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

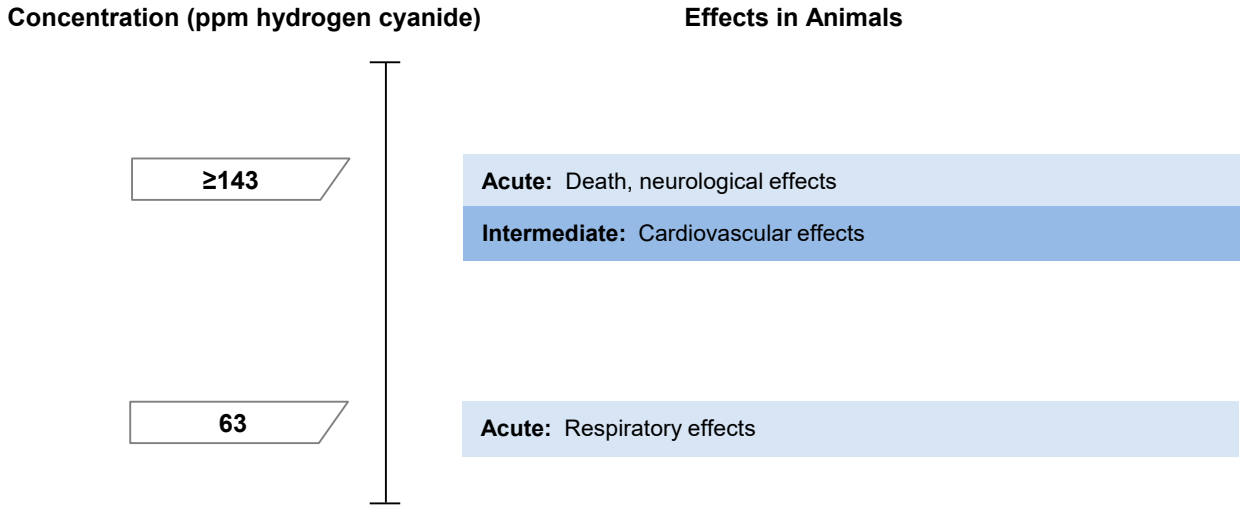
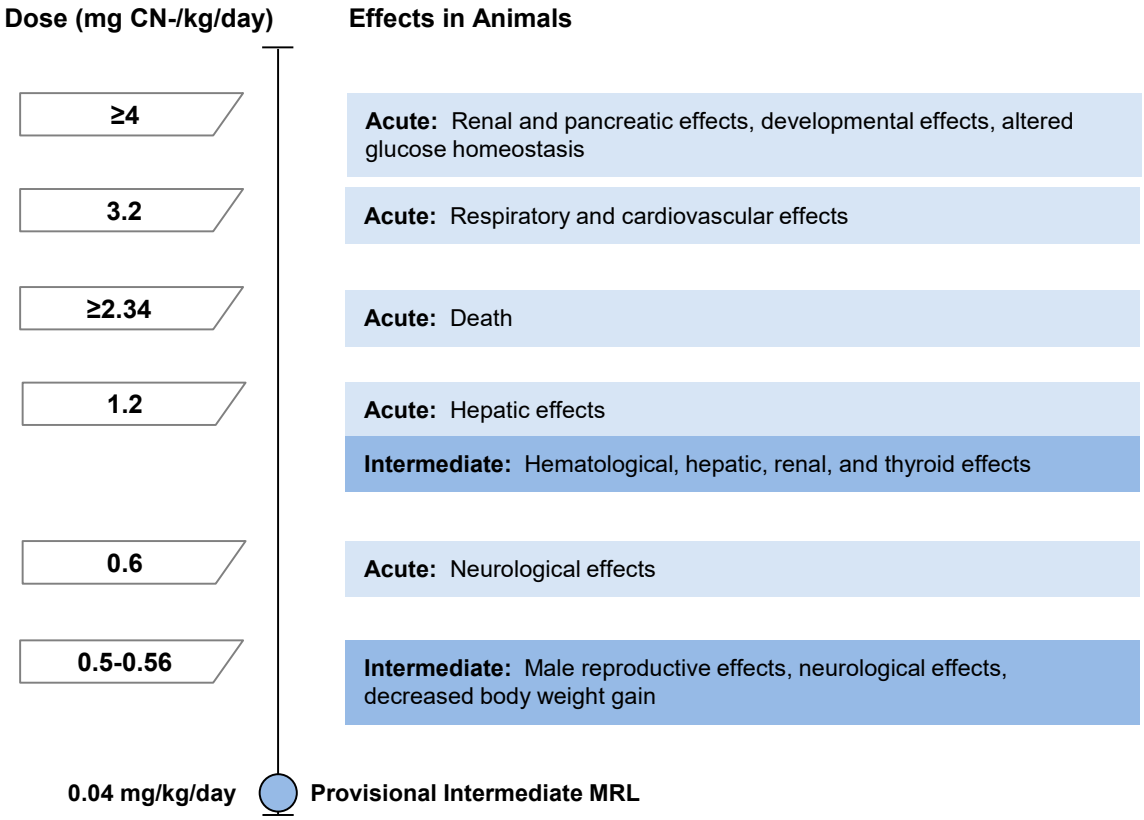


Figure 1-2. Health Effects Found in Animals Following Oral Exposure to Cyanide



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.

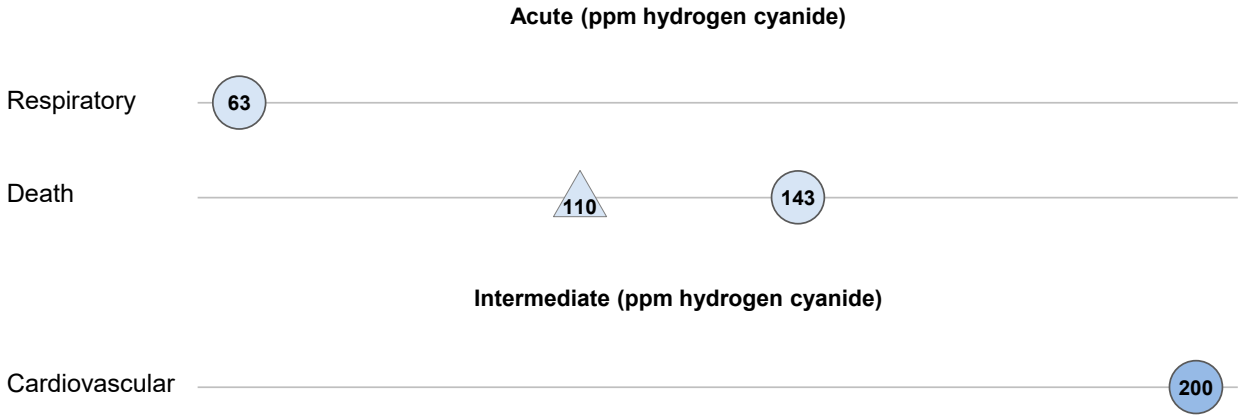
1.3 MINIMAL RISK LEVELS (MRLs)

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.

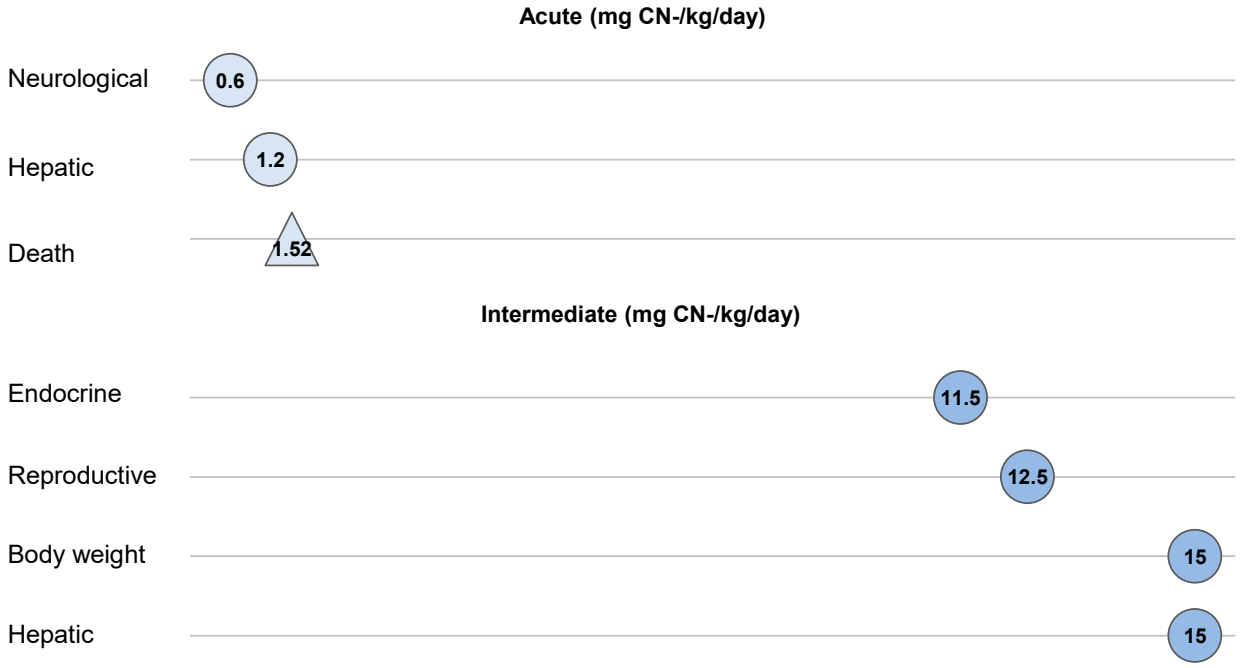


Table 1-1. Minimal Risk Levels (MRLs) for Cyanide[a]

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