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2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO CYANIDE IN THE UNITED STATES

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

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

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

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2.2 SUMMARY OF HEALTH EFFECTS

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

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

The signs of cyanide toxicity at concentrations leading to death in humans are well described.

Intoxication at $\geq 2,000$ ppm hydrogen cyanide is characterized by a brief sensation of dryness and burning in the throat due to local irritation, a suffusing warmth, and a hunger for air. Hyperpnea, and sometimes a brief outcry, follows the first breath. In <1 minute, apnea, a few gasps, loss of consciousness, and convulsions occur. Cardiovascular failure may also occur, although the heart may continue to beat for 3–4 minutes after the last breath. Reported signs sometimes include a bitter almond-like odor on the breath and (in light-toned individuals) a rose-colored hue of the skin. The total absorbed dose of hydrogen

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cyanide in such rapid deaths can be as low as 0.7 mg/kg. Dyspnea has been observed in survivors of inhalation poisoning incidents, and renal dysfunction (anuria followed by polyuria) was observed in one fatal inhalation exposure case. Similar signs of respiratory distress and renal dysfunction (albuminuria) were reported following ingestion of high doses of cyanide salts. Within a few minutes after swallowing the toxicant, the victim collapses, frequently with a scream. Dyspnea, convulsions, and death from asphyxia follow. Dermal exposure to cyanide results in comparable effects, but at higher doses. Based on case report studies, the following acute median lethal exposure levels for humans were estimated: an LC₅₀ of 524 ppm for a 10-minute inhalation exposure to hydrogen cyanide, an LD₅₀ of 1.52 mg/kg for the oral route, and an LD₅₀ of 100 mg/kg for the dermal route, assuming that CN⁻ is readily released from the compound. Animal studies also report dyspnea, convulsions, and asphyxiation as effects of high-acute exposure to cyanide by any route of exposure.

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

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

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

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

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

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

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

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

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

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

2.3 MINIMAL RISK LEVELS (MRLs)

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

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

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

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

Inhalation MRLs

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

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

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

Oral MRLs

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

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

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

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

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

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

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

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

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