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STATUS REPORT ON THE DEVELOPMENT OF DRAFT MCLGs FOR DISINFECTANTS AND BY-PRODUCTS

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How MCLGs Are Developed

MCLGs are set at concentration levels at which no known or anticipated adverse health effects occur, allowing for an adequate margin of safety. Establishment of an MCLG for each specific contaminant depends on the evidence of carcinogenicity from drinking water exposure or the Agency's oral Reference dose (RfD) based on noncarcinogenic data.

The cancer classification for a specific chemical and the RfD are adopted by two different Agency groups. Decisions on cancer classifications are made by the Cancer Risk Assessment Verification Endeavor (CRAVE) Work Group, which is composed of representatives of various EPA program offices. Decisions on EPA RfDs (using non-cancer endpoints only) are made through the Agency RfD work group, also composed of representatives of various EPA program offices. Decisions by CRAVE and the RfD groups represent consensus on risk assessments for the Agency and can be used by the respective regulatory programs as the basis for regulatory decisions. Summaries of the decisions by these two groups are available through the Agency's Integrated Risk Information System (IRIS). This system can be accessed by the public by contacting Mike McLaughlin of DIALCOM, Inc. at 202-488-0550.

The oral RfD (expressed in mg/kg/day) is an estimate, with uncertainty spanning perhaps an order of magnitude, of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious health effects during a lifetime. The RfD is derived from a no- or lowest-observed-adverse-effect level (called a NOAEL or LOAEL, respectively) that has been identified from a subchronic or chronic study of humans or animals. The NOAEL or LOAEL is then divided by an uncertainty factor(s) to derive the RfD.

Uncertainty factors are used in order to estimate the comparable "no-effect" level for a large heterogenous human population. The use of uncertainty factors accounts for intra- and inter-species differences in response to toxicity, the small number of animals tested compared to the size of the population, sensitive subpopulations and the possibility of synergistic action between chemicals (see 52 FR 25690 for further discussion on the use of uncertainty factors).

The use of an uncertainty factor (UF) is important in the derivation of the RfD. EPA has established certain guidelines (shown below) to determine how to apply uncertainty factors when establishing an RfD [USEPA, 1986].

Uncertainty Factors (UFs)

- Use a 1- to 10-fold factor when extrapolating from valid experimental results from studies using prolonged exposure to average healthy humans. This factor is intended to account for the variation in sensitivity among the members of the human population.

- Use an additional 10-fold factor when extrapolating from valid results of long-term studies on experimental animals when results of studies of human exposure are not available or are inadequate. This factor is intended to account for the uncertainty in extrapolating animal data to the case of humans.

- Use an additional 10-fold factor when extrapolating from less than chronic results on experimental animals when there are no useful long-term human data. This factor is intended to account for the uncertainty in extrapolating from less than chronic NOAELs to chronic NOAELs.

- Use an additional 10-fold factor when deriving an RfD from a LOAEL instead of a NOAEL. This factor is intended to account for the uncertainty in extrapolating from LOAELs to NOAELs.

An additional uncertainty factor may be used according to scientific judgment when justified.

- Use professional judgment to determine another uncertainty factor (also called a modifying factor, MF) that is greater than zero and less than or equal to 10. The magnitude of the MF depends upon the professional assessment of scientific uncertainties of the study and data base not explicitly treated above, e.g., the completeness of the overall data base and the number of species tested. The default value for the MF is 1.

From the RfD, a drinking water equivalent level (DWEL) is calculated. The DWEL represents a lifetime exposure concentration to a drinking water contaminant at which adverse non-cancer health effects are not expected to occur. The DWEL is calculated by multiplying the RfD by an assumed adult body weight (generally 70 kg) and then dividing by an average daily water consumption of 2 liters per day [NAS, 1977]. The DWEL assumes the total daily exposure to a substance is from drinking water exposure. The MCLG is determined by multiplying the DWEL by the percentage of the total daily exposure expected to be contributed by drinking water, called the relative source contribution (RSC). Generally, EPA assumes that the RSC from drinking water is 20 percent of the total exposure, unless other exposure data for the chemical are available [see 54 FR 22069 and 56 FR 3535].

Actual RSC's are calculated, when adequate data are available, between 20 and 80 percent.

The Agency is presently reviewing the RSC policy and the assumptions used in deriving an RSC. [The Agency's Science Advisory Board will review RSC issues during 1993.] Of critical importance is the issue of whether to incorporate contributions from air exposures into the RSC calculation given the fact that RfDs, which form the basis of DWELs and MCLGs, are all based on oral exposures. In this document, ambient air exposures have not been factored into the RSC.

The calculation below expresses the derivation of the MCLG:

$$\text{RfD} = \frac{\text{NOAEL or LOAEL}}{\text{uncertainty factor(s)}} = \text{mg/kg body weight/day}$$

$$\text{DWEL} = \frac{\text{RfD x body weight}}{\text{daily water consumption in l/day}} = \text{mg/L}$$

MCLG = DWEL x drinking water contribution = mg/L
(rounded to one significant figure)

For chemicals suspected to be carcinogenic to humans, the assessment for non-threshold toxicants consists of the weight of evidence of carcinogenicity in humans, using bioassays in animals and human epidemiological studies as well as information that provides indirect evidence (i.e., mutagenicity and other short-term test results). The objectives of the assessment are to determine the level or strength of evidence that the substance is a carcinogen and to provide an upperbound estimate of the possible risk of human exposure to the substance in drinking water. A summary of EPA's general carcinogen classification scheme is [USEPA, 1986]:

<u>Group A</u> -- Human carcinogen based on sufficient evidence from epidemiological or other human studies.

<u>Group B</u> -- Probable human carcinogen based on limited evidence of carcinogenicity in humans (Group B1) or based on sufficient evidence in animals with inadequate or no data in humans (Group B2).

<u>Group C</u> -- Possible human carcinogen based on limited evidence of carcinogenicity in animals in the absence of human data.

<u>Group D</u> -- Not classifiable based on lack of data or inadequate evidence of carcinogenicity from animal data.

<u>Group E</u> -- No evidence of carcinogenicity for humans (no evidence for carcinogenicity in at least two adequate animal tests in different species or in both epidemiological and animal studies).

EPA follows a three-category approach in developing MCLGs for drinking water contaminants (Table 1).

TABLE 1. EPA'S THREE-CATEGORY APPROACH FOR ESTABLISHING MCLGs

Category	Evidence of Carcinogenicity via Drinking Water	MCLG Approach
I	Strong evidence considering weight of evidence, pharmacokinetics, potency and exposure route	Zero
II	Limited evidence considering weight of evidence, pharmacokinetics, potency and exposure route	RfD approach with added safety margin of 1 to 10 or 10^{-5} to 10^{-6} cancer risk range
III	Inadequate or no animal evidence	RfD approach

Each chemical is evaluated for evidence of carcinogenicity from drinking water. For volatile contaminants, inhalation data are also considered. EPA takes into consideration the overall weight of evidence for carcinogenicity, pharmacokinetics, potency and exposure route.

EPA's policy is to set MCLGs for Category I contaminants at zero. The MCLG for Category II contaminants is calculated by using the RfD approach with an added margin of safety to account for possible cancer effects. If adequate data are not available to calculate an RfD, then the MCLG is based on a cancer risk range of 10^{-5} to 10^{-6}. MCLGs for Category III contaminants are calculated using the RfD approach.

Category I contaminants are those for which EPA has determined that there is strong evidence of carcinogenicity from drinking water. The MCLG for Category I contaminants is set at zero because it is assumed, in the absence of other data, that there is no threshold for carcinogenicity. In the absence of route specific data (e.g., oral) on the potential cancer risk from drinking water exposure, chemicals classified as Group A or B carcinogens are generally placed in Category I.

Category II contaminants include those contaminants which EPA has determined that there is limited evidence of carcinogenicity from drinking water considering weight of evidence, pharmacokinetics, potency and exposure. In the absence of route specific data, chemicals classified in Group C are generally placed in Category II. For Category II contaminants, two options are used to set the MCLG. The first option sets the MCLG based upon noncarcinogenic endpoints of toxicity (the RfD), then applying an additional safety factor of 1 to 10 to the MCLG to account for possible carcinogenicity. The second option is to set the MCLG based upon a theoretical lifetime excess cancer risk range of 10^{-5} to 10^{-6} using a conservative mathematical extrapolation model. EPA generally uses the first option; however, the second approach is used when valid noncarcinogenic data are not available to calculate an RfD and adequate experimental data are available to quantify the cancer risk.

Category III contaminants include those contaminants for which there is inadequate evidence of carcinogenicity from drinking water. If there is no additional information to consider, contaminants classified as Group D or E chemicals are generally placed in Category III. For these contaminants, the MCLG is established using the RfD approach.

Development of MCLGs for Disinfectants and By-Products
Chlorine, hypochlorite ion and hypochlorous acid

Chlorine (CAS # 7782-50-5) hydrolyses in water to form hypochlorite (CAS # as sodium salt 7790-92-3) and hypochlorous acid (CAS # 7681-52-9). Because of their oxidizing characteristic and solubility, chlorine and hypochlorites are used in water treatment to disinfect drinking water, sewage and wastewater, swimming pools and other types of water reservoirs. They are also used for general sanitation and control of bacterial odors in the food industry.

Chlorine is a highly reactive species and water soluble species. The fate, transport, and distribution of chlorine in natural waters is not well understood. Much of the available information comes from the addition and oxidation reactions with inorganic and organic compounds known to occur in aqueous solutions. Factors such as reactant concentrations, pH, temperature, salinity and sunlight influence these reactions.

Occurrence and Human Exposure

Chlorine exposures from swimming pools and hot tubs are not evaluated in this document. For the purpose of setting an MCLG, consideration is given to chlorine levels resulting from disinfection of drinking water. Persons who swim frequently or

use a hot tub may have greater dermal or inhalation exposure to chlorine.

Chlorine is added to drinking water as chlorine gas (Cl_2) or as calcium or sodium hypochlorite. In drinking water, the chlorine gas hydrolyses to hypochlorous acid and hypochlorite ion and can be measured as the free chlorine residual. Maintenance of a chlorine residual throughout the distribution system is important for minimizing bacterial growth and for indicating (by the absence of a residual) failures in the distribution system. Currently, maximum chlorine dosage is limited by taste and odor constraints and for systems needing to comply with the total trihalomethane (TTHM) standard regularly. Additionally, for systems using chlorination, the surface water treatment rule (SWTR) requires a minimum residual of 0.2 mg/L, measured as total chlorine, prior to the entry point to the distribution system and the presence of a detectable residual throughout the distribution system.

The following table presents the most recent and comprehensive occurrence information available for chlorine in drinking water. Descriptions of these surveys and other data are detailed in "Occurrence Assessment for Disinfectants and Disinfection By-Products (Phase 6a) in Public Drinking Water," USEPA August 1992. The table lists five surveys conducted by Federal, as well as private agencies. Median concentrations of chlorine in drinking water appear to range from <1 to 2 mg/L.

Occurrence of Chlorine in Drinking Water

Survey (Year)[1]	Location	Sample Information (No. of Samples)	Concentration (mg/L)		
			Range	Mean	Median
TSD, 1992[2] (1987-1991)	Disinfection By-Products Field Studies	Finished Water: At the Plant (71) Distribution System (45)	 0.1-5.0 0.0-3.2	 1.7 0.7	 1.4 0.5
AWWARF (1987) McGuire & Meadow, 1988	National Survey	Finished Water From: Lakes Flowing Streams Ground Waters Mixed-supplies			 2.2[3] 2.3[3] 1.2[3] 1.0[3]
EPA/AMWA/CDHS[2] (1988-1989) Krasner et al., 1989	35 Water Utilities Nationwide	Samples from Clearwell Effluent, 4 Quarters (17)	0.3-5.2	1.5	1.0
WIDB (1989-1990)	228 SW Plants 215 GW Plants	Residual Chlorine Provided to the Average Customer (systems >50,000 people)	0-3.5 0-5	0.937 0.872	0.80 0.325
AWWA Disinfection Survey (1991)	283 Utilities in the U.S.	Finished Water Entering Distribution System		0.07-5.0	1.10

[1] Dates indicate period of sample collection
[2] May not be representative of national occurrence
[3] Typical dosage used by treatment plants

SW Surface Water
GW Ground Water

AMWA Association of Metropolitan Water Agencies
AWWA American Water Works Association
AWWARF American Water Works Association Research Foundation
CDHS California Department of Health Services
TSD Technical Support Division
WIDB Water Industry Data Base

Exposure to chlorine residual varies both between systems and within systems. Chlorine residual within systems will vary based on where customers are located within the distribution system and changes in the system's disinfection needs over time. Using residual concentrations from the 1989-1991 AWWA Disinfection Survey and WIDB, exposure to chlorine due to drinking water can be estimated using a consumption rate of 2 liters per day. Based on the estimated 25 percentile and 75 percentile chlorine residuals in the 1991 AWWA Disinfection Survey, exposure was determined to range from 1.5 to 3.8 mg/day and the median would be 2.2 mg/day. Using the WIDB data, exposures to the average customer from surface and ground water sources using chlorination, respectively, were determined to be 1.9 mg/day and 1.7 mg/day.

Little information is available concerning the occurrence of chlorine in food and indoor air in the United States. The Food and Drug Administration (FDA) does not analyze for chlorine in foods. However, there are several uses of chlorine in food production; for example, disinfection of chicken in poultry plants and the superchlorination of water at soda and beer bottling plants (Borum, 1991). Therefore, the possibility exists for dietary exposure to chlorine from its use in food production. However, monitoring data are not available to characterize adequately the extent of such potential exposures. Additionally, preliminary discussions with FDA suggest that there are not approved uses for chlorine in most foods consumed in the typical diet. Similarly, the Indoor Air Division of EPA's Office of Air and Radiation is not currently conducting any sampling studies for chlorine in air. Data on levels of chlorine in ambient air are forthcoming from EPA's Office of Air Quality Planning and Standards.

Considering the limited number of food groups that are believed to contain chlorine and that no significant levels of chlorine are expected in ambient or indoor air, it is anticipated that drinking water is the predominant source of exposure to chlorine. Air and food are believed to provide only small contributions, although the magnitude and frequency of these potential exposures are issues currently under review. EPA, therefore, is considering setting an MCLG for chlorine in drinking water using a relative source contribution (RSC) value of 80%, the current exposure assessment policy ceiling. EPA requests any additional data on known concentrations of chlorine in drinking water, food and air.

Health Effects

The health effects information for chlorine is summarized from the draft Drinking Water Health Criteria Document for Chlorine, Hypochlorous Acid and Hyperchlorate Ion (USEPA, 1992a).

The studies cited within this section are summarized in the draft criteria document.

Chlorine and the hypochlorites are very reactive and thus can react with the constituents of saliva and possibly food and gastric fluid to yield a variety of reaction by-products (e.g., trihalomethanes). Thus, the health effects associated with the administration of chlorine and/or the hypochlorites in various animal studies may be due to these reaction by-products and not the disinfectant itself. Oxidizing species such as chlorine and the hypochlorites are probably short lived in biological systems due to both their reactivity and the large number of organic compounds found *in vivo*.

Oral studies with radiolabeled (i.e., ^{36}Cl) hypochlorite and hypochlorous acid indicate that, as measured by the radiolabel, these compounds may be well absorbed and distributed throughout the body with the highest levels measured in plasma and bone marrow. However, considering the reactivity of the hypochlorites, these results may only reflect the presence of reaction by-products (e.g., chloride). The major route of excretion appears to be urine and then the feces.

Acute oral LD_{50} values for calcium and sodium hypochlorite have been reported at 850 mg/kg in rats and 880 mg/kg in mice, respectively. Humans have consumed hyperchlorinated water for short periods of time at levels as high as 50 mg/L (1.4 mg/kg) with no apparent adverse effects.

Short-term oral studies in animals have indicated decreases in blood-glutathione levels, hemolysis and biochemical changes in liver in rodents following a gavage dose of hypochlorite in water. No adverse effects on reproduction (Druckery, 1968) or development (Abdel-Rahman et al., 1982) were observed in rats administered chlorine in drinking water at concentrations of 100 mg/L or less. However, Meier et al. (1985) observed an increase in sperm-head abnormalities in mice receiving hypochlorite at 200 mg/L, but not at 100 mg/L or less.

No systemic effects were observed in rodents following oral exposure to chlorine as hypochlorite in distilled water at levels up to 275 mg/L over a 2 years period.

Chlorinated water has been shown to be mutagenic to bacterial strains and mammalian cells. Investigations with rodents to determine the potential carcinogenicity of chlorine, or chlorinated water have been negative. In the most recent study, no apparent carcinogenic potential was demonstrated following oral exposure to chlorine in distilled drinking water as hypochlorite at levels up to 275 mg/L over a 2 years period (NTP, 1990). However, NTP observed a marginal increase in the

incidence of monocellular leukemia in mid-dose female F344 rats but not in male rats or male and female mice (NTP, 1990). Monocellular leukemia has a high spontaneous rate of occurrence in F344 rats. EPA believes that monocellular leukemia can not be solely attributed to exposures to chlorine in drinking water but rather may reflect the high background rate of monocellular leukemia in the test species.

EPA has not, as yet, evaluated the carcinogenic potential of chlorine, hypochlorite or hypochlorous acid. However, the International Agency for Research on Cancer (IARC, 1991) recently evaluated chlorinated drinking water and hypochlorite for potential human carcinogenicity. IARC determined that there was inadequate evidence for carcinogenicity of chlorinated drinking water and hypochlorite salts in humans and animals. IARC concluded that chlorinated drinking water and hypochlorite salts were not classifiable as to their carcinogenicity to humans and thus assigned these chemicals to IARC Group 3. This category is similar to EPA cancer classification Group D. EPA will initiate a cancer evaluation of these compounds in the fall of 1992.

Based on the previous discussion, EPA is considering placing chlorine, hypochlorite and hypochlorous acid in Category III for the purpose of setting an MCLG. The study selected for determining an RfD is the previously mentioned 2 year rodent study that was conducted by the National Toxicology Program (NTP, 1990). In this study, male and female F344 rats and B6C3F1 mice were given chlorine in distilled drinking water at levels of 0, 70, 140 and 275 mg/L for 2 years. Based on body weight and water consumption values, these concentrations correspond to doses of approximately 0, 8, 13 and 24 mg/kg/day for male rats; 0, 5, 7, and 15 mg/kg/day for female rats; 0, 8, 15, and 24 mg/kg/day for male mice and 0, 7, 13 and 22 mg/kg/day for female mice. There was a dose related decrease in water consumption for both rats and mice, presumably due to taste aversion. No effect on body weight or survival were observed for any of the treated animals.

A NOAEL of 15 mg/kg/day in female rats is proposed as the basis of the RfD (i.e., the highest dose received by female rats is lower than the highest dose received by either mice or male rats in the NTP study). The 15 mg/kg/day NOAEL is supported by EPA's analysis of other studies which reported NOAELs of 10 to 24 mg/kg/day for rodents.

An RfD of 0.15 mg/kg/day is calculated after dividing the NOAEL of 15 mg/kg/day by an uncertainty factor of 100, which is appropriate for use with a NOAEL from a chronic animal study. A DWEL of 5 mg/L is determined by adjusting the RfD for both human adult body weight and water consumption. EPA is considering adjusting the DWEL by an RSC of 80 percent to account for the likely exposure to chlorine, hypochlorite and hypochlorous acid from drinking water. This would result in an MCLG of 4 mg/L.

$$DWEL = \frac{0.15\ mg/kg/day \times 70\ kg}{2L} = 5\ mg/L$$

$$MCLG = 0.8 \times 5\ mg/L = 4\ mg/L$$

Issues

1. Setting an RSC percentage at 80%.

2. Placing chlorine, hypochlorite and hypochlorous acid in Category III.

3. Selection of the NTP study for the RfD.

Chlorine Dioxide, Chlorite and Chlorate

Chlorine dioxide is used as a disinfectant in drinking water treatment as well as an additive with chlorine to control tastes and odors in water treatment. It has also been used for bleaching pulp and paper, flour and oils and for cleaning and tanning of leather. Chlorine dioxide is a strong oxidizer that does not react with organics in the water, as does chlorine, to produce by-products such as the trihalomethanes. Chlorine dioxide is fairly unstable and rapidly dissociates into chlorite and chlorate in water. This dissociation is also reversible with chlorite converting back to chlorine dioxide. Chlorite ion is generally the primary product of chlorine dioxide reduction. The distribution of chlorite and chlorate is influenced by pH and sunlight.

Chlorite, (as the sodium salt), is used in the onsite production of chlorine dioxide and as a bleaching agent by itself, for pulp and paper, textiles and straw. Chlorite is also used to manufacture waxes, shellacs and varnishes. Chlorate, as the sodium salt, was once used as a weed killer - defoliant, to tan leather and in the manufacture of dyes, matches and explosives.

Occurrence and Human Exposure

Based on information from the Water Industry Data Base (WIDB), it has been estimated that for large systems (serving greater than 10,000 people), approximately 10% of community surface water systems serving 12.4 million people and 1% of community ground water systems, serving 0.2 million people currently use chlorine dioxide for disinfection in the United States. It was assumed that none of the smaller community systems (fewer than 10,000 people) use chlorine dioxide (WIDB, 1990).

The following table presents the most recent and comprehensive occurrence information available for chlorine

dioxide, chlorate, and chlorite in drinking water. Descriptions of these surveys and other data are detailed in "Occurrence Assessment for Disinfectants and Disinfection By-Products (Phase 6a) in Public Drinking Water," USEPA, August 1992. Typical dosages of chlorine dioxide used as a disinfectant in drinking water treatment facilities appear to range from 0.6 to 1.0 mg/L. For plants using chlorine dioxide, median concentrations of chlorite and chlorate were found to be 240 and 200 μg/L, respectively.

Occurrence of Chlorine Dioxide, Chlorate, and Chlorite in Drinking Water

Survey (Year)[1]	Location	Sample Information (No. of Samples)	Concentration (μg/L)			
			Range	Mean	Median	Other
AWWARF (1987) McGuire & Meadow, 1988		Finished Water From: Lakes Flowing Streams		 1.0 mg/L[3] 0.6 mg/L[3]		
TSD, 1992[2] (1987-1991)	Disinfection By-Products Field Studies	Plants Using ClO_2: Chlorite at the Plant (4) Chlorate at the Plant (4) Plants Not Using ClO_2: Chlorate at the Plant (30) Chlorate, Distr. System (4)	 15-740 21-330 <10-660 <10-47	 240 200 87 18	 110 220 16 13	Positive Detections 100% 100% 60% 75%

[1] Dates indicate period of sample collection
[2] May not be representative of national occurrence
[3] Typical dosage used by treatment plants

AWWARF American Water Works Association Research Foundation
TSD Technical Support Division

No information is available on the occurrence of chlorine dioxide, chlorate, and chlorite in food or ambient air. Currently, the Food and Drug Administration (FDA) does not analyze for these compounds in foods. Preliminary discussions with FDA suggest that there are not approved uses for chlorine dioxide in foods consumed in the typical diet. In addition, the EPA Office of Air and Radiation does not require monitoring for these compounds in air. However, chlorine dioxide is used as a sanitizer for air ducts (Borum, 1991).

EPA believes that drinking water is the predominant source of exposure for these compounds. Air and food exposures are considered to provide only small contributions to the total chlorine dioxide, chlorate, and chlorite exposures, although the magnitude and frequency of these potential exposures are issues currently under review. Therefore, EPA is considering proposing to regulate these compounds in drinking water with a relative source contribution value of 80 percent, the current exposure assessment policy ceiling. EPA requests any additional data on known concentrations of chlorine dioxide, chlorate and chlorite in drinking water, food and air.

Health Effects

The following health effects information is summarized from the draft Drinking Water Health Criteria Document for Chlorine Dioxide, Chlorite and Chlorate (USEPA, 1992b). Studies cited in this section are summarized in the draft criteria document.

The main health effects associated with chlorine dioxide and its anionic by-products include oxidative damage to red blood cells, decreased thyroxine hormone levels and delayed neurodevelopment. Chlorine dioxide, chlorite and chlorate are well absorbed by the gastrointestinal tract and excreted primarily in urine. Once absorbed, ^{36}Cl-radiolabeled chlorine dioxide, chlorite and chlorate are distributed randomly throughout the body. Lethality data for ingested chlorine dioxide have not been located in the available literature. A lethal concentration for guinea pigs by inhalation was reported at 150 ppm. Oral LD_{50} values for chlorite have been reported at 100 to 140 mg/kg in rats. Limited data suggest an oral LD_{50} value between 500 to 1500 mg/kg for chlorate in dogs.

In subchronic and chronic studies, animals given chlorine dioxide treated water exhibited osmotic fragility of red blood cells, decreased thyroxine hormone levels, possibly due to altered iodine metabolism and hyperplasia of goblet cells and inflammation of nasal tissues. It is not clear if the nasal effects are due to off-gassing of chlorine dioxide from the sipper tube of the animal water bottles, or from dermal contact while the animal drinks from the sipper tube.

Studies evaluating developmental or reproductive effects have described decreases in the number of implants and live fetuses per dam in female rats that were exposed before mating and during pregnancy. Delayed neurodevelopment has been reported in rat pups exposed perinatally to chlorine dioxide treated water. Delayed neurodevelopment was assessed by decreased locomotor activity and decreased brain development.

Subchronic studies with chlorite administered to rats via drinking water resulted in transient anemia and decreased red blood cell glutathione levels. Chlorite administration to cats produced 10 to 40 percent methemoglobin formation within a couple of hours following dosing. Exposure to chlorite in drinking water resulted in the destruction of red blood cells in cats rather than oxidation of hemoglobin.

Studies with chlorate also demonstrate effects on hematological parameters and formation of methemoglobin, but at much higher doses than chlorite.

No tumorigenic activity has been observed in chlorine dioxide, chlorite or chlorate treated animals. Chlorine dioxide concentrates did not increase the incidence of lung tumors in mice nor was any initiating activity observed in mouse skin or rat liver bioassays. Lung and liver tumors were increased in mice given sodium chlorite; however, the incidence was within the historical range for these tumor types. Carcinogenic studies on chlorate were not located in the available literature. Chlorate has been reported to be mutagenic in bacterial and Drosophila tests.

There are a number of cases of poisoning in humans using chlorate as a weed killer. Effects observed following exposures to 11 to 3400 mg/kg include cyanosis, renal failure, convulsions and death. The lowest lethal dose reported in adults is approximately 200 mg/kg. In an epidemiology study of a community where chlorine dioxide was used as the primary drinking water disinfectant for 12 weeks, no consistent changes were observed in the clinical parameters measured.

Several studies have been selected as the basis for the RfD and DWEL for chlorine dioxide. These studies identify a NOAEL of 3 mg/kg/d and a LOAEL of approximately 10 μg/kg/d. A NOAEL of 3 mg/kg/d has been identified in an 8 week rat study by Orme et al. (1985). In the rat study, chlorine dioxide was administered to female rats via drinking water at concentrations of 0, 2, 20 and 100 mg/L before mating, during gestation and lactation. Based on body weight and water consumption data, these concentrations correspond to doses of 1, 3 and 14 mg/kg/d. No effects were noted in dams. Pups in the high dose group (14 mg/kg/d) exhibited decreased exploratory and locomotor activity anda significant depression of thyroxine and. These effects were not

observed at the 3 mg/kg/d dose level. In a second experiment, pups were given 14 mg/kg/d chlorine dioxide directly by gavage during postnatal days 5 through 20. A greater and more consistent delay in neurobehavioral activity was observed along with a greater depression in thyroxine. Analysis of the DNA content of cells in the cerebellum from animals in the high dose drinking water group at postnatal day 21 and the gavage group at day 11 indicated a significant depression (Taylor and Pfohl, 1985). Another study confirmed 14 mg/kg/d as a LOAEL based on decreased brain cell proliferation in rats exposed postnatally by gavage (Toth et al., 1990).

In a monkey study (Bercz et al., 1982), animals were given chlorine dioxide at concentrations of 0, 30, 100 or 200 mg/L in drinking water following a rising dose protocol. These concentrations correspond to doses of 0, 3.5, 9.5 and 11 mg/kg/d based on animal body weight and water consumption. Animals showed signs of dehydration at the high dose and were discontinued at that dose. A slight depression of thyroxine was observed following exposure to 9.5 mg/kg/d. No effects were seen with 3.5 mg/kg/d, which is considered the NOAEL.

EPA is considering following a Category III approach for setting an MCLG for chlorine dioxide. Using a NOAEL of 3 mg/kg/d and an uncertainty factor of 100, an RfD of 0.03 mg/kg/d for chlorine dioxide is calculated. This RfD is approximately equal to the NOAEL of 0.03 mg/kg/d identified from the Lubbers et al. (1982) human clinical study (see USEPA, 1992b). Typically, an uncertainty factor of 1,000 would be used for a NOAEL from an animal study of less than lifetime duration. However, in this case an uncertainty factor of 100 is considered with the NOAEL instead of 1,000 since the endpoints of toxicity are observed following a short period of exposure.

A DWEL of 1 mg/L is derived by adjusting the RfD of 0.03 mg/kg/d for an adult body weight and water consumption. An RSC of 80 percent is used in calculating an MCLG of 0.8 mg/L, since most chlorine dioxide exposure is likely to come from a drinking water source.

$$\text{DWEL} = \frac{3\ \text{mg/kg/d} \times 70\ \text{kg}}{100 \times 2\ \text{L/day}} = 1\ \text{mg/L}$$

$$\text{MCLG} = 1\ \text{mg/L} \times 0.8 = 0.8\ \text{mg/L}$$

If the uncertainty factor were increased to 1,000, the resulting MCLG would be 0.08 mg/L. If the uncertainty factor were a total of 300 (100 for a NOAEL and 3 for less than lifetime), the resulting MCLG would be 0.3 mg/L.

The Drinking Water Committee of the Science Advisory Board (SAB) has suggested that a child's body weight of 10 kg and water

consumption of 1 L/d may be more appropriate for setting the DWEL than the adult parameters, given the acute nature of the toxicity. If a 10 kg weight and 1 L/d water consumption were used with an uncertainty factor of 1000, the resulting MCLG would be 0.2 mg/L.

Issues

1. Appropriateness of the 100-fold uncertainty factor.

2. Is an additional uncertainty factor of 3 is needed to account for the lack of a 2-generation reproduction study?

3. Use of a child's body weight and water consumption rate in setting an MCLG.

For chlorite, the subchronic rat study by Heffernan et al. (1979) would be selected as the basis for the RfD in following a Category III approach to set an MCLG. Rats were given 0, 10, 50, 100, 250, or 500 mg/L chlorite (as sodium salt; equivalent to 0, 1, 5, 10, 25, or 50 mg/kg/d) in drinking water for 30 to 90 days. In evaluating hematological parameters, the three highest doses were found to produce transient anemia after 30 days. At 90 days, red blood cell glutathione levels were 40 percent below controls in the 10 mg/kg/d group and 20 percent lower in the 5 mg/kg/d group. This NOAEL of 1 mg/kg/d is identified. This NOAEL is supported by a 2 year study in rats that identified a NOAEL of 0.7 mg/kg/d (Haag, 1949). However, the Haag study did not include histopathology on all treated animals and was never published.

An RfD of 0.01 mg/kg/d can be calculated from the NOAEL of 1 mg/kg/d divided by an uncertainty factor of 100. This RfD is approximately equal to the NOAEL of 0.03 mg/kg/d identified from the Lubbers et al. (1982) clinical study in humans (see USEPA, 1992b). Typically an uncertainty factor of 1,000 would be used with a NOAEL from an animal study of the less-than-lifetime duration. However, like chlorine dioxide, the endpoints of toxicity with chlorite occur after a short-term exposure. Thus, EPA is considering using an uncertainty factor of 100.

From the RfD, a DWEL of 0.4 mg/L is calculated after adjusting for an adult body weight and water consumption. An RSC of 80 percent is used since the majority of exposure is expected to come from drinking water. This yields an MCLG of 0.3 mg/L. If an uncertainty factor of 1,000 is used instead of 100, the resulting MCLG would be 0.03 mg/L.

$$\text{DWEL} = \frac{1\ \text{mg/kg/d} \times 70\ \text{kg}}{100 \times 2\ \text{L/day}} = 0.4\ \text{mg/L}$$

$$\text{MCLG} = 0.4 \times 0.80 = 0.3\ \text{mg/L}$$

The SAB made the same suggestion for chlorite as for chlorine dioxide. That is, to consider use of 10 kg and 1 L/d for determining the DWEL. The resulting MCLG would be 0.08 mg/L.

Data are considered inadequate to develop an MCLG for chlorate at this time. A NOAEL of 0.036 mg/kg/d was identified in the Lubbers et al. (1982) human clinical study following a 12 week exposure to chlorate in drinking water. NOAELs identified from animal studies are considerably higher (approximately 250 mg/kg/d). However, this is equivalent to doses that are lethal to humans (200 mg/kg/d). No information is available to characterize the potential human toxicity between the doses of 0.036 and 200 mg/kg/d. Thus, EPA considers the data base too weak to derive a separate MCLG for chlorate.

EPA is considering setting a Lifetime Health Advisory (HA) (a non-enforceable guidance) for chlorate as an interim measure to provide some health guidance while more data are being collected to set an MCLG. EPA is considering basing the Lifetime HA on the NOAEL from the Lubbers et al. (1982) study. An uncertainty factor of 10 would be used to account for a NOAEL from a human study. The resulting Lifetime HA value would be 0.1 mg/L.

$$\text{Lifetime HA} = \frac{0.036 \text{ mg/kg/d} \times 70 \times 0.8}{10 \times 2 \text{ L/d}} = 0.1 \text{ mg/L}$$

EPA currently has a guideline value of 1 mg/L for total residual oxidants when chlorine dioxide is used. Since chlorine dioxide, chlorite and chlorate are so reactive and undergo conversion from one form to another, it is likely that the experimental studies with chlorine dioxide actually include exposures to chlorite and chlorate as well. Although the toxicity elicited by each compound can vary, this variation may exist within the range of uncertainty employed in the risk assessment. Thus, EPA is considering establishing one MCLG for all residual oxidants when chlorine dioxide is used as a disinfectant. This MCLG could be based on the chlorine dioxide studies discussed above, resulting in a value of 0.8 mg/L. Alternatively, the MCLG for residual oxidants could be based on the chlorite (0.3 mg/L) value since it is the predominant degradation species.

Issues

1. Use of an uncertainty factior of 100.

2. Is it reasonable to set an MCLG for total residual oxidants and what would be the basis for that MCLG?

3. The chlorate MCLG issue as well as the separate MCLGs for chlorite and chlorine dioxide that are being considered.

4. Use of child's weight and water consumption rate in developing MCLG.

Chloramines

Inorganic chloramines (CAS. Nos. 10599-90-3 and 10025-85-1 for mono- and trichloramine, respectively) are formed in waters undergoing chlorination which contain ammonia. Monochloramines, dichloramines and trichloramines may be formed. Monochloramine is the principal chloramine formed in chlorinated natural and wastewater at a neutral pH and is much more persistent in the environment.

Chloramine is used as a disinfectant in drinking water to control taste and odor problems, limit the formation of chlorinated disinfection by-products, and maintain a residual in the distribution system for controlling biofilm growth. At typical pHs of most drinking waters, the predominant chloramine specie is monochloramine. For purposes of this regulation, only monochloramine will be considered since the other chloramines occur at much lower concentrations in almost all drinking waters. Monochloramine has also been much more extensively studied.

Chloramines are used as an intermediate in the manufacture of hydrazine.

Monochloramine, the principal chloramine formed in chlorinated natural and wastewaters at neutral pH, is persistent in the environment. First-order decay rate constants of 0.03 to 0.075 hr^{-1} for monochloramine in the laboratory, and higher rate constants of 0.28 to 0.31 hr^{-1} outdoors using chlorinated effluents, have been reported. If discharged into receiving waters containing bromide, monochloramine will decompose faster, probably through the formation of NHBrCl and decomposition of the dihalamine. The rate of monochloramine disappearance is primarily a function of pH and salinity. For example, at pH 7 and 25°C, the half-life of monochloramine is 6 hr at 5 parts per thousand (ppt) salinity and 0.75 hr at 35 ppt salinity; at pH 8.5 and 25°C, the half-life is 188 hr at 5 ppt salinity and 25 hr at 35 ppt salinity. Monochloramine is expected to decompose in wastewater discharges receiving waters via chlorine transfer to organic nitrogen-containing compounds.

Occurrence and Human Exposure

Chloramine occurs in drinking water both as a by-product and intentionally for disinfection. Chloramine is formed during chlorination when source waters contain ammonia. It is also used as a primary or secondary disinfectant, usually with chloramine being generated on site by the addition of ammonia to water following treatment by chlorination. The use of chloramines has

been shown to reduce the formation of certain by-products, notably trihalomethanes, relative to chlorination alone. Chlorination by-product formation can be minimized when the ammonia is added prior to or in combination with chlorine by reducing the chlorine residual of the water being treated. In most plants, however, ammonia is added some time after the addition of chlorine, to allow for more effective disinfection since chlorine is a much stronger disinfectant than chloramines.

The following table presents the most recent and comprehensive occurrence information available for chloramine in drinking water. Descriptions of these surveys and other data are detailed in "Occurrence Assessment for Disinfectants and Disinfection By-Products (Phase 6a) in Public Drinking Water," USEPA, August 1992. Typical dosages of chloramine used as a disinfectant in drinking water treatment facilities range from 1.5 to 2.7 mg/L. Median concentrations of chloramine in drinking water were found to range from 1.1 to 1.8 μg/L.

Occurrence of Chloramine in Drinking Water

Survey (Year)[1]	Location	Sample Information (No. of Samples)	Concentration (μg/L)			
			Range	Mean	Median	Other
AWWARF (1987) McGuire & Meadow, 1988	National Survey	Finished Water From: Lakes Flowing Streams				Typical dosages: 1.5 mg/L 2.7 mg/L
EPA/AMWA/CDHS[2] (1988-1989) Krasner et al., 1989	35 Water Utilities Nationwide	Samples from Clearwell Effluent, 4 Quarters (13)	0.9-5.5	2.3	1.8	
TSD, 1992[2] (1987-1991)	Disinfection By-Products Field Studies	At the Plant (11) Distribution System (8)	1.2-3.6 0.1-3.3	2.1 1.4	1.5 1.1	

[1] Dates indicate period of sample collection
[2] May not be representative of national occurrence

AMWA Association of Metropolitan Water Agencies
AWWARF American Water Works Association Research Foundation
CDHS California Department of Health Services
TSD Technical Support Division

Based on the residual concentrations given above, a high and low estimate for exposure to chloramine from drinking water can be calculated using an assumed consumption of 2 liters per day. Using the target range of 1.5 to 2 mg/L, the exposure may range from 3 to 5 mg/day. Some systems may deviate significantly from this range.

No information is available on the occurrence of chloramine in food or air. Currently, the Food and Drug Administration (FDA) does not measure for chloramine in foods since the analytical methods have not been developed. Preliminary discussions with FDA suggest that there are not approved uses for chloramine in foods consumed in the typical diet. Similarly, the Air Division of EPA's Office of Air and Radiation is not sampling chloramines in air (Borum, 1991).

Based on the previous discussion, EPA assumes that drinking water is the predominant source of exposure to chloramine. Air and food intakes are believed to provide only small contributions, although the magnitude and frequency of these potential exposures are issues currently under review. EPA, therefore, is proposing to establish an MCLG for chloramine in drinking water with a relative source contribution (RSC) value of 80%, the current exposure assessment policy ceiling. EPA requests any additional data on known concentrations of chloramine in drinking water, food and air.

Health Effects

The health effects information in this section is summarized from the draft Drinking Water Health Criteria Document for Chloramines (USEPA, 1992c). Studies mentioned in this section are summarized in the Criteria Document.

Short-term inhalation exposures to high levels (500 ml of 5% household ammonia mixed with 5% hypochlorite bleach) chloramines in humans result in burning in the eyes and throat, dyspnea, coughing, nausea and vomiting. Inhalation of the chloramine fumes resulted in pneumonitis but did not result in permanent pulmonary damage.

Short-term exposures in drinking water, in which human subjects were administered concentrations ranging between 1 and 24 mg/L (1, 8, 18 or 24 mg/L), have not resulted in any adverse effects reported in human subjects. Following human exposure, the subject's physical condition, urinalysis, hematology and clinical chemistry were evaluated. No adverse clinical effects were noted in any of the studies.

In another study, acute hemolytic anemia, characterized by oxidation of hemoglobin to methemoglobin and denaturation of hemoglobin, was reported in hemodialysis patients when tap water

containing chloramines was used for dialysis baths. Chloramines were reported to produce oxidant damage to red blood cells and inhibits the metabolic pathway used by red blood cells to prevent and repair such damage. Many dialysis centers have installed reverse osmosis units coupled with charcoal filtration or the addition of ascorbic acid to prevent hemolytic anemia.

Animal studies indicate varying sensitivity and conflicting results among different animal species. Toxic effects noted among rats are changes in blood glutathione and methemoglobin. Both monkeys and mice were unaffected during short-term assays with doses up to 200 mg/L chloramines. Based on studies up to 6 weeks in length, rats appear to be more sensitive than mice and monkeys.

Toxicokinetic studies of chloramines indicate absorption of chloramines is rapid, peaking within 8 hours of administration. In the rat, chloramines are metabolized to chloride ion and excreted mostly through the urine with a small portion excreted through the feces.

Longer-term studies (90 days or longer) should decrease body weight and organ weight, and have indicated that the liver is a primary target of toxicity in rodents. However, effects to the liver (weight changes and hypertrophy, chromatid pattern changes) appear to be related to overall body weight changes caused by the unpalatibility of chloramines to the test animals.

In addition, chloramine may induce immunotoxicity in rats in the form of increased prostaglandin E_2 synthesis, reduced antibody synthesis and spleen weight at levels as low as 9 to 19 mg/L chloramines for 90 days. Because these findings have not been corroborated by a follow-up study, the significance of these results are not presently clear.

Two lifetime rodent studies involving oral exposures to rats and mice via drinking water have been considered by EPA for the derivation of the MCLG for monochloramine. Both studies were performed by the National Toxicological Program (NTP) [NTP.1990. NTP Technical Report on the Toxicology and Carcinogenesis Studies of Chlorinated and Chloraminated Water in F344/N rats and B6C3F1 Mice (Drinking Water Studies). NTP TR 392, National Institutes of Health] and involved 70 animals/sex/dose exposed to drinking water containing 0, 50, 100 or 200 ppm chloramines.

The first NTP (1990) study was a 2-year study in mice to determine the potential chronic toxicity or carcinogenic activity of chloraminated drinking water. B6C3F1 mice were administered chloramine at doses of 0, 50, 100 and 200 ppm in drinking water. These doses were calculated based on a time-weighted average to be 0, 5.0, 8.9 and 15.9 mg/kg/day for male mice and 0, 4.9, 9.0

and 17.2 mg/kg/day for female mice. There was a dose-related decrease in the amount of water consumed by both sexes; this decrease was noted during the first week and continued throughout the study. Dosed male and female mice had similar food consumptions as controls except for females in the 200 ppm dose group that exhibited slightly lower consumption than controls.

Study results indicated that there was a dose-related decrease in mean body weights of dosed male and female mice throughout the study. Mean body weights of high-dose male mice were 10-22% lower than their control group after week 37 and the body weights of high-dose female mice were 10-35% lower after week 8. However, the survival of mice receiving monochloramine in drinking water was not significantly different than controls. Clinical findings observed were not attributed to the consumption of chloraminated drinking water. Body weight loss or systemic toxicity was not considered related to chloramine, but rather due to the unpalatability of chloramines in the test animals. Therefore, the highest dose tested, 17.2 mg/kg/day, is considered a NOAEL in mice.

In the second study F344/N rats were administered monochloramine for 2 years at doses of 0, 50, 100 and 200 ppm drinking water. These doses were calculated on the basis of a time-weighted average to be 0, 2.1, 4.8 and 8.7 mg/kg/day for male rats and 0, 2.8, 5.3 and 9.5 mg/kg/day for female rats. There was a dose-related decrease in the amount of water consumed by both sexes; this decrease was noted during the first week and continued throughout the study. Food consumption of treated rats was the same as the controls with males consuming more. In addition, mean body weights of 200 ppm dosed rats (both sexes) were lower than their control groups. However, mean body weights of rats receiving monochloramine in drinking water (at all levels) were within 10% of controls until week 97 for females and week 101 for males. Though several clinical changes were noted, no clinical changes were attributable to chloraminated drinking water. The survival of rats receiving chloraminated drinking water was not significantly different than controls except that, for the 50 ppm dose groups, survival was greater than that of controls. Therefore, EPA considers the highest dose tested, 9.5 mg/kg/day, as the NOAEL.

Based on two bacteria assays, monochloramine appears to be weakly mutagenic. One study examining the reproductive effects and another which examined developmental effects of chloramines concluded that there are no chemical-related effects due to chloramines.

The NTP evaluation, using the results of the two lifetime NTP bioassays, concluded that chloramines exhibited equivocal evidence of carcinogenic activity of chloraminated drinking water in female F344/N rats. This conclusion results from an increase

in mononuclear cell leukemia. There was no evidence of carcinogenic activity in male rats or mice of either sex. The findings do not establish a link between chloramine exposure and carcinogenicity because of the high historical background occurrence of this type of cancer in test animals. The incidence of mononuclear cell leukemia in the female control groups (16%) was substantially less than the incidence reported in untreated historical controls (25%). Incidence of mononuclear cell lukemia in test animals reached a high of 32% in the high dose female rats. This study also discovered incidence of renal tubular cell neoplasms in two high-dose male mice receiving chloraminated water. Since this type of tumor is rarely seen in historical controls, there is some concern that these may be treatment related. However, the overall evidence regarding the potential carcinogenicity of chloramines in drinking water can be described as inconclusive since no long-term study has linked any tumor development to actual chloramination exposure. On this basis, EPA is considering placing chloramine in Group D; inadequate evidence of carcinogenicity.

EPA believes that the lifetime study in rats (NTP, 1990) is the most suitable to calculate the MCLG for chloramines because the rat appears to be the more sensitive organism based on other short- and longer-term effects observed in the rat such as changes in biochemistry and immunology. Using the rat NOAEL of 9.5 mg/L from the NTP study, a DWEL of 3 mg/L can be derived for the 70-kg adult consuming 2 liters of water per day applying an uncertainty factor of 100, which is appropriate for use of a NOAEL derived from an animal study.

Following a Category III approach, EPA is considering proposing an MCLG of 3 mg/L (3.2 rounded to 3) based upon a DWEL of 4.0 mg/L, assuming a drinking water contribution of 80 percent.

$$RfD = \frac{9.5\ mg/kg/day}{100} = 0.095\ mg/kg/day$$
(rounded to 0.1mg/kg/day)

$$DWEL = \frac{0.1\ mg/kg/day \times 70}{2\ liters} = 3.5\ mg/L$$
(rounded to 4 mg/L)

$$MCLG = 4.0\ mg/L \times 0.8 = 3.2\ mg/L \text{ (rounded to 3 mg/L)}$$

Since chloramines, on a practical basis, will be measured as total chlorine, it is necessary to present the MCLG in terms of a chlorine equivalent concentration. Three mg/L chloramine is equivalent to 4 mg Cl_2/liter, based on the molecular weights of Cl_2 and NH_2Cl.

$$3 \text{ mg } NH_2Cl/L \times \frac{70.9 \text{ mg } Cl_2}{51.48 \text{ mg } NH_2Cl} = 4.13 \text{ mg } Cl_2/L$$

(rounded to 4 mg Cl_2/L)

EPA is considering proposing an MCLG of 4 mg Cl_2/liter.

Issues

1. The proposed MCLG for chloramines based on RSC of 80%.

2. The significance of the findings of immunotoxicity for setting the RfD instead of the NTPstudy.

3. The finding of mononuclear cell leukemia in female F344 rats.

4. The finding of tubular cell neoplasms in high-dose exposed mice.

5. Whether the adjusted MCLG, which takes into account the measurement of monochloramine as total chlorine, is appropriate?

Chloroform

Chloroform [trichloromethane, CAS No. 67-66-3] is a nonflammable, colorless liquid with a sweet odor and high vapor pressure (200 mm Hg at 25°C). It is moderately soluble in water (8 gm/L at 20°C) and soluble in organic solvents (log octanol/water partition coefficient of 1.97). Chloroform is used primarily to manufacture fluorocarbon-22 (chlorodifluoromethane) which in turn is used for refrigerants and fluoropolymer synthesis. A small percentage of the manufactured chloroform is used as an extraction solvent for various products (e.g. resins, gums). In the past, chloroform was used in anesthesia and medicinal preparations and as a grain fumigant ingredient. Chloroform can be released to the environment from direct (manufacturing) and indirect (processing/use) sources and chloroform is a prevalent chlorination disinfection by-product. Volatilization is the principle mechanism for removal of chloroform from lakes and rivers. Chloroform bioconcentrates slightly in aquatic organisms and adsorbs poorly to sediments and soil. Chloroform can be biodegraded in water and soil (half-life of weeks to months) and ground water (half-life of months to years), and photo-oxidized in air (half-life of months).

Occurrence and Human Exposure

Chloroform is a prevalent chlorination by-product in drinking water. The principle source of chloroform in drinking water is the chemical interaction of chlorine with commonly present natural humic and fulvic substances and other precursors produced by either normal organic decomposition or by the metabolism of aquatic biota. Because humic and fulvic material are generally found at much higher concentrations in surface water sources than in ground water

sources, surface water systems have higher frequencies of occurrence and higher concentrations of chloroform than ground water systems. Several water quality factors affect the formation of chloroform including Total Organic Carbon (TOC), pH, and temperature. Different treatment practices can reduce the formation of chloroform. These include the use of precursor removal technologies such as coagulation/filtration, granular activated carbon (GAC), and membrane filtration and the use of chlorine dioxide, chloramination, and ozonation.

The following table presents the most recent and comprehensive occurrence information available for chloroform in drinking water. Descriptions of these surveys and other data are detailed in "Occurrence Assessment for Disinfectants and Disinfection By-Products (Phase 6a) in Public Drinking Water," (USEPA, August 1992). The table lists six surveys conducted by Federal, as well as private agencies. Median concentrations of chloroform in drinking water appear to range from 14 to 57 $\mu g/L$ for surface water supplies and ≤ 0.5 $\mu g/L$ for ground-water supplies (many of which do not disinfect).

Occurrence of Chloroform in Drinking Water

Survey (Year)[1]	Location	Sample Information (No. of Samples)	Concentration (μg/L)			
			Range	Mean	Median	Other
CWSS (1978) Brass et al., 1981	450 Water Supply Systems	Finished Water (1,100): Surface Water Ground Water		 60[3] <0.5[3]		Positive Detections: 97%[4] 34%[4]
RWS (1978-1980) Brass, 1981	>600 Rural Systems (>2,000 Households)	Drinking Water from: Surface Water Ground Water		 84[3] 8.9[3]	 57 <0.5	Positive Detections: 82%[4] 17%[4]
GWSS (1980-1981) Westrick et al. 1983	945 GW Systems: (466 Random and 479 Nonrandom)	 Serving >10,000 (327) Serving <10,000 (618)	 Max. 300 Max. 430		 0.5 0	90th percentile: 17 7.8
TSD, 1991[2] (1984-1991)	Unregulated Contaminant Data Base - Treatment Facilities from 19 States	Sampled at the Plant (5,806)		17	5	
TSD, 1992[2] (1987-1991)	Disinfection By-Products Field Studies	Finished Water: At the Plant (73) Distribution System (56)	 <0.2-240 <0.2-340	 36 57	 28 42	Positive Detections: 96% 98%
EPA/AMWA/CDHS[2] (1988-1989) Krasner et al., 1989	35 Water Utilities Nationwide	Samples from Clearwell Effluent for 4 Quarters	Max. 130		9.6-15[5] 14	75% of Data was Below 33 μg/L

[1] Dates indicate period of sample collection
[2] May not be representative of national occurrence
[3] Mean of the positives
[4] Of systems sampled
[5] Range of medians for individual quarters

AMWA Association of Metropolitan Agencies
CDHS California Department of Health Services
CWSS Community Water Supply Survey
GWSS Ground Water Supply Survey
RWS Rural Water Survey
TSD Technical Support Division

Several studies have assessed inhalation exposure to chloroform. The major source of this data is from the USEPA's Total Exposure Assessment Methodology (TEAM) Studies, which measured chloroform exposure to approximately 750 persons in eight geographic areas from 1980 to 1987. Personal exposure to chloroform from air was measured over a 12-hour period (excluding showers) for individuals in three areas. The average exposures were reported to range from 4 to 9 $\mu g/m^3$ in New Jersey and Baltimore, and about 0.5 to 4 $\mu g/m^3$ in California cities (Wallace, 1991). In the 1987 Los Angeles TEAM Studies, chloroform in indoor air was measured in the living room and kitchen of private residences. Observed mean indoor concentrations ranged from 0.9 to 1.5 $\mu g/m^3$ (Pellizzari et al., 1989 and Wallace et al., 1990 in Wallace, 1992). For outdoor levels, the 12-hour average outdoor concentrations measured in the California and New Jersey TEAM Studies ranged from 0.2 to 0.6 $\mu g/m^3$ and 0.1 to 1.5 $\mu g/m^3$, respectively (Pellizzari et al., 1989 and Wallace et al., 1990 and PEI et al., 1989 in Wallace, 1992).

Given the limited exposure data in air, inhalation exposure can be estimated using an inhalation rate of 20 m^3/day. Resulting estimates for average ambient air exposures range from 2 to 30 $\mu g/d$ and 18-30 $\mu g/d$ for average indoor air exposures. However, based on the personal air monitoring data, a potentially higher average inhalation exposure is indicated with a range of 10 to 180 $\mu g/d$.

Two studies analyzed some foods for chloroform. In a pilot market basket survey of four food groups at five sites, measured chloroform levels were as follows: dairy composite, 17 ppb (1 of 5 sites); meat composite, not detected; oil and fat composite, trace amounts (1 of 5 sites); beverage composite, 6 to 32 ppb (4 of 5 sites) (Entz et al., 1982). In a study of 15 table-ready food items, chloroform was detected in 53% of the foods tested: butter, 670 ppb; cheddar cheese, 80 ppb; plain granola, 57 ppb; peanut butter, 29 ppb; chocolate chip cookies, 22 ppb; frozen fried chicken dinner, 29 ppb; and high meat dinner, 17 ppb (Heikes, 1987).

Limited data are available to characterize dietary exposure to chloroform. Although some uses of chlorine have been identified in the food production/food processing area, monitoring data are not adequate to characterize the magnitude or frequency of exposure to chloroform. Based on the limited number of food groups that are believed to contain chloroform and that there are often low levels expected in ambient and indoor air, EPA assumes that drinking water is the predominant source of chloroform intake. The characterization of potential food and air exposures are issues currently under review. EPA requests

any additional data on known concentrations of chloroform in drinking water, food, and air.

Health Effects

The health effects information is summarized from the draft Drinking Water Criteria Document for Trihalomethanes (USEPA, 1992d). Studies cited in this section are summarized in the criteria document.

Chloroform has been shown to be rapidly absorbed upon oral, inhalation and peritoneal administration and subsequently metabolized. The reported mean human lethal dose, from clinical observations of overdoses, was around 630 mg/kg. The LD50 values in mice and rats have been reported in the range of 908-1400 mg/kg. Several reactive metabolic intermediates (e.g. phosgene, carbene, dichloromethyl radicals) can be produced via oxidation (major pathway) or reduction (minor pathway) by microsomal preparations. Experimental studies suggested that these active metabolic intermediates are responsible for the hepatic and renal toxicity, and possibly, carcinogenicity, of the parent compound. Animal studies suggest that the extent of chloroform metabolism varies with species and sex. The retention of chloroform in organs after dosing was small. Due to the lipophilic nature of the compound, the residual concentration is in tissues with higher fatty content. In humans, the majority of the tested oral intake doses (0.1 to 1 gm) were excreted through the lungs in the form of a metabolite CO_2 or as the unchanged compound. Urinary excretion levels were below 1% .

Mammalian bioeffects following exposure to chloroform include effects on the central nervous system (CNS), hepatotoxicity, nephrotoxicity, reproductive toxicity and carcinogenicity. Chloroform caused CNS depression and affected liver and kidney function in humans in both accidental and long-term occupational exposure situations. In experimental animals, chloroform caused changes in kidney, thyroid, liver, and serum enzyme levels. These responses are discernible in mammals from exposure to levels of chloroform ranging from 15 to 2900 mg/kg; the intensity of response was dependent upon the dose and the duration of the exposure. Atoxia and sedation were noted in mice receiving a single dose of 500 mg/kg chloroform. Short-term exposure to the low levels of chloroform typically found in air, food, and water are not known to manifest acute toxic effects. The potential for human effects from chronic lifetime exposure is the basis for this regulation.

Developmental toxicity and reproductive toxicity have been investigated in animals. One developmental study reported maternal toxicity in rabbits administered with chloroform by the oral route. Decreased weight gain and mild fatty changes in

liver were observed in dams receiving 50 mg/kg/day (LOAEL); the maternal NOAEL was noted to be 35 mg/kg/day. There was no evidence of developmental effects.

The data from a 7.5-year oral study in dogs conducted by Heywood et al. (1979) were used to calculate the RfD and DWEL. EPA considers this study suitable for the RfD derivation since it is a chronic study and sensitive indices of hepatotoxicity (serum enzyme levels, liver histology) of sufficient numbers of experimental animals were monitored. In this study, chloroform was administered to beagle dogs (16 per dose group) in toothpaste base gelatin capsules at dose levels of 15 or 30 mg/kg/day 6 days/week for 7.5 years. A LOAEL of 15 mg/kg/day was established based on the observation of hepatic fatty cysts in treated animals at both doses. A RfD of 0.01 mg/kg/day has been derived from this LOAEL by the application of an uncertainty factor of 1,000, in accordance with NAS/EPA guidelines. From this RfD, a DWEL of 0.4 mg/L has been calculated for a 70-kg adult consuming 2 liters of drinking water per day.

The results of a number of assays to determine the mutagenicity potential of chloroform are inconclusive. Studies on the *in vitro* genotoxicity of chloroform reported negative results in bacteria (Ames assays), negative results for gene mutations and chromosomal aberrations in mammalian cells, and mixed results in yeasts. *in vivo* DNA damage tests in rats and mice were negative. Gene mutation tests in Drosophila were marginal; whereas tests for chromosomal aberrations and sperm abnormalities were mixed.

Several chronic animal studies confirmed the carcinogenicity of chloroform. Chloroform induced hepatocellular carcinomas in mice when administered by gavage in corn oil (NCI, 1976). Chloroform also induced renal adenomas and adenocarcinomas in male rats regardless of the carrier vehicle (oil or drinking water) employed (NCI, 1976; Roe et al., 1979; Jorgenson et al., 1985).

In the study by Jorgenson et al. (1985), chloroform was administered in drinking water to male Osborne-Mendel rats and female $B6C3F_1$ mice at doses of 0, 200, 400, 900 or 1,800 ppm (0, 19, 38, 81 or 160 mg/kg/day in rats and 0, 34, 65, 130 or 263 mg/kg/day in mice) for 2 years. Chloroform increased the incidence of kidney tumors in male rats in a dose-related manner. The combined incidence of renal tubular cell adenomas, renal tubular cell adenocarcinomas, and nephroblastomas in control, 200, 400, 900 and 1800 ppm groups were 5/301, 6/313, 7/148, 3/48, and 7/50, respectively. Jorgenson's study reported no statistically significant increase in the incidence of hepatocellular carcinomas in the female mice exposed to similar doses of chloroform as reported by the 1976 NCI study.

Since hepatic changes appeared to be dependent on the corn oil vehicle, the interaction of corn oil and chloroform could account for the enhanced hepatic toxicity and thus for the difference in the NCI and Jorgenson studies. Because the drinking water study did not replicate hepatic tumors in female mice and the potential role of corn oil in enhancing toxicity, the NAS Subcommittee on the Health Effects of Disinfectants and Disinfection By-Products recommended that male rat kidney tumor data obtained from Jorgenson's study be used to estimate the carcinogenic potency of chloroform. Until future studies can provide a better understanding of the corn oil effect on hepatic carcinogenicity, EPA agrees to adopt the aforementioned recommendation by the NAS Subcommittee.

Based on all kidney tumor data in male Osborne-Mendel rats reported by Jorgenson et al. (1985), EPA used a linearized multistage model and derived a carcinogenic potency factor for chloroform of 6.1×10^{-3} $(mg/kg/day)^{-1}$. Assuming a daily consumption of two liters of drinking water and an average human body weight of 70 kg, the 95% upper bound limit lifetime cancer risk levels of 10^{-6}, 10^{-5}, and 10^{-4} are associated with concentrations of chloroform in drinking water of 6, 60 and 600 $\mu g/L$, respectively.

EPA has classified chloroform in Group B2, probable human carcinogen, based on sufficient evidence of carcinogenicity in animals and inadequate evidence in humans (IRIS, 1985). The International Agency for Research on Cancer (IARC) has classified chloroform as a Group 2B carcinogen, agent possibly carcinogenic to humans. (IARC, 1982).

According to EPA's three-category approach for establishing MCLGs, chloroform would be placed in Category I since there is sufficient evidence of carcinogenicity via ingestion considering weight of evidence, potency, pharmacokinetics, and exposure. Thus, EPA is considering proposing an MCLG of zero for this contaminant.

Issues

1. The basis for the proposed MCLG for chloroform.

Bromodichloromethane (BDCM)

Bromodichloromethane [CAS No. 75-27-4] is a nonflammable, colorless liquid with a relatively high vapor pressure (50 mmHg at 20°C). BDCM is moderately soluble in water (3.3 gm/L at 30°C) and soluble in organic solvents (log octanol/water partition coefficient of 1.88). Only a small amount of BDCM is currently produced commercially in the United States. The chemical is used as an intermediate for organic synthesis and as a laboratory

reagent. The principal source of BDCM in drinking water is the chemical interaction of chlorine with the commonly present organic matter and bromide ions. Degradation of BDCM is not well studied, but probably involves photooxidation. The estimated atmospheric half-life of BDCM is two to three months. Volatilization is the principal mechanism for removal of BDCM from rivers and streams (half-life of hours to weeks). Limited studies reported that BDCM adsorbed poorly to sediments and soils. No study of bioaccumulation of BDCM was located. Based on the data of a few structurally similar chemicals such as chloroform, the bioconcentration potential of BDCM in aquatic organisms is low. Biodegradation of BDCM is limited under aerobic conditions and extensive (completion within days) under anaerobic conditions.

Occurrence and Human Exposure

BDCM, occurs in public water systems that chlorinate water containing humic and fulvic acids and bromine that can enter source waters through natural and anthropogenic means. Several water quality factors affect the formation of BDCM including Total Organic Carbon (TOC), pH, bromide and temperature. Different treatment practices can reduce the formation of BDCM. These include the use of chlorine dioxide, chloramination, and ozonation prior to chloramination, as well as the use of precursor removal technologies such as coagulation/filtration, granular activated carbon (GAC) and membrane filtration.

The following table presents the most recent and comprehensive occurrence information available for bromodichloromethane in drinking water. Descriptions of these surveys and other data are detailed in "Occurrence Assessment for Disinfectants and Disinfection By-Products (Phase 6a) in Public Drinking Water," USEPA, August 1992. The table lists six surveys conducted by Federal, as well as private agencies. Median concentrations of bromodichloromethane in drinking water appear to range from 6.6 to 15 $\mu g/L$ for surface water supplies and <0.5 $\mu g/L$ for ground-water supplies.

Occurrence of Bromodichloromethane						
Survey (Year)[1]	Location	Sample Information (No. of Samples)	Concentration (μg/L)			
			Range	Mean	Median	Other
CWSS (1978) Brass et al., 1981	450 Systems	Finished Water (1,100): Surface Water Ground Water		 12[3] 5.8[3]	 6.8 <0.5	Positive Detections: 94%[4] 33%[4]
RWS (1978-1980) Brass, 1981	>600 Rural Systems (>2,000 households)	Drinking Water from: Surface Water Ground Water		 17[3] 7.7[3]	 11 <0.5	Positive Detections: 76%[4] 13%[4]
GWSS (1980 1981) Westrick et al 1983	945 GW Systems: (466 Random and 479 Nonrandom)	 Serving >10,000 (327) Serving <10,000 (618)	 Max. 110 Max. 79		 0.4 0	90th Percentile 9.2 6.1
TSD, 1991[2] (1984-1991)	Unregulated Contaminant Data Base - Treatment Facilities from 19 States	Finished Water at Treatment Plants (4,439)		5.6	3	
TSD, 1992[2] (1987-1989)	Disinfection By-Products Field Studies	Finished Water: At the Plant (73) Distribution System (56)	 <0.2-90 <0.2-100	 13 17	 11 15	Positive Detections: 96% 98%
EPA/AMWA/CDHS[2] (1988-1989) Krasner et al., 1989	35 Water Utilities Nationwide	Samples from Clearwell Effluent for 4 Quarters	Max. 82	4.1-10[5]	6.6	75% of Data was Below 14 μg/L

[1] Dates indicate period of sample collection
[2] May not be representative of national occurrence
[3] Mean of the positives
[4] Of systems sampled
[5] Range of medians for individual quarters

AMWA Association of Metropolitan Water Agencies
CDHS California Department of Health Services
CWSS Community Water Supply Survey
GWSS Ground Water Supply Survey
RWS Rural Water Survey
TSD Technical Support Division

BDCM is usually found in air at low concentrations. Based on information obtained through a literature review, Howard (1990) estimated the average daily intake of BDCM from air using an inhalation rate of 20 m^3/day. Assuming a range of 6.7 to 670 ng/m^3, the average exposure may be as low as 0.134 µg/day or as high as 13.4 µg/day.

BDCM is not a common contaminant in food. In one market study of 39 different food items, BDCM was detected in one dairy composite (1.2 ppb), butter (7 ppb), and two beverages (0.3 and 0.6 ppb). Analysis of cola soft drinks found BDCM in three samples with reported concentrations of 2.3 ppb, 3.4 ppb, and 3.8 ppb (Entz et al., 1982 in Howard, 1990).

Limited data are available to characterize food and air exposures to BDCM. Although some uses of chlorine have been identified in the food production/food processing area, monitoring data are inadequate to characterize the magnitude and frequency of potential BDCM exposures. Based on the limited number of food groups that are believed to contain BDCM and that there are not significant levels expected in ambient or indoor air, EPA assumes that drinking water is the predominant source of BDCM intake. The EPA requests any additional data on known concentrations of BDCM in drinking water, food, and air.

Health Effects

The health effects information in this section is summarized from the draft Drinking Water Criteria Document for Trihalomethanes (USEPA, 1992d). Studies mentioned below are summarized in the criteria document.

Studies indicated that gastrointestinal absorption of BDCM is high in animals. No studies were located regarding BDCM in humans or animals following inhalation or dermal exposure. By analogy with the experimental data of a structurally-related halomethane chloroform, inhalation and dermal absorption may be high for BDCM. The reported LD_{50} values in mice and rats ranged from 450 to 969 mg/kg. Under both *in vivo* and *in vitro* conditions, several active metabolic intermediates (e.g. dichlorocarbonyl, dichloromethyl radicals) were produced via oxidation or reduction by microsomal preparations. Experimental studies suggested that these active metabolic intermediates may be responsible for hepatic and renal toxicity, and possibly, carcinogenicity, of the parent compound. Animal studies suggest that the extent of BDCM metabolism varies with species and sex. The retention of BDCM in organs after dosing was small, even after repeated doses. Urinary excretion levels were below 3%.

Mammalian bioeffects following exposure to BDCM include effects on the central nervous system (decreased operant

response), hepatotoxicity, nephrotoxicity, reproductive toxicity and carcinogenicity. In experimental mice and rats, BDCM caused changes in kidney, liver, and serum enzyme levels, and decrease of body weight. These responses were discernible in rodents from exposure to levels of BDCM that ranged from 25 to 300 mg/kg; the intensity of response was dependent upon the dose and the duration of the exposure. Ataxia and sedation were observed in mice receiving a single dose of 500 mg/kg BDCM.

One study investigated developmental and reproductive toxicity of BDCM in rodents. Ruddick et al. (1983) administered BDCM in corn oil to groups of pregnant rats by gavage at doses of 0, 50, 100 or 200 mg/kg/day on days 6 to 15 of gestation. At 200 mg/kg/day, BDCM significantly ($p < 0.05$) decreased maternal weight (25%) and increased relative kidney weights. There were no increases in the incidence of fetotoxicity or external/visceral malformations, but sternebral anomalies were more prevalent at 100 and 200 mg/kg than at 50 mg/kg. The sternebral anomalies were not considered by the authors to be evidence of a teratogenic effect, but of the maternal toxicity.

Data from a National Toxicology Program (NTP) chronic oral study in $B6C3F_1$ mice (NTP, 1987) was used to calculate the RfD and DWEL. BDCM in corn oil was given to mice by gavage 5 days/week for 102 weeks. Male mice (50/dose) were administered doses of 0, 25 or 50 mg/kg/day while female mice (50/dose) received doses of 0, 75 or 150 mg/kg/day. Following treatment, mortality, body weight and histopathology were observed. Renal cytomegaly and fatty metamorphosis of the liver was observed in male mice (≥25 mg/kg/day). Compound-related follicular cell hyperplasia of the thyroid gland was observed in both males and females. The survival rate decreased in females and decreases in mean body weights were observed in both males and females at high doses. Based on the observed renal, liver and thyroid effects in male mice, a LOAEL of 25 mg/kg/day was identified. A RfD of 0.02 mg/kg/day has been derived from the LOAEL of 25 mg/kg/day in mice by the application of an uncertainty factor of 1,000, in accordance with EPA guidelines for use of a LOAEL derived from a chronic animal study. From this RfD, a DWEL of 0.7 mg/L has been calculated for a 70-kg adult consuming 2 liters of drinking water per day.

In vitro genotoxicity studies reported mixed results in bacteria *Salmonella* strains and yeasts. BDCM was not mutagenic in mouse lymphoma cells without metabolic activation; but induced mutation with activation. An increase in frequency of sister chromatid exchange was reported in cultured human lymphocytes, rat liver cells, and mouse bone marrow cells (*in vivo*); but not in Chinese hamster ovary cells. Overall, more studies yielded positive results and evidence of mutagenicity for BDCM is considered adequate.

There are no epidemiologic studies which isolate BDCM exposure. A number of ecological studies and case-control studies reported positive association between the ingestion of chlorinated drinking water and cancer mortality rates for the stomach, large intestine, rectum and bladder. One study reported a strong correlation between bladder cancer and brominated trihalomethanes. In all studies, the studied populations were exposed to a mixture of compounds. Thus, these data are inadequate for assessing the carcinogenic potential of BDCM.

Evidence of the carcinogenicity of BDCM has been confirmed by a NTP (1987) chronic animal study. In this study BDCM in corn oil was administered via gavage to groups of 50 rats (Fischer 344/N) of each sex at doses of 0, 50 or 100 mg/kg, 5 days/week, for 102 weeks (NTP, 1987). Male $B6C3F_1$ mice (50/dose) were administered 0, 25 or 50 mg/kg by same route while females received 0, 75 or 150 mg/kg/day. BDCM caused statistically significant increases in kidney tumors in male mice, the liver in female mice, and the kidney and large intestine in male and female rats. In male mice, the combined incidence of tubular cell adenomas or adenocarcinomas of the kidneys increased significantly in the high-dose group (vehicle control, 1/46; low-dose, 2/49; high-dose 9/50). The combined incidences of hepatocellular adenomas or carcinomas in vehicle control, low-dose and high-dose female mice groups were 3/50, 18/48 and 29/50, respectively.

In rats from the NTP study, the combined incidences of tubular cell adenomas or adenocarcinomas in vehicle control, low-dose and high-dose groups were 0/50, 1/49 and 13/50 for males and 0/50, 1/50 and 15/50 for females, respectively. Tumors of large intestines were significantly increased in a dose-dependent manner in male rats, and only observed in high-dose female rats. The combined incidences of adenocarcinomas or adenomatous polyps were 0/50, 13/49, 45/50 for males and 0/46, 0/50, 12/47 for females, respectively. The combined tumor incidences of large intestine and kidney were 0/50, 13/49, 46/50 for male rats and 0/46, 1/50, 24/48 for female rats, respectively.

Using the linearized multistage model, several cancer potency factors for BDCM were derived based on the observed cancer incidence of various tumor types (large intestine, kidney, or combined) in mice or rats reported in the NTP bioassay. The resulting cancer potency factors are in the range of 4.9×10^{1} to 6.2×10^{-2} $(mg/kg/day)^{-1}$. A potency factor of 1.3×10^{-1} $(mg/kg/day)^{-1}$ was derived from the incidence of hepatic tumors in female mice (IRIS, 1990). However, hepatic tumor data should be interpreted with caution because studies of an analog chloroform indicated a possible role of corn oil vehicle in induction of these tumors. Until future studies can provide a better understanding of the corn oil effect on hepatic carcinogenicity

EPA considers carcinogenic risk quantification for BDCM based on kidney or large intestine tumor data to be more appropriate.

According to the Risk Assessment Guidelines of 1986 (USEPA, 1986), where two or more significantly elevated tumor sites or types are observed in the same study, the slope factor of the greatest sensitivity preferably should be used for carcinogenic risk estimation. Based on the potency factor of 6.2×10^{-2} $(mg/kg/day)^{-1}$ derived from the kidney tumor incidence in male mice, the estimated concentrations of BDCM in drinking water associated with excess cancer risks of 10^{-4}, 10^{-5} and 10^{-6} are 60, 6 and 0.6 $\mu g/L$, respectively.

EPA has classified BDCM in Group B2, probable human carcinogen, based on the sufficient evidence of carcinogenicity in animals and inadequate evidence in humans. The International Agency for Research on Cancer (IARC) has recently classified BDCM as a Group 2B carcinogen, agent probably carcinogenic to humans (IARC, 1991).

Following EPA's three-category approach for establishing MCLGs, BDCM would be placed in Category I since there is sufficient evidence for carcinogenicity via ingestion considering weight of evidence, potency, pharmacokinetics, and exposure. Thus, EPA is considering proposing an MCLG of zero for this contaminant.

Issues

1. Basis of the proposed MCLG for BDCM.

2. The use of tumor data of large intestine and kidney, but not liver, in quantitative estimation of carcinogenic risk of BDCM from oral exposure.

Dibromochloromethane (DBCM)

Dibromochloromethane [CAS No. 124-48-1] is a nonflammable, colorless liquid with a relatively high vapor pressure (76 mmHg at 20°C). DBCM is moderately soluble in water (4 gm/l at 20°C) and soluble in organic solvents (log octanol/water partition coefficient of 2.09). Currently DBCM is not produced commercially in the United States. The chemical has only limited uses as a laboratory agent. The principal source of DBCM in drinking water is the chemical interaction of the chlorine with the commonly present organic matter and bromide ions. Degradation of DBCM is not well studied, but probably involves photooxidation. The estimated atmospheric half-life of DBCM is one to two months. Volatilization is the principle mechanism for removal of DBCM from rivers and streams (half-life of hours to weeks). Studies reported that DBCM adsorbs poorly to soil and

sediments. No experimental study was found regarding the bioconcentration of DBCM. Based on the data of a few structurally similar chemicals, the bioconcentration potential of DBCM in aquatic organisms is assumed to be low. Biodegradation of DBCM is limited under aerobic condition and more extensive under anaerobic conditions.

Occurrence and Human Exposure

DBCM occurs in public water systems that chlorinate water containing humic and fulvic acids and bromine that can enter source waters through natural and anthropogenic means. Several water quality factors can affect the formation of DBCM, including Total Organic Carbon (TOC), pH, bromide, and temperature. Different treatment practices can reduce the formation of DBCM in drinking water. These include the use of precursor removal technologies such as coagulation/filtration, granular activated carbon (GAC), membrane filtration, and the use of chlorine dioxide, chloramination and ozonation.

The following table presents the most recent and comprehensive occurrence information available for dibromochloromethane in drinking water. Descriptions of these surveys and other data are detailed in "Occurrence Assessment for Disinfectants and Disinfection By-Products (Phase 6a) in Public Drinking Water," USEPA, August 1992. The table lists six surveys conducted by Federal, as well as private agencies. Median concentrations of dibromochloromethane in drinking water appear to range from 0.6 to 3.6 μg/L for surface water supplies and <0.5 μg/L for ground-water supplies.

Occurrence of Dibromochloromethane in Drinking Water

Survey (Year)[1]	Location	Sample Information (No. of Samples)	Concentration (μg/L)			
			Range	Mean	Median	Other
CWSS (1978) Brass et al., 1981	450 Systems	Finished Water (1,100): Surface Water Ground Water		 5.0[3] 6.6[3]	 1.5 <0.5	Positive Detections: 67%[4] 34%[4]
RWS (1978-1980) Brass, 1981	>600 Rural Systems (>2,000 households)	Drinking Water from: Surface Water Ground Water		 8.5[3] 9.9[3]	 0.8 <0.5	Positive Detections: 56%[4] 13%[4]
GWSS (1980-1981) Westrick et al. 1983	945 GW Systems: (466 Random and 479 Nonrandom)	 Serving >10,000 (327) Serving <10,000 (618)	 Max. 59 Max. 63		 0.7 0	90th Percentile: 9.2 5.6
TSD, 1991[2] (1984-1991)	Unregulated Contaminant Data Base - Treatment Facilities from 19 States	Sampled at the Plant (4,439)		3.0	1.7	
TSD, 1992[2] (1987-1989)	Disinfection By-Products Field Studies	Finished Water: At the Plant (73) In Distribution System (56)	 <0.2-41 <0.2-41	 4.9 6.6	 2.0 3.4	Positive Detections: 92% 93%
EPA/AMWA/CDHS[2] (1988-1989) Krasner et al., 1989	35 Water Utilities Nationwide	Samples from Clearwell Effluent for 4 Quarters	Max. 63		3.6 2.6-4.5[5]	75% of Data was Below 9.1 μg/L

[1] Dates indicate period of sample collection
[2] May not be representative of national occurrence
[3] Mean of the positives
[4] Of systems sampled
[5] Range of medians for individual quarters

AMWA Association of Metropolitan Water Agencies
CDHS California Department of Health Services
CWSS Community Water Supply Survey
GWSS Ground Water Supply Survey
RWS Rural Water Survey
TSD Technical Support Division

No information is available concerning the occurrence of DBCM in food in the United States. The Food and Drug Administration (FDA) does not analyze for DBCM in foods. However, there are several uses of chlorine in food production; for example, disinfection of chicken in poultry plants and the superchlorination of water at soda and beer bottling plants (Borum, 1991). Therefore, the possibility exists for dietary exposure from the by-products of chlorination in food products.

Based on information obtained through a literature review, Howard (1990) estimated the average daily intake of DBCM from air using an inhalation rate of 20 m^3/day. Assuming a range of 8.25 to 425 ng/m^3, the exposure may be as low as 0.17 μg/day or as high as 8.5 μg/day.

Although some uses of chlorine have been identified in the food production/food processing area, monitoring data are not available to adequately characterize the magnitude or frequency of potential exposure to DBCM. Additionally, preliminary discussions with FDA suggest that there are not approved uses for chlorine in most foods consumed in the typical diet. Based on the limited number of food groups that are believed to contain chlorinated chemicals and that there are not significant levels expected in ambient or indoor air, EPA assumes that drinking water is the predominant source of DBCM intake. Characterization of food and air exposure are issues currently under review. The EPA, therefore, is proposing to regulate DBCM in drinking water with a relative source contribution (RSC) value at the ceiling level of 80%. The EPA requests any additional data on known concentrations of DBCM in drinking water, food, and air.

Health Effects

The health effects information in this section is summarized from the Drinking Water Health Criteria Document for Trihalomethanes (USEPA, 1992d). Studies mentioned in this section are summarized in the criteria document.

Studies indicated that gastrointestinal absorption of DBCM is high in animals. No studies were located regarding DBCM in humans or animals following inhalation or dermal exposure. Based on the physical-chemical properties of DBCM, and by analogy with the structurally-related halomethanes such as chloroform, it is expected that the inhalation and dermal absorption could be significant for DBCM.

The LD50 values in mice and rats range from 800 to 1,200 mg/kg. Under both *in vivo* and *in vitro* conditions, several active metabolic intermediates (e.g. dihalocarbonyl, bromochloromethyl radicals) can be produced via oxidation or reduction by microsomal preparations. Environmental studies

suggest that these active metabolic intermediates are responsible for the hepatic and renal toxicity, and possibly carcinogenicity, of the parent compound. Animal studies suggest that the extent of DBCM metabolism varies with species and sex. The retention of DBCM in organs after dosing was small and relatively higher concentrations were found in stomach, liver and kidneys. Urinary excretion levels were below 2% .

Mammalian bioeffects following exposure to DBCM include effects on the central nervous system (decreased operant response), hepatotoxicity, nephrotoxicity, reproductive toxicity and carcinogenicity. In experimental mice and rats, DBCM caused changes in kidney, liver, and serum enzyme levels, and decreased body weight. These responses are discernible in mammals from exposure to levels of DBCM ranging from 39 to 250 mg/kg; the intensity of response was dependent upon the dose and the duration of the exposure. Ataxia and sedation were observed in mice receiving a single dose of 500 mg/kg DBCM.

Developmental and reproductive toxicity of DBCM was investigated in rodents. A multi-generation reproductive study of mice treated with DBCM in drinking water showed maternal toxicity (weight loss, liver pathological changes) and fetal toxicity (decreased pup weight & viability). The study identified a NOAEL of 17 mg/kg/day and a LOAEL of 171 mg/kg/day.

The National Toxicity Program (NTP, 1985) evaluated the subchronic and chronic toxicity of DBCM in F344/N rats and $B6C3F_1$ mice. In this study corn oil is used as the gavage vehicle. The chronic data indicated that doses of 40 and 50 mg/kg/day produced histopathological lesions in the liver of rats and mice, respectively. However, the chronic studies did not identify a reliable NOAEL. The subchronic study identified both a LOAEL and a NOAEL for hepatotoxicity, and was used to calculate the RfD and DWEL.

In the NTP subchronic study, DBCM in corn oil was administered to Fischer 344/N rats and $B6C3F_1$ mice via gavage at dose levels of 0, 15, 30, 60, 125 or 250 mg/kg/day, 5 days a week for 13 weeks. Following treatment, survival, body weight, clinical signs, histopathology and gross pathology were evaluated. Final body weights of rats that received 250 mg/kg/day were depressed 47% for males and 25% for females. Kidney and liver toxicity was observed in male and female rats and male mice at 250 mg/kg/day. A dose-dependent increase in hepatic vacuolation was observed in male rats. Based on this hepatic effect, the NOAEL and LOAEL in rats were 30 and 60 mg/kg/day, respectively.

Several studies on the mutagenicity potential of DBCM have reported inconclusive results. Studies on the *in vitro*

genotoxicity of DBCM reported mixed results in bacteria *Salmonella typhimurium* strains and yeasts. DBCM produced sister chromatid exchange uncultured human lymphocytes and Chinese hamster ovary cells (without activation). An increased frequency of sister chromatid exchange was observed in mouse bone marrow cells from mice dosed orally, but not via the intraperitoneal route.

No epidemiologic studies isolate DBCM exposure. A number of ecological studies and case-control studies reported positive association between the ingestion of chlorinated drinking water and cancer mortality rates for the stomach, large intestine, rectum and bladder. One study reported a strong correlation between bladder cancer and brominated trihalomethanes. In all studies, people were exposed to a mixture of compounds. Thus, these data are inadequate for assessing the carcinogenic potential of DBCM.

The carcinogenicity of DBCM was investigated by a NTP (1985) chronic animal study. In this study DBCM in corn oil was administered via gavage to groups of male and female F344/N rats at doses of 0, 40 or 80 mg/kg/day, 5 days/week for 104 weeks; and groups of male and female mice at 0, 50 or 100 mg/kg/day, 5 days/week for 105 weeks. Administration of DBCM showed a significant increase in the incidence of hepatocellular adenomas in high-dose female mice (vehicle control, 2/50; low dose, 4/49; high dose, 11/50) and combined incidence of hepatocellular adenomas or carcinomas (6/50; 10/49; 19/50). In high-dose male mice, administration of DBCM showed a significant increase in the incidence of hepatocellular carcinomas (10/50; 9/50; 19/50); however, the combined incidence of hepatocellular adenomas or carcinomas was only marginally increased (23/50; 14/50; 27/50). DBCM did not result in increased incidence of tumors in treated rats.

Using the linearized multistage model, EPA derived a cancer potency factor of 8.4×10^{-2} $(mg/kg/day)^{-1}$ (IRIS, 1990). The derivation was based on the tumor incidence of the hepatocellular adenomas or carcinomas in the female mice reported in the 1985 NTP study. Due to the possible role of the corn oil vehicle in induction of hepatic tumors as reported in studies on chloroform, some uncertainty exists regarding the relevance of this derived cancer potency factor to exposure via drinking water. However, the only tumor data currently available on DBCM are for liver tumors in mice. Until future studies can provide additional data, EPA considers this cancer potency factor valid for potential carcinogenic risk quantification for DBCM.

EPA has classified DBCM in Group C, possible human carcinogen, based on the limited evidence of carcinogenicity in animals (only in one species) and inadequate evidence of

carcinogenicity in humans. The International Agency for Research on Cancer (IARC) has classified DBCM as a Group 3 carcinogen: agent not classifiable as to its carcinogenicity to humans.

Using EPA's three-category approach for establishing MCLG, DBCM would be placed in Category II since there is limited evidence for carcinogenicity via drinking water considering weight of evidence, potency, pharmacokinetics, and exposure. As a Category II chemical, EPA would follow the first option and set the MCLG for DBCM on noncarcinogenic endpoints (the RfD) with the application of an additional safety factor to account for possible carcinogenicity. A RfD of 0.02 mg/kg/day has been derived from the NOAEL of 30 mg/kg/d, adjusted for dosing 5 days per week and divided by an uncertainty factor of 1,000. This factor is appropriate for use of a NOAEL derived from a subchronic animal study. EPA is considering proposing an MCLG of 0.06 mg/L for DBCM based on the DWEL of 0.7 mg/L, an additional safety factor of 10 for possible carcinogenicity, and an assumed drinking water contribution of 80 percent of total exposure.

$$\text{DWEL} = \frac{30\ \text{mg/kg/d} \times 70\ \text{k}}{1{,}000 \times 2\ \text{L/d}} = 0.7\ \text{mg/L}$$

$$\text{MCLG} = \frac{0.7\ \text{mg/L}}{10} \times 0.8 = 0.06\ \text{mg/L}$$

Issue

1. The basis for the proposed MCLG for DBCM.

2. The RSC of 80% for DBCM.

Bromoform

Bromoform [tribromomethane, CAS No. 75-25-2] is a nonflammable, colorless liquid with a sweet odor and a relatively high vapor pressure (5.6 mmHg at 25°C). Bromoform is moderately soluble in water (3.2 gm/L at 30°C) and soluble in organic solvents (log octanol/water partition coefficient of 2.38). Bromoform is not currently produced commercially in the United States. The chemical has only limited uses as a laboratory agent and as a fluid for mineral ore separation. The principal source of bromoform in drinking water is the chemical interaction of chlorine with commonly present organic matter and bromide ion. Degradation of bromoform is not well studied, but probably involves photooxidation. The estimated atmospheric half-life of bromoform is one to two months. Volatilization is the principle mechanism for removal of bromoform from rivers and streams (half-life of hours to weeks). Studies reported that bromoform adsorbs poorly to sediments and soils. No experimental studies were located regarding the bioconcentration of bromoform. Based on the data from a few structurally similar chemicals, the potential for bromoform to be bioconcentrated by aquatic organisms is low.

Biodegradation of bromoform is limited under aerobic condition but more extensive under anaerobic conditions.

Occurrence and Human Exposure

Bromoform occurs in public water systems that chlorinate water containing humic and fulvic acids and bromine that can enter source waters through natural and anthropogenic means. Several water quality factors affect the formation of bromoform including Total Organic Carbon (TOC), pH, and temperature. Different treatment practices can reduce the level of bromoform. These include the use of chloride dioxide, chloramination, and ozonation prior to chloramination.

The following table presents the most recent and comprehensive occurrence information available for bromoform in drinking water. Descriptions of these surveys and other data are detailed in "Occurrence Assessment for Disinfectants and Disinfection By-Products (Phase 6a) in Public Drinking Water," USEPA, August 1992. The table lists six surveys conducted by Federal, as well as private agencies. Median concentrations of bromoform in drinking water appear to range from <0.2 to 0.57 μg/L for surface water supplies and <0.5 μg/L for ground-water supplies.

Occurrence of Bromoform in Drinking Water

Survey (Year)[1]	Location	Sample Information (No. of Samples)	Concentration (μg/L)			
			Range	Mean	Median	Other
CWSS (1978) Brass et al., 1981	450 Systems	Finished Water (1,100): Surface Water Ground Water		2.1[3] 11[3]	<1.0 <0.5	Positive Detections: 13%[4] 26%[4]
RWS (1978-1980) Brass, 1981	>600 Rural Systems (>2,000 Households)	Drinking Water from: Surface Water Ground Water		8.7[3] 12[3]	<0.5 <0.5	Positive Detections: 18%[4] 12%[4]
GWSS (1980-1981) Westrick et al. 1983	945 GW Systems: (466 Random and 479 Nonrandom)	Serving >10,000 (327) Serving <10,000 (618)	Max. 68 Max. 110		0 0	90th Percentile: 8.3 4.1
TSD, 1991[2] (1984-1991)	Unregulated Contaminant Data Base - Treatment Facilities from 19 States	Sampled at the Plants (1,409)		2.5	1	
TSD, 1992[2] (1987-1989)	Disinfection By-Products Field Studies	Finished Water: At the Plant (73) In Distr. System (56)	<0.2-6.7 <0.2-10	0.7 1.0	<0.2 <0.2	Positive Detections: 45% 48%
EPA/AMWA/CDHS[2] (1988-1989) Krasner et al., 1989	35 Water Utilities Nationwide	Samples from Clearwell Effluent for 4 Quarters	Max. 72		0.33-0.88[5] 0.57	75% of Data was Below 2.8

[1] Dates indicate period of sample collection
[2] May not be representative of national occurrence
[3] Mean of the positives
[4] Of systems sampled
[5] Range of medians for individual quarters

AMWA Association of Metropolitan Water Agencies
CDHS California Department of Health Services
CWSS Community Water Supply Survey
GWSS Ground Water Supply Survey
RWS Rural Water Survey
TSD Technical Support Division

No information is available concerning the occurrence of bromoform in food in the United States. The Food and Drug Administration (FDA) does not analyze for bromoform in foods. However, there are several uses of chlorine in food production; for example, disinfection of chicken in poultry plants and the superchlorination of water at soda and beer bottling plants (Borum, 1991). Therefore, the possibility exists for dietary exposure from the by-products of chlorination in food products.

Bromoform is usually found in ambient air at low concentrations. One study reported ambient air concentrations from several urban locations across the U.S.. The overall mean concentration of positive samples was found to be 4.15 ng/m^3 and the maximum level was 71 ng/m^3 (Brodzinsky and Singh, 1983 in USEPA, 1991). Although the data are limited for bromoform, an inhalation intake could be estimated using the mean and maximum values from the Brodzinsky and Singh (1983) study, indicating a possible range of 0.08 to 1.4 μ/d.

Based on the limited number of food groups that are believed to contain bromoform and that significant levels are not expected in ambient or indoor air, EPA is assuming that drinking water is the predominant source of bromoform intake. Characterization of food and air exposures are issues currently under review. The EPA requests any additional data on known concentrations of bromoform in drinking water, food, and air.

Health Effects

The health effects information in this section is summarized from the Drinking Water Health Criteria Document for Trihalomethanes (USEPA, 1992d). Studies mentioned in this section are summarized in the criteria document.

Studies have indicated that gastrointestinal absorption of bromoform is high in humans and animals. No studies were located regarding bromoform in humans or animals following inhalation or dermal exposure. Based on the physical-chemical properties of bromoform, and by analogy with the structurally-related halomethanes such as chloroform, it is expected that both inhalation and dermal absorption could be significant for bromoform.

Bromoform was used as a sedative for children with whooping cough. Based on clinical observations of accidental overdose cases, the estimated lethal dose for a 10- to 20-kg child is about 300 mg/kg. The clinical signs in fatal cases were central nervous system (CNS) depression followed by respiratory failure.

The LD_{50} values in mice and rats have been reported in the range of 1,147-1550 mg/kg. Under both *in vivo* and *in vitro*

conditions, several active metabolic intermediates (e.g., dibromocarbonyl, dibromomethyl radicals) are produced via oxidation or reduction by microsomal preparations. Experimental studies suggested that these active metabolic intermediates are responsible for hepatic and renal toxicity, and possibly, carcinogenicity, of the parent compound. Animal studies suggest that the extent of bromoform metabolism varies with species and sex. The retention of bromoform in organs after dosing was small; relatively higher concentrations were found in tissues with higher lipophilic content. Urinary excretion levels were below 5%.

Mammalian bioeffects following exposure to bromoform include effects on the central nervous system (CNS), hepatotoxicity, nephrotoxicity, and carcinogenicity. Bromoform causes CNS depression in humans. The reported LOAEL which results in mild sedation in humans is 54 mg/kg. In experimental mice and rats, bromoform caused changes in kidney, liver, and serum enzyme levels, decrease of body weight, and decreased operant response. These responses are discernible in mammals from exposure to levels of bromoform ranging from 50 to 250 mg/kg; the intensity of response was dependent upon the dose and the duration of the exposure. Ataxia and sedation were noted in mice receiving a single dose of 1,000 mg/kg bromoform or 600 mg/kg for 14 days.

Few studies have investigated developmental and reproductive toxicity of bromoform in rodents. A developmental study in rats showed no fetal variations in a group fed with 50 mg/kg/day. An increased incidence of minor anomalies was noted at doses of 100 and 200 mg/kg/day. No maternal toxicity in rats was observed. One detailed reproductive toxicity study reported no apparent effects on fertility and reproduction when male and female rats were administered bromoform via gavage in corn oil at doses up to 200 mg/kg/day.

EPA used subchronic data from an oral study (NTP, 1989) to calculate the RfD and DWEL. In this study, bromoform was administered to rats in corn oil via gavage at dose levels of 0, 12, 25, 50, 100 or 200 mg/kg/day 5 days a week for 13 weeks. Based on the observation of hepatocellular vacuolization in treated male rats a NOAEL of 25 mg/kg/day was established. A RfD of 0.02 mg/kg/day has been derived from this NOAEL by the application of an uncertainty factor of 1,000, in accordance with EPA guidelines for use of a NOAEL from a subchronic study. From this RfD, a DWEL of 0.7 mg/L has been calculated for a 70-kg adult consuming 2 liters of drinking water per day.

A number of studies investigated the mutagenicity potential of bromoform. Studies on the *in vitro* genotoxicity of bromoform reported mixed results in bacteria *Salmonella typhimurium* strains. Bromoform produced mutations in cultured mouse lymphoma cells and sister chromatid exchange in human lymphocytes. Under

in vivo condition bromoform induced sister chromatid exchange, and chromosomal aberration and micronucleus in mouse bone marrow cells. Overall, most studies yielded positive results and evidence of mutagenicity for bromoform is considered adequate.

There are no epidemiologic studies which isolate bromoform exposure. A number of ecological studies and case-control studies reported positive association between the ingestion of chlorinated drinking water and cancer mortality rates for the stomach, large intestine, rectum and bladder. One study reported a strong correlation between bladder cancer and brominated trihalomethanes. In all studies, the cases were exposed to a mixture of compounds. Thus, EPA believes these data are inadequate for assessing the carcinogenic potential of bromoform.

The NTP (1989) conducted a chronic animal study to investigate the carcinogenicity of bromoform. In this study bromoform was administered in corn oil via gavage to F344/N rats (50/sex/group) at doses of 0, 100 or 200 mg/kg/day, 5 days/week for 105 weeks. An evaluation of the study results showed adenomatous polyps or adenocarcinoma (combined) of the large intestine (colon or rectum) were induced in three male rats (vehicle control, 0/50; low dose, 0/50; high dose, 3/50) and in nine female rats (0/50; 1/50; 8/50). The increase was considered to be significant since these tumors are rare in control animals. Neoplastic lesions in the large intestine in female rats reported was used to estimate carcinogenic potency of bromoform. EPA derived a cancer potency factor of 7.9×10^{-3} $(mg/kg/day)^{-1}$ using the linearized multistage model (IRIS, 1990). Assuming a daily consumption of two liters of drinking water and an average human body weight of 70 kg, the 95% upper bound limit lifetime cancer risks of 10^{-6}, 10^{-5} and 10^{-4} are associated with concentrations of bromoform in drinking water of 4, 40 and 400 $\mu g/L$, respectively.

EPA classified bromoform in Group B2, probable human carcinogen, based on the sufficient evidence of carcinogenicity in animals and inadequate evidence of carcinogenicity in humans. The International Agency for Research on Cancer (IARC) has recently classified bromoform in Group 3: agent not classifiable as to it carcinogenicity to humans (IARC, 1991).

Using EPA's three-category approach for establishing MCLG, bromoform would be placed in Category I since there is sufficient evidence for carcinogenicity from drinking water considering weight of evidence, potency, pharmacokinetics, and exposure. Thus, EPA is considering proposing an MCLG of zero for this contaminant.

Issues

The basis for the proposed MCLG for bromoform.

Dichloroacetic Acid

Chlorination of water containing organic material (humic, fulvic acids) results in the generation of many organic compounds, including dichloroacetic acid (DCA) (CAS. No. 79-43-6), a nonvolatile compound.

Though DCA is generally a concern due to its occurrence in chlorinated drinking water, dichloroacetic acid is used as a chemical intermediate, and an ingredient in pharmaceuticals and medicine. Previously, DCA was used experimentally to treat diabetes and hypercholesterolemia in human patients. In addition, DCA was used as an agricultural fungicide and topical astringent. It has also been extensively investigated for potential therapeutic use as a hypoglycemic, hypolactemic and hypolipidemic agent.

Occurrence and Human Exposure

DCA has been found to occur as a disinfection by-product in public water systems that chlorinate water containing humic and fulvic acids.

The following table presents the most recent and comprehensive occurrence information available for dichloroacetic acid in drinking water. Descriptions of these surveys and other data are detailed in "Occurrence Assessment for Disinfectants and Disinfection By-Products (Phase 6a) in Public Drinking Water," USEPA, August 1992. Median concentrations of dichloroacetic acid in drinking water were found to range from 6.4 to 17 μg/L.

Occurrence of Dichloroacetic Acid in Drinking Water

Survey (Year)[1]	Location	Sample Information (No. of Samples)	Concentration (μg/L)			
			Range	Mean	Median	Other
TSD, 1992[2] (1987-1989)	Disinfection By-Products Field Studies	Finished Water: At the Plant (72) In the Distr. System (56)	 <0.4-61 <0.4-75	 18 21	 16 17	Positive Detections: 93% 96%
EPA/AMWA/CDHS[2] (1988-1989) Krasner et al., 1989	35 Water Utilities Nationwide	Samples from Clearwell Effluent for 4 Quarters	<0.6-46		5.0-7.3[3] 6.4	75% of Data was Below 12 μg/L DL = 0.6 μg/L

[1] Dates indicate period of sample collection
[2] May not be representative of national occurrence
[3] Range of medians for individual quarters

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Based on the above data, a range of exposure to DCA from drinking water can be calculated using a consumption rate of 2 liters per day. The expected median exposure from drinking water would range from 13 to 34 μg/day, using these data sets.

No information is available concerning the occurrence of DCA in food and ambient or indoor air in the United States. The Food and Drug Administration (FDA) does not analyze for DCA in foods. However, there are several uses of chlorine in food production; for example, disinfection of chicken in poultry plants and the superchlorination of water at soda and beer bottling plants. Therefore, the possibility exists for dietary exposure from the by-products of chlorination in food products. However, monitoring data are not available to characterize adequately the magnitude or frequency of potential DCA exposure from diet. Additionally, preliminary discussions with FDA suggest that there are not approved uses for chlorine in most foods consumed in the typical diet. Similarly, the Air Division of EPA's Office of Air and Radiation is not currently sampling for DCA in air (Borum, 1991). Little exposure to DCA from air is expected since DCA is nonvolatile.

Since only a limited number of food groups are expected to contain chlorinated chemicals and no significant DCA levels are expected in ambient or indoor air, EPA believes that drinking water is the predominant source of DCA intake. Characterization of the potential exposures from food and air are issues currently under review. The EPA requests any additional data on known concentrations of DCA in drinking water, food, and air.

Health Effects

The health effects information in this section is summarized from the Drinking Water Health Criteria Document for Chlorinated Acetic Acids, Alcohols, Aldehydes and Ketones (USEPA, 1991a). Studies mentioned in this section are summarized in the criteria document.

Humans treated with DCA for 6 to 7 days at 43 to 57 mg/kg/day have experienced mild sedation, reduced blood glucose, reduced plasma lactate, reduced plasma cholesterol levels and reduced triglyceride levels. At the same time, the DCA treatment depressed uric acid excretion, resulting in elevated serum uric acid levels.

A longer term study in two young men receiving 50 mg/kg for 5 weeks up to 16 weeks, indicated that DCA significantly reduces serum cholesterol levels, and blood glucose, and causes peripheral neuropathy in the facial, finger, leg and foot muscles.

Estimates of acute oral LD50 values range from 2800 to 4500 mg/kg in rats and up to 5500 mg/kg in mice. Short term studies in dogs and rats indicate an effect on intermediary metabolism, as demonstrated by decreases in blood lactate and pyruvate. Exposures to DCA up to 3 months in dogs and rats result in a variety of adverse effects including effects to the neurological and reproductive systems. These effects are seen above 100 mg/kg/day in dogs and rats.

Studies on the toxicokinetics of DCA indicate that absorption is rapid and that DCA is quickly distributed to the liver and muscles in the rat. DCA is metabolized to glyoxylate which in turn is metabolized to oxalate. Although there are few studies regarding the excretion of DCA, studies in which rats, dogs and humans received intravenous injections of DCA indicated that the half-life of DCA in human blood plasma is much shorter than in rats or dogs. Urinary excretion of DCA was negligible after 8 hours. Total excretion of DCA was less than 1% of total dose.

EPA considered two studies for the derivation of a DWEL. A drinking water study by Bull, et al. (1990) reported a dose-related increase in hepatic effects in mice that received DCA at 270 mg/kg/day for 37 weeks and at 300 mg/kg/day for 52 weeks. Adverse effects included enlarged livers, marked cytomegaly with massive accumulation of glycogen in hepatocyte and focal necrosis. The NOAEL for this study was 137 mg/kg/day for 52 weeks.

The second study is a drinking water study by DeAngelo et al. (1991) in which mice received DCA at levels of 7.6, 77, 410, and 486 mg/kg/day for 60 or 75 weeks. While this study was intended as an assessment of carcinogenicity, other systemic effects were measured. This study concluded that levels at 77 mg/kg/day and above caused an extreme increase of relative liver weights and a significant increase in Neoplasia at levels of 410 mg/kg/day and above. This study indicates a NOAEL of 7.6 mg/kg/day for noncancer liver effects.

Based on the available data, DCA does not appear to be a potent mutagen. Studies in bacteria have indicated that DCA did not induce mutation or activate repair activity. Two studies have shown some potential for mutagenicity but these results have not been reproducible.

DCA appears to induce both reproductive and developmental toxicity. Damage and atrophy to sexual organs has been reported in male rats and dogs exposed to levels from 50 mg/kg/day to 2000 mg/kg/day for up 3 months. Malformation of the cardiovascular system has been observed in rats exposed to DCA, 140 mg/kg/day from day 6 to 16 of pregnancy.

Several studies indicate that DCA is a carcinogen in both mice and rats exposed via drinking water lifetime studies. These studies indicate that DCA induces liver tumors. In one study with male B6F3F1 mice, exposure to DCA at 0.5 g/L and 3.5 g/L for 104 weeks resulted in tumor formation in exposed animals at 75% (18/24) and 100% (24/24) respectively. In female mice exposed for 104 weeks to DCA at the same levels, tumor prevalence was 20% and 100%, respectively. In male rats exposed to 0.05, 0.5 or 5 g/L DCA for 104 weeks, tumor prevalence increased to 22% in the highest dose. No tumors were seen at the lower doses. However, at 0.5 g/L, there was an increase in the prevalence of proliferation of liver lesions. Some of these lesions are likely to progress into malignant tumors.

The liver appears to be the target organ of DCA toxicity. Consequently, the Agency has decided to use the NOAEL of 7.6 mg/kg/day from the DeAngelo et al. (1991) study as the basis for deriving noncancer risk values such as the RfD and DWEL. EPA selected this study since it has a subchronic exposure study in mice, which appear to be more sensitive to DCA than rats. An RfD of 0.0076 mg/kg/day has been derived from the NOAEL of 7.6 mg/kg/day by the application of an uncertainty factor of 1000, in accordance with NAS/EPA guidelines when using a NOAEL derived from less than lifetime animal study. From this RfD a DWEL of 0.3 mg/L has been derived for the 70 kg adult consuming 2 liters of water per day.

EPA is considering classifying DCA in Group B2; probable human carcinogen, based on positive carcinogenic findings in two animal species exposed to DCA in drinking water.

Based on the DeAngelo et al. (1991) studies in mice, a tentative cancer risk estimate for DCA can be derived. For a 70-kg adult drinking 2 liters of water per day, the upper-limit individual risk of 10-4, 10-5, and 10-6 correspond to concentrations of 0.01, 0.001, and 0.0001 mg/L.

EPA is considering following a Category I approach and thus proposing an MCLG for DCA of zero based on the evidence of carcinogenicity via drinking water.

Issues

1. The basis for the proposed MCLG for DCA in drinking water.

2. The tentative cancer classification of Group B2.

3. The appropriateness of using a less than lifetime cancer study as the basis for the RfD and DWEL.

Trichloroacetic Acid

Trichloroacetic acid (TCA) (CAS. No. 76-03-9) is also a major by-product of chlorinated drinking water. Chlorination of source waters containing organic materials (humic, fulvic acids) results in the generation of organic compounds such as TCA.

TCA is also sold as a pre-emergence herbicide. It is used in the laboratory to precipitate proteins and as a reagent for synthetic medicinal products. It is applied medically as a peeling agent for damaged skin, cervical dysplasia and removal of tatoos.

Occurrence and Human Exposure

Trichloroacetic acid (TCA) occurs in public water systems that chlorinate water containing humic and fulvic acids.

The following table presents the most recent and comprehensive occurrence information available for trichloroacetic acid in drinking water. Descriptions of these surveys and other data are detailed in "Occurrence Assessment for Disinfectants and Disinfection By-Products (Phase 6a) in Public Drinking Water," USEPA, August 1992. Median concentrations of trichloroacetic acid in drinking water were found to range from 5.5 to 15 μg/L. Based on the available data sets, and assuming a drinking water consumption rate of 2 L/day, median exposures from drinking water would range from 11 to 30 μg/day.

Occurrence of Trichloroacetic Acid in Drinking Water

Survey (Year)[1]	Location	Sample Information (No. of Samples)	Concentration (μg/L)			
			Range	Mean	Median	Other
TSD, 1992[2] (1987-1989)	Disinfection By-Products Field Studies	Finished Water: At the Plant (72) Distribution System (56)	 <0.4-54 <0.4-77	 13 15	 11 15	Positive Detections: 90% 91%
EPA/AMWA/CDHS[2] (1988-1989) Krasner et al., 1989	35 Water Utilities Nationwide	Samples from Clearwell Effluent for 4 Quarters			4.0-5.8 5.5	75% of Data was Below 15.3 μg/L DL = 0.6

[1] Dates indicate period of sample collection
[2] May not be representative of national occurrence
[3] Range of medians for individual quarters

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No information is available concerning the occurrence of TCA in food and ambient or indoor air in the United States. The Food and Drug Administration (FDA) does not analyze for TCA in foods. However, there are several uses of chlorine in food production; for example, disinfection of chicken in poultry plants and the superchlorination of water at soda and beer bottling plants. Therefore, the possibility exists for dietary exposure from the by-products of chlorination in food products. Also, TCA has limited use as a herbicide. However, monitoring data are not available to characterize adequately the magnitude or frequency of potential TCA exposure from diet. Similarly, the Air Division of EPA's Office of Air and Radiation is not currently measuring for TCA in air (Borum, 1991). The exposure from air for TCA is probably not a large source since TCA is nonvolatile.

Since only a limited number of food groups are expected to contain chlorinated chemicals and no significant TCA levels are expected in ambient or indoor air, EPA assumes that drinking water is the predominant source of TCA intake. Characterization of potential exposures from food and air are issues currently under review. The EPA is, therefore, proposing to regulate TCA in drinking water with a relative source contribution (RSC) value at the ceiling level of 80%. The EPA requests any additional data on known concentrations of TCA in drinking water, food, and air.

Health Effects

The health effects information in this section is summarized from the Drinking Water Health Criteria Document for Chlorinated Acetic Acids/Alcohols, Aldehydes and Ketones (USEPA, 1991a). Studies mentioned in this section are summarized in the criteria document.

No studies were located on short- or long-term exposure of humans to TCA.

Estimates of acute and LD_{50} values for TCA range from 3.3 to 5 g/kg in rats to 4.97 g/kg in mice. Short-term studies, up to 30 days, in rats demonstrate few effects other than decreased weight gain after administration of 240-312 mg/kg/day.

Few studies on toxicokinetics of TCA were located; however, a human study and a dog study show TCA to respond pharmacokinetically similar to DCA. The response indicates a rapid absorption, distribution to the liver and predominant excretion through the urine. The two studies indicate that TCA is readily absorbed from all sections of the intestine and that the urinary bladder may be significant in the absorption of TCA. TCA is also a major metabolite of trichloroethylene.

Longer-term studies in animals indicate that TCA affects the liver, kidney and spleen by altering weights, focal hepatocellular enlargement, intracellular swelling, glycogen accumulation, focal necrosis, an accumulation of lipofuscin and ultimately tumor generation in mice.

EPA is considering three chronic studies for the derivation of the MCLG for TCA. The first study by Mather et al. (1990) involves male rats receiving TCA in their drinking water at 0, 4.1, 36.5 or 355 mg/kg/day. The high dose resulted in spleen weight reduction and increased relative liver and kidney weights. Hepatic peroxisomal β-oxidation activity was increased. Liver effects at the high dose included focal hepatocellular enlargement, intracellular swelling and glycogen accumulation. The NOAEL for this study was 36.5 mg/kg/day.

In the second study, Parnell et al. (1988) exposed male rats to TCA in their drinking water at 2.89, 29.6 or 277 mg/kg/day for up to one year. No significant changes were detected in body weight, organ weight or histopathology over the study duration. This study identified a NOAEL as the highest dose tested, 277 mg/kg/day.

The third study, Bull et al. (1990) investigated the effects of TCA on liver lesions and tumor induction in male and female $B6C3F_1$ mice. Mice received TCA in their drinking water at 0, 1 or 2 g/L (164 or 329 mg/kg/day) for 37 or 52 weeks. Dose-related increases in relative and absolute liver weights were seen in females and males exposed to 1 and 2 g/L for 52 weeks. Small increases in liver cell size, accumulation of lipofuscin and focal necrosis were also seen. A LOAEL of 164 mg/kg/day (1 g/L) was identified.

Several studies show that TCA can produce developmental malformations in fetal Long Evans rats, particularly in the cardiovascular system. Teratogenic effects were observed at the lowest dose tested, 330 mg/kg/day.

With regard to mutagenicity tests, TCA was negative in Ames mutagenicity tests using Salmonella strain TA100, but was positive for bone marrow chromosomal aberrations and sperm abnormalities in mice. It also induced single-strand DNA breaks in rats and mice exposed by gavage.

TCA has induced hepatocellular carcinomas in two tests with $B6C3F_1$ mice, one of 52 weeks and another of 104 weeks. In the Bull et al. (1990) study, a dose-related increase in the incidence of hepatoproliferative lesions was observed in male $B6C3F_1$ mice exposed to 1 or 2 g/L for 52 weeks. An increase in hepatocellular carcinomas was observed in males at both dose levels. Carcinomas were not found in females.

DeAngelo et al. (1991) administered mice and rats with TCA over their lifetime. Male and female B6C3F1 mice were exposed to 4.5 g/L TCA for 104 weeks. Male mice at 4.5 g/L TCA had a tumor prevalence of 86.7%. Female mice appeared to be less sensitive to TCA than males: 60% prevalence over a 104-week exposure to 4.5 g/L. At 104 weeks, 0.5 g/L TCA did not result in a significant increase in tumors. In a preliminary study of 60 weeks exposure to 0.05, 0.5 and 5 g/L, no significant additional increase in tumors was seen at 0.05 g/L, but tumor prevalence was 37.9% and 55.2% at 0.5 and 5 g/L, respectively.

F344 male rats administered TCA over a lifetime at 0.05 to 5 g/L did not produce a significant increase in carcinogenicity.

EPA believes that the 90-day study by Mather et al. (1990) is the most suitable to calculate the MCLG for TCA because a NOAEL exists which is lower than any of the other NOAELs or LOAELs from less than lifetime studies. Using the rat NOAEL from the Mather et al. (1990) study, a DWEL of 0.128 mg/L can be derived for the 70-kg adult consuming 2 liters of water per day by applying an uncertainty factor of 1,000 (which is in accordance with NAS/EPA guidelines to use an uncertainty factor of 1,000 with a NOAEL derived from a less than lifetime study).

Given the overall data base on TCA and carcinogenicity, EPA is considering placing TCA in Group C: possible carcinogen in humans. Group C is normally given to a chemical which shows carcinogenicity in only one species, as in this case the mouse. However, since tumor generation occurred in both sexes at a high rate of prevalence, it may be classified in Group B2. EPA requests comment on the appropriate cancer classification for TCA.

EPA is considering following a Category II approach for setting an MCLG for TCA. This approach would yield an MCLG for TCA of 0.1 mg/L based on the DWEL of 1.28 mg/L, an additional safety factor of 10 for Category II contaminants to account for possible carcinogenicity, and assuming a drinking water contribution of 80 percent.

$$\text{DWEL} = \frac{36.5 \text{ mg/kg/day} \times 70}{(1{,}000) \times 2 \text{ l/day}} = 1.28 \text{ mg/L}$$

$$\text{MCLG} = \frac{1.28 \text{ mg/L} \times 0.8}{10} = 0.102 \text{ mg/L (rounded to 0.1 mg/L)}$$

<u>Issues</u>

1. Is the Mather et al. (1990) study appropriate on which to base the RfD and DWEL?

2. Should TCA be regulated on the basis of its carcinogenicity with an MCLG of zero (Category I), or should the MCLG for TCA be based on noncarcinogenic endpoints?

Trichloroacetaldehyde (Chloral Hydrate)

Chlorination of water containing organic materials (humic, fulvic acids) results in the generation of organic compounds such as trichloroacetaldehyde monohydrate or chloral hydrate (CH) (CAS. No. 302-17-0).

Trichloroacetaldehyde monohydrate (chloral hydrate, CH) is used as a hypnotic or sedative drug (i.e., knockout drops) in humans, including neonates. CH is also used in the manufacture of DDT.

Occurrence and Human Exposure

CH has been found to occur as a disinfection by-product in public water systems that chlorinate water containing humic and fulvic acids.

The following table presents the most recent and comprehensive occurrence information available for chloral hydrate in drinking water. Descriptions of these surveys and other data are detailed in "Occurrence Assessment for Disinfectants and Disinfection By-Products (Phase 6a) in Public Drinking Water," USEPA, August 1992. Median concentrations of chloral hydrate in drinking water were found to range from 2.1 to 4.4 μg/L.

Occurrence of Chloral Hydrate in Drinking Water

Survey (Year)[1]	Location	Sample Information (No. of Samples)	Concentration (μg/L)			
			Range	Mean	Median	Other
TSD, 1992[2] (1987-1989)	Disinfection By-Products Field Studies	Finished Water: At the Plant (67) Distribution System (53)	<0.2-25 <0.2-30	5.0 7.8	2.5 4.4	Positive Detections: 90% 91%
EPA/AMWA/CDHS[2] (1988-1989) Krasner et al., 1989	35 Water Utilities Nationwide	Samples from Clearwell Effluent for 4 Quarters	Max. 22		1.7-3.0[3] 2.1	75% of Data was Below 4.1 μg/L[4]

[1] Dates indicate period of sample collection
[2] May not be representative of national occurrence
[3] Range of medians for individual quarters
[4] Detection limit was 0.02 μg/L in the first quarter and 0.1 μg/L thereafter

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Based on the available data sets, median exposures from CH due to drinking water would range from 3.4 to 8.8 μg/day, based on the consumption of 2 liters per day.

No information is available concerning the occurrence of CH in food and ambient or indoor air in the United States. The Food and Drug Administration (FDA) does not analyze for CH in foods since the analytical methods for such an evaluation have not been developed (Borum, 1991). However, the FDA is considering research in this area. CH has been used as a sedative of hypnotic drug (see Health Effects Section). There are several uses of chlorine in food production; for example, disinfection of chicken in poultry plants and the superchlorination of water at soda and beer bottling plants. Therefore, the possibility exists for dietary exposure from the by-products of chlorination in food products. However, monitoring data are not available to adequately characterize the magnitude or frequency of potential CH exposure from the diet. Similarly, the Air Division of EPA's Office of Air and Radiation is not currently measuring for CH in air (Borum, 1991). But, CH from indoor air may contribute to exposure due to the volatilization from tap water.

Since only a limited number of food groups are expected to contain chlorinated chemicals and no significant levels are expected in ambient or indoor air, EPA believes that drinking water is the predominant source of CH intake. Characterization of potential food and air exposures are issues currently under review. The EPA is, therefore, proposing to regulate CH in drinking water with a relative source contribution (RSC) value at the ceiling level of 80%. The EPA requests any additional data on known concentrations of CH in drinking water, food, and air.

Health Effects

The health effects information in this section is summarized from the Drinking Water Health Criteria Document for Chlorinated Acetic Acids/Alcohols, Aldehydes and Ketones (USEPA, 1991a). Studies mentioned in this section are summarized in the criteria document.

In its use as a sedative or hypnotic drug in humans, a history of adverse effects related to CH exposure have been recorded. The acute and toxic dose to humans is about 10 g (or 140 mg/kg) causing severe respiratory depression and hypertension. Adverse reactions such as central nervous system depression and gastrointestinal disturbances are seen between 0.5 and 1.0 g CH. Cardiac arrhythmias are seen when patients receive levels between 10 and 20 g (167-333 mg/kg). Chronic use of CH may result in development of tolerance, physical dependence and addiction.

Estimates of acute oral LD_{50}s in mice range from 1,265 to 1,400 mg/kg with central nervous system depression and inhibition of respiration being the cause of death. Rats may be more sensitive than mice with acute oral LD_{50} values ranging from 285 mg/kg in newborn to 500 mg/kg in adults.

Short-term studies in mice indicate that the liver is the target of CH toxicity with changes in liver weight as the primary effect. NOAELs vary between 14 and 144 mg/kg/day.

Toxicokinetic studies of CH indicate that absorption is rapid and complete in dogs and humans. CH is metabolized to trichloroacetic acid (TCA) and trichloroethanol. CH is rapidly excreted primarily through the urine as trichloroethanol glucuronide and more slowly as TCA.

Three 90-day studies in mice were considered by EPA to derive the MCLG for CH. Each used the same dose levels (16 or 160 mg/kg/day) in mice. The first study (Kallman et al., 1984) exposed groups of 12 male mice to drinking water containing chloral hydrate at concentrations of 70 and 700 mg/L. This corresponded to doses of 15.7 and 160 mg/kg/day. Exposure was for 90 days. No treatment-related effects were observed for mortality, body weight, physical appearance, behavior, locomotor activity, learning in repetitive tests of coordination, response to painful stimuli, strength, endurance or passive avoidance learning. Both doses resulted in a decrease of about 1° in mean body temperature ($p < 0.05$). The biological significance of this hypothermic effect is uncertain.

In the second study, Sanders et al. (1982) supplied groups of 32 male and female CD-1 mice with chloral hydrate in deionized drinking water (70 or 700 mg/L, corresponding to time-weighted average doses of approximately 16 mg/kg/day or 160 mg/kg/day, respectively). After 90 days, the liver appeared to be the tissue most affected. Males appeared to be more sensitive than females. In males, there was a dose-related hepatomegaly and microsome proliferation, accompanied by small changes in serum chemistry values for potassium, cholesterol and glutathione. Females did not show hepatomegaly, but did display changed hepatic microsomal parameters. Based on hepatomegaly, this study identifies a LOAEL of 16 mg/kg/day for chloral hydrate (the lowest dose tested).

In the third study, Kauffman et al. (1982) studied the effect of chloral hydrate on the immune system. Groups of 13 to 18 male and female CD-1 mice were supplied with water containing 70 or 700 mg/L (corresponding to time-weighted average doses of approximately 16 or 160 mg/kg/day, respectively) for 90 days. In males, no effects were detected in either humoral or cell-mediated immunity at either dose level. In females,

exposure to the high dose (160 mg/kg/day) resulted in decreased humoral immune function ($p < 0.05$), but no effects on cell-mediated immunity were noted. Based on this study, a NOAEL of 16 mg/kg/day and a LOAEL of 160 mg/kg/day were identified.

CH is weakly mutagenic in *Salmonella*, yeast and mold. It has also caused chromosomal aberration in yeast and nondisjunction of chromosomes during spermatogenesis.

One study has observed neurobehavioral effects on mice pups from female mice receiving CH at 205 mg/kg/day for three weeks prior to breeding. Exposure of females continued until pups were weaned at 21 days of age. Pups from the high dose group (205 mg/kg/day) showed impaired retention in passive avoidance learning tasks. This can be construed as a developmental effect of CH.

Two studies on the carcinogenicity of CH indicate that CH produces mouse liver tumors. In one study, Rijhsinghani et al. (1986), B6C3F1 mice given a single oral dose of CH at 5 or 10 mg/kg developed a significant increase in liver tumors after 92 weeks.

In the second study, Daniel et al. (1991), male mice receiving 166 mg/kg/day CH for 104 weeks showed a total liver tumor prevalence of 71 percent (17/24). Proliferative liver lesions recognized and tabulated in this study included hyperplastic nodules, hepatocellular adenomas and hepatocellular carcinomas. No other studies were located on the carcinogenicity of CH in other test species.

Based on the limited evidence of carcinogenicity in these two studies and the extensive mutagenicity of CH, the Agency is considering classifying CH in Group C: possible human carcinogen.

EPA believes the 90-day study by Sanders et al. (1982) is most appropriate to calculate the MCLG for CH because the effects observed in this study (change to hepatic microsomal parameters and hepatomegaly) appear to be more severe than the other studies have indicated at similar dose levels. From the mouse LOAEL, a DWEL of 56 μg/L was derived for the 70-kg adult consuming 2 liters of water per day by applying an uncertainty factor of 10,000 (this is in accordance with NAS/EPA guidelines to use with a LOAEL from a less than lifetime study .

EPA is considering placing CH in Category II for setting an MCLG based on limited evidence of carcinogenicity from drinking water. The proposed MCLG for CH is 5 μg/L based upon a DWEL of 56 μg/L, an additional safety factor of 10 for possible carcinogenicity, and assuming a drinking water contribution of 30 percent.

$$DWEL = \frac{16\ mg/kg/d \times 70}{1{,}000 \times 2\ L/d} = 56\ \mu g/L$$

$$MCLG = \frac{56\ \mu g/L \times 0.8}{10} = 5\ \mu g/L$$

Issues

1. Is it appropriate to set the MCLG following a Category II approach and applying an extra uncertainty factor of 10.

2. Is the endpoint of liver weight increase and hepatomegaly a LOAEL or should it be considered a NOAEL given the lack of histopathology?

Bromate

Bromate (CAS #7789-38-0 as sodium salt) is a white crystal that is very soluble in water. Bromate may be formed by the reaction of bromine with sodium carbonate. Sodium bromate can be used with sodium bromide to extract gold from gold ores. Bromate is also used to clean boilers and in the oxidation of sulfur and vat dyes. It is formed in water following disinfection via ozonation of water containing bromide ion. In laboratory studies, the rate and extent of bromate formation depends on the ozone concentration used in disinfection, pH and contact time.

Occurrence and Human Exposure

Bromide and organobromine compounds occur in raw waters from both natural and anthropogenic sources. Bromide can be oxidized to bromate or hypobromous acid; however, in the presence of excess ozone, bromate is the principal product.

The following table presents the most recent occurrence information available for bromate in drinking water. Descriptions of this data are detailed in "Occurrence Assessment for Disinfectants and Disinfection By-Products (Phase 6a) in Public Drinking Water," USEPA, August 1992. Significant bromate concentrations may occur in ozonated water with bromide.

Occurrence of Bromate in Drinking Water						
Survey (Year)[1]	Location	Sample Information (No. of Samples)	Concentration (μg/L)			
			Range	Mean	Median	Other
McGuire et al., 1990[2]	MWD Pilot Plant Studies	Ozonation: Hydrogen Peroxide/Ozone:	Max. 60 Max. 90			
TSD, 1992[2] (1987-1991)	Disinfection By-Products Field Studies	Finished Water, Plants Not Using Ozone (33)	<10			Detection Limit of 5 μg/L

[1] Dates indicate period of sample collection
[2] May not be representative of national occurrence

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Although bromate is used as a maturing agent in malted beverages, as a dough conditioner, and in confectionery products (Borum, 1991), monitoring data are not available to adequately characterize the magnitude or frequency of potential bromate exposure from the diet. Currently, the Food and Drug Administration does not have available data for bromate in foods, as bromate is not a part of their Total Diet Study program. Similarly, the Air Division of EPA's Office of Air and Radiation is not currently measuring for bromate in air (Borum 1991).

Since only a limited number of food groups are expected to contain bromate and no significant bromate levels are expected in ambient or indoor air, EPA believes that drinking water is the predominant source of intake for bromate, and contributions from air and food would be small. Characterization of potential exposures from food and air are issues currently under review. The EPA requests any additional data on known concentrations of bromate in drinking water, food, and air.

Health Effects

The health effects information in this section is summarized from the Drinking Water Health Criteria Document for Ozone and By-Products (USEPA, 1991b). Studies mentioned in this section are summarized in the criteria document.

The noncancer effects of ingested bromate have not been well studied. Bromate is rapidly absorbed, in part unchanged, from the gastrointestinal tract following ingestion. It is distributed throughout the body, appearing in plasma and urine as bromate and in other tissues as bromide. Following exposure to bromate, bromide concentrations were significantly increased in kidney, pancreas, stomach, small intestine, red blood cells and plasma. Bromate is reduced in tissues probably by glutathione or by other sulfhydryl-containing compounds. Excretion occurs via urine and to a lesser extent feces.

Acute oral LD_{50} values range from 222 to 360 mg bromate/kg for mice and 500 mg/kg for rats. Acute symptoms of toxicity include decreased locomotion and ataxia, tachypnea, hypothermia, hyperemia of the stomach mucosa, kidney damage and lung congestion. In subchronic drinking water studies, decreased body weight gain and marked kidney damage were observed in treated rodents. These effects were observed at the lowest doses tested (30 mg/kg/d).

Bromate was positive in a rat bone marrow assay to determine chromosomal aberrations. Positive findings for bromate were also reported in a mouse micronucleus assay. Bromate has also been found to be carcinogenic to rodents following long-term oral

administration. In these studies, an increased incidence in kidney tumors was reported for male and female rats. Other tumors observed include thyroid follicular cell tumor and peritoneal mesothelioma. No carcinogenic effects have been seen in mice. Dose and time studies indicate that the minimum exposure time to produce tumors in rats is 13 weeks.

The available data are considered insufficient to calculate an RfD or DWEL. Only one noncarcinogenic toxicity study (Nakano et al. 1989. Renal changes induced by chronic oral administration of potassium bromate or ferric nitrilotriacetate in Wistar rats. Jpn. Arch. of Internal Med. 36:41-47) was located in the literature. The study failed to provide dose response data and did not identify a NOAEL. Histopathological lesions in kidney tubules that coincided with decreased renal function were noted in rats exposed to 30 mg bromate/kg/d for 15 months.

Kurokawa et al. (1986a) supplied groups of about 50 male and 50 female F344 rats (4-6 weeks old) with drinking water containing 0, 250 or 500 mg/L (the maximum tolerated dose) of $KBrO_3$. The high dose (500 mg/L) caused a marked inhibition of weight gain in males, and so at week 60 this dose was reduced to 400 mg/L. Exposure was continued through week 110. The authors stated the average doses for low dose and high dose groups were 12.5 or 27.5 mg $KBrO_3$/kg/day in males (equivalent to 9.6 and 21.3 mg BrO_3/kg/day) and 12.5 or 25.5 mg $KBrO_3$ in females (equivalent to 9.6 and 21.3 mg BrO_3). The incidence of renal tumors in the three groups (control, low dose, high dose) was 6%, 60% and 88% in males and 0%, 56% and 80% in females. The effects were statistically significant ($p < 0.001$) in all exposed groups. The incidence of peritoneal mesotheliomas in males at three doses was 11% (control), 33% (250 mg/L, $p < 0.05$) AND 59% (500 mg/L, $p < 0.001$). The authors concluded that $KBrO_3$ was carcinogenic in rats of both sexes.

In a subsequent study, Kurokawa et al. (1986b) supplied F344 rats with water containing $KBrO_3$ at 0, 154, 30, 60, 125, 250 or 500 mg/L for 104 weeks. The authors reported that these exposures resulted in average doses of 0, 0.9, 1.7, 3.3, 7.3, 16.0 or 43.4 mg/kg/day of $KBrO_3$, equivalent to doses of 0, 0.7, 1.3, 2.5, 5.6, 12 or 33.4 mg/kg/day of BrO_3. The incidence of renal cell tumors in these dose groups was 0%, 0%, 4%, 21% ($p < 0.05$), 50% ($p < 0.001$), 95% ($p < 0.001$) and 95% ($p < 0.001$). Using the linearized multistage model, estimates of cancer risks were derived. Combining incidence of renal adenomas and adenocarcinomas in rats, and a daily water consumption for an adult, lifetime risks of 10^{-4}, 10^{-5} and 10^{-6} are associated with bromate concentrations in water at 5, 0.5 and 0.05 μg/L, respectively. Equivalent concentrations in terms of $KBrO_3$, lifetime risks would be 7, 0.7 and 0.07 μg/L, respectively.

The International Agency for Research on Cancer place bromate in Group 2B, for agents that are probably carcinogenic to humans. EPA has not officially classified bromate as to its carcinogenic potential to humans. However, the EPA is currently performing a cancer weight of evidence evaluation, and is considering placing bromate in group B2: probable human carcinogen based on the following evidence. Bromate has been shown to produce several types of tumors in both sexes of rats following drinking water exposures. In addition, positive mutagenicity studies have been reported include indications of DNA interactions with bromate. As a result of bromate formation following disinfection, particularly with ozone, there is a potential for considerable exposure in drinking water. Thus, EPA is considering establishing an MCLG based on a Category I approach. The resulting MCLG would be zero.

The EPA is also interested in examining the mechanism of toxicity of bromate in rats in terms of whether renal tumor formation is due to direct action of bromate or indirectly through formation of specific adduct in kidney DNA of rats treated with bromate.

Issues

1. MCLG of zero based on carcinogenic weight of evidence.

2. Mechanism of action related to DNA adduct.

Other Disinfection By-products

EPA has also considered establishing MCLGs for other by-products of disinfection including cyanogen chloride, chloropicrin, chlorophenols, haloacetonitriles, formaldehyde and other aldehydes, and hydrogen peroxide. At this time, it is not likely that EPA will propose MCLGs for these compounds due to lack of health or exposure information.

Cyanogen chloride (CAS No. 506-77-4) usually occurs as a gas and has been produced as a chemical warfare agent, for use in tear gas and as a fumigant. It has also been formed as a by-product of chlorination and chloramination.

In humans, exposure to cyanogen chloride following inhalation results in eye and lung irritation. Death results after ten minutes exposure to 400 mg/m^3. No information is available on the health risks following ingestion of cyanogen chloride. EPA believes that the available data are insufficient to calculate an MCLG for cyanogen chloride. EPA considered using the data base for hydrogen cyanide. However, given the uncertainty in using this data to predict the risk for cyanogen chloride, EPA will follow the recommendations of the Science

Advisory Board and pursue additional research to better characterize the toxicity of the ingested compound.

Chloropicrin (CAS No. 76-06-2) is a colorless liquid that is formed from the reaction of chlorine with humic acids, amino acids and nitrophenols. Typical concentrations appear to be less than 10.58 μg/L in finished water. Like cyanogen chloride, chloropicrin has also been used as a chemical warfare agent. It has also been used as a grain fumigant, insecticide and fungicide. Chloropicrin is acutely toxic following ingestion and inhalation. The oral LD_{50} in rats is 250 mg/kg. Chronic oral data are not available to calculate an MCLG at this time. EPA will pursue additional research to determine the potential risks from chronic low level exposure to chloropicrin.

Mono- (CAS No. 95-57-8), di- (CAS No. 120-83-2) and trichlorophenol (CAS No. 88-06-2) are also potential by-products of disinfection. Recent surveys, however, have not detected the presence of the chlorophenols following disinfection. As a result of the apparent low exposure from drinking water, EPA is not planning to set an MCLG but has developed a Health Advisory for chlorophenols. The Health Advisory provides information on the health effects, analytical methods, treatment technologies and quantitative risk assessments for these compounds in the event that they are found in drinking water.

Health Advisories rather than MCLGs have also been developed for the haloacetonitriles and formaldehyde as a result of low exposure from drinking water. Many of these by-products are associated with chlorination. By-products of other disinfection methods including ozonation are currently being evaluated for their health effects, available analytical methods and treatment technologies. These compounds include MX, brominated acetic acids and other halogenated aldehydes that may be formed. These compounds will likely be addressed in a later rulemaking for disinfection by-products.

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