939 Agency for Toxic Substances and Disease Registry (ATSDR) toxicological profile for hydrogen cyanide contained in the cyanide profile

http://www.atsdr.cdc.gov/toxprofiles/tp8.pdf

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**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 (Fe3+) 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 hyp oxia 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 ≥2,000 ppm hydrogen cyanide is characterized by a brief sensation of dryness and burning in the throat due to local irritation, a suffusing warmt h, 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. 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 (albumin uria) 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 hydro gen 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 c ontact 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 b een 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.

In tropical countries, maternal ingestion of cassava during pregnancy has been associated with congenital hypothryoidism 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 int o 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 a nd 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 tha t may occur in the central nervous system during acute exposure to high doses may complicate recovery. Severe Parkinsion-like symptoms have been noted in several cases of severe acute oral exposure to lethal amounts of cyanide (after antidotes were adminis tered), 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, a nd 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 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 h umans 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 cyani de, 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 dos es 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 sett ings 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 exposu re 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 a ddition, 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 avai lable for neurotoxicity in exposed animals.

**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. Reproduc tive 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 proe strus 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 inge sting 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 expos ure 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.