

## Monochloramine; CASRN 10599-90-3

Human health assessment information on a chemical substance is included in the IRIS database only after a comprehensive review of toxicity data, as outlined in the [IRIS assessment development process](#). Sections I (Health Hazard Assessments for Noncarcinogenic Effects) and II (Carcinogenicity Assessment for Lifetime Exposure) present the conclusions that were reached during the assessment development process. Supporting information and explanations of the methods used to derive the values given in IRIS are provided in the [guidance documents located on the IRIS website](#).

### STATUS OF DATA FOR Monochloramine

**File First On-Line 11/01/1992**

Category (section)	Assessment Available?	Last Revised
<b>Oral RfD (I.A.)</b>	yes	03/01/1994*
<b>Inhalation RfC (I.B.)</b>	not evaluated	
<b>Carcinogenicity Assessment (II.)</b>	yes	12/01/1993*

\*A comprehensive review of toxicological studies was completed (05/27/05) - please see sections I.A.6. and II.D.2. for more information.

## I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

### I.A. Reference Dose for Chronic Oral Exposure (RfD)

Substance Name — Monochloramine

CASRN — 10599-90-3

Last Revised — 03/01/1994

The oral Reference Dose (RfD) is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. It is expressed in units of mg/kg-day. In general, the RfD 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 effects during a lifetime. Please refer to the Background Document for an elaboration of these concepts. RfDs can also be derived for the noncarcinogenic health effects of substances that are also carcinogens. Therefore, it is essential to refer to other sources of information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

NOTE: Chloramines are formed when free chlorine is added to water containing ammonia. Free chlorine refers to the concentrations of elemental chlorine, hypochlorous acid and hypochlorite ion that collectively occur in water. The type of chloramine formed is dependent on the chlorine to ammonia ratio, pH, temperature, and contact time. Monochloramine is formed when the pH of ammonia containing water is >8 and the molar ratio of hypochlorite to ammonia is <1. At hypochlorite to ammonia ratios of >1 or at lower pH values dichloramine and trichloramine are formed. Chloramines eventually decompose by several mechanisms, not all of which have been elucidated. For more information about the chemistry of chloramines see U.S. EPA, 1992.

### I.A.1. Oral RfD Summary

Critical Effect	Experimental Doses*	UF	MF	RfD
<b>No observed effects</b>	NOAEL: 200 ppm (9.5 mg/kg-day)	100	1	1E-1 mg/kg-day
<b>Rat Chronic Oral Study</b>	LOAEL: None			
<b>NTP, 1992</b>				

\*Conversion Factors -- 200 ppm = 9.5 mg/kg-day computed from summary water consumption data provided by the investigators.

### I.A.2. Principal and Supporting Studies (Oral RfD)

NTP (National Toxicology Program). 1992. Toxicology and Carcinogenesis Studies of Chlorinated and Chloraminated Water (CAS Nos. 7782-50-5, 7681-52-9 and 10599-90-3) in F344/N Rats and B6C3F1 Mice (drinking water studies). NTP TR 392.

The long-term effects of chloraminated water were examined in F344/N rats and B6C3F1 mice (NTP, 1992). Groups of rats (70/sex/dose) and mice (70/sex/dose) were administered chloraminated drinking water at 0 (controls), 50, 100 or 200 ppm for 103-104 weeks. Based on

body weight and water consumption data provided in the study, the intake of chloramine was 0, 2.6, 4.8 and 8.7 mg/kg-day for male rats; 0, 3.4, 5.3 and 9.5 mg/kg-day for female rats. Consumption of chloramine in mice was 0, 5.0, 8.9 and 15.9 mg/kg-day for males; and 0, 4.9, 9.0 and 17.2 mg/kg-day for females. Interim sacrifices (10/sex/dose) were conducted at weeks 14 and 66. At these times, a complete hematologic examination and necropsy were performed in all sacrificed animals. In addition, histopathologic examination was conducted in all control and high-dose animals. At the completion of the study, a complete histopathologic evaluation was performed in all animals. A dose-related decrease in water consumption was evident in rats throughout the study; food consumption was not affected by treatment. Mean body weights of high-dose male and female rats were lower than their respective controls. However, mean body weights were within 10% of controls until week 97 for females and week 101 for males. Decreases ( $p < 0.05$ ) in liver and kidney weight in the high-dose males and increases ( $p < 0.05$ ) in the brain- and kidney-to-body weight ratios in the high-dose rats (both sexes) were related to lower body weights in these groups and were not considered toxicologically significant. Results from pathologic evaluation at weeks 14 and 66 were unremarkable. The authors found no clinical changes attributable to consumption of chloraminated water. There were no non-neoplastic lesions after the 2-year treatment with chloraminated water. A NOAEL for rats of 200 ppm chloramine, or 9.5 mg chloramine/kg/day, can be defined in this study.

In treated mice, water consumption throughout the study was also decreased in a dose-related manner. Food consumption was slightly lower in high-dose females compared with controls. Body weights of treated male and female mice were lower than in controls; the effect was dose-related. On the average, body weights of high-dose males were 10-22% lower than controls after week 37; those of high-dose females were 10-35% lower than controls after week 8. Mice exhibited no adverse clinical signs attributed to treatment with chloramine. Survival rates between treated and control mice were not significantly different. Interim evaluations revealed no biologically significant differences in organ weights or in relative organ weights. There were occasional statistically significant differences, such as decreases in liver weights and increases in brain- and kidney-to-body weight ratios in high-dose male and female mice, but these were attributed to the lower body weights and were not considered toxicologically significant. Results from hematology tests, and gross or microscopic examination of tissues and organs were unremarkable. The 2-year evaluation revealed no non-neoplastic lesions attributable to chloramine treatment. The concentration of 200 ppm chloramine, or 17.2 mg chloramine/kg/day is considered a NOAEL for mice in this study.

The NOAEL of 9.5 mg chloramine/kg/day in rats is chosen as the basis for the chronic oral RfD. Although a higher NOAEL in the study of 17.2 mg/kg-day is found for mice, rats may be the more sensitive species since doses between 9.5 and 17.2 mg/kg-day were not tested in rats. Significant decreased weight gain in subchronic rat studies, such as Daniel et al. (1990), at 200

ppm was considered a consequence of decreased water consumption associated with taste aversion.

### **I.A.3. Uncertainty and Modifying Factors (Oral RfD)**

UF — The uncertainty factor of 100 reflects 10 for interspecies extrapolation and 10 for the protection of sensitive human subpopulations. An additional factor for the lack of reproductive and developmental toxicity data is not considered necessary because data from existing studies across chemical class (monochloramine and chlorine) provide sufficient confidence that the reproductive and developmental issues have been addressed. Although the studies with chlorine are marginal in quality, they do give an indication that adverse effects from monochloramine are not likely to occur.

MF — None

### **I.A.4. Additional Studies/Comments (Oral RfD)**

Daniel et al. (1990) conducted a 90-day drinking water study with monochloramine at 0, 25, 50, 100 and 200 mg/L in Sprague-Dawley rats (10/sex/dose group). Based on body weight and water consumption data, the investigators estimated the chloramine intake to be 0, 1.8, 3.4, 5.8 and 9.0 mg/kg-day for males and 0, 2.6, 4.3, 7.7 and 12.1 mg/kg-day for females. Endpoints examined included mortality, clinical signs, body weight, food consumption, hematology, clinical chemistry, organ weights, gross pathology, and histopathology. Water consumption was significantly reduced ( $p < 0.05$ ) in all treated groups in a concentration-related manner. Food consumption was significantly reduced in high-dose males. At the 200 mg/L dose level, the average weight gain for male and female treated rats was 51% of controls; water consumption at this dose level was 31-34% of controls. Significant changes ( $p < 0.05$ ) in hematologic and clinical chemistry parameters included decreased hematocrit at 100 mg/L, decreased red blood cell counts at 100 and 200 mg/L in males, and decreased serum calcium levels in all treated male groups. These findings were not dose-related, were within the normal ranges, and were not considered biologically significant. There were significant reductions ( $p < 0.05$ ) in organ weights (absolute, relative or both); as spleen and liver weight reductions occurred in both males and females at the highest dose but, histopathologic examinations did not reveal any treatment-related changes in these tissues. The authors suggested that to clearly identify the NOAEL, a matched watering and feeding study would be useful for distinguishing between systemic toxic effects and weight gain depression from taste aversion.

Male and female B6C3F1 mice (10/sex/dose group) were treated with monochloramine in the drinking water for 90 days (Daniel et al., 1991). The concentration levels of the disinfectant in water were 0 (controls), 12.5, 25, 50, 100 and 200 mg/L, and provided doses (calculated by the

investigators from water consumption and body weight data) of 0, 2.5, 5.0, 8.6, 11.1 and 15.6 mg monochloramine/kg/day for males; and 0, 2.8, 5.3, 9.2, 12.9 and 15.8 mg chloramine/kg/day for females. Endpoints examined in control and high-dose groups included mortality, clinical signs, body weight, food consumption, hematology, clinical chemistry, organ weights, gross pathology and histopathology. A significant, dose-related decrease in water consumption ( $p < 0.05$ ) occurred in females at all dose levels and in males at the two highest dose levels. Food consumption was decreased in females at the two highest dose levels. Final body weight and body weight gain were decreased ( $p < 0.05$ ) in both sexes at the two highest concentration levels. No overt clinical signs of toxicity and gross or histopathologic changes could be detected. Changes in hematologic and clinical chemistry parameters were not concentration-related and were attributed to the decrease in water and nutrient consumption and altered electrolyte balance. Changes in organ weights included a significant ( $p < 0.05$ ) decrease in liver, heart, and lung weight in males and in liver, heart, and spleen weight in females at concentrations of 100 and 200 mg/L. Minor weight changes occurred at 100 mg/L, including minor (less than 10%) depression of body weight relative to controls. These effects were considered a consequence of decreased water consumption associated with taste aversion and not chemically induced.

Male Sprague-Dawley rats (16/dose group) were administered monochloramine in the drinking water (ad libitum) at 0 (controls), 1, 10 or 100 mg/L for up to 12 months (Abdel-Rahman et al., 1984). This intake corresponds to 0.12, 1.2 and 12 mg monochloramine/kg/day based on reference body weight and water intake data for mature male rats of this strain (U.S. EPA, 1987). Hematologic parameters, as well as blood glutathione (GSH) levels, were monitored throughout the treatment period. Incorporation of 3H-thymidine was studied in liver, kidney, testes, intestinal mucosa, and spleen after 3 months of treatment. Treatment-related ( $p < 0.05$ ) decreases in blood GSH were observed at 6 and 12 months; changes in GSH levels at other times were inconsistent. A significant increase in red blood cell fragility was detected after 2 and 10 months of treatment at the mid-dose level, and after 2 and 6 months at the high-dose level. Significant changes in hematologic parameters were limited to decreased red blood cell count and hematocrit at the 10 and 100 mg/L levels at 3 months and a reduced hemoglobin concentration and mean corpuscular hemoglobin at the 100 mg/L level after 10 months of treatment. Increased incorporation of 3H-thymidine was observed in the kidney and spleen at 1 and 10 mg/L, and in testes at 100 mg/L at 3 months; other time periods were not examined. Body weights were reported to be significantly reduced relative to controls after 3 months of treatment at 100 mg/L and remained lower than controls throughout the experiment. Blood levels of chloroform monitored during the study were no different than in untreated rats. Single gavage doses of 0.19, 0.38 and 0.75 mg monochloramine/kg (estimated from initial body weights given by the investigators) significantly increased blood GSH for 1 hour following dosing, but GSH levels returned to control levels after 2 hours. The increased osmotic fragility observed was not corroborated by NTP (1992) and was not affected in the acute experimental series. The

significance of these changes to health is uncertain, particularly in the absence of food consumption and water intake data.

GSRI (1981) conducted a subchronic study of chloramine in the drinking water of F344 rats and B6C3F1 mice (10/sex/group for the two species) at concentrations of 0, 25, 50, 100, 200 and 400 ppm for 13 weeks. Based on body weight and water consumption data provided in the study, the intake of chloramine was estimated to be 0, 2.6, 5.0, 10.2, 19.4 and 40.7 mg/kg-day for male rats and 0, 4.1, 6.9, 15.1, 28.7 and 51.7 mg/kg-day for female rats. Intake of chloramine for mice was 0, 5.1, 8.4, 15.9, 30.7 and 50 for males and 0, 8.3, 12.9, 23.3, 35.2 and 92 mg/kg-day for females. Water consumption was not significantly altered in rats. There was a dose-related decrease in body weight gain in treated male rats. Results of microscopic examination of organs and tissues did not reveal any compound-related lesions in rats. Mice exhibited a dose-related reduction in water consumption. Male and female mice gained less weight than controls at the 200 and 400 ppm levels. Absolute and relative liver weight was reduced in high dose males; absolute liver weight was reduced in females at 100 ppm or greater. Histopathologic examination revealed a pattern of necrotic changes in the liver at the low doses and inflammatory response in the livers of female mice at the 100-400 ppm levels. (Confidence in this study is low due to questions regarding the conduct of this study, the histopathological evaluations, and lack of corroboration of its findings.)

Bercz et al. (1982) evaluated the toxicity of monochloramine administered in drinking water to five adult male and seven adult female African Green monkeys for 6 weeks at 100 mg/L. Each animal served as its own control. Chloramine was only one of several water disinfectants tested in the animals; between each chemical, the animals were rested for 6-9 weeks. The mean daily dose was 10 mg/kg-day. No effects were detectable on various hematologic parameters, including red cell glutathione levels. No evidence of thyroid suppression was detected in serum. A NOAEL of 10 mg/kg-day, the only dose tested, was reported.

Bull (1980) administered monochloramine to rats (number, sex and strain not reported) at doses of 0, 10, 50 or 100 mg/L in drinking water for 45 days. Based on default reference body weight and water consumption values for F344 male and female rats for subchronic exposure (U.S. EPA, 1987), the corresponding intake of monochloramine was 0, 1.6, 8.1 and 16 mg/kg-day. Body weight gain (no data provided) and hematologic parameters in exposed animals did not differ significantly from control animals. A significant decrease in methemoglobin was reported at 100 mg/L, the biologic significance of which is unclear. A NOAEL of 16 mg monochloramine/kg/day was defined in this study.

Immunotoxic effects were reported by Exon et al. (1987) when monochloramine was administered to male Sprague-Dawley rats (12/sex/dose group) from weaning to 12 weeks of age at doses of 0, 9, 19 and 38 ppm in drinking water. Based on reference body weight and water

consumption values for subchronic exposure (U.S. EPA, 1987), the corresponding intake of monochloramine was 0, 1.3, 2.6 and 5.3 mg/kg-day. Parameters monitored were body weight, spleen and thymus weight, antibody production, delayed-type hypersensitivity (DTH) reactions, natural killer cell (NKC) cytotoxicity, oxidative metabolism response and phagocytosis by macrophages, and production of interleukin 2 (IL2) and prostaglandin E2 (PGE2). The effects attributed to monochloramine treatment were limited to a significant reduction in relative spleen weight at 38 ppm, decreased antibody synthesis (9 and 19 ppm) and augmented PGE2 production at 19 and 38 ppm. These changes were not considered to be biologically significant. There were not significant effects on the other endpoints monitored. A NOAEL and/or LOAEL are not defined in this study.

In a reproductive study by Carlton et al. (1986), chloramine was administered by gavage in deionized water at doses of 0, 2.5, 5.0 and 10 mg chloramine/kg/day to male (12/dose group) and female (24/dose group) Long Evans rats for a total of 66-76 days. Males were treated for 56 days and females for 14 days prior to mating. Dosing continued during the 10-day mating period and afterwards females were dosed with chloramine daily during gestation and lactation. Males were necropsied at the end of the mating period. Dams and some offspring were necropsied at 21 days after birth. Other offspring were dosed with chloramine after weaning until they were 28-40 days old. No statistical differences were observed between control and exposed rats in fertility, viability, litter size, day of eye opening or average day of vaginal patency. There were no alterations in sperm count, direct progressive sperm movement, percent mobility or sperm morphology in adult males. Weights of male and female reproductive organs were not significantly different among control and test groups, and there were no significant morbid anatomic changes evident on tissue examination. There were no signs of toxicity, changes in blood counts, or effects on body weight in adult rats of either sex at any dose level. The mean weight of the pups was not affected by chloramine treatment. A NOAEL of 10 mg/kg-day for reproductive effects can be defined from this study.

Abdel-Rahman et al. (1982) administered monochloramine in the drinking water to female Sprague-Dawley rats (6/dose group) at 0, 1, 10 and 100 mg/L for 2.5 months prior to and throughout gestation. By using body weights provided by the investigators and a reference water consumption value (U.S. EPA, 1987), the intake of monochloramine was estimated to be to 0, 0.15, 1.5 and 15 mg monochloramine/kg/day. Treatment with monochloramine did not increase the number of fetal resorptions or affect fetal weight. In addition, monochloramine did not induce soft-tissue anomalies or skeletal malformations. A developmental NOAEL of 15 mg monochloramine/kg/day is provided by this study, although confidence is low due to the small number of animals exposed.

### **I.A.5. Confidence in the Oral RfD**

Study — High  
Database — Medium  
RfD — Medium

Confidence in the principal study (NTP, 1992) is high-to-medium. Relevant endpoints in two animal species were examined after prolonged exposure by an appropriate route. However, an effect level was not achieved in the study, and higher dose levels may not be practicable due to taste aversion (and therefore reduced water consumption). Confidence in the data base is medium. Information is available for mice, rats and monkeys on the noncarcinogenic toxicity of oral exposure to monochloramine for subchronic periods. The developmental toxicity and reproductive toxicity of monochloramine have been examined in rats, but with suboptimal studies. Due to the chemical relationship between monochloramine and chlorine (U.S. EPA, 1992), reproductive and developmental studies for chlorine (Druckrey, 1968; McKinney et al., 1976; Chernoff et al., 1979; Staples et al., 1979; Meier et al., 1985) may be used to satisfy these data gaps for monochloramine. The overall confidence of the RfD is medium.

### **I.A.6. EPA Documentation and Review of the Oral RfD**

Source Document — U.S. EPA, 1992

The Drinking Water Criteria Document for Chloramines has undergone a limited Agency Review.

Other EPA Documentation — None

Agency Work Group Review — 06/23/1992, 10/14/1993, 12/15/1993

Verification Date — 06/23/1992

A comprehensive review of toxicological studies published through May 2005 was conducted. No new health effects data were identified that would be directly useful in the revision of the existing RfD for Monochloramine and a change in the RfD is not warranted at this time. For more information, IRIS users may contact the IRIS Hotline at [hotline.iris@epa.gov](mailto:hotline.iris@epa.gov) or 202-566-1676.

### **I.A.7. EPA Contacts (Oral RfD)**

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (FAX) or [hotline.iris@epa.gov](mailto:hotline.iris@epa.gov) (internet address).

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### **I.B. Reference Concentration for Chronic Inhalation Exposure (RfC)**

Substance Name — Monochloramine  
CASRN — 10599-90-3

Not available at this time.

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## **II. Carcinogenicity Assessment for Lifetime Exposure**

Substance Name — Monochloramine  
CASRN — 10599-90-3  
Last Revised — 12/01/1993

Section II provides information on three aspects of the carcinogenic assessment for the substance in question; the weight-of-evidence judgment of the likelihood that the substance is a human carcinogen, and quantitative estimates of risk from oral exposure and from inhalation exposure. The quantitative risk estimates are presented in three ways. The slope factor is the result of application of a low-dose extrapolation procedure and is presented as the risk per (mg/kg)/day. The unit risk is the quantitative estimate in terms of either risk per ug/L drinking water or risk per ug/cu.m air breathed. The third form in which risk is presented is a drinking water or air concentration providing cancer risks of 1 in 10,000, 1 in 100,000 or 1 in 1,000,000. The rationale and methods used to develop the carcinogenicity information in IRIS are described in The Risk Assessment Guidelines of 1986 (EPA/600/8-87/045) and in the IRIS Background Document. IRIS summaries developed since the publication of EPA's more recent Proposed Guidelines for Carcinogen Risk Assessment also utilize those Guidelines where indicated (Federal Register 61(79):17960-18011, April 23, 1996). Users are referred to Section I of this IRIS file for information on long-term toxic effects other than carcinogenicity.

### **II.A. Evidence for Human Carcinogenicity**

#### **II.A.1. Weight-of-Evidence Characterization**

Classification — D; not classifiable as to human carcinogenicity

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Basis — Based on inadequate human data and equivocal evidence of carcinogenicity from animal bioassays. A 2-year bioassay showed a marginal increase in mononuclear cell leukemia in female F344/N rats. No evidence of carcinogenic activity was reported in male rats or in male or female B6C3F1 mice. Genotoxicity studies, both in vitro and in vivo, gave negative results.

## **II.A.2. Human Carcinogenicity Data**

Inadequate. There are no epidemiologic studies of monochloramine itself. Numerous studies have attempted to assess the relationship between drinking water quality and cancer, however, these studies differ greatly in both their objectives and design, thus precluding specific inferences being drawn from their findings. In general, these studies were intended to assess whether trihalomethanes or other organic compounds occurring in drinking water as a result of chlorination are associated with an increase in gastrointestinal and urinary cancer.

A pilot study by Zierler et al. (1986) found no correlation between cancer mortality and consumption of chloraminated water in individuals who resided for over 40 years in communities with chloraminated drinking water. A small excess of bladder cancer, however, occurred in residents of communities using chlorine as a disinfectant. These data were preliminary, and the investigators indicated that considerable potential for error exist in the classification of exposure and disease status. A subsequent report by the same group of investigators (Zierler et al., 1988) presented data on 614 individuals who died of primary bladder cancer who had been exposed to water disinfected with either chlorine or chloramine for 40-46 years. Potential confounders were controlled by a multiple logistic regression model. A control group (1074 individuals) comprised five disease groups: cardiovascular disease, cerebrovascular disease, lung cancer, chronic obstructive pulmonary disease, and lymphatic cancer. The mortality odds ratio for bladder cancer among individuals who resided only in communities supplied with chlorinated drinking water was significantly elevated at 1.6 (95% confidence interval = 1.2-2.1) relative to individuals who resided only in communities supplied with chloraminated drinking water using all controls. When only lymphoma controls were utilized, the bladder cancer risk rose to 2.7 (statistically significant with 95% CI=1.7-4.3). The use of deceased controls and the difference in the two odds ratios suggest the possibility that some of the underlying causes of death in the controls may have been a result of increased exposure to either chloramines or chlorines. This would have the effect of reducing the odds ratios toward the null. Unfortunately, it is impossible to find controls who have not been exposed to chlorine or chloramine. Hence the true cancer risk from exposure to chloraminated drinking water relative to unchloraminated drinking water absent chlorination cannot be determined at this time. Furthermore, the relationship between consumption of chloraminated water and bladder cancer incidence cannot be defined based on the results of these studies.

### II.A.3. Animal Carcinogenicity Data

Inadequate. NTP (1990) administered monochloramine in the drinking water of rats and mice for 103-104 weeks. The incidence of mononuclear cell leukemia was marginally increased in treated female rats. NTP (1990) considered this evidence of carcinogenicity to be equivocal. Small numbers of renal tubular cell neoplasms in male mice were considered unrelated to consumption of chloraminated water.

The potential carcinogenicity of chloraminated water was examined in F344/N rats (NTP, 1990). Groups of rats (70/sex/dose) were administered chloraminated drinking water at 0 (controls), 50, 100 or 200 ppm for 103-104 weeks. Based on body weight and water consumption data provided in the study, the intake of chloramine was 0, 2.6, 4.8, and 8.7 mg/kg/day for male rats; 0, 3.4, 5.3, and 9.5 mg/kg/day for female rats. The rate-limiting factor in administering monochloramine in drinking water was its palatability (Daniel et al., 1990). Interim sacrifices (10/sex/dose) were conducted at weeks 14 and 66 for evaluation. At these times, a complete hematological examination and necropsy were performed in all animals. In addition, histopathologic examination was conducted in all control and high dose animals. At the completion of the study, a complete histopathologic evaluation was performed in all animals. A dose-related decrease in water consumption was evident in rats throughout the study; food consumption was not affected by treatment. Mean body weights of high-dose male and female rats were lower than their respective controls. However, mean body weights were within 10% of controls until week 97 for females and week 101 for males. No treatment-related clinical findings were observed in rats. Survival of rats was not reduced by chloramine treatment, instead, low-dose males lived longer than controls. Results from pathologic evaluation at weeks 14 and 66 were unremarkable. There were no nonneoplastic lesions after the 2-year treatment with chloraminated water. Splenic histiocytic lymphoid hyperplasia was marginally increased in high-dose female rats (3/50 controls, 4/50 low-dose, 2/50 mid-dose, 6/50 high dose). Because of the lack of dose-response, the marginal increase in incidence, and small numbers, this lesion was considered unrelated to treatment with chloraminated water. The incidence of mononuclear cell leukemia was also marginally increased in treated female rats. The incidence of mononuclear cell leukemia was: 8/50 (controls), 11/50 (low-dose), 15/50 (mid-dose), and 16/50 (high-dose). A life table trend test was positive ( $p=0.021$ ). The mean time to observations for leukemia among early deaths was similar among control and dosed groups. There was no decrease in tumor latency associated with treatment. Because the overall evidence is weakly supportive of an association between occurrence of mononuclear leukemia in female rats and consumption of chloraminated water, NTP (1990) considered the evidence of carcinogenicity equivocal.

The potential carcinogenicity of chloraminated water was also examined in B6C3F1 mice (NTP, 1990). Groups of mice (70/sex/dose) were administered chloraminated drinking water at 0 (controls), 50, 100 or 200 ppm (highest palatable dose) for 103-104 weeks. Consumption of

chloramine in mice was 0, 5.0, 8.9 and 15.9 mg/kg/day for males, and 0, 4.9, 9.0 and 17.2 for females.

In treated mice, water consumption throughout the study was decreased in a dose-related manner. Food consumption was slightly lower in high-dose females compared with controls. Body weights of treated male and female mice were lower than in controls; the effect was dose-related. On the average, body weights of high dose-males were 10-22% lower than controls after week 37; those of high-dose females were 10-35% lower after week 8. Mice exhibited no adverse clinical signs attributed to treatment with chloramine. Survival rates between treated and control mice were not significantly different. Interim evaluations revealed no biologically significant differences in organ weights or in relative organ weights. Results from hematology tests, and gross or microscopic examination of tissues and organs were unremarkable. The 2-year evaluation revealed no nonneoplastic lesions attributable to chloramine treatment. Renal tubular cell adenomas occurred in two high-dose males, while one low-dose, two mid-dose, and one high-dose male showed focal tubule hyperplasia. Examination of additional kidney sections of all male mice showed hyperplasia in two controls and one mid-dose male, and an adenoma in one low-dose male. Since no additional neoplasms were found in the mid-dose and high-dose groups, and since focal hyperplasia was found at similar incidences in the control and treated groups, the small number of renal tubular cell neoplasms in male mice were considered unrelated to consumption of chloraminated water.

#### **II.A.4. Supporting Data for Carcinogenicity**

The initiation-promotion activity of chloramine was tested in rats in a rat liver focus bioassay (Herren-Freund and Pereira, 1986). In this assay, an increased incidence of gamma-glutamyltranspeptidase-(GGT-) positive foci serves as an indicator of early events in a carcinogenic process. Male Sprague-Dawley or Fischer 344 rats were administered 14.75 mg chloramine/kg body weight (presumably in the drinking water) 24 hours after a partial (two-thirds) hepatectomy. One week after initiation, nine rats received 500 ppm phenobarbital in the drinking water for 10 weeks. Diethylnitrosamine was used as positive control. Under the conditions of the study, chloramine did not induce GGT foci.

Miller et al. (1986) tested concentrates of monochloramine treated drinking water samples from a pilot-scale water plant as initiators in the GGT focus bioassay and the concentrates did not induce an incidence of GGT foci greater than that of the vehicle control (2% Emulphor). Miller et al. (1986) also tested these water sample concentrates in the mouse lung adenoma assay. Three control groups, a negative control, a vehicle control (2% Emulphor), and a positive control (10 mg urethane/mouse by gavage) were used. Lung adenomas were observed in the positive controls with a mean of 11.5 adenomas per animal, the vehicle control had 0.1 adenoma per

animal and the monochloramine- treated animals had a mean number of tumors of less than or equal to 0.09 adenomas per animal.

Bull (1980) and Bull et al. (1982) conducted initiation-promotion studies in SENCAR mice (25/treatment group, sex distribution not specified) using concentrates from several alternately disinfected waters. In these studies, settled, coagulated and sand-filtered river water was treated with chloramine at 3 mg/L; the residual disinfectant was allowed to dissipate for 48 hours. The water was then concentrated (concentration factor was 142X) by reverse osmosis and a total of 1.5 mL of this concentrate was injected subcutaneously to the back of mice in six doses over a 2-week period. Two weeks after the last dose of concentrate was applied, phorbol myristate acetate in acetone was applied 3 times weekly to the backs of the animals for 20 weeks. Controls were treated with acetone. Nondisinfected water samples (untreated water concentrates) and samples treated with dimethylbenzanthracene (positive controls) were also tested. Chloraminated water concentrate induced tumors in 5/25 mice, whereas none of the animals treated with nondisinfected water exhibited tumors. Lesions included papillomas (1/25), squamous cell carcinomas (2/25), and lung adenomas (5/50, nonpromoted animals included). Results from three additional experiments (Bull et al., 1982) showed a 19% incidence of papillomas in mice treated with chloraminated water concentrates compared with 11 and 13% in mice treated with saline and nondisinfected water concentrates, respectively. This increase was not statistically significant. In the last two of these three initiation promotion experiments, 23 and 15% of animals treated with concentrated monochloramine-treated waters developed papillomas. For these assays, papillomas were also observed in 15 and 13% of mice treated with saline and in 20% of mice exposed to nondisinfected water concentrates. The increase in the response rate for the nondisinfected water concentrate in these two experiments over that of the first experiment may be due to greater concentration factors. The carcinogenic activity associated with chloramine disinfected water concentrate did not significantly exceed that in the nondisinfected water concentrates in these two experiments.

Using a similar protocol, Miller et al. (1986) used concentrated monochloramine-treated drinking water samples from a pilot-scale water plant in the SENCAR mouse initiation-promotion assay (in addition to the GGT focus and lung adenoma bioassays described previously). Mice treated with this concentrated chloraminated water did not exhibit an increase in tumors.

Chloramine was weakly mutagenic when assayed in *Bacillus subtilis* for the reversion of *trpC* locus (Lu Shih and Lederberg, 1976). Treatment of *B. subtilis* with high concentrations of chloramine resulted in single-strand breaks in the DNA and a few double-strand scissions (Lu Shih and Lederberg, 1976). Thomas et al. (1987) reported that while monochloramine slightly increased the number of revertant colonies over controls in *Salmonella typhimurium* strains TA97a, TA100 and TA102, cytotoxicity eclipsed mutation before a doubling of revertants was reached. Drinking water samples treated with monochloramine collected at a pilot-scale drinking

water treatment plant were not mutagenic in *Salmonella typhimurium* strains TA98 or TA100 with or without metabolic activation (Miller et al., 1986). Gavage administration of chloramine at doses of 40, 100 or 200 mg/L to CD-1 mice did not induce chromosomal aberrations or micronuclei, nor did it induce sperm-head abnormalities in B6C3F1 mice (Meier et al., 1985).

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## **II.B. Quantitative Estimate of Carcinogenic Risk from Oral Exposure**

Not available.

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## **II.C. Quantitative Estimate of Carcinogenic Risk from Inhalation Exposure**

Not available.

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## **II.D. EPA Documentation, Review, and Contacts (Carcinogenicity Assessment)**

### **II.D.1. EPA Documentation**

Source Document — U.S. EPA, 1992

The Draft Final Drinking Water Criteria Document for Monochloramine has been reviewed by the Office of Health and Environmental Assessment (OHEA/ORD) and by the Science Advisory Board (SAB) of the U.S. EPA.

### **II.D.2. EPA Review (Carcinogenicity Assessment)**

Agency Work Group Review — 10/21/1992, 12/02/1992

Verification Date — 12/02/1992

A comprehensive review of toxicological studies published through May 2005 was conducted. No new health effects data were identified that would be directly useful in the revision of the existing carcinogenicity assessment for Monochloramine and a change in the assessment is not warranted at this time. For more information, IRIS users may contact the IRIS Hotline at [hotline.iris@epa.gov](mailto:hotline.iris@epa.gov) or 202-566-1676.

### **II.D.3. EPA Contacts (Carcinogenicity Assessment)**

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (FAX) or [hotline.iris@epa.gov](mailto:hotline.iris@epa.gov) (internet address).

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**III. [reserved]**

**IV. [reserved]**

**V. [reserved]**

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## **VI. Bibliography**

Substance Name — Monochloramine  
CASRN — 10599-90-3

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### **VI.B. Inhalation RfD References**

None

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### **VI.C. Carcinogenicity Assessment References**

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## VII. Revision History

Substance Name — Monochloramine  
CASRN — 10599-90-3

Date	Section	Description
11/01/1992	I.A.	Oral RfD summary on-line
12/01/1993	II.	Carcinogenicity assessment on-line
03/01/1994	I.A.	Oral RfD revised; study and number unchanged
10/28/2003	I.A.6., II.D.2.	Screening-Level Literature Review Findings message has been added.
06/22/2005	I.A.6., II.D.2	Screening-Level Literature Review Findings message has been removed and replaced by comprehensive literature review conclusions.

## VIII. Synonyms

Substance Name — Monochloramine

CASRN — 10599-90-3

Last Revised — 08/01/1992

- 10599-90-3
- Chloramide
- Chloramine
- Chloramine [inorganic compound]
- Chloroamine
- HSDB 4293
- Monochloramine
- Monochloroamine
- Monochloroammonia