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HEALTH ADVISORIES FOR LEGIONELLA AND SEVEN INORGANICS

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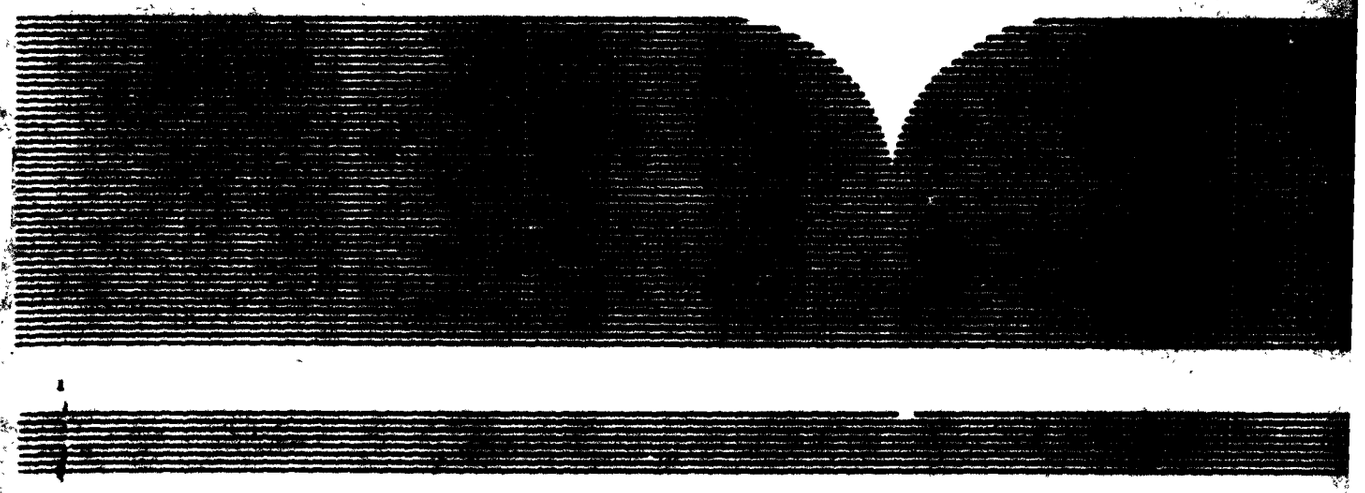

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16. Abstract

These documents summarize the health effects of Legionella and seven inorganics including: barium, cadmium, chromium, cyanide, mercury, nickel and nitrate/nitrite. Topics discussed include: General Information and Properties, Pharmacokinetics, Health Effects in Humans and Animals, Quantification of Toxicological Effects, Other Criteria Guidance and Standards, Analytical Methods and Treatment Technologies.

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CONTROL OF LEGIONELLA IN PLUMBING SYSTEMS

Health Advisory
Office of Drinking Water
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The Health Advisory (HA) Program, sponsored by the Office of Drinking Water (ODW), provides information on the health effects, analytical methodology and treatment technology that would be useful in dealing with the contamination of drinking water. Most of the Health Advisories prepared by the Office of Drinking Water are for chemical substances. This Health Advisory is different in that it addresses contamination of drinking water by a microbial pathogen and examines pathogen control rather than recommending a maximum allowable exposure level. Thus, for a variety of reasons, the format and contents of this Health Advisory necessarily vary somewhat from the usual Health Advisory document.

Health Advisories serve as informal technical guidance to assist Federal, State and local officials responsible for protecting public health when emergency spills or contamination situations occur. They are not to be construed as legally enforceable Federal standards. The HAs are subject to change as new information becomes available.

This Health Advisory (HA) is based upon information presented in the Office of Drinking Water's Criteria Document (CD) for Legionella. Individuals desiring further information should consult the CD. The CD is available for review at each EPA Regional Office of Drinking Water counterpart (e.g., Water Supply Branch or Drinking Water Branch), or for a fee from the National Technical Information Service, U.S. Department of Commerce, 5285 Port Royal Rd., Springfield, VA 22161, PB # 86-117843/AS. The toll-free number is (800) 336-4700; in the Washington, D. C. area: (703) 487-4650.

INTRODUCTION

Legionellae are bacteria that have been identified as the cause of legionellosis. Based upon an attack rate of about 1.2 cases of legionellosis per 10,000 persons per year (Foy et al., 1979), it has been estimated that more than 25,000 cases of this disease occur annually within the United States, and are caused primarily by one of the 23 currently recognized species of the genus Legionella. Most people who have developed Legionnaires Disease, the pneumonia form of legionellosis, were immunosuppressed or appeared to be more susceptible because of an underlying illness, heavy smoking, alcoholism, or age (more than 50 years old). In contrast, while some apparently healthy individuals have developed Legionnaires Disease, outbreaks involving healthy people have been limited mostly to the milder non-pneumonia form of the disease called Pontiac Fever.

Legionellae are widespread in lakes and rivers (Fliermans et al., 1979, 1981). There is some indication that these organisms may be either very sparse or absent in groundwater (Fliermans et al., 1982; Spino et al., 1984). Spino et al. (1984) was unable to isolate legionellae after aeration of groundwater through a redwood-slat aerator. The possibility that humans may

be exposed transiently to legionellae because of their high rate of contact with water is highly probable, given the high frequency of seropositivity to legionellae in healthy populations (Wentworth et al., 1984) and the widespread occurrence of legionellae in water environments.

In a number of outbreaks of legionellosis that have occurred in the United States, aerosols of water documented to contain the specific type of legionellae that was recovered from the patient have been identified as the vehicle for transmission (Cordes et al., 1981; Stout et al., 1982; Garbe et al., 1985). It has been hypothesized that legionellae enter buildings in very low numbers via the treated drinking water. These bacteria may proliferate in warm water when factors not yet fully determined allow them. Even when this occurs, as has been shown in numerous buildings, disease usually does not result. Cases and outbreaks of legionellosis occur only when aerosols containing legionellae possessing specific virulence factors (not as yet determined) are inhaled (possibly ingested) by susceptible individuals. Foodborne outbreaks or secondary spread have not been reported.

This Health Advisory discusses the control of legionellae in drinking water. This includes finished water at the treatment facility, the distribution system, and plumbing systems. Plumbing systems include hot water tanks, taps, showerheads, mixing valves, the faucet aerators, all of which have been associated with the proliferation of legionellae. This guidance does not discuss legionellae control for whirlpools, respirators, or heat-rejection equipment such as cooling towers and air conditioners. These have all been associated with cases of Legionnaires Disease.

Presence of Legionellae in the Distribution System and Plumbing Systems

Legionellae are found in raw water, in treated waters, and in plumbing systems (Fliermans et al., 1981; Hsu et al., 1984; Witherell et al., 1984), but the occurrence and fate of these organisms in the distribution system between these points are unknown. The organism may survive the treatment and disinfection process and pass intact through the distribution system. In addition, opportunities exist for their introduction into the system by means of broken or corroded piping, repair of existing mains, installation of new mains, back siphonage and cross connections, any of which may result in contamination of the water supply. In older distribution systems, especially those dependent on gravity flow, deterioration of piping may be so severe that the treated water comes in intimate contact with soil and is subject to infiltration by surface water. Thus, legionellae may be introduced into potable water by these routes.

Legionellae surviving initial water treatment may colonize pipe joints and corroded areas or adhere to the surface or sediment of storage tanks, especially those constructed of wood. Here, they may find a habitat suitable for survival and growth (Engelbrecht, 1983). Cul-de-sacs, intermittently used storage tanks and other sites in which waterflow is absent or restricted also may be appropriate habitats for legionellae.

New distribution systems or their components that were not appropriately cleaned and disinfected before being put into use may introduce legionellae into the system. Although this has not been documented, it may not be

coincidence that some of the serious outbreaks of Legionnaires Disease have occurred in newly-opened institutions or buildings (Haley et al., 1979; Marks et al., 1979; Helms et al., 1983). Construction activities may have included intervention into the water supply mains with introduction of contaminated water or, possibly, disturbance of sediment and sloughing of scale bearing high concentrations of legionellae by means of hydraulic shock or other perturbations.

There are numerous reports of legionellae occurring in plumbing systems, especially in hot water systems. Most of these investigations have been carried out in hospitals, and many were prompted by outbreaks of nosocomial (hospital-acquired) Legionnaires Disease. The primary reservoirs in hospitals are apparently hot water tanks in which water is maintained at temperatures below 55°C. Legionellae also have been found in showerheads, rubber fittings, aerator screens, faucet spouts, and other plumbing fixtures. This group of organisms has also been found in residential plumbing systems such as apartment buildings and homes (Wadowsky, 1982; Arnow and Weil, 1984), but disease has not been associated with these findings.

Control at the Water Treatment Facility

Only a few studies have been published on the effectiveness of various types of treatment for eradicating or reducing legionellae numbers at the water treatment utility. In one study, Tison and Seidler (1983) examined raw water and three kinds of distribution water supplies: (1) those treated by chlorine (free residual 0.2-0.6 mg/L); (2) those treated by sand filtration and chlorination (free residual 0.0-0.4 mg/L); and (3) those treated by flocculation, mixed media filtration, and chlorination (free residual 0.5-2.0 mg/L). Legionella were enumerated by direct fluorescent antibody (DFA) tests and all distribution waters contained about one order of magnitude fewer Legionella-like cells than did the raw waters, i.e., 10^3-10^4 per liter. While the evidence suggests that legionellae are common in treated water, the significance of these results is questionable because the authors were unable to isolate any legionellae by animal inoculation or culture procedures, and there are uncertainties about the specificity of the DFA technique used for legionellae detection.

Most water treatment plants in the United States use chlorine disinfection. Although extrapolation of laboratory studies to treatment plant situations is somewhat tenuous, Kuchta et al. (1983) reported that both L. pneumophila and L. micdadei (laboratory-adapted environmental and clinical strains) were much more resistant to chlorine than was Escherichia coli. At 21°C, pH 7.6, and 0.1 mg/L of free chlorine residual, a 99 percent kill was achieved in less than one minute for E. coli compared to 40 minutes for L. pneumophila. Under the same conditions, 0.5 mg/L of free chlorine resulted in a 99.9 percent legionellae kill in about 5 minutes. The contact time for a 99 percent kill of L. pneumophila at 4°C was twice as long as it was at 21°C. The authors concluded that legionellae can survive low levels of chlorine for rather long periods of time. In a subsequent study, Kuchta et al. (1984) compared agar-passaged (laboratory-adapted) and tap water-grown strains of L. pneumophila with respect to chlorine resistance, and showed that the latter were considerably more resistant. At 0.25 mg/L free residual chlorine, 21°C, and pH 7.6-8.0, a 99 percent kill of agar-passaged L. pneumophila was usually

achieved within 10 minutes, compared to 60 to 90 minutes for tap water-maintained strains. These data suggest that normal chlorination practices at treatment facilities may not control legionellae.

In contrast to these data, Hsu et al. (1984) reported that survivals of L. pneumophila and E. coli in various concentrations of chlorine were similar. In an in vitro study, laboratory-adapted strains of L. pneumophila Flint 1 serogroup 1 and E. coli B were inoculated into several dilutions of sodium hypochlorite in sterile tap water, and incubated at 24°C. At 0.2 mg/L residual chlorine, about an order of magnitude reduction occurred in two hours for both organisms. Neither organism could be recovered after two hours at concentrations equal to or exceeding 2.0 mg/L. The pH values were not reported. The reason for the discrepancy between this study and the Kuchta et al. (1983, 1984) studies may be due to strain or pH differences.

Control of Legionellae in Plumbing Systems

Chlorine and Heat

Studies on controlling legionellae in plumbing systems have examined primarily the effectiveness of heat and chlorine. The results of several of these are described below.

In an attempt to eradicate L. pneumophila from showers in a transplantation unit experiencing cases of Legionnaires Disease, Tobin et al. (1980) emptied the hot and cold water tanks and filled them with water containing 50 mg/L free chlorine. After three hours, this process was repeated. Shower fittings were removed and held at 65°C for 18 hours before replacement. Legionellae were not isolated from the shower samples after six months, but were found again at nine months.

Massanari et al. (1984) controlled a nosocomial outbreak of L. pneumophila infection by shock chlorination (15 mg/L) of both hot and cold water supplies for 12 hours. The system then was flushed and the hot water temperature raised from 41°C to 64°C for 41 days. These measures significantly reduced the frequency of positive cultures, but 3/35 of the outlets were still positive. Thereafter, a continuous-flow proportional chlorination unit was installed that provided free chlorine levels of 8 and 7.3 mg/L in hot and cold water, respectively. During the first 16 months of its use, virtually no samples (N=355) contained L. pneumophila and no new cases of legionellosis were identified. The few positive samples were obtained from rooms which had been vacant for at least 32 days. In this hospital, water is distributed in copper pipes.

Baird et al. (1984) hyperchlorinated their hospital water supply at a constant level of 4 mg/L of free chlorine. The rate of nosocomial Legionnaires Disease decreased by almost two-thirds and the total numbers of legionellae decreased, but the organisms persisted.

Witherell et al. (1984) attempted to eradicate L. pneumophila in hospital plumbing by adding chlorine to the cold water make-up that supplied the hot water heating system, in proportion to the water demands on the system. This was to avoid corrosion damage resulting from constant feed chlorination units

during periods of low demand. A free chlorine residual of 3.0 mg/L was maintained in the hot water system for 10 days and then reduced to 1.5 mg/L. The organism was not detected by direct culture methods subsequent to disinfection. The corrosivity of the hot water increased slightly (Langelier index = -0.3).

Fisher-Hoch et al. (1981) used hypochlorite to obtain a level of 1-2 mg/L of free chlorine at all cold water outlets in Kingston Hospital where legionellae were present in both cold and hot water. The free chlorine levels in the hot water could not be maintained above 0.2 mg/L and legionellae were recoverable at this level. The water temperature was 45°C, which was warm enough to volatilize the chlorine and cool enough to allow growth of legionellae. Eradication was accomplished successfully by maintaining the hot water temperature at 55°-60°C, in addition to disinfection of cold water. Subsequently, these investigators reported that when a disconnected hot water tank containing stagnant water was turned on again, L. pneumophila was found in the water and a case of nosocomial Legionnaires Disease occurred (Fisher-Hoch et al., 1982). A second disconnected tank which had been drained incompletely contained a thick brown liquid deposit at the bottom. This deposit contained 5.4×10^8 L. pneumophila/L. Filling the second tank with water containing 50 mg/L of chlorine for 24 hours followed by descaling did not successfully eliminate the legionellae. Maintaining a constant water temperature of 70°C throughout the tank for 1 hour, however, eliminated the organism. Ciesielski et al. (1984) also noted that legionellae can proliferate in stagnant water inside hot water tanks.

Dennis et al. (1982) examined water samples from the plumbing of 52 hotels, none of which was associated with cases of legionellosis. Ten isolates of L. pneumophila were obtained from water samples from eight hotels. Seven of these were from hot water taps or hot-cold mixer showers with water temperatures ranging from 40° to 54°C at the time of sampling. Evidence that these temperatures are not sufficient for Legionella control was also provided by Meenhorst et al. (1983). In their study, guinea pigs exposed to aerosolized legionellae from contaminated hot tapwater (48°C) contracted pneumonia. The strain of L. pneumophila used was isolated from a series of patients in the Netherlands.

Beam et al. (1984) attempted to control legionellosis outbreaks in two state development centers for the severely handicapped. In one center, hot water tanks that were positive for legionellae were heated to 71°C for 72 hours, followed by flushing for 15 minutes. Because of legionellae regrowth, a monthly heating schedule was established. Subsequently, the chlorine level was raised from 0.5 mg/L to 2 mg/L. This approach was successful in eradicating legionellae from water sources, but this chlorine level caused leaching from the iron pipes and consequent discoloration of the water, and was thus discontinued. Cement liners were installed in the hot water tanks and the first samples were positive for legionellae. The water temperature was not reported. Soon after, an outbreak of legionellosis occurred.

Plouffe et al. (1983) examined the relationship between the presence of L. pneumophila in potable water, nosocomial Legionnaires Disease, and hot water temperatures in six buildings. L. pneumophila was found in the hot water of all four buildings in which hot water was maintained at 43-49°C

(110°-120°F), and nosocomial Legionnaires Disease was found in three of these buildings. No organism and no disease was found in the two buildings where hot water was maintained at 57-60°C (135°-140°F). When the plumbing system of one of the buildings experiencing both L. pneumophila and Legionnaires Disease was flushed with 71°C water and the hot water then maintained at 57-60°C, no L. pneumophila and no new cases of Legionnaires Disease occurred for at least six months. The authors concluded that colonization and nosocomial Legionnaires Disease can be prevented by maintaining the hot water at 57-60°C.

In another attempt to eradicate L. pneumophila and nosocomial Legionnaires Disease, Yu et al. (1982) raised the temperature in the hot water storage tanks from 45° to 60°C for 72 hours and flushed 50 showers and 360 faucets for 20 minutes with the 60°C water to eliminate the organism from the sediment. A substantial reduction in counts occurred. After three months, colony counts increased rapidly from four colonies/mL to over 300 colonies/mL and nosocomial Legionnaires Disease again appeared. The authors concluded that a periodic schedule of short-term temperature elevation of the hot water system may control nosocomial Legionnaires Disease.

Stout et al. (1986) tested 75 legionellae isolates for their ability to withstand high temperatures. Tubes containing buffered yeast extract broth, sterile water, or hot water tank water plus sediment were inoculated and placed in 60°C, 70°C or 80°C water baths. At 60°C, four minutes were required for a one log reduction of L. pneumophila in the water plus sediment tube. Approximately 25 minutes were required at this temperature to sterilize a suspension of L. pneumophila which contains 10^8 colonies/mL. The authors recommend that when flushing distal outlets, that a flush temperature exceeding 60°C should be maintained for at least 30 minutes.

Muraca et al. (1987) compared the relative efficacies of heat (60°C), ozone (1-2 mg/L), UV (30,000 uW-scm^2 at 254 nm) and hyperchlorination (4-6 mg/L) to eradicate L. pneumophila in a model plumbing system. Non-turbid water at 25°C and 43°C and turbid water at 25°C were tested. When samples were taken of the circulated water, a 5-log kill of a 10^7 bacteria/mL concentration was achieved with all treatments within six hours. However, it is noteworthy that heat completely eradicated the Legionella in less than three hours, whereas UV light had produced its 5-log decrease in 20 minutes and no further inactivation was seen during the six-hour observation period. Chlorine and ozone required five hours to effect a similar 5-log decrease and chlorine achieved complete eradication only in the non-turbid samples during the six hours, while ozone killed the organisms in both turbid and non-turbid water in four to five hours.

Ozone Treatment

Edelstein et al. (1982) used ozone in an attempt to eradicate legionellae from the potable water supply of an unused wing of a hospital that was known to be contaminated with bacteria. The results were inconclusive because the organisms were eliminated from both the experimental wing and the control wing that was untreated. The latter was thought to be due to excess mechanical flushing and an unexpected rise in the chlorine content of the main water supply. The in vitro susceptibility of L. pneumophila to ozone was on the order of 0.36 mg ozone/L, but was not consistent. The ozone mean residual concentration used in the hospital water system was 0.79 mg/L.

Ultraviolet Radiation Treatment

Antopol and Ellner (1979) reported that 90 percent of L. pneumophila cells in distilled water were killed by 920 microwatt-sec/cm^2 of UV radiation. This could be compared with exposures ranging from 2,100 to 5,000 microwatt-sec/cm^2 for killing of E. coli, Salmonella, Serratia and Pseudomonas. If the latter values were obtained under the same conditions as those used for L. pneumophila, it would indicate that legionellae may be more than twice as susceptible to UV radiation than are the other organisms.

Gilpin (1984) reported laboratory and field experiments using UV radiation to inactivate Legionella spp. in standing and recirculating water systems. Times of exposure to one microwatt/cm^2 of UV radiation to produce 90 percent killing of six species of Legionella ranged from 17 to 44 minutes. A commercial UV apparatus killed 99 percent of the organism in less than 30 seconds in a three-liter recirculating water system.

In addition, Knudson (1985) reported that when agar plates seeded with L. pneumophila were exposed to 240 microwatt/cm^2 for 25 seconds or less, a reduction of six to seven orders of magnitude was observed. However, when UV-irradiated legionellae were exposed to indirect sunlight for 60 minutes, the recovery rates were two orders of magnitude greater than those not exposed to sunlight, due to photoreactivation.

Ethylene Oxide Treatment

Cordes et al. (1981) sterilized Legionella-contaminated showerheads with ethylene oxide but they were soon recontaminated.

Design of Hot Water Tanks

Legionellae often have been reported in hot water tanks, particularly in the bottom sediment. The design of these tanks is important in the control of these bacteria. Most residential hot water tanks are heated from the bottom near the cold water entrance pipe and are more likely to maintain a bottom temperature high enough (>55°C) to prevent growth of legionellae. However, if thermostats in homes have been set low (<55°C) as an energy conservation measure, growth of legionellae may result. Thermostats for hot water heaters in hospitals and other health care facilities are usually set at lower temperatures in conformity with the recommendations of the Joint Commission on Accreditation of Hospitals that the water temperature be "safe" (JCAH, 1985). This practice, which is done to prevent scalding of patients using the hot water, may promote the growth of legionellae. Larger institutional tanks also are heated more often by internal steam coils or by other heaters located midway from top to bottom of the tank. The water at the bottom may not be heated sufficiently to kill legionellae. Periodic partial draining of these tanks from the bottom to eliminate sediment may control legionellae proliferation. This is especially important, since environmental microflora in the sediment are known to produce metabolites, possibly including cysteine, which stimulate legionellae growth (Stout et al., 1985). Removal from other areas of the plumbing system where water stagnates may also prevent or control legionellae growth (Stout et al., 1985).

Type of Water Fittings

Information on the specific types of gaskets and fittings that support the colonization of legionellae is not well documented. One study of water fittings as sources of L. pneumophila in a hospital plumbing system was carried out by Colbourne et al. (1984a, 1984b). In well-controlled experiments, L. pneumophila was isolated from rubber washers and gaskets, but not from fiber or plastic fittings. The ability of the bacteria to multiply when in contact with the rubber fittings was demonstrated. When the rubber fittings were replaced with plastic fittings, L. pneumophila could not be isolated up to one year later. The authors concluded that shower and tap fittings that support growth of legionellae provide habitats protected from chlorine and heat. These foci may be seeded constantly or intermittently with legionellae from hot water tanks or other amplifiers within the distribution system.

When to Control Legionellae in Plumbing Systems

Legionellae are often found in the plumbing systems of hospitals which have not experienced any cases of Legionnaires Disease. One reason may be that some strains are more virulent than others. Currently, there is no practical method for distinguishing the virulent strains from avirulent strains. For this reason, some experts feel that the mere presence of legionellae in the absence of the disease is not sufficient grounds to undertake control measures (Jakubowski et al., 1984). They believe that health care institutions should focus initially on surveillance for respiratory illness, especially in high risk patients, rather than to control legionellae in plumbing systems. If nosocomial legionellosis is identified and environmental strains match patient isolates, then control in plumbing systems is indicated.

In contrast, Edelstein (1985) states that most authorities would probably agree that disinfection of a contaminated site is indicated when:

- it is implicated as a source of an outbreak of Legionnaires Disease or Pontiac Fever;
- it is present in a hospital ward housing especially high-risk patients, such as an organ transplantation unit, regardless of epidemiological findings; in this case, selective decontamination of certain ward areas may be feasible; and when
- it is found in a building which has not been used for some time and in which the water has stagnated.

Because of the virulence of some of these strains and the fact that at least 25,000 cases/year or more occur in the U.S., a stronger preventive approach could also be supported.

In summary, there is no consensus on when measures should be undertaken to control legionellae in the plumbing system of health care institutions. Once virulence factors can be identified and virulent strains differentiated from avirulent strains, routine monitoring of the plumbing system may become more practical.

Until then, the Office of Drinking Water recommends that, on the basis of the high incidence and mortality rate, health care institutions consider preventive measures for the control of legionellae in their plumbing systems. These measures could also control other opportunistic pathogens in the system which might cause nosocomial infections.

Summary

Legionellae are abundant in ambient water, and may survive water treatment, especially since they are relatively resistant to chlorine. Once in the treated water, they then pass, probably at low levels, through the distribution system. It is also possible that legionellae enter the distribution system through broken or corroded piping, repair of existing mains, installation of new mains, back siphonage, and cross connections. When legionellae enter hot water tanks, they settle to the bottom and, under certain circumstances, will proliferate. If they proliferate, plumbing fixtures such as aerators, water fittings, and showerheads may be seeded, resulting in colonization and growth at these sites.

Inhalation of aerosolized potable water has been suggested from outbreak investigations as a primary route of infection, although ingestion is also a possibility. The most susceptible individuals are those with underlying diseases, especially those involving immunosuppression therapy. In several outbreaks, however, apparently healthy individuals have developed legionellosis. Other risk factors include alcohol abuse, surgery and smoking.

In order to reduce legionellae levels in drinking water, the presence of organic matter and growth of algae and protozoa should be minimized in storage reservoirs. Moreover, newly-repaired or constructed components of the water distribution system should be flushed thoroughly and disinfected before being put into operation. Even after flushing and disinfection, one cannot assume legionellae have been controlled, since design factors in the distribution system may impede the efficiency of these measures.

In order to control legionellae growth in hot water plumbing, several approaches may be considered. Most of the published data have examined the effectiveness of chlorine and/or heat. The maintenance of free chlorine has been found effective for controlling legionellae. Shock chlorination also is effective, but unless free chlorine is maintained within a system, the organism may reappear. Control probably can be achieved if free chlorine levels in the hot water are maintained at 8 mg/L, but at this level corrosion of pipes may occur. In some cases, control may be achieved at 1.5-2 mg/L free chlorine. Undoubtedly, the level of chlorine found effective will depend, in part, on the design criteria of the plumbing system. A pertinent facet in controlling legionellae is the difficulty of controlling batch chlorination and of maintaining a chlorine residual in hot water. This problem can be minimized by using a continuous-flow proportional chlorinator in the hot water system.

Heat shock may eradicate legionellae in hot water tanks, if the temperature at the bottom of the tank is maintained at 70°C for one hour, but this is a temporary measure which must be done routinely to be effective. Maintenance

of hot water at 55°C or higher apparently controls the organism, while lower temperatures may not. If legionellae are controlled by heat, care must be taken to prevent scalding of persons using the water, especially in health care institutions.

Disinfection of a plumbing system by heat treatment or chlorine treatment alone may not be as effective as a combination of the two. For example, growth of legionellae may theoretically be enhanced on the cold water side of a hot-cold water mixing valve in a heat-treated plumbing system, a location where chlorine may be effective.

Effective disinfection of legionellae by ozone, ultraviolet radiation or ethylene oxide has not been demonstrated by field tests.

In addition to chemical and heat disinfection, other procedures may be effective in controlling legionellae. Hot water tanks should be designed to give uniform temperatures throughout. Hot or cold water tanks used intermittently should be disconnected from the system, drained, flushed, and disinfected before being reconnected. Hot water tanks should be drained regularly or at least bled to remove accumulated sludge that may serve as a substrate for growth of legionellae and other microorganisms. Taps and showers in unused areas of health care facilities should at least be flushed before patients are exposed to them. Finally, faucet sieves and aerators, and rubber washers and gaskets in the plumbing system should be used with caution, especially in institutions housing physically compromised individuals and where hot water is maintained at temperatures lower than 55°C.

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BARIUM

Health Advisory
Office of Drinking Water
U.S. Environmental Protection Agency

I. INTRODUCTION

The Health Advisory (HA) Program, sponsored by the Office of Drinking Water (ODW), provides information on the health effects, analytical methodology and treatment technology that would be useful in dealing with the contamination of drinking water. Health Advisories describe nonregulatory concentrations of drinking water contaminants at which adverse health effects would not be anticipated to occur over specific exposure durations. Health Advisories contain a margin of safety to protect sensitive members of the population.

Health Advisories serve as informal technical guidance to assist Federal, State and local officials responsible for protecting public health when emergency spills or contamination situations occur. They are not to be construed as legally enforceable Federal standards. The HAs are subject to change as new information becomes available.

Health Advisories are developed for One-day, Ten-day, Longer-term (approximately 7 years, or 10% of an individual's lifetime) and Lifetime exposures based on data describing noncarcinogenic end points of toxicity. Health Advisories do not quantitatively incorporate any potential carcinogenic risk from such exposure. For those substances that are known or probable human carcinogens, according to the Agency classification scheme (Group A or B), Lifetime HAs are not recommended. The chemical concentration values for Group A or B carcinogens are correlated with carcinogenic risk estimates by employing a cancer potency (unit risk) value together with assumptions for lifetime exposure and the consumption of drinking water. The cancer unit risk is usually derived from the linear multistage model with 95% upper confidence limits. This provides a low-dose estimate of cancer risk to humans that is considered unlikely to pose a carcinogenic risk in excess of the stated values. Excess cancer risk estimates may also be calculated using the One-hit, Weibull, Logit or Probit models. There is no current understanding of the biological mechanisms involved in cancer to suggest that any one of these models is able to predict risk more accurately than another. Because each model is based on differing assumptions, the estimates that are derived can differ by several orders of magnitude.

This Health Advisory is based on information presented in the Office of Drinking Water's Health Effects Criteria Document (CD) for barium (U.S. EPA, 1985). The HA and CD formats are similar for easy reference. Individuals desiring further information on the toxicological data base or rationale for risk characterization should consult the CD. The CD is available for review at each EPA Regional Office of Drinking Water counterpart (e.g., Water Supply Branch or Drinking Water Branch), or for a fee from the National Technical Information Service, U.S. Department of Commerce, 5285 Port Royal Rd., Springfield, VA 22161, PB #86-118031/45. The toll-free number is (800) 336-4700; in the Washington, D.C. area: (703) 487-4650.

II. GENERAL INFORMATION AND PROPERTIES

CAS No.

- Barium --
  Barium Chloride -- 10361-37-2
  Barium Sulfate -- 7727-43-7

Synonyms

- Barium Sulfate; Barite (Windholz, 1976)

Uses

- Depending upon the specific compound, barium salts are used for a number of purposes including drilling mud (Kirkpatrick, 1978), pigment (Miner, 1969), and as x-ray contrast medium (Miner, 1969). Other uses are summarized by Pidgeon (1964).

Properties (Pidgeon, 1964; Preisman, 1964; Miner, 1969; Chilton, 1973; Kirkpatrick, 1978; Reeves, 1979)

- The properties of barium compounds vary with the specific compound; some examples are as follows:

	Barium	Barium Chloride	Barium Sulfate
Chemical Formula	Ba	$BaCl_2$	$BaSO_4$
Atomic/Molecular Weight	137.33	208.24	233.40
Physical State	Silver-white solid	White solid	Colorless solid
Boiling Point	1637-1638°C	1560°C	--
Melting Point	729-730°C	960°C	1580°C
Density (20°C)	3.6 g/cm^3	3.856 g/cm^3	4.50 g/cm^3
Vapor Pressure	1810 x 10^{-5} mm Hg	--	--
Water Solubility (pph)	reacts	31 (0°C)	0.000285 (30°C)
Log Octanol/Water Partition Coefficient	--	--	--
Taste Threshold	--	--	--
Odor Threshold	--	--	--

Occurrence

- Barium is a reactive metal which is not found free in nature but exists as a number of salts. Barium occurs in nature chiefly as the mineral barite ($BaSO_4$) and in much smaller amounts as witherite ($BaCO_3$). The mineral forms are relatively insoluble in water, having high melting and boiling points and very low vapor pressures (Preisman, 1964). Barium compounds occur in most geologic materials at levels of 300-500 ppm. Barium occurs at low levels in most surface and ground waters with reported levels of less than 340 ug/L. While barium compounds are used commercially in a number of processes, contamination of drinking water is usually the result of naturally-occurring barium and not industrial releases (U.S. EPA, 1987).

- There are limited survey data on the occurrence of barium in drinking water. Most supplies contain less than 200 ug/L of barium. Currently, 60 ground water supplies and 1 surface water supply exceed the interim maximum contaminant level (MCL) of 1,000 ug/L. Barium also occurs in most foods as a low level contaminant. Based upon the limited information available on barium exposure, food is the major source of barium exposure (U.S. EPA, 1987).

III. PHARMACOKINETICS

Absorption

- In laboratory animals, the absorption of barium varies with a number of factors including the species of animal (U.S. EPA, 1985), the compound tested (McCauley and Washington, 1983), the age of the animal (Taylor et al., 1962) and the composition of the diet (Lengemann, 1959).

- While no definitive human barium absorption studies were found (U.S. EPA, 1985), barium absorption has been estimated to be approximately 5% in the adult (ICRP, 1973). However, other data (Harrison et al., 1967) suggest that barium absorption probably is greater than this. While data in laboratory animals (Lengemann, 1959) suggest that barium absorption in children may be significantly greater than in adults, there is currently inadequate information to resolve this issue.

Distribution

- In the mouse, intravenously injected barium ($^{133}BaCl_2$) is distributed widely throughout the organism, but is localized principally in the bone (Dencker et al., 1976).

- Based on autopsy data, barium levels in human bone are relatively constant and do not appear to increase with age, ranging from an average value of 7.0 ppm in bone at age 0 to 3 months to an average of 8.5 ppm at age 33 to 74 years (Sowden and Stitch, 1957).

Metabolism

° The skeletal metabolism of barium in humans is qualitatively similar to that of calcium, although the incorporation of these two elements is quantitatively very different (Bauer et al., 1956,1957).

Excretion

° In humans, ingested barium is eliminated principally via fecal excretion (approximately 72%) following oral exposure (Tipton et al., 1966).

IV. HEALTH EFFECTS

Humans

° Acute barium toxicity is associated with hypokalemia and electrocardiographic changes as well as other symptoms (Diengott et al., 1964; Gould et al., 1973; Talwar and Sharma, 1979).

° NAS (1977) has concluded that: "The fatal dose of barium chloride for man has been reported to be about 0.8 - 0.9 g, or 550 - 600 mg of barium."

° Schroeder and Kraemer (1974) concluded that there was a significant negative correlation between barium in drinking water and atherosclerotic heart disease.

° In an epidemiology study, Brenniman et al. (1981) concluded that there was no statistically significant difference in blood pressure between those ingesting drinking water containing barium at 7.3 mg/L as compared to 0.1 mg/L. A concentration of 7.3 mg/L corresponds to a dose of 0.20 mg/kg/day (assuming a 70-kg adult drinks 2 L per day). The duration of exposure was not identified.

Animals

Short-term Exposure

° The acute oral LD_{50} of barium varies markedly with species, compound, age and other factors (U.S. EPA, 1985). For example, the acute oral LD_{50} of barium chloride is 220 mg/kg in weanling rats and 132 mg/kg in adult rats (Tardiff et al., 1980).

Long-term Exposure

° Tardiff et al. (1980) exposed rate to barium at 0, 10, 50, or 250 ppm in drinking water for 4, 8 and 13 weeks. The barium concentrations were approximately 0, 2.75, 13.7 and 66.25 mg/kg/day at the beginning of the study and 0, 1.7, 6.6 and 31.5 mg/kg/day at the end of the study. Although the barium body burden increased with increasing barium dosage, no conclusive signs of barium toxicity were observed in these animals. A weakness of this study is that, unlike Perry et al. (1983) below, blood pressure was not measured.

- Perry et al. (1983) exposed weanling rats to barium at 1, 10 or 100 ppm in drinking water for up to 16 months (average daily barium doses of 0.051, 0.51 and 5.1 mg/kg, respectively). With the exception of an increase in blood pressure, there were no signs of toxicity at any barium dose level. Systolic blood pressure measurements revealed no increase in pressure in animals exposed to 1 ppm for 16 months, an increase of 4 mm Hg ($p \hat{} .01$) in animals exposed to 10 ppm barium for 16 months, and an increase in systolic pressure of 16 mm Hg ($p < 0.001$) in animals exposed to 100 ppm barium for 16 months. The animals in this study were maintained in a special contaminant-free environment and fed a diet designed to reduce exposure to trace metals. It is possible that the restricted intake of certain beneficial metals (e.g., Ca and K) may have predisposed the test animals to the hypertensive effects of barium (U.S. EPA, 1985).

- Schroeder and Mitchener (1975a,b) exposed rats and mice to 5 mg/L barium in drinking water for a lifetime (approximately 0.25 mg/kg/day for rats and 0.825 mg/kg/day for mice). No compound related adverse effects were observed. A weakness of this study is that, unlike Perry et al. (1983) above, blood pressure was not measured.

Reproductive Effects

- No adequate mammalian study on the potential reproductive effects of barium was identified (U.S. EPA, 1985).

Developmental Effects

- No adequate mammalian study on the potential developmental effects of barium was identified (U.S. EPA, 1985).

Mutagenicity

- No adequate studies on the mutagenicity of barium were identified (U.S. EPA, 1985).

Carcinogenicity

- No adequate studies on the carcinogenicity of barium were identified (U.S. EPA, 1985).

V. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

Health Advisories (HAs) are generally determined for One-day, Ten-day, Longer-term (approximately 7 years) and Lifetime exposures if adequate data are available that identify a sensitive noncarcinogenic end point of toxicity. The HAs for noncarcinogenic toxicants are derived using the following formula:

$$HA = \frac{(NOAEL \text{ or } LOAEL) \times (BW)}{(UF) \times (\_\_\_ \text{ L/day})} = \_\_\_ \text{ mg/L } (\_\_\_ \text{ ug/L})$$

where:

NOAEL or LOAEL = No- or Lowest-Observed-Adverse-Effect-Level in mg/kg bw/day.

BW = assumed body weight of a child (10 kg) or an adult (70 kg .

UF = uncertainty factor (10, 100 or 1,000), in accordance with NAS/ODW guidelines.

___ L/day = assumed daily water consumption of a child (1 L/day) or an adult (2 L/day).

One-day Health Advisory

The available data are insufficient to develop a One-day HA for barium. It is recommended that the modified DWEL of 0.51 mg/L (adjusted for a 10-kg child) be used as the One-day HA for the 10-kg child.

Ten-day Health Advisory

The available data are insufficient to develop a Ten-day HA for barium. It is recommended that the modified DWEL of 0.51 mg/L (adjusted for a 10-kg child) be used as the Ten-day HA for the 10-kg child.

Longer-term Health Advisory

The available data are insufficient to develop Longer-term HAs for barium. It is recommended that the DWEL of 1.8 mg/L be used as the Longer-term HA for the 70-kg adult and the modified DWEL of 0.51 mg/L (adjusted for a 10-kg child) be used as the Longer-term HA for the 10-kg child.

Lifetime Health Advisory

The Lifetime HA represents that portion of an individual's total exposure that is attributed to drinking water and is considered protective of noncarcinogenic adverse health effects over a lifetime exposure. The Lifetime HA is derived in a three step process. Step 1 determines the Reference Dose (RfD), formerly called the Acceptable Daily Intake (ADI). The RfD is an estimate of a daily exposure to the human population that is likely to be without appreciable risk of deleterious effects over a lifetime, and is derived from the NOAEL (or LOAEL), identified from a chronic (or subchronic) study, divided by an uncertainty factor(s). From the RfD, a Drinking Water Equivalent Level (DWEL) can be determined (Step 2). A DWEL is a medium-specific (i.e., drinking water) lifetime exposure level, assuming 100% exposure from that medium, at which adverse, noncarcinogenic health effects would not be expected to occur. The DWEL is derived from the multiplication of the RfD by the assumed body weight of an adult and divided by the assumed daily water consumption of an adult. The Lifetime HA is determined in Step 3 by factoring in other sources of exposure, the relative source contribution (RSC). The RSC from drinking water is based on actual exposure data or, if data are not available, a value of 20% is assumed for synthetic organic chemicals and a value of 10%

is assumed for inorganic chemicals. If the contaminant is classified as a Group A or B carcinogen, according to the Agency's classification scheme of carcinogenic potential (U.S. EPA, 1986), then caution should be exercised in assessing the risks associated with lifetime exposure to this chemical.

Considering the kind, nature and partially contradictory results of the various barium studies, ODW does not believe that it is appropriate to use any simplistic formula to determine a Lifetime HA for barium in drinking water. Rather:

° No single study, considered alone, is appropriate to calculate a Lifetime HA for barium.

° A barium HA must be based on the weight of all the pertinent data, considered together.

In the Perry et al. (1983) rat drinking water study, 10 ppm barium (0.51 mg/kg/day) produced a small (4 to 7 mm Hg) but statistically significant increase in blood pressure by 8 to 16 months; 100 ppm barium (5.1 mg/kg/day) produced clear hypertension and cardiotoxic effects.

A major shortcoming of the Perry, et al. (1983) study is that the animals were maintained in a special environment and received both a special diet and special water, all intended to reduce exposure to trace metals. Because of the beneficial effects of some metals (i.e., cadmium) and the interactions of barium with other metals, it is possible that the restricted intake of other metals may have contributed to the apparent toxicity of barium. In addition, the results of the Perry, et al. (1983) rat study clearly contradict the results of the Brenniman, et al. (1981) human study which suggests that barium in drinking water has no appreciable effect upon blood pressure in humans, at least at a level of 7.3 ppm (0.20 mg/kg/day) in drinking water.

While the 4 to 7 mm Hg increase in blood pressure observed at 10 ppm barium (0.51 mg/kg/day) in the Perry, et al. (1983) study may be a compound related effect, ODW has serious doubts as to whether this 4 to 7 mm Hg increase in rat blood pressure should be considered an adverse effect in the light of the negative effects observed in the Brenniman, et al. (1981) human study. Considering the contradiction between the rat and human data, it was ODW's judgment that it was not prudent either to ignore the results of Perry et al. (1983) or to treat the results with the same seriousness they would warrant, had they been observed in humans.

In ODW's judgment, the most appropriate way to balance the contradiction between the Perry, et al. (1983) rat study and the Brenniman, et al. (1981) human study is to use the results of the Perry, et al. (1983) study, with a reduced uncertainty factor of 10x and to treat the 0.51 mg/kg/day value as if it were a NOAEL.

Thus, based on the previous discussion, the Lifetime Health Advisory is derived as follows:

Step 1: Determination of the Reference Dose (RfD)

$$RfD = \frac{(0.51 \text{ mg/kg/day})}{(10)} = 0.051 \text{ mg/kg/day}$$

where:

0.51 mg/kg/day = NOAEL (see discussion above).

10 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a NOAEL from an animal study. However, as previously discussed, ODW believes that an uncertainty factor of 10 is appropriate in this specific case (see discussion above).

Step 2: Determination of the Drinking Water Equivalent Level (DWEL)

$$DWEL = \frac{(0.051 \text{ mg/kg/day})\ (70 \text{ kg})}{(2 \text{ L/day})} = 1.8 \text{ mg/L } (1{,}800 \text{ ug/L})$$

where:

0.051 mg/kg/day = RfD.

70 kg = assumed body weight of an adult.

2 L/day = assumed daily water consumption of an adult.

Step 3: Determination of the Lifetime Health Advisory

Lifetime HA = (1.8 mg/L) (83%) = 1.5 mg/L (1,500 ug/L)

where:

1.8 mg/L = DWEL.

83% = assumed relative source contribution from water (Federal Register, November 13, 1985).

Evaluation of Carcinogenic Potential

- Due to the absence of toxicological evidence to classify barium as a potential carcinogen, a quantification of carcinogenic risks for barium is not appropriate.

- No information was located in the available literature regarding the carcinogenic potential of barium in humans nor were any animal studies found which were adequate to evaluate the carcinogenic potential of barium.

- Applying the criteria described in EPA's guidelines for assessment of carcinogenic risk (U.S. EPA, 1986) barium is classified in Group D: Not classified. This category is for agents with inadequate animal and human evidence.

- The International Agency for Research on Cancer has not evaluated the carcinogenic potential of barium.

VI. OTHER CRITERIA, GUIDANCE AND STANDARDS

- The National Interim Primary Drinking Water Regulations of 1975 established a Maximum Contaminant Level (MCL) drinking water standard for barium of 1 mg/L (U.S. EPA, 1976).

- The National Academy of Sciences (NAS, 1982) derived a 1-day Suggested No-Adverse-Response Level (SNARL) for barium of 6.0 mg/L.

- The National Academy of Sciences (NAS, 1982) derived a chronic Suggested No-Adverse-Response Level (SNARL) value for barium of 4.7 mg/L.

- The American Conference of Governmental Industrial Hygienists established an occupational threshold limit value (TLV) of 0.5 mg/m^3 for barium nitrate in air (ACGIH, 1980).

- The USSR standard for waterborne barium is 4 mg/L (NAS, 1977).

- The OSHA 8-hour time-weighted average exposure limit for soluble barium compounds is 0.5 mg/m^3 in workplace air (OSHA, 1985).

VII. ANALYTICAL METHODS

- Determination of barium is by atomic absorption (AA) using either direct aspiration into a flame (U.S. EPA, 1979a) or a furnace technique (U.S. EPA, 1979b).

- The direct aspiration AA procedure is a physical method based on the absorption of radiation at 553.6 nm by barium. The sample is aspirated into an air-acetylene flame and atomized. A light beam is directed through the flame into a monochromator, and onto a detector that measures the amount of light absorbed. Absorbance is proportional to the concentration of barium in the sample. The detection limit is 100 ug/L using this procedure.

- The furnace AA procedure is similar to direct aspiration AA except a furnace, rather than a flame, is used to atomize the sample. The detection limit is 2 ug/L using this procedure.

VIII. TREATMENT TECHNOLOGIES

- Experience indicates that ion exchange, lime softening and reverse osmosis are effective to remove barium from drinking water. Conventional coagulation/filtration processes are not effective to remove barium from drinking water (U.S. EPA, 1977).

- Weinberg (1973) and Logsdon et al. (1974) reported that ion exchange softening systems are highly efficient (93 to 98 percent) for reducing

barium in water, even after water hardness breakthrough. Field data from two Midwestern full-scale ion exchange softening plants showed that barium removal was comparable to hardness removal on well water containing 11-19 mg/L of barium and 225-230 mg/L of hardness as $CaCo_3$ (BIF, 1970). When these softening units were performing efficiently and removing all of the hardness from the water, they also removed all of the barium.

- Experience indicates that lime softening is very effective in removing barium from drinking water. Lime softening achieved greater than 90 percent removal in the 10-11 pH range on well water containing 7-8.5 mg/L of naturally occurring barium. Removals decreased below and above this range. Pilot plant studies conducted at the EPA Municipal Research Laboratory and full-scale treatment information on similar types of ground water verified the laboratory data. Pilot plant test runs on water containing 10-12 mg/L of barium at pH 9.2, 10.5 and 11.6 resulted in removals of 84, 93 and 82 percent, respectively. Grab samples from two full-scale lime softening plants showed removals of 88 and 95 percent. These plants operated at pH 10.5 and 10.3; the raw water barium concentrations were measured at 7.5 and 17.4 mg/L, respectively (BIF, 1970).

- A number of studies indicate that reverse osmosis membranes can remove more than 90 percent of the barium from drinking water. In an experimental long term study, 99 percent barium removal was obtained using cellulose acetate membrane at 400-800 psi operating pressures (BIF, 1970). Other studies by Sorg et al. (1980) achieved similar results, where 95-99 percent removals were obtained by passing water containing 7 mg/L barium through cellulose acetate membranes at 165-180 psi operating pressures.

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March 31, 1987

CADMIUM

Health Advisory Draft
Office of Drinking Water
U.S. Environmental Protection Agency

I. INTRODUCTION

The Health Advisory (HA) Program, sponsored by the Office of Drinking Water (ODW), provides information on the health effects, analytical methodology and treatment technology that would be useful in dealing with the contamination of drinking water. Health Advisories describe nonregulatory concentrations of drinking water contaminants at which adverse health effects would not be anticipated to occur over specific exposure durations. Health Advisories contain a margin of safety to protect sensitive members of the population.

Health Advisories serve as informal technical guidance to assist Federal, State and local officials responsible for protecting public health when emergency spills or contamination situations occur. They are not to be construed as legally enforceable Federal standards. The HAs are subject to change as new information becomes available.

Health Advisories are developed for One-day, Ten-day, Longer-term (approximately 7 years, or 10% of an individual's lifetime) and Lifetime exposures based on data describing noncarcinogenic end points of toxicity. Health Advisories do not quantitatively incorporate any potential carcinogenic risk from such exposure. For those substances that are known or probable human carcinogens, according to the Agency classification scheme (Group A or B), Lifetime HAs are not recommended. The chemical concentration values for Group A or B carcinogens are correlated with carcinogenic risk estimates by employing a cancer potency (unit risk) value together with assumptions for lifetime exposure and the consumption of drinking water. The cancer unit risk is usually derived from the linear multistage model with 95% upper confidence limits. This provides a low-dose estimate of cancer risk to humans that is considered unlikely to pose a carcinogenic risk in excess of the stated values. Excess cancer risk estimates may also be calculated using the One-hit, Weibull, Logit or Probit models. There is no current understanding of the biological mechanisms involved in cancer to suggest that any one of these models is able to predict risk more accurately than another. Because each model is based on differing assumptions, the estimates that are derived can differ by several orders of magnitude.

This Health Advisory (HA) is based on information presented in the Office of Drinking Water's Health Effects Criteria Document (CD) for cadmium (U.S. EPA, 1985). The HA and CD formats are similar for easy reference. Individuals desiring further information on the toxicological data base or rationale for risk characterization should consult the CD. The CD is available for review at each EPA Regional Office of Drinking Water counterpart (e.g., Water Supply Branch or Drinking Water Branch), or for a fee from the National Technical Information Service, U.S. Department of Commerce, 5285 Port Royal Rd., Springfield, VA 22161, PB #86-117942/AS. The toll-free number is (800) 336-4700; in the Washington, D.C. area: (703) 487-4650.

II. GENERAL INFORMATION AND PROPERTIES

CAS No.

- Cadmium -- 7440-43-9
  Cadmium Chloride -- 10108-64-2
  Cadmium Oxide -- 1306-19-0

Synonyms

- None

Uses

- Cadmium is used for a number of purposes including the following (Stubbs, 1978): batteries, electroplating, stabilizer, pigments, and as an alloy with other metals.

Properties (Schindler, 1967; Weast, 1971; IARC, 1976; Parker, 1978)

- The properties of cadmium compounds vary with the specific compound; some examples are as follows:

	Cadmium	Cadmium Chloride	Cadmium Oxide
Chemical Formula	Cd	$CdCl_2$	CdO
Atomic/Molecular Weight	112.40	183.32	128.40
Physical State	Soft white solid	Solid	Solid
Boiling Point	765°C	--	1,559°C
Melting Point	320.9°C	568°C	900°C
Density	8.642 g/cm^3	4.047 g/cm^3	8.15 g/cm^3
Vapor Pressure (400°C)	1.4 mmHg	--	--
Water Solubility	--	Soluble	Insoluble
Log Octanol/Water Partition Coefficient	--	--	--
Taste Threshold	--	--	--
Odor Threshold	--	--	--

Occurrence

- Cadmium is a naturally-occurring metallic element, present in most of the earth's crust at levels below 1 ppm. Cadmium is commercially obtained as a byproduct during the production of zinc. Commercial uses of cadmium and its compounds include metal plating, electronics, paints, and pigments. Cadmium is released to the environment during its uses and from other commercial activities. However, these releases have not resulted in the contamination of ground and surface waters (U.S. EPA, 1987).

- Naturally occurring levels of cadmium in surface and ground water normally fall in the range of 1-10 ug/L. State monitoring data have reported that 21 ground water supplies and 4 surface water supplies currently exceed 10 ug/L. Cadmium occurs at low levels in food and air. The FDA Total Diet Study reports that adults currently receive 34 ug/day of cadmium from their diets. Based upon this information food appears to be the major route of exposure for cadmium (U.S. EPA, 1987).

- Cadmium is found in both cigarettes and cigarette smoke and as the absorption of inhaled cadmium can approach levels as high as 96% (CEC, 1978), smoking can account for a substantial fraction of the body burden of cadmium (Ellis et al., 1979)

III. PHARMACOKINETICS

Absorption

- The absorption of cadmium following oral administration to laboratory animals, and presumably humans, is modified by many factors including dose (Engstrom and Nordberg, 1979), age (Kostial et al., 1983), diet (Suzuki et al., 1969) and by the presence of other metals such as calcium (Washko and Cousins, 1976).

- Cadmium does not readily cross the skin (CEC, 1978).

- Cadmium is very readily absorbed following inhalation; as much as 96% of the cadmium deposited in the lungs may be absorbed (CEC, 1978).

Distribution

- In both rats (Sabbioni et al., 1978) and humans (Sumunio et al., 1975), cadmium distributes throughout the body and accumulates in the kidney and liver where it may attain levels 10 to 100 times greater than those of other tissues.

Metabolism

- Whole cadmium is not metabolized to other compounds as is the typical organic drinking water contaminant; once within the body, cadmium readily combines with the the low molecular weight protein(s) metallothionein (Foulkes, 1982).

Excretion

- Once absorbed, cadmium is eliminated in humans principally via the urine (U.S. EPA, 1985).

- Cadmium is eliminated very slowly in humans; a half-life for elimination of cadmium has been estimated to be 10 to 33 years (Ellis et al., 1979). The long half-life of cadmium in humans is principally accounted for by the marked accumulation and retention of cadmium in the kidney and liver (Friberg et al., 1974)

- In humans, average body retention of radiolabelled cadmium chloride, measured one to five weeks post exposure, was approximately 4.6% (McLellan et al., 1978).

IV. HEALTH EFFECTS

Humans

- In humans, the symptoms of cadmium toxicity following acute exposure include nausea, vomiting, diarrhea, muscular cramps and salivation (Arena, 1963). In the case of severe intoxication, sensory disturbances, liver injury and convulsions may result, which, in fatal intoxications, are followed by shock and/or renal failure and cardiopulmonary depression (CEC, 1978).

- The estimated acute lethal dose of cadmium is 350 to 35,000 mg for a 70-kg adult (CEC, 1978).

- For emesis, the NOAEL for cadmium in adults is 0.043 mg/kg/day following an acute oral exposure to cadmium salts (Lauwerys, 1979).

- Chronic non-occupational oral exposure to very high levels of cadmium has resulted in such adverse health effects as the Itai-Itai disease observed in Japan (principally in multiparous women), which is characterized by pain, osteomalacia, osteoporosis, proteinuria, glucosuria, and anemia (U.S. EPA, 1985).

- While it has been suggested that cadmium may play a role in hypertension, there is considerable uncertainty concerning what, if any, role cadmium may play in this disease. (Perry et al., 1977a and b; Kopp et al., 1982, 1983).

- Renal toxicity (e.g. proteinuria) following low level chronic oral exposure to cadmium is believed to be the most sensitive manifestation of cadmium toxicity (CEC, 1978; U.S. EPA, 1985). It has been estimated that the concentration at which 10% of the population is likely to display signs of renal dysfunction is 180 to 220 ug Cd/g renal cortex. Individuals with values over 285 ug/g usually display signs of renal dysfunction (U.S. EPA, 1985).

- Friberg et al. (1974) hypothesized that renal damage may occur when, over a 50 year period, a person's daily cadmium intake equals or exceeds 0.352 mg/day.

Animals

Short-term Exposure

- The acute oral LD_{50} of cadmium compounds in the rat varies with the compound and ranges from 16 mg/kg for cadmium cyanide to > 5,000 mg/kg for cadmium sulfide (CEC, 1978).

- Toxic effects, resulting from oral exposure to various cadmium compounds, have been observed in a variety of animal tissues (U.S. EPA, 1985) including the nervous system (Gabbiani et al., 1967), kidney (CEC, 1978), liver (Stowe et al., 1972), bone (Larsson and Piscator, 1971), hematopoietic system (Stowe et al., 1972), cardiovascular system (Kopp et al., 1978) and immune system (Koller, 1973).

Long-term Exposure

- Cadmium-induced renal toxicity (e.g. proteinuria) has been observed in animals in the absence of renal histopathology (CEC, 1978).

- In a 24-week male rat drinking water study, animals exposed to 2.15 and 6.44 mg cadmium/kg/day developed a significant level of proteinuria ($P < 0.05$), while animals exposed to the lowest level tested, 0.84 mg cadmium/kg/day (NOAEL), did not develop proteinuria (Kotsonis and).

  12 month rat drinking water study, no adverse effects were observed in animals exposed to 0.008, 0.035, 0.181, 0.361 or 0.375 (NOEL) mg cadmium/kg/day. However, at three months, the animals exposed to the highest level tested, 3.04 mg cadmium/kg/day, developed anemia and did not gain weight normally (Decker et al., 1958).

Reproductive Effects

- In a rat oral study, cadmium was administerted at 0, 0.1, 1.0 and 10.0 mg cadmium/kg/day (as $CdCl_2$) respectively, to groups of male and female adult rats for six weeks; males and females were mated for three weeks, and cadmium was administered during the mating period; pregnant females were given cadmium during the gestation period. In the 10 mg/kg group, the number of total implants and live fetuses decreased significantly ($p < 0.05$) while resorptions increased significantly ($p < 0.01$); fetuses showed decreased body weight ($p < 0.05$) and delayed ossification of the sternebrae and caudal vertebrae. No effects were observed at 0.1 or 1.0 mg cadmium/kg/day (Sutou et al., 198).

Developmental Effects

- In a rat drinking water study, fetal growth retardation was observed in animals whose dams were exposed to 100 mg cadmium/L but not in those exposed to 0.1 or 10 mg cadmium/L during gestation (Ahokas et al., 1980).

Mutagenicity

- While cadmium has been observed to cause chromosomal aberrations in several in vitro studies (e.g., Watanabe et al., 1979, and Di Paolo and Casto, 1979), strong evidence of mutagenic effects following oral ingestion is not available (U.S. EPA, 1985).

Carcinogenicity

- Cadmium and cadmium compounds have been shown to induce sarcomas at local injection sites (Haddow et al., 1964; Gunn et al., 1967). In addition, cadmium chloride administered to rats by aerosol for 18 months has produced lung tumors (Takenaka et al., 1983). These data are not believed relevant to the consumption of cadmium in drinking water (U.S. EPA, 1985).

- Although cancers of the prostate and lung have been noted in cadmium smelter workers in an epidemiological study (Lemen et al., 1976), evidence regarding the carcinogenicity of cadmium in humans following oral exposure is largely conjectural (U.S. EPA, 1985).

- No evidence of cadmium oncogenicity has been found in chronic oral animal studies (Schroeder et al., 1965; Kanisawa and Schroeder, 1969; Loser, 1980).

V. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

Health Advisories (HAs) are generally determined for One-day, Ten-day, Longer-term (approximately 7 years) and Lifetime exposures if adequate data are available that identify a sensitive noncarcinogenic end point of toxicity. The HAs for noncarcinogenic toxicants are derived using the following formula:

$$HA = \frac{(NOAEL \text{ or } LOAEL) \times (BW)}{(UF) \times (\_\_\_ \text{ L/day})} = \_\_\_ \text{ mg/L } (\_\_\_ \text{ ug/L})$$

where:

NOAEL or LOAEL = No- or Lowest-Observed-Adverse-Effect-Level in mg/kg bw/day.

BW = assumed body weight of a child (10 kg) or an adult (70 kg).

UF = uncertainty factor (10, 100 or 1,000), in accordance with NAS/ODW guidelines.

___ L/day = assumed daily water consumption of a child (1 L/day) or an adult (2 L/day).

One-day Health Advisory

The study by Lauwerys (1979) was selected to serve as the basis for the One-day HA for cadmium. In this study, the NOAEL for cadmium-induced emesis in adult humans following a single dose of cadmium was 0.043 mg cadmium/kg/day. This study was selected because it is of appropriate duration and was conducted in the most appropriate species, humans; more suitable data are not available.

The HA for a 10-kg child is calculated as follows:

$$\text{One-day HA} = \frac{(0.043 \text{ mg/kg/day})\ (10 \text{ kg})}{(10)\ (1 \text{ L/day})} = 0.043 \text{ mg/L } (43 \text{ ug/L})$$

where:

0.043 mg cadmium/kg/day = NOAEL for emesis following acute exposure to adults (Lauwerys, 1979).

10 kg = assumed body weight of a child.

10 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a NOAEL from a human study.

1 L/day = assumed daily water consumption of a child.

Ten-day Health Advisory

A 24-week oral exposure study in rats (Kotsonis and Klaassen, 1978) was considered for use as the basis of the Ten-day HA. In this study a NOAEL of 0.84 mg/kg/day was identified for proteinuria. If this NOAEL and an uncertainty factor of 100 were used, the Ten-day HA value would be 0.08 mg/L. This value is not markedly different from the One-day HA of 0.043 mg/L (based on a study which demonstrated cadmium-induced emesis in adult humans). However, since the Ten-day HA value of 0.08 mg/L would be greater than the One-day HA value, it is recommended that the more conservative One-day HA of 0.043 mg/L (43 ug/L) be used as the Ten-day HA.

Longer-term Health Advisory

The available data are insufficient to develop Longer-term HAs for cadmium. It is recommended that the DWEL of 18 ug/L be used as the Longer-term HA for the 70-kg adult and the modified DWEL of 5 ug/L (adjusted for a 10-kg child) be used as the Longer-term HA for the 10-kg child.

Lifetime Health Advisory

The Lifetime HA represents that portion of an individual's total exposure that is attributed to drinking water and is considered protective of noncarcinogenic adverse health effects over a lifetime exposure. The Lifetime HA is derived in a three step process. Step 1 determines the Reference Dose (RfD), formerly called the Acceptable Daily Intake (ADI). The RfD is an estimate of a daily exposure to the human population that is likely to be without

appreciable risk of deleterious effects over a lifetime, and is derived from the NOAEL (or LOAEL), identified from a chronic (or subchronic) study, divided by an uncertainty factor(s). From the RfD, a Drinking Water Equivalent Level (DWEL) can be determined (Step 2). A DWEL is a medium-specific (i.e., drinking water) lifetime exposure level, assuming 100% exposure from that medium, at which adverse, noncarcinogenic health effects would not be expected to occur. The DWEL is derived from the multiplication of the RfD by the assumed body weight of an adult and divided by the assumed daily water consumption of an adult. The Lifetime HA is determined in Step 3 by factoring in other sources of exposure, the relative source contribution (RSC). The RSC from drinking water is based on actual exposure data or, if data are not available, a value of 20% is assumed for synthetic organic chemicals and a value of 10% is assumed for inorganic chemicals. If the contaminant is classified as a Group A or B carcinogen, according to the Agency's classification scheme of carcinogenic potential (U.S. EPA, 1986), then caution should be exercised in assessing the risks associated with lifetime exposure to this chemical.

There are no adequate oral exposure studies in humans which provide a NOAEL for the chronic effects of cadmium. Friberg et al. (1974) concluded that the critical concentration of cadmium in the renal cortex of humans associated with renal dysfunction is 200 ug/g wet weight; this is supported by the recent reassessment by Kjellstrom et al. (1984). The 200 ug/g critical concentration was based on a comprehensive review of evidence from animal experiments and from analyses of kidneys from workers occupationally exposed to cadmium. The 200 ug/g value is probably the most widely accepted estimate of the critical concentration for renal dysfunction (NAS, 1977; CEC, 1978). However, Roels et al. (1983) reported that the critical concentration in the human renal cortex is 216 ug/g tissue wet weight and that less than 10% of occupationally exposed males may develop renal dysfunction at this concentration.

Several models have been proposed to estimate the daily intake (exposure) of cadmium required to produce the critical concentration in the renal cortex. Each model has inherent limitations. Friberg et al. (1974) estimated that a daily cadmium intake of 0.352 mg/day for 50 years would result in a renal cortex concentration of 200 ug/g. This model assumes 4.5% absorption of the daily oral dose and 0.01% excretion per day of the total body burden, both reasonable estimates. Thus, 0.352 mg of cadmium per day in a 70-kg adult (0.005 mg/kg/day) is a reasonable estimate of the daily cadmium intake that would result in renal dysfunction. In that the Friberg et al., (1974) value of 0.005 mg/kg/day is associated with renal dysfunction, 0.005 mg/kg/day is a LOAEL value which normally would require that an uncertainty factor of 100 be used. However, considering the relatively low level of uncertainty concerning cadmium toxicity in this case, it is judged that an uncertainty factor of 100 is unreasonably high and that an uncertainty factor of 10 is more appropriate.

As previously discussed, the study by Friberg et al., (1974) is the most appropriate from which to derive the Lifetime Health Advisory. From these results, a LOAEL of 0.005 mg/kg was identified. Using this LOAEL, the Lifetime Health Advisory is derived as follows:

Step 1: Determination of the Reference Dose (RfD)

$$RfD = \frac{(0.005 \text{ mg/kg/day})}{(10)} = 0.0005 \text{ mg/kg/day}$$

where:

0.005 mg/kg/day = LOAEL based on renal dysfunction in humans.

10 = uncertainty factor; this uncertainty factor, while smaller than would normally be required by NAS/ODW guidelines, was judged to best reflect the uncertainty concerning cadmium toxicity in humans.

Step 2: Determination of the Drinking Water Equivalent Level (DWEL)

$$DWEL = \frac{(0.0005 \text{ mg/kg/day})(70 \text{ kg})}{(2 \text{ L/day})} = 0.018 \text{ mg/L (18 ug/L)}$$

where:

0.0005 mg/kg/day = RfD.

70 kg = assumed body weight of an adult.

2 L/day = assumed daily water consumption of an adult.

Step 3: Determination of the Lifetime Health Advisory

Lifetime HA = (0.018 mg/L) (25%) = 0.005 mg/L (5 ug/L)

where:

0.018 mg/L = DWEL.

25% = assumed relative source contribution from water.

Evaluation of Carcinogenic Potential

- A quantitative evaluation of the carcinogenicity of cadmium has not been conducted since there is no conclusive evidence that cadmium is carcinogenic following oral exposure.
- U.S. EPA has recommended that cadmium not be considered a suspect human carcinogen for the purpose of calculating an ambient water quality criterion (U.S. EPA, 1980).
- Based on exposure to cadmium via inhalation, IARC (1982) has classified cadmium and certain cadmium compounds in Group 2B: Limited evidence for carcinogenicity in humans, sufficient evidence for carcinogenicity in animals.

° Applying the criteria described in EPA's guidelines for assessment of carcinogenic risk (U.S. EPA, 1986), cadmium, on the basis of inhalation data, may be classified in Group B1: Probable human carcinogen. This category is for agents for which there is inadequate evidence from human studies and sufficient evidence from animal studies. However, as there are inadequate data to conclude that cadmium is carcinogenic via ingestion, cadmium is dealt with here as Group D: Not classified. This category is for agents with inadequate animal evidence of carcinogenicity.

VI. OTHER CRITERIA, GUIDANCE, AND STANDARDS

° The National Academy of Sciences (NAS, 1982) has calculated a one-day Suggested No-Adverse Response Level (SNARL) of 0.150 mg/L for cadmium in drinking water for 70-kg adults.

° The National Academy of Sciences (NAS, 1982) has calculated a seven-day SNARL of 0.021 mg/L of drinking water for 70-kg adults.

° The National Academy of Sciences (NAS, 1982) has calculated a chronic exposure SNARL of 0.005 mg/L for cadmium in drinking water for 70-kg adults; this value is based on the assumption that water contributes 20% of the daily cadmium intake.

° A FAO/WHO expert committee has proposed a provisional tolerable weekly standard of no more than 57.1 to 71.4 ug Cd/week (WHO, 1972).

° The World Health Organization (WHO, 1984) has recommended that the concentration of cadmium in drinking water not exceed 0.005 mg/L.

° The Commission of the European Communities (CEC, 1975) has recommended that the concentration of cadmium in drinking water not exceed 0.005 mg/L.

° The current U.S. EPA primary drinking water standard for cadmium is 0.010 mg/L of drinking water (U.S. EPA, 1976).

° The recommended threshold limit values (TLVs) for cadmium dusts, salts and oxide fumes for occupational eight hour time-weighted average exposure is 0.05 mg/m^3 (ACGIH, 1980).

° The OSHA 8-hour time-weighted average exposure limit for cadmium fume is 0.1 mg/m^3 in workplace air; the acceptable ceiling concentration for cadmium fume is 0.3 mg/m^3 (OSHA, 1985).

° The OSHA 8-hour time-weighted average exposure limit for cadmium dust is 0.2 mg/m^3 in workplace air; the acceptable ceiling concentration for cadmium dust is 0.6 mg/m^3 (OSHA, 1985).

VII. ANALYTICAL METHODS

- Determination of cadmium is by atomic absorption (AA) using either direct aspiration into a flame (U.S. EPA, 1979a) or a furnace technique (U.S. EPA, 1979b).

- The direct aspiration AA procedure is a physical method based on the absorption of radiation at 228.8 nm by cadmium. The sample is aspirated into an air-acetylene flame and atomized. A light beam is directed through the flame into a monochromator and onto a detector that measures the amount of light absorbed. Absorbance is proportional to the concentration of cadmium in the sample. The detection limit is 5 ug/L using this procedure.

- The furnace AA procedure is similar to direct aspiration AA except a furnace, rather than a flame, is used to atomize the sample. The detection limit is 0.1 ug/L using this procedure.

VIII. TREATMENT TECHNOLOGIES

- Effective removal of cadmium from source waters may be achieved with treatment methods such as coagulation with alum or iron salts, lime softening, ion exchange and reverse osmosis. Laboratory experiments and pilot plant studies indicate that the effectiveness of cadmium removal by coagulation is pH dependent. Ferric sulfate coagulation studies on river water containing 0.3 mg/L of cadmium showed removals to increase from 20 % at pH 7.2 to above 90 % at pH 8 and above. Alum coagulation results on river water also increased with pH, but the data indicated that, above pH 8, removals may depend on the turbidity of the raw water. In some tests with low turbidity water (1-10 jtu), removals decreased as the pH increased (U.S. EPA, 1978).

- Experience indicates that lime softening is capable of achieving cadmium removal from water greater than 98 % in the pH range in well water containing 0.3 mg/L of cadmium. Removals equally as good were obtained at pH 11.2-11.3 when the initial cadmium concentration was increased up to 10 mg/L (U.S. EPA, 1978).

- There are limited performance data on the use of ion exchange as a treatment method for removal of cadmium from drinking water. The plating industry uses ion exchange for reducing cadmium in wastewaters and other wastewater streams studied have successfully used ion exchange for removing cadmium (Lindstedt et al., 1976; Nippon, 1976; Amax, 1977; Laszlo, 1977; Ameron, 1978). However, there is one report of 99 % removal efficiency for cadmium from drinking water using a home ion exchange softener (Personal communications, Ciccone Engineering, V.J. from Culligan Co., 1982). Tap water spiked with 0.10 mg/L of cadmium chloride and used as feed water to a cation exchanger on the sodium cycle produced product water with a cadmium level less than 0.01 mg/L.

- Experience indicates that reverse osmosis can effectively remove cadmium from drinking waters. A study by Mixon (1973) showed a 90 and 9.8% cadmium removal, respectively, from 0.10 mg/L and 0.98 mg/L spiked water samples, using three laboratory-scale cellulose acetate membranes operated at 400 psi. No difference in cadmium rejection was noted when barium, chromium, copper, lead and zinc were introduced. Another study by Hindin et al. (data) indicated a 70 percent removal for cadmium concentrations of 0.097, 0.959 and 9.25 mg/L using a laboratory size reverse osmosis cellulose acetate cell. A study performed by Huxstep (1982) in Florida related to inorganic contaminant removal from potable water by reverse osmosis resulted in a 96-98 % removal of cadmium.

- Protection against cadmium from corrosion of water distribution systems, in general, may be achieved by a number of methods including pH adjustment, addition of lime, increasing alkalinity, or addition of phosphates or silicates. The extent and type of treatment selection is dependent on the characteristics of the water and the compatibility of existing treatment with regard to various materials used to convey the water through the distribution system.

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March 31, 1987

CHROMIUM

Health Advisory
Office of Drinking Water
U.S. Environmental Protection Agency

I. INTRODUCTION

The Health Advisory (HA) Program, sponsored by the Office of Drinking Water (ODW), provides information on the health effects, analytical methodology and treatment technology that would be useful in dealing with the contamination of drinking water. Health Advisories describe nonregulatory concentrations of drinking water contaminants at which adverse health effects would not be anticipated to occur over specific exposure durations. Health Advisories contain a margin of safety to protect sensitive members of the population.

Health Advisories serve as informal technical guidance to assist Federal, State and local officials responsible for protecting public health when emergency spills or contamination situations occur. They are not to be construed as legally enforceable Federal standards. The HAs are subject to change as new information becomes available.

Health Advisories are developed for One-day, Ten-day, Longer-term (approximately 7 years, or 10% of an individual's lifetime) and Lifetime exposures based on data describing noncarcinogenic end points of toxicity. Health Advisories do not quantitatively incorporate any potential carcinogenic risk from such exposure. For those substances that are known or probable human carcinogens, according to the Agency classification scheme (Group A or B), Lifetime HAs are not recommended. The chemical concentration values for Group A or B carcinogens are correlated with carcinogenic risk estimates by employing a cancer potency (unit risk) value together with assumptions for lifetime exposure and the consumption of drinking water. The cancer unit risk is usually derived from the linear multistage model with 95% upper confidence limits. This provides a low-dose estimate of cancer risk to humans that is considered unlikely to pose a carcinogenic risk in excess of the stated values. Excess cancer risk estimates may also be calculated using the One-hit, Weibull, Logit or Probit models. There is no current understanding of the biological mechanisms involved in cancer to suggest that any one of these models is able to predict risk more accurately than another. Because each model is based on differing assumptions, the estimates that are derived can differ by several orders of magnitude.

This Health Advisory is based on information presented in the Office of Drinking Water's Health Effects Criteria Document (CD) for chromium (U.S. EPA, 1985). The HA and CD formats are similar for easy reference. Individuals desiring further information on the toxicological data base or rationale for risk characterization should consult the CD. The CD is available for review at each EPA Regional Office of Drinking Water counterpart (e.g., Water Supply Branch or Drinking Water Branch), or for a fee from the National Technical Information Service, U.S. Department of Commerce, 5285 Port Royal Rd., Springfield, VA 22161, PB #86-118072/AS. The toll-free number is (800) 336-4700; in the Washington, D.C. area: (703) 487-4650.

II. GENERAL INFORMATION AND PROPERTIES

CAS No.

- Chromium -- 7440-47-3
  Chromium (III) Chloride -- 10025-73-7
  Chromic Acid, Dipotassium Salt -- 7789-00-6

Synonyms

- None

Uses

Chromium and its salts have a variety of uses including the following (for additional information see Hartford, 1979):

- Hexavalent chromium compounds are used widely in industry for chrome alloy and chromium metal production, for metal finishing and corrosion control (Love, 1947) and as mordants in the textile industry (Iler, 1954).

- Chromium salts are used as anticorrosive agents in cooling waters, in the leather tanning industry, in the manufacture of catalysts, in pigments and paints, and in fungicides and wood preservatives (Hartford, 1979).

Properties (Hem, 1970; Weast, 1971; Windholz, 1976)

° The properties of chromium compounds vary with the specific compound; some examples are as follows:

	Chromium	Chromium (III) Chloride	Chromic Acid, Dipotassium Salt
Chemical Formula	Cr	$CrCl_3$	K_2CrO_4
Atomic/Molecular Weight	51.996	122.90	194.20
Physical State	blue-white solid	solid	solid
Boiling Point	2,642°C	--	--
Melting Point	1,900°C	83°C	968.3°C
Density	7.14 gm/cm^3	2.76 g/cm^3 (15°C)	2.732 g/cm^3 (18°C)
Vapor Pressure	--	--	--
Water Solubility	0.5 ug/L	inslouble	62.9 g/100 mL (20°C)
Log Octanol/Water Partition Coefficient	--	--	--
Taste Threshold	--	--	--
Odor Threshold	--	--	--

Occurrence

° Chromium is a relatively rare, naturally occurring element in the earth's crust. Chromium occurs in most rocks and minerals at levels of 200 ppm. A few minerals contain chromium at levels of 2-3,000 ppm. Chromium is not mined in the U.S. commercially; it is imported. Chromium is released to the environment during industrial activities. However, current data suggest that surface and ground water levels of chromium are the result of naturally-occurring chromium leaching from mineral deposits. Soluble chromium has been reported to occur in surface waters at levels up to 84 ug/L and in ground water at levels of 50 ug/L (U.S. EPA, 1987).

° Federal surveys of surface and ground water drinking water supplies have reported that most supplies contain less than 5 ug/L. Currently, 17 ground water supplies and one surface water supply exceed the interim standard of 50 ug/L (U.S. EPA, 1987).

III. PHARMACOKINETICS

Absorption

In general, with the exception of the Cr III glucose tolerance factor (GTF), Cr VI is more readily absorbed than Cr III:

° In humans and experimental animals, gastrointestinal absorption of inorganic salts of Cr III is low (from 0.5% to 3%). However, Cr VI and organic complexes of Cr III are more readily absorbed (approximately 2% to 10% for Cr VI and 10% to 25% for organic complexes of Cr III) (U.S. EPA, 1985).

- In humans administered 20 ng of Cr III as $^{51}CrCl_3$ in water, 0.5% of the dose was recovered in the urine, indicating little absorption (Donaldson and Berreras, 1966). In rats, Mertz et al. (1965) reported 2% to 3% absorption of Cr(III) based on total body counting of animals administered $^{51}CrCl_3$ by intubation at doses ranging from 1.5 to 100 ug/kg.

- GTF, an organic complex of Cr III with nicotinic acid and an amino acid that is found in brewer's yeast, was absorbed in rats at 10% to 25% of the administered dose (Mertz, 1976; Mertz et al., 1978).

- An estimate of 2.1% absorption of Cr VI based on recovery in urine was reported for humans administered 20 ng of $Na_2{}^{51}CrO_4$ in water (Donaldson and Barreras, 1966).

- Rats administered drinking water containing 25 mg/L Cr III as chromic chloride had 12.5 times greater tissue levels of chromium than rats whose drinking water contained 25 mg/L Cr VI as potassium chromate (Mackenzie et al., 1958).

Distribution

Depending on the particular compound (e.g., GTF) Cr III and Cr VI differ in their distribution within an organism; in general Cr III crosses membranes much more slowly than Cr VI (U.S. EPA, 1985):

- Chromium circulates in the plasma primarily in a nondiffusible form. A small fraction (9% to 12%) is in a more diffusible form which is filtered and partially reabsorbed in the kidney (Collins et al., 1961). An approximate plasma half-life of 6 hours for ^{51}Cr III in rats was reported by Hopkins (1965) after intravenous administration of either 0.1 or 1.0 ug/kg.

- Cr III has an affinity for iron-binding proteins (Gray and Sterling, 1950; Hopkins and Schwarz, 1964).

- The spleen and kidneys were shown to have the highest concentrations of chromium when rats were administered Cr III as chromium chloride in intravenous doses of 0.1 or 1.0 ug/kg (Hopkins, 1965). Similar results were reported by Mackenzie et al. (1958) when rats received drinking water containing 25 mg/L of either Cr III as chromic chloride or Cr VI as potassium chromate. The calculated doses were 1.87 mg/kg/day for males and 2.41 mg/kg/day for females.

- The placenta appears to be highly selective in its permeability to the various forms of chromium. Inorganic Cr III administered as $^{51}CrCl_3$ (chromium chloride) intravenously or by stomach intubation does not cross the placental barrier to an appreciable extent in rats (Mertz et al., 1969). However, Cr III administered by stomach intubation to pregnant rats in the form of GTF (obtained from yeast) is recovered readily from the fetus (Mertz and Roginski, 1971). The dosages in these two studies were unspecified.

- Cr VI traverses biological membranes by diffusion or facilitated transport, possibly via an anion transport system (Alexander et al., 1982). It is reduced to Cr III intracellularly by the cytochrome P-450 system in the presence of NADPH. Cr III reacts with nucleophilic ligands and cellular macromolecules (Gruber and Jennette, 1978).

Metabolism

- The metabolism of chromium in mammalian species is not well understood and is complicated by the presence of the two oxidation states, Cr III and Cr VI (U.S. EPA, 1985).

Excretion

The kidney appears to be the principal route of excretion of chromium compounds:

- The urinary system is the major excretory route for absorbed chromium, accounting for 80% or more of chromium excretion (Kraintz and Talmage, 1952). Very little is known about the form in which chromium is excreted.

- After intravenous administration, chromium is also excreted in the feces, although reports in the literature vary considerably on the percentage. Hopkins (1965) reported that 0.5% to 1.7% of the initial dose of Cr III was excreted in the feces of rats eight hours after intravenous administration of $^{51}CrCl_3$ at 0.1 ug/100 g.

IV. HEALTH EFFECTS

Humans

In general, Cr VI compounds are more toxic than Cr III compounds:

- The toxicity of chromium has been attributed primarily to Cr VI, which has been shown to produce liver and kidney damage, internal hemorrhage, dermatitis and respiratory problems. The immediate symptoms are generally nausea, repeated vomiting and diarrhea (U.S. EPA, 1985).

- Doses of 0.5 to 1.5 g of $K_2Cr_2O_7$ have been fatal in humans. The estimated LD_{LO} for $K_2Cr_2O_7$ in children is 26 mg/kg (Cr VI at 9.2 mg/kg) (NIOSH, 1983).

- Subchronic and chronic dermal exposure to Cr VI in the form of chromic acid may cause contact dermatitis and ulceration of the skin (Burrows, 1978). For example, Denton et al. (1954) reported information on an individual who was patch-tested on three occasions with 0.005% potassium dichromate solution and the filtrate of two cement samples which contained 0.0001% and 0.0004% Cr VI. The individual repeatedly showed a positive erythematous, edematous, papulovesicular patch-test reaction to each test solution.

- Chronic inhalation of dust or air containing Cr VI may cause respiratory problems including perforated or ulcerated nasal septa and decreased spirometric values (U.S. EPA, 1985). For example, Bloomfield and Blum (1928) reported perforated/ulcerated nasal septa and inflamed nasal mucosa in workers exposed to chromic acid (Cr VI) (0.1 to 5.6 mg/m^3 air) for one week to three years.

Animals

Short-term Exposure

In general, Cr VI compounds are more toxic than Cr III compounds:

- The oral LD_{50} for various salts of Cr III range from 600 to 2,600 mg/kg (Smyth et al., 1969).
- The oral LD_{50} of Cr VI (as $Na_2Cr_2O_7$) in rats is 19.8 mg/kg (NIOSH, 1983).
- Rats were exposed to drinking water containing Cr VI (K_2CrO_4) at levels of both 80 and 134 mg Cr VI/L for 60 days (8.3 and 14.4 mg Cr VI/kg/day respectively) without adverse effect (Gross and Heller, 1946).

Long-term Exposure

- In a one year rat drinking water study, consumption of water containing 0 to 25 mg/L of either Cr III ($CrCl_3$) or Cr VI (K_2CrO_4) (0 to 1.87 mg/kg/day for male rats and 0 to 2.41 mg/kg/day for female rats) produced no significant differences in weight gain, appearance or pathological changes in the blood or other tissues (Mackenzie et al., 1958). NOAELs of 1.87 mg/kg/day (males) and 2.41 mg/kg/day (females) can be identified from the results of this study.
- In a rat drinking water study in which 5 mg/L Cr III (about 0.42 mg/kg/day) was administered from the time of weaning until death, no adverse effects were observed (Schroeder et al., 1965). A NOAEL of 0.42 mg/kg/day can be identified from the results of this study.
- In a four year female dog drinking water study (five dose groups with two animals per group), Cr VI (K_2CrO_6) at 0.45 to 11.2 mg/L (0.012 to 0.30 mg/kg Cr VI) was without effect in terms of changes in physical condition, food consumption, growth rate, organ weights, urinalysis results and hematological analyses. Therefore, a NOAEL of 0.30 mg/kg/day can be identified from the results of this study (Anwar et al., 1961).

Reproductive Effects

- No information was found in the available literature on the reproductive effects of chromium.

Developmental Effects

- No information was found in the available literature on the developmental effects of chromium.

Mutagenicity

- The genotoxic effects of chromium are well documented both in in vivo and in vitro studies. The pathway by which chromium exerts these effects is believed to involve penetration of the cell membrane by Cr VI, followed by intracellular reduction to Cr III. Extracellular Cr III crosses the cell membrane, but less efficiently. Once inside the cell, Cr III can form tight complexes with DNA, accounting for its mutagenic potential (U.S. EPA, 1985).

- Compounds of both Cr III and Cr VI increase non-complementary nucleotide incorporation into DNA (Raffetto et al., 1977; Majone and Rensi, 1979), with Cr VI producing effects at lower doses. Exposure of cells from rat liver and kidney to Cr VI leads to increased cross-linking in DNA. Petrilli and De Flora (1978) reported positive Ames tests for Cr VI. However, Cr III exerted no effect at relatively high concentrations (presumably because of its inability to penetrate cells). Similar results were reported by Gentile et al. (1981).

- The difficulty of observing mutagenic effects of Cr III may be related to its slight uptake by cells under most conditions. Warren et al. (1981), studied the mutagenicity of a series of hexacoordinate Cr III compounds and concluded that, in the proper ligand environment, the metal possesses considerable genetic toxicity.

Carcinogenicity

There is inadequate evidence to determine whether or not oral exposure to chromium can lead to cancer:

- No increase in tumor rates over that of the control animals was observed in rats exposed rats to Cr III (chromium oxide pigments) at 293, 586 or 1,466 mg/kg/day in the diet for two years (Ivankovic and Preussmann, 1975).

- While the carcinogenicity of inhaled Cr VI is well established for occupational exposure of humans (Hayes et al., 1979), the effects are observed only in the respiratory passages and in the lungs, and are believed to have no bearing on carcinogenic risk following oral exposure to the metal (U.S. EPA, 1985).

V. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

Health Advisories (HAs) are generally determined for One-day, Ten-day, Longer-term (approximately 7 years) and Lifetime exposures if adequate data are available that identify a sensitive noncarcinogenic end point of toxicity. The HAs for noncarcinogenic toxicants are derived using the following formula:

$$HA = \frac{(NOAEL \text{ or } LOAEL) \times (BW)}{(UF) \times (\_\_\_ \text{ L/day})} = \_\_\_ \text{ mg/L } (\_\_\_ \text{ ug/L})$$

where:

NOAEL or LOAEL = No- or Lowest-Observed-Adverse-Effect-Level in mg/kg bw/day.

BW = assumed body weight of a child (10 kg) or an adult (70 kg).

UF = uncertainty factor (10, 100 or 1,000), in accordance with NAS/ODW guidelines.

___ L/day = assumed daily water consumption of a child (1 L/day) or an adult (2 L/day).

In considering the toxicity of chromium compounds, it is important to realize that chromium III is an essential nutrient required in trace quantities for normal glucose metabolism - i.e. GTF. Some forms of chromium may also be important in the metabolism of lipids and other carbohydrates (U.S. EPA, 1985).

The Health Advisories will be determined on the basis of the effects of Cr VI measured as total chromium. Separate Health Advisories will not be established for Cr III for the following reasons:

1. Based on the work of Schroeder and Lee (1975), there is reason to believe that oxidizing agents (e.g. due to chlorination of water) may accelerate the normal conversion of Cr III to Cr VI at the point of consumption (i.e., the tap).

2. Health Advisories based on total chromium will allow for the possible conversion of Cr III to Cr VI.

3. As discussed in this document, there is reason to believe that Cr VI is more toxic than Cr III. Thus Health Advisories based on the effects of Cr VI will conservatively protect against the toxic effects of any Cr III not converted to Cr VI.

One-day Health Advisory

The available data are insufficient to develop a One-day HA for chromium. It is recommended that the Ten-day HA of 1.4 mg/L be used as the One-day HA for the 10 kg child.

Ten-day Health Advisory

Gross and Heller (1946) exposed both male and female rats for 60 days to drinking water containing K_2CrO_4 at either 300 or 500 mg/L (Cr VI at 80 mg/L and 134 mg/L, respectively). Using reported average body weights of 270 and 260 g, respectively, and assuming consumption of 28 mL water per day, the average ingested doses of Cr VI are calculated to be 8.3 and 14.4 mg/kg/day, respectively. After two months, the rats receiving Cr VI at 8.3 mg/kg/day were described as normal. A "slight roughness of coat" was noted in rats receiving 14.4 mg/kg/day, but this is not considered to be an adverse health effect; this observation is not associated with other adverse health effects. Therefore, 14.4 mg/kg/day represents the NOAEL for Cr VI in this study.

The Ten-day HA for a 10-kg child is calculated as follows:

$$\text{Ten-day HA} = \frac{(14.4 \text{ mg/kg/day})\ (10 \text{ kg})}{(100)\ (1 \text{ L/day})} = 1.4 \text{ mg/L } (1400 \text{ ug/L})$$

where:

14.4 mg/kg/day = NOAEL based on the absence of adverse effects in rats exposed to chromium in drinking water.

10 kg = assumed body weight of a child.

100 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a NOAEL from an animal study.

1 L/day = assumed daily water consumption of a child.

Longer-term Health Advisory

Mackenzie et al. (1958) studied the effects of chronic ingestion of Cr III and Cr VI in rats. Both male and female Sprague Dawley rats (34 days old) were supplied with drinking water containing Cr as $CrCl_3$ (Cr III) or as K_2CrO_4 (Cr VI) in a series of doses up to 25 mg/L for a period of one year. Assuming an average weight of 375 g for males and 290 g for females, and an average daily water intake of 28 mL (Arrington, 1972), the average dose for males and females receiving 25 mg/L is calculated to be 1.87 and 2.41 mg Cr VI/kg/day, respectively. No significant adverse effects on appearance, weight gain, food consumption or blood chemistry were noted at any of the dose levels. However, the animals receiving the highest dose (25 mg/L) of Cr VI showed an approximate 20% reduction in water consumption.

Cr VI at 2.41 mg/kg/day was identified as the NOAEL in this study. The Longer-term HAs are calculated as follows:

For a 10-kg child:

$$\text{Longer-term HA} = \frac{(2.41 \text{ mg/kg/day})\ (10 \text{ kg})}{(100)(1 \text{ L/day})} = 0.24 \text{ mg/L } (240 \text{ ug/L})$$

where:

2.41 mg/kg/day = NOAEL based on the absence of adverse effects in rats exposed to chromium in drinking water.

10 kg = assumed body weight of a child.

100 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a NOAEL from an animal study.

1 L/day = assumed daily water consumption of a child.

For a 70-kg adult:

$$\text{Longer-term HA} = \frac{(2.41 \text{ mg/kg/day})\ (70 \text{ kg})}{(100)\ (2 \text{ L/day})} = 0.84 \text{ mg/L } (840 \text{ ug/L})$$

where:

2.41 mg/kg/day = NOAEL based on the absence of adverse effects in rats exposed to chromium in drinking water.

70 kg = assumed body weight of an adult.

100 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a NOAEL from an animal study.

2 L/day = assumed daily water consumption of an adult.

Lifetime Health Advisory

The Lifetime HA represents that portion of an individual's total exposure that is attributed to drinking water and is considered protective of noncarcinogenic adverse health effects over a lifetime exposure. The Lifetime HA is derived in a three step process. Step 1 determines the Reference Dose (RfD), formerly called the Acceptable Daily Intake (ADI). The RfD is an estimate of a daily exposure to the human population that is likely to be without appreciable risk of deleterious effects over a lifetime, and is derived from the NOAEL (or LOAEL), identified from a chronic (or subchronic) study, divided by an uncertainty factor(s). From the RfD, a Drinking Water Equivalent Level (DWEL) can be determined (Step 2). A DWEL is a medium-specific (i.e., drinking water) lifetime exposure level, assuming 100% exposure from that medium, at which adverse, noncarcinogenic health effects would not be expected to occur. The DWEL is derived from the multiplication of the RfD by the assumed body weight of an adult and divided by the assumed daily water consumption of an adult. The Lifetime HA is determined in Step 3 by factoring in other sources of exposure, the relative source contribution (RSC). The RSC from drinking water is based on actual exposure data or, if data are not available, a value of 20% is assumed for synthetic organic chemicals and a value of 10% is assumed for inorganic chemicals. If the contaminant is classified as a Group A or B carcinogen, according to the Agency's classification scheme of carcinogenic potential (U.S. EPA, 1986), then caution should be exercised in assessing the risks associated with lifetime exposure to this chemical.

The study by MacKenzie et al. (1958) (described under the Longer-term HA) is considered appropriate to serve as the basis for the Lifetime HA. The Anwar et al. (1961) study was not selected because only two animals per dose group were used.

Using the NOAEL of 2.41 mg/kg/day, the Lifetime HA is derived as follows:

Step 1: Determination of the Reference Dose (RfD)

$$\text{RfD} = \frac{(2.41 \text{ mg/kg/day})}{(100)\ (5)} = 0.0048 \text{ mg/kg/day}$$

where:

2.41 mg/kg/day = NOAEL based upon the absence of adverse effects in rats exposed to chromium in drinking water.

100 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a NOAEL from an animal study.

5 = additional uncertainty factor to compensate for less-than-lifetime exposure.

Step 2: Determination of the Drinking Water Equivalent Level (DWEL)

$$DWEL = \frac{(0.0048 \text{ mg/kg}) (70 \text{ kg})}{(2 \text{ L/day})} = 170 \text{ ug/L}$$

where:

0.0048 mg/kg = RfD.

70 kg = assumed body weight of an adult.

2 L/day = assumed daily water consumption of an adult.

Step 3: Determination of Lifetime Health Advisory

Lifetime HA = (170 ug/L) (71%) = 120 ug/L

where:

170 ug/L = DWEL.

71% = assumed relative source contribution from water.

Evaluation of Carcinogenic Potential

- There is no evidence of carcinogenic effects following oral exposure to chromium. Thus, no assessments for carcinogenic risks from oral exposure to chromium have been conducted. Inhalation of chromium, however, is associated with an increased frequency of lung cancer in humans.

- EPA's CAG has estimated the lifetime cancer risk due to a constant exposure to air containing 1 ug/m^3 of elemental chromium to be 1.2×10^{-2} (U.S. EPA, 1983).

- Based on exposure to chromium via inhalation, IARC (1982) has classified chromium and certain chromium compounds in Group 1 (Chromium VI); sufficient evidence for carcinogenicity in humans and animals.

- Applying the criteria described in EPA's guidelines for assessment of carcinogenic risk (U.S. EPA, 1986), chromium may be classified in Group A: Human carcinogen. This category is for agents for which

there is sufficient evidence to support the causal association between exposure to the agents and cancer. However, as there are inadequate data to conclude that chromium is carcinogenic via ingestion, chromium is dealt with here as Group D: Not classified. This category is for agents with inadequate animal evidence of carcinogenicity.

VI. OTHER CRITERIA, GUIDANCE AND STANDARDS

Recommended or established standards for chromium in the United States include:

- 50 ug Cr VI per liter for drinking water (U.S. PHS, 1962).
- 50 ug total chromium per liter for drinking water (NAS, 1974; U.S. EPA, 1976).
- 1 ug/m^3 for carcinogenic forms of Cr VI in workplace air (NIOSH, 1975).
- 25 ug/m^3 TWA or 50 ug/m^3 ceiling for non-carcinogenic forms of Cr VI in workplace air (NIOSH, 1975).
- The recommended ambient water quality criterion for Cr VI is 50 ug/L (U.S. EPA, 1980).
- An estimated adequate and safe intake for chromium of 50 to 200 ug/day for adults has been established (NAS, 1980a,b). This range is based on the absence of signs of chromium deficiency in the major portion of the U.S. population which consumes an average of 60 ug of chromium per day.
- The OSHA 8-hour time-weighted average exposure limit for chromium, soluble chromic, and chromous salts as chromium is 0.5 mg/m^3 (OSHA, 1985).

VII. ANALYTICAL METHODS

- Determination of chromium is by atomic absorption (AA) using either direct aspiration into a flame (U.S. EPA, 1979a) or a furnace technique (U.S. EPA, 1979b).
- The direct aspiration AA procedure is a physical method based on the absorption of radiation at 357.9 nm by chromium. The sample is aspirated into an air-acetylene flame and atomized. A light beam is directed through the flame into a monochromator, and onto a detector that measures the amount of light absorbed. Absorbance is proportional to the concentration of chromium in the sample. The detection limit is 50 ug/L using this procedure.
- The furnace AA procedure is similar to direct aspiration AA except that a furnace, rather than a flame, is used to atomize the sample. The detection limit is 1 ug/L using this procedure.

VIII. TREATMENT TECHNOLOGIES

- The treatment technologies that are available to remove chromium from water include coagulation/filtration, lime softening, ion exchange and reverse osmosis. However, the type of treatment that may be applied is dependent on the species of chromium present.

- Laboratory and pilot plant studies indicated that using ferric sulfate, Cr III removals were near 100 percent in the range of pH 6.5 to 9.5. Alum was less effective between pH 7.5 and 8.5, with removals around 90 percent or better. Above and below this pH range, removals were slightly lower, 80 to 90 percent. In removing Cr VI, laboratory and pilot-plant tests confirmed that of the three coagulants used, only ferrous sulfate was effective. With alum and ferric sulfate, Cr VI removals did not exceed 30 percent. By comparison, ferrous sulfate coagulation achieved 90 percent removal or better (U.S. EPA, 1977).

- Results of jar and pilot-plant tests indicate that Cr III removal efficiencies with lime softening were approximately 72 percent at pH 8.5 to 9.5 and greater than 99 percent at pH 11 to 11.5. Results with Cr VI in the same tests in all cases were less than 10 percent (U.S. EPA, 1977; Sorg, 1979).

- Since Cr III occurs in cationic species and Cr VI in anionic species, a cation exchanger in series with an anion exchanger may be required for their removal. Removal of Cr VI from sewage (Sorg, 1979), industrial wastewater, rinse waters from chromium plating operations (Miller and Mindler, 1978), cooling tower blowdown (Richardson et al., 1968; Miller and Mindler, 1978), and metal recovery (Sussman et al., 1945) has been demonstrated. Laboratory tests on a simulated Arizona well water (TDS 174 mg/L, pH 7.85) having 0.019 mg/L of Cr VI showed a breakthrough of Cr VI at roughly 12,000 bed volumes (U.S. EPA, 1982). Reports concerning industrial wastewater treatment indicate that ion exchange can successfully remove Cr III to below 0.05 mg/L (Patterson, 1975). Strong acid cationic resins have been used for removing Cr III as a contaminant from metal plating rinse waters and from chromate treated cooling waters. Vendor information indicates that operating pH levels of between 6 and 8 are adequate for Cr III removal with pH above 7 being slightly better than pH below 7 (Rohm and Haas Co., 1980). Ion exchange softening using standard strong acid synthetic resins operating in the sodium cycle should effectively remove Cr III with 90 percent or greater efficiency (Amore, 1977). In tests of home softeners with tap water spiked with 1 mg/L of chromium nitrate, the chromium content continued to be reduced to 0.020 mg/L after 192 cycles, at which point the test was discontinued.

- Reverse osmosis (RO) membranes can efficiently remove from 82 to 99 percent of the chromium in a feed water source (Fox, no date; Mixon, 1973; Johnston et al., 1978). Pilot plant tests using both cellulose acetate and hollow fiber (polyamide) membranes demonstrated their effectiveness in removing both Cr III and Cr VI. Cr III removal ranged from 90 to 98 percent and Cr VI removal ranged from 82 to 97 percent. Slightly better removal was achieved with the hollow fiber than with the cellulose acetate membranes (Fox, no date).

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March 31, 1987

CYANIDE

Health Advisory
Office of Drinking Water
U.S. Environmental Protection Agency

I. INTRODUCTION

The Health Advisory (HA) Program, sponsored by the Office of Drinking Water (ODW), provides information on the health effects, analytical methodology and treatment technology that would be useful in dealing with the contamination of drinking water. Health Advisories describe nonregulatory concentrations of drinking water contaminants at which adverse health effects would not be anticipated to occur over specific exposure durations. Health Advisories contain a margin of safety to protect sensitive members of the population.

Health Advisories serve as informal technical guidance to assist Federal, State and local officials responsible for protecting public health when emergency spills or contamination situations occur. They are not to be construed as legally enforceable Federal standards. The HAs are subject to change as new information becomes available.

Health Advisories are developed for One-day, Ten-day, Longer-term (approximately 7 years, or 10% of an individual's lifetime) and Lifetime exposures based on data describing noncarcinogenic end points of toxicity. Health Advisories do not quantitatively incorporate any potential carcinogenic risk from such exposure. For those substances that are known or probable human carcinogens, according to the Agency classification scheme (Group A or B), Lifetime HAs are not recommended. The chemical concentration values for Group A or B carcinogens are correlated with carcinogenic risk estimates by employing a cancer potency (unit risk) value together with assumptions for lifetime exposure and the consumption of drinking water. The cancer unit risk is usually derived from the linear multistage model with 95% upper confidence limits. This provides a low-dose estimate of cancer risk to humans that is considered unlikely to pose a carcinogenic risk in excess of the stated values. Excess cancer risk estimates may also be calculated using the One-hit, Weibull, Logit or Probit models. There is no current understanding of the biological mechanisms involved in cancer to suggest that any one of these models is able to predict risk more accurately than another. Because each model is based on differing assumptions, the estimates that are derived can differ by several orders of magnitude.

This Health Advisory (HA) is based on information presented in the Office of Drinking Water's Health Effects Criteria Document (CD) for cyanide (U.S. EPA, 1985). The HA and CD formats are similar for easy reference. Individuals desiring further information on the toxicological data base or rationale for risk characterization should consult the CD. The CD is available for review at each EPA Regional Office of Drinking Water counterpart (e.g., Water Supply Branch or Drinking Water Branch), or for a fee from the National Technical Information Service, U.S. Department of Commerce, 5285 Port Royal Rd., Springfield, VA 22161, PB # 86-117793/AS. The toll free number is (800) 336-4700; in the Washington, D.C. area: (703) 437-4650.

II. GENERAL INFORMATION AND PROPERTIES

- Cyanides are a group of organic and inorganic compounds that contain the cyano (CN) group. Free cyanide is defined as the sum of cyanide present as HCN and as CN^-. The organic cyanides are called nitriles and few of them dissociate to yield CN^- or HCN. In this Health Advisory, only a few widely used industrial inorganic cyanides will be discussed.

CAS No.

- Hydrogen Cyanide -- 74-90-8
  Sodium Cyanide -- 143- 33-9
  Potassium Cyanide -- 151-50-8

Synonyms

- Hydrogen Cyanide: Prussic Acid

Uses (U.S. EPA, 1985)

- Cyanide is used in rat and pest poisons, silver and metal polishes, photographic solutions, fumigating products, in the production of various resins such as acrylates, methyl acrylate and nitriles and in electroplating.

- Although there are a number of organic and inorganic compounds that contain the CN group, in this document only a few widely used industrial inorganic cyanides will be considered.

Properties (Weast, 1980; Towill et al., 1978)

° The properties of cyanide compounds vary with the specific compound; some examples are as follows:

	Hydrogen Cyanide	Sodium Cyanide	Potassium Cyanide
Chemical Formula	HCN	NaCN	KCN
Molecular Weight	27.03	49.01	65.12
Physical State	colorless gas or liquid	colorless solid	colorless solid
Boiling Point	25.70°C	14.96°C	--
Melting Point	-13.24°C	563.7°C	634.5°C
Density (g/cm^3)	0.688 (20°C)	1.60-1.62	1.553 (20°C)
Vapor Pressure	--	--	--
Water Solubility (g/100 mL)	miscible	48 (10°C)	71.6 (20°C)
Octanol/Water Partition Coefficient	0.66	-0.44	--
Taste Threshold	--	--	--
Odor Threshold	--	--	--
Conversion Factor	1.123	2.037	2.707

Occurrence

° In 1978, cyanide production in the United States exceeded 700 million pounds. Cyanide wastes are released from the pyrolysis of natural and synthetic materials (Towill et al., 1978).

° Despite numerous potential sources of pollution, cyanide is relatively uncommon in U.S. drinking water. In 1970, a survey of 969 water supplies failed to reveal cyanide concentrations above 0.2 mg/L. Of 2,595 samples examined, the highest cyanide concentration found was 8 ug/L and the average concentration was 0.09 ug/L (McCabe et al., 1970).

III. PHARMACOKINETICS

Absorption

° Free cyanides are absorbed readily from the lungs, the gastrointestinal tract and the skin by animals and humans. Inhalation exposure to HCN provides the most rapid route of entry (U.S. EPA, 1985).

° Dogs treated with KCN at single gavage doses equivalent to 20, 50 and 100 mg HCN (1.57, 4.42 or 8.40 mg HCN/kg bw) absorbed 72%, 24% and 16.6%, respectively, through the GI tract (Gettler and Baine, 1938). The dogs died within 155, 21 and 8 minutes, respectively, after dosing.

Distribution

- Once cyanide is absorbed, it is distributed rapidly by the blood throughout the body. Distribution patterns vary with the route of exposure (U.S. EPA, 1985).

- High levels of cyanide were found in brains and livers of 3 human subjects who ingested fatal doses of cyanide (Gettler and Baine, 1938).

- In rabbits, intramuscular injection of HCN gave higher levels of CN in blood and tissues than did KCN administration (Ballantyne et al., 1972).

- When radiolabeled KCN (5 mg/kg) was administered orally to rats over 24 hours, a rapid decline of radioactivity from whole blood and plasma was observed with a small increase in the levels in erythrocytes (Farooqui and Ahmed, 1982). The majority of the radioactivity in the erythrocytes (94.3%) was found in the hemolysate rather than the membranes. The heme fraction contained 70% of the radioactivity while 14 to 25% and 5 to 10% were found in the globin and cell membrane, respectively.

- Cyanide does not accumulate in blood and tissues following chronic exposure. Virtually no cyanide was found in the plasma or kidneys of rats treated with dietary concentrations of 100 and 300 ppm (mg/kg diet) for two years (Howard and Hanzal, 1955). Low levels were found in erythrocytes (mean of 1.97 ug). Increased levels of thiocyanate were found in plasma (1123 ug), erythrocytes (246 ug), liver (665 ug) and kidney (1188 ug).

- Yamamoto et al. (1982) found that rats on oral (gavage) exposure to cyanide (NaCN) (7 and 21 mg CN/kg/bw) showed higher levels of cyanide in lungs and liver compared to blood. On inhalation exposure to HCN at concentrations of 356 and 1,180 ppm (392 and 1,298 mg/m^3), concentration in the lungs exceeded that in the blood.

Metabolism

- Cyanide is detoxified by an intramitochondrial enzyme, rhodanese, which catalyzes the transfer of sulfur from a donor to cyanide to form the less toxic thiocyanate. Rhodanese is widely distributed throughout the body; high doses are found in the liver (U.S. EPA, 1985).

- Other minor detoxification pathways include spontaneous reaction with cystine to form 2-imino-4-thiozolidene carboxylic acid and with hydroxycobalamine to form cyanocobalamine - i.e. vitamin B_{12} (U.S. EPA, 1985).

Excretion

- The major route of cyanide elimination is as the thiocyanate in the urine, although some cyanide enters the metabolism of one-carbon compounds and CO_2 is eliminated in expired air. A small amount of HCN is eliminated in expired air (U.S. EPA, 1985).

- Rats eliminated 80% of subcutaneously-injected cyanide as thiocyanate in the urine, while 15% was eliminated as urinary 2-imino-thiozolidine carboxylic acid (Wood and Cooley, 1956).

- A man who had ingested 3 to 5 g KCN (at least 1.2 g HCN was present in the blood 3 hours later) eliminated a total of 237 mg thiocyanate in 72-hour urine (Liebowitz and Schwartz, 1948).

IV. HEALTH EFFECTS

- The enzyme cytochrome oxidase enables cells to utilize oxygen. Cyanide inhibits this enzyme thus resulting in effective cellular anoxia (U.S. EPA, 1985).

Humans

- Acute exposure to cyanide by the oral route has usually occurred from suicide attempts (NIOSH, 1976). Signs of acute poisoning by cyanide include rapid breathing, gasping, tremors, convulsions and death (DiPalma, 1971).

- The fatal oral doses of cyanide compounds range from 50 to 200 mg (0.7 to 2.9 mg CN^-/kg bw) (U.S. EPA, 1985). Within 20 minutes of ingestion of fatal doses, events progress from hyperventilation, vomiting, unconsciousness, convulsions, rapid and irregular heart rate, gasping, vascular collapse and cyanosis, to death.

- Although data regarding chronic oral exposure of humans to HCN, KCN or NaCN are not available, there are a number of reports on the etiology of thyroid disorders and neuropathies characterized by optic atrophy, nerve deafness and spinal ataxia in people living in certain tropical areas of Africa where the staple diet consists largely of cassava. Cassava contains a high level of the cyanogenic glycoside, linamarin, which releases cyanide on metabolism or acid hydrolysis *in vivo* (Osuntokun et al., 1969; Makene and Wilson, 1972).

- Case studies and epidemiological studies of case-hardeners, electroplaters, metal polishers, photographic material workers and HCN fumigators have revealed effects in workers typical of sublethal cyanide poisoning, including headache, dizziness and thyroid enlargement (NIOSH, 1976).

Animals

Short-term Exposure

- The acute oral LD_{50} for KCN was 10 mg/kg (4 mg CN^-/kg) in rats (Hayes, 1967; Gaines, 1969) and 8.5 mg KCN/kg (3.4 mg CN^-/kg) in mice (Sheehy and Way, 1968). The LD_{50} of intraperitoneally administered NaCN for mice was 3.2 mg CN^-/kg (Kruszyna et al., 1982).

- Mice administered 1 or 2 mg KCN/kg (0.4 or 0.8 mg/CN^-/kg) intraperitoneally showed minimal or no effects, while 3 to 5 mg KCN/kg (1.2-2.0 mg CN^-/kg) resulted in signs of toxicity (convulsions, agitation) (Isom et al., 1982). A dose of 6 mg KCN/kg (2.4 mg CN^-/kg) resulted in 20% mortality.

- Doses that are fatal to one species may be harmless to others. An oral dose of 3.8 mg KCN/kg (1.5 mg CN^-/kg) was fatal to a dog in 155 minutes (Gettler and Baine, 1938) but a higher dose of 8 mg KCN/kg (3.2 mg CN^-/kg), equal to the LD_{50} in mice, had only minimal effects on guinea pigs (Basu, 1983).

- Rats tolerated higher doses of cyanide (80 mg CN^-/kg bw/day) when mixed in the diet (Kreutler et al., 1978) than when administered by gavage (4.0 mg CN^-/kg bw) (Ferguson, 1962).

- Rats tolerated 25 daily doses of 10 mg KCN/kg bw (4 mg CN^-/kg bw) when the chemical was mixed in the diet; each of these doses was equal to the acute oral LD_{50} (Hayes, 1967).

- Rats tolerated higher oral doses of KCN (approximately 30 mg KCN/kg bw/day or 12 mg CN^-/kg bw/day for 21 days) when administered in drinking water (Palmer and Olsen, 1979) than when KCN was administered in a bolus (approximately 10 mg/kg bw KCN; 4.5 mg CN^-/kg bw) by gavage with water as the vehicle (Hayes, 1967; Gaines, 1969).

- Rats receiving approximately 12 mg CN^-/kg bw/day for 21 days in drinking water had significantly increased liver weights compared with controls, while rats receiving approximately 8 mg CN^-/kg bw/day in the diet did not (Palmer and Olsen, 1979).

- Beagle dogs consuming 3 mg CN^-/kg bw/day in the diet for 30 days showed no clinical signs of toxicity, effects on body weight, hematology or histopathologic lesions (American Cyanamid Co., 1959).

Long-term Exposure

- Animals can tolerate higher doses of cyanide when administered in the diet or in the drinking water during longer-term exposures (Hayes, 1967; Palmer and Olsen, 1979) than as a bolus dose by gavage.

- Pigs (sows) maintained on diets containing cyanide (30.3, 276.6 and 520.7 mg CN^-/kg diet) throughout gestation and lactation showed hyperplasia of kidney glomerular cells and accumulation of colloid and morphological changes in follicular cells of the thyroid (Tewe and Maner, 1981b). (See also discussion under Developmental Effects, below.)

- Weanling rats maintained on a diet containing 1,500 ppm KCN for 11.5 months (approximately 30 mg CN^-/kg bw/day) had a significantly reduced body weight gain, increased excretion of thiocyanate at 4 months and at 11 months, decreased plasma thyroxine levels, and decreased thyroxine secretion rates at 4 months (Philbrick et al., 1979). The

effects appeared to be greater in the animals on the vitamin B_{12}- and methionine-deficient diet. There were no definitive histopathologic lesions in the optic or CNS tissues, thyroid or sciatic tissues; however, vacuolization and myelin degeneration were observed in spinal cord sections.

- Dogs receiving $\geq$ 0.27 mg CN^-/kg bw/day, administered in a capsule for 15 months, had degenerative changes in ganglion cells of the CNS (Hertting et al., 1960). These effects may be due to the fact that CN^- was administered in a capsule (similar to a bolus dose by gavage).

- Rats maintained for 104 weeks on diets that had been fumigated with HCN to give average dose levels of 76 mg/kg diet and 190 mg/kg diet (i.e., approximately 3.6 and 7.5 mg CN^-/kg bw/day for males and 4.6 and 10.8 mg CN^-/kg bw/day for females) resulted in no effects clinically or histologically (Howard and Hanzel, 1955). The only effects of treatment were increased CN^- levels in the red blood cells, increased thiocyanate levels in the plasma, red blood cells, liver and kidneys of animals from both treatment groups.

Reproductive Effects

- No effects were seen on the reproductive performance of pregnant rats fed 500 mg CN^-/kg diet (KCN) through gestation and lactation (Tewe and Maner, 1981a). Offspring that were continued on the test diet after weaning consumed less food and grew at a significantly reduced rate compared to control offspring.

Developmental Effects

- Severe teratogenic effects were seen in hamsters administered cyanide by subcutaneously implanted osmotic minipumps that delivered cyanide at a rate of 3.3-3.4 mg CN^-/kg bw/hour (79.2-81.6 mg CN^-/kg bw/day) from day 6-9 of gestation (Doherty et al., 1982).

- Piglets born to pigs maintained on diets containing cyanide (30.3, 276.6 and 520.7 mg CN^-/kg diet) throughout gestation and lactation showed reduced organ-to-body weight ratios of the thyroid, spleen and heart in the high and/or medium dose groups relative to the low-dose group piglets (Tewe and Maner, 1981b). (See also discussion under Long-term Exposure, above.)

Mutagenicity

- Potassium cyanide was not mutagenic in Salmonella typhimurium with or without metabolic activation (De Flora, 1981).

- A study using HCN gas reported marginally mutagenic activity in S. typhimurium strain TA100 (Kushi, 1983). Addition of S-9 mix decreased the mutagenic activity.

- Cyanide was negative in a modified rec assay in Bacillus subtilis (Karube et al., 1981).

Carcinogenicity

- No information was located in the available literature on the carcinogenicity of cyanides.

V. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

Health Advisories (HAs) are generally determined for One-day, Ten-day, Longer-term (approximately 7 years) and Lifetime exposures if adequate data are available that identify a sensitive noncarcinogenic end point of toxicity. The HAs for noncarcinogenic toxicants are derived using the following formula:

$$HA = \frac{(NOAEL \text{ or } LOAEL) \times (BW)}{(UF) \times (\_\_\_ L/day)} = \_\_\_ mg/L \ (\_\_\_ ug/L)$$

where:

NOAEL or LOAEL = No- or Lowest-Observed-Adverse-Effect-Level in mg/kg bw/day.

BW = assumed body weight of a child (10 kg) or an adult (70 kg).

UF = uncertainty factor (10, 100 or 1,000), in accordance with NAS/ODW guidelines.

___ L/day = assumed daily water consumption of a child (1 L/day) or an adult (2 L/day).

One-day Health Advisory

The available data are insufficient to develop a One-day HA for cyanide. It is recommended that the modified DWEL of 0.22 mg/L (adjusted for the 10-kg child) be used as the One-day HA for the 10-kg child.

Ten-day Health Advisory

While the study by Palmer and Olsen (1979) was considered as the basis for the Ten-day HA, it is recommended that the modified DWEL of 0.22 mg/L (adjusted for a 10-kg child) be used as the Ten-day HA for the 10-kg child. The NOAEL observed by Howard and Hanzal (1955) in a two-year rat study (which serves as the basis for the DWEL and Lifetime HA) was 10.8 mg/kg/day, in good general agreement with the NOAEL of 8 mg/kg/day observed by Palmer and Olsen (1979) in a 21-day rat study. As the NOAELs in the two studies were little different and as greater confidence was placed in the Howard and Hanzal (1955) study, it was determined that it was appropriate to use the modified DWEL as the Ten-day HA.

Longer-term Health Advisory

The available data are insufficient to develop Longer-term HAs for cyanide. It is recommended that the DWEL of 0.77 mg/L be used as the Longer-term HA for the 70-kg adult and the modified DEWL of 0.22 mg.L (adjusted for a 10-kg child) be used as the Longer-term HA for the 10-kg child.

Lifetime Health Advisory

The Lifetime HA represents that portion of an individual's total exposure that is attributed to drinking water and is considered protective of noncarcinogenic adverse health effects over a lifetime exposure. The Lifetime HA is derived in a three step process. Step 1 determines the Reference Dose (RfD), formerly called the Acceptable Daily Intake (ADI). The RfD is an estimate of a daily exposure to the human population that is likely to be without appreciable risk of deleterious effects over a lifetime, and is derived from the NOAEL (or LOAEL), identified from a chronic (or subchronic) study, divided by an uncertainty factor(s). From the RfD, a Drinking Water Equivalent Level (DWEL) can be determined (Step 2). A DWEL is a medium-specific (i.e., drinking water) lifetime exposure level, assuming 100% exposure from that medium, at which adverse, noncarcinogenic health effects would not be expected to occur. The DWEL is derived from the multiplication of the RfD by the assumed body weight of an adult and divided by the assumed daily water consumption of an adult. The Lifetime HA is determined in Step 3 by factoring in other sources of exposure, the relative source contribution (RSC). The RSC from drinking water is based on actual exposure data or, if data are not available, a value of 20% is assumed for synthetic organic chemicals and a value of 10% is assumed for inorganic chemicals. If the contaminant is classified as a Group A or B carcinogen, according to the Agency's classification scheme of carcinogenic potential (U.S. EPA, 1986), then caution should be exercised in assessing the risks associated with lifetime exposure to this chemical.

The study of Howard and Hanzal (1955) has been selected to serve as the basis for the DWEL and Lifetime HA. In this study, rats were maintained for 104 weeks on diets that had been fumigated with HCN to give average dose levels of 76 or 190 mg/kg diet (i.e., approximately 3.6 and 7.5 mg/kg/day for male rats and 4.6 and 10.8 for female rats). No clinical or histological effects were observed at either dose level.

Using the NOAEL of 10.8 mg/kg/day, the DWEL and Lifetime HA are derived as follows:

Step 1: Determination of the Reference Dose (RfD)

$$RfD = \frac{(10.8 \text{ mg/kg/day})}{(100)\ (5)} = 0.022 \text{ mg/kg/day} *$$

* NB: The RfD is in good general agreement with the observation (NIOSH, 1976) that 1 mg HCN/m^3 is without effect in humans via inhalation.

where:

10.8 mg/kg/day = NOAEL for absence of clinical and histological effects in rats exposed to HCN in the diet for 104 weeks.

100 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a NOAEL from an animal study.

5 = additional uncertainty factor selected to allow for possibly greater absorption of cyanide from water than from the diet.

Step 2: Determination of the Drinking Water Equivalent Level (DWEL)

$$DWEL = \frac{(0.022 \text{ mg/kg/day})\ (70 \text{ kg})}{(2 \text{ L/day})} = 0.77 \text{ mg/L } (770 \text{ ug/L})$$

where:

0.02 mg/kg/day = RfD.

70 kg = assumed body weight of an adult.

2 L/day = assumed daily water consumption of an adult.

Step 3: Determination of the Lifetime Health Advisory

The DWEL of 770 ug/L assumes that 100% of the exposure to cyanide is via drinking water. It is probable, however, that exposure occurs via other routes. Therefore, if one assumes that drinking water contributes 20% of daily exposure to cyanide, then the Lifetime Health Advisory would be 154 ug/L. The Lifetime HA is calculated as follows:

$$\text{Lifetime HA} = (770 \text{ ug/L})\ (20\%) = 154 \text{ ug/L}$$

where:

770 ug/L = DWEL.

20% = assumed relative source contribution from water.

Evaluation of Carcinogenic Potential

- There is no available information pertaining to the carcinogenicity of cyanides.
- IARC has not calculated the carcinogenic potential of cyanides.
- Applying the criteria described in EPA's final guidelines for assessment of carcinogenic risk (U.S. EPA, 1986), cyanide may be classified in Group D: Not classified. This category is for agents with inadequate human and animal evidence of carcinogenicity.

VI. OTHER CRITERIA, GUIDANCE AND STANDARDS

- The ambient water quality criterion for cyanide has been proposed at 3.77 mg/L assuming that a 70 kg human consumes 2 L of water and 6.5 g of fish per day with a bioconcentration factor of 1.0 (U.S. EPA, 1982).
- The U.S. PHS (1962) recommended that concentrations of cyanide in water supplies not exceed 0.2 mg/L in order to protect human health. The U.S. PHS (1962) also recommended that concentrations in drinking water be kept below 0.01 mg/L since this level or lower can be achieved by proper treatment.

- ACGIH (1980) has recommended a TLV for alkali cyanides in workroom air of 5 mg CN^-/m^3.

- NIOSH has recommended a TLV of 5 mg/m^3 for CN^- which was adopted by OSHA (1981).

VII. ANALYTICAL METHODS

- Determination of cyanide is by volumetric titration or colorimetry (U.S. EPA, 1979). The cyanide as hydrocyanic acid (HCN) is released from cyanide complexes by means of a reflux-distillation operation and absorbed in a scrubber containing sodium hydroxide solution. The cyanide ion in the absorbing solution is then determined by volumetric titration or colorimetrically. The titration procedure uses a standard solution of silver nitrate and an indicator. The detection limit is 1 mg/L. In the colorimetric measurement, the cyanide is converted to cyanogen chloride, a reagent is added to form a colored complex and the absorbance is measured. The detection limit is 20 ug/L.

VIII. TREATMENT TECHNOLOGIES

- Several treatment technologies for the removal of cyanide are available, although most of what has been reported in the literature involves wastewater applications. The treatment of high concentrations of cyanide (and cyanide complexes) in industrial waste streams and mine drainage runoff has been studied extensively, but only limited information is available on reductions of low cyanide levels in drinking water supplies.

- The general treatment technologies that may be practical for reducing cyanide levels in drinking water include oxidation by chlorine or ozone, ion exchange and reverse osmosis.

- Oxidation by chlorine may be the cheapest and most practical method to remove cyanide from the water. In addition to the removal of cyanide, chlorine oxidation may cause secondary beneficiary effects. These include disinfection of the water, oxidation of iron and manganese, oxidation of taste and odor causing compounds. Practical experience in the wastewater industry and the laboratory indicate that chlorine oxidation is capable of removing 99% or more of the cyanide from the water (Gott, 1978; Smith et al., 1980).

- Oxidation by ozone may be used to destroy cyanide in water if the formation of trihalomethanes is to be avoided. The use of ozone oxidation for cyanide is a relatively new technique. Laboratory and pilot studies by Cullivan (Cullivan, no date) indicated that complete destruction of cyanide in water required a 1.3 to 1 ozone to cyanide molar ratio. These results were achieved with 5 to 15 mg/L of cyanide in the influent water. However, the results of study indicated that at cyanide concentrations of less than 5 mg/L, the rate of destruction is decreased.

° Although reverse osmosis and ion exchange can reduce cyanide levels in the water, their application may not be practical in the economical sense if cyanide is the only contaminant to be removed. Experience by Moore (1976) and Trachtenberg et al. (1979) indicates that a well-designed ion exchange facility can remove over 99% of the cyanide present in the water. Pilot plant studies performed by Rosehart (1973) treating mine-waters by reverse osmosis, resulted in cyanide removal ranging from 28.7 to 81.6 percent, respectively.

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MERCURY

Health Advisory
Office of Drinking Water
U.S. Environmental Protection Agency

I. INTRODUCTION

The Health Advisory (HA) Program, sponsored by the Office of Drinking Water (ODW), provides information on the health effects, analytical methodology and treatment technology that would be useful in dealing with the contamination of drinking water. Health Advisories describe nonregulatory concentrations of drinking water contaminants at which adverse health effects would not be anticipated to occur over specific exposure durations. Health Advisories contain a margin of safety to protect sensitive members of the population.

Health Advisories serve as informal technical guidance to assist Federal, State and local officials responsible for protecting public health when emergency spills or contamination situations occur. They are not to be construed as legally enforceable Federal standards. The HAs are subject to change as new information becomes available.

Health Advisories are developed for One-day, Ten-day, Longer-term (approximately 7 years, or 10% of an individual's lifetime) and Lifetime exposures based on data describing noncarcinogenic end points of toxicity. Health Advisories do not quantitatively incorporate any potential carcinogenic risk from such exposure. For those substances that are known or probable human carcinogens, according to the Agency classification scheme (Group A or B), Lifetime HAs are not recommended. The chemical concentration values for Group A or B carcinogens are correlated with carcinogenic risk estimates by employing a cancer potency (unit risk) value together with assumptions for lifetime exposure and the consumption of drinking water. The cancer unit risk is usually derived from the linear multistage model with 95% upper confidence limits. This provides a low-dose estimate of cancer risk to humans that is considered unlikely to pose a carcinogenic risk in excess of the stated values. Excess cancer risk estimates may also be calculated using the One-hit, Weibull, Logit or Probit models. There is no current understanding of the biological mechanisms involved in cancer to suggest that any one of these models is able to predict risk more accurately than another. Because each model is based on differing assumptions, the estimates that are derived can differ by several orders of magnitude.

This Health Advisory (HA) is based on information presented in the Office of Drinking Water's Health Effects Criteria Document (CD) for Mercury (U.S. EPA, 1985). The HA and CD formats are similar for easy reference. Individuals desiring further information on the toxicological data base or rationale for risk characterization should consult the CD. The CD is available for review at each EPA Regional Office of Drinking Water counterpart (e.g., Water Supply Branch or Drinking Water Branch), or for a fee from the National Technical Information Service, U.S. Department of Commerce, 5285 Port Royal Rd., Springfield, VA 22161, PB # 86-117827/AS. The toll-free number is (800) 336-4700; in the Washington, D.C. area: (703) 487-4650.

II. GENERAL INFORMATION AND PROPERTIES

CAS Nos.

- Mercury -- 7439-97-6
  Mercury (II) Chloride -- 7487-94-7
  Mercury (II) Sulfate -- 7783-36-0

Synonyms

- Mercury (II) chloride: mercuric bichloride; mercury perchloride.
  Mercury (II) sulfate: mercuric sulfate.

Uses (U.S. EPA, 1985)

- While this document is concerned with the toxic effects of ionic mercury, it is metallic mercury that has the most uses. Some uses of metallic mercury include use as a cathode in the electrolytic preparation of chlorine and caustic soda, and in electrical apparatuses, dental amalgams, catalysts and in pulp and paper manufacture.

Properties (Weast, 1971)

- The properties of inorganic mercury compounds vary with the specific compound; some examples are as follows:

	Mercury	Mercury (II) Chloride	Mercury (II) Sulfate
Chemical Formula	Hg	$HgCl_2$	$HgSO_4$
Atomic/Molecular Weight	200.59	271.49	296.65
Physical State	Silver liquid	White powder	White powder
Boiling Point	356.58°C	302°C	--
Melting Point	-38.87°C	276°C	Decomposes
Density	13.5939	5.44	6.47
Vapor Pressure	--	--	--
Water Solubility	Insoluble	6.9 g/100 cm^3 (20°C)	Decomposes
Log Octanol/Water Partition Coefficient	--	--	--
Taste Threshold	--	--	--
Odor Threshold	--	--	--

Occurrence

- Mercury, although a relatively rare element, is ubiquitous in the earth's crust, occurring at levels from 10 to 500 ppb as a sulfide, chloride or oxide. However, mercury can form organic compounds that can bioaccumulate in the food chain and become a significant toxicological concern. Only a small fraction of mercury in ground and surface waters occurs in the organic form (U.S. EPA, 1987).

- The majority of mercury used commercially in the United States is imported. These commercial Uses have resulted in releases of mercury and its compounds to surface waters. Naturally occurring levels of mercury in ground and surface water are less than 0.5 ug/L, although higher levels may occur in ground water from local mineral deposits. Ground water surveys have found mercury at levels above 0.5 ug/L in 15 to 30% of wells tested. Surface water surveys report that about 20% of surface waters exceed 0.5 ug/L. State compliance data report that 16 ground water and 16 surface water wells currently exceed the maximum contaminant level of 2 ug/L (U.S. EPA, 1987).

III. PHARMACOKINETICS

Absorption

- It is estimated that between 7 and 15% of orally administered inorganic mercury is absorbed by humans (Rahola et al., 1971; Task Group on Metal Accumulation, 1973).

Distribution

- Rothstein and Hayes (1960) administered a single dose of ^{203}Hg (as $Hg(NO_3)_2$; 0.2 mg/kg) by intravenous injection to seven male Wistar rats. Distribution of mercury was primarily to kidney, liver, blood, skin and muscle. Other tissues contained only fractional percentages of the administered dose. In general, each tissue except the kidney showed a maximum value four hours or one day post-treatment, followed by rapid clearance. The kidney continued to accumulate mercury with maximum concentrations reached at 6 to 15 days. For example, after four hours, only 9% of the body burden of mercury was found in the kidney; by the fifteenth day post-treatment 86% of the remaining mercury was in the kidney.

- Jugo (1976) administered single intravenous injections of ^{203}Hg (as $HgCl_2$; 0.15 mg/kg) to 2- or 21-week old female albino rats (strain not specified). Approximately 28 and 51% of the administered dose was present in the kidneys of the 2- and 21-week old rats, respectively, after 144 hours. Approximately 9% of the dose was present in the liver of 2-week old rats; less than 1% was present in the liver of older rats. In both groups of rats, the blood and brain contained less than 1% of the administered dose.

Metabolism

- No information was found in the available literature on the metabolism of inorganic mercury.

Excretion

- Rahola et al. (1971) administered single oral doses of protein bound methyl mercury (14 ug/subject) and inorganic mercury (6 ug/subject) to human volunteers. Approximately 85% of the administered inorganic mercury was eliminated in the feces within 4 to 5 days; only about 0.2% was excreted in the urine. After 50 days the daily excretion of inorganic mercury in the urine and feces was about 0.02% of the administered dose. Approximately 6% of the administered dose of methyl mercury was eliminated in the feces within 3 to 4 days; excretion in the urine was negligible at first, but increased slowly. After 100 days, 20% of the daily excretion of mercury was via the urine.

- Rothstein and Hayes (1960) reported on the excretion of mercury in rats administered single intravenous injections of ^{203}Hg (as $Hg(NO_3)_2$; 0.2 mg/kg). These authors indicated that the clearance of mercury from rats occurred in three phases: a rapid phase invoking 35% of the dose lasting for a few days; a slower phase involving 50% of the dose with a half-time of 30 days; and a slow phase involving 15% of the dose with a half-time of approximately 100 days. Since mercury was found to accumulate in the kidney in the first few days following dosing, the two slow phases of excretion represent primarily clearance from the kidney.

IV. HEALTH EFFECTS

Humans

Short-term Exposure

- Gleason, et al. (1957) estimated that the lethal oral dose for mercuric salts in humans is 1 to 4 g (equivalent to 14 to 57 mg/kg body weight).

- Ingestion of a dose of 1.5 g of mercuric chloride ($HgCl_2$) produced emesis after 5 minutes, followed by severe abdominal pain with a brief period of loss of consciousness (Pesce et al., 1977).

Long-term Exposure

- No information was found in the available literature on the human health effects of long-term exposure to inorganic mercury.

Animals

Short-term Exposure

° Male and female Brown-Norway rats (varying numbers per dose group) were given subcutaneous injections of mercuric chloride, three times per week for a maximum of 12 weeks. The dose levels administered were 0, 0.05, 0.1, 0.25, 0.5, 1.0 or 2.0 mg/kg/injection. Rats that received doses of 0.1 mg/kg/injection or higher developed renal disease characterized by antiglomerular basement membrane antibodies and the appearance of deposits in the glomerular tufts and in the small renal arteries. Proteinurea and a nephrotic syndrome were also observed in these rats. Based on these results, a NOAEL of 0.05 mg/kg/injection is identified (Druet et al., 1978).

Long-term Exposure

° Male and female rats (strain not specified; 20 to 24/group) were administered mercury (as mercuric acetate) in the diet for up to 2 years at concentrations of 0, 0.5, 2.5, 10, 40 or 160 ppm. Assuming that 1 ppm in the diet of rats is equivalent to 0.05 mg/kg/day (Lehman, 1959), these dose levels correspond to 0, 0.025, 0.125, 0.50, 2.0 or 8.0 mg/kg/day. At the highest dose level (8.0 mg/kg/day), body weight was slightly depressed in male rats only (statistical significance not specified). Kidney weights were significantly increased ($p < 0.05$) in the 2.0 and 8.0 mg/kg/day dose groups. Pathological changes originating in the proximal convoluted tubules were also noted at these dose levels, with more severe effects in females than in males. Based on these results, a NOAEL of 10 ppm (0.5 mg/kg/day) is identified. A number of deficiencies limit the usefulness of this study. These deficiencies include the small number of animals surviving past 18 months, lack of information on the number of animals in each group having detectable pathological changes and the absence of statistical analysis of body weight changes in males (Fitzhugh et al., 1950).

Reproductive Effects

° No information was found in the available literature on the reproductive effects of inorganic mercury.

Developmental Effects

° Oral dosing of Syrian golden hamsters with mercuric acetate on day 8 of gestation at levels ranging from 4 to 100 mg/kg produced a dose-related response in numbers of resorptions and abnormal embryos. While these findings were evident at the 4 mg/kg dose level, the percentage of change was not significantly different from controls at this low level (Gale, 1974).

Mutagenicity

° No evidence is currently available to indicate that the mercuric salts are mutagenic.

Carcinogenicity

- No evidence was found in the available literature on the carcinogenicity of inorganic mercury.

V. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

Health Advisories (HAs) are generally determined for One-day, Ten-day, Longer-term (approximately 7 years) and Lifetime exposures if adequate data are available that identify a sensitive noncarcinogenic end point of toxicity. The HAs for noncarcinogenic toxicants are derived using the following formula:

$$HA = \frac{(NOAEL \text{ or } LOAEL) \times (BW)}{(UF) \times (\_\_\_ \text{ L/day})} = \_\_\_ \text{ mg/L } (\_\_\_ \text{ ug/L})$$

where:

NOAEL or LOAEL = No- or Lowest-Observed-Adverse-Effect-Level in mg/kg bw/day.

BW = assumed body weight of a child (10 kg) or an adult (70 kg).

UF = uncertainty factor (10, 100 or 1,000), in accordance with NAS/ODW guidelines.

___ L/day = assumed daily water consumption of a child (1 L/day) or an adult (2 L/day).

One-day Health Advisory

The available data are insufficient to develop a One-day HA for mercury. It is, therefore, recommended that the modified DWEL (1.58 ug/L) be used at this time as a conservative estimate of the One-day HA value.

Ten-day Health Advisory

The available data are insufficient to develop a Ten-day HA for mercury. It is, therefore, recommended that the modified DWEL (1.58 ug/L) be used at this time as a conservative estimate of the Ten-day HA value.

Longer-term Health Advisory

The available data are insufficient to develop Longer-term HAs for mercury. It is, therefore, recommended that the modified DWEL (1.58 ug/L) be used at this time as a conservative estimate of the Longer-term HA value for the 10-kg child.

Lifetime Health Advisory

The Lifetime HA represents that portion of an individual's total exposure that is attributed to drinking water and is considered protective of noncarcinogenic adverse health effects over a lifetime exposure. The Lifetime HA is derived in a three step process. Step 1 determines the Reference Dose (RfD), formerly called the Acceptable Daily Intake (ADI). The RfD is an estimate of a daily exposure to the human population that is likely to be without appreciable risk of deleterious effects over a lifetime, and is derived from the NOAEL (or LOAEL), identified from a chronic (or subchronic) study, divided by an uncertainty factor(s). From the RfD, a Drinking Water Equivalent Level (DWEL) can be determined (Step 2). A DWEL is a medium-specific (i.e., drinking water) lifetime exposure level, assuming 100% exposure from that medium, at which adverse, noncarcinogenic health effects would not be expected to occur. The DWEL is derived from the multiplication of the RfD by the assumed body weight of an adult and divided by the assumed daily water consumption of an adult. The Lifetime HA is determined in Step 3 by factoring in other sources of exposure, the relative source contribution (RSC). The RSC from drinking water is based on actual exposure data or, if data are not available, a value of 20% is assumed for synthetic organic chemicals and a value of 10% is assumed for inorganic chemicals. If the contaminant is classified as a Group A or B carcinogen, according to the Agency's classification scheme of carcinogenic potential (U.S. EPA, 1986), then caution should be exercised in assessing the risks associated with lifetime exposure to this chemical.

The study by Druet et al. (1978) has been selected to serve as the basis for the Lifetime Health Advisory. In this study, Brown-Norway rats were given subcutaneous injections of mercuric chloride, three times per week for up to 12 weeks at dose levels of 0, 0.05, 0.1, 0.25, 0.5, 1.0 or 2.0 mg/kg/injection. Kidney damage, characterized by proteinurea and a nephrotic syndrome, was observed in rats that received doses of 0.1 mg/kg/injection or higher. Based on these results, a NOAEL of 0.05 mg/kg/injection is identified.

Using this NOAEL, the Drinking Water Equivalent Level and Lifetime Health Advisory are derived as follows:

Step 1: Determination of the Reference Dose (RfD)

$$RfD = \frac{(100)\ (0.05\ mg/kg/injection)\ (0.739)\ (36)}{(10)\ (84\ days)\ (1{,}000)} = 0.158\ ug/kg/day$$

where:

0.05 mg/kg/injection = NOAEL for absence of renal effects in rats.

36 = number of doses.

0.739 = percentage of mercury in mercuric chloride.

84 days = exposure period.

1,000 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a NOAEL from an animal study of less-than-lifetime duration.

100/10 = assumed subcutaneous absorption factor relative to ingestion.

Step 2: Determination of the Drinking Water Equivalent Level (DWEL)

$$DWEL = \frac{(0.158 \text{ ug/kg/day})(70 \text{ kg})}{(2 \text{ L/day})} = 5.5 \text{ ug/L}$$

where:

0.158 ug/kg/day = RfD.

70 kg = assumed body weight of an adult.

2 L/day = assumed daily water consumption of an adult.

Step 3: Determination of the Lifetime Health Advisory

Lifetime HA = (5.5 ug/day) (20%) = 1.1 ug/L

where:

5.5 ug/L = DWEL.

20% = assumed relative source contribution from water.

Evaluation of Carcinogenic Potential

- The International Agency for Research on Cancer has not evaluated the carcinogenic potential of mercury.
- Applying the criteria described in EPA's guidelines for assessment of carcinogenic risk (U.S. EPA, 1986), mercury may be classified in Group D: not classified. This group is for substances with inadequate animal evidence of carcinogenicity.

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VI. OTHER CRITERIA, GUIDANCE AND STANDARDS

- The U.S. EPA has recommended an ambient water quality criterion for the protection of health of 144 ng/L (U.S. EPA, 1980) and for drinking water of 2 ug/L (U.S. EPA, 1973).

- A WHO expert group has recommended an international standard for mercury in drinking water at 1 ug Hg/L (WHO, 1971).

VII. ANALYTICAL METHODS

- Determination of mercury is by flameless atomic absorption using either a manual cold vapor technique (U.S. EPA, 1979a) or an automated cold vapor technique (U.S. EPA, 1979b).

- The flameless atomic absorption procedure is a physical method based on the absorption of radiation at 253.7 nm by mercury vapor. The mercury is reduced to the elemental state and aerated from solution in a closed system. The mercury vapor passes through a cell positioned in the light path of an atomic absorption spectrophotometer. Absorbance is measured as a function of mercury concentration. The detection limit for mercury is 0.2 ug/L using either the manual or automated technique.

VIII. TREATMENT TECHNOLOGIES

- Laboratory and pilot plant studies indicate that coagulation/filtration is moderately effective in removal of inorganic mercury from drinking water. Ferric sulfate coagulation achieved 66% removal at pH 7 and 97% removal at pH 8 from water containing 0.05 mg/L of inorganic mercury. Alum coagulation was shown to be much less effective: 47% of the mercury was removed at pH 7 and 38% at pH 8. It has been found that coagulation/filtration is less effective for removal of organic mercury. However, the mercury removal efficiency of existing coagulation/filtration systems can be improved by the addition of powdered activated carbon (PAC) to the raw water influent. Laboratory tests by Logsdon and Symons (1973) have shown that each milligram per liter of PAC added removes 0.0001 mg/L of either inorganic or organic mercury.

- Lime softening is essentially ineffective for removal of organic mercury but moderately effective for removal of inorganic mercury, depending on the pH of the water. Laboratory studies by Logsdon and Symons (1973) have shown that in the 10.7-11.4 pH range, lime softening removed 60 to 80% of the inorganic mercury, whereas only about 30% removal was achieved at pH 9.4.

- The use of activated carbon as a process to remove mercury from drinking water has been reported by various investigators (Logsdon and Symons, 1973; Sigworth and Smith, 1972; Sorg, 1979; Theim et al., 1976). Laboratory tests were performed by pumping solutions of tap

water and either soluble inorganic or organic mercury through columns of granular activated carbon for extended periods of time. The results showed that 80 to 99% of the mercury may be removed from the water by this technology (Sigworth, et al. 1972; Logsdon and Symons, 1973).

- Limited pilot-plant studies have been reported by Sorg (1977) on the use of reverse osmosis for mercury removal. One study investigating the removal of heavy metals, pesticides and other toxic chemicals from secondary wastewater effluent resulted in inorganic and organic mercury removals of 82 and 83%, respectively. Another test involved a hollow fiber membrane with raw water flow of 1.25 gpm, 170 to 200 psi, and 40 to 50% water recovery. The spiral wound membrane system showed a 25% mercury removal, while the hollow fiber system efficiency removal was 79 to 81%.

- Several preliminary ion exchange experiments have been carried out by Ebersole and O'Connor (1972) to investigate organic and inorganic mercury removal from drinking water. These studies showed that as much as 98% of inorganic mercury added to distilled water could be removed by cation and anion exchange resins operated in series. Although these experiments were very preliminary, the results indicated that ion exchange may be an effective method for inorganic mercury removal.

March 31, 1987

NICKEL

Health Advisory
Office of Drinking Water
U.S. Environmental Protection Agency

I. INTRODUCTION

The Health Advisory (HA) Program, sponsored by the Office of Drinking Water (ODW), provides information on the health effects, analytical methodology and treatment technology that would be useful in dealing with the contamination of drinking water. Health Advisories describe nonregulatory concentrations of drinking water contaminants at which adverse health effects would not be anticipated to occur over specific exposure durations. Health Advisories contain a margin of safety to protect sensitive members of the population.

Health Advisories serve as informal technical guidance to assist Federal, State and local officials responsible for protecting public health when emergency spills or contamination situations occur. They are not to be construed as legally enforceable Federal standards. The HAs are subject to change as new information becomes available.

Health Advisories are developed for One-day, Ten-day, Longer-term (approximately 7 years, or 10% of an individual's lifetime) and Lifetime exposures based on data describing noncarcinogenic end points of toxicity. Health Advisories do not quantitatively incorporate any potential carcinogenic risk from such exposure. For those substances that are known or probable human carcinogens, according to the Agency classification scheme (Group A or B), Lifetime HAs are not recommended. The chemical concentration values for Group A or B carcinogens are correlated with carcinogenic risk estimates by employing a cancer potency (unit risk) value together with assumptions for lifetime exposure and the consumption of drinking water. The cancer unit risk is usually derived from the linear multistage model with 95% upper confidence limits. This provides a low-dose estimate of cancer risk to humans that is considered unlikely to pose a carcinogenic risk in excess of the stated values. Excess cancer risk estimates may also be calculated using the One-hit, Weibull, Logit or Probit models. There is no current understanding of the biological mechanisms involved in cancer to suggest that any one of these models is able to predict risk more accurately than another. Because each model is based on differing assumptions, the estimates that are derived can differ by several orders of magnitude.

This Health Advisory (HA) is based on information presented in the Office of Drinking Water's Health Effects Criteria Document (CD) for Nickel (U.S. EPA, 1985). The HA and CD formats are similar for easy reference. Individuals desiring further information on the toxicological data base or rationale for risk characterization should consult the CD. The CD is available for review at each EPA Regional Office of Drinking Water counterpart (e.g., Water Supply Branch or Drinking Water Branch), or for a fee from the National Technical Information Service, U.S. Department of Commerce, 5285 Port Royal Rd., Springfield, VA 22161, PB # 86-117801/AS. The toll-free number is (800) 336-4700; in the Washington, D.C. area: (703) 487-4650.

II. GENERAL INFORMATION AND PROPERTIES

CAS No.

- Nickel -- 7440-02-0
  Nickel Chloride -- 7718-54-9
  Nickel Oxide -- 1313-99-1

Synonyms

- Nickel Chloride: Nickelous Chloride
  Nickel Oxide: Bunsenite

Uses (U.S. EPA, 1985)

- While this document is concerned with the toxic effects of ionic nickel, it is metallic nickel which has the most uses. Some uses of metallic nickel include use in the manufacture of stainless steel, various other alloys and in electroplating.

Properties (Weast, 1971)

- The properties of nickel compounds vary with the specific compound; some examples are as follows:

	Nickel	Nickel Chloride	Nickel Oxide
Chemical Formula	Ni	$NiCl_2$	NiO
Atomic/Molecular Weight	58.71	129.62	74.71
Physical State	silver metal	yellow solid	green-black solid
Boiling Point	2,732°C	973°C (sublimes)	--
Melting Point	1,453°C	1,001°C	1,990°C
Density	8.90	3.55	6.67
Vapor Pressure	--	--	--
Water Solubility	insoluble	64.2 g/100cc (20°C)	--
Log Octanol/Water Partition Coefficient	--	--	--
Taste Threshold	--	--	--
Odor Threshold	--	--	--

Occurrence

- Nickel is a metallic element which is not found free in nature but exists as a number of salts. Nickel compounds are found in most geologic materials at levels up to several thousand ppm. Nickel occurs at low levels in most surface and ground waters. Because nickel compounds are relatively insoluble, the levels of nickel in most surface and ground waters are less than 100 ppb. Since nickel compounds are used commercially in a number of industries, contamination of drinking water is the result of naturally occurring nickel compounds proliferated during industrial activities (U.S. EPA, 1979a; 1983a).

- Nickel is a component of some plumbing material. When pipes and other materials corrode, nickel can be released to drinking water. However, available information suggests that releases from this source are small (U.S. EPA, 1979a; 1983a).

- There are limited survey data on the occurrence of nickel in drinking water. Based upon these data, most supplies contain less than 40 ug/L of nickel. The highest level reported for a drinking water supply was 490 ug/L. Nickel also occurs at low levels in food. Based upon the limited information available, diet is the major source of nickel exposure with water making only a minor contribution (U.S. EPA, 1979a; 1983a).

III. PHARMACOKINETICS

- The major routes of nickel intake for both humans and animals are inhalation and ingestion, and to a lesser extent percutaneous absorption. The extent of nickel absorption is dependent not only on the concentration of inhaled or ingested nickel, but also on the chemical and physical forms of nickel (U.S. EPA, 1985). Since inhalation and percutaneous exposures are not relevant to drinking water, emphasis will be placed on studies using the oral route of exposure.

Absorption

- Very little of the nickel ingested in food is absorbed. Total dietary intake of nickel ranges from 107 to 900 ug/day with average values of 160-500 ug daily (U.S. EPA, 1985); about 1-10% of this is absorbed (Horak and Sunderman, 1973).

- In rats, intubation of ^{63}Ni in dilute acid solutions resulted in 3-6% absorption of radiolabelled nickel (Ho and Furst, 1973).

- There was no uptake of nickel in rats chronically exposed to drinking water at levels of 5 ppm over the lifetime of an animal (Schroeder et al., 1974).

- Transplacental transfer of nickel to the fetus takes place in both humans and animals. Newborn rats of mothers fed 1000 ppm Ni in the diet showed whole body levels of 22-30 ppm nickel (Phatak and

Patwardhan, 1950). Also, similar levels of nickel (0.04-2.8 ppm) were seen in the liver, heart and muscle of fetuses as were seen in adult humans (Casey and Robinson, 1978).

° Absorption from inhalation exposure to nickel carbonyl is both rapid and extensive. Sunderman and Selin (1968) exposed rats to nickel carbonyl at 100 mg Ni/L of air for 15 minutes. It was estimated that half of the inhaled amount was initially absorbed. On the other hand, inhalation exposure to insoluble particulate nickel (e.g., the oxide or the subsulfide) results in very little absorption.

Distribution

° The tissue distribution in animals orally exposed to Ni is dependent upon the concentration of the compound. Calves fed supplemental nickel in the diet at levels of 62.5, 250 or 1000 ppm showed somewhat elevated levels of nickel in pancreas, testes and bone at 250 ppm; pronounced increases were seen in these tissues at 1000 ppm (O'Dell et al., 1971).

° Weanling rats exposed to nickel (acetate) in diet up to levels of 1000 ppm showed increased levels of nickel in kidney, liver, heart and testes as nickel concentration was increased, with the greatest accumulation in the kidneys (Whanger, 1973).

Metabolism

° Serum albumin is the main carrier protein for nickel in the sera of humans, rabbits, rats and bovine species. In the sera of rabbits and humans the nickel-rich metalloproteins α_1-macroglobulin (nickeloplasmin) and 9.5 S α_1-glycoprotein, respectively have been identified (NAS, 1975).

Excretion

° The main excretory route of absorbed nickel in humans and animals appears to be the urine (Ho and Furst, 1973) with biliary excretion also occurring in experimental animals (Onkelinx et al., 1973). The deposition of nickel in hair of humans also appears to be an excretory mechanism (Nechay and Sunderman, 1973). Unabsorbed dietary nickel is excreted in the feces.

IV. HEALTH EFFECTS

Humans

° No clinical or epidemiologic studies dealing with the toxicity of nickel following oral exposure were found in the available literature.

° The toxicity of nickel to humans and animals is a function of the chemical form of the element and the route of exposure. There has been a suggestion of a correlation between chronic inhalation exposure

to nickel carbonyl and respiratory tract cancer from epidemiological studies which have been confirmed in experimental animals. Dermatitis (nickel itch) is another frequent effect of exposure to nickel (EPA, 1983b). However, these data are not pertinent to the effects due to ingestion of nickel in drinking water.

Animals

Short-term Exposure

° The oral LD_{50} values converted to mg nickel/kg bw range from 105 mg/kg bw for nickel chloride in male rats to 186 mg/kg for nickelocene in mice (U.S. EPA, 1985).

° Nickel chloride administered orally to rats at doses of 0.5 to 5.0 mg/kg/day for 2 to 4 weeks led to a significantly decreased thyroid absorption of iodine (Lestrovoi et al., 1974).

° Nickel acetate in the diet of weanling OSU brown rats for six weeks at concentrations of 100, 500 or 1000 ppm (i.e., 10, 50 or 100 mg Ni/kg bw) resulted in a significantly reduced weight gain at 500 ppm; rats exposed to 1000 ppm lost weight. At 500 and 1000 ppm, there was a dose-related decrease in blood hemoglobin concentration, packed cell volume and plasma alkaline phosphate activity. Cytochrome oxidase activity was decreased significantly ($p< 0.005$) in both heart and liver in the high-dose group. Iron concentration was increased significantly ($p< 0.05$) in red blood cells, heart, kidney, liver and testes in the 1000 ppm group; elevated levels of iron concentration also were seen in the 500 ppm group. No significant effects were seen on body weights, mineral content and enzyme activity in the 100 ppm group in comparison with control levels. The 100 ppm (10 mg Ni/kg bw) is considered a NOAEL while 500 ppm (50 mg Ni/kg bw) is a LOAEL (Whanger, 1973).

Long-term Exposure

° Nickel added to the diet of mice resulted in reduced body weight gain in females at a dietary concentration of 1100 ppm nickel and reduced body weight gain in both males and females at 1600 ppm (Weber and Reid, 1969b).

° Studies in chicks (Weber and Reid, 1968a; Ling and Leach, 1979) and calves (O'Dell et al., 1970) have shown adverse effects at dietary levels ranging from 250 to 700 mg Ni/kg diet.

° Nickel (as nickel chloride) administered to rats at a concentration of 225 ppm in drinking water (17.6 mg Ni/kg bw) for four months led to a significant reduction in body weight ($p< 0.05$) compared with controls (Clary, 1975). Daily urinary volume and urinary zinc and calcium concentrations were reduced significantly. Also, at sacrifice, serum lipid and cholestrol concentrations were reduced significantly ($p< 0.05$).

- Daily doses of 25 mg/kg bw of nickel sulphate administered by oral intubation to male rats for 120 days caused degenerative cellular changes in the liver and kidney (von Waltschewa et al., 1972). In the treated rats, testes were smaller than in controls. Other testicular changes included interstitial cell proliferation, transparent vessel walls, reduced number of spermatozoa and their precursors and decreased concentrations of succinodehydrogenase and steroid 3-B-dehydrogenase.

- Rats fed a diet containing nickel acetate at concentrations of 0.1 to 10% (16.6-166 mg Ni/kg bw) for 10-190 days led to a high rate of mortality, hypoplasia of bone marrow, thymus and spleen, progressive renal tubular degeneration, mural exudative pulmonary alveolar lesions and noninflammatory lysis of pancreatic exocrine cells (Ashrof and Sybers, 1974).

- In a chronic study with mice fed a diet devoid of cadmium and low in other metals with 5 ppm nickel added to their drinking water (approximately 0.85 mg Ni/kg bw/day) no significant effects were observed. Only body weights of animals dying after one year were depressed by 4% to 13% over controls (Schroeder et al., 1964).

- The mean body weights of both male and female rats were reduced significantly ($p<0.025$) compared to controls at 18 months in a study where rats were administered 5 ppm nickel (average daily dose estimated to be 0.41 mg Ni/kg bw) in drinking water for life (Schroeder et al., 1974). Lifespan was not affected. Histopathology revealed an increased incidence ($p<0.025$) of focal myocardial fibrosis (13.3%) in the experimental group compared to the control.

- In a two-year feeding study with beagle dogs administered nickel sulfate hexahydrate at dietary levels of 0, 100, 1,000 or 2,500 ppm (0, 3, 29 or 70 mg Ni/kg bw), no significant effects on body weight, hematology, urinalysis, organ-to-body weight ratios or histopathology were noted at 100 or 1,000 ppm. At 2,500 ppm, body weight gain was depressed, hemoglobin and hematocrit values tended to be lower and kidney- and liver-to-body weight ratios were significantly higher ($p <0.05$). Pathological changes in the lungs and granulocytic hyperplasia of the bone also were noted in the high dose group. Based on these findings, the NOAEL from this study is 1,000 ppm (29 mg/kg bw) (Ambrose et al., 1976).

- In a two-year feeding study in rats given 0, 100, 1,000 or 2,500 ppm nickel sulfate in milk (0, 5, 50 and 125 mg Ni/kg bw), no significant effects were reported at 100 ppm (Ambrose et al., 1976). Body weight was reduced significantly ($p<0.05$) in both male and female rats fed 2,500 ppm nickel when compared with controls. At 1,000 ppm, body weight also was reduced in both sexes. Animals fed 1,000 or 2,500 ppm nickel diets had significantly higher ($p<0.05$) heart-to-body weight ratios and significantly lower liver-to-body weight ratios than controls. The 1,000 ppm (50 mg/kg bw) represents a LOAEL from this study and 100 ppm (5 mg/kg bw) is a NOAEL.

Reproductive Effects

- In a three-generation reproduction study in rats, nickel sulfate hexahydrate fed at levels of 0, 250, 500 or 1,000 ppm (0, 12.5, 25 or 50 mg Ni/kg/day) led to a slight decrease in adult body weight at mating and weaning in the 1000 ppm group over controls. Fertility, gestation, viability and lactation indices were not affected. The body weights of weanlings from the 1,000 ppm group were reduced in all generations. The incidence of stillborn pups was 19%, 12% and 15% in the F_{1a} and 4%, 20% and 25% in the F_1b generations in the 250, 500 and 1000 ppm groups, respectively, compared to 4% and 2% in the control F_{1a} and F_{1b} generations. Elevated incidence of fetal mortality was not observed in the F_2 and F_3 generations (Ambrose et al., 1976).

- In another three-generation reproduction study, rats were provided drinking water containing 5 ppm nickel (salt not specified, estimated total daily dose was 0.43 mg/kg) (Schroeder and Mitchener, 1971). Neonatal mortality was increased significantly ($p < 0.025$) in all generations of exposed rats compared to controls. The number of runts were increased significantly in the first ($p < 0.025$) and third ($p < 0.0001$) generations. Average litter size was reduced somewhat in the F_3 generation. In this study, the diet was found to be deficient in trace metals (particularly chromium).

- No significant differences were observed in the litter size and initial body weight of pups when male and female rats were fed diets containing 250, 500 or 1,000 ppm nickel (daily dose of 10, 20 or 40 mg Ni/kg bw) for 8 weeks before breeding and continuing through lactation (Phatak and Patwardhan, 1950).

Developmental Effects

- Transplacental transfer of nickel is well documented in laboratory animals (U.S.EPA, 1985).

- In a three-generation reproduction study in rats (Ambrose et al., 1976) (described above) no evidence of teratogenicity was seen in weanlings of rats fed nickel sulfate hexahydrate at levels of 0, 250, 500 or 1,000 ppm (0, 12.5, 25 or 50 mg Ni/kg/day).

Mutagenicity

- Nickel chloride was not mutagenic in *Escherichia coli* and *Bacillus subtilis* (U.S. EPA, 1985).

- Nickel chloride and nickel sulfate were mutagenic or weakly mutagenic in eukaryotic test systems (U.S. EPA, 1985).

- Nickel induced chromosomal aberrations in cultured mammalian cells and sister chromatid exchanges in both cultured mammalian cells and in human lymphocytes (U.S. EPA, 1985).

Carcinogenicity

- It has been demonstrated that the incidence of respiratory tract cancers in nickel refinery workers is statistically significantly elevated (NIOSH, 1977; IARC, 1976; NAS, 1975); these data are not, however, relevant to the consumption of nickel in drinking water.

- Repeated i.p. injections of nickel acetate at a dose of 360 mg/kg have induced lung carcinomas in mice (Stoner et al., 1976). This is not, however, relevant to the consumption of nickel in drinking water.
- No evidence of carcinogenicity has been found in those chronic studies in which nickel was administered orally to laboratory animals (Schroeder et al., 1964, 1974; Schroeder and Mitchner, 1975).

V. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

Health Advisories (HAs) are generally determined for One-day, Ten-day, Longer-term (approximately 7 years) and Lifetime exposures if adequate data are available that identify a sensitive noncarcinogenic end point of toxicity. The HAs for noncarcinogenic toxicants are derived using the following formula:

$$HA = \frac{(NOAEL \text{ or } LOAEL) \times (BW)}{(UF) \times (\_\_\_ \text{ L/day})} = \_\_\_ \text{ mg/L } (\_\_\_ \text{ ug/L})$$

where:

NOAEL or LOAEL = No- or Lowest-Observed-Adverse-Effect-Level in mg/kg bw/day.

BW = assumed body weight of a child (10 kg) or an adult (70 kg).

UF = uncertainty factor (10, 100 or 1,000), in accordance with NAS/ODW guidelines.

___ L/day = assumed daily water consumption of a child (1 L/day) or an adult (2 L/day).

One-day Health Advisory

The available data are insufficient to develop a One-day HA for nickel. It is recommended that the Ten-day HA of 1.0 mg/L be used as the One-day HA for the 10-kg child.

Ten-day Health Advisory

The study by Whanger (1973) has been selected for the derivation of a Ten-day HA. Dose-response relationships were observed in this 6-week dietary study defining a NOAEL for nickel of 100 ppm in diet (10 mg/kg bw/day) and a LOAEL of 500 ppm in diet (50 mg/kg bw/day). The biological endpoints included body weight gain, hematology parameters and cytochrome oxidase activity.

The Ten-day HA for Ni for a 10-kg child is calculated as follows:

$$\text{Ten-day HA} = \frac{(10 \text{ mg/kg/day})\ (10 \text{ kg})}{(1 \text{ L/day})\ (100)} = 1.0 \text{ mg/L } (1{,}000 \text{ ug/L})$$

where:

10 mg Ni/kg bw/day = NOAEL for absence of effects on weight gain, hematology parameters and cytochrome oxidase activity in rats following 6-week oral exposure.

10 kg = assumed body weight of a child.

100 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a NOAEL from an animal study.

1 L/day = assumed daily water consumption of a child.

Longer-term Health Advisory

The available data are insufficient to develop Longer-term HAs for nickel. It is recommended that the DWEL of 0.35 mg/L be used as the Longer-term HA for the 70-kg adult and the modified DWEL of 0.1 mg/L (adjusted for a 10-kg child) be used as the Longer-term HA for the 10-kg child.

The Agency is in the process of reviewing a draft report of a 90-day gavage study in rats (Mayhew, 1987). The final report is expected to be available in July or August, 1987. After the official final report has been reviewed and considered, it may serve as the basis for a longer-term health advisory.

Lifetime Health Advisory

The Lifetime HA represents that portion of an individual's total exposure that is attributed to drinking water and is considered protective of noncarcinogenic adverse health effects over a lifetime exposure. The Lifetime HA is derived in a three step process. Step 1 determines the Reference Dose (RfD), formerly called the Acceptable Daily Intake (ADI). The RfD is an estimate of a daily exposure to the human population that is likely to be without appreciable risk of deleterious effects over a lifetime, and is derived from the NOAEL (or LOAEL), identified from a chronic (or subchronic) study, divided by an uncertainty factor(s). From the RfD, a Drinking Water Equivalent Level (DWEL) can be determined (Step 2). A DWEL is a medium-specific (i.e., drinking water) lifetime exposure level, assuming 100% exposure from that medium, at which adverse, noncarcinogenic health effects would not be expected to occur. The DWEL is derived from the multiplication of the RfD by the assumed body weight of an adult and divided by the assumed daily water consumption of an adult. The Lifetime HA is determined in Step 3 by factoring in other sources of exposure, the relative source contribution (RSC). The RSC from drinking water is based on actual exposure data or, if data are not available, a value of 20% is assumed for synthetic organic chemicals and a value of 10% is assumed for inorganic chemicals. If the contaminant is classified as a Group A or B carcinogen, according to the Agency's classification scheme of

carcinogenic potential (U.S. EPA, 1986), then caution should be exercised in assessing the risks associated with lifetime exposure to this chemical.

Because of various problems with the two teratogenicity/reproductive toxicity studies of Schroeder and Mitchner (1971) and Ambrose et al., (1976), the two-year rat feeding study of Ambrose et al., (1976) is used for the derivation of the Lifetime HA. In this study, rats were given 0, 100, 1,000 or 2,500 ppm nickel sulfate (approximate daily dose was 0, 5, 50 or 125 mg Ni/kg bw) in their diet. No significant effects were reported at 100 ppm. Body weight was reduced significantly ($p < 0.05$) in both male and female rats fed 2500 ppm nickel compared to controls. At 1000 ppm also, the body weight was reduced for the male and female rats. The NOAEL identified in this study is 100 ppm (5 mg/kg bw).

Using this NOAEL, the Lifetime Health Advisory is derived as follows:

Step 1: Determination of the Reference Dose (RfD)

$$RfD = \frac{(5 \text{ mg/kg/day})}{(100)\ (5)} = 0.01 \text{ mg/kg/day}$$

where:

5 mg/kg/day = NOAEL for absence of effects on weight gain in rats.

100 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a NOAEL from an animal study.

5 = additional uncertainty factor selected to allow for possibly greater absorption of nickel from water than from the diet.

Step 2: Determination of the Drinking Water Equivalent (DWEL)

$$DWEL = \frac{(0.01 \text{ mg/kg/day})\ (70 \text{ kg})}{(2 \text{ L/day})} = 0.35 \text{ mg/L } (350 \text{ ug/L})$$

where:

0.01 mg/kg/day = RfD.

70 kg = assumed body weight of an adult.

2 L/day = assumed daily water consumption of an adult.

Step 3: Determination of the Lifetime Health Advisory

The DWEL of 350 ug/L assumes 100% of the exposure to nickel occurs via drinking water. The available data indicate that the estimated intake of nickel from food and air are 400 ug/day and 0.6 ug/day (negligible), respectively. Factoring in these data on human exposure, a Lifetime HA of 0.150 mg/L (150 ug/L) would result.

Evaluation of Carcinogenic Potential

- Nickel has not been shown to be carcinogenic through oral exposure. Data are not available concerning the potential carcinogenic effects of ingested nickel compounds in humans.

- A relative high degree of evidence exists to demonstrate that certain nickel compounds or mixtures of nickel compounds are carcinogenic to humans via inhalation. Nickel refinery dust and nickel subsulfide (which is believed to be the major nickel component of the refinery dust) are classified in Group A: Human carcinogen, based on the EPA final guidelines for assessment of carcinogen risk (U.S. EPA, 1986). In the case of nickel carbonyl, while there is insufficient evidence from epidemiological studies, there is sufficient evidence from animal studies to classify it in Group B2: Probable human carcinogen.

- Based upon an evaluation of the carcinogenic potential of nickel from inhalation and intramuscular injection, IARC has concluded that nickel and certain nickel compounds are group 2A chemicals (IARC, 1976). However, at the present time there is insufficient evidence to classify nickel as a carcinogen following oral exposure.

- Applying the criteria described in EPA's final guidelines for assessment of carcinogenic risk (U.S. EPA, 1986), nickel via inhalation or intramuscular injection may be classified in Group B: Probable human carcinogen. This category is for agents for which there is inadequate evidence from human studies and sufficient evidence from animal studies. However, as there are inadequate data to conclude that nickel is carcinogenic via ingestion, nickel is dealt with here as Group D: Not classifiable as to human carcinogenicity. This category is for agents with inadequate human and animal evidence of carcinogenicity.

VI. OTHER CRITERIA, GUIDANCE AND STANDARDS

- ACGIH (1983) has established a TWA-TLV of 1.0 mg Ni/m^3 for metallic nickel salts and 0.1 mg Ni/m^3 for soluble nickel salts.

- The NIOSH (1977) criterion for occupational exposure to nickel is a TWA of 15 ug Ni/m^3.

- EPA (U.S. EPA, 1980; 1982) derived an ADI of 1.46 mg Ni/day and established an ambient water quality criterion of 0.632 mg Ni/L.

VII. ANALYTICAL METHODS

- Determination of nickel is by atomic absorption (AA) using either direct aspiration into a flame (U.S. EPA, 1979b) or a furnace technique (U.S. EPA, 1979c).

- The direct aspiration AA procedure is a physical method based on the absorption of radiation at 232.0 nm by nickel. The sample is aspirated into an air-acetylene flame and atomized. A light beam is directed through the flame into a monochromator and onto a detector that measures the amount of light absorbed. Absorbance is proportional to the concentration of nickel in the sample. The detection limit is 40 ug/L using this procedure.

- The furnace AA procedure is similar to direct aspiration AA except a furnace, rather than a flame, is used to atomize the sample. The detection limit is 1 ug/L using this procedure.

VIII. TREATMENT TECHNOLOGIES

- Treatment techniques that may be capable of removing nickel from drinking water include lime softening, ion exchange and reverse osmosis. Conventional coagulation is moderately effective in removing nickel from drinking water. Although the removal of nickel from drinking water supplies by these technologies have not been extensively studied, some information is available from waste water technology surveys.

- Culp et al. (1978) reported excellent removal of nickel with lime softening, ranging from 90.9 to 99.9 percent, for wastewater with nickel concentrations from 5 mg/L to 160 mg/L. Maruyama et al. (1975) reported removal efficiencies of 95 percent with low lime softening (260 mg/L lime dosage) and 98 percent with high lime softening (600 mg/L dosage) from domestic wastewater containing 5 mg/L of nickel.

- Cation exchange has been used extensively in the plating industry to recover nickel. Normally, these operations have employed cation resins in the hydrogen cycle because of the need to recover both acid and metal for recycle. Nickel was eluted with sulfuric acid, 6 to 10 lb H_2SO_4/ft^3 of resin in 10 percent solution. The reported efficiencies of removing nickel from plating industry wastewater are 96 to 100 percent (Keramida and Etzel, 1982).

- Reverse osmosis (RO) membranes have been tested and shown to remove nickel effectively from source water. A laboratory scale study evaluating the performance of cellulose acetate membrane with plating rinse showed that cellulose acetate has a rejection efficiency for Ni^{+2} of 99.6 percent. Other membranes are commercially available: cellulose acetate butyrate, nylon hollow fibers, polyurethanes (Golomb, 1972). These membranes, however, have not been tested for their efficiencies to remove nickel. The cellulose acetate membrane was field tested on a small industrial automatic plating line. The wastewater nickel concentration was varied: 1,700 mg/L, 50 mg/L, 12 mg/L. Tests by Golomb (1974) have shown that cellulose acetate membrane can be used to remove effectively 99+ percent of nickel from the waste rinse streams.

- Pilot plant studies evaluating the efficiency of coagulation indicated that alum was only 25-45 percent effective to remove nickel from water (Maruyama et al., 1975; Hannah et al., 1977).

° Another study by Nillson (1978), investigating the removal of trace metals from tap water and municipal wastewater, determined the efficiency of calcium hydroxide proved to be 91.3 percent effective in removing nickel from tap water and 63.3 percent effective in removing nickel from wastewater at a pH of 9.5.

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March 31, 1987

NITRATE/NITRITE

Health Advisory
Office of Drinking Water
U.S. Environmental Protection Agency

I. INTRODUCTION

The Health Advisory (HA) Program, sponsored by the Office of Drinking Water (ODW), provides information on the health effects, analytical methodology and treatment technology that would be useful in dealing with the contamination of drinking water. Health Advisories describe nonregulatory concentrations of drinking water contaminants at which adverse health effects would not be anticipated to occur over specific exposure durations. Health Advisories contain a margin of safety to protect sensitive members of the population.

Health Advisories serve as informal technical guidance to assist Federal, State and local officials responsible for protecting public health when emergency spills or contamination situations occur. They are not to be construed as legally enforceable Federal standards. The HAs are subject to change as new information becomes available.

Health Advisories are developed for One-day, Ten-day, Longer-term (approximately 7 years, or 10% of an individual's lifetime) and Lifetime exposures based on data describing noncarcinogenic end points of toxicity. Health Advisories do not quantitatively incorporate any potential carcinogenic risk from such exposure. For those substances that are known or probable human carcinogens, according to the Agency classification scheme (Group A or B), Lifetime HAs are not recommended. The chemical concentration values for Group A or B carcinogens are correlated with carcinogenic risk estimates by employing a cancer potency (unit risk) value together with assumptions for lifetime exposure and the consumption of drinking water. The cancer unit risk is usually derived from the linear multistage model with 95% upper confidence limits. This provides a low-dose estimate of cancer risk to humans that is considered unlikely to pose a carcinogenic risk in excess of the stated values. Excess cancer risk estimates may also be calculated using the One-hit, Weibull, Logit or Probit models. There is no current understanding of the biological mechanisms involved in cancer to suggest that any one of these models is able to predict risk more accurately than another. Because each model is based on differing assumptions, the estimates that are derived can differ by several orders of magnitude.

This Health Advisory (HA) is based on information presented in the Office of Drinking Water's Health Effects Criteria Document (CD) for nitrate and nitrite (U.S. EPA, 1985). The HA and CD formats are similar for easy reference. Individuals desiring further information on the toxicological data base or rationale for risk characterization should consult the CD. The CD is available for review at each EPA Regional Office of Drinking Water counterpart (e.g., Water Supply Branch or Drinking Water Branch), or for a fee from the National Technical Information Service, U.S. Department of Commerce, 5285 Port Royal Rd., Springfield, VA 22161, PB #86-117959/AS. The toll-free number is (800) 336-4700; in the Washington, D.C. area: (703) 487-4650.

II. GENERAL INFORMATION AND PROPERTIES

CAS No.

- Potassium Nitrate -- 7757-79-1
  Potassium Nitrite -- 7758-09-0

Synonyms

- Potassium Nitrate: Saltpeter (Windholz, 1976)

Uses

Among other uses, nitrate and nitrite have a variety of uses including the following (U.S. EPA, 1985):

- The major use of nitrate is in inorganic fertilizers.
- Nitrate is used in the manufacture of explosives, glassmaking and as a heat-transfer fluid and a heat-storage medium for solar heating applications.
- Both nitrate and nitrite are used in curing meats.

Properties (Weast, 1974)

- The properties of nitrate and nitrite compounds vary with the specific compound; some examples are as follows:

	Potassium Nitrate	Potassium Nitrite
Chemical Formula	KNO_3	KNO_2
Molecular Weight	101.11	85.11
Physical State	solid	solid
Boiling Point	400°C (decomposes)	decomposes
Melting Point	334°C	440°C
Density	2.109 (16 C)	1.915
Vapor Pressure	--	--
Water Solubility (0°C)	13.3 g/100cc	281 g/100cc
Log Octanol/Water Partition Coefficient	--	--
Taste Threshold	--	--
Odor Threshold	--	--

Occurrence

- Nitrate and nitrite are naturally occurring inorganic ions which make up part of the nitrogen cycle. Wastes containing organic nitrogen enter the soil and are decomposed first to ammonia which is subsequently oxidized to nitrite and nitrate. Because nitrite is easily oxidized to form nitrate, nitrate predominates in ground and surface waters. Nitrate then is taken up by plants during their growth and converted back to organic form. Levels of nitrate in water can be raised as the result of the contamination by nitrogen containing fertilizers or human and animal wastes. Nitrate and nitrite ions are very mobile in soil and readily move with ground water (U.S. EPA, 1987).

- Surveys of naturally occurring levels of nitrate and nitrite in ground and surface water have found that levels normally do not exceed 1 to 2 mg/L for nitrate and 0.1 mg/L for nitrite. Surface waters generally contain lower levels of nitrate and nitrite than ground water. Nitrate has been included in a number of drinking water surveys. Nitrates occur at levels of less than 1 mg/L in most surface and ground water supplies. Nitrates occur at levels exceeding 5 mg/L in about 3% of surface waters and 6% of ground waters. Currently, 40 surface water supplies and 568 ground water supplies exceed the nitrate MCL of 10 mg/L. Systems which exceed the MCL are usually contaminated by nitrates from the use of fertilizers or from animal wastes or septic systems. Nitrite levels have not been surveyed in drinking water supplies but are expected to be much lower than 1 mg/L (U.S. EPA, 1987).

- Nitrates occur naturally in a number of foods, particularly vegetables. Nitrates also are added to meat products as a preservative. For adults, the major source of nitrates appears to be from dietary sources. For infants, water appears to be the major source of exposure (U.S. EPA, 1987).

III. PHARMACOKINETICS

Absorption

Both nitrate and nitrite are readily and completely absorbed following oral administration:

- Nitrate is absorbed by active transport from the upper small intestine and nitrite is absorbed by diffusion across the gastric mucosa and also through the wall of the intestinal tract (U.S. EPA, 1985).

- Following oral administration, both nitrate and nitrite are readily and completely absorbed: both $^{13}NO_3^-$ and $^{13}NO_2^-$ were completely absorbed within ten minutes after administration of 10 to 100 mg/kg in mice (Parks et al., 1981). Similar results for nitrate (dose not specified) in rats were reported by Witter et al. (1979).

Distribution

Both nitrate and nitrite readily distribute throughout the tissues but do not bioaccumulate:

- Rapid, homogeneous distribution of nitrate (dose unspecified) was observed in rats 45 to 60 minutes after dosing by gavage (Witter et al., 1979).
- Both $^{13}NO_3^-$ and $^{13}NO_2^-$ achieved transient equilibrium in mice within five minutes after intratracheal administration of 10 to 100 mg/kg (Parks et al., 1981). Equilibrium between the intravascular and extravascular compartments of rabbits was reached within five minutes after injection of either radiochemical into rabbits.
- Nitrate secretion in saliva by humans was reported by Spiegelhalder et al. (1976) after ingestion of vegetables and vegetable juices. Secretion of nitrate by the gastric mucosa in rats was observed by Bloomfield et al. (1962) following intraperitoneal doses of sodium nitrate ranging from 60 to 200 mg/kg.
- In rats, nitrite has been shown to cross the placenta (Shuval and Greuner, 1977).
- No evidence was found for bioaccumulation of nitrate or nitrite in any tissue (U.S. EPA, 1985).

Metabolism

While nitrate is not directly metabolized to other compounds in humans, nitrate is metabolized by bacteria in humans - particularly infants - to nitrite which, by reacting with hemoglobin, can markedly decrease the ability of blood to carry oxygen to the tissues:

- While there is no evidence that mammals metabolize nitrate into other compounds (Parks et al.,1981), the bacteria found in human saliva and the stomach can reduce nitrate to nitrite (U.S. EPA, 1985).
- Due to decreased acidity (increased pH), particularly in the stomach of the bottle-fed infant, bacteria capable of reducing nitrate to nitrite may proliferate in the stomach thus leading to an increased formation of nitrite in infants 3 months old or less (U.S. EPA, 1985).
- Nitrite reacts with the hemoglobin (the chemical responsible for the ability of blood to transport oxygen to the tissues) in erythrocytes to form methemoglobin which is unable to transport oxygen (Parks et al., 1981).
- The enzyme methemoglobin reductase converts methemoglobin to hemoglobin and nitrate, thus, reversing the process induced by nitrite (Smith and Beutler, 1966).
- Bacteria in the saliva reduce 5% of absorbed nitrate into nitrite (Spiegelhalder et al.,).

In animals:

- Gruener et al. (1973) observed that the activity of methemoglobin reductase in rat fetuses was nearly ten times higher than that of adult rats.

- Nitrite in the stomach can react with secondary amines and other amine substrates to form N-nitroso compounds that may be oncogenic (Sander et al., 1968; Oshima and Bartsch, 1981). Vitamin C and vitamin E can inhibit the formation of nitrosamines (Archer et al., 1975; Kamm et al., 1977).

Excretion

- Nitrate is readily excreted by the kidneys (U.S. EPA, 1985).

- In humans, about 25% of the nitrate absorbed is secreted in saliva (Spiegelhalder et al., 1976).

- While it has been suggested that appreciable amounts of nitrate are eliminated in human (Donahoe, 1949) and cows milk (Davison et al., 1964), there are inadequate data to support this conclusion.

- The half-life for elimination of nitrite in dogs, sheep and Shetland ponies (0.5-0.6 hrs) is too rapid to be accounted for by renal excretion, thus suggesting that metabolism may be significant (Schneider and Yeary, 1975).

IV. HEALTH EFFECTS

Humans

- The lethal dose of potassium nitrate for an adult ranges from 54 to 462 mg/kg; the lethal dose of sodium nitrite ranges from 32 to 154 mg/kg (Burden, 1961).

- The toxicity of nitrate in humans is due to the reduction of nitrate to nitrite. By reacting with hemoglobin, nitrite forms methemoglobin which will not transport oxygen to the tissues and thus can lead to asphyxia (see Metabolism, above) (U.S. EPA, 1985).

- The normal methemoglobin level in humans has been shown to range between 1 and 2% (Shuval and Greuner, 1977). A level greater than 3% is defined as methemoglobinemia. However, there is a consistent elevation of the methemoglobin concentration in pregnant women from the 14th week through delivery (Skrivan, 1971).

- Walton (1951) published a survey by the American Public Health Association which found that more than 278 cases of cyanosis in infants were associated with nitrate-contaminated water. No cases of cyanosis in infants were associated with water containing 10 mg/L or less of nitrate-nitrogen. See also the discussion under Ten-day HA, below.

- Winton et al. (1971) compared methemoglobin levels with nitrate ion intake in 111 infants younger than six months old. Only three infants had methemoglobin levels above 2.9%. They were the youngest of five infants who had received more than 10 mg/kg/day of nitrate ion.

- Craun et al. (1981) conducted an epidemiologic study of 102 children aged one to eight years in Washington County, Illinois. Of the study subjects, 64 consumed water with high nitrate levels (22 to 111 mg/L nitrate-nitrogen) and 38 consumed water with low nitrate levels (less than 10 mg/L nitrate-nitrogen). Ingestion of water containing 22 to 111 mg/L nitrate-nitrogen did not produce abnormal mean methemoglobin levels and was not related to increased methemoglobin levels in comparison to controls. See also the discussion under Ten-day HA, below.

- Hegesh and Shiloah (1982) demonstrated that nitrites were synthesized in infants with acute diarrhea. See also the discussion under Ten-day HA, below.

- In pregnant woman, the level of methemoglobin increases from the normal methemoglobin level (between 0.5 and 2.5% of total hemoglobin) to a maximum, 10.5%, at the 30th week of pregnancy and subsequently declines to normal after delivery (Skrivan, 1971). Thus, pregnant women may be more sensitive to the induction of clinical methemoglobinemia by nitrite at approximately the 30th week of pregnancy.

Animals

Short-term Exposure

- In the rabbit and rat, acute oral LD_{50} values for potassium nitrate of 1,166 mg/kg and 1,986 mg/kg, respectively, have been reported (Windholz, 1976; WHO, 1962). The acute oral LD_{50} of sodium nitrate in the rabbit has been reported to be 1,955 mg/kg (Windholz, 1976).

- In the rat, reported acute oral LD_{50} values for sodium nitrate range from 46 to 120 mg/kg (Druckery et al., 1963; Imaizumi et al., 1980; Windholz, 1976; WHO, 1962).

- Unlike humans, in which nitrite toxicity relates to the formation of methemoglobin (see Metabolism, above), the immediate toxic effect of nitrite in some species (e.g. the horse) is due to nitrite induced vasodilation which results in cardiovascular collapse and shock (U.S. EPA, 1985).

- In a three week mouse drinking water study, elevated methemoglobin levels were observed in 50-day-old mice administered nitrite ion (as sodium nitrite) at levels of 133 and 178 mg/kg/day but not at 88 mg/kg/day (Shuval and Greuner, 1977).

Long-term Exposure

- In a six month rat feeding study, 2,500 mg nitrate/kg/day produced a marked diuretic effect within two months when compared with rats fed

equimolar levels of sodium chloride; 250 mg nitrate/kg/day caused no diuresis and is identified as the NOAEL in this study (Fritsch et al., 1980).

- In a six month rat feeding study, both 250 and 2,500 mg nitrate/kg/day as well as 25 and 250 mg nitrite/kg/day induced hemorrhagic areas in the spleen (Fritsch et al. , 1980). Therefore, 250 mg nitrate/kg/day and 25 mg nitrite/kg/day are identified as LOAELs in this study.

- Two long-term studies using ICR mice reported increases in amyloidosis (starchy deposits) and hemosiderosis after ingestion of very high doses of sodium nitrate (2,500 and 5,000 mg nitrate/kg/day: Sugiyama et al., 1979) and sodium nitrite (208, 416 and 833 mg nitrite/kg/day: Inai, et al., 1979). LOAELs of 2,500 mg nitrate/kg/day and 208 mg nitrite/kg/day can be identified from the results of these studies.

Reproductive Effects

- In a developmental toxicity study reported by Globus and Samuel (1976) (described below) no evidence of sodium nitrite-induced adverse reproductive effects was observed.

Developmental Effects

- Groups of mice were intubated with sodium nitrite at 16.7 mg/kg/day on days 0 through 14, 16 or 18 of gestation (Globus and Samuel, 1978). Analysis of fetal livers indicated that maternally administered sodium nitrite stimulated fetal hepatic erythropoiesis. No evidence of a nitrite related effect upon fetal mortality, resorptions, mean weight, number of offspring or incidence of skeletal malformation was observed.

- The nitrosation of amides or amines in the stomach produces N-nitroso compounds which may pass through the placenta to exert teratogenic or fetotoxic effects (Ivankovic, 1979; Teramoto et al., 1980).

Mutagenicity

- Both sodium nitrite and sodium nitrate were negative in host-mediated assays in mice (FDA, 1972a and b). Other host mediated assays did not find sodium nitrite to be mutagenic in mice (Couch and Friedman, 1975) or in either rats or mice (Whong et al., 1979).

- Dominant lethal gene tests in rats were negative for both sodium nitrate and nitrite (FDA, 1972a and b); a cytogenetic assay in rat bone marrow cells was also negative for both compounds.

- Kodama et al. (1976) reported that sodium nitrite induced mutations to azaquanine resistance in cultured FM3A cells (a C3H mouse mammary carcinoma cell line). Sodium nitrite was mutagenic in Salmonella typhimurium (FDA, 1972a,b) and E. coli Sd-4 (Hussain and Ehrenberg, 197).

Carcinogenicity

- It was judged (U.S. EPA, 1985) that the available animal studies (Newberne 1978, 1979; Maekawa et al., 1982) provided inconclusive evidence regarding the carcinogenicity of nitrate and nitrite administered orally in the absence of nitrosatable compounds .

- Many studies have documented carcinogenesis (adult and prenatal) in which both nitrite and nitrosatable compounds were orally administered to animals (NAS, 1981); tumors were induced in many organs including the stomach, esophagus and nasal cavity.

- More than 120 N-nitroso compounds have been tested for carcinogenicity and greater than 75% of these compounds have been shown to be carcinogenic (Shank and Magee, 1981). These compounds have been demonstrated to be carcinogenic in at least 22 species and carcinogenic transplacentally in at least five species (Schmahl and Habs, 1980). All species tested have shown tumor formation following treatment with at least one of the N-nitroso compounds tested. Tumors have been induced in every organ and tissue and most cell types. While organ specificity is observed within a species even after administration by different routes, clear differences in target tissue have been noted between species (Lijinsky et al., 1975).

V. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

Health Advisories (HAs) are generally determined for One-day, Ten-day, Longer-term (approximately 7 years) and Lifetime exposures if adequate data are available that identify a sensitive noncarcinogenic end point of toxicity. The HAs for noncarcinogenic toxicants are derived using the following formula:

$$HA = \frac{(NOAEL \text{ or } LOAEL) \times (BW)}{(UF) \times (\_\_\_ \text{ L/day})} = \_\_\_ \text{ mg/L } (\_\_\_ \text{ ug/L})$$

where:

NOAEL or LOAEL = No- or Lowest-Observed-Adverse-Effect-Level in mg/kg bw/day.

BW = assumed body weight of a child (10 kg) or an adult (70 kg).

UF = uncertainty factor (10, 100 or 1,000), in accordance with NAS/ODW guidelines.

___ L/day = assumed daily water consumption of a child (1 L/day) or an adult (2 L/day).

The available data suggest that calculation of the HA values for nitrate/nitrite should:

- Recognize the newborn infant as the population group at greatest risk

- Recognize and consider the conversion of orally ingested nitrate to nitrite.

- Utilize human data wherever possible due to the extreme species variation (both quantitative and qualitative) observed in nitrate and nitrite toxicity.

HA values are presented below for a 4-kg infant (assumed to consume 0.64 L of formula per day) and a 70-kg adult. Normally, HAs are determined for the 10-kg child and the 70-kg adult. However, newborn infants (assumed to weigh 4 kg) are the population subgroup at greatest risk and thus HAs are provided for the 4-kg infant.

While no separate HAs for the 10 kg child are provided, the HAs for the 70-kg adult will be protective for all age groups other than the 4-kg infant, in that they are based upon data obtained in children (Craun et al., 1981).

Nitrate is toxic because it is converted to nitrite and thus the toxicity of nitrate and nitrite must be additive. Thus, nitrate and nitrite cannot be considered independently. Each HA is presented in terms of both mg nitrate-nitrogen/L drinking water and mg nitrite-nitrogen/L drinking water. Appropriate use of these values requires information on both the nitrate and nitrite content of drinking water so that a total "effective" nitrate concentration can be calculated and used as follows :

- The "effective" nitrate-nitrogen concentration (mg/L) for all age groups is equal to nitrate-nitrogen + 10x nitrite-nitrogen.

- The "effective" nitrate-nitrogen concentration (mg/L) should not exceed the appropriate nitrate standard for the appropriate group (4-kg infant or 70-kg adult) or exposure period.

One-day Health Advisory

The available data are insufficient to develop One-day HAs for nitrate and nitrite. The Ten-day HA should be protective of one-day exposures.

Ten-day Health Advisory

Populations other than the 4-kg infant:

Craun et al. (1981) conducted an epidemiologic study of 102 children aged one to eight years in Washington County, Illinois. Of the study subjects, 64 consumed water with high nitrate levels (22 to 111 mg/L nitrate-nitrogen) and 38 consumed water with low nitrate levels (less than 10 mg/L nitrate-nitrogen). Ingestion of water containing 22 to 111 mg/L nitrate-nitrogen did not result in abnormal mean methemoglobin levels and was not related to increased methemoglobin levels in comparison to controls. In the entire study group of 102 children, only five had methemoglobin levels greater than 2% (maximum of 3.1% in a child from the low exposure group).

For a 70-kg adult and all age groups other than the 4-kg infant, the Ten-day nitrate HA value is 111 mg/L nitrate-nitrogen, the NOAEL observed by

Craun et al. (1981). Since the study was based on observations in humans and since the most sensitive subgroup (i.e., infants) is considered separately, no uncertainty factor has been employed in deriving the Ten-day nitrate HA from the NOAEL.

There are no studies that provide a direct measure of the NOAEL for nitrite in children. The Ten-day nitrite HA for a 70 kg adult and all other age groups other than the 4 kg infant can be calculated from the NOAEL for nitrate, assuming 10% conversion of nitrate to nitrite, as follows:

$$(111 \text{ mg/L nitrate-nitrogen})(0.10) = 11 \text{ mg/L nitrite-nitrogen}$$

where:

111 mg/L = NOAEL for nitrate based on the absence of methemoglobinemia in children.

0.10 = assumed 10% conversion of nitrate to nitrite by 10-kg child.

For a 4-kg infant:

Walton (1951) published a survey by the American Public Health Association which found more than 278 cases of cyanosis in infants that were definitely associated with consumption of nitrate-contaminated water by the infant or the nursing mother. No cases associated with water containing 10 mg/L or less of nitrate-nitrogen were found. As previously noted, Hegesh and Shiloah (1982) demonstrated that nitrites were synthesized in infants with acute diarrhea. Nitrites are responsible for methemoglobinemia and thus it is possible that infants with diarrhea may be the population most sensitive to the toxic effects of both nitrate and nitrite. As diarrhea is relatively common in infants, it is believed that at least some of the infants noted in Walton (1951) had diarrhea (U.S. EPA, 1985). Thus it was concluded that Walton (1951) could serve as a basis for the protection of all infants including those with diarrhea.

Based on the previous discussion, the Ten-day nitrate HA for 4-kg infants is 10 mg/L nitrate-nitrogen, the NOAEL for methemoglobinemia observed by Walton (1951). Studes by Donahoe (1949), Winton, et al. (1971) and Toussaint and Wurkert (1982) support this HA.

No study provides a direct measure of the NOAEL for nitrite in infants. However, the Ten-day nitrite HA for the 4-kg infant can be calculated from the NOAEL for nitrate as follows:

$$\frac{(10 \text{ mg/L nitrate-nitrogen})(100\%)}{10} = 1 \text{ mg/L nitrite-nitrogen}$$

where:

10 mg/L = NOAEL for nitrate-nitrogen based on the absence of methemoglobinemia in infants.

100% = assumed 100% conversion of nitrate to nitrite by 4-kg infant.

10 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with data from a study in humans.

Longer-term Health Advisory

The available data are insufficient to develop Longer-term HAs for nitrate and nitrite. However, for both nitrate and nitrite, it is judged that the Ten-day HA for the 4-kg infant will offer protection against the formation of methemoglobin induced by the ingestion of either nitrate or nitrite in all age groups.

Lifetime Health Advisory

The Lifetime HA represents that portion of an individual's total exposure that is attributed to drinking water and is considered protective of noncarcinogenic adverse health effects over a lifetime exposure. The Lifetime HA is derived in a three step process. Step 1 determines the Reference Dose (RfD), formerly called the Acceptable Daily Intake (ADI). The RfD is an estimate of a daily exposure to the human population that is likely to be without appreciable risk of deleterious effects over a lifetime, and is derived from the NOAEL (or LOAEL), identified from a chronic (or subchronic) study, divided by an uncertainty factor(s). From the RfD, a Drinking Water Equivalent Level (DWEL) can be determined (Step 2). A DWEL is a medium-specific (i.e., drinking water) lifetime exposure level, assuming 100% exposure from that medium, at which adverse, noncarcinogenic health effects would not be expected to occur. The DWEL is derived from the multiplication of the RfD by the assumed body weight of an adult and divided by the assumed daily water consumption of an adult. The Lifetime HA is determined in Step 3 by factoring in other sources of exposure, the relative source contribution (RSC). The RSC from drinking water is based on actual exposure data or, if data are not available, a value of 20% is assumed for synthetic organic chemicals and a value of 10% is assumed for inorganic chemicals. If the contaminant is classified as a Group A or B carcinogen, according to the Agency's classification scheme of carcinogenic potential (U.S. EPA, 1986), then caution should be exercised in assessing the risks associated with lifetime exposure to this chemical.

No suitable studies for calculation of a Lifetime Health Advisory were located. However, for both nitrate and nitrite, it is judged that the Ten-day HA for the 4-kg infant (10 mg/L nitrate-nitrogen and 1 mg/L nitrite-nitrogen) will offer protection against the formation of methemoglobin induced by the ingestion of either nitrate or nitrite in all age groups.

As previously discussed, the 4-kg infant is the most sensitive member of the population with respect to the formation of methemoglobin induced by either nitrite directly or by the in vivo reduction of nitrate to nitrite.

In addition, as the 4-kg infant ages, e.g., to a 10-kg child, the sensitivity to the effects of methemoglobin as well as the amount of nitrate reduced to nitrite decrease, thus rendering the older child and the adult less sensitive to the effects of both nitrate and nitrite. Thus, it has been concluded that the Ten-day HA for the 4-kg infant for both nitrate and nitrite (10 mg/L nitrate-nitrogen and 1 mg/L nitrite-nitrogen) will offer adequate protection against methemoglobin formation in all other age groups as well.

Evaluation of Carcinogenic Potential

- A number of animal studies provided inconclusive evidence regarding the carcinogenicity of nitrate and nitrite administered in the absence of nitrosatable compounds (U.S. EPA, 1985).

- Applying the criteria described in EPA's guidelines for assessment of carcinogenic risk (U.S. EPA, 1986), both nitrate and nitrite may be classified in Group D: Not classified. This category is for agents with inadequate animal evidence of carcinogenicity.

VI. OTHER CRITERIA, GUIDANCE AND STANDARDS

- The interim Maximum Contaminant Level for nitrate-nitrogen is 10 mg/L (U.S. EPA, 1976b).

- The U.S. Public Health Service recommended a limit of 10 mg/L nitrate-nitrogen or 45 mg/L nitrate ion (U.S. PHS, 1962).

- The Committee on Water Quality Criteria of the National Academy of Sciences recommended that nitrate-nitrogen concentration in public water supplies not exceed 10 mg/L and nitrite-nitrogen not exceed 1 mg/L (NAS, 1972).

- The EPA Quality Criteria for Water (U.S. EPA, 1976a) suggested that the maximum concentrations of nitrate-nitrogen and nitrite-nitrogen in domestic water supplies not exceed 10 mg/L and 1 mg/L, respectively.

VII. ANALYTICAL METHODS

- Determination of nitrite alone, or nitrite and nitrate combined, is by colorimetry or spectrophotometry (U.S. EPA, 1979a;b). In these methods, a sample is passed through a column containing granulated copper-cadmium to reduce nitrate to nitrite. The nitrite (that which was originally present plus reduced nitrate) is determined by diazotizing with sulfanilamide and coupling with N-(1-naphthyl)-ethylenediamine dihydrochloride to form a highly colored azo dye which then is measured colorimetrically or spectrophotometrically. Separate, rather than combined, nitrate-nitrite values are obtained by carrying out the procedure first with, and then without, the copper-cadmium reduction step. The applicable range of the colorimetric and spectrophotometric methods is 0.05 to 10 mg/L nitrate-nitrogen and 0.01 to 1 mg/L nitrite-nitrogen, respectively.

- An alternative reduction procedure may be used (U.S. EPA, 1979c). In this method, nitrate is reduced to nitrite with hydrazine sulfate. The applicable range of this method is 0.01 to 10 mg/L.

VIII. TREATMENT TECHNOLOGIES

- Ion exchange and reverse osmosis are the practical methods currently in use to remove nitrates from water. Conventional coagulation and lime softening are not effective treatment methods for the removal of this contaminant (U.S. EPA, 1977; Laverentz, 1974).

- The application of ion exchange resins for nitrate removal has a well established history and is recognized as a practical treatment for drinking water systems (U.S. EPA, 1977; Gillies, 1978; Sorg, 1978; Sorg, 1980).

- Laboratory experiments and pilot plant studies have shown that some strong base and weak base ion exchange resins are nitrate selective and can reduce the nitrate concentration from as high as 50 mg/L (as N) to 0.5 mg/L (Holzmacher, 1971; Gregg, 1973; Korngold, 1973; Gaundett, 1975; Kuelow et al., 1975). One full-scale ion exchange plant has been operating successfully on Long Island, New York, since 1974. This plant lowers the nitrate level of 20-30 mg/L in the raw water to 0.5 mg/L. The finished water is a blend of treated and raw water and contains about 5 mg/L of nitrate (as N). Other installations removing nitrate include a 40,000 gpd plant at Curryville, Pennsylvania and the 2,500 gpd plant in the Virgin Islands.

- An important feature of the commercial nitrate ion exchange resin is that nitrate is not the most preferred ion in the exchange but rather the sulfate ion. However, field studies by Guter (1982) in McFarland, California have shown that nitrates can be removed effectively in the presence of sulfates as high as 380 mg/L.

- Although reverse osmosis (RO) systems have not been installed to remove specifically nitrates, removal efficiencies of 67 to 95% (high pressure) have been demonstrated. There are two plants currently operating which can provide data on nitrate removal. Laverentz (1974) reported that in Greenfield, Iowa, nitrate is reduced from 0.2 mg/L NO_3-N to 0.014 ng/L NO_3-N. In San Diego Country Estates, Romona, California, the nitrate is reduced from 12.4 mg/L NO_3-N to 4.2 mg/L NO_3-N. However, there are considerable experimental field data obtained when cellulose acetate was the only commercial membrane as well as more recent field tests that indicate nitrate rejection ranges for cellulose acetate membranes from 70 to 80% (Sourirajan, 1977), 80 to 90% (Metcalf and Eddy, Inc., 1979), and 58 to 86% (Weber, 1972).

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