "Mutagenicity Tests"[mh] OR "Chromosome Aberrations"[mh] OR "DNA Damage"[mh] OR "DNA Repair"[mh] OR "DNA Replication/drug effects"[mh] OR "DNA/drug effects"[mh] OR "DNA/metabolism"[mh] OR "Genomic Instability"[mh] OR "Salmonella typhimurium/drug effects"[mh] OR "Salmonella typhimurium/genetics"[mh] OR "Sister Chromatid Exchange"[mh] OR strand-break*[tiab])))))) OR ("Cyanides"[mh:noexp] AND ("Cyanides/toxicity"[mh] OR "Cyanides/adverse effects"[mh] OR "Cyanides/poisoning"[mh] OR "Cyanides/pharmacokinetics"[mh] OR "Cyanides/blood"[mh] OR "Cyanides/cerebrospinal fluid"[mh] OR "Cyanides/urine"[mh] OR "Cyanides/antagonists and inhibitors"[mh] OR ("Cyanides/metabolism"[mh] AND ("humans"[mh] OR "animals"[mh])) OR "Cyanides/pharmacology"[majr] OR ("Cyanides"[mh] AND ("environmental exposure"[mh] OR "chemically induced"[sh] OR toxicokinetics[mh:noexp] OR "endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh] OR "computational biology"[mh] OR "medical informatics"[mh] OR genomics[mh] OR genome[mh] OR proteomics[mh] OR proteome[mh] OR metabolomics[mh] OR metabolome[mh] OR genes[mh] OR "gene expression"[mh] OR phenotype[mh] OR genetics[mh] OR genotype[mh] OR transcriptome[mh] OR ("systems biology"[mh] AND ("environmental exposure"[mh] OR "epidemiological monitoring"[mh] OR analysis[sh])) OR "transcription, genetic "[mh] OR "reverse transcription"[mh] OR "transcriptional activation"[mh] OR "transcription factors"[mh] OR ("biosynthesis"[sh] AND (RNA[mh] OR DNA[mh])) OR "RNA, messenger"[mh] OR "RNA, transfer"[mh] OR "peptide biosynthesis"[mh] OR "protein biosynthesis"[mh] OR "reverse transcriptase polymerase chain reaction"[mh] OR "base sequence"[mh] OR "trans-activators"[mh] OR "gene expression profiling"[mh])) OR ("Cyanides"[mh] AND ((indexingmethod_automated OR indexingmethod_curated) AND ("RNA"[mh] OR "DNA"[mh] OR "DNA Replication"[mh] OR "Salmonella typhimurium"[mh] OR antagonist*[tw] OR inhibitor*[tw] OR "blood"[tw] OR "serum"[tw] OR "plasma"[tw] OR pharmacokinetic*[tw] OR toxicokinetic*[tw] OR "pbpk"[tw] OR "poisoned"[tw] OR "poisoning"[tw] OR "urine"[tw] OR "urinary"[tw] OR "toxicity"[sh] OR "occupational diseases"[mh] OR "hazardous substances"[mh] OR "epidemiology"[sh] OR "epidemiologic studies"[mh])))) OR ("Cyanides"[mh] AND (("Neoplasms"[mh] OR "Carcinogens"[mh] OR "Lymphoproliferative disorders"[mh] OR "Myeloproliferative disorders"[mh] OR "Toxicity Tests"[mh] OR ((cancer*[tiab] OR carcinogen*[tiab]) AND (risk*[tiab] OR health[tiab]) AND assessment*[tiab]) OR "Mutagens"[mh] OR "Mutagenicity Tests"[mh] OR "Chromosome Aberrations"[mh] OR "DNA Damage"[mh] OR "DNA Repair"[mh] OR "DNA Replication/drug effects"[mh] OR "DNA/drug effects"[mh] OR "DNA/metabolism"[mh] OR "Genomic Instability"[mh] OR "Salmonella typhimurium/drug effects"[mh] OR "Salmonella typhimurium/genetics"[mh] OR "Sister Chromatid Exchange"[mh] OR strand-break*[tiab])))))) OR ("Sodium Cyanide/toxicity"[mh] OR "Sodium Cyanide/adverse effects"[mh] OR "Sodium Cyanide/poisoning"[mh] OR "Sodium Cyanide/pharmacokinetics"[mh] OR "Sodium Cyanide/blood"[mh] OR "Sodium Cyanide/cerebrospinal fluid"[mh] OR "Sodium Cyanide/urine"[mh] OR "Sodium Cyanide/antagonists and inhibitors"[mh] OR ("Sodium Cyanide/metabolism"[mh] AND ("humans"[mh] OR "animals"[mh])) OR "Sodium Cyanide/pharmacology"[majr] OR ("Sodium Cyanide"[mh] AND ("environmental exposure"[mh] OR "chemically induced"[sh] OR toxicokinetics[mh:noexp] OR "endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh] OR "computational biology"[mh] OR "medical informatics"[mh] OR genomics[mh] OR

Table B-2. Database Query Strings

Database search date	Query string
	genome[mh] OR proteomics[mh] OR proteome[mh] OR metabolomics[mh] OR metabolome[mh] OR genes[mh] OR "gene expression"[mh] OR phenotype[mh] OR genetics[mh] OR genotype[mh] OR transcriptome[mh] OR ("systems biology"[mh] AND ("environmental exposure"[mh] OR "epidemiological monitoring"[mh] OR analysis[sh])) OR "transcription, genetic "[mh] OR "reverse transcription"[mh] OR "transcriptional activation"[mh] OR "transcription factors"[mh] OR ("biosynthesis"[sh] AND (RNA[mh] OR DNA[mh])) OR "RNA, messenger"[mh] OR "RNA, transfer"[mh] OR "peptide biosynthesis"[mh] OR "protein biosynthesis"[mh] OR "reverse transcriptase polymerase chain reaction"[mh] OR "base sequence"[mh] OR "trans-activators"[mh] OR "gene expression profiling"[mh])) OR ("Sodium Cyanide"[mh] AND ((indexingmethod_automated OR indexingmethod_curated) AND ("RNA"[mh] OR "DNA"[mh] OR "DNA Replication"[mh] OR "Salmonella typhimurium"[mh] OR antagonist*[tw] OR inhibitor*[tw] OR "blood"[tw] OR "serum"[tw] OR "plasma"[tw] OR pharmacokinetic*[tw] OR toxicokinetic*[tw] OR "pbpk"[tw] OR "poisoned"[tw] OR "poisoning"[tw] OR "urine"[tw] OR "urinary"[tw] OR "toxicity"[sh] OR "occupational diseases"[mh] OR "hazardous substances"[mh] OR "epidemiology"[sh] OR "epidemiologic studies"[mh]))) OR ("Sodium Cyanide"[mh] AND (("Neoplasms"[mh] OR "Carcinogens"[mh] OR "Lymphoproliferative disorders"[mh] OR "Myeloproliferative disorders"[mh] OR "Toxicity Tests"[mh] OR ((cancer*[tiab] OR carcinogen*[tiab]) AND (risk*[tiab] OR health[tiab]) AND assessment*[tiab]) OR "Mutagens"[mh] OR "Mutagenicity Tests"[mh] OR "Chromosome Aberrations"[mh] OR "DNA Damage"[mh] OR "DNA Repair"[mh] OR "DNA Replication/drug effects"[mh] OR "DNA/drug effects"[mh] OR "DNA/metabolism"[mh] OR "Genomic Instability"[mh] OR "Salmonella typhimurium/drug effects"[mh] OR "Salmonella typhimurium/genetics"[mh] OR "Sister Chromatid Exchange"[mh] OR strand-break*[tiab]))))) OR ("Potassium Cyanide/toxicity"[mh] OR "Potassium Cyanide/adverse effects"[mh] OR "Potassium Cyanide/poisoning"[mh] OR "Potassium Cyanide/pharmacokinetics"[mh] OR "Potassium Cyanide/blood"[mh] OR "Potassium Cyanide/cerebrospinal fluid"[mh] OR "Potassium Cyanide/urine"[mh] OR "Potassium Cyanide/antagonists and inhibitors"[mh] OR ("Potassium Cyanide/metabolism"[mh] AND ("humans"[mh] OR "animals"[mh])) OR "Potassium Cyanide/pharmacology"[majr] OR ("Potassium Cyanide"[mh] AND ("environmental exposure"[mh] OR "chemically induced"[sh] OR toxicokinetics[mh:noexp] OR "endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh] OR "computational biology"[mh] OR "medical informatics"[mh] OR genomics[mh] OR genome[mh] OR proteomics[mh] OR proteome[mh] OR metabolomics[mh] OR metabolome[mh] OR genes[mh] OR "gene expression"[mh] OR phenotype[mh] OR genetics[mh] OR genotype[mh] OR transcriptome[mh] OR ("systems biology"[mh] AND ("environmental exposure"[mh] OR "epidemiological monitoring"[mh] OR analysis[sh])) OR "transcription, genetic "[mh] OR "reverse transcription"[mh] OR "transcriptional activation"[mh] OR "transcription factors"[mh] OR ("biosynthesis"[sh] AND (RNA[mh] OR DNA[mh])) OR "RNA, messenger"[mh] OR "RNA, transfer"[mh] OR "peptide biosynthesis"[mh] OR "protein biosynthesis"[mh] OR "reverse transcriptase polymerase chain reaction"[mh] OR "base sequence"[mh] OR "trans-activators"[mh] OR "gene expression profiling"[mh])) OR ("Potassium Cyanide"[mh] AND ((indexingmethod_automated OR indexingmethod_curated) AND ("RNA"[mh] OR "DNA"[mh] OR "DNA Replication"[mh] OR "Salmonella typhimurium"[mh] OR antagonist*[tw] OR inhibitor*[tw] OR "blood"[tw] OR "serum"[tw] OR "plasma"[tw] OR pharmacokinetic*[tw] OR toxicokinetic*[tw] OR "pbpk"[tw] OR "poisoned"[tw] OR "poisoning"[tw] OR "urine"[tw] OR "urinary"[tw] OR "toxicity"[sh] OR "occupational diseases"[mh] OR "hazardous substances"[mh] OR "epidemiology"[sh] OR "epidemiologic studies"[mh]))) OR ("Potassium Cyanide"[mh] AND (("Neoplasms"[mh] OR

Table B-2. Database Query Strings

Database search date	Query string
	"Carcinogens"[mh] OR "Lymphoproliferative disorders"[mh] OR "Myeloproliferative disorders"[mh] OR "Toxicity Tests"[mh] OR ((cancer*[tiab] OR carcinogen*[tiab]) AND (risk*[tiab] OR health[tiab]) AND assessment*[tiab]) OR "Mutagens"[mh] OR "Mutagenicity Tests"[mh] OR "Chromosome Aberrations"[mh] OR "DNA Damage"[mh] OR "DNA Repair"[mh] OR "DNA Replication/drug effects"[mh] OR "DNA/drug effects"[mh] OR "DNA/metabolism"[mh] OR "Genomic Instability"[mh] OR "Salmonella typhimurium/drug effects"[mh] OR "Salmonella typhimurium/genetics"[mh] OR "Sister Chromatid Exchange"[mh] OR strand-break*[tiab]))))) OR ("cyanogen"[nm] AND ("Nitriles/toxicity"[mh] OR "Nitriles/adverse effects"[mh] OR "Nitriles/poisoning"[mh] OR "Nitriles/pharmacokinetics"[mh] OR "Nitriles/blood"[mh] OR "Nitriles/cerebrospinal fluid"[mh] OR "Nitriles/urine"[mh] OR "Nitriles/antagonists and inhibitors"[mh] OR ("Nitriles/metabolism"[mh] AND ("humans"[mh] OR "animals"[mh])) OR "Nitriles/pharmacology"[majr] OR ("Nitriles"[mh] AND ("environmental exposure"[mh] OR "chemically induced"[sh] OR toxicokinetics[mh:noexp] OR "endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh] OR "computational biology"[mh] OR "medical informatics"[mh] OR genomics[mh] OR genome[mh] OR proteomics[mh] OR proteome[mh] OR metabolomics[mh] OR metabolome[mh] OR genes[mh] OR "gene expression"[mh] OR phenotype[mh] OR genetics[mh] OR genotype[mh] OR transcriptome[mh] OR ("systems biology"[mh] AND ("environmental exposure"[mh] OR "epidemiological monitoring"[mh] OR analysis[sh])) OR "transcription, genetic "[mh] OR "reverse transcription"[mh] OR "transcriptional activation"[mh] OR "transcription factors"[mh] OR ("biosynthesis"[sh] AND (RNA[mh] OR DNA[mh])) OR "RNA, messenger"[mh] OR "RNA, transfer"[mh] OR "peptide biosynthesis"[mh] OR "protein biosynthesis"[mh] OR "reverse transcriptase polymerase chain reaction"[mh] OR "base sequence"[mh] OR "trans-activators"[mh] OR "gene expression profiling"[mh])) OR ("Nitriles"[mh] AND ((indexingmethod_automated OR indexingmethod_curated) AND ("RNA"[mh] OR "DNA"[mh] OR "DNA Replication"[mh] OR "Salmonella typhimurium"[mh] OR antagonist*[tw] OR inhibitor*[tw] OR "blood"[tw] OR "serum"[tw] OR "plasma"[tw] OR pharmacokinetic*[tw] OR toxicokinetic*[tw] OR "pbpk"[tw] OR "poisoned"[tw] OR "poisoning"[tw] OR "urine"[tw] OR "urinary"[tw] OR "toxicity"[sh] OR "occupational diseases"[mh] OR "hazardous substances"[mh] OR "epidemiology"[sh] OR "epidemiologic studies"[mh])))) OR ("Nitriles"[mh] AND (("Neoplasms"[mh] OR "Carcinogens"[mh] OR "Lymphoproliferative disorders"[mh] OR "Myeloproliferative disorders"[mh] OR "Toxicity Tests"[mh] OR ((cancer*[tiab] OR carcinogen*[tiab]) AND (risk*[tiab] OR health[tiab]) AND assessment*[tiab]) OR "Mutagens"[mh] OR "Mutagenicity Tests"[mh] OR "Chromosome Aberrations"[mh] OR "DNA Damage"[mh] OR "DNA Repair"[mh] OR "DNA Replication/drug effects"[mh] OR "DNA/drug effects"[mh] OR "DNA/metabolism"[mh] OR "Genomic Instability"[mh] OR "Salmonella typhimurium/drug effects"[mh] OR "Salmonella typhimurium/genetics"[mh] OR "Sister Chromatid Exchange"[mh] OR strand-break*[tiab])))))) OR ((1762-95-4[rn] OR 333-20-0[rn] OR 540-72-7[rn]) AND ("Thiocyanates/toxicity"[mh] OR "Thiocyanates/adverse effects"[mh] OR "Thiocyanates/poisoning"[mh] OR "Thiocyanates/pharmacokinetics"[mh] OR "Thiocyanates/blood"[mh] OR "Thiocyanates/cerebrospinal fluid"[mh] OR "Thiocyanates/urine"[mh] OR "Thiocyanates/antagonists and inhibitors"[mh] OR ("Thiocyanates/metabolism"[mh] AND ("humans"[mh] OR "animals"[mh])) OR "Thiocyanates/pharmacology"[majr] OR ("Thiocyanates"[mh] AND ("environmental exposure"[mh] OR "chemically induced"[sh] OR toxicokinetics[mh:noexp] OR "endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh] OR "computational biology"[mh] OR "medical informatics"[mh] OR genomics[mh] OR genome[mh] OR proteomics[mh] OR proteome[mh] OR

Table B-2. Database Query Strings

Database search date	Query string
	metabolomics[mh] OR metabolome[mh] OR genes[mh] OR "gene expression"[mh] OR phenotype[mh] OR genetics[mh] OR genotype[mh] OR transcriptome[mh] OR ("systems biology"[mh] AND ("environmental exposure"[mh] OR "epidemiological monitoring"[mh] OR analysis[sh])) OR "transcription, genetic "[mh] OR "reverse transcription"[mh] OR "transcriptional activation"[mh] OR "transcription factors"[mh] OR ("biosynthesis"[sh] AND (RNA[mh] OR DNA[mh])) OR "RNA, messenger"[mh] OR "RNA, transfer"[mh] OR "peptide biosynthesis"[mh] OR "protein biosynthesis"[mh] OR "reverse transcriptase polymerase chain reaction"[mh] OR "base sequence"[mh] OR "trans-activators"[mh] OR "gene expression profiling"[mh])) OR ("Thiocyanates"[mh] AND ((indexingmethod_automated OR indexingmethod_curated) AND ("RNA"[mh] OR "DNA"[mh] OR "DNA Replication"[mh] OR "Salmonella typhimurium"[mh] OR antagonist*[tw] OR inhibitor*[tw] OR "blood"[tw] OR "serum"[tw] OR "plasma"[tw] OR pharmacokinetic*[tw] OR toxicokinetic*[tw] OR "pbpk"[tw] OR "poisoned"[tw] OR "poisoning"[tw] OR "urine"[tw] OR "urinary"[tw] OR "toxicity"[sh] OR "occupational diseases"[mh] OR "hazardous substances"[mh] OR "epidemiology"[sh] OR "epidemiologic studies"[mh]))) OR ("Thiocyanates"[mh] AND (("Neoplasms"[mh] OR "Carcinogens"[mh] OR "Lymphoproliferative disorders"[mh] OR "Myeloproliferative disorders"[mh] OR "Toxicity Tests"[mh] OR ((cancer*[tiab] OR carcinogen*[tiab]) AND (risk*[tiab] OR health[tiab]) AND assessment*[tiab]) OR "Mutagens"[mh] OR "Mutagenicity Tests"[mh] OR "Chromosome Aberrations"[mh] OR "DNA Damage"[mh] OR "DNA Repair"[mh] OR "DNA Replication/drug effects"[mh] OR "DNA/drug effects"[mh] OR "DNA/metabolism"[mh] OR "Genomic Instability"[mh] OR "Salmonella typhimurium/drug effects"[mh] OR "Salmonella typhimurium/genetics"[mh] OR "Sister Chromatid Exchange"[mh] OR strand-break*[tiab])))) OR ("Calcid"[tw] OR "Calcium cyanide"[tw] OR "Calcium dicyanide"[tw] OR "Calcyan"[tw] OR "Calcyanide"[tw] OR "Cyanide of calcium"[tw] OR "Cyanogas"[tw] OR "Degesch Calcium Cyanide A-Dust"[tw] OR "Copper cyanide"[tw] OR "Copper monocyanide"[tw] OR "Copper(+1) cyanide"[tw] OR "Copper(1+) cyanide"[tw] OR "Copper(I) cyanide"[tw] OR "Cupricin"[tw] OR "Cuprous cyanide"[tw])) AND 2004:3000[dp] (((("Cyanide"[tw] OR "Aero Liquid HCN"[tw] OR "Agent AC"[tw] OR "Ammonium isothiocyanate"[tw] OR "Ammonium rhodanate"[tw] OR "Ammonium rhodanide"[tw] OR "Ammonium sulfocyanate"[tw] OR "Ammonium sulfocyanide"[tw] OR "Ammonium thiocyanate"[tw] OR "Calcium dicyanide"[tw] OR "Calcyan"[tw] OR "Calcyanide"[tw] OR "Carbon hydride nitride"[tw] OR "Carbononitridic chloride"[tw] OR "CHLORCYAN"[tw] OR "Chlorocyan"[tw] OR "Chlorocyanide"[tw] OR "Chlorocyanogen"[tw] OR "Chloronitrile"[tw] OR "Copper monocyanide"[tw] OR "Cupricin"[tw] OR "Cyanasalt H"[tw] OR "Cyanasalt S"[tw] OR "Cyanic chloride"[tw] OR "Cyanides"[tw] OR "Cyanobrik"[tw] OR "Cyanochloride"[tw] OR "Cyanogas"[tw] OR "Cyanogen"[tw] OR "Cymag"[tw] OR "Cynanide"[tw] OR "Dicyan"[tw] OR "Dicyanogen"[tw] OR "EDN Fumigas"[tw] OR "Ethanedinitrile"[tw] OR "Evercyn"[tw] OR "Feratox"[tw] OR "Formic anammonide"[tw] OR "Formonitrile"[tw] OR "Hydrocyanic acid"[tw] OR "M-44 capsules"[tw] OR "Nitriloacetonitrile"[tw] OR "Oxalic acid dinitrile"[tw] OR "Oxalonitrile"[tw] OR "Potassium argentocyanide"[tw] OR "Potassium bis(cyano-C)argentate"[tw] OR "Potassium cyanoargentate"[tw] OR "Potassium dicyanoargentate"[tw] OR "Potassium isothiocyanate"[tw] OR "Potassium rhodanate"[tw] OR "Potassium sulfocyanate"[tw] OR "Potassium thiocyanate"[tw] OR "Potassium thiocyanide"[tw] OR "Prussic acid"[tw] OR "Prussite"[tw] OR "Rhodanid"[tw] OR "Rhodanine, ammonium salt"[tw] OR "Sodium isothiocyanate"[tw] OR "Sodium rhodanate"[tw] OR "Sodium rhodanide"[tw] OR "Sodium sulfocyanate"[tw] OR "Sodium sulfocyanide"[tw] OR "Sodium thiocyanate"[tw] OR "Sodium thiocyanide"[tw] OR "Thiocyanate sodium"[tw] OR "Thiocyanic acid, ammonium salt"[tw]

Table B-2. Database Query Strings

Database search date	Query string
	OR "Thiocyanic acid, potassium salt"[tw] OR "Thiocyanic acid, sodium salt"[tw] OR "Weedazol tl"[tw] OR "Zaclondiscoids"[tw] OR "Zyklon B"[tw]) NOT medline[sb]) AND (toxicity[ti] OR death OR lethal OR fatal OR fatality OR necrosis OR LC50* OR LD50* OR "body weight" OR "weight loss" OR "weight gain" OR weight-change* OR overweight OR obesity OR inhal* OR respiratory OR "pulmonary edema" OR "pulmonary effect" OR "pulmonary system" OR "pulmonary function" OR "pulmonary organ" OR "pulmonary toxicity" OR airway OR trachea OR tracheobronchial OR lung OR lungs OR nose OR nasal OR nasopharyngeal OR larynx OR laryngeal OR pharynx OR bronchial OR bronchi OR bronchioles OR bronchitis OR hemothorax OR alveolar OR alveoli OR irritation OR irritant OR sensitization OR sensitizer OR cilia OR mucocilliary OR cvd OR cardio OR vascular OR cardiovascular OR "circulatory system" OR "circulatory function" OR "circulatory effect" OR "circulatory organ" OR "circulatory toxicity" OR "cardiac arrest" OR "cardiac palpitation" OR "cardiac arrhythmia" OR "cardiac edema" OR "heart rate" OR "heart failure" OR "heart attack" OR "heart muscle" OR "heart beat" OR "myocardial-infarction" OR "chest pain" OR artery OR arteries OR veins OR venules OR cardiotox* OR "gastro-intestinal" OR gastrointestinal OR "digestive system" OR "digestive function" OR "digestive effect" OR "digestive organ" OR "Intestinal system" OR "intestinal function" OR "intestinal microbiota" OR "intestinal effect" OR "intestinal organ" OR "gi tract" OR "gi disorder" OR abdominal OR esophagus OR stomach OR intestine OR pancreas OR pancreatic OR diarrhea OR nausea OR vomit OR ulcer OR constipation OR emesis OR "gut microbes" OR "gut flora" OR "gut microflora" OR anorexia OR hematological OR hematology OR hemato OR haemato OR blood OR anemia OR cyanosis OR erythrocytopenia OR leukopenia OR thrombocytopenia OR hemoglobin OR erythrocyte OR hematocrit OR "bone marrow" OR reticulocyte OR methemoglobin OR red-blood-cell OR musculoskeletal OR skeletal OR muscle OR muscular OR arthritis OR "altered bone" OR "joint pain" OR "joint-ache" OR "limb pain" OR "limb ache" OR hepatic OR "liver system" OR "liver function" OR "liver effect" OR "liver organ" OR "Liver enzyme" OR "liver weight" OR "liver congestion" OR "liver changes" OR "liver biochemical changes" OR "liver toxicity" OR hepatocytes OR gallbladder OR cirrhosis OR jaundice OR "hepatocellular degeneration" OR "hepatocellular hypertrophy" OR hepatomegaly OR hepatotox* OR renal OR "kidney system" OR "kidney function" OR "Kidney effect" OR "kidney toxicity" OR "urinary system" OR "urinary function" OR "urinary effect" OR "Urinary toxicity" OR "bladder system" OR "bladder effect" OR "bladder function" OR "bladder toxicity" OR "Urine volume" OR "blood urea nitrogen" OR bun OR nephropathy OR nephrotox* OR dermal OR "skin rash" OR "skin itch" OR "skin irritation" OR "skin redness" OR "skin effect" OR "skin necrosis" OR "skin exposure" OR "skin contact" OR acanthosis OR dermatitis OR psoriasis OR edema OR ulceration OR acne OR ocular OR "eye function" OR "eye effect" OR "eye irritation" OR "eye drainage" OR "eye tearing" OR blindness OR myopia OR cataracts OR endocrine OR "hormone changes" OR "hormone excess" OR "hormone deficiency" OR "hormone gland" OR "hormone secretion" OR "hormone toxicity" OR "sella turcica" OR thyroid OR adrenal OR pituitary OR immunological OR immunologic OR immune OR lymphoreticular OR lymph-node OR spleen OR thymus OR macrophage OR leukocyte* OR white-blood-cell OR immunotox* OR neurological OR neurologic OR neurotoxic OR neurotoxicity OR neurodegenerat* OR "nervous system" OR brain OR neurotoxicant OR neurochemistry OR neurophysiology OR neuropathology OR "motor activity" OR motor change* OR behavior-change* OR behavioral-change* OR sensory-change* OR cognitive OR vertigo OR drowsiness OR headache OR ataxia OR reproductive OR "reproduction system" OR "reproduction function" OR "reproduction effect" OR "reproduction toxicity" OR fertility OR "maternal toxicity" OR developmental OR "in utero" OR terata* OR terato* OR embryo* OR fetus* OR foetus* OR fetal* OR foetal*

Table B-2. Database Query Strings

Database search date	Query string
	OR prenatal* OR "pre-natal" OR perinatal* OR "post-natal" OR postnatal* OR neonat* OR newborn* OR zygote* OR child OR children OR infant* OR offspring OR elderly OR "altered food consumption" OR "altered water consumption" OR "metabolic effect" OR "metabolic toxicity" OR fever OR cancer OR cancerous OR neoplas* OR tumor OR tumors OR tumour* OR malignan* OR carcinoma OR carcinogen OR carcinogen* OR angiosarcoma OR blastoma OR fibrosarcoma OR glioma OR leukemia OR leukaemia OR lymphoma OR melanoma OR meningioma OR mesothelioma OR myeloma OR neuroblastoma OR osteosarcoma OR sarcoma OR mutation OR mutations OR genotoxicity OR genotoxic OR mutagenicity OR mutagenic OR "mechanism of action"[tiab:~0] OR "mechanism of absorption"[tiab:~0] OR "mechanism of distribution"[tiab:~0] OR "mechanism of excretion"[tiab:~0] OR "mechanism of metabolism"[tiab:~0] OR "mechanism of toxic effect"[tiab:~0] OR "mechanism of toxicity" OR "adverse effect" OR "adverse effects" OR "health effects" OR noncancer OR poisoning OR morbidity OR inflammation OR antagonist OR inhibitor OR metabolism OR "environmental exposure" OR toxicokinetics OR pharmacokinetics OR "gene expression" OR "population health" OR epidemiology OR epidemiological OR case-control* OR case-referent OR case-report OR case-series OR cohort* OR correlation-stud* OR cross-sectional-stud* OR ecological-studies OR ecological-study OR follow-up-stud* OR longitudinal-stud* OR metaanalyses OR metaanalysis OR meta-analysis OR prospective-stud* OR record-link* OR retrospective-stud* OR seroepidemiologic-stud* OR occupation* OR worker* OR workmen* OR workplace* OR "human health" OR "oral intake" OR "oral feed" OR "oral ingestion" OR "oral exposure" OR "oral administration" OR ingest* OR gavage* OR "drinking-water" OR NHANES OR "National Health and Nutrition Examination Survey" OR (human AND (risk OR toxic* OR safety)) OR mammal* OR ape OR apes OR baboon* OR balb OR beagle* OR boar OR boars OR bonobo* OR bovine OR C57 OR C57bl OR callithrix OR canine OR canis OR capra OR capuchin* OR cats OR cattle OR cavia OR chicken OR chickens OR chimpanzee* OR chinchilla* OR cow OR cows OR cricetinae OR dog OR dogs OR equus OR feline OR felis OR ferret OR ferrets OR flying-fox OR Fruit-bat OR gerbil* OR gibbon* OR goat OR goats OR guinea-pig* OR guppy OR hamster OR hamsters OR horse OR horses OR jird OR jirds OR lagomorph* OR leontopithecus OR longevans OR macaque* OR marmoset* OR medaka OR merione OR meriones OR mice OR monkey OR monkeys OR mouse OR muridae OR murinae OR murine OR mustela-putorius OR nomascus OR non-human-primate* OR orangutan* OR pan-paniscus OR pan-troglodytes OR pig OR piglet* OR pigs OR polecat* OR pongopygmaeus OR quail OR rabbit OR rabbits OR rat OR rats OR rhesus OR rodent OR rodentia OR rodents OR saguinus OR sheep OR sheeps OR siamang* OR sow OR sows OR Sprague-Dawley OR swine OR swines OR symphalangus OR tamarin* OR vervet* OR wistar OR wood-mouse OR zebra-fish OR zebrafish)) AND 2004:3000[dp]
NTRL	
07/2023	Limited to 2004-present, Terms in the title or keyword "Cyanide" OR "Aero Liquid HCN" OR "Agent AC" OR "Ammonium isothiocyanate" OR "Ammonium rhodanate" OR "Ammonium rhodanide" OR "Ammonium sulfocyanate" OR "Ammonium sulfocyanide" OR "Ammonium thiocyanate" OR "Calcium dicyanide" OR "Calcyan" OR "Calcyanide" OR "Carbon hydride nitride" OR "Carbononitridic chloride" OR "CHLORCYAN" OR "Chlorocyan" OR "Chlorocyanide" OR "Chlorocyanogen" OR "Chloronitrile" OR "Copper monocyanide" OR "Cupricin" OR "Cyanasalt H" OR "Cyanasalt S" OR "Cyanic chloride" OR "Cyanides" OR "Cyanobrik" OR "Cyanochloride" OR "Cyanogas" OR "Cyanogen" OR "Cymag" OR "Cynanide" OR "Dicyan" OR "Dicyanogen" OR "EDN Fumigas" OR "Ethanedinitrile" OR "Evercyn" OR "Feratox" OR "Formic anammonide" OR "Formonitrile" OR "Hydrocyanic acid" OR "M-44 capsules" OR

Table B-2. Database Query Strings

Database search date	Query string
	"Nitriloacetonitrile" OR "Oxalic acid dinitrile" OR "Oxalonitrile" OR "Potassium argentocyanide" OR "Potassium bis(cyano-C)argentate" OR "Potassium cyanoargentate" OR "Potassium dicyanoargentate" OR "Potassium isothiocyanate" OR "Potassium rhodanate" OR "Potassium sulfocyanate" OR "Potassium thiocyanate" OR "Potassium thiocyanide" OR "Prussic acid" OR "Prussite" OR "Rhodanid" OR "Rhodanine, ammonium salt" OR "Sodium isothiocyanate" OR "Sodium rhodanate" OR "Sodium rhodanide" OR "Sodium sulfocyanate" OR "Sodium sulfocyanide" OR "Sodium thiocyanate" OR "Sodium thiocyanide" OR "Thiocyanate sodium" OR "Thiocyanic acid, ammonium salt" OR "Thiocyanic acid, potassium salt" OR "Thiocyanic acid, sodium salt" OR "Weedazol tl" OR "Zaclondiscoids" OR "Zyklon B"
Toxcenter	
08/2023	FILE 'TOXCENTER' ENTERED AT 17:32:05 ON 15 AUG 2023 L1 1317 SEA FILE=TOXCENTER ((540-72-7 OR 333-20-0) AND PY>2003) NOT PATENT/DT L2 QUE (CHRONIC OR IMMUNOTOX? OR NEUROTOX? OR TOXICOKIN? OR BIOMARKER? OR NEUROLOG?) L3 QUE (PHARMACOKIN? OR SUBCHRONIC OR PBPK OR EPIDEMIOLOGY/ST,CT,IT) L4 QUE (ACUTE OR SUBACUTE OR LD50# OR LD(W)50 OR LC50# OR LC(W)50) L5 QUE (TOXICITY OR ADVERSE OR POISONING)/ST,CT,IT L6 QUE (INHAL? OR PULMON? OR NASAL? OR LUNG? OR RESPIR?) L7 QUE ((OCCUPATION? OR WORKPLACE? OR WORKER?) AND EXPOS?) L8 QUE (ORAL OR ORALLY OR INGEST? OR GAVAGE? OR DIET OR DIETS OR DIETARY OR DRINKING(W)WATER?) L9 QUE (MAXIMUM AND CONCENTRATION? AND (ALLOWABLE OR PERMISSIBLE)) L10 QUE (ABORT? OR ABNORMALIT? OR EMBRYO? OR CLEFT? OR FETUS?) L11 QUE (FOETUS? OR FETAL? OR FOETAL? OR FERTIL? OR MALFORM? OR OVUM?) L12 QUE (OVA OR OVARY OR PLACENTA? OR PREGNAN? OR PRENATAL?) L13 QUE (PERINATAL? OR POSTNATAL? OR REPRODUC? OR STERIL? OR TERATOGEN?) L14 QUE (SPERM OR SPERMAC? OR SPERMAG? OR SPERMATI? OR SPERMAS? OR SPERMATOB? OR SPERMATOC? OR SPERMATOG?) L15 QUE (SPERMATOI? OR SPERMATOL? OR SPERMATOR? OR SPERMATOX? OR SPERMATOZ? OR SPERMATU? OR SPERMI? OR SPERMO?) L16 QUE (NEONAT? OR NEWBORN? OR DEVELOPMENT OR DEVELOPMENTAL?) L17 QUE (ENDOCRIN? AND DISRUPT?) L18 QUE (ZYGOTE? OR CHILD OR CHILDREN OR ADOLESCEN? OR INFANT?) L19 QUE (WEAN? OR OFFSPRING OR AGE(W)FACTOR?) L20 QUE (DERMAL? OR DERMIS OR SKIN OR EPIDERM? OR CUTANEOUS?) L21 QUE (CARCINOG? OR COCARCINOG? OR CANCER? OR PRECANCER? OR

Table B-2. Database Query Strings

Database search date	Query string
	NEOPLAS?)
	L22 QUE (TUMOR? OR TUMOUR? OR ONCOGEN? OR LYMPHOMA? OR CARCINOM?)
	L23 QUE (GENETOX? OR GENOTOX? OR MUTAGEN? OR GENETIC(W)TOXIC?)
	L24 QUE (NEPHROTOX? OR HEPATOTOX?)
	L25 QUE (ENDOCRIN? OR ESTROGEN? OR ANDROGEN? OR HORMON?)
	L26 QUE (OCCUPATION? OR WORKER? OR WORKPLACE? OR EPIDEM?)
	L27 QUE L2 OR L3 OR L4 OR L5 OR L6 OR L7 OR L8 OR L9 OR L10 OR L11 OR L12 OR L13 OR L14 OR L15 OR L16 OR L17 OR L18 OR L19 OR L20 OR L21 OR L22 OR L23 OR L24 OR L25 OR L26

	L35 QUE L2 OR L3 OR L4 OR L5 OR L6 OR L7 OR L8 OR L9 OR L10 OR L11 OR L12 OR L13 OR L14 OR L15 OR L17 OR L18 OR L19 OR L20 OR L23 OR L24 OR L25 OR L26
	L36 309 SEA FILE=TOXCENTER L1 AND L35
	L37 1 SEA FILE=TOXCENTER L1 AND (NEONAT? OR NEWBORN? OR DEVELOPMENTAL ?)
	L38 79 SEA FILE=TOXCENTER (L1 AND (DEVELOPMENT OR L21 OR L22)) NOT (SYNTHESIS/TI OR DESIGN/TI OR DRUG? OR TREATMENT? OR THERAP? OR ANTI-TUMOR? OR ANTI-TUMOUR? OR ANTI-CANCER OR ANTICANCER OR ANTI-NEOPLASTIC OR ANTINEOPLASTIC OR ANTI-CARCINOGEN? OR ANTICARCINOGEN?)
	L39 366 SEA FILE=TOXCENTER L36 OR L37 OR L38
	L41 16 SEA FILE=TOXCENTER L39 AND BIOSIS/FS
	D SCAN L41
	L111 11591 SEA FILE=TOXCENTER ((74-90-8 OR 143-33-9 OR 151-50-8 OR 592-01-8 OR 544-92-3 OR 506-61-6 OR 460-19-5 OR 506-77-4 OR 1762-95-4 OR 57-12-5) AND PY>2003) NOT PATENT/DT
	L112 5165 SEA FILE=TOXCENTER L111 AND L27
	L113 95 SEA FILE=TOXCENTER L111 AND (NEONAT? OR NEWBORN? OR DEVELOPMENT AL?)
	L114 810 SEA FILE=TOXCENTER (L111 AND (DEVELOPMENT OR L21 OR L22)) NOT (SYNTHESIS/TI OR DESIGN/TI OR DRUG? OR TREATMENT? OR THERAP? OR ANTI-TUMOR? OR ANTI-TUMOUR? OR ANTI-CANCER OR ANTICANCER OR ANTI-NEOPLASTIC OR ANTINEOPLASTIC OR ANTI-CARCINOGEN? OR ANTICARCINOGEN?)
	L115 5165 SEA FILE=TOXCENTER L112 OR L113 OR L114
	L116 670 SEA FILE=TOXCENTER L115 AND MEDLINE/FS
	L117 4495 SEA FILE=TOXCENTER L115 NOT MEDLINE/FS
	L118 1035 SEA FILE=TOXCENTER L115 AND BIOSIS/FS
	L119 4618 DUP REM L116 L117 (547 DUPLICATES REMOVED)
	L*** DEL 670 S L115 AND MEDLINE/FS
	L*** DEL 670 S L115 AND MEDLINE/FS

Table B-2. Database Query Strings

Database search date	Query string
	L120 670 SEA FILE=TOXCENTER L119 L*** DEL 4495 S L115 NOT MEDLINE/FS L*** DEL 4495 S L115 NOT MEDLINE/FS L121 3948 SEA FILE=TOXCENTER L119 L122 3948 SEA FILE=TOXCENTER (L120 OR L121) NOT MEDLINE/FS L124 3393 SEA FILE=TOXCENTER L122 AND (L35 OR L113 OR L114) D SCAN

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
TSCATS via ChemView	
07/2023	Compounds searched: 74-90-8, 143-33-9, 151-50-8, 592-01-8, 544-92-3, 506-61-6, 460-19-5, 506-77-4, 1762-95-4, 57-12-5, 333-20-0, 540-72-7
NTP	
07/2023	"Cyanide" "Cyanides" "Ammonium thiocyanate" "Cyanogen" 74-90-8 143-33-9 151-50-8 592-01-8 544-92-3 506-61-6 460-19-5 506-77-4 1762-95-4 57-12-5 333-20-0 "Ammonium rhodanate" "Chlorocyan" "Chloronitrile" "Cyanochloride" "Cyanogas" "Cynanide" "Dicyan" "Ethanedinitrile" "Formonitrile" "Hydrocyanic acid" "Potassium dicyanoargentate" "Potassium thiocyanate" "Prussic acid" "Rhodanid" "Sodium thiocyanate" "Zyklon B"
Regulations.gov	
07/2023	Limited to 2004-present; dockets/notices "74-90-8"

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
	"143-33-9" "151-50-8" "592-01-8" "544-92-3" "506-61-6" "460-19-5" "506-77-4" "1762-95-4" "57-12-5" "333-20-0" "Cyanide" "Cyanides" "Ammonium rhodanate" "Ammonium thiocyanate" "Chlorocyan" "Chloronitrile" "Cyanochloride" "Cyanogas" "Cyanogen" "Cynanide" "Dicyan" "Ethanedinitrile" "Formonitrile" "Hydrocyanic acid" "Potassium dicyanoargentate" "Prussic acid" "Rhodanid" "Zyklon B" "Potassium thiocyanate" "Sodium thiocyanate"
NPIRS	
08/2023	Compounds searched: 74-90-8, 143-33-9, 151-50-8, 592-01-8, 544-92-3, 506-61-6, 460-19-5, 506-77-4, 1762-95-4, 57-12-5, 333-20-0, 540-72-7
NIH RePORTER	
01/2024	Search Criteria-- Fiscal Year: Active Projects; Text Search: "Cyanide" OR "Aero Liquid HCN" OR "Agent AC" OR "Ammonium isothiocyanate" OR "Ammonium rhodanate" OR "Ammonium rhodanide" OR "Ammonium sulfocyanate" OR "Ammonium sulfocyanide" OR "Ammonium thiocyanate" OR "Calcid" OR "Calcium dicyanide" OR "Calcyan" OR "Calcyanide" OR "Carbon hydride nitride" OR "Carbononitridic chloride" OR "CHLORCYAN" OR "Chlorocyan" OR "Chlorocyanide" OR "Chlorocyanogen" OR "Chloronitrile" OR "Copper monocyanide" OR "Cupricin" OR "Cyanasalt H" OR "Cyanasalt S" OR "Cyanic chloride" OR "Cyanides" OR "Cyanobrik" OR "Cyanochloride" OR "Cyanogas" OR "Cyanogen" OR "Cymag" OR "Cynanide" OR "Dicyan" OR "Dicyanogen" OR "EDN Fumigas" OR "Ethanedinitrile" OR "Evercyn" OR "Feratox" OR "Formic anammonide" OR "Formonitrile" OR "Hydrocyanic acid" OR "M-44 capsules" OR "Nitriloacetonitrile" OR "Oxalic acid dinitrile" OR "Oxalonitrile" OR "Potassium argentocyanide" OR "Potassium bis(cyano-C)argentate" OR "Potassium cyanoargentate" OR "Potassium dicyanoargentate" OR "Potassium isothiocyanate" OR "Potassium rhodanate" OR "Potassium sulfocyanate" OR "Potassium thiocyanate" OR "Potassium thiocyanide" OR "Prussic acid" OR

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
	"Prussite" OR "Rhodanid" OR "Rhodanine, ammonium salt" OR "Sodium isothiocyanate" OR "Sodium rhodanate" OR "Sodium rhodanide" OR "Sodium sulfocyanate" OR "Sodium sulfocyanide" OR "Sodium thiocyanate" OR "Sodium thiocyanide" OR "Thiocyanate sodium" OR "Thiocyanic acid, ammonium salt" OR "Thiocyanic acid, potassium salt" OR "Thiocyanic acid, sodium salt" OR "Weedazol tl" OR "Zaclondiscoids" OR "Zyklon B" (advanced) Limit to: Project Title, Project Terms, Project Abstracts
Other	Identified throughout the assessment process

The 2023 results were:

- Number of records identified from PubMed, NTRL, and TOXCENTER (after duplicate removal): 5,213
- Number of records identified from other strategies: 134
- Total number of records to undergo literature screening: 5,347

B.1.2 Literature Screening

A two-step process was used to screen the literature search to identify relevant studies on cyanide:

- Title and abstract screen
- Full text screen

Title and Abstract Screen. Within the reference library, titles and abstracts were screened manually for relevance. Studies that were considered relevant (see Table B-1 for inclusion criteria) were moved to the second step of the literature screening process. Studies were excluded when the title and abstract clearly indicated that the study was not relevant to the toxicological profile.

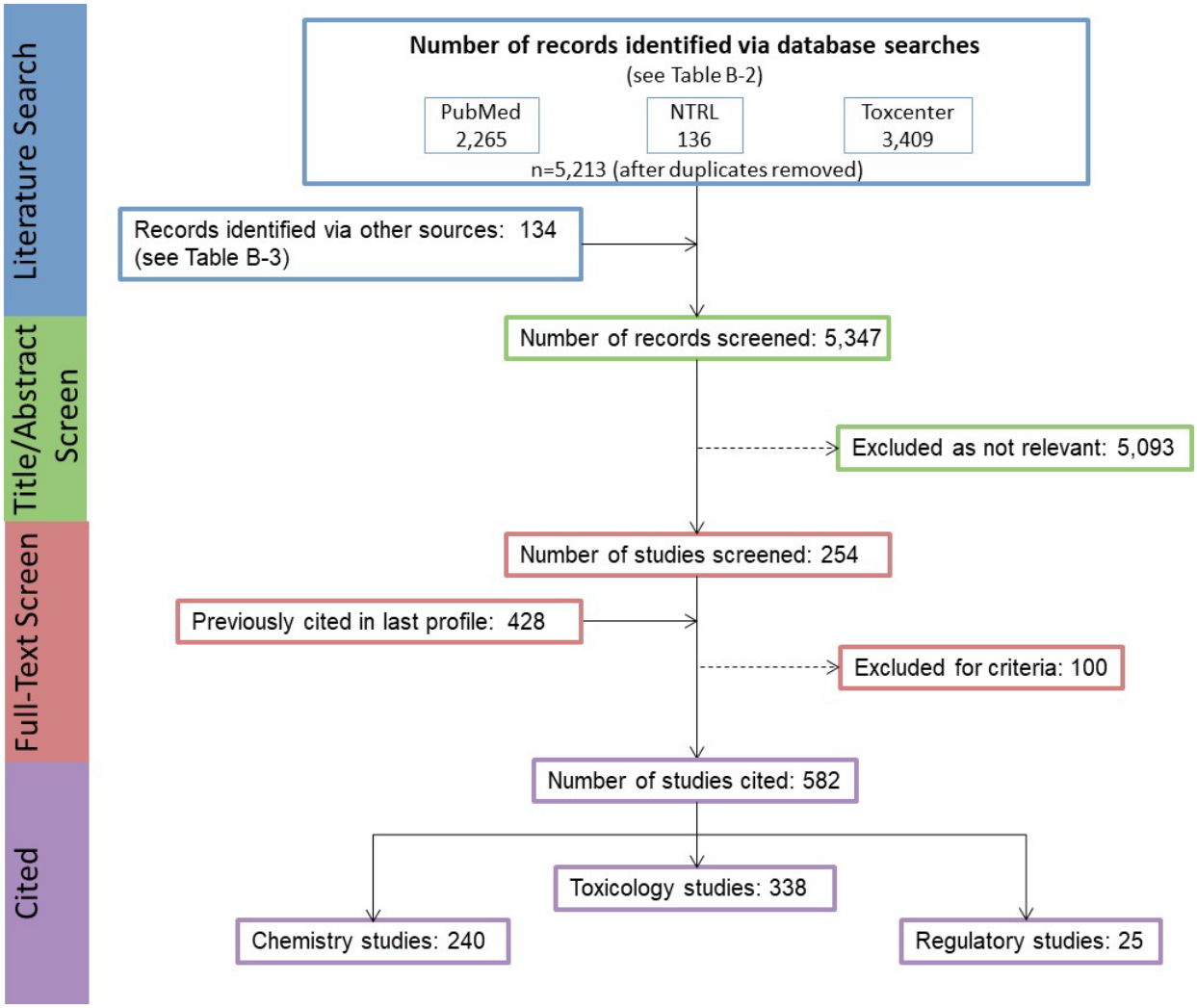
- Number of titles and abstracts screened: 5,347
- Number of studies considered relevant and moved to the next step: 254

Full Text Screen. The second step in the literature screening process was a full text review of individual studies considered relevant in the title and abstract screen step. Each study was reviewed to determine whether it was relevant for inclusion in the toxicological profile.

- Number of studies undergoing full text review: 254
- Number of studies cited in the pre-public draft of the toxicological profile: 428
- Total number of studies cited in the profile: 582

A summary of the results of the literature search and screening is presented in Figure B-1.

Figure B-1. August 2023 Literature Search Results and Screen for Cyanide



APPENDIX C. FRAMEWORK FOR ATSDR'S SYSTEMATIC REVIEW OF HEALTH EFFECTS DATA FOR CYANIDE

To increase the transparency of ATSDR's process of identifying, evaluating, synthesizing, and interpreting the scientific evidence on the health effects associated with exposure to cyanide, ATSDR utilized a slight modification of NTP's Office of Health Assessment and Translation (OHAT) systematic review methodology (NTP 2013, 2015; Rooney et al. 2014). ATSDR's framework is an eight-step process for systematic review with the goal of identifying the potential health hazards of exposure to cyanide:

- Step 1. Problem Formulation
- Step 2. Literature Search and Screen for Health Effects Studies
- Step 3. Extract Data from Health Effects Studies
- Step 4. Identify Potential Health Effect Outcomes of Concern
- Step 5. Assess the Risk of Bias for Individual Studies
- Step 6. Rate the Confidence in the Body of Evidence for Each Relevant Outcome
- Step 7. Translate Confidence Rating into Level of Evidence of Health Effects
- Step 8. Integrate Evidence to Develop Hazard Identification Conclusions

C.1 PROBLEM FORMULATION

The objective of the toxicological profile and this systematic review was to identify the potential health hazards associated with inhalation, oral, or dermal/ocular exposure to cyanide. The inclusion criteria used to identify relevant studies examining the health effects of cyanide are presented in Table C-1.

Data from human and laboratory animal studies were considered relevant for addressing this objective. Human studies were divided into two broad categories: observational epidemiology studies and controlled exposure studies. The observational epidemiology studies were further divided: cohort studies (retrospective and prospective studies), population studies (with individual data or aggregate data), and case-control studies.

Table C-1. Inclusion Criteria for Identifying Health Effects Studies

Species
Human
Laboratory mammals
Route of exposure
Inhalation
Oral
Dermal (or ocular)
Parenteral (these studies will be considered supporting data)
Health outcome
Death
Systemic effects
Body weight effects
Respiratory effects
Cardiovascular effects

Table C-1. Inclusion Criteria for Identifying Health Effects Studies

Gastrointestinal effects
Hematological effects
Musculoskeletal effects
Hepatic effects
Renal effects
Dermal effects
Ocular effects
Endocrine effects
Immunological effects
Neurological effects
Reproductive effects
Developmental effects
Other noncancer effects
Cancer

Prioritization of Human Data. The database of case-reports and case-series reviews of cyanide-related deaths and poisonings is extensive. Due to the well-established acute lethality of cyanide via all routes, as well as the mechanism of acute toxicity, comprehensive review and inclusion of these studies was not performed for this profile. Case reports were included when the provided key information on dose-response or hazard identification, and recent reviews were relied upon when available.

C.2 LITERATURE SEARCH AND SCREEN FOR HEALTH EFFECTS STUDIES

A literature search and screen were conducted to identify studies examining the health effects of cyanide. The literature search framework for the toxicological profile is discussed in detail in Appendix B.

C.2.1 Literature Search

As noted in Appendix B, the current literature search was intended to update the 2006 Toxicological Profile for Cyanide; thus, the literature search was restricted to studies published between January 2004 and August 2023. See Appendix B for the databases searched and the search strategy.

A total of 5,347 records relevant to all sections of the toxicological profile were identified (after duplicate removal).

C.2.2 Literature Screening

As described in Appendix B, a two-step process was used to screen the literature search to identify relevant studies examining the health effects of cyanide.

Title and Abstract Screen. In the Title and Abstract Screen step, 5,347 records were reviewed; 21 documents were considered to meet the health effects inclusion criteria in Table C-1 and were moved to the next step in the process.

Full Text Screen. In the second step in the literature screening process for the systematic review, a full text review of 115 health effect documents (documents identified in the update literature search and

documents cited in older versions of the profile) was performed. From those 115 documents (143 studies), 29 documents (37 studies) were included in the qualitative review.

C.3 EXTRACT DATA FROM HEALTH EFFECTS STUDIES

Relevant data extracted from the individual studies selected for inclusion in the systematic review were collected in customized data forms. A summary of the type of data extracted from each study is presented in Table C-2. For references that included more than one experiment or species, data extraction records were created for each experiment or species.

Table C-2. Data Extracted From Individual Studies

Citation
Chemical form
Route of exposure (e.g., inhalation, oral, dermal)
Specific route (e.g., gavage in oil, drinking water)
Species
Strain
Exposure duration category (e.g., acute, intermediate, chronic)
Exposure duration
Frequency of exposure (e.g., 6 hours/day, 5 days/week)
Exposure length
Number of animals or subjects per sex per group
Dose/exposure levels
Parameters monitored
Description of the study design and method
Summary of calculations used to estimate doses (if applicable)
Summary of the study results
Reviewer's comments on the study
Outcome summary (one entry for each examined outcome)
No-observed-adverse-effect level (NOAEL) value
Lowest-observed-adverse-effect level (LOAEL) value
Effect observed at the LOAEL value

A summary of the extracted data for each study is presented in the Supplemental Document for Cyanide and overviews of the results of the inhalation, oral, and dermal exposure studies are presented in Sections 2.2–2.18 of the profile and in the Levels Significant Exposures tables in Section 2.1 of the profile (Tables 2-1, 2-2, and 2-3, respectively).

C.4 IDENTIFY POTENTIAL HEALTH EFFECT OUTCOMES OF CONCERN

Overviews of the potential health effect outcomes for cyanide identified in human and animal studies are presented in Tables C-3 and C-4, respectively. Available human studies evaluating noncancer effects include numerous case studies and case-series reports; as indicated in Section C-1, only a limited number of case studies and case-series reports were included in the profile. Case studies and case-series reports included in the report were not included in the formal systematic review due to inherent high risk of bias and low confidence based on study design. However, where appropriate, consistent findings from

numerous case studies were considered during the adjustment of the confidence rating (with regards to consistency and/or severity of observed effects). Available epidemiological studies include a limited number of occupational exposure studies and population-based studies of communities with high dietary cassava intake. When evaluated together, these studies suggest that the thyroid and neurological system may be susceptible to cyanide toxicity at sublethal exposure levels. Animal studies evaluated a comprehensive set of endpoints following oral exposure, with only limited information at sublethal exposure levels via inhalation and dermal routes. Based on oral studies, animal data suggest that the thyroid, neurological system, and male reproductive systems may be susceptible to cyanide toxicity. Therefore, thyroid, neurological, and male reproductive effects were considered sensitive outcomes following oral exposure and underwent systematic review. Due to paucity of data, particularly a lack of dose-response information, systematic review was not conducted via the inhalation route. There were 37 studies (published in 29 documents) examining these potential outcomes carried through to Steps 4–8 of the systematic review. Hertting et al. (1960) was not carried through systematic review, despite evaluating the male reproductive system in dogs following oral exposure, because it is a foreign language study with an English abstract; therefore, systematic review questions could not be answered. However, due to use of a single animal per exposure group and lack of a concurrent control, it is not considered a reliable study (therefore, it was not translated into English for systematic review).

APPENDIX C

Table C-3. Overview of the Health Outcomes for Cyanide Evaluated In Human Studies

	Body weight	Respiratory	Cardiovascular	Gastrointestinal	Hematological	Musculoskeletal	Hepatic	Renal	Dermal	Ocular	Endocrine	Immunological	Neurological	Reproductive	Developmental	Other Noncancer	Cancer
Inhalation studies																	
Cohort	1 1	1 1	1 1	1 1					1 1	1 1	1 1		2 2				
Case control																	
Cross-sectional		3 3	2 2	1 1	2 2		2 2	1 0	1 0	4 4	1 1	1 1	4 4			1 0	
Case series		3 3	2 2					1 1	1 1				7 7				
Controlled exposure		1 1								1 1							
Oral studies																	
Cohort																	
Case control																	
Population											2 2		4 4				
Case series		7 7	2 2	4 4	1 0	2 2		1 1		1 1			21 21			3 3	
Dermal studies																	
Cohort																	
Case control																	
Population																	
Case series		3 3	2 2				1 1						4 4				
Number of studies examining endpoint				0	1	2	3	4	5–9	≥10							
Number of studies reporting outcome				0	1	2	3	4	5–9	≥10							

APPENDIX C

Table C-4. Overview of the Health Outcomes for Cyanide Evaluated in Experimental Animal Studies

	Body weight	Respiratory	Cardiovascular	Gastrointestinal	Hematological	Musculoskeletal	Hepatic	Renal	Dermal	Ocular	Endocrine	Immunological[a]	Neurological[a]	Reproductive[a]	Developmental	Other Noncancer	Caner
Inhalation studies																	
Acute-duration		5 5	2 2						1 0	1 1			10 9				
Intermediate-duration	1 1	3 1	2 0	1 1	2 0	2 0	2 0	2 0					2 2				
Chronic-duration																	
Oral studies																	
Acute-duration	4 0	4 2	5 2				9 4	6 3			4 2		13 11	8 4	5 3	4 2	
Intermediate-duration	18 10	5 3	7 1	4 1	6 3		15 9	9 6	4 2	3 2	11 7	2 0	9 7	10 9	4 3	3 2	
Chronic-duration		1 0	1 0	1 1			1 0	2 1					2 1				
Dermal studies																	
Acute-duration		6 6		1 1					1 1	3 3			8 8				
Intermediate-duration																	
Chronic-duration																	

Number of studies examining endpoint	0	1	2	3	4	5–9	≥10
Number of studies reporting outcome	0	1	2	3	4	5–9	≥10

[a]Number of studies examining endpoint includes study evaluating histopathology, but not evaluating function.

C.5 ASSESS THE RISK OF BIAS FOR INDIVIDUAL STUDIES

C.5.1 Risk of Bias Assessment

The risk of bias of individual studies was assessed using OHAT's Risk of Bias Tool (NTP 2015). The risk of bias questions for observational epidemiology studies, human-controlled exposure studies, and animal experimental studies are presented in Tables C-5, C-6, and C-7, respectively. Each risk of bias question was answered on a four-point scale:

- **Definitely low risk of bias (++)**
- **Probably low risk of bias (+)**
- **Probably high risk of bias (-)**
- **Definitely high risk of bias (– –)**

In general, "definitely low risk of bias" or "definitely high risk of bias" were used if the question could be answered with information explicitly stated in the study report. If the response to the question could be inferred, then "probably low risk of bias" or "probably high risk of bias" responses were typically used.

Table C-5. Risk of Bias Questionnaire for Observational Epidemiology Studies

Selection bias
Were the comparison groups appropriate?
Confounding bias
Did the study design or analysis account for important confounding and modifying variables?
Attrition/exclusion bias
Were outcome data complete without attrition or exclusion from analysis?
Detection bias
Is there confidence in the exposure characterization?
Is there confidence in outcome assessment?
Selective reporting bias
Were all measured outcomes reported?

Table C-6. Risk of Bias Questionnaire for Human-Controlled Exposure Studies

Selection bias
Was administered dose or exposure level adequately randomized?
Was the allocation to study groups adequately concealed?
Performance bias
Were the research personnel and human subjects blinded to the study group during the study?
Attrition/exclusion bias
Were outcome data complete without attrition or exclusion from analysis?
Detection bias
Is there confidence in the exposure characterization?
Is there confidence in outcome assessment?
Selective reporting bias
Were all measured outcomes reported?

Table C-7. Risk of Bias Questionnaire for Experimental Animal Studies

Selection bias
Was administered dose or exposure level adequately randomized?
Was the allocation to study groups adequately concealed?
Performance bias
Were experimental conditions identical across study groups?
Were the research personnel blinded to the study group during the study?
Attrition/exclusion bias
Were outcome data complete without attrition or exclusion from analysis?
Detection bias
Is there confidence in the exposure characterization?
Is there confidence in outcome assessment?
Selective reporting bias
Were all measured outcomes reported?

After the risk of bias questionnaires were completed for the health effects studies, the studies were assigned to one of three risk of bias tiers based on the responses to the key questions listed below and the responses to the remaining questions.

- Is there confidence in the exposure characterization? (only relevant for observational studies)
- Is there confidence in the outcome assessment?
- Does the study design or analysis account for important confounding and modifying variables? (only relevant for observational studies)

First Tier. Studies placed in the first tier received ratings of "definitely low" or "probably low" risk of bias on the key questions **AND** received a rating of "definitely low" or "probably low" risk of bias on the responses to at least 50% of the other applicable questions.

Second Tier. A study was placed in the second tier if it did not meet the criteria for the first or third tiers.

Third Tier. Studies placed in the third tier received ratings of "definitely high" or "probably high" risk of bias for the key questions **AND** received a rating of "definitely high" or "probably high" risk of bias on the response to at least 50% of the other applicable questions.

The results of the risk of bias assessment for the different types of cyanide health effects studies (observational epidemiology and animal experimental studies) are presented in Tables C-8 and C-9, respectively.

Table C-8. Summary of Risk of Bias Assessment for Cyanide—Observational Epidemiology Studies

Reference	Risk of bias criteria and ratings						Risk of bias tier
	Selection bias	Confounding bias	Attrition / exclusion bias	Detection bias		Selective reporting bias	
	Were the comparison groups appropriate?	Did the study design or analysis account for important confounding and modifying variables?*	Were outcome data complete without attrition or exclusion from analysis?	Is there confidence in the exposure characterization?*	Is there confidence in the outcome assessment?*	Were all measured outcomes reported?	
Outcome: Thyroid effects							
Population							
Delange and Ermans 1971	+	–	+	– –	+	+	Second
Cliff et al. 1986	+	–	+	–	+	+	Second
Outcome: Neurological effects							
Population							
Money 1958	– –	– –	+	– –	+	+	Second
Osuntokun 1968	+	–	+	–	++	+	Second
Osuntokun 1972	+	–	+	–	++	+	Second
Osuntokun et al. 1969	++	–	+	–	++	+	Second

++ = definitely low risk of bias; + = probably low risk of bias; – = probably high risk of bias; – – = definitely high risk of bias; na = not applicable

*Key question used to assign risk of bias tier

Table C-9. Summary of Risk of Bias Assessment for Cyanide—Experimental Animal Studies

Reference	Risk of bias criteria and ratings: Selection bias: Was administered dose or exposure level adequately randomized?	Selection bias: Was the allocation to study groups adequately concealed?	Performance bias: Were experimental conditions identical across study groups?	Performance bias: Were the research personnel blinded to the study group during the study?	Attrition/ exclusion bias: Were outcome data complete without attrition or exclusion from analysis?	Detection bias: Is there confidence in the exposure characterization?	Detection bias: Is there confidence in the outcome assessment?*	Selective reporting bias: Were all measured outcomes reported?	Other bias: Did the study clearly identify if reported doses were in terms of administered compound or cyanide ion?	Risk of bias tier
Outcome: Thyroid effects										
Oral acute exposure										
de Sousa et al. 2007	+	+	+	+	–	+	–	–	++	Second
Hawk et al. 2016	–	+	+	+	+	++	–	+	++	Second
Sabourin et al. 2016	++	+	–	+	–	++	–	–	++	Second
Oral intermediate exposure										
Avais et al. 2018	++	+	++	+	++	–	–	–	++	Second
Kamalu 1991, 1993; Kamalu and Agharanya 1991	+	+	–	+	++	–	–	++	++	Second
NTP 1993 (rat)	++	+	++	+	++	+	–	++	++	Second
NTP 1993 (mice)	++	+	++	+	++	+	–	++	++	Second
Philbrick et al. 1979	–	–	++	–	++	–	–	++	+	Third
Soto-Blanco et al. 2002	++	+	++	+	++	+	++	++	++	First
Sousa et al. 2002	+	+	+	+	++	++	+	++	++	First
Tyner 2024; Tyner and Greeley 2023	++	+	++	+	++	++	++	++	++	First

Table C-9. Summary of Risk of Bias Assessment for Cyanide—Experimental Animal Studies

Reference	Risk of bias criteria and ratings: Selection bias — Was administered dose or exposure level adequately randomized?	Selection bias — Was the allocation to study groups adequately concealed?	Performance bias — Were experimental conditions identical across study groups?	Performance bias — Were the research personnel blinded to the study group during the study?	Attrition/ exclusion bias — Were outcome data complete without attrition or exclusion from analysis?	Detection bias — Is there confidence in the exposure characterization?	Detection bias — Is there confidence in the outcome assessment?*	Selective reporting bias — Were all measured outcomes reported?	Other bias — Did the study clearly identify if reported doses were in terms of administered compound or cyanide ion?	Risk of bias tier
Outcome: Neurological effects										
Oral acute exposure										
de Sousa et al. 2007	+	+	+	+	–	+	–	–	++	Second
Hawk et al. 2016	–	–	+	–	+	++	+	+	++	First
Ishaku et al. 2018	++	+	++	++	++	+	–	++	++	Second
Ogundele et al. 2014b	+	+	++	+	++	+	+	++	++	First
Rice et al. 2018 (dose-finding)	++	–	+	–	+	+	–	+	++	Second
Rice et al. 2018 (operant training)	++	+	+	+	+	+	–	+	++	Second
Sabourin et al. 2016	++	+	–	+	–	++	–	–	++	Second
Oral intermediate exposure										
Gerhart 1986	–	–	–	–	++	+	–	++	++	Third
Gerhart 1987	–	–	–	–	++	+	–	++	++	Third
Ishaku et al. 2018	++	+	++	++	++	+	–	++	++	Second
Kamalu 1991, 1993	+	–	–	–	+	–	– –	+	++	Third
Mathangi et al. 2011	+	+	++	+	++	+	+	++	++	Second
NTP 1993 (rat)	++	+	++	+	++	+	+	++	++	First
NTP 1993 (mice)	++	+	++	+	++	+	+	++	++	First
Philbrick et al. 1979	–	–	++	–	++	–	–	++	+	Second

Table C-9. Summary of Risk of Bias Assessment for Cyanide—Experimental Animal Studies

Reference	Risk of bias criteria and ratings									Risk of bias tier
	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	Other bias	
	Was administered dose or exposure level adequately randomized?	Was the allocation to study groups adequately concealed?	Were experimental conditions identical across study groups?	Were the research personnel blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Is there confidence in the exposure characterization?	Is there confidence in the outcome assessment?*	Were all measured outcomes reported?	Did the study clearly identify if reported doses were in terms of administered compound or cyanide ion?	
Soto-Blanco et al. 2002	++	+	++	+	++	+	+	++	++	First
Oral chronic exposure										
Howard and Hanzal 1955	–	–	–	–	–	– –	–	–	++	Third
Outcome: Male reproductive effects										
Oral acute exposure										
Hawk et al. 2016	–	+	+	+	+	++	–	+	++	Second
Sabourin et al. 2016	++	+	–	+	–	++	–	–	++	Second
Oral intermediate exposure										
Gerhart 1986	–	+	–	+	++	+	–	++	++	Second
Gerhart 1987	–	+	–	+	++	+	–	++	++	Second
Kamalu 1991, 1993	+	+	–	+	+	–	– –	++	++	Second
NTP 1993 (rat)	++	+	++	+	++	+	–	++	++	Second
NTP 1993 (mice)	++	+	++	+	++	+	–	++	++	Second
Oyewopo et al. 2021a	+	+	++	+	++	+	–	++	++	Second
Oyewopo et al. 2021b	++	+	++	+	++	–	–	++	+	Second
Shivanoor and David 2015	+	+	+	+	+	–	+	+	–	First
Tyner 2024; Tyner and Greeley 2023	++	+	++	+	++	++	++	++	++	First
Oral chronic exposure										

Table C-9. Summary of Risk of Bias Assessment for Cyanide—Experimental Animal Studies

Reference	Risk of bias criteria and ratings									Risk of bias tier
	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	Other bias	
	Was administered dose or exposure level adequately randomized?	Was the allocation to study groups adequately concealed?	Were experimental conditions identical across study groups?	Were the research personnel blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Is there confidence in the exposure characterization?	Is there confidence in the outcome assessment?*	Were all measured outcomes reported?	Did the study clearly identify if reported doses were in terms of administered compound or cyanide ion?	
Howard and Hanzal 1955	–	–	–	–	–	– –	–	–	++	Third

++ = definitely low risk of bias; + = probably low risk of bias; – = probably high risk of bias; – – = definitely high risk of bias; na = not applicable

*Key question used to assign risk of bias tier

C.6 RATE THE CONFIDENCE IN THE BODY OF EVIDENCE FOR EACH RELEVANT OUTCOME

Confidences in the bodies of human and animal evidence were evaluated independently for each potential outcome. ATSDR did not evaluate the confidence in the body of evidence for carcinogenicity; rather, the Agency defaulted to the cancer weight-of-evidence assessment of other agencies including HHS, EPA, and IARC. The confidence in the body of evidence for an association or no association between exposure to cyanide and a particular outcome was based on the strengths and weaknesses of individual studies. Four descriptors were used to describe the confidence in the body of evidence for effects or when no effect was found:

- **High confidence:** the true effect is highly likely to be reflected in the apparent relationship
- **Moderate confidence:** the true effect may be reflected in the apparent relationship
- **Low confidence:** the true effect may be different from the apparent relationship
- **Very low confidence:** the true effect is highly likely to be different from the apparent relationship

Confidence in the body of evidence for a particular outcome was rated for each type of study: case-control, case series, cohort, population, human-controlled exposure, and experimental animal. In the absence of data to the contrary, data for a particular outcome were collapsed across animal species, routes of exposure, and exposure durations. If species (or strain), route, or exposure duration differences were noted, then the data were treated as separate outcomes.

C.6.1 Initial Confidence Rating

In ATSDR's modification to the OHAT approach, the body of evidence for an association (or no association) between exposure to cyanide and a particular outcome was given an initial confidence rating based on the key features of the individual studies examining that outcome. The presence of these key features of study design was determined for individual studies using four "yes or no" questions, which were customized for epidemiology, human controlled exposure, or experimental animal study designs. Separate questionnaires were completed for each outcome assessed in a study. The key features for observational epidemiology (cohort, population, and case-control) studies, human controlled exposure, and experimental animal studies are presented in Tables C-10, C-11, and C-12, respectively. The initial confidence in the study was determined based on the number of key features present in the study design:

- **High Initial Confidence:** Studies in which the responses to the four questions were "yes".

- **Moderate Initial Confidence:** Studies in which the responses to only three of the questions were "yes".

- **Low Initial Confidence:** Studies in which the responses to only two of the questions were "yes".

- **Very Low Initial Confidence:** Studies in which the response to one or none of the questions was "yes".

Table C-10. Key Features of Study Design for Observational Epidemiology Studies

Exposure was experimentally controlled
Exposure occurred prior to the outcome
Outcome was assessed on individual level rather than at the population level
A comparison group was used

Table C-11. Key Features of Study Design for Human-Controlled Exposure Studies

A comparison group was used or the subjects served as their own control
A sufficient number of subjects were tested
Appropriate methods were used to measure outcomes (i.e., clinically-confirmed outcome versus self-reported)
Appropriate statistical analyses were performed and reported or the data were reported in such a way to allow independent statistical analysis

Table C-12. Key Features of Study Design for Experimental Animal Studies

A concurrent control group was used
A sufficient number of animals per group were tested
Appropriate parameters were used to assess a potential adverse effect
Appropriate statistical analyses were performed and reported or the data were reported in such a way to allow independent statistical analysis

The presence or absence of the key features and the initial confidence levels for studies examining thyroid effects, neurological, and male reproductive effects observed in the observational epidemiology and animal experimental studies are presented in Tables C-13 and C-14, respectively.

Table C-13. Presence of Key Features of Study Design for Cyanide—Observational Epidemiology Studies

	Key features				
Reference	Controlled exposure	Exposure prior to outcome	Outcomes assessed on an individual level	Comparison group	Initial study confidence
Outcome: Thyroid effects					
Case series					
Delange and Ermans 1971	No	Yes	Yes	Yes	Moderate
Cliff et al. 1986	No	Yes	Yes	Yes	Moderate

Table C-13. Presence of Key Features of Study Design for Cyanide—Observational Epidemiology Studies

Reference	Key features: Controlled exposure	Exposure prior to outcome	Outcomes assessed on an individual level	Comparison group	Initial study confidence
Outcome: Neurological effects					
Population					
Money 1958	No	Yes	Yes	No	Low
Osuntokun 1968	No	Yes	Yes	Yes	Moderate
Osuntokun 1972	No	Yes	Yes	Yes	Moderate
Osuntokun et al. 1969	No	Yes	Yes	Yes	Moderate

Table C-14. Presence of Key Features of Study Design for Cyanide—Experimental Animal Studies

Reference	Key feature: Concurrent control group	Sufficient number of animals per group	Appropriate parameters to assess potential effect	Adequate data for statistical analysis	Initial study confidence
Outcome: Thyroid effects					
Oral acute exposure					
de Sousa et al. 2007	Yes	No	No	No	Very Low
Hawk et al. 2016	Yes	Yes	No	Yes	Moderate
Sabourin et al. 2016	Yes	No	No	No	Very Low
Oral intermediate exposure					
Avais et al. 2018	Yes	No	No	Yes	Low
Kamalu 1991, 1993; Kamalu and Agharanya 1991	Yes	Yes	No	Yes	Moderate
NTP 1993 (rat)	Yes	Yes	No	Yes	Moderate
NTP 1993 (mice)	Yes	Yes	No	Yes	Moderate
Philbrick et al. 1979	Yes	Yes	No	Yes	Moderate
Soto-Blanco et al. 2002	Yes	No	Yes	Yes	Moderate
Sousa et al. 2002	Yes	No	Yes	Yes	Moderate
Tyner and Greeley 2023	Yes	Yes	Yes	Yes	High

Table C-14. Presence of Key Features of Study Design for Cyanide—Experimental Animal Studies

Reference	Key feature: Concurrent control group	Key feature: Sufficient number of animals per group	Key feature: Appropriate parameters to assess potential effect	Key feature: Adequate data for statistical analysis	Initial study confidence
Outcome: Neurological effects					
Oral acute exposure					
de Sousa et al. 2007	Yes	No	No	No	Very Low
Hawk et al. 2016	Yes	Yes	Yes	Yes	High
Ishaku et al. 2018	Yes	Yes	Yes	Yes	Moderate
Ogundele et al. 2014a	Yes	No	Yes	Yes	Moderate
Rice et al. 2018	No	No	Yes	Yes	Low
Rice et al. 2018	No	Yes	Yes	Yes	Moderate
Sabourin et al. 2016	Yes	No	No	No	Low
Oral intermediate exposure					
Gerhart 1986	Yes	Yes	No	Yes	Moderate
Gerhart 1987	Yes	Yes	No	Yes	Moderate
Ishaku et al. 2018	Yes	Yes	Yes	Yes	Moderate
Kamalu 1993	Yes	Yes	No	Yes	Moderate
Mathangi et al. 2011	Yes	Yes	Yes	Yes	High
NTP 1993 (rat)	Yes	Yes	No	Yes	Moderate
NTP 1993 (mice)	Yes	Yes	No	Yes	Moderate
Philbrick et al. 1979	Yes	Yes	No	No	Low
Soto-Blanco et al. 2002	Yes	No	No	Yes	Low
Oral chronic exposure					
Howard and Hanzal 1955	Yes	No	No	No	Very Low
Outcome: Male reproductive effects					
Oral acute exposure					
Hawk et al. 2016	Yes	Yes	No	Yes	Moderate
Sabourin et al. 2016	Yes	No	No	No	Low
Oral intermediate exposure					
Gerhart 1986	Yes	Yes	Yes	Yes	High
Gerhart 1987	Yes	Yes	Yes	Yes	High
Kamalu 1991, 1993	Yes	Yes	Yes	Yes	High
NTP 1993 (rat)	Yes	Yes	Yes	Yes	High
NTP 1993 (mice)	Yes	Yes	Yes	Yes	High
Oyewopo et al. 2021a	Yes	Yes	No	Yes	Low

Table C-14. Presence of Key Features of Study Design for Cyanide—Experimental Animal Studies

Reference	Key feature: Concurrent control group	Key feature: Sufficient number of animals per group	Key feature: Appropriate parameters to assess potential effect	Key feature: Adequate data for statistical analysis	Initial study confidence
Oyewopo et al. 2021b	Yes	Yes	Yes	Yes	Moderate
Shivanoor and David 2015	Yes	Yes	Yes	Yes	High
Tyner and Greeley 2023	Yes	Yes	Yes	Yes	High
Oral chronic exposure					
Howard and Hanzal 1955	Yes	No	Yes	No	Low

A summary of the initial confidence ratings for each outcome is presented in Table C-15. If individual studies for a particular outcome and study type had different study quality ratings, then the highest confidence rating for the group of studies was used to determine the initial confidence rating for the body of evidence; any exceptions were noted in Table C-15.

Table C-15. Initial Confidence Rating for Cyanide Health Effects Studies

	Initial study confidence	Initial confidence rating
Outcome: Thyroid effects		
Oral acute exposure		
Animal studies		
de Sousa et al. 2007	Very Low	Moderate
Hawk et al. 2016	Moderate	
Sabourin et al. 2016	Very Low	
Oral intermediate exposure		
Animal studies		
Avais et al. 2018	Low	High
Kamalu 1991, 1993; Kamalu and Agharanya 1991	Moderate	
NTP 1993 (rat)	Moderate	
NTP 1993 (mice)	Moderate	
Philbrick et al. 1979	Moderate	
Soto-Blanco et al. 2002	Moderate	
Sousa et al. 2002	Moderate	
Tyner and Greeley 2023	High	

Table C-15. Initial Confidence Rating for Cyanide Health Effects Studies

	Initial study confidence	Initial confidence rating
Oral chronic exposure		
Human studies		
Delange and Ermans 1971	Moderate	Moderate
Cliff et al. 1986	Moderate	
Outcome: Neurological effects		
Oral acute exposure		
Animal studies		
de Sousa et al. 2007	Very Low	High
Hawk et al. 2016	High	
Ishaku et al. 2018	Moderate	
Ogundele et al. 2014a	Moderate	
Rice et al. 2018	Low	
Rice et al. 2018	Moderate	
Sabourin et al. 2016	Low	
Oral intermediate exposure		
Animal studies		
Gerhart 1986	Moderate	High
Gerhart 1987	Moderate	
Ishaku et al. 2018	Moderate	
Kamalu 1993	Moderate	
Mathangi et al. 2011	High	
NTP 1993 (rat)	Moderate	
NTP 1993 (mice)	Moderate	
Philbrick et al. 1979	Low	
Soto-Blanco et al. 2002	Low	
Oral chronic exposure		
Human studies		
Money 1958	Low	Moderate
Osuntokun 1968	Moderate	
Osuntokun 1972	Moderate	
Osuntokun et al. 1969	Moderate	
Animal studies		
Howard and Hanzal 1955	Low	Low
Outcome: Male reproductive effects		
Oral acute exposure		
Animal studies		
Hawk et al. 2016	Moderate	Moderate
Sabourin et al. 2016	Low	

Table C-15. Initial Confidence Rating for Cyanide Health Effects Studies

	Initial study confidence	Initial confidence rating
Oral intermediate exposure		
Animal studies		
Gerhart 1986	High	High
Gerhart 1987	High	
Kamalu 1991, 1993	High	
NTP 1993 (rat)	High	
NTP 1993 (mice)	High	
Oyewopo et al. 2021a	Low	
Oyewopo et al. 2021b	Moderate	
Shivanoor and David 2015	High	
Tyner 2024; Tyner and Greeley 2023	High	
Oral chronic exposure		
Animal studies		
Howard and Hanzal 1955	Low	Low

C.6.2 Adjustment of the Confidence Rating

The initial confidence rating was then downgraded or upgraded depending on whether there were substantial issues that would decrease or increase confidence in the body of evidence. The nine properties of the body of evidence that were considered are listed below. The summaries of the assessment of the confidence in the body of evidence for thyroid, neurological, and male reproductive effects following oral exposure are presented in Table C-16. If the confidence ratings for a particular outcome were based on more than one type of human study, then the highest confidence rating was used for subsequent analyses. An overview of the confidence in the body of evidence for all health effects associated with cyanide exposure is presented in Table C-17.

Table C-16. Adjustments to the Initial Confidence in the Body of Evidence

	Initial confidence	Adjustments to the initial confidence rating	Final confidence
Outcome: Thyroid effects			
Human studies	Moderate	-1 risk of bias	Low
Animal studies	High	-1 risk of bias	Moderate
Outcome: Neurological effects			
Human studies	Moderate	-1 risk of bias +1 large magnitude of effect +1 consistency in body of evidence	High
Animal studies	High	-1 risk of bias +1 large magnitude of effect	High

Table C-16. Adjustments to the Initial Confidence in the Body of Evidence

	Initial confidence	Adjustments to the initial confidence rating	Final confidence
Outcome: Male reproductive			
Animal studies	High	-1 risk of bias -1 unexplained inconsistency (drinking water studies) +1 consistency in body of evidence (gavage studies)	Moderate

Table C-17. Confidence in the Body of Evidence for Cyanide

	Confidence in body of evidence	
Outcome	Human studies	Animal studies
Thyroid effects (oral exposure)	Low	Moderate
Neurological effects (oral exposure)	High	High
Male reproductive effects (oral exposure)	No data	Low

Five properties of the body of evidence were considered to determine whether the confidence rating should be downgraded:

- **Risk of bias.** Evaluation of whether there is substantial risk of bias across most of the studies examining the outcome. This evaluation used the risk of bias tier groupings for individual studies examining a particular outcome (Tables C-8 and C-9). Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for risk of bias:
  - No downgrade if most studies are in the risk of bias first tier
  - Downgrade one confidence level if most studies are in the risk of bias second tier
  - Downgrade two confidence levels if most studies are in the risk of bias third tier

- **Unexplained inconsistency.** Evaluation of whether there is inconsistency or large variability in the magnitude or direction of estimates of effect across studies that cannot be explained. Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for unexplained inconsistency:
  - No downgrade if there is little inconsistency across studies or if only one study evaluated the outcome
  - Downgrade one confidence level if there is variability across studies in the magnitude or direction of the effect
  - Downgrade two confidence levels if there is substantial variability across studies in the magnitude or direct of the effect

- **Indirectness.** Evaluation of four factors that can affect the applicability, generalizability, and relevance of the studies:
  - Relevance of the animal model to human health—unless otherwise indicated, studies in rats, mice, and other mammalian species are considered relevant to humans

- Directness of the endpoints to the primary health outcome—examples of secondary outcomes or nonspecific outcomes include organ weight in the absence of histopathology or clinical chemistry findings in the absence of target tissue effects
- Nature of the exposure in human studies and route of administration in animal studies—inhalation, oral, and dermal exposure routes are considered relevant unless there are compelling data to the contrary
- Duration of treatment in animal studies and length of time between exposure and outcome assessment in animal and prospective human studies—this should be considered on an outcome-specific basis

Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for indirectness:

- No downgrade if none of the factors are considered indirect
- Downgrade one confidence level if one of the factors is considered indirect
- Downgrade two confidence levels if two or more of the factors are considered indirect

- **Imprecision.** Evaluation of the narrowness of the effect size estimates and whether the studies have adequate statistical power. Data are considered imprecise when the ratio of the upper to lower 95% CIs for most studies is ≥10 for tests of ratio measures (e.g., odds ratios) and ≥100 for absolute measures (e.g., percent control response). Adequate statistical power is determined if the study can detect a potentially biologically meaningful difference between groups (20% change from control response for categorical data or risk ratio of 1.5 for continuous data). Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for imprecision:
  - No downgrade if there are no serious imprecisions
  - Downgrade one confidence level for serious imprecisions
  - Downgrade two confidence levels for very serious imprecisions

- **Publication bias.** Evaluation of the concern that studies with statistically significant results are more likely to be published than studies without statistically significant results.
  - Downgrade one level of confidence for cases where there is serious concern with publication bias

Four properties of the body of evidence were considered to determine whether the confidence rating should be upgraded:

- **Large magnitude of effect.** Evaluation of whether the magnitude of effect is sufficiently large so that it is unlikely to have occurred as a result of bias from potential confounding factors.
  - Upgrade one confidence level if there is evidence of a large magnitude of effect in a few studies, provided that the studies have an overall low risk of bias and there is no serious unexplained inconsistency among the studies of similar dose or exposure levels; confidence can also be upgraded if there is one study examining the outcome, provided that the study has an overall low risk of bias

- **Dose response.** Evaluation of the dose-response relationships measured within a study and across studies. Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be upgraded:
  - Upgrade one confidence level for evidence of a monotonic dose-response gradient
  - Upgrade one confidence level for evidence of a non-monotonic dose-response gradient where there is prior knowledge that supports a non-monotonic dose-response and a non-monotonic dose-response gradient is observed across studies

- **Plausible confounding or other residual biases.** This factor primarily applies to human studies and is an evaluation of unmeasured determinants of an outcome such as residual bias towards the null (e.g., "healthy worker" effect) or residual bias suggesting a spurious effect (e.g., recall bias). Below is the criterion used to determine whether the initial confidence in the body of evidence for each outcome should be upgraded:
  - Upgrade one confidence level for evidence that residual confounding or bias would underestimate an apparent association or treatment effect (i.e., bias toward the null) or suggest a spurious effect when results suggest no effect

- **Consistency in the body of evidence.** Evaluation of consistency across animal models and species, consistency across independent studies of different human populations and exposure scenarios, and consistency across human study types. Below is the criterion used to determine whether the initial confidence in the body of evidence for each outcome should be upgraded:
  - Upgrade one confidence level if there is a high degree of consistency in the database

C.7 TRANSLATE CONFIDENCE RATING INTO LEVEL OF EVIDENCE OF HEALTH EFFECTS

In the seventh step of the systematic review of the health effects data for cyanide, the confidence in the body of evidence for specific outcomes was translated to a level of evidence rating. The level of evidence rating reflected the confidence in the body of evidence and the direction of the effect (i.e., toxicity or no toxicity); route-specific differences were noted. The level of evidence for health effects was rated on a five-point scale:

- **High level of evidence:** High confidence in the body of evidence for an association between exposure to the substance and the health outcome
- **Moderate level of evidence:** Moderate confidence in the body of evidence for an association between exposure to the substance and the health outcome
- **Low level of evidence:** Low confidence in the body of evidence for an association between exposure to the substance and the health outcome
- **Evidence of no health effect:** High confidence in the body of evidence that exposure to the substance is not associated with the health outcome
- **Inadequate evidence:** Low or moderate confidence in the body of evidence that exposure to the substance is not associated with the health outcome OR very low confidence in the body of evidence for an association between exposure to the substance and the health outcome

A summary of the level of evidence of health effects for cyanide is presented in Table C-18.

Table C-18. Level of Evidence of Health Effects for Cyanide

Outcome	Confidence in body of evidence	Direction of health effect	Level of evidence for health effect
Human studies			
Thyroid (oral)	Low	Effect	Low
Neurological (oral)	High	Effect	High
Animal studies			
Thyroid (oral)	Moderate	Effect	Moderate
Neurological (oral)	High	Effect	High
Male reproductive (oral)	Moderate	Effect	Moderate

C.8 INTEGRATE EVIDENCE TO DEVELOP HAZARD IDENTIFICATION CONCLUSIONS

The final step involved the integration of the evidence streams for the human and animal studies to allow for a determination of hazard identification conclusions. For health effects, there were four hazard identification conclusion categories:

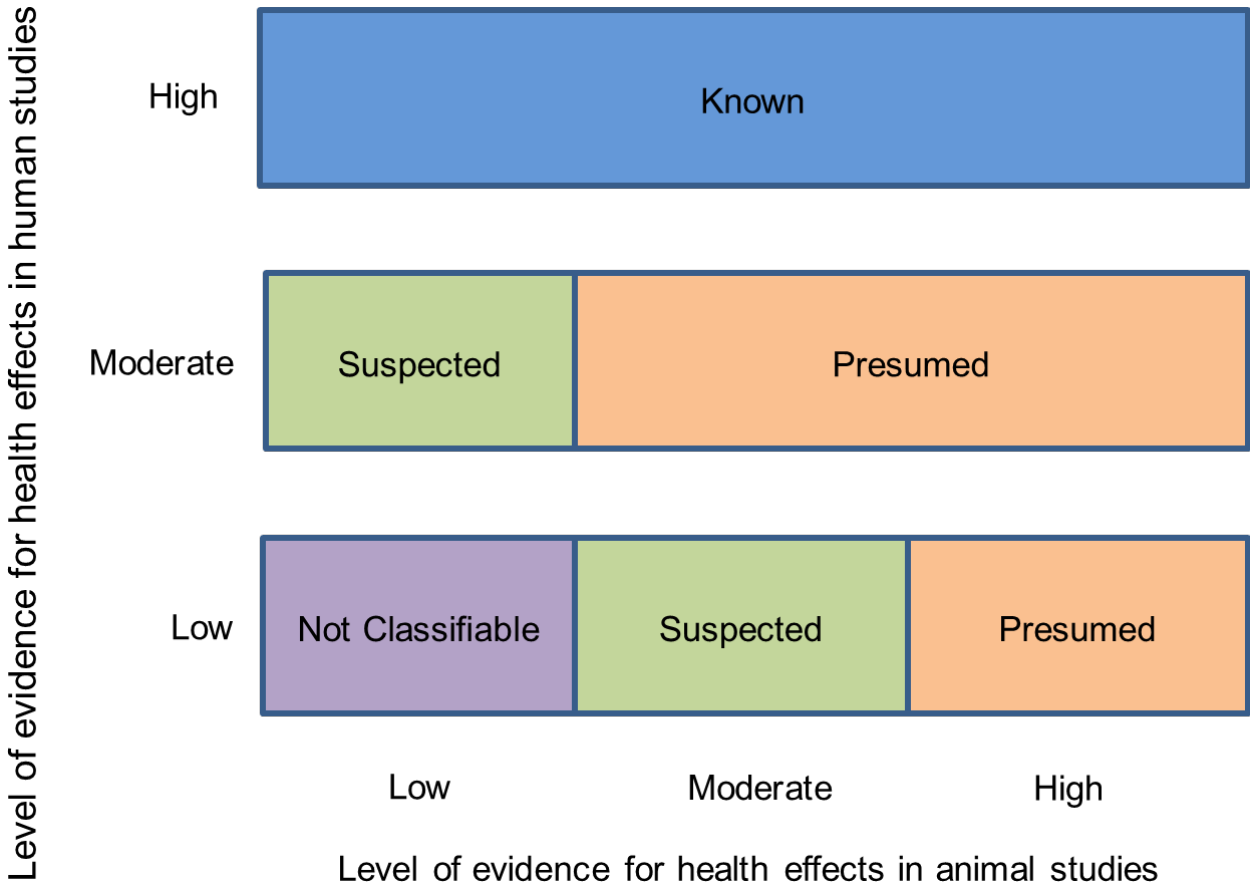
- **Known** to be a hazard to humans
- **Presumed** to be a hazard to humans
- **Suspected** to be a hazard to humans
- **Not classifiable** as to the hazard to humans

The initial hazard identification was based on the highest level of evidence in the human studies and the level of evidence in the animal studies; if there were no data for one evidence stream (human or animal), then the hazard identification was based on the one data stream (equivalent to treating the missing evidence stream as having low level of evidence). The hazard identification scheme is presented in Figure C-1 and described below:

- **Known:** A health effect in this category would have:
  - High level of evidence for health effects in human studies **AND** a high, moderate, or low level of evidence in animal studies.
- **Presumed:** A health effect in this category would have:
  - Moderate level of evidence in human studies **AND** high or moderate level of evidence in animal studies **OR**
  - Low level of evidence in human studies **AND** high level of evidence in animal studies
- **Suspected:** A health effect in this category would have:
  - Moderate level of evidence in human studies **AND** low level of evidence in animal studies **OR**
  - Low level of evidence in human studies **AND** moderate level of evidence in animal studies
- **Not classifiable:** A health effect in this category would have:
  - Low level of evidence in human studies **AND** low level of evidence in animal studies

Other relevant data such as mechanistic or mode-of-action data were considered to raise or lower the level of the hazard identification conclusion by providing information that supported or opposed biological plausibility.

Figure C-1. Hazard Identification Scheme



Two hazard identification conclusion categories were used when the data indicated that there may be no health effect in humans:

- **Not identified** to be a hazard in humans
- **Inadequate** to determine hazard to humans

If the human level of evidence conclusion of no health effect was supported by the animal evidence of no health effect, then the hazard identification conclusion category of "not identified" was used. If the human or animal level of evidence was considered inadequate, then a hazard identification conclusion category of "inadequate" was used. As with the hazard identification for health effects, the impact of other relevant data was also considered for no health effect data.

The hazard identification conclusions for cyanide are listed below and summarized in Table C-19.

Known Health Effects

- Neurological effects (oral exposure)
  - There is evidence of regional outbreaks of neurological disease in African communities reliant on a diet rich in cassava as a carbohydrate source (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). While other compounds in cassava may

contribute to observed effects, findings are strengthened by strong evidence of neurological effects from case reports and case-series reports that the CNS is a primary target following high-level cyanide exposure (see Section 2.15 for references). Even single exposures to high doses have resulted in permanent neurological dysfunction (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; Zaknun et al. 2005).

- Damage to the tissues of the CNS have been observed in animal studies following acute- and intermediate-duration exposure to cyanide compounds (de Sousa et al. 2007; Philbrick et al. 1979; Soto-Blanco et al. 2002). Data at nonlethal doses in animals are limited, with few studies evaluating sensitive neurobehavioral outcomes, particularly repeat-dose exposure via relevant exposure routes (drinking water or dietary exposures), increasing risk of bias. However, bolus administration studies are consistent with human poisoning cases, showing neurobehavioral changes at low doses (Hawk et al. 2016; Ishaku et al. 2018; Mathangi et al. 2011; Ogundele et al. 2014b) and overt and severe clinical signs of neurotoxicity prior to death at lethal doses (Gerhart 1987; Rice et al. 2018; Sabourin et al. 2016).
- Numerous plausible mechanisms of neurotoxicity have been proposed for cyanide; however, CNS effects are likely due to inhibition of cytochrome c oxidase activity and subsequent rapid biochemical changes in the brain such as changes in ion flux, neurotransmitter releases, and potentially oxidative stress (Chance and Erecinska 1971; Gibson and Greenwood 1963; Johnson and Isom 1985; Kanthasamy et al. 1991a, 1994; Persson et al. 1985; Pettersen and Cohen 1993; Smith 1996)

Presumed Health Effects

- Thyroid effects (oral exposure)
  - There is limited evidence of endemic goiter and altered thyroid function in African communities reliant on a diet rich in cassava as a carbohydrate source (Cliff et al. 1986; Delange and Ermans 1971).
  - Adverse thyroid effects (altered serum hormones, enlarged thyroid) have been reported in rats and rabbits following intermediate-duration oral exposure to cyanide compounds (Avais et al. 2018; Philbrick et al. 1979; Tyner and Greeley 2023). At lower doses, evidence of induction of potential homeostatic mechanisms for thyroid function (dose-related increases in the number of resorption vacuoles in the thyroid gland) in the absence of clear evidence of altered thyroid function have also been reported (de Sousa et al. 2007; Sousa et al. 2002)
  - The proposed mechanism of action for thyroid toxicity is competitive inhibition of the sodium-iodine symporter by the metabolite thiocyanate, which has a higher binding affinity than the physiological ligand, iodine (De Groef et al. 2006; EPA 2010; Tonacchera et al. 2004).
  - Considering the well-established competitive inhibition of the sodium-iodine symporter by thiocyanate, the hazard conclusion of suspected health effect based on low evidence in humans and moderate evidence in animals was upgraded to presumed health effect, incorporating evidence from all three data streams (human, animal, mechanistic).

Suspected Health Effects

- Male reproductive effects (oral exposure)
  - There are no data regarding potential male reproductive effects in humans following oral exposure to cyanide.
  - Data from drinking water studies in animals are inconsistent. Male reproductive effects were reported in rats (decreased weight of the testes, epididymis, cauda epididymis, and sperm effects) and mice (decreased cauda epididymis) in a 13-week study conducted by NTP (1993); however, these findings were not reproducible in a study in rats conducted by Tyner and Greeley (2023) designed to replicate the NTP (1993) study. Tyner and Greeley (2023)

attributed findings in the NTP (1993) study to decreased water intake at the highest dose. Tyner and Greeley (2023) also observed decreased water intake, to a lesser extent; no adverse male reproductive effect were observed compared to either water-restricted or ad libitum controls. Nonsignificant trends observed in sperm effects compared to *ad libitum* controls were no longer observed compared to water-restricted controls.

- Intermediate-duration gavage studies consistently reported mild, adverse effects on the male reproductive system (Gerhart 1986, 1987; Oyewopo et al. 2021a, 2021b; Shivanoor and David 2015). No adverse effects were noted in acute-duration bolus studies (Hawk et al. 2016; Sabourin et al. 2016).
- No animal studies evaluating male reproductive function (i.e., fertility) were identified, but the NTP (1993) study concluded that observed effects were unlikely to adversely impact fertility in rodents.
- No cyanide-specific mechanistic studies pertaining specifically to male reproductive toxicity were identified. EPA (2010) proposed that cyanide-associated hypothyroidism could potentially underlie male reproductive effects observed in some studies. However, a review by Williams and DeSesso (2023) challenged this proposal, pointing out that the perchlorate anion has a much higher affinity for the sodium iodide symporter compared to thiocyanide, but shows no evidence of adverse effects on the male reproductive system.

Table C-19. Hazard Identification Conclusions for Cyanide

Outcome	Hazard identification
Thyroid effects (oral)	Presumed
Neurological effects (oral)	Known
Male reproductive effects (oral)	Suspected

APPENDIX D. USER'S GUIDE

Chapter 1. Relevance to Public Health

This chapter provides an overview of U.S. exposures, a summary of health effects based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information, and an overview of the minimal risk levels. This is designed to present interpretive, weight-of-evidence discussions for human health endpoints 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?

Minimal Risk Levels (MRLs)

Where sufficient toxicologic information is available, ATSDR derives 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 hazardous substance 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. Section 1.2, Summary of Health Effects, contains basic information known about the substance. Other sections, such as Section 3.2 Children and Other Populations that are Unusually Susceptible and Section 3.4 Interactions with Other Substances, 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 endpoint 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 endpoint 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 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 that are provided in Chapter 2. Detailed discussions of the MRLs are presented in Appendix A.

Chapter 2. 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 and MRLs to humans for noncancer endpoints. The LSE tables and figures can be used 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 tables and figures follow. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

TABLE LEGEND

See Sample LSE Table (page D-5)

(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 figures are limited to the inhalation and oral routes. Not all substances will have data on each route of exposure and will not, therefore, have all five of the tables and figures. Profiles with more than one chemical may have more LSE tables and figures.

(2) Exposure period. Three exposure periods—acute (<15 days), intermediate (15–364 days), and chronic (≥365 days)—are presented within each relevant route of exposure. In this example, two oral studies of chronic-duration exposure are 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) Figure key. 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 51 identified NOAELs and less serious LOAELs (also see the three "51R" data points in sample LSE Figure 2-X).

(4) Species (strain) No./group. The test species (and strain), whether animal or human, are identified in this column. The column also contains information on the number of subjects and sex per group. Chapter 1, Relevance to Public Health, covers the relevance of animal data to human toxicity and Section 3.1, 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.

(5) Exposure parameters/doses. The duration of the study and exposure regimens are provided in these columns. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 51), rats were orally exposed to “Chemical X” via feed for 2 years. For a

more complete review of the dosing regimen, refer to the appropriate sections of the text or the original reference paper (i.e., Aida et al. 1992).

(6) Parameters monitored. This column lists the parameters used to assess health effects. Parameters monitored could include serum (blood) chemistry (BC), biochemical changes (BI), body weight (BW), clinical signs (CS), developmental toxicity (DX), food intake (FI), gross necropsy (GN), hematology (HE), histopathology (HP), immune function (IX), lethality (LE), neurological function (NX), organ function (OF), ophthalmology (OP), organ weight (OW), reproductive function (RX), urinalysis (UR), and water intake (WI).

(7) Endpoint. This column lists the endpoint examined. The major categories of health endpoints included in LSE tables and figures are death, body weight, respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, dermal, ocular, endocrine, immunological, neurological, reproductive, developmental, other noncancer, and cancer. "Other noncancer" refers to any effect (e.g., alterations in blood glucose levels) not covered in these systems. In the example of key number 51, three endpoints (body weight, hematological, and hepatic) were investigated.

(8) NOAEL. A NOAEL is the highest exposure level at which no adverse effects were seen in the organ system studied. The body weight effect reported in key number 51 is a NOAEL at 25.5 mg/kg/day. NOAELs are not reported for cancer and death; with the exception of these two endpoints, this field is left blank if no NOAEL was identified in the study.

(9) LOAEL. A LOAEL is the lowest dose used in the study that caused an adverse 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 endpoint used to quantify the adverse effect accompanies the LOAEL. Key number 51 reports a less serious LOAEL of 6.1 mg/kg/day for the hepatic system, which was used to derive a chronic exposure, oral MRL of 0.008 mg/kg/day (see footnote "c"). MRLs are not derived from serious LOAELs. A cancer effect level (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. If no LOAEL/CEL values were identified in the study, this field is left blank.

(10) Reference. The complete reference citation is provided in Chapter 8 of the profile.

(11) Footnotes. Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. For example, footnote "c" indicates that the LOAEL of 6.1 mg/kg/day in key number 51 was used to derive an oral MRL of 0.008 mg/kg/day.

FIGURE LEGEND

See Sample LSE Figure (page D-6)

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.

(12) Exposure period. The same exposure periods appear as in the LSE table. In this example, health effects observed within the chronic exposure period are illustrated.

(13) Endpoint. These are the categories of health effects for which reliable quantitative data exist. The same health effect endpoints appear in the LSE table.

(14) 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.

(15) LOAEL. In this example, the half-shaded circle that is designated 51R identifies a LOAEL critical endpoint in the rat upon which a chronic oral exposure MRL is based. The key number 51 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 6.1 mg/kg/day (see entry 51 in the sample LSE table) to the MRL of 0.008 mg/kg/day (see footnote "c" in the sample LSE table).

(16) CEL. Key number 59R is one of studies for which CELs were derived. The diamond symbol refers to a CEL for the test species (rat). The number 59 corresponds to the entry in the LSE table.

(17) Key to LSE figure. The key provides the abbreviations and symbols used in the figure.

Table 2-X. Levels of Significant Exposure to [Chemical X] – Oral (1)

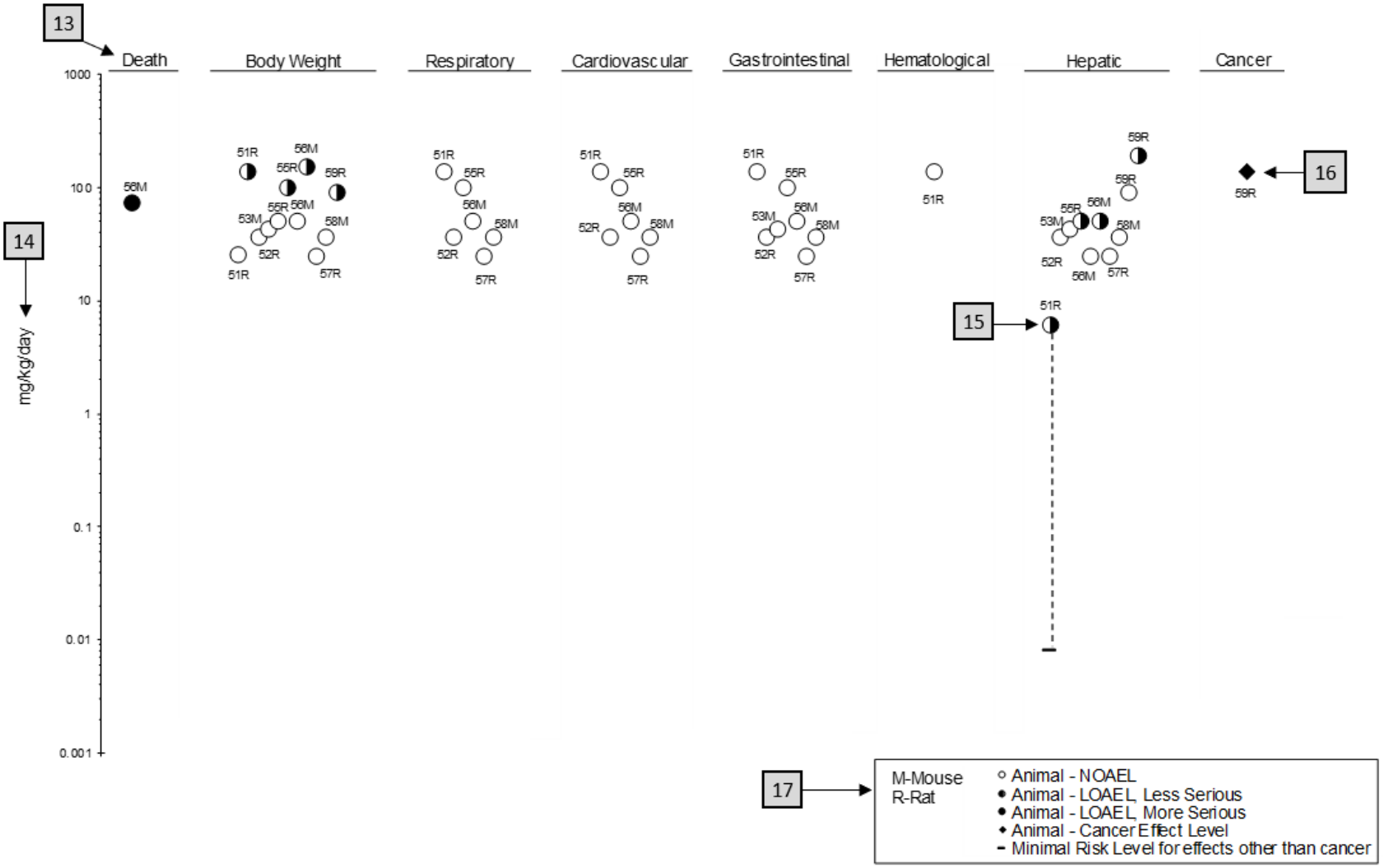
Figure key[a] (3)	Species (strain) No./group (4)	Exposure parameters (5)	Doses (mg/kg/day) (5)	Parameters monitored (6)	Endpoint (7)	NOAEL (mg/kg/day) (8)	Less serious LOAEL (mg/kg/day) (9)	Serious LOAEL (mg/kg/day) (9)	Effect
CHRONIC EXPOSURE (2)									
51	Rat (Wistar) 40 M, 40 F	2 years (F)	M: 0, 6.1, 25.5, 138.0 F: 0, 8.0, 31.7, 168.4	CS, WI, BW, OW, HE, BC, HP	Bd wt	25.5	138.0		Decreased body weight gain in males (23–25%) and females (31–39%)
					Hemato	138.0			
					Hepatic		6.1[c]		Increases in absolute and relative weights at ≥6.1/8.0 mg/kg/day after 12 months of exposure; fatty generation at ≥6.1 mg/kg/day in males and at ≥31.7 mg/kg/day in females, and granulomas in females at 31.7 and 168.4 mg/kg/day after 12, 18, or 24 months of exposure and in males at ≥6.1 mg/kg/day only after 24 months of exposure
Aida et al. 1992 (10)									
52	Rat (F344) 78 M	104 weeks (W)	0, 3.9, 20.6, 36.3	CS, BW, FI, BC, OW, HP	Hepatic	36.3			
					Renal	20.6	36.3		Increased incidence of renal tubular cell hyperplasia
					Endocr	36.3			
George et al. 2002									
59	Rat (Wistar) 58M, 58F	Lifetime (W)	M: 0, 90 F: 0, 190	BW, HP	Cancer		190 F		Increased incidence of hepatic neoplastic nodules in females only; no additional description of the tumors was provided
Tumasonis et al. 1985									

[a]The number corresponds to entries in Figure 2-x.

(11) [b]Used to derive an acute-duration oral minimal risk level (MRL) of 0.1 mg/kg/day based on the $BMDL_{05}$ of 10 mg/kg/day and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

[c]Used to derive a chronic-duration oral MRL of 0.008 mg/kg/day based on the $BMDL_{10}$ of 0.78 mg/kg/day and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

Figure 2-X. Levels of Significant Exposure to [Chemical X] - Oral



APPENDIX E. 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 may find the following information helpful for fast answers to often-asked questions.

Primary Chapters/Sections of Interest

Chapter 1: Relevance to Public Health: The Relevance to Public Health Section provides an overview of exposure and health effects and evaluates, interprets, and assesses the significance of toxicity data to human health. A table listing minimal risk levels (MRLs) is also included in this chapter.

Chapter 2: Health Effects: Specific health effects identified in both human and animal studies are reported by type of health effect (e.g., death, hepatic, renal, immune, reproductive), route of exposure (e.g., inhalation, oral, dermal), and length of exposure (e.g., acute, intermediate, and chronic).
NOTE: Not all health effects reported in this section are necessarily observed in the clinical setting.

Pediatrics:

Section 3.2 Children and Other Populations that are Unusually Susceptible
Section 3.3 Biomarkers of Exposure and Effect

ATSDR Information Center

Phone: 1-800-CDC-INFO (800-232-4636) or 1-888-232-6348 (TTY)
Internet: http://www.atsdr.cdc.gov

ATSDR develops educational and informational materials for health care providers categorized by hazardous substance, clinical condition, and/or by susceptible population. The following additional materials are available online:

Clinician Briefs and Overviews discuss health effects and approaches to patient management in a brief/factsheet style. They are narrated PowerPoint presentations with Continuing Education credit available (see https://www.atsdr.cdc.gov/emes/health_professionals/clinician-briefs-overviews.html).

Managing Hazardous Materials Incidents is a set of recommendations for on-scene (prehospital) and hospital medical management of patients exposed during a hazardous materials incident (see https://www.atsdr.cdc.gov/MHMI/index.html).

Fact Sheets (ToxFAQs™) provide answers to frequently asked questions about toxic substances (see https://www.atsdr.cdc.gov/toxfaqs/Index.asp).

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 • Web Page: https://www.cdc.gov/nceh/.

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, 400 7th Street, S.W., Suite 5W, Washington, DC 20024 • Phone: 202-245-0625 or 1-800-CDC-INFO (800-232-4636) • Web Page: https://www.cdc.gov/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 • Web Page: https://www.niehs.nih.gov/.

Clinical Resources (Publicly Available Information)

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 • Web Page: http://www.acoem.org/.

The American College of Medical Toxicology (ACMT) is a nonprofit association of physicians with recognized expertise in medical toxicology. Contact: ACMT, 10645 North Tatum Boulevard, Suite 200-111, Phoenix AZ 85028 • Phone: 844-226-8333 • FAX: 844-226-8333 • Web Page: http://www.acmt.net.

The Pediatric Environmental Health Specialty Units (PEHSUs) is an interconnected system of specialists who respond to questions from public health professionals, clinicians, policy makers, and the public about the impact of environmental factors on the health of children and reproductive-aged adults. Contact information for regional centers can be found at http://pehsu.net/findhelp.html.

The American Association of Poison Control Centers (AAPCC) provide support on the prevention and treatment of poison exposures. Contact: AAPCC, 515 King Street, Suite 510, Alexandria VA 22314 • Phone: 701-894-1858 • Poison Help Line: 1-800-222-1222 • Web Page: http://www.aapcc.org/.

APPENDIX F. GLOSSARY

Absorption—The process by which a substance crosses biological membranes and enters systemic circulation. Absorption can also refer to 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, 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.

Benchmark Dose (BMD) or Benchmark Concentration (BMC)—is the dose/concentration corresponding to a specific response level estimate using a statistical dose-response model applied to either experimental toxicology or epidemiology data. For example, a BMD_{10} would be the dose corresponding to a 10% benchmark response (BMR). The BMD is determined by modeling the dose-response curve in the region of the dose-response relationship where biologically observable data are feasible. The BMDL or BMCL is the 95% lower confidence limit on the BMD or BMC.

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—Indicators signaling events in biologic systems or samples, typically classified as markers of exposure, effect, and susceptibility.

Cancer Effect Level (CEL)—The lowest dose of a chemical in a study, or group of studies, that produces significant increases in the incidence of cancer (or malignant 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-control study, a group of people with a specified and well-defined outcome is identified and compared to a similar group of people without the outcome.

Case Report—A report that describes a single individual with a particular disease or exposure. These reports may suggest some potential topics for scientific research, but are not actual research studies.

Case Series—Reports that describe the experience of a small number of individuals with the same disease or exposure. These reports may suggest potential topics for scientific research, but are not actual research studies.

Ceiling Value—A concentration that must not be exceeded.

Chronic Exposure—Exposure to a chemical for ≥365 days, as specified in the Toxicological Profiles.

Clastogen—A substance that causes breaks in chromosomes resulting in addition, deletion, or rearrangement of parts of the chromosome.

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, and who are disease-free at start of follow-up. Often, at least one exposed group is compared to one unexposed group, while in other cohorts, exposure is a continuous variable and analyses are directed towards analyzing an exposure-response coefficient.

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 a specific point in time.

Data Needs—Substance-specific informational needs that, if met, would reduce the uncertainties of human health risk 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 response or amount of the response.

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 effect occurs. Effects include malformations and variations, altered growth, and *in utero* death.

Epidemiology—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.

Excretion—The process by which metabolic waste products are removed from the body.

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.

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

Immediately Dangerous to Life or Health (IDLH)—A condition that poses a threat of life or health, or conditions that pose an immediate threat of severe exposure to contaminants that are likely to have adverse cumulative or delayed effects on health.

Immunotoxicity—Adverse effect on the functioning of the immune system that may result from exposure to chemical substances.

Incidence—The ratio of new cases 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.

Metabolism—Process in which chemical substances are biotransformed in the body that could result in less toxic and/or readily excreted compounds or produce a biologically active intermediate.

Minimal LOAEL—Indicates a minimal adverse effect or a reduced capacity of an organ or system to absorb additional toxic stress that does not necessarily lead to the inability of the organ or system to function normally.

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—The state of being diseased; the morbidity rate is the incidence or prevalence of a disease in a specific population.

Mortality—Death; the 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, which are changes 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 hazardous substance.

No-Observed-Adverse-Effect Level (NOAEL)—The exposure level 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. Although effects may be produced at this exposure level, 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 odds ratio that is greater than 1 is considered to indicate greater risk of disease in the exposed group compared to the unexposed group.

Permissible Exposure Limit (PEL)—An Occupational Safety and Health Administration (OSHA) regulatory limit on the amount or concentration of a substance not to be exceeded in workplace air averaged over any 8-hour work 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 (insects or other organisms harmful to cultivated plants or animals).

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 endpoints. 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—A type of physiologically based dose-response model that is 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, including tissue volumes, blood flow rates to tissues, cardiac output, alveolar ventilation rates, and possibly membrane permeabilities. The models also utilize biochemical information, such as blood:air partition coefficients, and metabolic parameters. PBPK models are also called biologically based tissue dosimetry models.

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 a group is followed over time and the pertinent observations are made on events occurring after the start of the study.

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 RfC is 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 oral exposure of the human population to a potential hazard that is likely to be without risk of deleterious noncancer health effects during a lifetime. The oral RfD is expressed in units of mg/kg/day.

Reportable Quantity (RQ)—The quantity of a hazardous substance that is considered reportable under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA). RQs are (1) ≥1 pound 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 hazardous substance. 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 hazardous substance.

Risk Factor—An aspect of personal behavior or lifestyle, an environmental exposure, existing health condition, or an inborn or inherited characteristic that is associated with an increased occurrence of disease or other health-related event or condition.

Risk Ratio/Relative Risk—The ratio of the risk among persons with specific risk factors compared to the risk among persons without risk factors. A risk ratio that is greater than 1 indicates greater risk of disease in the exposed group compared to the unexposed group.

Serious LOAEL—A dose that evokes failure in a biological system and can lead to morbidity or mortality.

Short-Term Exposure Limit (STEL)—A STEL is a 15-minute TWA exposure that should not be exceeded at any time during a workday.

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 it is believed that nearly all workers may be repeatedly exposed, day after day, for a working lifetime without adverse effect. The TLV may be expressed as a Time-Weighted Average (TLV-TWA), as a Short-Term Exposure Limit (TLV-STEL), or as a ceiling limit (TLV-C).

Time-Weighted Average (TWA)—An average exposure within a given time period.

Toxicokinetic—The absorption, distribution, metabolism, and elimination of toxic compounds in the living organism.

Toxics Release Inventory (TRI)—The TRI is an EPA program that tracks toxic chemical releases and pollution prevention activities reported by industrial and federal facilities.

Uncertainty Factor (UF)—A factor used in operationally deriving the Minimal Risk Level (MRL), 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 substance that is foreign to the biological system.

APPENDIX G. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

AAPCC	American Association of Poison Control Centers
ACGIH	American Conference of Governmental Industrial Hygienists
ACOEM	American College of Occupational and Environmental Medicine
ACMT	American College of Medical Toxicology
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AEGL	Acute Exposure Guideline Level
AIC	Akaike's information criterion
AIHA	American Industrial Hygiene Association
ALT	alanine aminotransferase
AOEC	Association of Occupational and Environmental Clinics
AP	alkaline phosphatase
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BCF	bioconcentration factor
BMD/C	benchmark dose or benchmark concentration
BMD_X	dose that produces a X% change in response rate of an adverse effect
$BMDL_X$	95% lower confidence limit on the BMD_X
BMDS	Benchmark Dose Software
BMR	benchmark response
BUN	blood urea nitrogen
C	centigrade
CAA	Clean Air Act
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	cancer effect level
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CI	confidence interval
cm	centimeter
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
DNA	deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
DWEL	drinking water exposure level
EAFUS	Everything Added to Food in the United States
ECG/EKG	electrocardiogram
EEG	electroencephalogram
EPA	Environmental Protection Agency
ERPG	emergency response planning guidelines
F	Fahrenheit
F1	first-filial generation
FDA	Food and Drug Administration
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FR	Federal Register

FSH	follicle stimulating hormone
g	gram
GC	gas chromatography
gd	gestational day
GGT	γ-glutamyl transferase
GRAS	generally recognized as safe
HEC	human equivalent concentration
HED	human equivalent dose
HHS	Department of Health and Human Services
HPLC	high-performance liquid chromatography
HSDB	Hazardous Substances Data Bank
IARC	International Agency for Research on Cancer
IDLH	immediately dangerous to life and health
IRIS	Integrated Risk Information System
Kd	adsorption ratio
kg	kilogram
kkg	kilokilogram; 1 kilokilogram is equivalent to 1,000 kilograms and 1 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
LC_{Lo}	lethal concentration, low
LD_{50}	lethal dose, 50% kill
LD_{Lo}	lethal dose, low
LDH	lactate dehydrogenase
LH	luteinizing hormone
LOAEL	lowest-observed-adverse-effect level
LSE	Level of Significant Exposure
LT_{50}	lethal time, 50% kill
m	meter
mCi	millicurie
MCL	maximum contaminant level
MCLG	maximum contaminant level goal
MF	modifying factor
mg	milligram
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
MRL	Minimal Risk Level
MS	mass spectrometry
MSHA	Mine Safety and Health Administration
Mt	metric ton
NAAQS	National Ambient Air Quality Standard
NAS	National Academy of Science
NCEH	National Center for Environmental Health
ND	not detected
ng	nanogram
NHANES	National Health and Nutrition Examination Survey
NIEHS	National Institute of Environmental Health Sciences

NIOSH	National Institute for Occupational Safety and Health
NLM	National Library of Medicine
nm	nanometer
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NTP	National Toxicology Program
OR	odds ratio
OSHA	Occupational Safety and Health Administration
PAC	Protective Action Criteria
PAH	polycyclic aromatic hydrocarbon
PBPD	physiologically based pharmacodynamic
PBPK	physiologically based pharmacokinetic
PEHSU	Pediatric Environmental Health Specialty Unit
PEL	permissible exposure limit
PEL-C	permissible exposure limit-ceiling value
pg	picogram
PND	postnatal day
POD	point of departure
ppb	parts per billion
ppbv	parts per billion by volume
ppm	parts per million
ppt	parts per trillion
REL	recommended exposure limit
REL-C	recommended exposure limit-ceiling value
RfC	reference concentration
RfD	reference dose
RNA	ribonucleic acid
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
SD	standard deviation
SE	standard error
SGOT	serum glutamic oxaloacetic transaminase (same as aspartate aminotransferase or AST)
SGPT	serum glutamic pyruvic transaminase (same as alanine aminotransferase or ALT)
SIC	standard industrial classification
SLOAEL	serious lowest-observed-adverse-effect level
SMR	standardized mortality ratio
sRBC	sheep red blood cell
STEL	short term exposure limit
TLV	threshold limit value
TLV-C	threshold limit value-ceiling value
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TWA	time-weighted average
UF	uncertainty factor
U.S.	United States
USDA	United States Department of Agriculture
USGS	United States Geological Survey

USNRC	U.S. Nuclear Regulatory Commission
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