2. RELEVANCE TO PUBLIC HEALTH

2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO CYANIDE IN THE UNITED STATES

Cyanides, a diverse family of compounds containing the highly reactive cyanide anion (CN^-), are produced from both anthropogenic (of human origin) 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; hydrogen cyanide is widely dispersed and persistent in the atmosphere. 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 160–166 ppt (0.180–0.187 mg/m^3); assuming a ventilation rate of 20 m^3/day, the average intake from air is about 3.8 :g/day for the non-urban, nonsmoking population. Cyanide levels in smoke from U.S. commercial cigarettes range from 10 to 400 :g/cigarette for mainstream (inhaled) smoke and from 0.006 to 0.27 :g/cigarette for sidestream smoke. The cyanide content in drinking water in 71 out of 73 urban areas in Canada was <1 :g/L; the value for two other cities was 11 :g/L. Assuming that adults ingest two liters of water per day, the cyanide intake from drinking water ranges from <2 to 22 :g/day. Mean cyanide concentrations have been reported for some food products: cereal grains (0.002–0.45 :g/g), soy protein products (0.07–0.3 :g/g), canned unpitted fruits (0–4 :g/g), commercial fruit juices (1.9–4.6 mg/L), and U.S. lima beans (0.10–0.17 mg/g). There are no comprehensive data on the cyanide content of total diet samples in the United States, so it is not possible to estimate the average daily intake from foods.

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

2.2 SUMMARY OF HEALTH EFFECTS

Exposure to cyanide can lead to death from asphyxiation within minutes. 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. Effects reported following exposure to cyanide compounds containing iron or copper may not parallel the effects for CN^- or hydrogen cyanide; certain iron-containing cyanide compounds do not release CN^- readily and therefore are less toxic, whereas some effects of copper-containing cyanide compounds may be attributed to copper rather than cyanide. In humans and animals exposed to cyanide by any route, the cyanide anion rapidly binds to enzymes and other proteins that contain ferric iron, resulting in inactivation and loss of function. The high toxicity of cyanide is related to its affinity for the ferric iron of cytochrome c oxidase, which is a key enzyme in the use of oxygen by mitochondria. The rapid cell death that occurs on exposure to cyanide is related to the cessation of cellular respiration. In addition, cyanide also binds the iron of hemoglobin, with the concomitant reduction in the oxygen-carrying capacity of the blood. The central nervous system is the most sensitive target of acute cyanide exposure, with death resulting from the inactivation of centers controlling respiration. Since cyanide is well known to act rapidly, it has often been used with suicidal and homicidal intent, as a chemical warfare agent, and as a lethal agent for executions in the United States. Detoxification of cyanide by thiosulfate results in the formation of thiocyanate, most of which is excreted in urine, but which itself, by interfering with iodine uptake by the thyroid gland and thyroid peroxidase, is a suppressor of thyroxine synthesis. Poor dietary protein intake reduces the amount of available thiosulfate (derived from sulfur-containing amino acids), thereby exacerbating the effects of cyanide exposure. The following discussion omits oral toxicity data on goats which, as ruminants, are not appropriate models for monogastric humans.

Case reports in humans and studies in animals indicate that the central nervous system is the primary target associated with inhalation, oral, or dermal exposure to cyanide; it should be noted that the evidence for neurotoxicity as the major effect following intermediate-duration oral exposure in animals is weak. High exposure levels result in convulsions, unconsciousness, and death, whereas survivors of poisoning incidents may, weeks later, develop a Parkinsonian-type syndrome or other neurological deficits, the bases of which are shown by the regional pattern of brain lesions detected by magnetic resonance imaging (MRI). In chronic inhalation exposures in humans, serious neurological effects (dizziness, hallucinations,

headache) occur at concentrations that cause relatively mild effects in other organ systems. In acute- and intermediate-duration inhalation or oral studies and limited dermal evidence, irregularities in respiration and cardiac physiology have been reported. Thyroid effects have been reported in humans and animals following cyanide exposure and result from the interference of thiocyanate, a metabolite of cyanide, with iodine uptake and utilization in the thyroid gland. In intermediate- and chronic-duration studies, reduction of plasma thyroid hormone levels has been reported. In tropical countries, long-term ingestion of cassava has been associated with the development of goiter; effects in these populations are intensified since cassava is a poor source of dietary protein. Gastrointestinal effects can be caused by central nervous system stimulation (nausea) or by direct contact (necrosis) with cyanide salts. There is no evidence that cyanide exposure is correlated with carcinogenicity. Cyanide has an indirect genotoxic effect *in vitro* and *in vivo* in that dying cells release endonucleases into the cytosol, ultimately resulting in DNA fragmentation.

In tropical countries, maternal ingestion of cassava during pregnancy has been associated with congenital hypothryoidism in some of the offspring, resulting from the increased levels of thiocyanate, which interfere with iodine accumulation by the thyroid gland. 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 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.

The following sections discuss significant effects resulting from exposure to cyanide in greater detail: death, neurotoxicity, respiratory effects, cardiovascular, and reproductive effects.

Death. The signs of cyanide toxicity at concentrations leading to death in humans are well described. Intoxication at ≥2,000 ppm hydrogen cyanide is characterized by a brief sensation of dryness and burning in the throat due to local irritation, a suffusing warmth, and a hunger for air. Hyperpnea, and sometimes a brief outcry, follows the first breath. In <1 minute, apnea, a few gasps, loss of consciousness, and convulsions occur. Cardiovascular failure may also occur, although the heart may continue to beat for 3–4 minutes after the last breath. Reported signs sometimes include a bitter almond-like odor on the breath and (in light-toned individuals) a rose-colored hue of the skin. The total absorbed dose of hydrogen cyanide in such rapid deaths can be as low as 0.7 mg/kg. Similar signs were reported following ingestion of high doses of cyanide salts. Within a few minutes after swallowing the toxicant, the victim collapses,

frequently with a scream. Dyspnea, convulsions, and death from asphyxia follow. Dermal exposure to cyanide results in comparable effects, but at higher doses. Based on case report studies, the following acute median lethal exposure levels for humans were estimated: an LC_{50} of 524 ppm (median lethal concentration) for a 10-minute inhalation exposure to hydrogen cyanide, an LD_{50} (median lethal dose) of 1.52 mg/kg for the oral route, and an LD_{50} of 100 mg/kg for the dermal route, assuming that CN^- is readily released from the compound.

In general, signs of toxicity preceding death are the same in humans and animals. Dyspnea, convulsions, and asphyxiation occur in animals following all routes of exposure to cyanide. LC_{50} values were provided for inhalation exposures to hydrogen cyanide at different durations in rats, mice, and rabbits. Lethal concentrations were also reported in dogs. Lower cyanide concentrations required longer periods of exposure to produce death; for example, in rats, the 10-second LC_{50} was 3,417 ppm and the 60-minute LC_{50} was 143 ppm for hydrogen cyanide. The difference in species susceptibility to cyanide poisoning was indicated by lower lethal concentrations in rabbits compared with rats.

Following oral exposure in animals, LD_{50} values greater than 2 mg CN^-/kg were calculated for rats dosed with cyanide as sodium cyanide and in rabbits treated with cyanide as hydrogen cyanide, sodium cyanide, and potassium cyanide. For oral exposure, the molar lethal toxicities of hydrogen cyanide, sodium cyanide, and potassium cyanide are similar. Rabbits appeared to be more susceptible to the lethal toxicity of these three compounds than were rats. Cyanide toxicity was influenced by dilution of gavage doses; the more dilute the solution, the higher the mortality for the same total dose.

Deaths can occur after dermal exposure to hydrogen cyanide, sodium cyanide, or potassium cyanide. The lowest LD_{50} of 6.7 mg CN^-/kg, indicating the highest toxicity, was calculated for cyanide applied to the skin in the form of hydrogen cyanide. Potassium cyanide was the least toxic compound. A similar pattern in cyanide toxicity was observed among these three compounds when applied into the inferior conjunctival sac of rabbits but the lethal doses were lower, as expected considering that the conjunctiva is less of a barrier to absorption than the skin; transocular LD_{50} values were between 1 and 3.2 mg CN^-/kg. Dermal absorption and consequent mortality were also observed in guinea pigs and dogs following unspecified doses of hydrogen cyanide. Cyanide absorption and, therefore, toxicity differed in rabbits with dry intact, moist, or abraded skin as expected. The lowest LD_{50} for cyanide given as sodium cyanide was calculated for rabbits with abraded skin.

Cyanide can inhibit enzymatic activity by binding to the metallic cofactor in metalloenzymes. Cytochrome c oxidase (an enzyme in the mitochondrial respiratory chain) is sensitive to cyanide action. Due to its inhibition, oxygen cannot be utilized, histotoxic hypoxia develops, and this can lead to deaths of humans and animals. 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. These reactions may make contributions to the signs of cyanide toxicity. Signs of cyanide intoxication include an initial hyperpnea followed by dyspnea and then convulsions. These effects are due to initial stimulation of carotid and aortic bodies and effects on the central nervous system. Death is caused by respiratory collapse resulting from central nervous system toxicity.

The inorganic cyanides and their cyanohydrins are highly toxic chemicals that should be handled only by properly trained personnel, with appropriate protective equipment (masks, respirators, gloves, and protective clothing), using extreme caution. Death can result from exposure by all routes that humans are likely to experience, including transocular. Although cyanides are among the most acutely toxic of all industrial chemicals, are produced in large quantities, and are used in many applications, they have caused few serious accidents or deaths. This appears to be due to the fact that it is common knowledge that the cyanides are very toxic materials that need to be treated with due caution.

Neurological Effects. The central nervous system, which has a high metabolic demand for oxygen, is the primary target for cyanide toxicity in humans and animals. 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.

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 humans and animals, and a loss of memory, a decrease in visual acuity, psychomotor ability, and visual learning was 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.

The severity of neurological effects in humans after acute oral exposure to cyanide are dose-related. The symptoms vary from tremor and headache to deep coma and death in central respiratory arrest. Pathological changes that may occur in the central nervous system during acute exposure to high doses may complicate recovery. Severe Parkinsonism was one of the effects noted in seven cases of severe acute oral exposure to 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 due to a shortening of the cassava processing time. It should be mentioned, however, that a study reported the isolation of scopoletin, a potent hypotensive and spasmolytic agent, from cassava roots and it is possible that this substance, which remains in cassava during processing (rather than cyanide), contributes to the tropical ataxic neuropathy observed among cassava eaters.

Depending on the dose and form of cyanide given to animals, neurological effects of varying severity occurred. The determination of apparent neurotoxic doses of cyanide is confounded when the compounds contain metals such as silver or copper, which also have neurotoxic properties. Tremors, convulsions, and lethargy were seen in rats treated with potassium silver cyanide for 90 days. Depressed activity was the only neurological sign found in rats exposed to lower doses of total cyanide given as copper cyanide for the same period. Myelin degeneration of spinal cord tracts was found in rats treated with 30 mg CN^-/kg/day potassium cyanide for 11.5 months. Similar to inhalation exposure effects, behavioral changes were found in pigs following intermediate-duration oral exposure to 0.4 mg cyanide/kg/day as potassium cyanide. In many studies, however, neurological effects occurred at high cyanide exposure levels. 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.

Convulsions and coma were also reported in humans and animals following acute dermal exposure to cyanide. It is likely that absorption by the inhalation route also occurred in these cases.

Inhalation and oral studies in animals have shown that cyanide exposure leads to encephalopathy in both white and gray matter. At the lowest tested oral concentrations in intermediate-duration (15 days to <12 months) studies, neurohistopathology of the central nervous system was observed without overt signs of neurotoxicity in rats. In rats, neurohistopathology of the spinal cord (spheroids or axonal swellings), hippocampus (neuronal degeneration), and cerebellum (degeneration of Purkinje cells) were observed at 0.24 mg CN^-/kg/day exposure to sodium cyanide. This study was not selected as the basis for the intermediate inhalation MRL (see Section 2.3) because of reporting inadequacies. The intermediate-duration oral study conducted by NTP in rats did not examine the spinal cord for histopathology and reported only results for the corpus callosum in the brain. A review of the slides in this study is under consideration.

Other studies have observed cyanide-induced histopathological damage in regions such as the deep cerebral white matter, the corpus callosum, hippocampus, corpora striata, pallium, and substantia nigra. White matter may be more sensitive because of its relatively low cytochrome c oxidase content. These effects have been observed following acute inhalation exposures to hydrogen cyanide lasting less than 2 hours and in dogs exposed orally to 0.27 mg CN^-/kg as sodium cyanide for 14.5 months. Partial remyelination after cessation of exposure has been reported, but it is apparent that this process is slow and incomplete. The topographic selectivity of cyanide-induced encephalopathy may be related to the depth of acute intoxication and the distribution of the blood flow, which may result in selected regions of vascular insufficiency.

Respiratory Effects. Respiratory effects commonly occur after inorganic cyanide poisoning by any route of exposure. Following inhalation, the first breath of a lethal concentration of hydrogen cyanide causes hyperpnea. The victims experience shortness of breath that may be rapidly (>1 minute) followed by apnea. Dyspnea was reported in patients who survived acute inhalation exposure to hydrogen cyanide. Similarly, dyspnea was observed in humans following acute oral exposure to cyanide as sodium cyanide, as potassium cyanide, or as cyanogenic glycosides in apricot pits. Likewise, dyspnea occurred following dermal exposure to cyanide as copper cyanide and potassium cyanide in occupational accidents. In general, dyspnea following single oral exposures of humans was associated with doses between 0.03 and 15 mg CN^-/kg. Humans acutely exposed to cyanogen, which dissociates into hydrogen cyanide and hydrocyanic acid, experienced nasal irritation.

Various symptoms indicating respiratory effects were reported in humans exposed to hydrogen cyanide or its salts in occupational settings. Upper respiratory irritation, cough, altered sense of smell, nasal congestion, epistaxis, hemoptysis, and dyspnea were among the clinical signs of cyanide toxicity. The severity of these effects correlated with cyanide levels in workplace air. It must be pointed out, however, that in occupational settings such as electroplating operations or gold recovery, exposure to other chemicals also occurs. Exposure to inorganic cyanide, its salts, or cyanohydrins by any route produces similar respiratory effects in animals.

Cardiovascular Effects. Hypotension was the main effect reported in patients after acute inhalation exposure to hydrogen cyanide, as well as after oral exposure to potassium cyanide or after ingestion of cyanogenic glycosides in apricot pits. Palpitations were recorded in men exposed dermally to hydrogen cyanide. Peripheral vasoconstriction and gross plasma extravasation were found in a man whose whole body was exposed to liquid copper cyanide in a cistern. In many of these cases, the effects reported may reflect an indirect action mediated by the nervous system. Workers exposed to cyanide during electroplating and silver-reclaiming jobs complained of precordial pains. During electroplating operations, however, exposure to other chemicals such as cleaners and cutting oils also occurs. Acute inhalation of hydrogen cyanide resulted in bradycardia, arrhythmia, and T-wave abnormalities, and increased cardiac-specific creatinine phosphokinase activity in monkeys.

Reproductive Effects. No studies were located regarding reproductive effects in humans after any route of exposure. Increased resorptions were noted following oral exposure of rats to cyanogenic glycosides in a cassava diet and increased gonadal weight was observed in male rats exposed 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 fed rice with sodium cyanide added and in dogs fed a cassava diet. A number of reproductive effects were observed following exposure of rats and mice to sodium cyanide in the drinking water for 13 weeks. In male rats, decreases in the left caudal epididymal weight left epididymis weight, left testis weight, spermatid heads, and spermatid counts were noted. In female rats, significantly more time was spent in proestrus and diestrus stages, and less time was spent in estrus and metestrus stages, while in male mice, a significant decrease in the left epididymal and caudal epididymal weights was noted, but no changes in sperm motility or spermatid head density were observed. This study was used as the basis for the intermediate oral MRL. In contrast, no reproductive effects were reported in hamsters exposed to cassava during gestation. Thus, it is possible that exposure to cyanide could lead to reproductive effects in humans.

2.3 MINIMAL RISK LEVELS (MRLs)

The derivation of MRLs omits oral exposure studies in goats, because of their ruminant stomachs, and studies that tested cyanide compounds containing copper or silver, because the known toxicities of these metals would confound calculation of the dose-response for cyanide.

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. Acute hydrogen cyanide inhalation studies in humans and laboratory rodents reported increased mortality or LC_{50} values of 143 ppm and higher (AMRL 1971; Ballantyne 1983a; DOA 1976; Higgins et al. 1972; Hume et al. 1995; Matijak-Schaper and Alarie 1982; Singh et al. 1989). Nonlethal acute inhalation exposures resulted in serious adverse effects at 63 ppm and higher: suppression of the central nervous system and respiration, and irregularities of cardiac physiology (Bonsall 1984; Matijak-Schaper and Alarie 1982; 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).

The available intermediate-duration inhalation studies in animals reported mortality and serious neurological effects (tremors, ataxia, cell death in cerebellar neurons and glia cells) at concentrations of 45 ppm and above (O'Flaherty and Thomas 1982; Valade 1952). Chronic occupational inhalation studies in humans described serious neurological effects (paresthesia, hallucination, headache, weakness, dizziness) as well as respiratory, cardiovascular, and thyroid effects at 6.4 ppm and above (Blanc et al. 1985; El Ghawabi et al. 1975). These studies, however, either lacked information about exposure levels or used small cohorts of workers. Neurological effects were noted in workers who were also exposed to gasoline, hydrochloric acid, copper cyanide, and sodium carbonate (El Ghawabi et al. 1975). This study was not considered for the basis of an inhalation MRL because of the multiple exposures.

Oral MRLs

An acute oral MRL was not derived for cyanide because the available studies were not suitable, reporting increased lethality or other serious effects in exposed organisms. Acutely-exposed rodents exhibited 50–95% lethality at the tested doses of 4–22 mg CN^-/kg/day (Ferguson 1962; Smyth et al. 1969). Decreased

fetal weight in a developmental study in hamsters ingesting 1 mg CN^-/kg/day in cassava (Frakes et al. 1986a) and neurotoxicity (brain lesions, Parkinsonian-like syndrome, coma) with suppression of respiratory and cardiac physiology in humans ingesting 7.4–15 mg CN^-/kg as potassium cyanide were considered serious adverse effects (Liebowitz and Schwartz 1948; Rosenow et al. 1995).

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

This MRL was derived from a NOAEL of 4.5 mg/kg/day in a study in which groups of 10 male and 10 female rats were given 0, 0.2, 0.5, 1.4 (males), 1.7 (females), 4.5 (males), 4.9 (females), or 12.5 mg/kg/day cyanide, as sodium cyanide, in the drinking water for 13 weeks (NTP 1993). At the end of the study, the animals were evaluated for histopathology, clinical chemistry, urine chemistry, and reproductive toxicity. A number of reproductive effects, such as decreases in left epididymis weight, left cauda epididymis weight, left testis weight, spermatid heads, and spermatid counts were observed at 12.5 mg/kg/day. At 1.4 and 4.5 mg/kg/day, significantly decreased weight of the left cauda epididymis and spermatozoa motility were observed; however, these effects alone were not considered to be adverse. The 12.5 mg/kg/day dose was identified as the lowest-observed-adverse-effect level (LOAEL), based on the reproductive effects in male rats, and the 4.5 mg/kg/day dose was identified as the NOAEL. This 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 LOAEL of 1.04 mg/kg/day for cyanide based on systemic and reproductive effects (reduced spermatogenesis, degeneration of germ cells of the testis) was identified dogs exposed to sodium cyanide in feed for 14 weeks (Kamalu 1993). However, this study was not used to derive the intermediate oral MRL because dogs have very low levels of the detoxifying enzyme rhodanese and are therefore not a good model for human toxicity. A rat gavage study by Soto-Blanco et al. (2002a) indicated that neurotoxicity was the most sensitve end point, but because of reporting deficiencies, this study was not used as the basis for the intermediate oral MRL. The study reported neurohistopathology in the spinal cord (spheroids in the white matter of the spinal cord), cerebellum (damage to Purkinje cells and loss of white matter) and hippocampus (neuronal loss) in male Wistar rats exposed daily by gavage to 0.24 mg CN^-/kg/day as potassium cyanide for 3 months. There were no overt clinical signs of neurotoxicity and no indication of thyroid effects. In pigs that had nutritional deficiencies and were exposed to potassium cyanide by gavage for 24 weeks, both neurological (reduced activity) and endocrine effects (reduced serum thyroid hormones) were noted at 0.4 mg CN^-/kg/day, which was the no-effect level for gastrointestinal effects (Jackson 1988). This study was not used to derive the intermediate-duration MRL

because the bolus administration would likely overwhelm the detoxification apparatus and not accurately represent likely human exposure to cyanide in drinking water. It should be noted that the NTP (1993) study, because of the lack of overt clinical signs of neurotoxicity, did not evaluate the spinal cord for histopathology and only reported histopathology results in the brain for the corpus callosum. A re-evaluation of the histological slides of the NTP study is under consideration.

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 investigated effects in rats exposed to hydrogen cyanide in the diet for 2 years (Howard and Hanzal 1955). The reliability of this study is low because evaporation of the cyanide from the feed resulted in unstable cyanide levels throughout the experiment and because the observed effects were not based solely on the toxicity of cyanide. Furthermore, no effects were observed other than nondose-related changes in body weight gain in female rats, but not in male rats. Therefore, the data are not sufficient to derive an MRL value for chronic oral exposure.