Monochloramine in Drinking-water

Background document for development of WHO *Guidelines for Drinking-water Quality*

Preface

One of the primary goals of WHO and its member states is that "all people, whatever their stage of development and their social and economic conditions, have the right to have access to an adequate supply of safe drinking water." A major WHO function to achieve such goals is the responsibility "to propose ... regulations, and to make recommendations with respect to international health matters ...."

The first WHO document dealing specifically with public drinking-water quality was published in 1958 as *International Standards for Drinking-water*. It was subsequently revised in 1963 and in 1971 under the same title. In 1984–1985, the first edition of the WHO *Guidelines for Drinking-water Quality* (GDWQ) was published in three volumes: Volume 1, Recommendations; Volume 2, Health criteria and other supporting information; and Volume 3, Surveillance and control of community supplies. Second editions of these volumes were published in 1993, 1996 and 1997, respectively. Addenda to Volumes 1 and 2 of the second edition were published in 1998, addressing selected chemicals. An addendum on microbiological aspects reviewing selected microorganisms was published in 2002.

The GDWQ are subject to a rolling revision process. Through this process, microbial, chemical and radiological aspects of drinking-water are subject to periodic review, and documentation related to aspects of protection and control of public drinking-water quality is accordingly prepared/updated.

Since the first edition of the GDWQ, WHO has published information on health criteria and other supporting information to the GDWQ, describing the approaches used in deriving guideline values and presenting critical reviews and evaluations of the effects on human health of the substances or contaminants examined in drinking-water.

For each chemical contaminant or substance considered, a lead institution prepared a health criteria document evaluating the risks for human health from exposure to the particular chemical in drinking-water. Institutions from Canada, Denmark, Finland, France, Germany, Italy, Japan, Netherlands, Norway, Poland, Sweden, United Kingdom and United States of America prepared the requested health criteria documents.

Under the responsibility of the coordinators for a group of chemicals considered in the guidelines, the draft health criteria documents were submitted to a number of scientific institutions and selected experts for peer review. Comments were taken into consideration by the coordinators and authors before the documents were submitted for final evaluation by the experts meetings. A "final task force" meeting reviewed the health risk assessments and public and peer review comments and, where appropriate, decided upon guideline values. During preparation of the third edition of the GDWQ, it was decided to include a public review via the world wide web in the process of development of the health criteria documents.

During the preparation of health criteria documents and at experts meetings, careful consideration was given to information available in previous risk assessments carried out by the International Programme on Chemical Safety, in its Environmental Health Criteria monographs and Concise International Chemical Assessment Documents, the International Agency for Research on Cancer, the joint FAO/WHO Meetings on Pesticide Residues and the joint FAO/WHO Expert Committee on Food Additives (which evaluates contaminants such as lead, cadmium, nitrate and nitrite, in addition to food additives).

Further up-to-date information on the GDWQ and the process of their development is available on the WHO internet site and in the current edition of the GDWQ.

Acknowledgements

Acronyms and abbreviations used in the text

CAS	Chemical Abstracts Service
DPD	N,N-diethyl-p-phenylenediamine
EPA	Environmental Protection Agency (USA)
IARC	International Agency for Research on Cancer
IPCS	International Programme on Chemical Safety
LOAEL	lowest-observed-adverse-effect level
NADPH	reduced nicotinamide adenine dinucleotide phosphate
NOAEL	no-observed-adverse-effect level
NTP	National Toxicology Program (USA)
TDI	tolerable daily intake
THM	trihalomethane
USA	United States of America

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1. GENERAL DESCRIPTION

1.1 Identity

CAS No.:	10599-90-3
Molecular formula:	NH_2Cl

Monochloramine, dichloramine ($NHCl_2$) and trichloramine (NCl_3) are 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 (*1–4*). The production of monochloramine, dichloramine and trichloramine is highly dependent upon pH, the ratio of chlorine to ammonia-nitrogen and, to a lesser extent, temperature and contact time (*5,6*). A pH between approximately 7.5 and 9.0 is optimum for the formation of monochloramine (*6*); the ideal pH is 8.3 (*7*).

Only monochloramine, the most abundant chloramine, will be considered here, as it has been the most extensively studied.

1.2 Physicochemical properties[1]

Property	Value
Physical state	Colourless, unstable liquid
Melting point	-66 °C
Water solubility	Soluble

1.3 Organoleptic properties

Most individuals are able to taste chlorine and its by-products, including chloramines, at concentrations below 5 mg/litre, and some at levels as low as 0.3 mg/litre (*8*).

Free chlorine or combined chlorine can create, prevent or help in the removal of undesirable 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.

1.4 Major uses

The chloramines are used as intermediates in the manufacture of hydrazine when formed *in situ* from ammonia and chlorine (*9*). 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 (*3,10*). It is recognized as a less effective disinfectant than chlorine. Chloramines are considered to have moderate

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[1] Conversion factor in air: 1 ppm = 2.1 mg/m^3.

biocidal activity against bacteria and low biocidal activity against viruses and protozoan cysts (*3,10*).

1.5 By-product formation

It has been shown that the use of chloramines for disinfection instead of chlorine reduces the formation of THMs in drinking-water supplies, often by as much as 40–80% (*6*). Compared with chlorine, use of monochloramine resulted in lower levels of total chlorinated by-products, as measured by such parameters as total organic halides, non-purgeable organic halides and non-purgeable organic chlorine (*6*). Another study indicated that while chloramination significantly reduces the formation of purgeable organic halides, significant amounts of non-purgeable organic halides are still formed (*11*).

Although chloramination significantly reduces THM levels, formation of other by-products, such as haloketones, chloropicrin, cyanogen chloride, haloacetic acids, haloacetonitriles, aldehydes and chlorophenols, has been reported (*12–14*). However, in a field study with water disinfected with monochloramine (ammonia was added to convert all but approximately 0.5 mg/litre of the free chlorine; a free chlorine residual was released into the distribution system), concentrations of THMs increased with increasing residence time in the distribution system, but concentrations of haloacetonitriles, haloketones, chloropicrin and haloacetic acids decreased with increasing residence time (*15*).

The mutagenicity of drinking-water obtained from river water and treated by several common disinfection methods was assessed using *Salmonella typhimurium* strains TA100 and TA98 without metabolic activation. Use of either chlorination or chloramination greatly increased the mutagenic potency of concentrated water extracts compared with raw or ozonated water (*16*). In another study, the mutagenic potencies of concentrates from drinking-water treated with a variety of disinfection schemes incorporating ozone, monochloramine, chlorine dioxide and chlorine were tested using *S. typhimurium* strains TA100, TA98, TA102 and TA97 with and without metabolic activation. The results showed that disinfection with chloramine resulted in a lower level of mutagenic activity compared with disinfection with chlorine (*17*).

1.6 Nitrification

Nitrification is a microbiological process during which ammonia is oxidized sequentially to nitrite and nitrate (*18*). 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 (*19*). Two groups of 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 (*18,20*). Nitrite has been reported in a number of chloramine-containing distribution systems, with levels sometimes reaching 2 mg/litre (*19*). The presence of nitrite in a water supply is undesirable because of health concerns (e.g., methaemoglobinaemia in infants) (*3*).

Nitrite may also accelerate the decomposition of monochloramine (*21)* and interfere with chlorine residual measurements (*7*).

1.7 Environmental fate

Monochloramine is persistent in the environment. It hydrolyses slowly in aqueous solutions (*4*). 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/litre per sunlight hour between 10 a.m. and 2 p.m. (latitude 30–40°N) (*7*). Monochloramine has been reported at concentrations ranging from 0.03 to 1.0 mg/litre in secondary sewage effluents and cooling water samples (*22*). Its rate of disappearance is primarily a function of pH and salinity: its half-life increases with increasing pH and decreases with increasing salinity. It decomposes more quickly if discharged into receiving waters containing bromide, presumably as a result of the formation of bromochloramine and the decomposition of the dihalamine. Monochloramine is expected to decompose via chlorine transfer to give organic nitrogen-containing compounds in receiving waters (*23*).

2. ANALYTICAL METHODS

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 multistage 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-CI D) and the *N,N*-diethyl-*p*-phenylenediamine (DPD) ferrous titrimetric (4500-CI F) and colorimetric (4500-CI G) methods (*24*).

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 concentration and pH. Possible interferences with this method include trichloramine, 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 (*24*). It is generally not suitable for field use, owing to the complexity of the instrumentation (*25*).

The DPD methods have been widely accepted and have become the standard testing procedures in the field (*25*). They allow complete differentiation of chlorine species by using a small amount of iodide ion (as potassium iodide) 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/litre as chlorine gas and requires careful pH control for accurate results (*24*). The DPD colorimetric method has a detection limit of 0.010 mg/litre under ideal conditions (*24*).

3. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

No data are available on levels of monochloramine in air or food.

3.1 Water

Typical chloramine concentrations of 0.5–2 mg/litre are found in drinking-water supplies where chloramine is used as a primary disinfectant or to provide a chlorine residual in the distribution system (*26*). Chloramine residuals in the USA range from 0.6 to 5.0 mg/litre; 75% of utilities have finished water with chloramine residual levels between 1.0 and 3.0 mg/litre entering the distribution system (*6*). In one survey, mono- and dichloramines were found in secondary sewage effluents and cooling water at levels in the range of 0.03–1.0 mg/litre and 0.002–0.70 mg/litre, respectively (*22*).

Chloramines may be present in swimming pools due to the reaction of chlorine or hypochlorites used for disinfection with ammonia in the water from urea decomposition (*27*).

4. KINETICS AND METABOLISM IN LABORATORY ANIMALS AND HUMANS

Monochloramine administered by the oral route in the rat is rapidly and readily absorbed from the gastrointestinal tract (*28*). In humans, most of the monochloramine from drinking-water would reach the stomach intact but would rapidly decay in stomach fluid, and free monochloramine is not expected to enter systemic circulation (*29*). It has been suggested that at low concentrations, 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 (*30*).

Five days after administration, the highest concentrations of monochloramine, measured as labelled chloride ion, were found in plasma, followed by whole blood, skin, testes, packed cells, bone marrow, kidney, lung, stomach, thyroid and thymus, carcass, liver, ileum and fat (*28*). The peak plasma level was reached 8 h following administration, with an elimination half-life from plasma of 39 h (*31*).

Monochloramine is metabolized to the chloride ion, which is excreted mainly in the urine and to a lesser extent in the faeces (*28*).

5. EFFECTS ON LABORATORY ANIMALS AND IN VITRO TEST SYSTEMS

5.1 Short-term exposure

Male A/JAX mice (12 per dose) were exposed to monochloramine at concentrations of 0, 2.5, 25, 50, 100 or 200 mg/litre (approximately 0, 0.4, 4, 8, 15 or 30 mg/kg of body weight per day) for 30 days. No significant adverse effects on various haematological parameters, including blood cell counts, haemoglobin, glutathione levels and glucose-6-phosphate dehydrogenase activity, were reported at any dose level tested. The NOAEL in this study was 30 mg/kg of body weight per day (*32*).

Monochloramine at 0, 25, 50, 100 or 200 mg/litre (corresponding to 0, 1.8, 3.4, 5.8 and 9.0 mg/kg of body weight per day for males and 0, 2.6, 4.3, 7.7 and 12.1 mg/kg of body weight per day for females) was administered in drinking-water to Sprague-Dawley rats for 90 days. The authors considered the highest dose a LOAEL for both sexes, based on reductions in liver and spleen weights. In addition, overall reductions in body weight gain were observed at 50 mg/litre and higher, but significant reductions only at 200 mg/litre. The authors concluded that 100 mg/litre (7.7 and 5.8 mg/kg of body weight per day for female and male rats, respectively) can be considered a NOAEL (*33*).

In a 90-day study, male and female $B6C3F_1$ mice received monochloramine in their drinking-water at 0, 12.5, 25, 50, 100 or 200 mg/litre, equivalent to 0, 2.5, 5.0, 8.6, 11.1 and 15.6 mg/kg of body weight per day for males and 0, 2.8, 5.3, 9.2, 12.9 and 15.8 mg/kg of body weight per day for females (*34*). Food consumption was decreased in both sexes; the decrease was significant for females at the two highest dose levels. Water consumption was significantly decreased at the two highest doses for males and at all doses for females. 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 and 200 mg/litre, final mean body weights and body weight gains were reduced. The authors concluded that, based on the decreased organ weights, weight gain and food and water consumption, 50 mg/litre (8.6 mg/kg of body weight per day in males; 9.2 mg/kg of body weight 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. A 13-week oral study in male Sprague-Dawley rats confirmed that monochloramine at 200 mg/litre in drinking-water can cause reduced body weight gain and other changes observed in earlier investigations, largely related to the reduced water intake and food consumption (*35*).

5.2 Long-term exposure

Monochloramine was administered for 2 years to male and female F344/N rats at 0, 50, 100 or 200 mg/litre in the drinking-water, corresponding to average doses of 0, 2.9, 5.2 and 9.4 mg/kg of body weight per day in males and 0, 3.1, 5.7 and 10.2 mg/kg of body weight per day in females. The authors failed to find any clinical changes attributable to the consumption of chloraminated water. Mean body weights of rats given the highest dose were lower than those of their respective control groups. Based on these considerations, the authors considered the NOAELs for this study to be 5.2 and 5.7 mg/kg of body weight per day for male and female rats, respectively. However, it is probable that the observed weight decreases were a direct result of the unpalatability of the drinking-water (*36*).

In a second bioassay, B6C3F$_1$ mice were exposed for 2 years to monochloramine in their drinking-water at levels of 0, 50, 100 or 200 mg/litre, corresponding to average doses of 0, 5.4, 9.8 and 17.0 mg/kg of body weight per day for males and 0, 5.8, 10.6 and 19.0 mg/kg of body weight per day for females. As was observed in rats, there were dose-related decreases in water consumption and mean body weights of both sexes. The authors reported that there were no clinical changes attributable to the consumption of chloraminated water. Based on changes in body weight at the highest dose, the NOAELs were 9.8 and 10.6 mg/kg of body weight per day for male and female mice, respectively (*36*).

5.3 Reproductive and developmental toxicity

Monochloramine was administered by gavage at doses of 0, 2.5, 5.0 or 10 mg/kg of body weight per day to male and female Long-Evans rats for 66–76 days before and during mating and throughout gestation and lactation. No significant differences were observed between controls and exposed rats in fertility, viability, litter size, mean weight of pups or day of eye opening. There were no alterations in sperm count, direct progressive sperm movement, percentage mobility or sperm morphological characteristics in adult males. The weights of male and female reproductive organs were not significantly different between the test and control groups, and no significant anatomical changes were seen on tissue examination. A NOAEL of 10 mg/kg of body weight per day was identified (*37*).

In a study in which monochloramine was administered to female Sprague-Dawley rats (six per dose) at 0, 1, 10 or 100 mg/litre daily (approximately 0, 0.1, 1 or 10 mg/kg of body weight per day) in drinking-water before mating and throughout gestation, it was found not to be teratogenic or embryotoxic. The reliability of these findings is reduced because of the small number of dams exposed and the lack of data on maternal toxicity (*38*).

5.4 Mutagenicity and related end-points

In *in vitro* studies without metabolic activation, monochloramine was reported to be weakly mutagenic at the *trpC* locus of *Bacillus subtilis* (*39*) and showed little or no mutagenic activity in assays employing *Salmonella typhimurium* strains TA97, TA100 and TA102 (*40*).

Concentrated extracts of water samples treated with monochloramine showed mutagenic activity in the Ames/*Salmonella* assay as well as in a mammalian cell assay (mouse lymphoma L51784$^{+/-}$) without metabolic activation (*41*). It is possible that other agents, such as 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) — caused this result. These compounds have previously been identified in mutagenic extracts of aqueous monochloraminated fulvic acid (*42*).

In *in vivo* studies, there was no significant increase in bone marrow chromosomal aberrations or micronuclei in CD-1 mice after intraperitoneal administration of monochloramine (*43*), and no mutagenic activity was detected in the mouse bone marrow micronucleus test following oral administration (*44*). While another *in vivo* study reported positive results for rat bone marrow chromosomal aberrations after treatment with monochloramine, this study did not appear to have been published, and sufficient detail was not provided to allow a critical evaluation (*45*).

Based on the existing studies, monochloramine appears to have some mutagenic potential *in vitro*, but no significant mutagenic properties *in vivo*.

5.5 Carcinogenicity

In 2-year bioassays, mice and rats were exposed to monochloramine at 0, 50, 100 or 200 mg/litre in drinking-water, the highest doses being equivalent to 9.4 and 10.2 mg/kg of body weight per day for male and female rats, respectively, and 17.0 and 19.0 mg/kg of body weight per day for male and female mice, respectively. The studies provided equivocal evidence of the carcinogenic activity of chloraminated drinking-water in female F344/N rats, as indicated by an increase, in comparison with concurrent controls, in the incidence of mononuclear cell leukaemia. The following factors did not support an association between the occurrence of mononuclear cell leukaemia and the consumption of chloraminated drinking-water: 1) the increases in leukaemia incidence in dosed female rats were small and not clearly dose-related; 2) there was no decrease in tumour latency in the dosed groups; 3) the effect was not observed in male rats or either sex of mouse; and 4) the incidence in concurrent controls was less than the mean incidence in historical control groups (*46*).

6. EFFECTS ON HUMANS

Chloramine was administered at increasing doses (approximately 0.0001, 0.01, 0.11, 0.26 or 0.34 mg/kg of body weight per day) to five groups of 10 human subjects each,

over a 16-day period. There were no adverse effects on clinical signs, urinalysis, haematology or clinical chemistry in comparison with controls. In a second phase of the study, 10 healthy adult males were given a 5 mg/litre monochloramine solution (0.04 mg/kg of body weight per day). There were no adverse effects on physical condition, urinalysis or clinical chemistry and no serious objections to the taste of monochloramine at the dose tested (*47*). Forty-eight men received monochloramine in drinking-water at concentrations of 0, 2 or 15 mg/litre for 4 weeks. At 15 mg/litre, increases in the level of plasma apolipoprotein B were observed. The authors concluded that monochloramine at 2 mg/litre 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 (*48*).

Acute haemolytic anaemia, methaemoglobinaemia and haemolysis in haemodialysis patients have been reported when tap water containing chloramines was used for dialysis (*13,49–51*). More recently, there was an outbreak of erythropoietin resistance despite only subtle signs of haemolysis in patients in a haemodialysis unit. The dialysate chloramine levels in this unit had risen from <0.1 mg/litre to 0.25–0.3 mg/litre just prior to the outbreak (*52*). While the dialysed route of exposure appears not to be relevant to exposure via drinking-water, it is useful for elucidation of potential mechanisms of toxicity. Chloramine oxidizes haemoglobin to methaemoglobin and induces damage to the hexose monophosphate shunt, which protects the red cells from oxidant damage through generation of NADPH (*50,53*).

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. A preliminary report from a study conducted in Massachusetts, USA, examining mortality patterns of residents living in communities using drinking-water treated either by chlorine or by chloramines reported a slight excess of deaths from pneumonia and influenza in communities where water was disinfected by chloramines (*54*). The authors indicated that these preliminary observations required clarification due to the possibility of the influence of uncontrolled or unidentified confounding factors. A later report by the same authors, conducting a case–control study of inhabitants of 43 communities, investigated the possible association between chlorinated drinking-water and bladder cancer (*55*). Persons from communities with chloraminated water were considered to be "non-exposed." The study results were 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 that in 1992, the US 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 (*56*).

7. GUIDELINE VALUE

Although monochloramine has been shown to be mutagenic in some *in vitro* studies, it has not been found to be genotoxic *in vivo*. In the absence of data on human cancer and on the basis of inadequate evidence for the carcinogenicity of monochloramine in experimental animals, monochloramine was evaluated by IARC as not classifiable as to its carcinogenicity (Group 3) (*57*). The US EPA classified monochloramine in group D, not classifiable as to its human carcinogenicity, in that there is inadequate human and animal evidence (*58*). IPCS did not consider that the increase in mononuclear cell leukaemia was treatment-related (*59*). In the NTP bioassay in two species, the incidence of mononuclear cell leukaemias in female F344/N rats was increased, but no other increases in tumour incidence were observed (*36*).

A TDI of 94 µg/kg of body weight can be calculated by applying an uncertainty factor of 100 (for intra- and interspecies variation) to a NOAEL of 9.4 mg/kg of body weight per day (the highest dose administered to males in the 2-year NTP rat drinking-water study, chosen because of the probability that the lower body weights were caused by the unpalatability of the drinking-water) (*36*). An additional uncertainty factor for possible carcinogenicity was not applied, because equivocal cancer effects reported in the NTP study in only one species and in only one sex were within the range observed in historical controls. A guideline value of 3 mg/litre (rounded figure) can be calculated by allocating 100% of the TDI to drinking-water.

The guideline value is analytically achievable using common chlorine residual determination procedures. Although it is possible to reduce the concentration of chloramines effectively to zero (<0.1 mg/litre) by reduction using sulfur dioxide or a sulfite compound (sodium disulfite, sodium hydrogen sulfite, sodium sulfite or sodium thiosulfate) (*6*), it is normal practice to supply water with a chloramine residual of a few tenths of a milligram per litre to act as a preservative during distribution.

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