CHLORAMINE

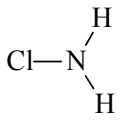
1. Exposure Data

1.1 Chemical and physical data

1.1.1 *Nomenclature*

Chem. Abstr. Serv. Reg. No.: 10599-90-3
Chem. Abstr. Name: Chloramide
IUPAC Systematic Name: Chloramide
Synonyms: Chloroamine; monochloramine; monochloroamine; monochloroammonia

1.1.2 *Structural and molecular formulae and relative molecular mass*



ClH_2N Relative molecular mass: 51.47

1.1.3 *Chemical and physical properties of the pure substance* (Ura & Sakata, 1986)

(*a*) *Description*: Colourless liquid with a strong pungent odour
(*b*) *Melting-point*: –66 °C
(*c*) *Stability*: Stable in aqueous solution, but unstable and explosive in pure form

1.1.4 *Technical products and impurities*

Monochloramine is not known to be a commercial product but is generated *in situ* as needed.

1.1.5 *Analysis*

Chloramines have been determined in water by amperometric titration. Free chlorine is titrated at a pH of 6.5–7.5, a range at which chloramines react slowly. Chloramines are then

titrated in the presence of the correct amount of potassium iodide in the pH range 3.5–4.5. The tendency of monochloramine to react more readily with iodide than dichloramine provides a means for estimation of monochloramine content (American Public Health Association/American Water Works Association/Water Environment Federation, 1999).

In another method, *N,N*-diethyl-*para*-phenylenediamine is used as an indicator in the titrimetric procedure with ferrous ammonium sulfate. In the absence of an iodide ion, free chlorine reacts instantly with the *N,N*-diethyl-*para*-phenylenediamine indicator to produce a red colour. Subsequent addition of a small amount of iodide ion (as potassium iodide) catalytically causes monochloramine to colour. For accurate results, careful pH and temperature control is essential. A simplified colorimetric version of this procedure is commonly used for monitoring levels of chloramine in municipal water systems (American Public Health Association/American Water Works Association/Water Environment Federation, 1999).

1.2 Production and use

1.2.1 *Production*

Chloramines are inorganic nitrogen compounds that contain one or more chlorine atoms attached to a nitrogen atom. A familiar example is monochloramine, the existence of which has been known since the beginning of the nineteenth century. Monochloramine is prepared in pH-controlled reactions by the action of hypochlorous acid or chlorine on ammonia (Ura & Sakata, 1986; Wojtowicz, 1993).

Free chlorine reacts readily with ammonia to form chloramines: monochloramine, dichloramine and trichloramine (nitrogen trichloride). The presence and concentrations of these chloramines depend chiefly on pH, temperature, initial chlorine-to-nitrogen ratio, absolute chlorine demand and reaction time. Both free chlorine and chloramines may be present simultaneously. Chloramines may be formed in water supplies during the treatment of raw waters containing ammonia or by the addition of ammonia or ammonium salts. Typical water treatment practices are designed to produce mainly monochloramine. Chloramines are also formed in swimming pools from the chlorination of ammonia or other nitrogen-containing contaminants (American Public Health Association/American Water Works Association/Water Environment Federation, 1999).

The chemistry of chloramines is fairly well understood and can be summarized in its simplest form by three reversible reactions involving ammonia (NH_3), hypochlorous acid (HOCl), monochloramine (NH_2Cl), dichloramine ($NHCl_2$) and trichloramine (NCl_3):

$$NH_3 + HOCl \rightleftharpoons NH_2Cl + H_2O \quad (1)$$

$$NH_2Cl + HOCl \rightleftharpoons NHCl_2 + H_2O \quad (2)$$

$$NHCl_2 + HOCl \rightleftharpoons NCl_3 + H_2O \quad (3)$$

Monochloramine is generally the dominant species produced during drinking-water disinfection. The production of dichloramine is favoured as the chlorine-to-nitrogen ratio increases and the pH decreases. Hydrolysis reactions (the reverse reactions in equations 1–3 above) are also of considerable interest because they generate hypochlorous acid, which may be important in the formation of the chlorine-substituted organic compounds, hypobromous acid–hypobromite and bromamines. Also, the hydrolysis reaction with monochloramine liberates ammonia. At equilibrium, no more than several per cent of monochloramine is hydrolysed to free chlorine (Diehl *et al*., 2000).

In addition to hydrolysis and conversion to trichloramine (equation 3), dichloramine decomposes by several other reactions, two of which are base-catalysed. The decomposition of dichloramine accelerates as pH, the concentration of bases (e.g. alkalinity), or both increase. Therefore, dichloramine is much less stable than monochloramine under most conditions of practical interest; however, its greater instability does not necessarily mean that dichloramine is of little significance in the formation of disinfection by-products (Diehl *et al*., 2000).

Monochloramine decomposes in a stepwise fashion, being converted first to dichloramine; the subsequent decomposition of dichloramine is primarily responsible for loss of total residual chlorine. The two major pathways for the decomposition of monochloramine are its hydrolysis and subsequent reaction with free chlorine (equations 1 and 2 above) and general acid catalysis:

$$NH_2Cl + NH_2Cl + H^+ \rightleftharpoons NHCl_2 + NH_3 + H^+ \quad (4)$$

The rate of general acid catalysis (equation 4) is a function of the concentration of proton donors and increases as their concentration increases and pH decreases. It has been noted that the carbonate system, via carbonic acid and bicarbonate, may significantly increase the rate of acid-catalysed decomposition at concentrations and pH values typical of many drinking-water systems. Therefore, the decomposition rate of both monochloramine and dichloramine may increase as alkalinity increases (Diehl *et al*., 2000).

Data on the production of monochloramine for water treatment are not available.

1.2.2 *Use*

Chloramines, including monochloramine, are used in synthetic reactions (e.g. as an oxidizing agent for trisubstituted phosphines) and as bleaching agents, disinfectants and bactericides because they function as chlorinating agents and oxidants (undergoing hydrolysis to varying degrees to form hypochlorous acid). Chloramine is widely used in the primary and secondary disinfection of drinking-water (chloramination, in-situ NH_2Cl formation, is increasingly being used to disinfect public water supplies in order to reduce the formation of trihalomethanes). The use of chloramine in water treatment is increasing in the USA to meet stricter standards for disinfection by-products. In addition, chloramine is generally thought to produce a more stable residual than free chlorine and thus to

provide more protection against bacterial regrowth in the distribution system (Ura & Sakata, 1986; Wojtowicz, 1993; Zhang & DiGiano, 2002).

A recent survey of water-treatment plants that serve more than 10 000 people in the USA showed an increase in the percentage of those that use chloramine disinfection, from 20% in 1989 to 29% in 1998 (Oldenburg *et al*., 2002). In addition, the Environmental Protection Agency (1998) in the USA has predicted that an additional 25% will change to chloramine disinfection to comply with stricter standards for disinfection by-products.

Monochloramine has been used in the synthesis of a wide range of other chemicals. The chemistry of monochloramine involves chlorination, amination, addition, condensation, redox, acid-base and decomposition reactions. When monochloramine is added to ketones, it forms vicinal chloroamines and when condensed with aldehydes gives *N*-chloroimines. In the presence of excess base, monochloramine decomposes to ammonia and nitrogen. The reaction of equimolar amounts of monochloramine and caustic with excess ammonia is the basis of the industrial-scale production of hydrazine and, in 1990, it was estimated that 55 000 tonnes of monochloramine were consumed worldwide in the production of hydrazine (Wojtowicz, 1993). Monochloramine is also used in organic synthesis for preparation of amines and substituted hydrazines (Wojtowicz, 1993).

1.3 Occurrence

1.3.1 *Natural occurrence*

Chloramines are not known to occur as natural products. *N*-Chloramines, including monochloramines, are formed *in vivo* secondary to the formation of hypochlorous acid in phagocytes and neutrophils (Carr *et al*., 2001).

1.3.2 *Occupational exposure*

In studies of occupational exposures around swimming pools, Hery *et al.* (1995) measured concentrations of chloramines (expressed as trichloramine) ranging from values below the limit of detection (around 0.05 mg/m^3) to 1.94 mg/m^3 in the air of swimming pools, depending on the characteristics of the pool, water temperature, water-surface stirring and air filtration. Massin *et al.* (1998) measured the levels of trichloramine in the air of indoor swimming pools and found average concentrations of 0.24 mg/m^3 (standard deviation [SD], 0.17) in public pools and 0.67 mg/m^3 (SD, 0.37) in leisure-centre pools. Two public pools had concentrations as high as 0.60 mg/m^3 and two leisure-centre pools had concentrations as low as 0.14 mg/m^3. Thickett *et al.* (2002) measured concentrations of trichloramine in air varying from 0.1 to 0.57 mg/m^3 in indoor swimming pools, where they found cases of occupational asthma among swimming instructors and lifeguards.

Highly irritant and odour-intensive chloramine compounds are also responsible for the typical ‘indoor swimming pool smell’. Due to their different volatilities, pool water releases dichloramine about three times faster and trichloramine about 300 times faster than monochloramine (Holzwarth *et al.*, 1984). Dichloramine imparts a chlorinous odour

to water, while monochloramine does not. Trichloramine has a strong unpleasant odour at concentrations in water as low as 0.02 mg/L (Kirk & Othmer, 1993).

Hery *et al.* (1998) measured total concentrations of chloramines ranging from 0.4 to 16 mg/m^3 in ambient air samples and from 0.2 to 5 mg/m^3 in personal air samples in a green salad-processing plant. In personal air samples, concentrations of soluble chlorine (hypochlorite, mono- and dichloramine) ranged from < 0.1 to 3.7 mg/m^3, while concentrations of trichloramine ranged from < 0.1 to 2.3 mg/m^3. Area samples in the plant contained 0.1–10.9 mg/m^3 soluble chlorine and 0.1–5.9 mg/m^3 trichloramine.

1.3.3 *Air*

See Section 1.3.2, Occupational exposure.

1.3.4 *Water*

Chloramines, mainly monochloramine, are used to provide a disinfection residual in drinking-water distribution systems where it is difficult to maintain free chlorine residual or where the formation of disinfection by-products is a problem (Vikesland *et al.,* 2001). Levels up to 4 mg/L are typically added and decrease with length of residence to around 0.6 mg/L (Zhang & DiGiano, 2002). The decay of chloramines in water distribution systems is dependent on, for example, pH, temperature, length of residence, assimilable organic carbon, and nitrite and bromide content (Vikesland *et al.,* 2001; Zhang & DiGiano, 2002).

Knowledge of the occurrence of organic chloramines in swimming-pool water is very limited, as there are currently no suitable analytical methods for their determination and characterization. Organic chloramines are formed when urine is present in the pools. The distribution of total nitrogen among relevant nitrogen compounds in swimming pools has been calculated. Although more than 80% of the total nitrogen content in urine is present in the form of urea and the ammonia content in urine, at approximately 5%, is comparatively low, swimming-pool water exhibits considerable concentrations of ammonia, which are evidently formed secondarily by degradation of urea following chemical reactions with chlorine. Ammonia reacts rapidly with hypochlorous acid to form monochloramine, dichloramine and trichloramine, whereas nitrogen-containing organic compounds, such as amino acids, may react with hypochlorite to form organic chloramines (Taras, 1953; Isaac & Morris, 1980; WHO, 2000).

1.4 Regulations and guidelines

The WHO (1998) has established a drinking-water guideline for monochloramine of 3 mg/L. The WHO also notes that insufficient data on health effects are available for di- and trichloramine to establish a numerical guideline.

Australia and New Zealand have also established a guideline of 3 mg/L for monochloramine (National Health and Medical Research Council and Agriculture and Resource Management Council of Australia and New Zealand, 1996). In Canada, the maximum allowable concentration for total chloramines has been established at 3.0 mg/L (Health Canada, 2003).

The Environmental Protection Agency (1998) in the USA established a maximum residual disinfectant level for chloramine of 4.0 mg/L (as Cl_2). This level can be exceeded under emergency conditions such as a major line break or a natural disaster.

2. Studies of Cancer in Humans

See Introduction to the monographs on chloramine, chloral and chloral hydrate, dichloroacetic acid, trichloroacetic acid and 3-chloro-4-(dichloromethyl)-5-hydroxy-2(5*H*)-furanone.

3. Studies of Cancer in Experimental Animals

3.1 Oral administration

3.1.1 *Mouse*

Groups of 70 male and 70 female B6C3F$_1$ mice, 5–6 weeks of age, were given chloraminated, deionized, charcoal-filtered drinking-water[1] that contained 50, 100 or 200 ppm [mg/L] monochloramine expressed as available atomic chlorine or deionized, charcoal-filtered drinking-water (controls). The dose levels of chloramine were based on a previous study that indicated that 200 ppm was the maximum concentration that mice will drink. Interim sacrifices of 9–10 mice each were carried out at 14 or 15 and 66 weeks, leaving 50–51 mice of each sex that were killed after 103–104 weeks of exposure. At 2 years, survival of mice that received chloraminated drinking-water was not significantly different from that of controls. Within the first week of chloramine treatment, a dose-related decrease in drinking-water consumption was observed in both males and females, which continued throughout the study. There was also a dose-related decrease in the body weights of males and females administered chloramine, which occurred earlier and to a greater extent in females than in males. The chloraminated water decreased the body weight of female mice by approximately 10% (50 ppm), 15% (100 ppm) and 30% (200 ppm). No neoplastic or

[1] The chloramine formulations were prepared from buffered sodium hypochlorite (pH 9) stock solutions to which dilute ammonium hydroxide was added. The sodium hypochlorite stock solution was prepared by bubbling chlorine gas into charcoal-filtered, deionized water and was raised to pH 9 with sodium bicarbonate/carbonate.

non-neoplastic lesions associated with the consumption of chloraminated drinking-water was observed in male or female mice (National Toxicology Program, 1992).

3.1.2 *Rat*

Groups of 70 male and 70 female Fischer 344/N rats, 5–6 weeks of age, were given chloraminated, deionized, charcoal-filtered drinking-water[1] that contained 50, 100 or 200 ppm [mg/mL] monochloramine expressed as available atomic chlorine or deionized, charcoal-filtered drinking-water (controls). The dose levels of chloramine were based on a previous study that indicated that 200 ppm was the maximum concentration that rats will drink. Interim sacrifices of 9–10 rats each were carried out at 15 and 66 weeks, leaving 50–51 rats of each sex that were killed after 103–104 weeks of exposure. Survival of male and female rats that received chloraminated drinking-water was not significantly different from that of controls except for the low-dose male group in which survival was greater. Within the first week of chloramine administration, a dose-related decrease in drinking-water consumption by males and females was observed, which remained reduced throughout the study. Chloraminated water did not affect the body weight of female and male rats until weeks 97 and 101, at which time a 10% reduction relative to controls occurred in the high-dose female and male rats, respectively. The incidence of mononuclear-cell leukaemia was higher in female rats that received the high dose of chloramine than in controls: 8/50 (16%), 11/50 (22%), 15/50 (30%) and 16/50 (32%) for the 0-, 50-, 100- and 200-ppm chloramine-treated groups, respectively. When adjusted for intercurrent mortality (Kaplan-Meier estimated tumour incidence), the rate of leukaemia was 20.8, 29.0, 39.9 and 41.4% for the 0-, 50-, 100- and 200-ppm chloramine-treated groups, respectively. The results were analysed by the life table test (Haseman, 1984) for an overall dose–response trend, resulting in a p-value of 0.02. This was followed by pairwise comparison between the controls and the treated groups resulting in p-values of 0.280, 0.077 and 0.036 for the 50-, 100- and 200-ppm chloramine-treated groups, respectively. The authors reported that the incidence of leukaemia in the concurrent control group was lower than that in untreated historical controls (170/680 [25%], with a range of 14–36%). There was a marginal increase in spleenic histiocytic lymphoid hyperplasia in females (controls, 3/50; 50 ppm, 4/50; 100 ppm, 2/50; and 200 ppm, 6/50). Since this apparent increase lacked a dose–response relationship and was only marginally significant, it was not considered by the authors to be related to the chloraminated water. There were no other neoplastic or non-neoplastic lesions associated with the consumption of chloraminated drinking-water. The report concluded that there was no evidence for the carcinogenic activity of chloraminated drinking-water in male rats and equivocal evi-

[1] The chloramine formulations were prepared from buffered sodium hypochlorite (pH 9) stock solutions to which dilute ammonium hydroxide was added. The sodium hypochlorite stock solution was prepared by bubbling chlorine gas into charcoal-filtered, deionized water and was raised to pH 9 with sodium bicarbonate/carbonate.

dence in female rats based on an increased incidence of mononuclear-cell leukaemia (National Toxicology Program, 1992).

3.2 Administration with known carcinogens or modifying factors

Rat: *Helicobacteria pylori* has been associated with an increased risk for stomach cancer that could result from the interaction of ammonia produced by its urease activity and hypochlorous acid produced by neutrophils. Ammonia and hypochlorous acid interact to form chloramine. Hence, administering ammonia and hypochlorous acid to rats in order to form chloramine has been used as a model for the ulcerogenic and carcinogenic activity of the bacterium (Iishi *et al*., 1997; Iseki *et al*., 1998; Narahara *et al*., 2001; Kato *et al*., 2002).

Early studies demonstrated that the combination of 20% ammonium acetate in the diet and 30 mM sodium hypochlorite in the drinking-water enhanced the incidence of *N*-methyl-*N*′-nitro-*N*-nitrosoguanidine (MNNG)-induced stomach cancer, which was increased from 10/20 (50%) to 17/20 (85%) by the combination. The number of stomach cancers per tumour-bearing rat was not altered: 1.8 ± 0.4 versus 1.7 ± 0.2 (Iishi *et al*., 1997). In another report, the combination increased the incidence of rats with stomach cancer from 12/19 (63%) to 19/19 (100%), while again not altering the number of stomach cancers per tumour-bearing rat: 1.3 ± 0.2 versus 1.9 ± 0.2 (Iseki *et al*., 1998). Neither 20% ammonium acetate nor 30 mM sodium hypochlorite administered alone affected the incidence of MNNG-induced stomach cancer (Iishi *et al*., 1997; Iseki *et al*., 1998).

Groups of 20 male Wistar rats [age unspecified] received 25 μg/mL MNNG in the drinking-water for 25 weeks and, at week 26, received 20% ammonium acetate in the diet and 30 mM sodium hypochlorite in the drinking-water. Some groups of rats also received subcutaneous injections of 25 or 50 mg/kg bw ambroxol, a clinical mucoregulatory agent with antioxidant activity, every other day, to determine its ability to prevent the enhancement of stomach cancer by chloramine. All surviving rats were killed at week 52 and were evaluated for stomach tumours as were rats that survived to at least week 50. The incidence of MNNG-induced stomach adenocarcinomas was significantly increased ($p < 0.01$) from 7/20 (35%) in animals not administered chloramine to 17/20 (85%) in animals administered chloramine. Ambroxol reduced the incidence of stomach cancer in rats treated with MNNG plus chloramine to 6/19 (32%) and 5/20 (25%) for the 25- and 50-mg/kg doses, respectively. Neither dose level of ambroxol affected the incidence of stomach cancer induced by MNNG. In rats that did not receive chloramine as chloraminated water, the incidence of MNNG-induced stomach cancer was 8/20 (40%) and 9/20 (45%) for the low- and high-dose ambroxol-treated groups, respectively (Narahara *et al*., 2001).

4. Other Data Relevant to an Evaluation of Carcinogenicity and its Mechanisms

4.1 Absorption, distribution, metabolism and excretion

4.1.1 *Humans*

No studies on the absorption, distribution, metabolism and excretion of monochloramine in humans have been reported.

4.1.2 *Experimental systems*

Male Sprague-Dawley rats (220–240 g) were given 1.1 mg per animal [^{36}Cl]-labelled chloramine [$NH_2\ ^{36}Cl$] orally as 3 mL of a solution containing 370 mg/L chloramine. The peak plasma concentration of ^{36}Cl (10.3 μg/L) was reached 8 h after dosing, and the absorption and elimination half-lives were 2.5 h and 38.8 h, respectively. The distribution of radioactivity was highest in plasma and lowest in fat. Approximately 25% and 2% of the administered dose of radiolabelled chloramine was excreted in the urine and faeces, respectively, during 120 h after treatment. Only 0.35% of the administered dose of monochloramine was present in plasma as [^{36}Cl]chloride 120 h after treatment. No evidence for enzymatic intervention in the metabolism of monochloramine was presented (Abdel-Rahman *et al*., 1983).

The effect of 15 μM monochloramine as hepatic function was investigated in isolated perfused male Sprague-Dawley rat liver. The uptake of monochloramine averaged 98%. Approximately 0.7% of the amount taken up by the liver was reduced by glutathione (GSH) and appeared in the bile in the form of GSH disulfide (Bilzer & Lauterburg, 1991).

Monochloramine inactivated bovine liver catalase *in vitro*, either by reacting with reduced nicotinamide adenine dinucleotide phosphate (NADPH) or by hydrolysis to hypochlorous acid, which may ligate with the haeme iron of catalase, or both (Mashino & Fridovich, 1988). Subsequent studies showed that the reaction of monochloramine with NADH yields a pyridine chlorohydrin (Prütz *et al*., 2001).

Monochloramine inhibited purified rat liver enzymes, N^{10}-formyl tetrahydrofolate dehydrogenase (0.56–3.35 μM) and formaldehyde dehydrogenase (2.7–101 μM), *in vitro* (Minami *et al*., 1993).

4.2 Toxic effects

4.2.1 *Humans*

(*a*) *Inhalation*

Chloramines are volatile and, as a result, an important route of human exposure is through inhalation. Numerous case reports have documented the effects of inhalation exposures in households as a result of mixing bleach and liquid ammonia for cleaning. A more limited set of information relates to the inhalation of chloramine in occupational settings. Few studies have investigated the potential effects of inhaling chloramine while bathing. The following is a summary of representative studies of these exposure conditions.

Instances of inhalation of chloramines in the home have been reported as case studies, which give little opportunity for accurate assessment of exposure. However, they do provide a qualitative description of the symptoms and damage that ensued.

Tanen *et al*. (1999) documented acute lung injury that progressed to severe pneumonitis, caused by the use of combined hypochlorite and ammonia for cleaning in an occupational setting. A tracheostomy was necessary, but the patient recovered within 7 days.

Hery *et al*. (1998) reported an analysis of concentrations of chloramine and complaints of irritation of the eye and upper respiratory tract of workers in a green-salad processing plant. The irritant agents were chloramines that resulted from the reaction of hypochlorite with nitrogen compounds in the sap proteins that were released when the vegetables were cut. The study documented the relationship between concentrations of chloramine in the processing water and those in the air at different workstations. The air measurements included nitrogen trichloride (trichloroamine) as a separate entity and clearly showed that the exposure was not entirely composed of monochloramine. Concentrations of chlorine (5–60 mg/L) in combination with amino-containing chemicals resulted in levels of total soluble chlorine compounds in the air of 0.1–0.8 mg/m^3 chlorine and 0.2–0.9 mg/m^3 nitrogen trichloride. This exposure assessment was linked to a second study in which irritation phenomena were studied among 334 swimming-pool lifeguards (Massin *et al*., 1998). Exposure of these individuals was primarily by inhalation, and eye, nose and throat irritation showed a dose–response relationship with exposures to nitrogen trichloride. There was little evidence that chronic respiratory symptoms increased with increasing exposure (e.g. chronic bronchitis). The irritant effects became apparent at nominal air concentrations of 0.5 mg/m^3 nitrogen trichloride. The extent to which nitrogen trichloride would be formed in the air from use of chloraminated water in confined spaces (e.g. showers) in the home has not been studied.

A recent account of case studies of two lifeguards and one swimming instructor reported that two subjects had decreased forced expiratory volume in response to a challenge of nitrogen trichloride at 0.5 mg/m^3 and the third showed a positive response in the workplace (Thickett *et al*., 2002). These authors concluded that nitrogen trichloride was a cause of occupational asthma.

(*b*) *Ingestion*

A few studies have specifically evaluated the potential effects of ingested chloramine. Lubbers and Bianchine (1984) and Lubbers *et al*. (1984) studied acute and repeated doses of monochloramine in comparison with other drinking-water disinfectants. In a rising-dose tolerance study (Lubbers & Bianchine, 1984), groups of 10 adult male volunteers drank two 500-mL portions of water containing 0.01, 1.0, 8, 18 or 24 mg/L chloramine, or hypochlorite, sodium chlorite, sodium chlorate or chlorine dioxide or served as controls. A battery of measures, including blood and urine biochemistry, blood cell counts and morphology, and physical examination were conducted following each dose. No statistically significant changes were noted in the chloramine-treated group. In the subsequent repeated-dose study (Lubbers *et al*., 1984), 10 volunteers were required to drink a 500-mL portion of water containing 5 ppm [5 mg/L] chloramine daily for 12 weeks followed by an 8-week wash-out period. The volunteers were required to consume the entire 500-mL portion within 15 min. The other treatment groups involved comparisons with other drinking-water treatments as described in the rising-dose study. The same set of biochemical, clinical and haematological tests and physical examinations were conducted. The only statistically significant change in the chloramine-treated group was an increase in triiodothyronine (T_3) uptake. However, this change remained within the normal range and was considered to be clinically irrelevant.

Wones *et al*. (1993) reported the results of a study focused on measures of lipid metabolism and thyroid function that involved three groups of 16 adult male volunteers who received 1.5 L distilled water or 2 or 15 ppm [2 or 15 mg/L] chloramine daily for 4 weeks, followed by a 4-week acclimatization period during which all subjects were provided distilled drinking-water and a standardized diet that was relatively high in total fat, saturated fat and cholesterol. The diet was maintained whereas the water provided was changed in the subsequent 4-week experimental period. The only statistically significant change was a 12% increase in plasma apolipoprotein B in men consuming 15 ppm chloramine. The only parameter that tended to parallel this trend was an increase in plasma triglycerides, but this was not statistically significant ($p = 0.07$).

(*c*) *Haemodialysis patients*

Two studies are representative of broad findings in patients undergoing haemodialysis treatment when the municipal drinking-water that was used in the preparation of dialysis fluid contained appreciable concentrations of chloramine. Fluck *et al*. (1999) reported that chloramine-induced haemolysis was responsible for erythropoeitin-resistant anaemia that developed in a haemodialysis unit in the United Kingdom. An increase in mean methaemoglobinaemia of 23% and a fall in mean haptoglobin of 21% was noted in these patients. Following installation of columns that contained activated carbon to remove the chloramine, these effects were reversed. The concentrations of chloramine prior to installation of the columns were 0.25–0.3 ppm [mg/L] but fell to < 0.1 ppm [mg/L] following installation of carbon column filtration.

There is some evidence of varying sensitivity to the haemolytic effects of chloramine among haemodialysis patients. Weinstein *et al*. (2000) studied differences between 24 responders and nine non-responders to chloramine in dialysis fluid. The initial water analysis indicated a concentration of 0.19 mg/L chloramine in the water supply. An inverse correlation between concentrations of serum GSH and haemoglobin was observed in these patients.

4.2.2 *Experimental systems*

(*a*) *Inhalation*

No study of exposure to chloramine via inhalation has been reported. One study in mice of sensory irritation responses to nitrogen trichloride found that the airborne concentration of nitrogen trichloride that resulted in a 50% decrease in respiratory rate was 2.5 ppm [12.3 μg/mL] (Gagnaire *et al*., 1994). The maximal response was observed within 10 min.

(*b*) *Oral*

Monochloramine was administered in the drinking-water at concentrations of 0, 1, 10 and 100 mg/L to male Sprague-Dawley rats (Abdel-Rahman *et al*., 1984) and haematological parameters were examined after 3 and 10 months of treatment. Only four animals per group were sampled at each time-point. A statistically significant decrease in haematocrit was observed after 3 months of treatment with 10 and 100 mg/L. While a similar trend was apparent at 10 months, the results were not statistically significant.

Daniel *et al*. (1990) compared the subchronic toxicity of chloramine with that of chlorine and chlorine dioxide in Sprague-Dawley rats. Chloramine was administered in the drinking-water at concentrations of 0, 25, 50, 100 and 200 mg/L for 90 days to groups of five males or females. Parameters of haematology and clinical chemistry were measured after 90 days. Tissues were sampled and examined for gross lesions and histopathology. At the 200-mg/L dose, weight gain was decreased and the relative kidney weights were increased by chloramine in both male and female rats. Male animals had significantly decreased haematocrits at 100 mg/L and decreased red blood cell counts at both 100 and 200 mg/L. No treatment-related pathology was noted.

The effects of monochloramine were compared with those of chlorine in 10 male and female B6C3F_1 mice given 0, 12.5, 25, 50, 100 and 200 mg/L of the two compounds in the drinking-water (Daniel *et al*., 1991). Body weight gain was significantly decreased at 100 and 200 mg/L in both male and female mice. Red blood cell counts, haemoglobin and haematocrit levels in male mice were significantly increased at 200 mg/L. Only red blood cell counts were elevated in female mice at this dose. Relative kidney weights were increased at 200 mg/L in males and females, but not at lower doses of monochloramine. No treatment-related pathology was observed.

Bercz *et al*. (1982) studied the ability of chloramine to induce haematological effects and alterations in clinical chemistry measures including serum thyroxine (T_4) concentrations

in adult African green monkeys (five males and seven females). Chloramine was administered in the drinking-water at a concentration of 100 mg/L for a period of 6 weeks (total body dose, 10 mg/kg bw per day). No significant effects were observed.

An immunotoxicological evaluation was made in groups of 12 male Sprague-Dawley rats treated with sodium hypochlorite or 9, 19 or 38 ppm [mg/L] chloramine in the drinking-water (Exon *et al*., 1987). No remarkable findings were noted with respect to relative spleen and thymus weights, delayed hypersensitivity reactions, natural killer cell activity or the phagocytic activity of macrophages. A substantial and dose-related increase in prostaglandin E_2 activity was observed in adherent resident peritoneal cells from animals treated with 19 and 38 ppm. However, no corresponding alterations in immune function were found.

A study of plasma cholesterol and thyroid hormone levels was conducted in white Carneau pigeons treated with various disinfectants (Revis *et al*., 1986). Increases in plasma levels of low-density lipoprotein cholesterol were observed with 2 and 15 ppm [mg/L] hypochlorite (chlorine pH 8.5), and 15 ppm [mg/L] chloramine and chlorine dioxide when administered with a high-cholesterol diet. These changes appeared to be correlated with an increase in the size of atherosclerotic plaques and a very large decrease in T_4 and T_3 concentrations in serum. It must be noted that these results are substantially different from those observed in primates (Bercz *et al*., 1982), in an independent study in pigeons (Penn *et al*., 1990), in rats (Poon *et al*., 1997) and in humans (Wones *et al*., 1993) receiving comparable treatments with a variety of disinfectants, including chloramine.

Poon *et al*. (1997) specifically examined the effects of 200 ppm [mg/L] (equivalent to 21.6 mg/kg per day) monochloramine in drinking-water in male Sprague-Dawley rats treated for 13 weeks. The study included a group of control rats that were given the same volume of water as that consumed by the chloramine-treated animals. The animals were monitored for changes in levels of T_4, hepatic drug metabolizing enzymes, haematological parameters and measures of immune response. The authors concluded that the minor changes seen in these parameters were largely associated with decreased water and food consumption.

The role of monochloramine and related organic chloramines formed *in situ* has been studied extensively with respect to the development of stomach lesions. This interest arises from investigations of mechanisms by which *H. pylori* might induce gastritis, peptic ulcers and stomach cancer (Suzuki *et al.*, 1992; Dekigai *et al.*, 1995; Xia & Talley, 2001). This organism produces a high concentration of ammonia in the stomach of infected patients, which is postulated to interact with neutrophil-derived hypochlorous acid to produce chloramine.

Monochloroamine exerts biological effects in isolated systems at concentrations that would commonly be seen in drinking-water. At concentrations of 1–10 μM [0.5–5 mg/L], monochloramine inhibited the growth of the normal rat gastric mucosa cell line, RGM-L (Naito *et al*., 1997). This growth inhibition was in part attributed to evidence of increased apoptosis (characterized by a fraction of subdiploid cells and nuclear fragmentation) with concomitant accumulation of cells in the G2/M phase of the cell cycle.

The application of chloramine to the serosal side of the colonic mucosa of rats at concentrations of 50 μM increased mucosal secretion of prostaglandin E_2 (Tamai *et al*., 1991). The 50% maximum effective for monochloramine was 3.2 μM [0.165 mg/L] compared with 6.5 μM [0.34 mg/L] for hypochlorous acid and 6.5 μM [0.22 mg/L] for hydrogen peroxide.

Apoptosis induced by etoposide was inhibited in human Jurkat T cells (acute T-cell leukaemia cell line) by 70 μM [3.6 mg/L] monochloramine (Than *et al*., 2001). This effect was associated with an increase in the number of cells arrested in the G_0/G_1 phase and a decrease in the number of cells in the S phase. Cells that survived had an increased incidence of aneuploidy, probably attributable to treatment with etoposide.

Monochloramine, at a concentration range of 30–50 μM [1.5–2.6 mg/L], inhibited the respiratory burst that is induced in neutrophils by phorbol esters. These concentrations did not affect cell viability, but decreased protein kinase C activity, which fell to zero with 70 μM [3.6 mg/L] chloramine (Ogino *et al*., 1997).

Experiments that examined the ability of monochloramine solutions to damage the gastric mucosa used higher concentrations than those encountered in drinking-water. Umeda *et al*. (1999) gave 5 mL/kg [30.9 mg/kg] of a 120-mM [6.18 g/L] concentration of chloramine to rats to induce gastric mucosal damage. However, the aim of the study was to demonstrate that Lafutidine, a histamine H_2-receptor antagonist, substantially decreased the size of the lesions produced. The authors indicated that concentrations of 60 mM [3.09 g/L] were needed to induce lesions.

(*c*) *Dermal*

Solutions of up to 1000 mg/L monochloramine produced no evidence of hyperplasia when applied to the skin of Sencar mice for 10 min per day for 4 days (Robinson *et al*., 1986). This was in sharp contrast to results obtained with hypochlorous acid, which more than doubled skin thickness in parallel experiments at concentrations as low as 300 mg/L.

4.3 Reproductive and developmental effects

4.3.1 *Humans*

No data were available to the Working Group.

4.3.2 *Experimental systems*

Carlton *et al*. (1986) examined the effects of chloramine on reproductive parameters of Long-Evans rats. Twelve males were treated by gavage with either 0, 2.5, 5 or 10 mg/kg bw monochloramine for 56 days prior to mating and throughout the 10-day mating period; 24 females were treated with the same doses for 14 days before mating and throughout mating, gestation and lactation, and 21 days postpartum. No clinical signs of toxicity, haematological changes or changes in reproductive parameters were found. No treatment-related histopathology was observed in the reproductive tracts of either male or female rats.

4.4 Genetic and related effects

4.4.1 *Humans*

No data were available to the Working Group.

4.4.2 *Experimental systems* (see Table 1 for details and references)

All the results given in Section 4.4.2 correspond to single studies.

After exposure of *Bacillus subtilis* cells or *B. subtilis* DNA to monochloramine, single-strand breaks as well as loss of DNA-transforming activity were observed. Monochloramine did not induce a mutagenic effect in *Salmonella typhimurium* strain TA100 and was a weak mutagen in the reversion of trpC to trp^+ in *B. subtilis*. [The Working Group noted that the procedure followed by these authors was less sensitive than the standard Maron and Ames plating method.]

The water obtained after treatment of a non-mutagenic raw water with monochloramine showed mutagenic activity to *S. typhimurium* in the presence and in the absence of metabolic activation (Cheh *et al.*, 1980). [The Working Group noted that the mutagenic activity is probably not due to monochloramine but to by-products of the reaction of monochloramine with organic carbon contained in the raw water.] Treatment of fulvic acid solutions or of drinking-water with monochloramine induced the appearance of significant mutagenicity in *S. typhimurium* strains TA100 and TA98 (Cozzie *et al.*, 1993; DeMarini *et al.*, 1995) [The Working Group noted that the mutagenic activity observed was not attributable to monochloramine itself but to by-products of the reaction of monochloramine with organic compounds.]

Monochloramine caused double-strand DNA breakage in plasmid pUC18, and chlorogenic acid prevented this effect. *In vitro*, it induced DNA double-strand breaks and chromatin condensation in rabbit gastric mucosal cells and human stomach carcinoma KATO III cells, and DNA fragmentation in rabbit gastric mucosal cells and in human stomach adenocarcinoma MKN45 cells. The precursors of monochloramine, ammonia and hypochlorous acid did not induce DNA double-strand breaks or chromatin condensation in either rabbit gastric mucosal or KATO III cells (Suzuki *et al.*, 1997).

In a single in-vivo study, monochloramine did not induce micronucleus formation, chromosomal aberrations or aneuploidy in the bone marrow of CD-1 mice or sperm abnormalities in $B6C3F_1$ mice. Monochloramine induced the formation of micronuclei in erythrocytes of newt larvae *in vivo*.

Table 1. Genetic and related effects of chloramine

Test system	Result[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic activation		
DNA strand breaks, *Bacillus subtilis* culture	+	NT	112 µM [5.7]	Shih & Lederberg (1976a)
Salmonella typhimurium TA100, reverse mutation	–	NT	60 µM [3]	Thomas *et al.* (1987)
Bacillus subtilis, reverse mutation	+	NT	56 µM [2.9]	Shih & Lederberg (1976b)
DNA double-strand breaks, plasmid pUC18 DNA *in vitro*	+	NT	3 mM [154.5]	Shibata *et al.* (1999)
DNA double-strand breaks, rabbit gastric mucosal cells *in vitro*	+	NT	0.1 mM [5.15]	Suzuki *et al.* (1997)
DNA fragmentation, rabbit gastric mucosal cells *in vitro*	+	NT	0.1 mM [5.15]	Suzuki *et al.* (1997)
DNA double-strand breaks, human gastric carcinoma KATO III cells *in vitro*	+	NT	0.1 mM [5.15]	Suzuki *et al.* (1997)
Chromatin condensation, rabbit gastric mucosal cells *in vitro*	+	NT	0.1 mM [5.15]	Suzuki *et al.* (1997)
DNA fragmentation, human gastric adenocarcinoma MKN45 cells *in vitro*	+	NT	0.001 mM [0.05]	Suzuki *et al.* (1998)
DNA fragmentation, human gastric carcinoma KATO III cells *in vitro*	–	NT	0.001 mM [0.05]	Suzuki *et al.* (1998)
Chromatin condensation, human gastric carcinoma KATO III cells *in vitro*	+	NT	0.1 mM [5.15]	Suzuki *et al.* (1997)
Micronucleus formation, CD-1 mouse bone-marrow erythrocytes *in vivo*	–		200[c] po × 5	Meier *et al.* (1985)
Micronucleus formation, *Pleurodeles waltl* newt larvae peripheral erythrocytes *in vivo*	+		0.15[d]	Gauthier *et al.* (1989)
Chromosomal aberrations, CD-1 mouse bone-marrow cells *in vivo*	–		200[c] po × 5	Meier *et al.* (1985)
Aneuploidy, bone-marrow cells of CD-1 mouse *in vivo*	–		200[c] po × 5	Meier *et al.* (1985)
Sperm morphology, B6C3F1 mice *in vivo*	–		200[c] po × 5	Meier *et al.* (1985)

[a] +, positive; –, negative; NT, not tested
[b] LED, lowest effective dose; HID, highest ineffective dose; in-vitro tests, µg/mL; in-vivo tests, mg/kg bw; po, orally
[c] Amount of chloramine (in µg) administered daily to each animal by gavage for 5 days
[d] Larvae reared in chloramine-containing water

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Chloramine, formed by the reaction of ammonia with chlorine, is increasingly being used in the disinfection of drinking-water. Monochloramine, dichloramine and trichloramine are in equilibrium, with monochloramine predominating. Exposure to milligram-per-litre levels occurs through ingestion of chloraminated water. Chloramines are also formed in swimming pools from the reaction of chlorine with nitrogen-containing contaminants, and trichloramine has been measured in swimming-pool air. Chloramine generated *in situ* is also used as an intermediate in the production of hydrazines, organic amines and other industrial chemicals.

5.2 Human carcinogenicity data

Several studies were identified that analysed risk with respect to one or more measures of exposure to complex mixtures of disinfection by-products that are found in most chlorinated and chloraminated drinking-water. No data specifically on chloramine were available to the Working Group.

5.3 Animal carcinogenicity data

Chloraminated drinking-water (predominantly in the form of monochloramine) was tested for carcinogenicity by oral administration in female and male mice and rats without demonstrating clear evidence of carcinogenic activity. In carcinogen-initiated rats, chloramine generated by ammonium acetate (in feed) and sodium hypochlorite (in drinking-water) promoted stomach cancer.

5.4 Other relevant data

^{36}Cl-Labelled chloramine is readily absorbed after oral administration to rats. About 25% of the administered radioactivity is excreted in the urine over 120 h.

Nitrogen trichloride (trichloroamine) is volatilized from food-processing water disinfected with chloramine and from swimming-pool waters disinfected with chlorine, and reacts with ammonia in water to form chloramine. Upon inhalation, it produces lung irritation and may be a cause of occupational asthma. Ingestion of monochloramine produced no clinical abnormalities in male volunteers at concentrations as high as 15 mg/L. No reproductive or developmental effects have been associated with monochloramine.

Chloramine induced single-strand breaks and loss of DNA-transforming activity and was a weak mutagen in *Bacillus subtilis*. It was not mutagenic to *Salmonella typhimurium*. *In vitro*, chloramine caused double-strand DNA breakage in plasmid pUC18, and DNA fragmentation and DNA double-strand breaks as well as chromatin condensation in rabbit gastric mucosal cells and human stomach cancer cells. Monochloramine did not induce micronuclei, chromosomal aberration, aneuploidy or sperm abnormality in mice *in vivo*, but induced the formation of micronuclei in erythrocytes of newt larvae *in vivo*.

5.5 Evaluation

There is *inadequate evidence* in humans for the carcinogenicity of chloramine.

There is *inadequate evidence* in experimental animals for the carcinogenicity of monochloramine.

Overall evaluation

Chloramine is *not classifiable as to its carcinogenicity to humans (Group 3)*.

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