

# Chloramines

## Guideline

*The recommended maximum acceptable concentration (MAC) for chloramines in drinking water is 3.0 mg/L (3000 µg/L). This MAC is based on a risk evaluation for monochloramine only, as monochloramine is usually the predominant chloramine and as information on dichloramine and trichloramine toxicity is insufficient to establish guidelines for these two compounds.*

## Identity, Use and Sources in the Environment

Pure monochloramine ( $\text{NH}_2\text{Cl}$ ) is a colourless and unstable liquid with a melting point of  $-66^\circ\text{C}$ . Monochloramine is soluble in cold water, alcohol and ether and slightly soluble in carbon tetrachloride and benzene.<sup>1-3</sup> Monochloramine should be recognized as being different from the commercial products known as chloramine B, chloramine T and dichloramine T, which are organic compounds produced by chlorinating benzenesulphonamide or para-toluenesulphonamide.<sup>2</sup> Monochloramine is produced by adding chlorine to a solution containing ammonia, by adding ammonia to a solution containing free residual chlorine or by adding premixed solutions of ammonia and chlorine to water.<sup>4</sup> The production of monochloramine, dichloramine ( $\text{NHCl}_2$ ) and trichloramine ( $\text{NCl}_3$ ) is highly dependent upon pH, the ratio of chlorine to ammonia-nitrogen and, to a lesser extent, temperature and contact time.<sup>5,6</sup> A pH between approximately 7.5 and 9.0 is optimum for the formation of monochloramine<sup>6</sup>; the ideal pH is 8.3.<sup>7</sup> A lower pH favours the formation of dichloramine (pH 4–6) and trichloramine (pH <4.4). A chlorine to ammonia-nitrogen ratio of 3–5:1 is optimum for monochloramine formation. A ratio of between 5:1 and 7.6:1 favours dichloramine production, and trichloramines are produced at higher ratios. Contact times between chlorine and ammonia in the chloramination process may have to be increased if the pH is beyond the optimum range and the temperature is below  $20^\circ\text{C}$ .<sup>6</sup>

Monochloramine may be a by-product of drinking water chlorination, or it may be added to maintain residual disinfection activity in a potable water distribution system, as persistence of residual chloramine in the distribution system is excellent.<sup>2,8</sup> Monochloramine is recognized as a less effective disinfectant than chlorine. Chloramine is considered to have moderate biocidal activity against bacteria and low biocidal activity against viruses and protozoan cysts.<sup>2,8</sup> Some bacteria may be inactivated by disinfection with chloramine; however, much longer contact times are required for viruses and cysts.<sup>7,9</sup> Chloramine has been labelled by the U.S. Environmental Protection Agency (EPA) as a secondary disinfectant.<sup>7</sup> Inactivation of organisms using monochloramine requires larger concentrations and a longer contact time than chlorine disinfection.<sup>10</sup> Monochloramine efficacy has, however, been demonstrated in a number of studies. Brodtmann and Russo<sup>11</sup> evaluated the bacteriological quality of the Jefferson Parish Water Department, a water system that used chloramine as the primary disinfectant for 30 years. They reported that chloramine treatment was effective in destroying 60% of the total bacterial population and 88% of the coliform bacteria in the clarified effluent before sand filtration with a contact time of less than 10 minutes. Furthermore, Lechevallier *et al.*<sup>12</sup> stated that monochloramine was better than or as effective as free chlorine for inactivation of biofilm bacteria, as the greater penetrating power of monochloramine seemed to compensate for its limited disinfection activity. In a model distribution system study, results suggested that biofilms can be controlled using monochloramine levels ranging from 2 to 4 mg/L, but further research is needed to confirm these results in a full-scale distribution system.<sup>13</sup>

Bull and Kopfler<sup>14</sup> determined that the concentration of chloramine required for a stable residual in the distribution system is between 0.5 and 2.0 mg/L, whereas the American Water Works Association recommends a goal of 2.0 mg/L combined chlorine residual for water leaving the treatment plant and a level of 1.0 mg/L combined chlorine throughout the distribution system.<sup>6</sup>

In chlorination of either potable water or wastewater, both free chlorine and monochloramine can react with organic nitrogen compounds to form organochloramines, which are generally non-germicidal.<sup>7</sup> Transfer of active chlorine ( $\text{Cl}^+$ ) to nitrogenous organic compounds can occur by a direct transfer and by hydrolysis of monochloramine to hypochlorous acid ( $\text{HOCl}$ ), which can then react with the substrate.<sup>15</sup> Monochloramine is an intermediate in the Raschig process for the industrial production of hydrazine.<sup>16,17</sup>

### Exposure

No data are available on levels of monochloramine in air or food, and there are few data on concentrations of monochloramine in Canadian drinking water supplies. Neden *et al.*<sup>18</sup> reported a study by the Greater Vancouver Water District, which compared the effects of using either chlorine or chloramine as the secondary disinfectant on bacterial regrowth in a distribution system. In their study, it was determined that chloramine was better able to attain and maintain a disinfection residual. Total chloramine residuals (after 10 minutes) ranged between 1.5 and 2.0 mg/L in cold months and between 2.5 and 3.0 mg/L in warmer-water months. A residual of  $\geq 1.0$  mg/L was observed throughout the distribution system; however, this target level was inadequate to maintain an acceptable coliform level, and the average residual level was later increased to  $>2.0$  mg/L. Generally, the chloraminated water had a lower heterotrophic plate count, fewer taste and odour complaints, fewer positive coliform counts and a more stable residual than chlorinated water.

A telephone survey on chloramination practices in Edmonton, Toronto, Brantford and Ottawa–Carleton was summarized in a report prepared for the Greater Vancouver Regional District.<sup>19</sup> Chloramine was used in these cities as a secondary disinfectant, providing a chloramine residual ranging between 0.7 and 2.0 mg/L. Chloramine residuals in the United States range from 0.6 to 5.0 mg/L; 75% of utilities have finished water with chloramine residual levels between 1.0 and 3.0 mg/L entering the distribution system.<sup>6</sup>

The switch from secondary chlorination to chloramination by the Regional Municipality of Ottawa–Carleton in the summer of 1992 resulted in an average chloramine residual of 0.92 mg/L (95% of which was monochloramine) leaving the plant and an average residual of 0.71 mg/L in the distribution system. The switch to chloramination, to control the formation of trihalomethanes (THMs), produced no observable changes in the bacteriological quality of the drinking water.<sup>20</sup> More recently, the municipality increased the average residual in the distribution to 1 mg/L to achieve

an acceptable level at the end of the distribution system.<sup>21</sup>

Aqueous solutions of monochloramine, formed by the chlorination of natural water containing ammonia, are of primary environmental significance.<sup>2</sup> Monochloramine is persistent in the environment. Under normal conditions, monochloramine is the principal chloramine in water and chlorinated wastewater.<sup>22</sup> Jolley *et al.*<sup>23</sup> reported monochloramine and dichloramine at concentrations ranging from 0.0321 to 0.9979 mg/L and from 0.0020 to 0.6950 mg/L, respectively, in secondary sewage effluents or cooling water samples. Chloramines may also be present in swimming pools.<sup>24</sup>

### Analytical Methods and Treatment Technology

Chloramines are usually measured as “combined” chlorine residual using chlorine residual determination procedures. The “combined” chlorine residual is calculated as the difference between the total and free chlorine residuals. Analytical procedures must be able to distinguish between free and combined chlorine. The speciation of the individual chloramines can be determined by multi-stage procedures of the chlorine residual determination.

As the analysis of these “combined” chlorine species can be influenced by several factors, including pH, temperature, reaction time and the presence of other ions in the water source, analysts should be aware of the potential effect of these factors in each analytical approach. Analysts should also be aware of potential problems resulting from the instability of residual chlorine and of the requirement for immediate residual chlorine determination to obtain accurate results.

The chlorine residual can be determined by various standard methods. Choice methods for analysing combined chlorine residuals include the amperometric titration method (4500-Cl D) and the N,N-diethyl-p-phenylenediamine (DPD) ferrous titrimetric (4500-Cl F) and colorimetric (4500-Cl G) methods.<sup>25</sup>

The amperometric titration method can be used to determine total chlorine and to differentiate between free and combined chlorine. A further differentiation into monochloramine and dichloramine fractions is then possible by control of the potassium iodide (KI) concentration and pH. Possible interferences with this method include nitrogen trichloride, chlorine dioxide, free halogens, certain organic chloramines, copper and silver. This method is very accurate, but it requires great care and technical skill to obtain accurate results.<sup>25</sup> It is generally not suitable for field use, owing to the complexity of the instrumentation.<sup>26</sup>

The DPD methods have been widely accepted and have become the standard testing procedures in the field.<sup>26</sup> They allow complete differentiation of chlorine species by using a small amount of iodide ion (as KI) as a catalyst. Compounds that may interfere with the analysis include oxidized manganese, copper and chromate. A high concentration of combined chlorine can break through into the free chlorine fraction; procedure modifications can be used to avoid this problem. The DPD titrimetric method has a detection limit as low as 0.018 mg/L as Cl<sub>2</sub> and requires careful pH control for accurate results.<sup>25</sup> The DPD colorimetric method has a detection limit of 0.010 mg/L under ideal conditions.<sup>25</sup>

Monochloramine hydrolyses slowly in aqueous solutions.<sup>4</sup> Aeration and boiling of water are not effective for the removal of monochloramine<sup>27</sup>; a minimal aeration loss of 10–15% has been reported with monochloramine.<sup>7</sup> Ultraviolet light depletes only free chlorine, whereas chloramines seem to be quite stable in sunlight. Chloramine decay has been suggested to be at most 0.2 mg/L per sunlight hour between 10 a.m. and 2 p.m. (latitude 30–40°N).<sup>7</sup> Pure chloramines can be removed by granular activated carbon.<sup>7</sup> Two reducing agents commonly used for removing chloramine for special water uses are sodium thiosulphate and ascorbic acid.<sup>6</sup>

## Health Effects

### Kinetics and Metabolism

Abdel-Rahman *et al.*<sup>28</sup> reported that the half-life for <sup>36</sup>Cl absorption following oral administration of NH<sub>2</sub><sup>36</sup>Cl in rats was 2.49 hours, whereas the elimination half-life from plasma was 38.8 hours. The peak plasma level of <sup>36</sup>Cl was reached eight hours following administration. The <sup>36</sup>Cl plasma level remained at a plateau for 8–48 hours after administration. The distribution scheme of <sup>36</sup>Cl after oral administration of NH<sub>2</sub><sup>36</sup>Cl showed that the highest <sup>36</sup>Cl activity was in the plasma and whole blood and the lowest activity was in the liver, ileum and fat. The chloride metabolite is excreted mainly in the urine.<sup>28</sup> In humans, it appears that most of the monochloramine from drinking water would reach the stomach intact; however, monochloramine rapidly decays in stomach fluid, and free monochloramine is not expected to enter systemic circulation.<sup>29</sup>

Scully and White<sup>30</sup> discussed the types of transformation that monochloramine might undergo in the body. The authors suggested that the formation of disinfection by-products from the reaction of organic or inorganic compounds present in the saliva or gastric fluid could be expected, rather than the absorption of intact inorganic monochloramine at low concentrations. Organic chloramino acids can potentially form in gastric

fluid exposed to inorganic monochloramine. Monochloramine may transfer its chlorine atom to organic amines and amino acids.<sup>31</sup>

Scully and White<sup>30</sup> stated that monochloramine can react with organic compounds by three basic mechanisms: oxidation of the molecule, substitution of the chlorine atom for another atom, and addition to an unsaturated molecule. The chemical reactions of the disinfectants may vary between the saliva and stomach owing to differences in pH, chloride ion concentration and organic substance concentrations. The authors concluded that different products could be formed at different dose levels and that more toxicologically significant products may be formed at low dosages that would be destroyed at higher doses. Slight inhibition of glutamine and glucose transport systems has been reported using HeLa cells and rat mesenteric lymphocytes. This inhibition may be due to the monochloramine binding to the thiol groups present on the membrane.<sup>32</sup> Inactivation of a number of enzyme systems has been reported with chloramine.<sup>33</sup>

### Effects in Humans

Mixing solutions of ammonia and sodium hypochlorite results in acrid monochloramine and dichloramine fumes.<sup>34</sup> Inhalation of chloramine fumes from mixing household cleaning agents (ammonia and sodium hypochlorite bleach) results in burning in eyes and throat, transient cough, dyspnoea, nausea and vomiting. In mucosa, chloramines decompose to ammonia and hypochlorous acid, which can combine with moisture to form hydrochloric acid and nascent oxygen. Corrosive effects of ammonia and hydrochloric acid also contribute to chloramine-induced respiratory tract damage.<sup>35</sup> Metabolic acidosis related to chloramine exposure has also been hypothesized in a case report. Enzymological measures were used to investigate the possible toxic mechanism of chloramine. The authors reported an enzyme inhibition of carbonic anhydrase and aldehyde dehydrogenase and an enhancement of superoxide dismutase in a simulated *in vitro* experiment using monochloramine in the inhibition assay.<sup>36</sup> Chloramine exposure may also account for some of the eye irritation observed in swimming pools.<sup>24,37</sup>

Methaemoglobinaemia and haemolysis in dialysis patients have been reported with chloramine use.<sup>14,38,39</sup> In 1987, 100 patients receiving haemodialysis at a special outpatient dialysis centre (OPDC) were exposed to chloramine-contaminated dialysate when the carbon filter in the centre's water processing system failed.<sup>40</sup> During the subsequent three weeks, at least 41 patients required transfusions to treat the haemolytic anaemia that resulted from the chloramine exposure. There was, however, no evidence of a relationship between the chloramine exposure incident and deaths at the OPDC

during that time. Chloramine oxidizes haemoglobin to methaemoglobin and induces damage to the hexose monophosphate shunt (HMPS), which protects the red cells from oxidant damage through generation of reduced nicotinamide adenine dinucleotide phosphate.<sup>38,39</sup> The HMPS damage in red cells reduces the cells' capacity to protect themselves against oxidant damage. Individuals with a glucose-6-phosphate dehydrogenase (G6PD) deficiency may be at increased risk from a variety of oxidant compounds. Although global in its distribution, G6PD deficiency has been encountered with greatest frequency in the tropical and subtropical zones of the eastern hemisphere.<sup>41</sup> Some groups may, therefore, be more sensitive to exposure to chloramines.<sup>42</sup> It should be noted, however, that these haematological effects have not been observed in some experimental animal studies following oral administration of monochloramine.<sup>14,43</sup> The dialysed route of exposure appears not to be relevant to exposure via drinking water but is useful for elucidation of potential mechanisms of toxicity.

No significant changes were observed in 10 healthy male volunteers receiving monochloramine in drinking water at concentrations of 0, 0.01, 1.0, 8.0, 18.0 or 24.0 mg/L; each volunteer had five three-day sequences at each of the five dose levels. On the first day of each three-day treatment sequence, each volunteer ingested 1 L of water in two 500-mL portions. The second 500-mL portion was administered four hours after the first. No disinfectant was administered on the second and third day, as these two days served as follow-up observation days on which a battery of parameters was monitored to assess the biochemical and physiochemical response. The control group received untreated water. In a second phase, groups of 10 subjects received 5 mg/L monochloramine in their drinking water for 12 weeks. Each subject received 500 mL daily. Physiological examinations, including blood and urine samples and taste evaluations, were conducted on a weekly basis during the treatment period and for eight weeks following cessation of treatment. The authors concluded that under the conditions of the experiment, no definitive detrimental physiological impacts were identified in either of these phases.<sup>44</sup>

Forty-eight men received monochloramine in drinking water at concentrations of 0, 2 or 15 mg/L for four weeks. Almost all subjects had consumed chlorinated drinking water prior to the study. In individuals exposed to 2 mg/L, there were no significant changes in total cholesterol, triglycerides, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, apolipoproteins A1, A2 and B, and thyroid function when compared with the control group. At 15 mg/L, increases in the level of plasma apolipoprotein B were observed. The authors concluded that

monochloramine at 2 mg/L did not affect lipid or thyroid metabolism in healthy men; however, limitations of the study, including relatively brief baseline and treatment periods and consumption by almost all subjects of chlorinated drinking water from local water supplies before entry into the study, suggested that further research was required.<sup>45</sup>

There have been a number of epidemiological studies that have associated chlorinated drinking water with bladder and colon cancer, but few studies were found that specifically involved chloraminated drinking water. In a preliminary report, Zierler *et al.*<sup>46</sup> examined mortality patterns of residents in Massachusetts living in communities using drinking water treated either by chlorine or by chloramine. They reported a slight excess of deaths from pneumonia and influenza in communities where water was disinfected by chloramine. There was also some indication that bladder cancer mortality was excessive among residents of communities with chlorinated drinking water when compared with residents of communities with chloraminated drinking water. The authors noted, however, that the study may have been influenced by unidentified or uncontrolled confounding factors.

Later, Zierler *et al.*<sup>47</sup> conducted a case-control study of inhabitants of 43 communities to investigate the possible association between chlorinated drinking water and bladder cancer. The study was based on data records and interviews with informants of 614 people (cases) who had died from bladder cancer and of 1074 people (controls) who had died from other causes. Persons from the 20 communities with chloraminated water were considered to be "non-exposed." THM levels were 2–9 times lower in the chloraminated water than in the chlorinated water. The authors concluded that, as previously reported, there was a positive association between the incidence of bladder cancer and the consumption of chlorinated drinking water, as there was an increase in the frequency of bladder cancer mortality (odds ratio [OR] = 1.6; confidence interval = 1.2–2.1) among lifetime residents of communities receiving chlorinated drinking water compared with residents of communities receiving chloraminated drinking water. Some slight evidence of a dose-response relationship was also seen, with an OR of 1.6 for lifetime consumers of chlorinated water and an OR of 1.4 for people exposed for half or more of their lives. The study results were thus consistent with the interpretation that risk for this concern was lower for use of chloramination than for chlorination, provided that the association was a real one. It should be noted, however, that, in 1992, the U.S. EPA pointed out that there were a number of flaws in published epidemiological studies reporting a link between chlorine and/or chloramine and cancers of the colon and bladder.<sup>48</sup>

### Toxicological Studies

In a study comparing chlorine dioxide, chlorate, chlorite and monochloramine, chemicals were administered in drinking water (dose levels for monochloramine were not stated clearly) to seven female and five male African green monkeys using 30- to 60-day subchronic rising dose protocols. Each animal served as its own control; between chemicals, the animals were rested for 6–9 weeks. Various effects, such as effects on thyroid metabolism and haematological changes, were reported for some chemicals, but not following administration of monochloramine at 100 mg/L.<sup>49</sup>

No induction of gamma-glutamyltranspeptidase foci, a potential indicator of carcinogenicity, was observed in nine male Sprague-Dawley and Fischer 344 rats exposed to 14.75 mg/kg chloramine (route not specified) 24 hours after a partial hepatectomy. Seven days after initiation, promotion by 500 ppm phenobarbital in the drinking water was begun; after 10 weeks of exposure, the rats were removed from exposure to the promoter for one week and then sacrificed.<sup>50</sup>

Administration of monochloramine in drinking water at 0, 2.5, 25, 50, 100 or 200 mg/L to A/J male mice (12 animals per treatment group) for 30 days resulted in body weight loss in the three highest dose groups. No evidence of haemolysis was reported.<sup>51</sup> In a limited study, changes in body weight and haematological parameters, such as decreased red blood cell count and haematocrit, reduced haemoglobin concentration and reduced mean corpuscular haemoglobin, were observed in four male Sprague-Dawley rats exposed for up to 12 months to maximum monochloramine concentrations of 100 mg/L.<sup>52</sup> Body weights decreased by 8% after three months and by 17% by the end of treatment. Administration of single monochloramine doses (3 mL) of 0, 10, 20 or 40 mg/L by gavage to groups of four male Sprague-Dawley rats resulted in increases of glutathione (GSH) at 30 and 60 minutes after treatment, although concentrations returned to normal after two hours. In a subsequent experiment, decreases in GSH were observed in rats four months after receiving monochloramine at doses of 1 or 100 mg/L in their drinking water. After 12 months, GSH levels were reduced in all treatment groups (1, 10 or 100 mg/L). Decreased red blood cell count and haematocrit were reported at concentrations of 10 and 100 mg/L after three months, and haemoglobin and mean corpuscular haemoglobin concentrations were reduced at 100 mg/L after 10 months. An increased osmotic fragility was also observed in the 10 and 100 mg/L groups after two months' treatment. Treatment effects were analysed using analysis of variance (ANOVA); however, the statistical tests for significance in this study may not have been appropriate.

Revis *et al.*<sup>53</sup> reported changes in liver metabolism (liver cholesterol and liver triglycerides) in New Zealand white rabbits (five or six animals per treatment group) exposed to 15 ppm monochloramine in drinking water for nine months. Although some increases were reported in this study, a clear dose–response relationship between monochloramine and these lipids was not observed. Lipid droplet increases in the liver were also reported (dose not specified). Immunotoxic effects were reported in male Sprague-Dawley rats (12 animals per treatment group) exposed to monochloramine at concentrations of 0, 9, 19 or 38 mg/L in drinking water for nine weeks.<sup>54</sup> The doses were calculated to be approximately equivalent to 0, 0.9, 1.9 and 3.8 mg/kg bw per day.<sup>55,56</sup> At the highest dose, there was a reduction in spleen weight; at the middle and highest doses, there was augmented production of prostaglandin E<sub>2</sub>; and at the lowest and middle doses, a decrease in antibody synthesis was observed.

In a subchronic study, monochloramine was administered to Fischer 344 rats and B6C3F<sub>1</sub> mice (10 animals of each sex per dose level) at concentrations of 0, 25, 50, 100, 200 and 400 mg/L in drinking water for 13 weeks. The most significant toxicological findings in mice were associated with liver damage. In treated mice, cytological alterations, characterized by an increase in the frequency of mitotic figures, bizarre chromatin patterns and increased cell size, were reported in males at 100, 200 and 400 mg/L. Liver cell necrosis was seen at the three lowest doses, and inflammation of the liver of females was observed at 100, 200 and 400 mg/L.<sup>57</sup> Although this subchronic study was completed and the results reported, the results are highly suspect. This study, run by the Gulf South Research Institute, was terminated because there was inadequate cataloguing of lesions, etc. Furthermore, the effects on the liver were not confirmed in the two-year chronic study conducted by the National Toxicology Program (NTP)<sup>58</sup> or in the subchronic study by Daniel *et al.*<sup>59</sup> For these reasons, this study has not been considered further in this report.

In an adequate subchronic study, Daniel *et al.*<sup>43</sup> exposed Crl:CD BR Sprague-Dawley rats (10 animals of each sex per treatment group) to 0, 25, 50, 100 or 200 mg/L monochloramine in drinking water for 90 days; corresponding doses were equivalent to 0, 1.8, 3.4, 5.8 and 9.0 mg/kg bw per day in males and 0, 2.6, 4.3, 7.7 and 12.1 mg/kg bw per day in females. There was a significant dose-related reduction in daily water consumption in both sexes and a dose-related decrease in the average daily food consumption of males, significant at the highest dose only. Average body weight gains in both sexes of the highest treatment groups were approximately 51% those of the controls. Final mean body weights were significantly reduced in

both sexes at 200 mg/L (approximately 21% in males and 11% in females), and mean weight gains were significantly reduced in females at 200 mg/L only and at  $\geq 50$  mg/L in males. Absolute liver and spleen weights were decreased in both sexes at the highest dose level. Although these weight reductions appeared to be dose-related in males, subsequent histopathological examination did not reveal any target organs or any treatment-related changes. Reductions in red blood cell count at 100 and 200 mg/L, the significant decrease in haematocrit at 100 mg/L and a reduction in serum calcium levels in males were not considered treatment-related. Based on the decrease in organ and body weights observed in both sexes, the authors concluded that 200 mg/L was the lowest-observed-adverse-effect level (LOAEL) and that 100 mg/L — equivalent to 5.8 and 7.7 mg/kg bw per day in male and female rats, respectively — was the no-observed-adverse-effect level (NOAEL).

In a second subchronic study by Daniel *et al.*,<sup>59</sup> male and female (10 animals of each sex per treatment group) B6C3F<sub>1</sub> mice received 0, 12.5, 25, 50, 100 and 200 mg/L monochloramine in their drinking water for 90 days. Corresponding doses were equivalent to 0, 2.5, 5.0, 8.6, 11.1 and 15.6 mg/kg bw per day for males and 0, 2.8, 5.3, 9.2, 12.9 and 15.8 mg/kg bw per day for females. Food consumption was decreased in both males and females; the decrease was significant for females at the two highest dose levels. Water consumption was significantly decreased in males at the two highest doses and at all doses for females. A number of haematological and clinical changes were observed (increase in white blood cells, decrease in mean corpuscular volume, several minor changes in serum enzymes, etc.); however, none was considered treatment-related. Significantly decreased organ weights (including liver, heart, lung and spleen) were observed at the two highest dose levels. Some increases in relative organ weights were also reported at the highest dose. At 100 mg/L, final mean body weights were reduced by approximately 10% and 7% for males and females, respectively; at 200 mg/L, body weight reductions reached approximately 25% in males and 19% in females. Average body weight gains in males at 100 mg/L and 200 mg/L were approximately 69% and 19% of those of controls, respectively; in females, they were approximately 71% and 38% of those of controls, respectively. No compound-related gross or microscopic lesions were observed in the animals. The authors concluded that, based on the decreased organ weights, weight gain and food and water consumption, 50 mg/L (8.6 mg/kg bw per day in males; 9.2 mg/kg bw per day in females) was the NOAEL. The authors stated that the results suggest that monochloramine induces effects via

an indirect mechanism, e.g., nutritional deficiencies, rather than a direct toxicological effect on specific organs or tissues.

The carcinogenicity of monochloramine has been investigated in a recently completed NTP study.<sup>58</sup> Doses of 0, 50, 100 or 200 ppm were administered in drinking water to groups of 70 male and 70 female F344/N rats or B6C3F<sub>1</sub> mice for two years. In rats, calculated estimates of time-weighted average doses were 0, 2.6, 4.8 and 8.7 mg/kg bw per day in males and 0, 2.8, 5.2 and 9.5 mg/kg bw per day in females. There was a dose-related decrease in water consumption in both sexes; feed consumption in dosed rats was similar to that of controls. Mean body weights of high-dose rats of both sexes were consistently 5–10% lower than those of other dosed groups. However, at week 97, at the highest dose administered, female rats showed a mean body weight loss of 13%; at week 101, mean body weight was 12% lower than in controls in both sexes. Interim sacrifices (10 animals per sex per dose) were conducted at weeks 14 and 66. At week 14, the mean body weight of high-dose males was significantly lower (9%,  $P \leq 0.01$ ) than that of controls; at week 66, mean body weights were significantly lower ( $P \leq 0.05$ ) than those of controls for both sexes (females 8%; males 6%). Slight decreases in liver and kidney weights in the high-dose males and increases in brain to body weight and kidney to body weight ratios of high-dose male and female rats were related to decreases in body weight. No other clinical findings, effects on survival or gross microscopic lesions were attributable to the consumption of chloraminated water. There was, however, a marginal increase in the incidence of mononuclear cell leukaemia in females — i.e., 8/50 (16%), 11/50 (22%), 15/50 (30%) and 16/50 (32%) for control, low-, mid- and high-dose groups, respectively. Trend analysis tests were significant ( $P < 0.05$ ). However, there was no indication of reduced latency of leukaemia, and there was no supporting evidence of this effect in males.

In mice, in the same study, calculated estimates of time-weighted average doses were 0, 5.0, 8.9 or 15.9 mg/kg bw per day in males and 0, 4.9, 9.0 or 17.2 mg/kg bw per day in females. As was observed in rats, there were dose-related decreases in water consumption and mean body weights of both sexes. Feed consumption was similar to that of controls in males and only slightly lower than that of controls in high-dose females. After week 37, mean body weights of high-dose males were 10–22% lower than those of controls, and mean body weights were 10–35% lower than those of controls in high-dose females after week 8. Interim sacrifices (10 animals per sex per dose) were conducted at weeks 15 and 66. At week 15, the mean body weights of high-dose males and females were significantly lower than those of controls (9%,  $P \leq 0.05$

for males; 16%,  $P \leq 0.01$  for females). At week 66, the mean body weights of mid- and high-dose males were significantly lower (9%,  $P \leq 0.01$ ) than those of controls. Differences in organ weights and organ to body weight ratios observed in high-dose mice at weeks 15 and 66 were related to decreases in body weights. No other clinical findings or effects on survival rates were attributable to the consumption of chloraminated water. Renal tubular adenomas were observed in 0/50 (0%), 1/50 (2%), 0/50 (0%) and 2/51 (4%) males in the control, low-, mid- and high-dose groups, respectively. This rare tumour was observed in 0/129 (0%) drinking water historical controls and in only 1/563 (0.2%) feed historical controls. These tumours were, however, not considered to be treatment-related. The presence of focal renal tubular hyperplasia in males was also considered not to be treatment-related. It was concluded by the NTP that under conditions of the bioassay, there was *equivocal evidence* of carcinogenicity in female F344/N rats but *no evidence* of carcinogenicity in either male F344/N rats or B6C3F<sub>1</sub> mice of either sex.

In limited studies, no treatment-related developmental or reproductive effects have been observed in rats exposed to monochloramine in drinking water or by gavage at 100 mg/L and 10 mg/kg, respectively.<sup>60,61</sup>

### Mutagenicity

Monochloramine has been found to be weakly mutagenic in bacterial assays using *Bacillus subtilis*.<sup>62,63</sup> Water samples treated with monochloramine showed mutagenic activity in the Ames/*Salmonella* assay as well as in a mammalian cell assay (mouse lymphoma L51784<sup>+/−</sup>) without metabolic activation.<sup>64</sup> Little mutagenic activity for monochloramine was reported by Thomas *et al.*<sup>65</sup> using a modified pre-incubation protocol for the Ames/*Salmonella* assay.

In *in vivo* studies, there was no evidence of chromosomal damage, either micronuclei or bone marrow aberrations in CD-1 mice, nor was there evidence of mutagenic potential as expressed by sperm head abnormalities in B6C3F<sub>1</sub> mice, following exposure to acute or subchronic doses of monochloramine by gavage.<sup>66</sup>

Known mutagens — 3-chloro-4-(dichloromethyl)-5-hydroxy-2(5H)-furanone (MX), (E)-2-chloro-3-(dichloromethyl)-4-oxobutenoic acid (EMX) and (E)-2-chloro-3-(dichloromethyl)butenedioic acid (ox-EMX) — have been identified in mutagenic extracts of aqueous monochloraminated fulvic acid. These compounds account, respectively, for 9%, 26% and 2% of the mutagenic activity observed in the monochloramination extracts.<sup>67</sup>

### Other Considerations

Chlorine residual compounds may be responsible for taste and odour in drinking water. The taste and odour of monochloramine are less objectionable than those of hypochlorous acid, hypochlorite ion and di- and trichloramine.<sup>6</sup> Odour and taste threshold values for monochloramine are 0.65 mg/L and 0.48 mg/L, respectively.<sup>68</sup> Monochloramine will likely not result in complaints about taste and odour at concentrations of 3 mg/L<sup>68</sup> or even 5 mg/L<sup>7</sup> in drinking water supplies; however, dichloramines may cause complaints at concentrations of 0.8 mg/L<sup>7</sup> or 0.5 mg/L.<sup>68</sup> Odour is more closely related to the ratio of dichloramine to monochloramine than to their absolute concentrations. Problems with taste and odour may result when the concentration of dichloramine exceeds 20% of the monochloramine concentration.<sup>69</sup> As such, the formation of dichloramine and trichloramine in the treatment process should be kept to a minimum to avoid problems with taste and odour.<sup>6</sup> Free chlorine or combined chlorine can create, prevent or help in the removal of tastes and odours in drinking water. Reactions of these disinfectants with organic compounds may form by-products that cause tastes and odours that are evident at concentrations below the taste and odour thresholds for the disinfectants themselves. Generally, chloramines are weaker oxidants than free chlorine and are not very effective in reducing or removing tastes and odours already present. However, residual activity within the distribution system may prevent taste-and odour-related bacterial growth and regrowth. On the other hand, ammonia, which may be produced when the chloramine residual is depleted, may be used by bacteria as a nutrient, a situation that may result in bacterial growth. This growth and the by-products related to it could, in turn, cause taste and odour problems.<sup>6</sup>

Nitrification is a microbiological process during which ammonia is oxidized sequentially to nitrite and nitrate.<sup>70</sup> The addition of ammonia in the production of chloramine may provide the source of nitrogen, which under certain conditions can be used to produce nitrites/nitrates.<sup>71</sup> Two groups of chemolithotrophic bacteria (ammonia- and nitrite- oxidizing bacteria) commonly found in terrestrial and aquatic environments can oxidize ammonia into nitrite and nitrate sequentially. When incomplete nitrification occurs, an accumulation of nitrite may result.<sup>70,72</sup> The presence of nitrite in a water supply is undesirable, because of health concerns (e.g., methaemoglobinaemia<sup>2</sup>) (see also supporting document on Nitrate/nitrite) and because nitrite may accelerate the decomposition of monochloramine<sup>73</sup> and interfere with chlorine residual measurements.<sup>7</sup>

Nitrite and nitrate were not present at significant concentrations in the decomposition of monochloramine

or dichloramine solutions in a laboratory experiment.<sup>74</sup> However, nitrite has been reported in a number of chloramine-containing distribution systems, with levels sometimes reaching 2 mg/L.<sup>71</sup> A residual of approximately 2.0 mg/L also assists in limiting nitrification, and periodic burnout with free chlorine appears to be needed to kill off nitrifying populations.<sup>71</sup> Ammonia-oxidizing bacteria seem to grow best under conditions of mild alkalinity (pH 7.5–8.5), warm water temperature, darkness, extended detention time and the presence of free ammonia.<sup>7</sup> These organisms have been found to be about 13 times more resistant to monochloramine than to free chlorine. No ammonia-oxidizing bacteria were detected in a chloraminated reservoir when the water temperature was below 16–18°C.<sup>72</sup> Chloramine use should be closely monitored in areas where water temperatures exceed 15°C because of the increased risk of nitrification.<sup>9</sup>

Nitrite production is not the only disadvantage reported with the use of chloramine. Degradation of elastomer, a product often used in distribution systems, has also been reported to be greater with chloramine than with chlorine use.<sup>75</sup>

It has been shown that chloramination significantly reduces THM formation in drinking water supplies. In a pilot plant, THM concentrations following a 30-minute disinfectant contact time were 4 µg/L and 34 µg/L for chloramine and chlorine treatment systems, respectively, where the average residuals for chlorine and monochloramine were 1.0 mg/L and 2.1 mg/L, respectively.<sup>76</sup> Another study demonstrated that the direct transfer of Cl<sup>-</sup> from monochloramine to phloracetophenone, a naturally occurring plant compound,<sup>77</sup> resulted in chloroform concentrations two orders of magnitude less than when free available chlorine was the chlorinating agent.<sup>78</sup> Chloramination can result in reductions in THM concentrations in finished water of between 10 and 95%, although 40–80% is most common.<sup>6</sup> Concentrations of THMs in the drinking water of the Ottawa–Carleton distribution system decreased from an annual average of 0.117 mg/L to 0.041 mg/L (65%) after the introduction of chloramination.<sup>20</sup> Chloramination significantly reduced, but did not eliminate, the formation of organic halides and THMs in water treatment plants in the United States.<sup>79</sup>

Although chloramination significantly reduces THM levels, formation of other by-products, such as halo ketones, chloropicrin, cyanogen chloride, haloacetic acids, haloacetonitriles, aldehydes and chlorophenols, has been reported.<sup>9,14,80</sup> Chloroacetic acids are by-products often present in significant quantities.<sup>9</sup> Johnson and Jensen<sup>10</sup> stated that oxidation by chlorine may remove THM and total organic halogen (TOX) precursors, but chloramines do not oxidize precursors to any significant extent. According to these authors, in

some instances chlorine oxidizes organic material, whereas chloramines react to form chloro-organics. Thus, chloramine may produce substitution by-products without the advantage of oxidation provided by chlorine. Amy *et al.*<sup>79</sup> indicated that the fraction of TOX represented by non-purgeable organic halides (NPOX) was slightly higher in water derived from chloramination as opposed to free chlorination. However, Stephen *et al.*<sup>81</sup> reported a reduction of NPOX of around 85% using chloramine instead of chlorine in a solution of distilled water mixed with humic acid. The NPOX fraction has not been totally characterized, and the potential health effects of these compounds have not been adequately studied.<sup>79</sup> Kirmeyer *et al.*<sup>6</sup> reported that, compared with chlorine, chloramine produced lower levels of total chlorinated by-products, as measured by such parameters as TOX, NPOX and non-purgeable organic chlorine (NPOCl). In a study of 35 water utilities in the United States, Krasner *et al.*<sup>80</sup> demonstrated that, although chloramines have been used effectively to limit the formation of THMs and other disinfection by-products, chloramine use, compared with chlorine use, increased the production of cyanogen chloride, a respiratory irritant. Conversion of cyanogen chloride to cyanide and thiocyanate may also be responsible for some chronic toxicity. Although cyanogen chloride production does not appear to limit the use of any disinfectant, it should be noted that this chemical has not been appropriately evaluated by the oral route of administration.<sup>14</sup>

## Classification and Assessment

The use of monochloramine as a secondary disinfectant in the treatment of drinking water may yield advantages such as increased residual activity in the distribution system, reduction of the formation of THMs and other by-products associated with chlorine use, possible control of bacterial biofilm regrowth in the distribution systems and, in some circumstances, reduction of taste and odour problems associated with chlorination of drinking water supplies.

Monochloramine has been weakly mutagenic in several *in vitro* studies; however, there has been no evidence of clastogenic activity in *in vivo* studies conducted to date. No treatment-related developmental or reproductive effects have been observed in rats exposed to monochloramine in drinking water in limited studies. Some possible immunologic effects have been reported. Nevertheless, the biological significance of these effects is not clear, and no other studies report these effects. It should be noted, however, that an administered concentration of 38 mg/L (calculated dose of 3.8 mg/kg bw per day) has been reported to cause a reduction in spleen weight and augmented production of prostaglandin E<sub>2</sub> in male rats.<sup>54</sup>

Available epidemiological studies are inadequate for the assessment of carcinogenicity of monochloramine in humans. There has, however, been some equivocal evidence of neoplastic responses in rats and mice following chronic exposure to monochloramine in drinking water. Kidney tubular adenomas were observed in two male mice (4%) exposed to 15.9 mg/kg bw per day (200 mg/L).<sup>58</sup> This rare tumour in mice was not, however, considered to be treatment-related. In female rats, there was a dose-related marginal increase in the incidence of mononuclear cell leukaemia over the moderately high incidence (16%) seen in controls.<sup>58</sup> Evidence of carcinogenic activity was classified as equivocal, as there was no indication of reduced latency of leukaemia, and this effect was not observed in male rats or either sex of mouse. The evidence for the carcinogenicity of monochloramine is, therefore, considered to be limited, and the compound has been classified as being possibly carcinogenic to humans (inadequate evidence in humans, some evidence in animals).

For compounds classified as being possibly carcinogenic to humans, the tolerable daily intake (TDI) is derived on the basis of division of a NOAEL (or no-observed-effect level, NOEL) or LOAEL (or lowest-observed-effect level, or LOEL) by an uncertainty factor. The only significant effect related to exposure to monochloramine is the reduction in body weight gain in both chronic and subchronic studies in rats. Administration of 200 mg/L monochloramine in the drinking water of rats for 90 days, equivalent to 9.0 mg/kg bw per day in males and 12.1 mg/kg bw per day in females, resulted in decreases in body weight of approximately 21% in males and 11% in females, and body weight gains were only 51% of control values.<sup>43</sup> In a two-year chronic study, administration of 100 ppm in drinking water, equivalent to 4.8 mg/kg bw per day in males and 5.2 mg/kg bw per day in females, body weight decreases in both sexes were less than 10%.<sup>58</sup> It should be noted, however, that the reduction in body weight gains may have been related to the decrease in water consumption, owing to a taste aversion to monochloramine in the drinking water.

For monochloramine, the TDI is derived as follows:

$$\text{TDI} = \frac{4.8 \text{ mg/kg bw per day}}{100} = 0.048 \text{ mg/kg bw per day}$$

where:

- 4.8 mg/kg bw per day is the (calculated time-weighted average) estimated NOEL based on decreased mean body weights in male rats, observed in the chronic study with the most appropriate route and vehicle of administration (i.e., drinking water)<sup>58</sup>; the male rat model was chosen, as the estimated time-weighted average dose was lower for males than for females
- 100 is the uncertainty factor ( $\times 10$  for interspecies variation and  $\times 10$  for intraspecies variation).

## Rationale

A maximum acceptable concentration (MAC) for monochloramine in drinking water was derived from the TDI as follows:

$$\text{MAC} = \frac{0.048 \text{ mg/kg bw per day} \times 70 \text{ kg bw} \times 0.80}{1.5 \text{ L/d}} \approx 1.8 \text{ mg/L}$$

where:

- 0.048 mg/kg bw per day is the TDI, as derived above
- 70 kg bw is the average body weight of an adult
- 0.80 is the proportion of total monochloramine intake considered to be ingested in drinking water
- 1.5 L/d is the average daily consumption of drinking water for an adult.

Because monochloramine is classified as being possibly carcinogenic to humans and because of considerations of various factors mentioned above (possible immunotoxicity effects in rats, methaemoglobinaemia and haemolysis in dialysis patients, increases in levels of plasma apolipoprotein B in humans, etc.), a conservative approach was used in the derivation of the guideline. However, no definite toxic end-points have been reported following monochloramine administration, particularly as decreases in body weight may have been due to taste aversion, which resulted in lower water consumption and body weight loss.

Because the MAC must be measurable by available analytical methods, the PQL was also taken into consideration in its derivation. Therefore, a MAC of 3.0 mg/L for total chloramines was established on the basis of the following considerations:

(1) Because of the questionable significance of the toxicity end-point, the guideline is established at the lowest practicable level of 3.0 mg/L. The PQL for chloramines is approximately 0.1–0.2 mg/L, well below the proposed MAC. However, many small municipalities do not have the capacity to measure individual chloramines or total chloramines down to the sub-milligram level, and 3.0 mg/L is a realistic PQL in these cases.

(2) This level is considered to be close to the concentration calculated from the NOEL for monochloramine, in view of the uncertainties associated with this calculation. Moreover, although monochloramine normally represents a large fraction of the total chloramines, the specification for measurement of total chloramines ensures that monochloramine will be less than the maximum.

(3) Natural ammonia may be found at higher concentrations in groundwater and surface water during the colder winter months and therefore may present a potential plant operational control problem if the guideline is lower than 3.0 mg/L. Under conditions of high ammonia, the production of chloramines may increase.

It should be emphasized that this MAC is based on the risk evaluation for monochloramine only, as monochloramine is usually the predominant chloramine and as information on dichloramine and trichloramine toxicity is insufficient to establish guidelines for these two compounds.

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