

# Public Health Review of Monochloramine

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## **EXECUTIVE SUMMARY**

Water disinfection is necessary to prevent disease-causing pathogens from adversely affecting consumers. Water disinfection is achieved in two stages: primary disinfection inactivates more than 99 percent of pathogens, and secondary disinfection protects the water from pathogen re-growth during transit from the water treatment facility to the communities served.

Three chemicals are approved by the Environmental Protection Agency (EPA) for secondary disinfection of drinking water: free chlorine (chlorination), monochloramine (chloramination), and chlorine dioxide. Disinfection byproducts (DBPs) are formed from any type of water disinfection. EPA regulates two classes of DBPs, trihalomethanes (THMs) and haloacetic acids (HAAs). THMs and HAAs are associated with adverse health effects, such as cancer and reproductive effects. Water disinfection via free chlorine leads to high levels of THMs and HAAs in the drinking water. EPA recently enacted a new rule that will effectively decrease the levels of THMs and HAAs allowed in public drinking water. Water disinfection using monochloramine drastically reduces THMs and HAAs in drinking water. In the U.S., monochloramine has been used for water disinfection for 90 years, and millions of people currently drink and use chloraminated water. Monochloramine is also used extensively worldwide.

Studies on the health effects of monochloramine in animals do not show any evidence of cancer, immunotoxicity, organ-specific toxicity, oxidation of lipids, or lung toxicity, even at high doses. Studies on the health effects of monochloramine in humans do not reveal any alterations in blood biochemistry, lipid metabolism, or thyroid function that would indicate an adverse health effect. Epidemiological evidence indicates that people who drink chlorinated water are more likely to die from bladder cancer than those who drink chloraminated water; this is most likely due to the reduction in THMs and HAAs in chloraminated water. There is no large-scale epidemiology study of the health effects of monochloramine because one is not warranted by other scientific data. Carcinogenic studies in mice and rats do not support a carcinogenic effect of monochloramine, and other studies looking at health effects in animals and humans report no adverse effects.

Both free chlorine and monochloramine lead to the formation of unregulated DBPs. Many of these have only recently been characterized in drinking water, and toxicity data is therefore limited. Some are known carcinogens and mutagens. The concentrations at which the unregulated DBPs are found in

drinking water are possibly too low to cause a health effect. The Health Department recognizes that unregulated DBPs are at the forefront of drinking water research, and will continue to follow EPA as it considers the status of some unregulated DBPs. The most abundant DBPs are the regulated THMs and HAAs.

The Vermont Department of Health has conducted an extensive review of scientific literature on monochloramine. Health has determined that the use of monochloramine as a water disinfectant is not likely to result in adverse health effects. On the contrary, the Health Department believes that the use of monochloramine will reduce the concentration of regulated and possibly unregulated DBPs in drinking water. This reduction may contribute to fewer adverse health effects compared to drinking water treated with free chlorine as a disinfectant.

## FULL REPORT

### WATER DISINFECTION

Drinking water is disinfected in two stages. First, free chlorine is added to inactivate more than 99 percent of illness and disease-causing pathogens. As water is pumped away from the treatment plant for distribution to customers served by the water system, a secondary disinfectant is added to protect the water from pathogen re-growth while in transit.

Three chemicals are currently approved by the Environmental Protection Agency (EPA) for secondary disinfection of drinking water: free chlorine, monochloramine, and chlorine dioxide. When monochloramine is used as a water disinfectant, ammonium ion in the form of liquid or solid ammonium sulfate, gaseous anhydrous ammonia, or solid ammonium hydroxide is added in the appropriate ratio to the free chlorine to create monochloramine. The Maximum Residual Disinfectant Level (MRDL) is the highest level of a disinfectant allowed in drinking water without causing an unacceptable possibility of adverse health effects. The MRDL set by the EPA for both chlorine and monochloramine is 4 milligrams per liter (mg/L).

### NEED FOR A NEW WATER DISINFECTANT

Amendments to the Safe Drinking Water Act in 1996 required the EPA to provide a balance between microbial pathogens and disinfection byproducts (DBPs) in drinking water. Some DBPs, namely trihalomethanes (THMs) and haloacetic acids (HAAs) are carcinogenic in animals, and are thought to pose health risks to humans. The Stage 1 Disinfectants and Disinfection Byproducts Rule (DBPR) was promulgated in December 1998, and set maximum contaminant levels (MCLs) for the THMs and HAAs. The Stage 2 DBPR builds on the Stage 1 rule, and requires that each water system evaluate their distribution system to identify locations with high DBP concentrations. These locations will be used as sampling sites for the Stage 2 DBPR compliance monitoring. Once the Stage 2 DBPR is in effect, each sampling location must maintain a locational running annual average that is below the EPA's MCL of 80 micrograms per liter ( $\mu\text{g/L}$ ) for THMs and 60  $\mu\text{g/L}$  for HAAs. This contrasts with the previous law, which averaged DBP levels from all sampling locations in a water distribution system to obtain the yearly average; the prior method allowed some sampling sites to remain higher than acceptable. A system that is over the MCLs or just under the MCLs may risk becoming non-compliant once the locational running annual average is instituted.

The use of monochloramine as a water disinfectant leads to lower formation of THMs and HAAs compared to chlorination. Monochloramine has greater persistence in the distribution system compared to free chlorine. Thus, monochloramine is an effective method by which public water systems can lower their THM and HAA levels to comply with the Stage 2 DBPR.

## PUBLIC WATER SYSTEMS THAT USE MONOCHLORAMINE

Monochloramine is a popular water disinfectant, and is recognized by the EPA as the best available technology for drinking water utilities to lower the levels of HAAs and THMs in drinking water (Li, 2011). Thus, as the Stage 2 DBPR takes effect in 2013, more water systems in Vermont are expected to choose monochloramine as a water disinfectant.

The Denver, Colorado Water Department has used monochloramine as a water disinfectant since 1918. The city of Portland, Oregon has used monochloramine since 1924. Other water systems and the year they began using monochloramine include: the Massachusetts Water Resources Authority (i.e. the Boston Metro area; 1932); St. Louis Water Division, MO (1934); Portland, ME (1938); Indianapolis Water Company, IN (1954); Minneapolis, MN (1954); City of Dallas, TX (1959); the City of Milwaukee, WI (1964); Philadelphia, PA (1969); Houston, TX (1982); Miami-Dade Water Authority in FL (1982); San Diego, CA (1982); East Bay Municipal Utility District, CA (1998); The City of San Francisco, CA (2004); and the Champlain Water District, VT (2006). Millions of people in the U.S. are currently drinking chloraminated water, and monochloramine is used worldwide for water disinfection. In New England alone, over 3 million people are served by water systems using monochloramine as a water disinfectant.

In some water systems that use monochloramine, a small percentage of customers complained of health problems. Complaints were sent to the San Francisco Public Utilities Commission in California, and the Champlain Water District in Vermont. Reports of people claiming adverse effects due to monochloramine, including skin rashes, itchy eyes, and other dermal effects, have been addressed by public health officials from the San Francisco Department of Public Health and the Vermont Department of Health in conjunction with the Centers for Disease Control & Prevention (CDC).

Both San Francisco and Vermont analyzed less than 100 people who reported adverse reactions to monochloramine. Almost 2.5 million people are served by the two water districts combined. In the San Francisco investigation, the nature of complaints was heterogeneous, indicating that the symptoms could result from underlying or preexisting conditions; no further study was warranted (Weintraub et al., 2006). The Vermont/CDC investigation reported a strong bias introduced by anti-monochloramine literature and participation of anti-monochloramine group members in the survey. The CDC recommended that any future studies should be designed to eliminate bias, and to obtain a baseline occurrence for

common symptoms reported after monochloramine addition to the water (CDC, 2008).

Throughout this report, several references are made to the Champlain Water District's process. Champlain Water District switched to monochloramine as a water disinfectant in April of 2006, and have made many measurements of water quality data available for reference.

## ADVERSE HEALTH EFFECTS OF CHLORINATED WATER

### Cancer:

Several epidemiological studies have correlated an increase in cancer to years of residence in a chlorinated drinking water community. A Massachusetts study identified a 1.7 fold increase in mortality ratio due to chlorinated versus chloraminated water (Zierler et al., 1986). Results from the Iowa Women's Health Study Cohort identified a 1.7 fold increased risk for colon cancer for women exposed to the highest level of chloroform (a THM; 14-287 µg/L); the risk for all cancers relative to the highest chloroform exposure was 1.3 times greater (Doyle et al., 1997). Consumption of chlorinated water was associated with an increased risk (1.4-fold) of bladder cancer in men, and higher risk (1.2-fold) of bladder cancer in women (Villanueva et al., 2003). Several additional studies find increased risk of cancers in chlorinated water (Rahman et al., 2010), yet many face challenges in accurately characterizing exposure (Arbuckle et al., 2002).

If the route of exposure (showering/bathing/swimming) is stratified with occurrence of bladder cancer, there is a 2-fold increased risk for bladder cancer in men who showered or bathed in chlorinated water (Villanueva et al., 2007). This increase in cancer is irrespective of whether the men drank chlorinated or bottled water. These data support the hypothesis that inhalation exposure of THMs in addition to oral exposure contributes to the formation of bladder cancer (Richardson et al., 2007). Cancer risks in Canadian drinking water due to THMs are estimated to be mostly due to ingestion, although up to 40 percent of cancers may be attributable to inhalation and dermal exposure (Chowdhury et al., 2011).

Once the Stage 2 DBPR goes into effect, the EPA estimates that 280 bladder cancers will be prevented per year, 26 percent of which are fatal (EPA, 2005). Switching to chloramine to lower DBPs will theoretically prevent 73 deaths per year (EPA, 2005).

### Reproductive Effects:

Studies on adverse birth outcomes due to use of chlorinated water usually assess gestational age, birthweight, stillbirth, intrauterine growth retardation, and congenital anomalies. Several studies find clear associations between water chlorination and adverse reproductive outcomes (Nieuwenhuijsen et al., 2009),

while some find no association (Grellier et al., 2010). A large study of over 390,000 births revealed significant increased risks of ventricular septal defect, cleft palate, and anencephalus in children of women exposed to the highest levels of THMs (> 20 µg/L; Hwang et al., 2008).

A major limitation in epidemiological studies on cancer and reproductive effects is accurate measurement of DBP exposure. Since free chlorine is not carcinogenic (NTP, 1992), the individual DBPs responsible for the increase in cancer should be properly measured and used in future epidemiological studies.

Consistent data from animal models suggests that the regulated THMs and HAAs are associated with adverse reproductive outcomes. Pregnant mice were treated with either the four regulated THMs, the five regulated HAAs, or the nine combined (Narotsky et al., 2011). All three mixtures caused pregnancy loss and resorption; HAA treatment led to increased eye malformations in surviving pups.

The Department of Health agrees with the EPA that the weight of evidence to suggest an association between regulated DBPs and cancer or adverse reproductive outcomes is enough to warrant a reduction in the regulated DBPs in drinking water. This is why monochloramine, rather than free chlorine, is being used as a water disinfectant in the Champlain Water District treatment facility, and many other Vermont water systems are looking to institute this approach. This is detailed in the *Engineering feasibility study on the costs of treatment options for reducing disinfection byproducts in public drinking water systems*, required by the Vermont General Assembly and reported by the Vermont Department of Environmental Conservation (AECOM, 2010).

## MONOCHLORAMINE PROPERTIES

At the pH of Vermont surface water, monochloramine is formed by the addition of ammonium ion to free chlorine. There are three species of chloramines: monochloramine, dichloramine, and trichloramine. Dichloramine and trichloramine are formed at low pH (< 5) and only with a chlorine-to-ammonia ratio greater than 5:1 by weight. Thus, when properly managed, the addition of ammonia to free chlorine will yield predominantly monochloramine. Dichloramine and trichloramine are well-documented irritants, and are largely blamed for the irritating effects of swimming pool water (Dang et al., 2010). Airway irritation by trichloramine, the most irritating of the chloramine species, was of the same order of magnitude as irritation by chlorine (Gagnaire et al., 1994). The breakpoint curve of adding free chlorine to drinking water predicts formation of dichloramine and trichloramine at free chlorine concentrations above the breakpoint (Wolfe et al., 1984). Dichloramine and trichloramine are more readily formed in swimming pools due to the greatly increased nitrogen content from urea, creatinine, and histidine (components of sweat and urine) relative to that found in drinking water (Li and Blatchley, 2007). Several studies describe the volatility and toxicity of di- and trichloramine. Monochloramine, which is the

primary species formed in water disinfection, is not volatile. During a shower of 100° F, the San Francisco Public Utilities Commission reports that only 8 percent of monochloramine in water was volatilized, compared to up to 94 percent of chlorine.

## MONOCHLORAMINE AND LEAD

In some very old water systems, lead service lines (LSLs) were used to connect from the street to household plumbing. The Safe Drinking Water Act Amendments of 1986 required that only lead-free pipe, solder and flux could be used in the installation of any facility providing water to the public. Since many water systems were in use before 1986, many systems serve households that have lead solder joining copper pipes together. The use of free chlorine may lead to the formation of  $Pb^{4+}$ , which is very insoluble. The introduction of monochloramine may reduce the oxidation reduction potential (ORP) enough to convert  $Pb^{4+}$  to  $Pb^{2+}$ , which is soluble. Where LSLs exist, this can lead to leaching of lead from LSLs after switching to monochloramine. Under these conditions where LSLs exist, lead levels in water may reach elevated levels (EPA, 2007). To prevent the solubilization of lead, a water system planning to switch to monochloramine from free chlorine will review their corrosion control protocol. One option is to use an orthophosphate to create a lead species that is resistant to the oxidizing properties of monochloramine. Many water systems have used zinc orthophosphate for many years to limit lead leaching from customers' home plumbing.

## MONOCHLORAMINE AND NITRIFICATION

The ratio of ammonium ion to total chlorine is closely monitored to avoid nitrification as the consequence of excess ammonia. Nitrification is the microbial process by which reduced nitrogen compounds such as ammonia are sequentially oxidized to nitrite and nitrate. Ammonia is converted to nitrite by ammonia-oxidizing bacteria. Nitrite can then be converted to nitrate by nitrite-oxidizing bacteria (NOBs). Factors that increase the risk for nitrification include higher temperature, the distance (length) of the distribution system, and the age of pipes, with older pipes being more susceptible. A low chlorine-to-ammonia ratio (~3:1) favors the growth of NOBs. The technical review conducted by the Vermont Department of Environmental Conservation ensures that water utility systems have a nitrification monitoring strategy in place before switching to monochloramine, as well as a preventative maintenance program.

## POPULATIONS SENSITIVE TO MONOCHLORAMINE

### Concerns for dialysis patients:

As with chlorine, people who rely on dialysis may be vulnerable to monochloramine in water that is not treated to dialysis specifications. Both



chlorine and monochloramine must be removed prior to use in dialysis. When using water for dialysis that does not meet dialysis specifications, the monochloramine or chlorine in the water is directly absorbed into the blood, forming methemoglobin. Methemoglobin has a reduced capacity to carry oxygen, and may lead to a dangerous condition known as methemoglobinemia.

#### Effects on Aquatic Life:

Monochloramine is toxic to fish, as is free chlorine. Both must be removed before chloraminated or chlorinated water can be used for home fish tanks.

### MONOCHLORAMINE STUDIES

In the following section, peer-reviewed studies of monochloramine's toxicity will be summarized. Studies supplied from Vermonters for a Clean Environment were considered in this section.

#### Endogenous Role of Monochloramine:

Monochloramine is an endogenous chemical (i.e. it is found naturally in the body) that can be formed by the reaction of hypochlorous acid, produced by neutrophils, with endogenous amines (Grisham et al., 1984). The production of hypochlorous acid and its subsequent conversion to monochloramine by neutrophils represents the body's first line of defense against invading pathogens. Neutrophils are quickly recruited to sites of infection and play a crucial role in immunity.

#### Mutagenicity:

Monochloramine is reported to be a weak mutagen in the bacterial reversion assay (Shih and Lederberg, 1976). A later study showed that mixed chloramines were mutagenic, but only at 98° F in the presence of glucose (Thomas et. al., 1987). At room temperature or below, chloramine was not mutagenic. At 98° F without glucose present, chloramine was not mutagenic. Glucose is not expected to be present in drinking water; thus mutagenicity of chloramine at any drinking water temperature is not expected. Monochloramine is rapidly broken down in human stomach fluid (Kotiaho et al., 1992) and is not expected to be mutagenic upon ingestion. Oral administration of monochloramine to CD-1 mice did not lead to chromosomal aberrations or micronuclei in bone marrow cells (Meier et al., 1985). Thus, although monochloramine may be a weak mutagen *in vitro*, there is no evidence of *in vivo* mutagenicity.

#### Metabolism:

Monochloramine is quickly broken down in the presence of human stomach fluid to chloride and ammonia (Kotiaho et al., 1992). The ammonia enters the citric

acid cycle and is converted to urea, which is filtered out of blood by the kidney. Chloride derived from monochloramine is excreted in the urine (Abdel-Rahman et al., 1983). The conversion of ammonia to urea represents a normal facet of human metabolism and our bodies are quite capable of this process. It is estimated that the daily intake of ammonia from food sources is 18 mg/day (ATSDR, 2004). The concentration of ammonium ion in the Champlain Water District's water is approximately 0.2 mg/L, indicating one would need to drink 90 liters of chloraminated water per day just to equal the ammonia intake from food. Thus, chloraminated water is not a significant source of ammonia.

Monochloramine also interacts readily with Vitamin C, resulting in the break down of monochloramine (Ward, 1996; Peskin and Winterbourn, 2001). The City of San Francisco and the Champlain Water District describe the use of vitamin C in drinking water and bathing water to successfully break down monochloramine into chlorine and ammonia.

#### Short-term Studies in Animals:

Rats were given monochloramine in drinking water at concentrations up to 100 mg/L for 45 days (Bull, 1980; Table 1). No overt toxicity was observed in chloramine-treated animals. Hematological parameters measured including blood hemoglobin, packed cell volume, and glutathione were normal in treated and control groups. Methemoglobin was decreased in chloramine-treated animals, which is opposite of what was expected if monochloramine was available to bind hemoglobin and affect oxygen transport.

African Green monkeys were given monochloramine in the drinking water for six weeks at concentrations up to 100 mg/L (Bercz et al., 1982). Monochloramine had no effect on 18 hematological tests, including leukocyte and reticulocyte cell counts in blood, methemoglobin levels, red blood cell glutathione levels and total blood protein. There was no adverse effect of monochloramine on thyroid hormone levels.

Female CD-1 mice were given concentrated water (100x or 400x) originally treated with monochloramine at 2.1 mg/L (Miller et al., 1986). After 30 days, mice were examined for gross pathological changes. Some significant differences in organ weights in treated animals were observed, but in no consistent pattern. Therefore, the authors concluded that overt toxicity of concentrated chloraminated water was not observed.

Male Sprague-Dawley rats were given monochloramine in the drinking water at concentrations up to 38 mg/L from birth to 12 weeks of age (Exon et al., 1987). Several immunological endpoints measured were normal including thymus weights, delayed-type hypersensitivity reactions, natural killer cell cytotoxicity, oxidative metabolism response and phagocytosis by macrophages, and interleukin 2 synthesis. The monochloramine-treated rats showed slightly

reduced spleen weights, as well as a dose-dependent increase in prostaglandin synthesis. A decrease in total antibody synthesis was concluded by the authors; however the decrease was significant at only the lowest dose of monochloramine and was not dose-dependent. Thus, increased prostaglandin synthesis was the only consistent biological indicator of an effect of monochloramine treatment in rats. The significance of this finding is unclear.

To evaluate the toxicity of monochloramine, the EPA administered monochloramine in drinking water at concentrations up to 200 mg/L to male and female rats for 90 days (Daniel et al., 1990). Rats were observed for mortality; body weights; food and water consumption; hematological parameters including red blood cell count, white blood cell count, hemoglobin, hematocrit and mean corpuscular volume; serum levels of glucose, blood nitrogen urea, creatinine, inorganic phosphate, serum aspartate transaminase, serum alanine transaminase, cholesterol, lactate dehydrogenase and calcium; gross pathology of brain, liver, spleen, lung, adrenal glands, heart and gonads; and histopathology of the skin, lymph nodes, mammary glands, muscle, sciatic nerve, thymus, esophagus, stomach, small intestine, tongue, salivary gland, large intestine, colon, pancreas, bladder, seminal vesicles, prostate, uterus, aorta, thyroid and parathyroid. Mortality was not increased due to consumption of monochloramine. At the highest dose of monochloramine, all hematological parameters, serum levels, gross pathology and histopathology of organs were normal. The authors observed a dose-dependent decrease in water consumption, likely due to taste aversion, which led to decreased body weights in treated animals.

A similar EPA study on male and female B6C3F1 mice given monochloramine in drinking water at concentrations up to 200 mg/L for 90 days measured the same endpoints described above (Daniel et al., 1991). Female mice showed a dose-dependent increase in white blood cell counts; all other hematological parameters in male and female mice were normal. As observed in rats, the treated mice exhibited a dose-dependent decrease in water consumption, leading to lower body weights at the end of the study. No abnormal gross or histopathological endpoints were noted in treated mice. Thus, in both EPA studies of mice and rats, monochloramine treatment led to no direct toxicological effects on specific organs or tissues.

Administration of monochloramine in drinking water (up to 200 mg/L) for 13 weeks to male rats produced no significant cytological changes in red cells or bone marrow (Poon et al., 1997). In addition, the following parameters were normal: mitogen responsiveness to T cell and B cell mitogens; natural killer cell activities; serum IgG, IgA, IgM, serum thyroxin, liver phase I and phase II enzymes, serum and liver thiobarbituric acid reactive species (a measure of lipid peroxidation); bronchoalveolar lavage fluid protein and N-acetylglucosaminidase activity (measurements of lung function); and urinary metabolites.

A more recent study failed to find any immunotoxicological effects of monochloramine. Administration of monochloramine in drinking water up to 200 mg/L to rats for 28 days did not produce any immunotoxicological effects; B and T lymphocyte populations were normal, as were CD4+ and CD8+ T lymphocytes, natural killer cells, and macrophages (Guo et al., 2011).

#### Long-term Studies in Animals:

Male Sprague-Dawley rats were given monochloramine in drinking water at doses up to 100 mg/L for one year (Abdel-Rahman and Suh, 1984; Table 1). After 10 months of treatment, no effect was observed on red blood cell counts, hematocrit percent, hemoglobin percent, mean corpuscular volume, mean corpuscular hemoglobin, or mean corpuscular hemoglobin concentration. Blood glutathione levels were decreased at some points, but the changes were not consistent among all treatment points and were not dose-dependent. Osmotic fragility was not increased in a time- and dose-dependent manner by monochloramine.

Male and female F344/N rats and male and female B6C3F1 mice were given monochloramine in drinking water at concentrations up to 200 mg/L for two years (NTP, 1992). No changes in organ systems related to ingestion of monochloramine were observed in either species or sex. Both rats and mice receiving the highest dose of monochloramine showed a decrease in water consumption and body weight at the end of the study. This is most likely due to palatability of water treated with monochloramine at 200 mg/L, as animals who drink as much water as animals given chloraminated water also showed weight loss (Poon et al., 1997). Thus, monochloramine itself did not have any adverse effect on animals in the two-year studies.

#### Carcinogenicity Studies in Animals:

Monochloramine was tested for its ability to initiate tumor formation in rat liver (Herren-Freund and Pereira, 1986; Table 2). Male rats were given monochloramine at 14.75 mg/kg/day for seven days, followed by phenobarbitol. Under these conditions, monochloramine was not a tumor initiator. In a similar study, rats were given concentrated drinking water (2000x and 4000x) originally treated with 2.1 mg/L monochloramine (Miller et al., 1986). After seven days, rats were given phenobarbitol for 56 days. Monochloramine-treated water concentrates did not initiate tumor formation in this study.

In 1992, the National Toxicology Program published their two year study on the carcinogenicity of chloraminated water (NTP, 1992). Female and male B6C3F1 mice and female and male F344/N rats were given chloraminated water at doses up to 200 mg/L for two years. 70 animals were in each group. The water was charcoal-filtered to remove DBPs that could complicate results. There was no evidence of carcinogenicity in male or female B6C3F1 mice at any dose, and no

evidence of carcinogenicity in male 344/N rats at any dose. There was equivocal evidence of carcinogenicity of chloraminated water in female F344/N rats, based on a slight increase in mononuclear cell leukemia. Equivocal evidence is demonstrated by studies that show a marginal increase in neoplasms that may be chemically related. It should be noted that the incidence of mononuclear cell leukemia in the control group was 16 percent, which is lower than the historical average for F344/N rats (25 percent). Therefore, the incidence of mononuclear cell leukemia (32 percent) in the highest-dosed rats may not be significant. No observation of mononuclear cell leukemia was made in female mice, or male rats or mice, indicating the leukemia seen in female rats could be due to chance. The EPA concludes that there is inadequate evidence of human and animal carcinogenicity for monochloramine, and classifies monochloramine in class D; not classifiable as to human carcinogenicity. This classification can be used for negative results that are not sufficiently robust for the E classification; not likely to be carcinogenic to humans.

Administration of monochloramine to F344/N rats and B6C3F1 mice for two years at concentrations up to 200 mg/L did not result in the formation of liver, kidney or intestinal cancers (Dunnick and Melnick, 1993). Rather, lesions in all three tissues were observed in animals given THMs (bromoform, chloroform, bromodichloromethane, and dibromochloromethane) for two years.

#### Irritation Studies in Animals:

Using observable redness in rabbit eyes as an endpoint, mixed chloramines at or below 2 mg/L did not produce an irritation reaction when constantly administered for one hour (Eichelsdoerfer et al., 1975; Table 3). At 4 mg/L, the MRDL for monochloramine, mixed chloramines produced an irritation reaction when constantly administered for one hour (Eichelsdoerfer et al., 1975). It should be noted that these studies were conducted using a chloramine solution containing monochloramine, dichloramine, and trichloramine. Using a HET-CAM (Hen's Egg Test at the Chorion Allantois Membrane), no irritating effects of monochloramine (up to 2.4 mg/L) in the presence of free chlorine (up to 0.6 mg/L) were reported (Erdinger et al., 1997). Irritating effects were only observed at free chlorine concentrations of greater than 2 mg/L. Female mice submerged in water containing 1000 mg/L monochloramine for 10 minutes a day for four days did not display hyperplasia, as those exposed to chlorine did (Robinson et al., 1986). Thus, animal studies suggest that monochloramine at concentrations below the MRDL of 4 mg/L is not expected to cause irritating effects.

#### Reproductive and Developmental Toxicity Studies in Animals:

Female rats were treated with monochloramine (up to 100 mg/L in drinking water) for three months including gestation (Abdel-Rahman et al., 1982; Table 4). No increase in fetal resorption was found, and monochloramine did not produce any teratogenic effects at the highest doses.

Male and female Long-Evans rats were given monochloramine at doses up to 10 mg/kg/day for 76 days, including mating, gestation, and lactation periods (Carlton et al., 1986). No effect of monochloramine on fertility, viability, litter size, weight of pups or day of eye opening was observed. There were no adverse changes in sperm count, movement or mobility in male rats. There were no changes in reproductive organ weights of animals given monochloramine, and no other histopathological changes were observed.

#### Other Studies in Animals:

In an often misunderstood report, monochloramine was linked to the formation of gastric lesions in rats (Iishi et al., 1997). Rats were treated first with *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine (MNNG), which is a potent carcinogen. Following MNNG administration, rats were given food containing ammonium acetate and sodium hypochlorite for one year, with the assumption that these would combine in the stomach to produce monochloramine. The group given ammonium acetate and sodium hypochlorite showed an increase in gastric tumors compared to the control group (29 versus 18 tumors). However, there was also an increase of the same magnitude in the group receiving taurine (26 tumors), an amino acid the authors tested for scavenging properties. Thus, while the ammonium acetate plus sodium hypochlorite group did show an increase in total number of gastric tumors, so did the taurine group, which should be close to control levels. This points out that the assay system the authors used had high levels of background tumors, and conclusions can be difficult to determine. Another important consideration is that all animals, including controls, were treated with the potent carcinogen MNNG first; ammonium acetate and sodium hypochlorite alone was not tested. Further, the administration of ammonium acetate and sodium hypochlorite in food may have unknown pharmacokinetic interactions, and may not react in the stomach to form monochloramine. This route of exposure is not relevant to human drinking water health impacts.

Another misinterpreted paper is that of Ballester et al. (2005). Rats treated intrarectally with monochloramine develop an intense inflammatory reaction, which has been interpreted as due to monochloramine leading to the formation of inflammatory bowel disease. However, this study has limited relevance to human exposure from drinking water. Monochloramine will not reach the intestine, as monochloramine is quickly degraded in the stomach (Kotiaho et al., 1992). Therefore, the route of exposure is irrelevant to humans drinking chloraminated water. In addition, the dose given to the rat (3.2 mg) is equivalent to the amount of monochloramine in 487 L of water containing monochloramine at 2.3 mg/L (the concentration of monochloramine in Champlain Water District's water). This study does not support the claim that monochloramine leads to irritable bowel syndrome in humans.

#### Studies in Humans:

Lubbers et al. (1982) evaluated extensive biochemical parameters such as serum urea nitrogen, creatinine, uric acid, blood methemoglobin, and thyroxin levels in volunteers (10 per group, 6 groups) after ingestion of water containing monochloramine (5 mg/L) for 12 weeks (Table 5). No abnormal indices of the physical exam or any aberrant biochemical parameters were observed after monochloramine ingestion. In a second part of the study, volunteers (10 per group, 6 groups) drank water containing monochloramine at doses that increased daily for 13 days. The highest dose was 24 mg/L. No changes in any parameters were associated with monochloramine ingestion.

Volunteers (16 per group, 3 groups) drank water containing either 2 mg/L or 15 mg/L monochloramine for four weeks. Lipid and thyroid metabolism was measured at the end of the study; no changes in cholesterol, triglycerides, or thyroid hormones were observed (Wones et al., 1993). The group receiving 15 mg/L monochloramine did have increased Apolipoprotein B (a component of low-density lipoprotein, LDL, cholesterol), but no increase in corresponding LDL cholesterol. The significance of increased Apolipoprotein B independent of LDL cholesterol changes is unknown.

#### Reported Health Effects:

In 2004, a California water utility serving 2.4 million people switched from chlorine to monochloramine for secondary disinfection. After receiving a small number of complaints, the local department of health investigated 17 reports of symptoms. The complaints were heterogeneous and often accompanied by preexisting conditions; no further study was warranted (Weintraub et al., 2006).

In Vermont, after the Champlain Water District extensively publicized and then switched to monochloramine in 2006, complaints from the public led to a pilot study by CDC to determine if an epidemiological study was warranted. The pilot study determined there was a strong bias introduced by an anti-chloramine group, and no conclusive link between reported health symptoms and monochloramine could be made. At this time, CDC has no plans to further investigate in Vermont. Although undocumented by a physician, reports of self-diagnosed health effects reportedly from chloraminated water have been sent to the Health Department from Vermonters for a Clean Environment.

In April 2007, the Health Department surveyed 173 health care providers in Chittenden County to try to find out if there was a hidden prevalence of health problems related to monochloramine used by Champlain Water District.

Those surveyed included family practice and primary care physicians, pediatricians, pulmonologists, dermatologists, allergists and naturopaths. Of the 81 health care provider surveys returned, two providers reported having a patient whose underlying disease was exacerbated by the water, 11 providers reported

they were not sure if patient complaints were related to the water, and 59 providers reported the water did not cause patient complaints.

It is possible that some people may be sensitive to monochloramine in the water. We encourage anyone with symptoms to contact his or her physician.

#### Epidemiological Studies:

Zierler et al. (1986) compared the type of water disinfectant among over 50,000 cases of death due to cancer to over 200,000 controls who died from other diseases. The study revealed that drinking chlorinated water led to a mortality odds ratio of 1.7 for bladder cancer compared to chloraminated water, meaning that people who drank chlorinated water were 1.7 times more likely to die of bladder cancer than those who drank chloraminated water. There was a slight increase in deaths from pneumonia and influenza in chloraminated communities, but confounding factors such as smoking and occupational exposure were not accounted for. A follow-up report analyzed 614 cases of bladder cancer deaths and confirmed that people who drank chlorinated water, not chloraminated water, were more likely to die from bladder cancer (Zierler et al. 1988). When the risk of dying from bladder cancer was compared to the risk of dying from lymphoma, people who drank chlorinated water were 2.7 times more likely to die from bladder cancer than those who drank chloraminated water. Thus, the epidemiological evidence available does not indicate that chloraminated water increases the risk for cancer. On the contrary, the data indicate that those who drank chlorinated water were more likely to have and die from cancer than those who drank chloraminated water. This can possibly be explained by the reduction in carcinogenic THMs in chloraminated water compared to chlorinated water.

A study of bladder cancer patients in Colorado compared the odds ratio for developing bladder cancer based on the type of water disinfectant (McGeehin et al., 1993). Persons who drank chlorinated water were 1.8 times more likely to develop bladder cancer than people who drank untreated water. People who drank chloraminated water were less likely to develop bladder cancer than people who drank untreated water. This data indicates that chloraminated water poses less of a health risk than chlorinated water.

One reason that there are few large-scale epidemiology studies of the health effects of monochloramine is because one is not warranted by scientific data. Epidemiological studies are initiated when enough scientific evidence supports an inquiry; epidemiological studies often involve thousands of people and take several years to complete. Thus far, scientific evidence does not warrant a large-scale epidemiological study. This evidence includes lack of toxicity in animal and human studies, as well as lack of significance of pilot studies. Studies in mice and rats do not support a carcinogenic effect of monochloramine, and other studies looking at health effects in animals and humans generally report no adverse effects.



## DISINFECTION BYPRODUCTS OF MONOCHLORAMINE

Along with the recognized public health benefits derived from disinfection with chlorine, monochloramine and chlorine dioxide, each produces its own set of regulated and unregulated DBPs. THMs and HAAs are the most abundant classes of DBPs found in disinfected waters. The THMs and HAAs were observed to produce cancer in animal models and to have other toxic endpoints; epidemiological evidence points to a risk of THM and HAA exposure and bladder cancer and adverse reproductive outcomes. For these reasons, most governments limit the amounts of THMs and HAAs that can be present in drinking water.

Since the 1970s, some of the unregulated DBPs have been known to be carcinogenic and mutagenic in cellular assays, as well as *in vivo*. The Department of Health anticipates that EPA will release health assessments of seven nitrosamines in late 2012. Nitrosamines are a class of unregulated DBPs that can be formed by reactions of some naturally-occurring nitrogen precursors with chlorinated or chloraminated waters. Nitrosamines, particularly nitrosodiethylamine (NDMA) are probable human carcinogens (NTP 2005). NDMA is found predominantly in food, and is made endogenously inside our bodies. The contribution of NDMA from drinking water is most likely a minor source to total human exposure (Fristachi and Rice, 2007). California and Massachusetts both set drinking water notification levels for NDMA at 10 ng/L (10 ppt). The Champlain Water District has monitored for five nitrosamines, with none detected at ng/L levels (Champlain Water District, 2009).

One class of DBPs with high genotoxicity (toxicity to genes) and cytotoxicity (toxicity to cells) compared to the regulated THMs and HAAs are the haloacetamides (HANs; Muellner et al., 2007). Haloacetamides (HAMs) also have high cytotoxic and genotoxic potential (Plewa et al., 2008). For both the HANs, HAMs, and other unregulated halo-DBPs, iodo-containing compounds are most toxic, followed by bromo- and chloro- containing compounds. It is important to note that the HANs, HAMs and other unregulated DBPs are formed in water systems that use chlorine for primary and secondary disinfection, as well as those that use chlorine for primary disinfection and monochloramine for secondary disinfection (Richardson, 2005). Lake Champlain, the water source for the Champlain Water District and many other water districts, has non-detectable iodine levels. Thus, iodo-DBPs are not expected to be present in high levels in treated Lake Champlain water.

Bull et al., (2009) analyzed the DBPs reported in the EPA's 1989 35-utility study, and found that THMs, HAAs, dihaloacetamides, tri- and dihalopropanols and trihaloacetaldehydes were found in roughly the same concentrations in water systems that use free chlorine and monochloramine as secondary disinfectants.

One caveat to this study is that the data used was collected 14 years ago; detection methods have vastly improved since then. In this study, the greatest determinant of which classes of DBPs were formed was geography, as the organic material of the starting water is a major factor in DBP formation.

In waters from Scotland, disinfection with monochloramine produced less regulated THMs and HAAs than water disinfected with free chlorine (Goslan et al., 2009). Haloacetonitriles were produced to the same degree in each system, while chloropicrin was significantly reduced in chloraminated water compared to chlorinated.

In a 2010 report, DBPs formed from chlorinated and chloraminated water were quantitated; these DBPs included regulated and unregulated HAAs, regulated THMs, and unregulated iodo-trihalomethanes (i-THMs), HANs, haloketones (HKs), haloaldehydes (HAs), and halonitromethanes (HNMs; Bougeard et al., 2010). For 22 out of the 25 quantitated DBPs, chlorination resulted in much higher formation than chloramination. The two i-THMs were formed to roughly the same degree in chlorinated and chloraminated water, and 1,1-dichloropropanone was increased in chloraminated water compared to chlorinated water. Overall, this study indicates that with the exception of a few DBPs, chloramination leads to fewer regulated and unregulated DBPs than chlorination.

Another DBP that has been studied is hydrazine. Hydrazine can be formed from ammonia and monochloramine, but only at an alkaline pH (> 10; Rayson et al., 2010). Given that the pH of drinking water is usually around 7.6, hydrazine is not predicted to be a major DBP formed from monochloramine use. In addition, a large excess of ammonia must be present compared to monochloramine (Cahn and Powell, 1954). Monochloramine is present around 2.3 mg/L, while ammonia is present at 0.2 mg/L in Champlain Water District water, a ratio that does not favor the formation of hydrazine. Indeed, hydrazine is not detected in Champlain Water District water leaving the treatment plant (Champlain Water District, personal communication).

Although several of the unregulated DBPs are genotoxic and cytotoxic in cellular assays, the concentrations at which they occur in drinking water may very well limit their toxicity to humans. Pregnant rats were given drinking water spiked with iodide and bromide, then chlorinated and concentrated so that DBPs were 130 fold higher than concentrations observed in finished drinking water (Narotsky et al., 2008). No adverse developmental effects were observed, including gestational age or survival of pups. The same concentrated water containing iodinated and brominated DBPs was used to treat primary hepatocytes at either full strength, 1:10 or 1:20 dilution for 24 hours, and gene expression was measured (Crosby et al., 2008). The concentrated water, but neither dilutions, produced significant gene expression changes in pathways including cell cycle arrest, oxidative stress, and metabolism. The observation that no changes were

observed in the diluted concentrates (still 6-fold more concentrated than finished drinking water) indicates a threshold concentration, below which no cellular changes are observed.

It is important to recognize that unregulated DBPs are formed by both free chlorine and monochloramine in drinking water, and in many reports monochloramine leads to less total DBPs than chlorine. The Health Department recognizes that unregulated DBPs are at the forefront of drinking water research, and will continue to follow EPA as it considers the status of some unregulated DBPs.

Pharmaceuticals and personal care products (PPCPs) are found in some water systems that reuse waste water. In these waters, PPCPs may serve as precursors for the formation of unregulated DBPs. Some amine-containing PPCPs can combine with monochloramine to form NDMA in benchtop studies (Shen and Andrews, 2011). Ranitidine (Zantac) can be converted at a high percentage to NDMA in the presence on high concentrations of monochloramine. Quaternary amines are found in many consumer products, and may serve as precursors for nitrosamine formation (Kemper et al., 2010). Quaternary amines are used extensively in the cosmetics and personal hygiene industry, and are known to cause dermal and respiratory irritation (Bello et al., 2009). The most common cause of contact dermatitis is a quaternary amine, Quaternium-15 (Warshaw et al., 2007). Lake Champlain, the source of raw drinking water for many water districts, may receive small amounts of organic wastewater compounds from wastewater effluent and combined sewer overflows (Phillips and Chalmers, 2009).

## CONCLUSION

The Vermont Department of Health has determined that the use of monochloramine for water disinfection is not likely to result in adverse health effects. On the contrary, the Health Department believes that the use of monochloramine will reduce the concentration of regulated and possibly unregulated DBPs in drinking water. This reduction may contribute to fewer adverse health effects compared to drinking water treated with free chlorine as a disinfectant.

Table 1. Short-term and Long-term Studies on Monochloramine in Drinking Water in Animals

Species	Route	Highest Dose	Duration	Effect	Reference
<b>Short-term studies</b>					
Rats	Drinking water	100 mg/L	45 days	Normal hemoglobin, packed red cell volume, and glutathione; decreased methemoglobin	Bull, 1980
Monkeys	Drinking water	100 mg/L	6 weeks	Normal hematological parameters and thyroid hormone levels	Bercz, 1982
Mice	Concentrated drinking water *	4000x	30 days	Normal gross pathology, no overt toxicity observed	Miller, 1986
Rats	Drinking water	38 mg/L	12 weeks	Normal serum immunological endpoints; increased prostaglandin synthesis	Exon, 1987
Rats	Drinking water	200 mg/L	90 days	Normal hematological parameters, serum chemistry, gross observations and histological parameters; decreased body weight due to taste aversion.	Daniel, 1990
Mice	Drinking water	200 mg/L	90 days	Normal hematological parameters, serum chemistry, gross observations and histological parameters; decreased body weight due to taste aversion	Daniel, 1991
Rats	Drinking water	200 mg/L	13 weeks	Normal red cells and bone marrow cells, mitogen responsiveness, serum immunology, liver enzymes, and lung function; no evidence of lipid peroxidation	Poon, 1997
Rats	Drinking water	200 mg/L	28 days	Normal serum immunological endpoints	Guo, 2011
<b>Long-term studies</b>					
Rats	Drinking water	100 mg/L	1 year	Normal hematological parameters	Abdel-Rahman, 1984
Rats	Drinking water	200 mg/L	2 years	Normal gross pathology; decreased body weight due to taste aversion.	NTP, 1992
Mice	Drinking water	200 mg/L	2 years	Normal gross pathology; decreased body weight due to taste aversion.	NTP, 1992

\* drinking water was treated with monochloramine at 2.1 mg/L then concentrated 4000x.

Table 2. Carcinogenicity Studies on Monochloramine in Animals

Species	Route	Highest Dose	Duration	Effect	Reference
Rats	dermal	14.75 mg/kg/day	7 days	No evidence of tumor initiation	Freund, 1986
Rats	oral	2.1 mg/L (concentrated 4000x)	7 days	No evidence of tumor initiation	Miller, 1986
Rats	oral	200 mg/L	2 years	No evidence of carcinogenicity	NTP, 1992
Mice	oral	200 mg/L	2 years	Equivocal evidence of carcinogenicity in females	NTP, 1992

Table 3. Irritation Studies on Monochloramine in Animals

Species	Route	Highest Dose	Duration	Effect	Reference
Rabbit	ocular	4 mg/L	1 hour	No irritation below 4 mg/L; irritation at 4 mg/L	Eichelsdoerfer, 1975
Mice	dermal	1000 mg/L	10 min/day; 4 days	No skin hyperplasia observed	Robinson, 1986
HEN-CAM	n/a	2.4 mg/L	1 hour	No irritation observed	Erdinger, 1997

Table 4. Reproductive and Developmental Toxicity Studies in Animals

Species	Route	Highest Dose	Duration	Effect	Reference
Rats	Drinking water	100 mg/L	3 months including gestation	No effect on fetal resorption; no teratogenic effects on offspring	Abdel-Rahman, 1982
Rats	Oral gavage	10 mg/kg/day	76 days including mating, gestation and lactation	No effect on fertility, viability, litter size, weight of offspring, sperm count or mobility. Normal reproductive organ histopathology	Carlton, 1986

Table 5. Studies on Monochloramine in Drinking Water in Humans

Species	Route	Highest Dose	Duration	Effect	Reference
Humans	Drinking water	24 mg/L	13 days	Normal serum biochemical parameters, and physical parameters	Lubbers, 1982
Humans	Drinking water	15 mg/L	4 weeks	Normal lipid and thyroid metabolism; increased Apolipoprotein B	Wones, 1993

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