

**Public Health Goal for  
CYANIDE  
in Drinking Water**

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## PREFACE

### **Drinking Water Public Health Goal of the Office of Environmental Health Hazard Assessment**

This Public Health Goal (PHG) technical support document provides information on health effects from contaminants in drinking water. The PHG describes concentrations of contaminants at which adverse health effects would not be expected to occur, even over a lifetime of exposure. PHGs are developed for chemical contaminants based on the best available toxicological data in the scientific literature. These documents and the analyses contained in them provide estimates of the levels of contaminants in drinking water that would pose no significant health risk to individuals consuming the water on a daily basis over a lifetime.

The California Safe Drinking Water Act of 1996 (amended Health and Safety Code, Section 116365) requires the Office of Environmental Health Hazard Assessment (OEHHA) to adopt PHGs for contaminants in drinking water based exclusively on public health considerations. The Act requires OEHHA to adopt PHGs that meet the following criteria:

1. PHGs for acutely toxic substances shall be set at levels at which scientific evidence indicates that no known or anticipated adverse effects on health will occur, plus an adequate margin-of-safety.
2. PHGs for carcinogens or other substances which can cause chronic disease shall be based solely on health effects without regard to cost impacts and shall be set at levels which OEHHA has determined do not pose any significant risk to health.
3. To the extent the information is available, OEHHA shall consider possible synergistic effects resulting from exposure to two or more contaminants.
4. OEHHA shall consider the existence of groups in the population that are more susceptible to adverse effects of the contaminants than a normal healthy adult.
5. OEHHA shall consider the contaminant exposure and body burden levels that alter physiological function or structure in a manner that may significantly increase the risk of illness.
6. In cases of scientific ambiguity, OEHHA shall use criteria most protective of public health and shall incorporate uncertainty factors of noncarcinogenic substances for which scientific research indicates a safe dose-response threshold.
7. In cases where scientific evidence demonstrates that a safe dose-response threshold for a contaminant exists, then the PHG should be set at that threshold.
8. The PHG may be set at zero if necessary to satisfy the requirements listed above.
9. OEHHA shall consider exposure to contaminants in media other than drinking water, including food and air and the resulting body burden.
10. PHGs adopted by OEHHA shall be reviewed periodically and revised as necessary based on the availability of new scientific data.

PHGs adopted by OEHHA are for use by the California Department of Health Services (DHS) in establishing primary drinking water standards (State Maximum Contaminant Levels, or MCLs). Whereas PHGs are to be based solely on scientific and public health considerations without regard to economic cost considerations, drinking water standards adopted by DHS are to consider economic factors and technical feasibility. For this reason PHGs are only one part of the information used by DHS for establishing drinking water standards. PHGs established by

OEHHA exert no regulatory burden and represent only non-mandatory goals. By federal law, MCLs established by DHS must be at least as stringent as the federal MCL if one exists.

PHG documents are developed for technical assistance to DHS, but may also benefit federal, state and local public health officials. While the PHGs are calculated for single chemicals only, they may, if the information is available, address hazards associated with the interactions of contaminants in mixtures. Further, PHGs are derived for drinking water only and are not to be utilized as target levels for the contamination of environmental waters where additional concerns of bioaccumulation in fish and shellfish may pertain. Often environmental water contaminant criteria are more stringent than drinking water PHGs, to account for human exposures to a single chemical in multiple environmental media and from bioconcentration by plants and animals in the food chain.

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## SUMMARY

A Public Health Goal (PHG) of 150 ppb is developed for cyanide in drinking water. The U.S. Environmental Protection Agency's (U.S.EPA's) Maximum Contamination Level (MCL) for cyanide in drinking water is 200 ppb. Cyanide, which is also commonly referred to as hydrogen cyanide and hydrocyanic acid, does not appear to be carcinogenic to animals or humans or mutagenic in bacteria. The proposed PHG of 0.15 mg/L (150 ppb) is based on a chronic no-observed-adverse-effect-level (NOAEL) of 10.8 mg/kg-day in rats in which no clinical or histopathological effects were observed.

## INTRODUCTION

Cyanide is a naturally occurring chemical and is present naturally in many food items including many commonly consumed foods such as almonds, lima beans and mustard (Hebert, 1993; Salkowski and Penney, 1994).

The purpose of this document is to develop a PHG for cyanide in drinking water. Cyanide may be present in source water or may enter tap water in the distribution system of the individual household. Tap water is used for drinking directly and also for the preparation of foods and beverages. There are other sources for human exposure to cyanide. The public may be exposed to cyanide from contaminated air or from food containing cyanide as a natural constituent (ATSDR, 1995). Some of the typical sources of human exposure other than food or drinking water include: 1) industrial such as mining operations, fumigation, metal treatment, steel making, electronics, plastics, dyes, pharmaceutical manufacturing and metal processing, 2) fires (e.g., polyurethane foam, wool, nylon and tobacco), 3) consumer products such as nail glue remover and 4) drugs such as nitroprusside and nitriles (Salkowski and Penney, 1994).

High-doses of cyanide inhibit cellular enzymes resulting in histotoxic hypoxia. The central nervous system (CNS) effects include demyelinating lesions of the brain and a parkinsonian-like encephalopathy (Salkowski and Penney, 1994). The heart is also sensitive to cyanide induced hypoxia (U.S. EPA, 1992). Cyanide intoxication from the consumption of drinking water containing high concentrations of cyanide is uncommon.

U.S.EPA established an ambient water quality criterion for cyanides of 0.2 mg/L for the protection of human health from the toxic properties of cyanide in drinking water (U.S. EPA, 1996). The criterion is based on the U.S. Public Health Service drinking water standards of 1962 (U.S. EPA, 1980; U.S. EPA, 1981). A U.S. EPA lifetime health advisory of 0.15 mg/L considers contributions to cyanide exposure from routes other than drinking water.

## CHEMICAL PROFILE

Cyanides are organic or inorganic compounds which contain the  $\text{C}\equiv\text{N}$  group (Health Canada, 1991). The chemical and physical properties of hydrogen cyanide (HCN) are summarized in Table 1.

Table 1. Physical and Chemical Properties of Cyanide (NIOSH, 1994; U.S. EPA, 1978)

Molecular weight	27.0
Vapor pressure	664 Torr @ 0°C 807 Torr @ 27°C
Boiling point	78° F (25.6 °C)
Physical state	liquid below 78°F (25.6 °C)
Solubility in water	miscible
Flammability	flammable gas or liquid

Hydrogen cyanide (HCN), also known as hydrocyanic acid and prussic acid, is a colorless or pale blue gas with a bitter, almond like odor (NIOSH, 1994). Cyanide in water is generally considered as the sum of cyanide present as both HCN and  $\text{CN}^-$ , and expressed as the term “free cyanide” (U.S. EPA, 1980). Free cyanide is very reactive, however, and does not occur commonly in nature (U.S. EPA, 1980). At about pH 8 or above, HCN dissociates readily in water to  $\text{H}^+$  and  $\text{CN}^-$ . In aqueous solutions below pH 8, HCN remains undissociated as a weak and volatile acid (U.S. EPA, 1992).

## PRODUCTION AND USE

The projected industrial production of hydrogen cyanide for 1997 was 1.46 billion pounds (ATSDR, 1995). Inorganic cyanides have several industrial uses, chiefly electroplating and metal treatments. Organic cyanides are feedstock chemicals for such products as acrylic fibers and plastics (U.S. EPA, 1978). Cyanide is a waste component of several industrial processes including mining, steel production and paint manufacturing (Hebert, 1993).

## ENVIRONMENTAL OCCURRENCE AND HUMAN EXPOSURE

Cyanide is a naturally occurring chemical. It is found in certain foods, typically in insignificant amounts in food produced in the United States (U.S.). It is also generated in fires and is one of many toxic components of tobacco smoke. The distribution and transformation of cyanides in air, on land or in water has been well described. Cyanide is a reactive compound which does not accumulate in the environment (U.S. EPA, 1978; U.S. EPA, 1981).

### Air

Air emissions of cyanide during the 1970s were estimated to be 44 million pounds per year. Over 90 percent of this atmospheric cyanide burden was caused by automobile exhaust and is presumed to have declined significantly (U.S. EPA, 1981). More recent data on nationwide total cyanide emissions are not in the available literature (ATSDR, 1995). Industrial sources include mining operations, chemical processing, petroleum refineries, steel mills and solid waste incinerators. For 1996, the California Air Resources Board (ARB) estimates that about 1.2 million pounds of HCN were emitted into the air from industrial sources (ARB, 1997), with most arising from mining industry sources.

Fires can be a source of cyanide into the air, especially on a local scale. Hydrogen cyanide is liberated upon the combustion of several materials, most notably wool, silk, polyacrylonitrile, nylon, polyurethane and paper although the amounts vary considerably according to conditions of

combustion (Pauluhn, 1992; U.S. EPA, 1980). Cyanide gas may be an important cause of poisoning and death in victims of smoke inhalation from residential fires (Baud *et al.*, 1991; Sorokin, 1993).

The half-life for hydrogen cyanide in air is calculated as a range of 1.4 to 2.9 years (ATSDR, 1995). Significant concentrations of cyanides are not, however, usually found in air (U.S. EPA, 1978). The average inhalation exposure of the general U.S. nonurban, nonsmoking population is estimated to be 3.8 ug/day (ATSDR, 1995). Tobacco smoke is considered to be one of the major sources of cyanide exposure to the general public (U.S. EPA, 1978).

## **Soil**

Conclusive estimates of amounts of cyanide discharged to released to soil are not available (ATSDR, 1995; U.S. EPA, 1978), and excepting chemical accidents, this route of cyanide into the environment appears to be negligible. Hydrogen cyanide which has a high vapor pressure and is soluble in water, tends not to adsorb onto soils but instead volatilize into the atmosphere (U.S. EPA, 1978). Cyanide in soils can be degraded rapidly to CO<sub>2</sub> and NH<sub>3</sub> via microbial metabolism, helping to prevent accumulation within the soil. Under anaerobic conditions, microbes convert cyanides to gaseous nitrogen compounds (U.S. EPA, 1978).

## **Water**

The major sources of cyanide released to water are metal finishing industries, iron and steel making industries, organic chemical manufacturers and water treatment facilities (which may be downstream from cyanide releasing industries). Along with industrial point-sources, cyanide can enter waterways from agricultural runoff, runoff from roads which are salted in winter and atmospheric fallout and washout (ATSDR, 1995; U.S. EPA, 1981).

Certain microorganisms and many higher plants can also synthesize cyanide and cyanide-containing molecules. There are no known significant impacts to drinking water supplies from these natural sources (U.S. EPA, 1978).

According to U.S. EPA (1978), cyanides are uncommon in U.S. water supplies, and when found, usually do not exceed 10 ppb. Based on 1988 data establishing a mean cyanide concentration in drinking water from 35 U.S. water utilities (ATSDR, 1995), the estimated average daily intake from drinking water consumption is 0.4 to 0.7 µg of hydrogen cyanide. Volatilization is the dominant removal mechanism of cyanide from bodies of water, especially with a pH less than 9, in which most of the cyanide will exist as volatile HCN. The factors affecting the rate of cyanide volatilization from a body of water include water temperature, pH, wind speed and cyanide concentration (ATSDR, 1995; U.S. EPA, 1992). As in soil, various microbes are able to degrade cyanide to carbon dioxide and ammonia. Cyanide apparently does not bioaccumulate or biomagnify in food webs (U.S. EPA, 1978). Cyanide forms stable complexes with most transition metals which may be present in water.

## **Food**

Fiksel *et al.* (U.S. EPA, 1981) concluded that air, water and soil borne cyanide exposures to humans do not present significant risks to the general population when compared with potential



exposure from naturally occurring sources, such as certain plants or plant products used as food. Cyanide is a naturally occurring chemical and is present in many food items such as almonds, maize, apple seeds, millets, bamboo, mustard, beans, peas, elderberry, sorghum, cassava root, sugar cane, lemon, sweet potato, lima beans, wild cherry, lime and yam (Claus *et al.*, 1970; Hayes, 1989; Hebert, 1993; Salkowski and Penney, 1994).

Cyanide is widely distributed throughout the plant kingdom with approximately 1,000 to 2,000 cyanide-bearing species of higher plants among about 200 *genera* (Conn, 1981; Duke, 1977; U.S. EPA, 1981). Some commonly consumed, U.S. grown, foods such as peas, beans, lima beans and sweet potatoes contain small amounts of cyanogen glycoside compounds such as amygdalin which can be hydrolyzed to release hydrogen cyanide within the body (Claus *et al.*, 1970; Hebert, 1993; Hayes and Reddy, 1989; Salkowski and Penney, 1994). For example, two U.S. varieties of lima beans were found to contain 100 and 170 mg/kg cyanide (Montgomery, 1969). No precise estimate of daily cyanide intake from food can be found (ATSDR, 1995) although Fiksel *et al.* (U.S. EPA, 1981) described a dietary worst-case cyanide consumption of 300 mg/day. The authors added that in the U.S., this level of cyanide consumption via the food route is highly unlikely. In the U.S., human exposure to cyanide from foods containing cyanides is expected to be low, but likely to exceed cyanide intake from the airborne and drinking water routes (ATSDR, 1995; U.S. EPA, 1981).

## **METABOLISM AND PHARMACOKINETICS**

### **Absorption and Distribution**

Absorption of cyanide occurs rapidly, whether absorption by ingestion of cyanide salts, of HCN through the lungs or by dermal exposure to HCN gas or aqueous solutions of HCN, potassium cyanide or sodium cyanide (Hebert, 1993; U.S. EPA, 1992). This rapid absorption of cyanide occurs in both animals and humans. Data on actual absorption rates are not available. However, we know empirically from the extremely rapid onset of symptoms that cyanide is readily absorbed into the bloodstream and distributed throughout the body (Hebert, 1993; U.S. EPA, 1978). Once cyanide is in the bloodstream, it is distributed to other body tissues, and after the initial exposure to cyanide, the tissues show increased cyanide concentrations relative to blood (U.S. EPA, 1978). The distribution of cyanide among the various body tissues is somewhat uniform, although the highest levels are generally found within the liver, lungs, blood and brain (Gettler and Baine, 1938). Cyanide does not accumulate in blood and tissues following chronic exposure (Howard and Hanzal, 1955; U.S. EPA, 1992). In the mid-1950s, two researchers reported that the range of cyanide concentrations in the blood of normal humans was from 0 to 107 ug/L with an average concentration of 48 ug/L (Feldstein and Klendshoj, 1954).

### **Metabolism and Excretion**

The majority of cyanide detoxication metabolism occurs within the tissues and the principal metabolic product is the conversion of the cyanide ion to the less toxic thiocyanate via a reaction involving the enzyme rhodanese (Salkowski and Penney, 1994; Hebert, 1993; U.S. EPA, 1980). Rhodanese is the trivial name for the enzyme thiosulfate: cyanide sulfurtransferase (U.S. EPA, 1992). Rhodanese catalyses the transfer of sulfur of thiosulfate to the cyanide ion to form thiocyanate, which is excreted in the urine. Rhodanese is widely distributed in the body, but the

highest activity is in the mammalian liver (U.S. EPA, 1980). The body has a large capacity to detoxicate cyanide, but the rhodanese system responds slowly to a cyanide challenge, making the rate of absorption an important consideration (Clemedson *et al.*, 1955).

Minor metabolic detoxication pathways also exist. For example, about 15 percent of free cyanide conjugates with cysteine to form 2-iminothiazolidene-4-carboxylic acid (Salkowski and Penney, 1994; U.S. EPA, 1980). In the bloodstream, cyanide can bind reversibly with the Fe<sup>3+</sup> of methemoglobin and become sequestered (Hebert, 1993).

Most cyanide, about 80 percent, is excreted in the urine as thiocyanate (U.S. EPA, 1978). Cyanide does not appear to accumulate significantly in any body compartment with either repeated doses or chronic exposures. There are no known *in vivo* inhibitors of rhodanese (U.S. EPA, 1980).

## **TOXICOLOGY**

### **Toxicological Effects in Animals**

#### **Acute Toxicity**

Cyanide is a potent and rapidly acting poison. The toxic effects of HCN and soluble inorganic cyanide salts are principally due to the propensity for the <sup>-</sup>CN ion to complex with certain metal ions. The respiratory enzyme cytochrome c oxidase, which is necessary for intracellular utilization of oxygen, is especially sensitive to cyanide binding to the trivalent ion forming a stable coordination complex (U.S. EPA, 1981; ATSDR, 1995). This complex subsequently inhibits cellular respiration and disables oxidative phosphorylation. Cyanide does not interfere with the transfer of oxygen to the tissues, rather it prevents cellular use of oxygen in energy production (Gordon and Amdur, 1991). The cells are unable to utilize oxygen resulting is histotoxic hypoxia to which the central nervous system and the heart are particularly sensitive (Rieders, 1971; U.S. EPA, 1992). Cardiac irregularities are common, but death typically arises from respiratory arrest following CNS failure (Timbrell, 1994).

The acute effects of cyanide poisoning in all obligate aerobic species are ultimately caused by a single biochemical lesion, the inhibition of cytochrome c oxidase (Gosselin *et al.*, 1976). The acute LD<sub>50</sub> for animal exposure to cyanide, which will vary according to species, sex, route of administration and other variables, is approximately 10 mg/kg KCN, (or 4 mg/kg<sup>-</sup>CN) (Hebert, 1993; Hayes, 1967). The acute elimination half-life of cyanide in plasma is 14.1 minutes (Leuschner *et al.*, 1991). Cyanide will bind preferentially with methemoglobin over cytochrome oxidase, therefore amyl nitrate, which oxidizes hemoglobin to methemoglobin, may be used as one of many antidotes for acute cyanide intoxication (Timbrell, 1994).

#### **Subchronic Toxicity**

Hebert (1993) reported that relatively few experimental data exist on the effects of subchronic exposure to cyanide at concentrations not considered to be acutely toxic. Hebert (1993) performed a subchronic study in which groups of male or female rats and mice (10 per dose level, each sex) were administered drinking water containing sodium cyanide at the cyanide concentrations of 0, 3,

10, 30, 100 or 300 ppm for 13 weeks. The author reported no clinical signs attributable to sodium cyanide administration or to dehydration; no gross or microscopic changes specifically related to cyanide toxicity occurred at any site in males or females of either species, including the lack of lesions in the brain or thyroid gland.

Reproductive effects in male rats such as decreases in epididymis weight and testis weight; and in male rats, reductions in spermatid head size and count were observed at the 300 ppm (12.7 mg/kg-day) dose level. The 12.7 mg/kg-day level was identified as the subchronic NOAEL in light of the reproductive effects on male rats (ATSDR, 1995). This study was used by the Agency for Toxic Substances and Disease Registry (ATSDR) to derive an intermediate duration minimum risk level (MRL) (15 to 364 days) of 0.05 mg/kg-day.

### Chronic Toxicity

Philbrick *et al.* (1979) determined that weanling rats fed a diet supplemented with 1,500 ppm potassium cyanide for 48 weeks gained weight at a significantly lower rate than either those fed a diet supplemented with 240 ppm potassium thiocyanate or those of the control. The cyanide treated rats also showed decreased thyroid gland activity (as did the thiocyanate treated group). The authors reported no clinical signs of toxicity in either treatment group, and no deaths throughout the experimental period (Philbrick *et al.*, 1979).

Howard and Hanzal (1955) performed the chronic rat cyanide feeding study on which the U.S. EPA based a chronic NOAEL for the cyanide drinking water standard. In this experiment, male and female rats (at 10/sex/group) were administered diets containing HCN at levels of either 100 or 300 ppm for a period of two years. At the conclusion of the study, several tissues were examined microscopically from both the treated and control groups, including the heart, lung, liver, spleen, stomach, small and large intestines, kidney, adrenal gland, thyroid, testes, ovary and the cerebrum and cerebellum of the brain, with all findings compatible with those expected of aging animals. Similar results were recorded in both the control and experimental animals and no pathology was due to cyanide intoxication. The authors concluded that a diet containing 100 or 300 ppm HCN as a result of fumigation is nontoxic to male and female albino rats over a two-year period. Therefore, 300 ppm was identified as an NOAEL. The NOAEL of 300 ppm was adjusted to a daily dose of 10.8 mg CN/kg-day for female rats, and 7.5 mg/kg-day for male rats by correcting for HCN volatilization from the spiked diet and adjusting to average body weights (U.S. EPA, 1992). This value, 10.8 mg/kg-day, represents the highest NOAEL for use in determining the PHG for cyanide.

Jackson (1991) examined the effects of chronic potassium cyanide solution (administered once daily, orally, for 24 weeks) on body weight in neonatal swine. Twelve female and male littermates were apportioned into control (0 mg CN) and three treatment groups of 0.4, 0.7 or 1.2 mg/kg-day. Significant body weight differences were noticed as early as week 12. However, the work appears to be flawed as the administered doses were given as in one large daily bolus rather than via food or drinking water. Since cyanide detoxication in the liver, an enzymatically catalyzed reaction, reaches a maximum rate in the presence of excess substrate, the capacity of the liver to form thiocyanate upon first pass may be exceeded (U.S. EPA, 1992). Animals tolerate higher doses of cyanide when administered in the diet or drinking water during subchronic exposure (Hayes, 1967). Administration of cyanide doses via drinking water or food provide more valid correlation to drinking water guidance calculations.

## Developmental and Reproductive Toxicity

Cyanide was reported to be embryotoxic and teratogenic to Golden Syrian hamsters when exposed to high-doses (approximately 80 mg/kg-day) during gestation. Fetuses exhibited severe teratogenic effects, such as neural tube defects, and maternal toxicity ranging from mild to severe was also reported (Doherty *et al.*, 1982). As previously mentioned, Hebert (1993) performed a subchronic study in which rats and mice were administered drinking water containing sodium cyanide at cyanide concentrations of 0, 3, 10, 30, 100 and 300 ppm for 13 weeks. The author reported reproductive effects in male rats including decreases in epididymis weight and testis weight and reductions in spermatid head size and count at 300 ppm (12.7 mg/kg-day).

## Comparison of Acute and Chronic Toxicity

It should be noted that the chronic NOAEL of 10.8 mg/kg-day in the rat is higher than the acute oral LD<sub>50</sub> of a single exposure to 4 mg/kg also in the rat. This difference between acute and chronic responses has been described by Clemdeson *et al.*, (1955), Hayes (1967) and Leuschner *et al.* (1991). As mentioned earlier, if given over a sufficient length of time the body can detoxicate cyanide in amounts which would be lethal if given in a single bolus dose, since the rhodanese enzyme system responds slowly to the cyanide challenge. Hayes (1967) administered potassium cyanide (KCN) daily to rats in the diet at 25 times the acute oral LD<sub>50</sub> for 90 days with no mortality observed, and yielded a chronicity factor for oral KCN of less than 0.04. This tolerance indicated the ability of the body, especially the liver, to detoxicate cyanide provided there is time to accomplish the task without overloading the capacity of the rhodanese enzyme system (Hayes, 1967) making the rate of absorption an important consideration (Clemdeson *et al.*, 1955).

## Carcinogenicity

Cyanide is not suspected to be a carcinogen, and it has not been definitively tested for potential carcinogenic effects (U.S. EPA, 1981; NTP, 1997).

## Genetic Toxicity

Most of the assays for mutagenicity and effects on DNA syntheses have been negative for cyanide (U.S. EPA, 1992). Zeiger *et al.*, (1992) performed comprehensive mutagenicity testing using sodium cyanide (0.3 to 333 µg/plate in *Salmonella typhimurium* strains TA100, TA 1535, TA97 and TA98 with and without Aroclor-induced rat and hamster S9 at concentrations of 10 and 30 percent). All results were negative (Hebert, 1993). This work replicated some of the previous research performed by other researchers who obtained similarly negative results (U.S. EPA, 1992) with the exception of Kushi *et al.* (1983), who reported a marginally positive result in TA100 without S9.

## Toxicological Effects in Humans

### Acute Toxicity

Cyanide is a chemical asphyxiant that can cause death soon after exposure (Rorison and McPherson, 1992). Cyanide inhibits cytochrome oxidase preventing oxygen utilization leading to cytotoxic anoxia. Acute effects depend on the degree of histotoxic hypoxia. Death results from

CNS depression (U.S. EPA, 1978). Signs of acute intoxication by cyanide include rapid breathing, gasping, headache, salivation, nausea, anxiety, vertigo, cardiac arrhythmias, tremors, hypotension, respiratory failure, convulsions and death. Venous blood remains oxygenated and victim may appear pink (Timbrell, 1994). The mean lethal dose by mouth of cyanide in human adults is thought to be in the range of 50 to 200 mg and death is rarely delayed more than one hour (Gosselin *et al.*, 1976).

### Chronic Toxicity

Exposure to low levels of cyanide over a prolonged period produces symptoms which differ from acute exposures. Chronic cyanide intoxication has been associated with such human diseases as retrotubular neuritis in pernicious anemia, Leber's optic atrophy and Nigerian nutritional neuropathy (U.S. EPA, 1978).

Chronic exposure to tobacco smoke has been implicated in tobacco amblyopia, an eye disorder common to people who smoke (Hebert, 1993). Electroplaters and workers chronically exposed to cyanide solutions commonly suffer from dermatitis (Hamilton and Hardy, 1974).

As acutely toxic as cyanide is, repeated low-level doses of cyanide do not necessarily result in cumulative adverse effects. Cyanide may be highly acutely toxic, but it has lower toxicity on a chronic basis (U.S. EPA, 1980).

### Neurological Effects

Chronic human exposure to cyanide has been studied in regions of Africa with populations which consume large amounts of cyanide-containing cassava root. Neurological findings include symmetrical hyperreflexia of the upper limbs, symmetrical spastic paraparesis of the lower limbs, spastic dysarthria, diminished visual acuity, peripheral neuropathy, cerebellar signs and deafness (Ministry of Health, 1984).

### Sensitive Subpopulations

U.S. EPA (1992) describes certain groups which are at higher risk to the toxic effects of cyanide exposure than the general population. These groups include persons with defects in the rhodanese enzyme system, persons with vitamin B<sub>12</sub> deficiency or metabolism defect, iodine deficiency, protein deficiency and fetuses exposed to cyanide *in utero*.

## **DOSE-RESPONSE ASSESSMENT**

### **Noncarcinogenic Effects**

In 1992, U.S. EPA calculated the Drinking Water Equivalent Level (DWEL) as a function of the oral reference dose (RfD), for lifetime exposure to cyanide to be 0.7 mg/L (U.S. EPA, 1992). The value is currently reported as 0.8 mg/L apparently accounting for mathematical rounding in the original calculation (U.S. EPA, 1996). The DWEL is a lifetime exposure concentration protective of adverse, noncarcinogenic health effects under the assumption that all of the exposure to a contaminant is via drinking water (U.S. EPA, 1996).

The study by Howard and Hanzal (1955) has been selected to serve as the basis for an RfD and lifetime DWEL because it is the only long-term study for which an NOAEL was identified. From the chronic feeding study, U.S. EPA identified 10.8 mg/kg-day as an NOAEL for absence of clinical and histological effects following two years of feeding. From the NOAEL of 10.8 mg/kg-day, an RfD of 0.02 mg/kg-day was derived by applying a 500-fold uncertainty factor (100-fold for deriving an NOAEL from an animal study and five-fold to account for the use of a dietary study to develop drinking water criterion). From the RfD, the DWEL was calculated assuming an adult male body weight of 70 kg and the volume of drinking water consumed daily is 2 L/day. Therefore, the DWEL was calculated to be 0.8 mg/L.

We agree with U.S. EPA's identification of 10.8 mg/kg-day as the critical NOAEL. This level is used in the calculation of a PHG for cyanide in drinking water.

### CALCULATION OF PHG

The calculation of the public health-protective concentration (C, in mg/L) for cyanide follows the general formula for noncarcinogenic endpoints:

$$C = \frac{\text{NOAEL} \times \text{RSC} \times \text{BW}}{\text{UF} \times \text{L/day}} = \text{mg/L}$$

where,

- NOAEL = No-observed-adverse-effect-level (10.8 mg/kg-day)
- RSC = Relative source contribution of 20% (0.2)
- BW = Body weight for an adult male (70 kg)
- UF = Uncertainty factor of 500 (10-fold for inter-species variation, 10-fold for human variability, 5-fold to account for the use of a dietary study for drinking water criterion)
- L/day = Volume of drinking water consumed by an adult (2 L/day).

The RSC accounts for contribution of total exposure to cyanide from sources other than drinking water. A large percentage of cyanide exposure comes from food in nonsmokers, or tobacco smoke in smokers. We assume that the contribution of cyanide from these other sources is significantly larger than the contribution from drinking water, and an RSC for water of 20 percent (0.2) is used.

Therefore,

$$C = \frac{10.8 \text{ mg/kg-day} \times 0.2 \times 70 \text{ kg}}{500 \times 2 \text{ L/day}}$$

$$= 0.1512 \text{ mg/L} = 0.15 \text{ mg/L (rounded)} = 150 \text{ ppb.}$$

OEHHA calculates a PHG of 0.15 mg/L (150 ppb) for cyanide in drinking water. For comparison, U.S. EPA's DWEL calculation assumes that 100 percent of the human exposure to cyanide derives from drinking water. The DWEL was modified by U.S. EPA on the basis of relative source contribution (RSC) to arrive at a lifetime health advisory for cyanide of 0.15 mg/L, (U.S. EPA, 1997). The RSC is an assumption of the percentage of exposure we would receive via drinking water relative to other potential sources such as food and air.

## RISK CHARACTERIZATION

The PHG for cyanide is based on a thoroughly conducted dietary study in rats. Suitable long-term drinking water studies are not available, nor are suitable human chronic or subchronic studies available that contain well-defined exposure information. Concerning the mechanism of action, there is little doubt that the rat provides a relevant model for humans considering the well-known biochemical lesion produced in cyanide intoxication. However, considerable uncertainty may lie in the physiological response to the lesion or in the efficacy of detoxication mechanisms. In addition, appreciable uncertainty lies in determining the range of individual thresholds for adverse effects, especially in individuals with specific physiological (e.g., rhodanese or vitamin B<sub>12</sub> deficiencies) or behavioral factors (e.g., heavy smokers or consumption of high-cyanide foods) that may increase the risk of adverse effects of cyanide in drinking water. The combined uncertainty factor of 500, in addition to the RSC of 20 percent (0.2) recommended by both OEHHA and U.S. EPA is intended to account for all of these areas of uncertainty and variability.

## OTHER STANDARDS AND REGULATORY LEVELS

In 1962, the U.S. Public Health Service recommended that concentrations of cyanide in water supplies not exceed 0.2 mg/L in order to protect human health. This value was apparently calculated from the threshold limit value giving an approximate water level of 20 mg/L followed by the application of a 100-fold safety factor (U.S. EPA, 1992).

Table 2 includes selected international, national and state regulations and guidelines adapted from ATSDR (1995) and U.S. EPA (1996).

Table 2. Selected Guidelines And Regulations For Cyanide

Agency	Standard or Criterion	Level	Comment
ATSDR	Minimal Risk Level	0.05 mg/kg	subchronic
WHO	Drinking water guidelines	0.1 mg/L	
OSHA	Permissible Exposure Limit	5 mg/m <sup>3</sup>	occupational
U.S. EPA	Maximum Contaminant Level	0.2 mg/L	water
U.S. EPA	10-day Health Advisory	0.2 mg/L	10 kg child
U.S. EPA	Longer term Health advisory.	0.2 mg/L	10 kg child
U.S. EPA	Lifetime Health Advisory	0.15 mg/L	lifetime
ACGIH	Threshold Limit Value-Time Weighted Ave.	5 mg/m <sup>3</sup>	occupational
NIOSH	Immediately Dangerous to Life or Health	50 ppm	air
California DHS	Maximum Contaminant Level	200 ppb	1994

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