

2. CHEMISTRY OF DISINFECTANTS AND DISINFECTANT BY-PRODUCTS

2.1 Background

The use of chlorine (Cl_2) as a water disinfectant has come under scrutiny because of its potential to react with natural organic matter (NOM) and form chlorinated disinfectant by-products (DBPs). Within this context, NOM serves as the organic DBP precursor, whereas bromide ion (Br^-) serves as the inorganic precursor. Treatment strategies generally available to water systems exceeding drinking-water standards include removing DBP precursors and using alternative disinfectants for primary and/or secondary (distribution system) disinfection. Alternative disinfectant options that show promise are chloramines (NH_2Cl , monochloramine), chlorine dioxide (ClO_2) and ozone (O_3). While ozone can serve as a primary disinfectant only and chloramines as a secondary disinfectant only, both chlorine and chlorine dioxide can serve as either primary or secondary disinfectants.

Chloramine presents the significant advantage of virtually eliminating the formation of chlorination by-products and, unlike chlorine, does not react with phenols to create taste- and odour-causing compounds. However, the required contact time for inactivation of viruses and *Giardia* cysts is rarely obtainable by chloramine post-disinfection at existing water treatment facilities (monochloramine is significantly less biocidal than free chlorine). More recently, the presence of nitrifying bacteria and nitrite (NO_2^-) and nitrate (NO_3^-) production in chloraminated distribution systems as well as the formation of organic chloramines have raised concern.

The use of chlorine dioxide, like chloramine, can reduce the formation of chlorinated by-products during primary disinfection. However, production of chlorine dioxide, its decomposition and reaction with NOM lead to the formation of by-products such as chlorite (ClO_2^-), a compound that is of health concern.

If used as a primary disinfectant followed by a chloramine residual in the distribution system, ozone can eliminate the need for contact between DBP precursors and chlorine. Ozone is known to react both

with NOM to produce organic DBPs such as aldehydes and increase levels of assimilable organic carbon and with bromide ion to form bromate.

A thorough understanding of the mechanisms of DBP formation allows microbial inactivation goals and DBP control goals to be successfully balanced. This chapter examines a range of issues affecting DBP formation and control to provide guidance to utilities considering the use of various disinfecting chemicals to achieve microbial inactivation with DBP control.

2.2 Physical and chemical properties of common disinfectants and inorganic disinfectant by-products

The important physical and chemical properties of commonly used disinfectants and inorganic DBPs are summarized in Table 1.

2.2.1 Chlorine

Chlorine, a gas under normal pressure and temperature, can be compressed to a liquid and stored in cylindrical containers. Because chlorine gas is poisonous, it is dissolved in water under vacuum, and this concentrated solution is applied to the water being treated. For small plants, cylinders of about 70 kg are used; for medium to large plants, tonne containers are common; and for very large plants, chlorine is delivered by railway tank cars or road (truck) tankers. Chlorine is also available in granular or powdered form as calcium hypochlorite ($\text{Ca}(\text{OCl})_2$) or in liquid form as sodium hypochlorite (NaOCl ; bleach).

Chlorine is used in the form of gaseous chlorine or hypochlorite (OCl^-). In either form, it acts as a potent oxidizing agent and often dissipates in side reactions so rapidly that little disinfection is accomplished until amounts in excess of the chlorine demand have been added. As an oxidizing agent, chlorine reacts with a wide variety of compounds, in particular those that are considered reducing agents (hydrogen sulfide [H_2S], manganese(II), iron(II), sulfite [SO_3^{2-}], Br^- ,

Table 1. Physical and chemical properties of commonly used disinfectants and inorganic disinfectant by-products

Chemical ^a	E° (V) ^b	Oxidation number of Cl or Br	δ_{\max} (nm) ^c	ϵ (mol ⁻¹ litre ⁻¹ cm ⁻¹) ^d	p_i ° ^e	pK_a ^f
HOCl/Cl ⁻	+1.49	+1	254 292 (OCl ⁻)	60 419	+25.2	7.5
ClO ₂ /ClO ₂ ⁻	+0.95	+4	359	1250	+16.1	–
NH ₂ Cl	–	+1	245	416	–	–
O ₃ /O ₂	+2.07	–	254	3200	+35.0	
HOBr/Br ⁻	+1.33	+1	330	50	+22.5	8.7
ClO ₂ ⁻ /Cl ⁻	+0.76	+3	262	–	+12.8	1.96
ClO ₃ ⁻ /Cl ⁻	+0.62	+5	360	–	+10.5	1.45
BrO ₃ ⁻ /Br ⁻	+0.61	+5	195	–		0.72

^a Half-cell reactants/products.

^b E° = standard electrode potential (redox potential) in water at 25 °C. The oxidation–reduction state of an aqueous environment at equilibrium can be stated in terms of its redox potential. In the chemistry literature, this is generally expressed in volts, E , or as the negative logarithm of the electron activity, p_i . When p_i is large, the electron activity is low and the system tends to be an oxidizing one: i.e., half-reactions tend to be driven to the left. When p_i is small, the system is reducing, and reactions tend to be driven to the right.

^c δ_{\max} = maximum absorbance wavelength of that particular solution in nm.

^d ϵ = molar absorptivity (molar extinction coefficient), in mol⁻¹ litre⁻¹ cm⁻¹. This can be used for quantitative determination of the various species of chemicals and is the only direct physical measurement. There is often some background absorbance that may interfere with the measurement in natural waters that should be considered.

^e p_i ° = $-\log \{e^-\}$ where $\{e^-\}$ = electron activity.

^f pK_a = negative logarithm of the acid ionization constant (e.g., at pH 7.5, the molar concentration of HOCl is same as that of OCl⁻). As this parameter is dependent upon temperature, the values listed were determined at 25 °C.

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iodide [I⁻], nitrite). From the point of view of DBP formation and disinfection, these reactions may be important because they may be fast and result in the consumption of chlorine.

Chlorine gas hydrolyses in water almost completely to form hypochlorous acid (HOCl):

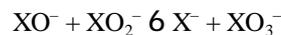


The hypochlorous acid dissociates into hydrogen ions (H⁺) and hypochlorite ions in the reversible reaction:



Hypochlorous acid is a weak acid with a pK_a of approximately 7.5 at 25 °C. Hypochlorous acid, the prime disinfecting agent, is therefore dominant at a pH below 7.5 and is a more effective disinfectant than hypochlorite ion, which dominates above pH 7.5.

The rates of the decomposition reactions of chlorine increase as the solution becomes more alkaline, and these reactions can theoretically produce chlorite and chlorate (ClO₃⁻); they occur during the electrolysis of chloride (Cl⁻) solutions when the anodic and cathodic compartments are not separated, in which case the chlorine formed at the anode can react with the alkali formed at the cathode. On the other hand, hypochlorous acid/hypochlorite (or hypobromous acid/hypobromite, HOBr/OBr⁻) can be formed by the action of chlorine (or bromine) in neutral or alkaline solutions. The decomposition of hypohalites (XO⁻) is favoured in alkaline solutions (2XO⁻ ⇌ X⁻ + XO₂⁻) and is such that there is no longer any domain of thermodynamic stability for the hypohalite ions. These oxyhalites are further converted to stable oxyhalates as follows:



Another reaction that occurs in waters containing bromide ion and hypochlorite is the production of hypobromous acid:



This reaction is irreversible, and the product hypobromous acid is a better halogenating agent than hypochlorous acid and interferes with

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common analytical procedures for free chlorine. The presence of bromide in hypochlorite solutions can ultimately lead to the formation of bromate (BrO_3^-).

Hypobromous acid is a weak acid ($\text{p}K_a = 8.7$); like hypochlorite, hypobromite is metastable. In alkaline solution, it decomposes to give bromate and bromide:



Bromic acid (HBrO_3) is a strong acid ($\text{p}K_a = 0.7$). Bromic acid and bromate can be obtained by the electrolytic oxidation of bromide solutions or bromine water using chlorine. Bromic acid and bromate are powerful oxidizing agents, but the speed of their oxidation reactions is generally slow (Mel et al., 1953).

2.2.2 Chlorine dioxide

Chlorine dioxide is one of the few compounds that exists almost entirely as monomeric free radicals. Concentrated chlorine dioxide vapour is potentially explosive, and attempts to compress and store this gas, either alone or in combination with other gases, have been commercially unsuccessful. Because of this, chlorine dioxide, like ozone, must be manufactured at the point of use. Chlorine dioxide in water does not hydrolyse to any appreciable extent. Neutral or acidic dilute aqueous solutions are quite stable if kept cool, well sealed and protected from sunlight.

Chlorine dioxide represents an oxidation state (+4) intermediate between those of chlorite (+3) and chlorate (+5). No acid or ion of the same degree of oxidation is known. Chlorine dioxide is a powerful oxidizing agent that can decompose to chlorite; in the absence of oxidizable substances and in the presence of alkali, it dissolves in water, decomposing with the slow formation of chlorite and chlorate:



Chlorine dioxide has an absorption spectrum with a maximum at 359 nm, with a molar absorptivity of $1250 \text{ mol}^{-1} \text{ litre}^{-1} \text{ cm}^{-1}$. This extinction coefficient is independent of temperature, pH, chloride and ionic strength. Chlorine dioxide is readily soluble in water, forming a

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greenish-yellow solution. It can be involved in a variety of redox reactions, such as oxidation of iodide ion, sulfide ion, iron(II) and manganese(II). When chlorine dioxide reacts with aqueous contaminants, it is usually reduced to chlorite ion. The corresponding electron transfer reactions are comparable to those occurring when singlet oxygen acts as an oxidant (Tratnyek & Hoigne, 1994).

Bromide (in the absence of sunlight) is not oxidized by chlorine dioxide. Therefore, water treatment with chlorine dioxide will not transform bromide ion into hypobromite and will not give rise to the formation of bromoform (CHBr₃) or bromate. This is an important difference between the use of chlorine dioxide as an oxidant and the use of chlorine or ozone as an oxidant.

2.2.3 Ozone

Ozone is a strong oxidizing agent ($E^{\circ} = 2.07$ V). Oxidation reactions initiated by ozone in water are generally rather complex; in water, only part of the ozone reacts directly with dissolved solutes. Another part may decompose before reaction. Such decomposition is catalysed by hydroxide ions (OH⁻) and other solutes. Highly reactive secondary oxidants, such as hydroxyl radicals (OH[•]), are thereby formed. These radicals and their reaction products can additionally accelerate the decomposition of ozone. Consequently, radical-type chain reactions may occur, which consume ozone concurrently with the direct reaction of ozone with dissolved organic material.

Many oxidative applications of ozone have been developed, including disinfection, control of algae, removal of tastes and odours, removal of colour, removal of iron and manganese, microflocculation, removal of turbidity by oxidative flocculation, removal of organics by oxidation of phenols, detergents and some pesticides, partial oxidation of dissolved organics and control of halogenated organic compounds. For disinfection and for oxidation of many organic and inorganic contaminants in drinking-water, the kinetics of ozone reactions are favourable; on the other hand, for many difficult-to-oxidize organic compounds, such as chloroform (CHCl₃), the kinetics of ozone oxidation are very slow (Hoigne et al., 1985).

2.2.4 Chloramines

Monochloramine has much higher CT values¹ than free chlorine and is therefore a poor primary disinfectant. Additionally, it is a poor oxidant and is not effective for taste and odour control or for oxidation of iron and manganese. However, because of its persistence, it is an attractive secondary disinfectant for the maintenance of a stable distribution system residual. The use of disinfectants such as ozone or chlorine dioxide combined with chloramines as a secondary disinfectant appears to be attractive for minimizing DBP formation (Singer, 1994b).

Monochloramine is the only useful ammonia-chloramine disinfectant. Dichloramine (NHCl₂) and nitrogen trichloride (NCl₃) are too unstable to be useful and highly malodorous. Conditions practically employed for chloramination are designed to produce only monochloramine.

2.3 Analytical methods for disinfectant by-products and disinfectants

Analytical methods for various DBPs and their detection limits are summarized in Table 2. Methods for disinfectants are summarized in APHA (1995).

2.3.1 Trihalomethanes, haloacetonitriles, chloral hydrate, chloropicrin and haloacetic acids

Gas chromatographic (GC) techniques are generally employed for organic DBPs. Detection and quantification of haloacetonitriles (HANs) and chloral hydrate in chlorinated natural waters are complicated by (i) hydrolysis of dihaloacetonitriles and chloral hydrate to dihaloacetic acids and chloroform, respectively; (ii) degradation of HANs by dechlorinating agents such as sodium sulfite and sodium thiosulfate; (iii) low purge efficiency for the HANs and chloral hydrate

¹ The CT value is the product of the disinfectant concentration *C* in mg/litre and the contact time *T* in minutes required to inactivate a specified percentage (e.g., 99%) of microorganisms.

Table 2. Summary of analytical methods for various DBPs and their minimum detection limits

DBPs	Analytical method	APHA ^a method	Minimum detection limit (: g/litre)	Major interferences	References
THMs	MTBE extraction	–	0.4	None	AWWARF (1991)
	Pentane extraction	6232B	0.1		
HAAs	Salted MTBE extraction and derivatization with diazomethane	6233B	0.5–1.0	None	AWWARF (1991)
HANs	Pentane extraction	6232B	0.05	None	Koch et al. (1988)
Cyanogen chloride	MTBE extraction	6233A	0.5	None	AWWARF (1991)
Chloramine	Derivatization with 2-mercaptobenzothiazole	–	–	None	Lukasewycz et al. (1989)
Haloketones ^b	Pentane extraction	6232B	0.2	None	Krasner et al. (1995) AWWARF (1991)
Chloral hydrate	MTBE extraction	–	0.5	None	AWWARF (1991)
Aldehydes	Extraction with hexane and derivatization with PFBHA	–	1.0	PFBHA sulfate	Scimienti et al. (1990)
Bromate	Ion chromatography (H ₃ BO ₃ /NaOH)	4500	2.0 ^c	Cl ⁻	Siddiqui et al. (1996a) Krasner et al. (1993) Weinberg et al. (1998)
			0.2		
Chlorate	Ion chromatography (H ₃ BO ₃ /NaOH)	4500	5	Cl ⁻ , acetate	Siddiqui (1996)
Chlorite	Ion chromatography (NaHCO ₃ /Na ₂ CO ₃)	4500	10	Cl ⁻ , acetate	AWWARF (1991)
TOC	UV/persulfate or combustion	5310	200	Metals	APHA (1995)

^a American Public Health Association.

^b Sum of 1,1-DCPN and 1,1,1-TCPN.

^c 1.0 : g/litre with high-capacity column.

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in the purge-and-trap technique; and (iv) low extraction efficiency for chloral hydrate with pentane in the liquid–liquid extraction normally used. Although chloral hydrate is not efficiently extracted from water with pentane, it can be extracted with an efficiency of approximately 36% when the ratio by volume of methyl *tert*-butyl ether (MTBE) to water is 1 : 5 (Amy et al., 1998). MTBE quantitatively extracts HANs, trihalomethanes (THMs), chloral hydrate and chloropicrin, permitting simultaneous analysis for all of these DBPs. Chloral hydrate decomposes on packed columns to trichloroacetaldehyde, resulting in considerable band broadening, although this does not appear to be a significant problem with DB-1 and DB-5 columns.

The extraction of THMs can be accomplished using MTBE (EPA Method 551) or pentane. Method 551 also permits simultaneous extraction and measurement of chloral hydrate, HANs, THMs, chloropicrin and haloketones. The pentane method can be used to extract THMs, HANs, haloketones and chloropicrin but not chloral hydrate in the same run (APHA, 1995).

The haloacetic acid (HAA) analytical method involves using an acidic salted ether or acidic methanol liquid–liquid extraction, requiring esterification with diazomethane prior to analysis on a gas chromatograph equipped with an electron capture detector (ECD). THMs and HANs can be analysed by extraction with pentane prior to analysis on a capillary-column GC equipped with an ECD. The analysis of cyanogen compounds involves extraction with MTBE prior to injection into GC–ECD. Aldehydes require derivatization with *O*-(2,3,4,5,6-pentafluorobenzyl)-hydroxylamine (PFBHA) (to form an oxime), extraction with hexane and GC–ECD analysis $[(C_6F_5)-CH_2ONH_2 + RCHO \rightarrow (C_6F_5)-CH_2ON=CHR + H_2O]$. It should be noted that PFBHA peaks are very large relative to other peaks in the chromatogram from a purge-and-trap system, whereas the peaks are comparable to other peaks in a GC–ECD chromatogram (Trehly et al., 1986).

2.3.2 *Inorganic disinfectant by-products*

An ion chromatography (IC) method (EPA Method 300) has been developed to determine inorganic by-products. The elution order is fluoride, chlorite, bromate, chloride, nitrite, bromide, chlorate, nitrate and sulfate ion. The eluent is a carbonate buffer. Ethylenediamine is used to preserve chlorite samples and to minimize the potential for chlorite ion reaction on the IC separating column. EPA Method 300

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involves measurement by an IC system using a separating column (e.g., Ion Pac AS9-SC) fitted with an anion micromembrane suppressor column. An eluent containing 2.0 mmol of sodium carbonate (Na_2CO_3) per litre / 0.75 mmol of sodium bicarbonate (NaHCO_3) per litre is used for bromide determination, and an eluent containing 40 mmol of boric acid (H_3BO_3) per litre / 20 mmol of sodium hydroxide (NaOH) per litre is used for bromate and chlorate determination. The analytical minimum detection limits for bromate and chlorate using a borate eluent have been reported as 2 : g/litre and 5 : g/litre, respectively (Siddiqui, 1996; Siddiqui et al., 1996a). For samples with high chloride ion content, a silver cartridge can be used to remove chloride prior to IC analysis to minimize its interference with bromate measurement. It should be noted that for natural sources and waters with high total organic carbon (TOC) levels, detection limits will be slightly different because of the masking effect of NOM and high concentrations of carbonate/bicarbonate ions that may interfere with bromate/chlorate measurement.

2.3.3 Total organic carbon and UV absorbance at 254 nm

TOC is the primary surrogate parameter for the measurement of NOM in water supplies. Several investigators have reported that the ultraviolet (UV)/persulfate oxidation method underestimates the TOC concentration in natural waters as compared with the combustion method because of the inability of the persulfate method to oxidize highly polymerized organic matter. It is generally assumed that the calibration of a TOC analyser with a potassium hydrogen phthalate standard is sufficient for the measurement of TOC in natural waters, but potassium hydrogen phthalate has a simple molecular structure and is easy to oxidize. Dissolved organic carbon (DOC) is operationally defined by a (0.45-: m) filtration step. UV absorbance at 254 nm (UVA_{254}) is used to describe the type and character of NOM, whereas TOC describes just the amount of NOM.

2.3.4 Chloramines

Knowledge of the amine content of the water during water treatment processes involving chloramination is important to define more adequately the content of a matrix described only as a combined chlorine residual. The presence of organic nitrogen and the instability

of many organic chloramines continue to challenge the analyst. Lukasewycz et al. (1989) developed a technique for the analysis of chloramines and organic chloramines present in water using 2-mercaptobenzothiazole as a derivatizing agent. The resulting sulfanilamides are stable and can be conveniently analysed by high-performance liquid chromatography (HPLC) using UV or electrochemical detection. This method appears to be superior to the use of diazotization or phenylarsine oxide as a method of detection. Organic chloramines are much weaker disinfectants than inorganic monochloramine but are indistinguishable by the common analytical methods.

2.4 Mechanisms involved in the formation of disinfectant by-products

2.4.1 Chlorine reactions

Chlorine reacts with humic substances (dissolved organic matter) present in most water supplies, forming a variety of halogenated DBPs, such as THMs, HAAs, HANs, chloral hydrate and chloropicrin, as follows:



It is generally accepted that the reaction between chlorine and humic substances, a major component of NOM, is responsible for the production of organochlorine compounds during drinking-water treatment. Humic and fulvic acids show a high reactivity towards chlorine and constitute 50–90% of the total DOC in river and lake waters (Thurman, 1985). Other fractions of the DOC comprise the hydrophilic acids (up to 30%), carbohydrates (10%), simple carboxylic acids (5%) and proteins/amino acids (5%). The reactivity of carbohydrates and carboxylic acids towards chlorine is low, and they are not expected to contribute to the production of organochlorine compounds. However, hydrophilic acids such as citric acid and amino acids will react with chlorine to produce chloroform and other products and may contribute towards total organochlorine production (Larson & Rockwell, 1979).

Free chlorine reacts with water constituents by three general pathways: oxidation, addition and substitution (Johnson & Jensen, 1986). Chlorine can undergo an addition reaction if the organic compound has a double bond. For many compounds with double bonds,

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this reaction is too slow to be of importance in water treatment. The oxidation reactions with water constituents such as carbohydrates or fatty acids (e.g., oleic acid) are generally slow.

Most chlorine DBPs are formed through oxidation and substitution reactions. THMs have the general formula CHX_3 , where X can be Cl or Br. Chloroform may be produced through a series of reactions with functional groups of humic substances. The major functional groups of humic substances include acetyl, carboxyl, phenol, alcohol, carbonyl and methoxyl. The reactions proceed much more rapidly at high pH than at low pH.

Rook (1977) proposed resorcinol structures to be the major precursor structure in humic material for chloroform formation. In accordance with this hypothesis in the chlorination of terrestrial and aquatic humic substances, a series of intermediates were detected that contained a trichloromethyl group and that could be converted to chloroform by further oxidation or substitution reactions (Stevens et al., 1976).

However, the production of chlorinated compounds such as dichloropropanedioic acid, 2,2-dichlorobutanedioic acid, cyanogen chloride (CNCl), HANs or the cyano-substituted acids cannot be explained on the basis of resorcinol structures, and possible production pathways require protein-type precursors (De Leer et al., 1986). The reaction pathway for amino acids involves initial rapid formation of the monochloramine and dichloramine, which can react further to form aldehyde or HANs, respectively. Trehy et al. (1986) demonstrated the formation of chloral hydrate along with HANs after chlorination of amino acids by substitution reactions, and aldehydes were shown to be the oxidation products. Luknitskii (1975) provided a detailed chemistry of chloral hydrate formation.

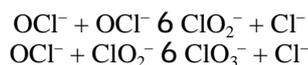
Christman et al. (1983) also identified chloroform, chloral hydrate, dichloroacetic acid (DCA), trichloroacetic acid (TCA) and 2,2-dichlorobutanedioic acid as the major products, accounting for 53% of the total organic halogen (TOX). A number of other minor products have been detected, including several chlorinated alkanolic acids and non-chlorinated benzene carboxylic acids. De Leer et al. (1985) extended these studies to incorporate chloroform intermediates, chlorinated aromatic acids and cyano-compounds as potential products

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in drinking-water. The presence of unhalogenated aldehydes and HANs in chlorinated natural waters can be attributed in part to the presence of amino acids or peptides in natural waters. Humic acids may also contribute to the presence of amino acids in natural waters, as they have amino acids associated with them either in a free or in a combined form. Several studies regarding the chlorination of amino acids have shown that the primary amino group on the amino acids can be converted to either an aldehyde or a nitrile group (Morris et al., 1980; Isaac & Morris, 1983). These studies indicate that with an equimolar amount of halogenating agent, the major product is an aldehyde. However, if an excess of halogenating agent is added, then the corresponding nitrile can also be formed, with the ratio of the aldehyde to nitrile formed increasing with pH.

Many treated waters contain not only chlorinated but also brominated compounds, such as bromoform. These compounds form because aqueous chlorine converts bromide in the water to hypobromous acid. The bromine can then react with the organic matter in the same way as hypochlorous acid to form various bromochlorinated DBPs. However, compared with hypochlorous acid, hypobromous acid is a weaker oxidant and stronger halogenating agent.

Chlorate, an inorganic by-product of chlorine, is formed in concentrated hypochlorite solutions during their production and storage through the following reactions (Gordon et al., 1997):



The first reaction proceeds at a much slower rate and is rate limiting, hence the generally observed second-order kinetics. Sodium hypochlorite is stored at pH greater than 12 to prevent rapid decomposition, and most of the sodium hypochlorite is present as hypochlorite ion. The average rate constant for the formation of chlorate is $85 \times 10^{-5} \text{ mol}^{-1} \text{ litre}^{-1} \text{ d}^{-1}$ (Gordon et al., 1995).

2.4.2 Chlorine dioxide reactions

The major chlorine dioxide by-products of concern are chlorite and chlorate. Chlorine dioxide reacts generally as an electron acceptor, and hydrogen atoms present in activated organic C–H or N–H structures are

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thereby not substituted by chlorine (Hoigne & Bader, 1994). Moreover, in contrast to chlorine, chlorine dioxide's efficiency for disinfection does not vary with pH or in the presence of ammonia, and it does not oxidize bromide. As opposed to chlorine, which reacts via oxidation and electrophilic substitution, chlorine dioxide reacts only by oxidation; this explains why it does not produce organochlorine compounds. In addition to this, chlorine dioxide is more selective in typical water treatment applications, as evidenced by its somewhat lower disinfectant demand as compared with chlorine.

Chlorine dioxide is generally produced by reacting aqueous (sodium) chlorite with chlorine (Gordon & Rosenblatt, 1996):



However, under conditions of low initial reactant concentrations or in the presence of excess chlorine, the reactant produces chlorate ion:



This reaction scenario is common in generators that overchlorinate to achieve high reaction yields based on chlorite ion consumption.

An alternative approach to chlorine dioxide generation is with hydrochloric acid (HCl), a process that results in less chlorate during production:



Chlorite ion is also produced when chlorine dioxide reacts with organics (Gordon & Rosenblatt, 1996):



Chlorine dioxide can also undergo a series of photochemically initiated reactions resulting in the formation of chlorate ion (Gordon et al., 1995).

While bromide is not generally oxidized by chlorine dioxide, bromate can be formed in the presence of sunlight over a wide range of

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pH values (Gordon & Emmert, 1996). Utilities need to be concerned with bromate ion in the chlorine dioxide treatment of drinking-water if the water contains bromide and is exposed to sunlight. Practically, this means minimizing exposure to sunlight when chlorine dioxide is applied in the presence of bromide ion. There appears to be a problem with chlorine dioxide producing odour-causing compounds at the tap. This has been linked to chlorine dioxide reacting with volatile organic compounds derived from new carpets and office products (Hoehn et al., 1990).

Hoigne & Bader (1994) described the kinetics of reaction between chlorine dioxide and a wide range of organic and inorganic compounds that are of concern in water treatment. Measured rate constants were high for nitrite, hydrogen peroxide, ozone, iodide, iron(II), phenolic compounds, tertiary amines and thiols. Bromide, ammonia, structures containing olefinic double bonds, aromatic hydrocarbons, primary and secondary amines, aldehydes, ketones and carbohydrates are unreactive under the conditions of water treatment. Chlorine dioxide rapidly oxidizes substituted phenoxide anions and many phenols, and second-order rate constants have been measured (Rav-Acha & Choshen, 1987).

2.4.3 Chloramine reactions

Chloramination of drinking-water produces THMs (if chloramine is formed by chlorination followed by ammonia addition), HAAs, chloral hydrate, hydrazine, cyanogen compounds, nitrate, nitrite, organic chloramines and 1,1-dichloropropanone (1,1-DCPN) (Dlyamandoglu & Selleck, 1992; Kirmeyer et al., 1993, 1995).

In the presence of even small quantities of organic nitrogen, it is possible for chloramination to produce organic chloramines. Several researchers have shown that monochloramine readily transfers its chlorine at a comparatively rapid rate to organic amines to form organohalogen amines (Isaac & Morris, 1983; Bercz & Bawa, 1986). Monochloramine was shown to cause binding of radiolabelled halogen to nutrients such as tyrosine and folic acid; the amount of binding varied with pH but was generally less at neutral pH than at higher pH (Bercz & Bawa, 1986). Organic chloramines are much weaker disinfectants than inorganic monochloramine but are indistinguishable by common analytical methods. Organic chloramine formation may

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necessitate changing chloramination conditions (e.g., ammonia and chlorine addition order, chlorine-to-ammonia ratios and contact time).

HANs and non-halogenated acetonitriles are produced when chloramines are reacted with humic materials and amino acids (Trehly et al., 1986). The reaction pathway for these products is quite complicated and very similar to that for chlorine, with many intermediates and by-products formed. In the case of aspartic acid, De Leer et al. (1986) demonstrated the presence of at least 11 other significant products.

2.4.4 Ozone reactions

Ozone has been shown to oxidize bromide to hypobromite and bromate, and hypochlorite to chlorate (Glaze et al., 1993; Siddiqui et al., 1995; Siddiqui, 1996).

Bromate generally forms through a combination of molecular ozone attack and reaction of bromide with free radical species. The molecular ozone mechanism does not account for hydroxyl radicals always formed as secondary oxidants from decomposed ozone during water treatment. Siddiqui et al. (1995) indicated that there is a radical pathway that is influenced by both pH and alkalinity. The hydroxyl radical and, to a lesser degree, the carbonate radical ($\text{CO}_3^{\cdot-}$) pathway may be more important than the molecular ozone pathway. Oxidants such as hydroxyl and carbonate radicals may interact with intermediate bromine species, leading to the formation of hypobromite radicals (BrO^{\cdot}), which eventually undergo disproportionation to form hypobromite and bromite (BrO_2^-). Bromate is then formed through oxidation of bromite by ozone. The radical mechanism for the formation of bromate includes two decisive reaction steps still involving molecular ozone: the formation of hypobromite and oxidation of bromite.

Bromate ion formed through reactions with molecular ozone contributes in the range of 30–80% to the overall bromate ion formation in NOM-containing waters (von Gunten and Hoigne, 1994). Siddiqui et al. (1995) reported up to 65% and 100% bromate ion formation through the radical pathway in NOM-free and NOM-containing waters, respectively. Differences in NOM-containing waters can be attributed to differences in the characteristics of the NOM present. A change in mechanism as a function of pH and the competitive

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roles of the free radical (one electron transfer) mechanism above pH 7 versus oxygen atom (two electron transfer) mechanism help explain both the large variations in bromate ion yield and the sensitivity to reactor design, concentration of organic precursors and ozone/bromide ion concentrations (Gordon, 1993).

The presence of bromide ion in a source water further complicates the reaction of ozone and leads to the formation of additional DBPs, such as bromoform, dibromoacetonitrile (DBAN) and dibromoacetone (DBAC) (Siddiqui, 1992; Amy et al., 1993, 1994).

2.5 Formation of organohalogen disinfectant by-products

Table 3 summarizes the DBPs identified as being formed from the use of chlorine, chlorine dioxide, chloramine and ozone.

The formation of organochlorine and organobromine compounds during drinking-water treatment is a cause of health concern in many countries. These compounds include THMs, HAAs, HANs, chloral hydrate, chloropicrin, acetaldehydes, halogenated furanones and other compounds.

2.5.1 Chlorine organohalogen by-products

Table 4 summarizes the range of concentrations of chlorinated DBPs formed from the reaction of chlorine with NOM, from various sources.

The major chlorination DBPs identified are THMs, HAAs, HANs, haloketones, chloropicrin and chloral hydrate. HAAs represent a major portion of the non-THM halogenated organic compounds (Miller & Uden, 1983; Reckhow & Singer, 1985). Many researchers have identified HANs and haloketones as other important DBPs (Trehly & Bieber, 1981; Miller & Uden, 1983; Oliver, 1983; Reckhow & Singer, 1985). According to an AWWARF (1991) study, for all eight utilities tested, 1,1,1-trichloropropanone (1,1,1-TCPN) was the more prevalent of the two measured haloketone compounds. In addition, Kronberg et al. (1988) identified the extremely mutagenic compound, MX.

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Table 3. Disinfectant by-products present in disinfected waters

Disinfectant	Significant organo-halogen products	Significant inorganic products	Significant non-halogenated products
Chlorine/hypochlorous acid	THMs, HAAs, HANs, chloral hydrate, chloropicrin, chlorophenols, N-chloramines, halofuranones, bromohydrins	Chlorate (mostly from hypochlorite use)	Aldehydes, cyanoalkanoic acids, alkanolic acids, benzene, carboxylic acids
Chlorine dioxide		chlorite, chlorate	unknown
Chloramine	HANs, cyanogen chloride, organic chloramines, chloramino acids, chloral hydrate, haloketones	nitrate, nitrite, chlorate, hydrazine	aldehydes, ketones
Ozone	bromoform, MBA, DBA, DBAC, cyanogen bromide	chlorate, iodate, bromate, hydrogen peroxide, hypobromous acid, epoxides, ozonates	aldehydes, ketoacids, ketones, carboxylic acids

Despite the fact that HAA formation and THM formation have very different pH dependencies, HAA formation correlates strongly with THM formation when treatment conditions are relatively uniform and when the water has a low bromide concentration (Singer, 1993). DBP formation and requisite chlorine dosage for disinfection strongly correspond to the concentration of TOC at the point of chlorine addition, suggesting that optimized or enhanced removal of organic carbon prior to chlorination will decrease the formation of DBPs.

HAA formation can be appreciable when drinking-water is chlorinated under conditions of slightly acidic pH and low bromide concentrations. The concentrations of DCA and TCA are similar to the concentrations of chloroform, and the total HAA concentration can be as much as 50% greater than the THM concentration in the finished water on a weight basis.

Table 4. Concentration range of chlorinated disinfectant by-products in drinking-water^a

DBPs	Peters et al. (1990); Peters (1991)	Krasner et al. (1989)	Nieminski et al. (1993)	Koch et al. (1991)	Reckhow et al. (1990)
THMs	3.1–49.5	30.0–44.0	17.0–51.0	49.0–81.0	201–1280
HAAs	<0.5–14.7	13.0–21.0	5.0–25.0	22.0–32.0	118–1230
HANs	0.04–1.05	2.5–4.0	0.5–5.0	2.0–2.6	3.0–12.0
Haloketones	–	0.9–1.8	0.2–1.6	1.0–2.0	4.8–25.3
Chlorophenols	–	–	0.5–1.0	–	–
Chloral hydrate	–	1.7–3.0	–	–	–
Chloropicrin	–	0.1–0.16	<0.1–0.6	–	–
TOC	1.7–5.6	2.9–3.2	1.5–6.0	2.5–3.0	4.8–26.6
Bromide	100–500	70–100	–	170–420	–

^a All values shown in : g/litre, except TOC (mg/litre).

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McGuire & Meadow (1988) reported that the national average THM concentration in the USA was 42 : g/litre for drinking-water utilities serving more than 100 000 persons, and only 3% of systems were above the US maximum contaminant level of 100 : g/litre. Amy et al. (1993) estimated that the national average THM concentration in the USA was 40 : g/litre, with an average TOC concentration of 3.0 mg/litre. The median annual average THM concentration found for utilities among the American Water Works Association's (AWWA) Water Industry Database was 35 : g/litre, as compared with 50 : g/litre for the non-database utilities (Montgomery Watson, Inc., 1993).

In Germany, 10% of the utilities produced disinfected drinking-water with a THM concentration above 10 : g/litre; the median annual average concentration was between 1 and 4 : g/litre, depending on raw water quality and size of facility (Haberer, 1994).

Total THM levels in treated drinking-water were reported in one survey in the United Kingdom (Water Research Centre, 1980): chlorinated water derived from a lowland river contained a mean level of 89.2 : g/litre, and that from an upland reservoir, 18.7 : g/litre. The study also showed that chlorinated groundwater was contaminated by THMs to a significantly lesser extent than chlorinated surface waters.

In a national survey of the water supplies of 70 communities serving about 38% of the population in Canada, conducted in the winter of 1976–1977, chloroform concentrations in treated water of the distribution system 0.8 km from the treatment plant, determined by the gas sparge technique, averaged 22.7 : g/litre. Levels of the other THMs were considerably lower, averaging 2.9 : g/litre for bromodichloromethane (BDCM), 0.4 : g/litre for dibromochloromethane (DBCM) and 0.1 : g/litre for bromoform. Using direct aqueous injection techniques, average concentrations of most of the THMs were higher (Health Canada, 1993).

Samples collected from the distribution systems of eight major cities in Saudi Arabia showed that THMs occurred in all the water supplies, at concentrations ranging between 0.03 and 41.7 : g/litre. Median total THM concentrations in several cities were higher during the summer than during the winter. In addition, THM concentrations were low in cities that did not mix groundwater and desalinated water.

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Brominated THMs dominated (with bromoform the most abundant) and existed at the highest concentration levels, whereas chloroform was the least prevalent compound. This is the opposite of the occurrence pattern found in almost all water distribution systems worldwide (Fayad, 1993).

The concentrations of chloral hydrate in drinking-water in the USA were summarized by IARC (1995) and varied from 0.01 to 28 : g/litre. The highest values were found in drinking-water prepared from surface water.

Chlorination of water as well as the combination of ozonation and chlorination can lead to the formation of chloropicrin (Merlet et al., 1985). In a study conducted for over 25 utilities, very low levels of chloropicrin were observed, and chlorination produced maximum concentrations of less than 2 : g/litre (AWWARF, 1991). The chloropicrin appeared to form slowly during the incubation period, with concentrations tending to level off at approximately 40 h.

Dichloroacetonitrile (DCAN) is by far the most predominant HAN species detected in water sources with bromide levels of 20 : g/litre or less. For sources with higher bromide levels (50–80 : g/litre), bromochloroacetonitrile (BCAN) was the second most prevalent compound. However, none of these sources had a DBAN concentration exceeding 0.5 : g/litre, including one source water that had a much higher bromide level, 170 : g/litre. Thus, it appears that ambient bromide concentration is not the only factor influencing the speciation of HAN compounds.

Chlorine can react with phenols to produce mono-, di- or trichlorophenols, which can impart tastes and odours to waters. The control of chlorophenolic tastes and odours produced when phenol-laden water is treated with chlorine is essential. The sources of phenolic compounds in water supplies are reported to be industrial wastes.

In natural waters, one of the most important sources of organic nitrogen is proteins and their hydrolysis products. The reaction of aqueous chlorine or monochloramine with organic nitrogen may form complex organic chloramines (Feng, 1966; Morris et al., 1980; Snyder

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& Margerum, 1982). The formation of *N*-chloramines resulting from the reaction of amines and chlorine has been reported (Weil & Morris, 1949; Gray et al., 1979; Morris et al., 1980). Likewise, the chlorination of amides has been reported (Morris et al., 1980).

Nieminski et al. (1993) reported the occurrence of DBPs for Utah (USA) water treatment plants. All plants used chlorine for primary and secondary disinfection purposes. Overall, THMs and HAAs represented 75% of the total specific DBPs analysed for the survey; however, total DBPs represented only 25–50% of the TOX concentration. THMs constituted 64% of the total DBPs by weight; HAAs were 30% of the total DBPs by weight and approximately one-half of the total THM concentrations. (However, in some waters, HAA concentrations may approach or possibly exceed THM concentrations.) HANs, halo ketones, chlorophenols and chloropicrin represented 3%, 1.5%, 1.0% and 0.5%, respectively, of the total surveyed DBPs.

The occurrence of DBPs in drinking-waters in the USA was evaluated at 35 water treatment facilities that had a broad range of source water qualities and treatment processes (Krasner et al., 1989). THMs were the largest class of DBPs, and HAAs were the next most significant class. Aldehydes, by-products of ozonation, were also produced by chlorination. Over four quarterly sampling periods, median total THM concentrations ranged from 30 to 44 : g/litre, with chloroform, BDCM, DBCM and bromoform ranges of 9.6–15, 4.1–10, 2.6–4.5 and 0.33–0.88 : g/litre, respectively. Median total HAA concentrations ranged from 13 to 21 : g/litre, with TCA, DCA, monochloroacetic acid (MCA), dibromoacetic acid (DBA) and monobromoacetic acid (MBA) ranges of 4.0–6.0, 5.0–7.3, <1–1.2, 0.9–1.5 and <0.5 : g/litre, respectively.

Concentrations of DCA and TCA measured in various water sources have been summarized by IARC (1995): in Japan, chlorinated drinking-water contained 4.5 and 7.5 : g of DCA and TCA per litre, respectively; rainwater in Germany contained 1.35 : g of DCA per litre and 0.1–20 : g of TCA per litre, whereas groundwater contained 0.05 : g of TCA per litre; in Australia, a maximum concentration of 200 : g/litre was found for DCA and TCA in chlorinated treated water; and chlorinated water in Switzerland contained 3.0 : g of TCA per litre.

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In a survey of 20 drinking-waters prepared from different source waters in the Netherlands, HAAs were found in all drinking-waters prepared from surface water, whereas they could not be detected in drinking-waters prepared from groundwaters. Brominated acetic acids accounted for 65% of the total acid concentration (Peters et al., 1991). In another survey of Dutch drinking waters, the average concentration of dihaloacetonitriles was about 5% of the average THM concentration (Peters, 1990).

2.5.2 Chloramine organohalogen by-products

Chloramine treatment practice involves three potential approaches: free chlorine followed by ammonia addition, ammonia addition followed by chlorine addition (*in situ* production) and pre-formed (off-line formation) chloramines. Generally, the objective is monochloramine formation. Chlorine followed by ammonia is a common approach, and, during the free-chlorine period, DBP formation may mimic that of chlorine. Chloramination results in the production of THMs (predominantly formed by chlorination followed by ammonia addition), HAAs, chloral hydrate, hydrazine, cyanogen compounds, organic chloramines and 1,1-DCPN (Diyamandoglu & Selleck, 1992; Singer, 1993; Kirmeyer et al., 1993, 1995). Chloramination significantly reduces but does not eliminate THM formation; cyanogen chloride and TOX represent the major DBP issues with respect to chloramines.

Scully et al. (1990) identified chloramino acids such as *N*-chloroglycine, *N*-chloroleucine and *N*-chlorophenylalanine as by-products after chlorination of water containing nitrogen or after chloramination.

2.5.3 Chlorine dioxide organohalogen by-products

Chlorine-free chlorine dioxide does not form THMs (Noack & Doerr, 1978; Symons et al., 1981). Several studies show that the TOX formed with chlorine dioxide is 1–15% of the TOX formed with chlorine under the same reaction conditions (Chow & Roberts, 1981; Symons et al., 1981; Fleischacker & Randtke, 1983).

Treatment of phenol-laden source waters with chlorine dioxide does not produce the typical chlorophenolic taste and odour compounds

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that are produced when the water is treated using chlorine and is effective in removing existing tastes and odours of this type.

2.5.4 Ozone organohalogen by-products

Ozonation of drinking-water containing bromide ion has been shown to produce hypobromous acid/hypobromite, with hypobromite ion serving as an intermediate to bromate formation. In the presence of NOM, hypobromous acid produces a host of brominated organic compounds, such as bromoform, MBA, DBA, DBAN, cyanogen bromide and DBAC (Glaze et al., 1993; Siddiqui & Amy, 1993). Cavanagh et al. (1992) and Glaze et al. (1993) reported the identification of bromohydrins, a new group of labile brominated organic compounds from the ozonation of a natural water in the presence of enhanced levels of bromide. However, results by Kristiansen et al. (1994) strongly suggest that the bromohydrins, such as 3-bromo-2-methyl-2-butanol, in extracts of unquenched disinfected water are artefacts formed from the reaction of excessive hypobromous acid with traces of olefins in the extraction solvents and not novel DBPs.

Table 5 compares the median concentrations of various DBPs after ozonation and chlorination.

2.6 Formation of inorganic disinfectant by-products

Although organic DBPs have been the subject of study over a longer time frame, the formation of many inorganic by-products is coming under increasing scrutiny.

2.6.1 Chlorine inorganic by-products

Chlorite and chlorate are inorganic by-products formed in some chlorine solutions. This is of interest because many small drinking-water utilities use hypochlorite solutions as a source of free chlorine for disinfection. Bolyard & Fair (1992) examined the occurrence of chlorate in samples of untreated source water, drinking-water and hypochlorite solutions from 14 sites that use hypochlorite solutions. The hypochlorite solutions used were found to contain significant levels of chlorate. Chlorite and bromate were also found in hypochlorite solutions from these same water utilities. Chlorate was present in drinking-water, either as a manufacturing by-product or from

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Table 5. Median concentrations of organic disinfectant by-products in drinking-water

DBPs	Median concentration (: g/litre): chlorination ^a	Median concentration (: g/litre): ozonation ^b
THMs	40	<1.0
Chloroform	15	–
BDCM	10	–
DBCM	4.5	–
Bromoform	0.57	<1.0
HANs	2.5	<1.0
TCAN	<0.012	–
DCAN	1.1	–
BCAN	0.58	–
DBAN	0.48	<1.0
Haloketones	0.94	–
DCPN	0.46	–
TCPN	0.35	–
HAAs	20	<5.0
MCA	1.2	–
DCA	6.8	–
TCA	5.8	–
MBA	<0.5	<1.0
DBA	1.5	<5.0
Aldehydes	7.8	45
Formaldehyde	5.1	20
Acetaldehyde	2.7	11
Glyoxal	–	9
Methylglyoxal	–	5
Chloral hydrate	3.0	–
Ketoacids	–	75
Trichlorophenol	<0.4	–

^a Krasner et al. (1989).

^b Siddiqui et al. (1993).

decomposition reactions occurring during storage. Approximately 0.2 mg of chlorate per litre was observed in water following the addition of chlorine as sodium hypochlorite at a dose sufficient to maintain a residual of 0.45 mg/litre (Andrews & Ferguson, 1995). The concentration of chlorite in commercial bleach solutions typically ranges from 0.002 to 0.0046 mol/litre; similarly, the chlorate concentration ranges from about 0.02 to 0.08 mol/litre (Gordon et al., 1995).

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A detailed study by Bolyard & Fair (1992) demonstrated that hypochlorite solutions used to disinfect drinking-water contain significant levels of chlorite and chlorate. The concentration of chlorite ranged from <2 to 130 mg/litre for free available chlorine concentrations ranging from 3 to 110 g/litre. The concentration of chlorate varied over the range 0.19–50 g/litre, with a median of 12 g/litre. These solutions also contained bromate levels ranging from <2 to 51 mg/litre. The concentrations of chlorate in treated source waters ranged from 11 to 660 g/litre. In another study involving 25 samples from plants using gaseous chlorine, no chlorate was detected, indicating that the use of gaseous chlorine does not produce chlorate (Bolyard & Fair, 1992). Nieminski et al. (1993) measured chlorate and chlorite for six water treatment plants that use liquid chlorine (i.e., hypochlorite) and found chlorate concentrations ranging from 40 to 700 g/litre, with no chlorite or bromate detected in finished waters. These chlorate concentrations may be attributed to high concentrations of chlorate, ranging from 1000 to 8000 mg/litre, detected in a bleach used for disinfection and resulting from the decomposition of hypochlorite stock solution. However, no chlorite or chlorate was detected in any of the samples of finished water of the treatment plants that apply gaseous chlorine. Chlorate formation is expected to be minimal in low-strength hypochlorite solutions freshly prepared from calcium hypochlorite, because of the low hypochlorite concentration and only mildly alkaline pH.

2.6.2 Chloramine inorganic by-products

Inorganic by-products of chloramination include nitrate, nitrite, hydrazine and, to some extent, chlorate (Dlyamandoglu & Selleck, 1992; Kirmeyer et al., 1995).

2.6.3 Chlorine dioxide inorganic by-products

The major inorganic by-products of chlorine dioxide disinfection have been identified as chlorite and chlorate. Andrews & Ferguson (1995) measured a chlorate concentration of 0.38 mg/litre when a chlorine dioxide residual of 0.33 mg/litre was maintained. The application of chlorine dioxide produces about 0.5–0.7 mg of chlorite and 0.3 mg of chlorate per mg of chlorine dioxide consumed or applied (Andrews & Ferguson, 1995).

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2.6.4 Ozone inorganic by-products

When bromide or iodide ions are present in waters, some of the halogen-containing oxidants that can be produced during ozonation include free bromine, hypobromous acid, hypobromite ion, bromate ion, free iodine, hypoiodous acid and iodate ion.

During the oxidation or chemical disinfection of natural waters containing bromide ion with ozone, bromate ion can be formed at concentrations ranging from 0 to 150 : g/litre under normal water treatment conditions (Siddiqui, 1992). Chlorate formation with an initial total chlorine concentration of 0.6 mg/litre was evaluated at pH levels of 8.0, 7.0 and 6.0, and chlorate concentrations ranging from 10 to 106 : g/litre were formed after ozonation (Siddiqui et al., 1996a).

It has been reported that ozone reacts with many metal ions and with cyanide ion (Hoigne et al., 1985; Yang & Neely, 1986). Bailey (1978) discussed the formation of ozonates, compounds of metal cations having the general formula $M^+O_3^-$. Hydrogen peroxide has been identified as a by-product of ozonation of organic unsaturated compounds (Bailey, 1978).

Table 6 provides the range of bromate concentrations normally encountered in drinking-waters with a variety of source water characteristics after ozonation.

2.7 Formation of non-halogenated organic disinfectant by-products

2.7.1 Chlorine organic by-products

Lykins & Clark (1988) conducted a 1-year pilot plant study of the effects of ozone and chlorine and determined that the concentration of aldehydes increased by 144% upon ozonation. In the chlorinated stream, the concentration of these aldehydes increased by 56%. This study indicates that aldehyde formation, although greater with ozone, is not unique to ozonation, but is associated with chlorination and other oxidants as well.

Table 6. Summary of bromate ion formation potentials in different source waters under different conditions following ozonation

<i>N</i> ^a	Bromide (: g/litre)	Ozone (mg/litre)	pH	Alkalinity (mg/litre)	DOC (mg/litre)	Bromate (: g/litre)	Reference
18	10–800	1–9.3	5.6–9.4	20–132	2.2–8.2	<5–60	Krasner et al. (1992)
4	60–340	3–12	6.5–8.5	90–230	3–7	<5–40	Siddiqui & Amy (1993)
28	10–100	2–4	6.8–8.8	20–120	0.3–11	<5–100	Amy et al. (1993, 1994)
4	12–37	0–3.97	7.8	N/A	N/A	<7–35	Hautman & Bolyard (1993)
1	500	2.3–9.5	7.2–8.3	N/A	N/A	13–293	Yamada (1993)
23	12–207	0.3–4.3	5.7–8.2	14–246	0.5–6.8	<2–16	Legube et al. (1993)
8	107–237	1–5	6.8–8.0	N/A	2–5	<5–50	Kruithof & Meijers (1993)

^a N = number of sources studied.

2.7.2 Chloramine organic by-products

When Suwannee River (USA) fulvic acid was reacted with aqueous solutions of ¹⁵N-labelled chloramine and ¹⁵N-labelled ammonia, lyophilized products exhibiting nuclear magnetic resonances between 90 and 120 ppm were observed, denoting the formation of amides, enamines and aminoquinones (Ginwalla & Mikita, 1992). This represents evidence for the formation of nitrogen-containing compounds from the chloramination of NOM in natural waters.

Amino acids, peptides and amino sugars were chlorinated under various chlorine/nitrogen ratios (Bruchet et al., 1992). Six natural amino acids (alanine, methionine, valine, phenylalanine, leucine and isoleucine) were shown to induce tastes and odours at concentrations in the range of 10–20 : g/litre. Detectable odours were consistently induced in a multicomponent mixture containing each of these amino acids after a 2-h contact time with chlorine. Investigation of the by-products indicated that the odours generated were systematically linked to the aliphatic aldehydes formed. The peptides investigated had varying degrees of odour formation potential, while the amino sugars did not impart any odour. Chlorinous odours occasionally detected during these experiments were found to be due to organic chloramines and other oxidation by-products.

2.7.3 Chlorine dioxide organic by-products

Gilli (1990) showed the formation of carbonyl compounds (34 : g/litre) such as *n*-valeraldehyde (7–15 : g/litre), formaldehyde (3.4–9 : g/litre), acetaldehyde (4.5 : g/litre) and acetone (3.2 : g/litre) after using chlorine dioxide.

2.7.4 Ozone organic by-products

Ozone aliphatic oxidation products from organic impurities in water are usually acids, ketones, aldehydes and alcohols. So-called ultimate oxidation products of organic materials are carbon dioxide, water, oxalic acid and acetic acid. However, ozonation conditions generally employed in treating drinking-water are rarely sufficient to form high concentrations of these ultimate products.

When source waters containing NOM and unsaturated organic compounds are ozonated, ozonides, peroxides, diperoxides, triperoxides and peroxy acids, for example, can be produced. The limited research that has been conducted in aqueous solutions indicates that these intermediates decompose readily in water to form products such as aldehydes, ketones, carboxylic acids and ketoacids.

Coleman et al. (1992) identified numerous compounds in addition to the following in ozonated humic samples: monocarboxylic acids up to C-24, dicarboxylic acids up to C-10, ketoacids, furan carboxylic acids, and benzene mono-, di- and tricarboxylic acids. Among the various aldehydes, Paode et al. (1997) found four (formaldehyde, acetaldehyde, glyoxal and methylglyoxal) to be dominant. Table 7 provides a range of concentrations for aldehydes from the ozonation of a variety of source waters.

2.8 Influence of source water characteristics on the amount and type of by-products produced

The extensive literature pertaining to DBP levels in disinfected source waters and control of DBPs by various treatment processes attests to the wide variety of factors influencing DBP formation and the complex interrelationships between these factors. Variables including the concentration and characteristics of precursor material, pH, chlorine concentration, bromide level, presence of chlorine-demanding substances such as ammonia, temperature and contact time all play a role in DBP formation reactions.

2.8.1 Effect of natural organic matter and UV absorbance at 254 nm

NOM consists of a mixture of humic substances (humic and fulvic acids) and non-humic (hydrophilic) material. Both the amount (as indicated by TOC or UVA_{254}) and the character (as described by UVA_{254}) of NOM can affect DBP formation. NOM provides the precursor material from which organic DBPs are formed; consequently, increasing concentrations of NOM lead to increasing concentrations of by-products. This relationship has led to the use of TOC and UVA_{254} measurements as surrogate parameters for estimating the extent of DBP formation.

Table 7. Effect of ozone dose and TOC on non-halogenated organic by-products

Ozone dose (mg/litre)	TOC (mg/litre)	Formal (: g/litre)	Acetal (: g/litre)	Glyoxal (: g/litre)	Methyl-glyoxal (: g/litre)	Reference
1.2–4.4	2.66	8–24	2–4	4–11	4–15	Miltner et al. (1992)
1.0–9.2	1.0–25.9	3–30	7–65	3–15	3–35	Weinberg et al. (1993)
5.5–28.5	5.4–17.4	58–567	6–28	15–166	17–54	Schechter & Singer (1995)

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The removal of NOM is strongly influenced by those properties embodying the size, structure and functionality of this heterogeneous mixture. The humic acids are more reactive than fulvic acids with chlorine (Reckhow et al., 1990) and ozone, in terms of both oxidant/disinfectant demand and DBP formation. Processes such as coagulation, adsorption and membrane filtration are separation processes that remove NOM intact, while ozonation transforms part of the NOM into biodegradable organic matter, potentially removable by biofiltration. Coagulation preferentially removes humic/higher molecular weight NOM; the selectivity of membranes for NOM removal is largely dictated by the molecular weight cutoff of the membrane; the use of granular activated carbon (GAC) requires a significant empty bed contact time; biofiltration can remove only the rapidly biodegradable NOM fraction.

In an investigation of the nature of humic and fulvic acids isolated from a variety of natural waters, Reckhow et al. (1990) found that the fulvic fractions had a lower aromatic content and smaller molecular size than the humic fractions. UV absorbance was correspondingly higher for the humic fractions, owing to the higher aromatic content and larger size. These researchers also found that for all of the organic material investigated, the production of chloroform, TCA, DCA and DCAN was higher upon chlorination of the humic fractions than upon chlorination of the corresponding fulvic fractions. These findings support the findings of other researchers and show that the UV absorbance measurement is an indicator of the nature of the precursor material present in a sample. This measurement, in conjunction with the TOC (or DOC) measurement, can be employed in the evaluation of data to provide an indication of the reactivity of NOM towards forming DBPs.

The reaction of ozone with NOM can occur directly or by radical processes. The disappearance of disinfecting chemical is influenced by the type and concentration of NOM present in natural waters. Direct consumption of these chemicals is greater when the UV absorbance (due to electrophilic and nucleophilic sites of NOM) of the source water is significant, resulting in decreased DBP formation potential.

It appears that the nature of the organic material in a source water may have some impact on the relative concentrations of THMs and HAAs formed upon chlorination. Treatment techniques that lower the

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levels of DOC without affecting bromide levels have been implicated in a shift from chlorinated to brominated THM compounds. This is of concern because the theoretical risk to humans varies for the individual THMs, with the brominated species generally being of more concern (Bull & Kopfler, 1991).

2.8.2 *Effect of pH*

The impact of pH on THM concentrations has been reported by a number of researchers since THMs in drinking-water first came to the attention of the water industry (Stevens et al., 1976; Lange & Kawczynski, 1978; Trussell & Umphres, 1978). More recently, the impact of pH on a number of other chlorination by-products has been reported (Miller & Uden, 1983; Reckhow & Singer, 1985). The rate of THM formation increases with the pH (Stevens et al., 1976). Kavanaugh et al. (1980) reported a 3-fold increase in the reaction rate per unit pH.

In general, increasing pH has been associated with increasing concentrations of THMs and decreasing concentrations of HAAs (pH primarily impacting TCA), HANs and haloketones. The concentrations of TCA tend to be higher in waters with pH levels less than 8.0 than in waters with pH levels greater than 8.0; a less marked trend is observed for DCA. Other researchers have reported similar findings with respect to the pH dependency of HAA concentrations. For example, Stevens et al. (1976) found that TCA concentrations were significantly lower at a pH of 9.4 than at pH levels of approximately 5 and 7. TCA was by far the most predominant of the measured HAA species at six of the eight utilities surveyed. Carlson & Hardy (1998) reported that at pH levels greater than 9.0, THM formation decreased with increasing pH. It is possible that the shift in chlorine species from hypochlorous acid to hypochlorite affects THM formation during short reaction times.

AWWARF (1991) observed no relationship between pH and the concentrations of THMs at eight utilities over time, suggesting that although THM concentrations for a particular water are known to be pH dependent, factors other than pH influence THM concentrations over a variety of source waters. Nieminski et al. (1993) reported that treatment plants with a pH of about 5.5 in finished water produced equal amounts of THMs and HAAs, whereas plants with pHs greater

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than 7.0 in finished water produced higher amounts of THMs as compared with HAAs.

No strong relationship has been observed between HAN concentration and pH over time. Within the approximate pH range 7–8.5, HAN concentrations increased slightly over time. In general, a trend of decreasing HAN concentrations with increasing pH would be expected, since these compounds are known to undergo base-catalysed hydrolysis and have been identified as intermediates in the formation of chloroform (Reckhow & Singer, 1985). Therefore, these compounds may be unstable in the presence of free chlorine or under basic conditions. In general, after an initial formation period, HAN and halo ketone concentrations level off or begin to decline over the remainder of the reaction period. This indicates that base-catalysed hydrolysis may not be a significant mechanism of reaction for the relatively low pH sources.

Stevens et al. (1989) evaluated the effects of pH and reaction time (4, 48 and 144 h) on the formation of chloral hydrate. Chloral hydrate formation increased over time at pH 5 and 7, whereas chloral hydrate that had formed within 4 h at pH 9.4 decayed over time at the elevated pH.

The pH of the source water can also affect the formation of by-products after chloramine addition. The disproportionation of mono-chloramine, which is an important reaction leading to an oxidant loss, has been shown by several researchers to be catalysed by hydrogen ion, phosphate, carbonate and silicate (Valentine & Solomon, 1987).

Humic acids have shown reaction rates with chlorine dioxide that increased by a factor of 3 per pH unit (pH 4–8) (Hoigne & Bader, 1994).

In addition to the impact of pH on THM and HAA formation noted above, overall TOX formation decreases with increasing pH. Many of the halogenated DBPs tend to hydrolyse at alkaline pH levels (>8.0) (Singer, 1994a). This has significant implications, for example, for precipitative softening facilities.

pH has a strong effect on aldehyde formation (Schechter & Singer, 1995). Higher ozonation pH values produced lower amounts of

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aldehydes, supporting the theory that these DBPs are formed primarily through the direct molecular ozone reaction pathway, as opposed to the radical pathway. These results may also reflect greater destruction of aldehydes by hydroxyl radicals at elevated pH levels.

2.8.3 *Effect of bromide*

The presence of bromide ion during water treatment disinfection can lead to the formation of DBPs such as brominated organics and bromate ion. Low but significant levels of bromide, the ultimate precursor to bromate and other brominated compounds, may occur in drinking-water sources as a result of pollution and saltwater intrusion in addition to bromide from natural sources. An understanding of the sources and levels of bromide ion in different source waters is crucial for an understanding of the bromate ion formation potential in drinking-waters. There are no known treatment techniques available for economically removing bromide ion present in source waters during drinking-water treatment.

The impact of bromide on the speciation of DBPs within a class of compounds such as THMs or HAAs has been discussed by Cooper et al. (1983, 1985) and Amy et al. (1998). Rook et al. (1978) reported that bromine is more effective than chlorine in participating in substitution reactions with organic molecules; furthermore, precursor materials may differ in their susceptibility to bromination versus chlorination reactions. Hypobromous acid formed from bromide may also react with ammonia to form bromamines (Galal-Gorchev & Morris, 1965).

2.8.4 *Effect of reaction rates*

After chlorine addition, there is a period of rapid THM formation for the initial few hours (e.g., 4 h), followed by a decline in the rate of THM formation, suggesting fast and slow NOM reactive sites. Many authors have indicated that the concentration of chloroform appears to increase slowly even after 96 h, suggesting that as long as low concentrations of free chlorine are present, chloroform continues to form. Bromochlorinated THM species have been found to form more rapidly than chloroform. Further data from many sources indicate that bromoform formation slows at approximately 7–8 h and levels off almost completely after 20 h (AWWARF, 1991; Koch et al., 1991).

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The same general kinetic trend observed for THMs also appears to apply to HAAs. A period of rapid formation occurs during the first 4–8 h, followed by a reduction in the formation rate. In general, for most sources, concentrations of chlorinated HAAs appear to slowly increase even after 96 h, while the formation of DBA levels off after about 18–20 h.

Miller & Uden (1983) observed that nearly 90% of the final concentrations of THMs, TCA and DCA form within the first 24 h of chlorine addition to waters containing NOM. Reckhow et al. (1990) found that although waters containing precursor materials isolated from six different water sources differed in their yields of chlorinated organic by-products, the formation curves for chloroform, TCA and DCA had the same general shapes for all six precursor materials. Some researchers have suggested that DCA may be an intermediate in TCA formation; however, for all eight source waters studied, both DCA and TCA concentrations increased or remained stable throughout the 96-h reaction period, suggesting that DCA was an end-product (AWWARF, 1991). Carlson & Hardy (1998) indicated that HAA formation followed a pattern similar to that of THM formation. As with the THMs, HAA formation rate appeared to be rapid for the first 30 min; after 30 min, HAAs formed at nearly a constant rate in four of the source waters studied.

Different trends were observed in the HAN concentrations of different source waters. For two source waters, HAN levels formed rapidly for the first 8 h and continued to increase slowly or levelled off after 96 h (AWWARF, 1991). DBAN levels remained relatively stable over the 96 h, as did BCAN and DCAN levels. For other sources, levels of HANs consisting mostly of DCAN increased rapidly up to 4–8 h and began to decline by the end of the 96-h period. For these sources, BCAN appeared to be slightly more stable than DCAN.

Very low levels of chloropicrin formation have been observed by many researchers (AWWARF, 1991). The highest concentration observed was 4.0 : g/litre. Chloropicrin appears to form slowly during the incubation period, with concentrations tending to level off at approximately 40 h.

2.8.5 *Effect of temperature*

The formation rates of THMs, HAAs, bromate ion and HANs have been shown to increase with temperature (AWWARF, 1991; Siddiqui & Amy, 1993). Both haloketone and chloropicrin levels were found to be higher at a lower temperature, while the concentrations of other DBP species were similar or not significantly different. These results suggest that a higher temperature allows for more rapid progression of the transformation of haloketones to other by-products. In studies on the effect of temperature on THMs, Peters et al. (1980) found an Arrhenius dependency between the rate constant and temperature with an activation energy of 10–20 kJ/mol.

The impact of temperature on THMs was strongest at longer contact times (Carlson & Hardy, 1998). On a conceptual basis, it may be that rapidly forming compounds are more reactive and form DBPs regardless of temperature. On the other hand, slowly forming compounds require higher activation energy, and an increase in the temperature supplies the energy. In addition to reaction kinetics, the temperature of a source water can also affect disinfection efficiency. The biocidal effectiveness of monochloramine is significantly less than that of free chlorine and is dependent on temperature, pH and residual concentration.

2.8.6 *Effect of alkalinity*

Although pH is a very influential variable and alkalinity affects pH, alkalinity itself does not appear to directly affect the formation of THMs and HAAs (by chlorination) and has only a slight effect on aldehydes and other organic by-products following ozonation (Andrews et al., 1996). However, the majority of studies on the effect of alkalinity on the formation of bromate during ozonation indicate that increased alkalinity increases bromate formation (Siddiqui et al., 1995). The quantity of aldehydes produced remains approximately constant for similar changes in alkalinity and pH; however, deviation from equivalent changes in pH and alkalinity results in increased aldehyde concentrations. Therefore, conditions of high alkalinity and low pH or low alkalinity and high pH produce greater quantities of aldehydes than do intermediate values of these parameters (Andrews et al., 1996).

2.9 Influence of water treatment variables on the amount and type of by-products produced

Since DBPs are formed by all of the above chemical disinfectants, the adoption of alternative disinfectants for DBP control often means only a trade-off between one group of DBPs and another. The most effective DBP control strategy is organic precursor (NOM) removal through enhanced coagulation, biofiltration, GAC or membrane filtration. There has been little success with bromide removal. Other DBP control options include water quality modifications — for example, acid or ammonia addition for bromate minimization.

2.9.1 Effect of ammonia

The presence of ammonia in source waters during disinfection can cause chlorine and ozone demand and participation in the formation of by-products such as nitrate, cyanogen chloride and other nitrogenous compounds.

Ammonia also does not consume chlorine dioxide. In contrast to chlorine, chlorine dioxide can therefore be considered as a virucide when ammonia is present. This might be one of the historical reasons why chlorine dioxide has been adopted as a disinfectant by some treatment plants using well oxidized waters but containing changing ammonia concentrations. The addition of ammonia has been shown to reduce the formation of bromate after ozonation (Siddiqui et al., 1995), and the ammonia has been shown to participate in the formation of HANs and cyanogen bromide (CNBr) (Siddiqui & Amy, 1993).

The growth of nitrifying bacteria is a potential problem in chloraminated water supplies or chlorination of sources containing nitrogen. In a study conducted by Cunliffe (1991), nitrifying bacteria were detected in 64% of samples collected from five chloraminated water supplies in South Australia and in 21% of samples that contained more than 5 mg of monochloramine per litre. Increased numbers of the bacteria were associated with monochloramine decay within the distribution systems.

2.9.2 *Effect of disinfectant dose*

Chlorine dose is a factor affecting the type and concentration of DBPs formed. The THM level rises with increasing chlorine dose (Kavanaugh et al., 1980). However, there is some disagreement regarding the quantitative relations between chlorine concentration and THM levels (or the rate of THM production). Most investigators found a linear relationship between chlorine consumption and THM production, with an order of reaction greater than or equal to unity (Trussell & Umphres, 1978; Kavanaugh et al., 1980). However, it is also possible that the order of reaction changes during the course of the reaction.

Reckhow & Singer (1985) found that the concentration of DBP intermediates such as DCAN and 1,1,1-TCPN formed after 72 h of reaction time was dependent on chlorine dose. DCAN, which was measured at a concentration of approximately 5 : g/litre at a chlorine dose of 10 mg/litre, was not detected in samples dosed with 50 mg of chlorine per litre. The concentration of chloroform was about 150 : g/litre in a sample dosed with 10 mg of chlorine per litre but was approximately 200 : g/litre in a sample dosed with 20 mg of chlorine per litre. Thus, it is imperative to have uniform chlorine doses for performing DBP formation kinetic measurements.

Since chloramine residuals are longer-lasting than free chlorine residuals, the doses for each set of chlorinated and chloraminated samples will be different in order to achieve the prescribed target residual. The disappearance of chloramines can be explained approximately by a second-order reaction. However, as the chlorine dose increased, the observed rate constant was found to decrease, then increased after reaching a minimum value (Diyamandoglu & Selleck, 1992). Below the chlorine dose at the minimum value of the observed rate constant, the rate constant was proportional to the 1.4 power of the chlorine dose, regardless of the ammonia concentration (Yamamoto et al., 1988).

2.9.3 *Effect of advanced oxidation processes*

Water utilities can add treatment processes that remove DBP precursors or DBPs. Many utilities will be using both approaches. The

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hydrogen peroxide/UV process, an advanced oxidation process, offers small water utilities a treatment process with the potential to provide primary disinfection and a method of DBP control (Symons & Worley, 1995). This process has been shown to oxidize dissolved organic halogens and decrease TOC. TOC removal as a function of UV dose has also been demonstrated by Worley (1994), with TOC removals of between 0% and 80%. Andrews et al. (1996) evaluated the effect of the hydrogen peroxide/UV process on THM formation and concluded that this process is only slightly effective in reducing the formation of DBPs. However, using hydrogen peroxide at 1 mg/litre in combination with UV effectively reduced or prevented the formation of aldehydes. Other advanced oxidation processes (e.g., hydrogen peroxide/ozone, ozone/UV) involving hydroxyl (and hydroperoxyl) radical formation may provide similar opportunities.

2.9.4 Effect of chemical coagulation

Enhanced coagulation and softening will remove TOC. Enhanced coagulation is characterized by coagulant doses greater than those required for optimum turbidity removal; as an alternative to higher doses, a combination of acid (pH depression) and coagulant addition can be practised.

All organic DBPs were reduced by the addition of commonly used coagulants. Iron-based coagulants, such as ferric chloride, were consistently more effective than alum in removing NOM (Crozes et al., 1995). Alum coagulation removed all DBP precursors to a significant extent. The percentage removals showed the same trends as, but were not identical to, the percentage removals of TOC and UV absorbance. UV absorbance was removed to a somewhat greater extent than TOC. Hence, TOC and UV absorbance can serve as surrogate parameters for DBP formation potential. A fairly good correlation was observed between the ratio of HAAs to THMs and the ratio of UV absorbance to TOC, indicating that the relative concentrations of HAAs and THMs do to some extent depend on the nature of the precursor material. However, more data from waters of different qualities would be required to evaluate the validity of this relationship.

The effectiveness of coagulants in removing DBP precursors is dependent upon the molecular size of the dissolved organic matter. Normally, higher molecular weight fractions are effectively removed

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through coagulation. In a study conducted by Teng & Veenstra (1995), water containing dissolved organic matter with molecular weights in the range 1000–10 000 daltons generally produced the largest amounts of THMs and HAAs under conditions of free chlorination. Coagulation and ozonation shift a proportionately greater amount of the THM and HAA formation potential to the smallest molecular weight range (<1000 daltons).

Coagulation and filtration remove NOM but not bromide, hence increasing the ratio of bromide to TOC. As a result, the subsequent use of chlorine generally favours the formation of brominated organic DBPs.

2.9.5 Effect of pre-ozonation

Several studies of ozone oxidation followed by chlorination showed increased, rather than decreased, levels of THMs (Trussell & Umphres, 1978). This is attributed, at least partially, to the formation of aldehydes by ozonation. Another possibility is hydroxylation of aromatic compounds to produce *m*-dihydroxy aromatic derivatives, which are known THM precursors (Lykins & Clark, 1988). Although the aldehydes produced contain polar groupings, they are nevertheless not easily removed during the flocculation step by complexation with aluminium or iron salts. A convenient and more appropriate method for the removal of the aldehydes formed during ozonation is the incorporation of a biological treatment step (biofiltration) in the water treatment process following ozone oxidation.

Pre-ozonation can have both positive and negative effects on DBP formation. Pre-ozonation with typical water treatment dosages and bicarbonate levels has been shown to remove TCA and DCAN precursors. However, such treatment can result in no net change in the DCA precursors and may lead to an increase in 1,1,1-TCPN precursors (Reckhow & Singer, 1985). According to Teng & Veenstra (1995), pre-ozonation resulted in enhanced formation of DCA during chlorination and chloramination in the presence of precursors in the <1000 dalton molecular weight range. They also indicated that pre-ozonation plus chloramination controlled the overall production of THMs and HAAs. However, the use of pre-ozonation coupled with free chlorination

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increased the yield of DCA for both the hydrophilic and hydrophobic fractions of NOM as compared with free chlorination alone.

With ozone–chlorine treatment, chloral hydrate formation can be enhanced. This behaviour, which has also been observed for DCA, suggests that the reaction that produces chloral hydrate is accelerated under the conditions of ozonation in combination with prechlorination and warm water temperatures (LeBel et al., 1995).

Ozonation in the presence of traces of hypochlorite ion can form inorganic by-products such as chlorate. Siddiqui et al. (1996a) showed that if there is any residual chlorine present, ozone can potentially oxidize hypochlorite ion to chlorate.

Coleman et al. (1992) suggested that brominated MX analogues and other mixed bromochlorinated by-products formed after ozonation and chlorination can possibly increase mutagenic activity.

2.9.6 *Effect of biofiltration*

Biofiltration (ozone–sand filtration or ozone–GAC) can potentially reduce TOC, organic by-products and the formation of halogenated DBPs.

Passage of ozonated water samples through a rapid sand filter reduced the concentration of aldehydes by 62% (Lykins & Clark, 1988). Chlorinated samples experienced a 26% reduction in aldehyde concentrations under the same conditions. These reductions in aldehyde levels are attributable to biological activity in the sand filters. If GAC filtration follows sand filtration, ozone oxidation can be expected to promote more bioactivity in the GAC filter, because a better colonization environment is provided for microorganisms on GAC particles than on sand. Thus, the biological conversion of oxidized water impurities to carbon dioxide and water will be greater during passage through GAC media. Similar aldehyde removals have been observed by several researchers (Van Hoof et al., 1985; Sketchell et al., 1995).

Drinking-water treatment techniques that remove organic contaminants without affecting bromide concentrations cause a shift in the formation of DBPs towards brominated DBPs. Sketchell et al. (1995)

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studied three sources containing three different DOC levels and ambient bromides, which were filtered through biologically active GAC filters. Analysis of treated waters showed no removal of bromide ion and a shift towards more brominated organo-DBPs. THM levels after treatment with GAC with no added ozone decreased from 900–1700 to 100–700 : g/litre. These water sources contained DOC levels ranging from 10 to 25 mg/litre and high concentrations of biodegradable DOC (DOC removals ranged from 60% to 80% after GAC treatment).

Table 8 summarizes the effects of ozonation and biofiltration on the formation of DBPs from various sources.

2.10 Comparative assessment of disinfectants

A comparative assessment (Table 9) of various disinfecting chemicals for pre-disinfection (or oxidation) and post-disinfection and maintaining a residual for 5 days to simulate concentrations in the distribution system showed that the use of free chlorine produces the largest concentration of halogenated DBPs (Clark et al., 1994). The concentration of DBPs may be reduced by adding ozone or chlorine dioxide as a preoxidant, although enhanced formation has been observed.

Table 10 summarizes the effects of water quality and treatment variables on the formation of DBPs.

2.11 Alternative strategies for disinfectant by-product control

The concern about chlorite, bromate, chlorate and other DBPs in drinking-water following treatment with disinfectants has stimulated research into ways to eliminate the production or enhance the removal of DBPs. Strategies for DBP control include source control, precursor removal, use of alternative disinfectants and removal of DBPs by technologies such as air stripping, activated carbon, UV light and advanced oxidation technologies. For DBPs that can arise in hypochlorite solutions (e.g., chlorate), the purity and storage conditions of the solutions are important concerns.

Table 8. Effects of ozonation and biofiltration on chlorine organic by-products

DBPs	Ozonation (% change)	Biofiltration (% change)	Ozonation + biofiltration (% change)	Reference
THMs	! 20	! 20	! 40 (chlorine)	Speitel et al. (1993)
HAAs	! 10	! 13	! 25 (chlorine)	Speitel et al. (1993)
Chloropicrin	+50 to +250		! 50 to ! 100 (chlorine)	Miltner et al. (1992)
Aldehydes	+425 to +1300	! 40 to ! 50	! 92 to ! 98	Miltner et al. (1992)
TOX	! 30		! 51 (chlorine)	Miltner et al. (1992)
TOX	! 10	! 38	! 47 (chlorine)	Shukairy & Summers (1992)
TOX	+32	! 69	! 60 (monochloramine)	Shukairy & Summers (1992)

Table 9. Comparative assessment of organic disinfectant by-products (: g/litre) in distribution systems^{a,b}

DBPs	Sand-Cl ₂	Cl ₂ -Sand-Cl ₂	O ₃ -Sand-Cl ₂	NH ₂ Cl-Sand-NH ₂ Cl	O ₃ -Sand-NH ₂ Cl	ClO ₂ -Sand-Cl ₂
THMs	236.0	225.0	154.0	9.0	3.2	138.0
HAAs	60.0	146.0	82.0	14.0	9.0	44.0
HANs	3.1	2.9	2.7	<0.1	<0.1	<0.1
Haloketones	2.1	2.6	2.6	<0.1	<0.1	4.2
Chloropicrin	1.3	1.3	7.7	<0.1	<0.1	1.4
Chloral hydrate	79.0	75.0	55.0	<0.1	<0.1	45.0
TOX	557.0	540.0	339.0	59.0	27.0	379.0

^a Clark et al. (1994).

^b TOC = 3.0 mg/litre; pH = 7.6.

Table 10. Summary of impact of water quality and treatment variables on disinfectant by-product formation

Variable	Impact on THMs	Impact on HAAs	Impact on aldehydes	Impact on chlorate/chlorite	Impact on bromate
Contact time	Curvilinear increase with increasing contact time Rapid formation <5 h 90% formation in 24 h Levels off at 96 h	Curvilinear increase with increasing contact time Rapid formation <5 h 90% formation in 24 h Levels off at 150 h	Linear increase as long as residual chemical present Secondary reactions between disinfectants and aldehydes possible	Linear increase in bleach solutions No discernible effects in dilute solutions If oxidation of hypochlorite, contact time has a positive effect	Curvilinear increase with most bromate forming in <5 min Formation is a function of ozone residual and bromide
Disinfectant dose	Rapid and curvilinear increase after TOC demand with dose, levelling off at 2.0 mg/litre for TOC of 2.0 mg/litre	Curvilinear increase after TOC demand with increasing dose, levelling off at 2.0 mg/litre	Curvilinear with increasing ozone dose or chlorine dose No appreciable effect after ozone/DOC = 2 : 1	Concentrations related to hypochlorite doses applied Ozone oxidation of hypochlorite increases with dose	Linear increase after TOC demand and then levelling off after ozone residual disappearance
pH	Curvilinear increase with increasing pH to pH 7.0 and possible pH maximum No positive effect at pH > 9.5	Mixed, possible pH maximum for DCAA and DBAA TCAA decreases up to pH > 9 DCAA maximum at pH 7-7.5	Negative effect (forms mostly through molecular ozone) 25% decrease for pH 7-8.5	Positive effect Decomposition of hypochlorite increases with pH Oxidation of hypochlorite by ozone increases	Strong linear positive effect Hydroxyl radical generation efficiency increases

Table 10 (Contd).

Variable	Impact on THMs	Impact on HAAs	Impact on aldehydes	Impact on chlorate/chlorite	Impact on bromate
Temperature	Linear increase with increasing temperature (10–30 °C; 15–25% increase)	Linear increase with increasing temperature (10–30 °C; 20–30% increase)	Terminal products such as carbon dioxide increase and total aldehydes slightly decrease	Positive effect Decomposition of hypochlorite increases	Curvilinear increase 20–30% increase for 15–25 °C
TOC	Increase with increasing TOC; precursor content important Humic acids more reactive than fulvic acids	Increase with increasing TOC; precursor content important Humic acids more reactive than fulvic acids	Positive effect (hydrophobic fraction mostly responsible) Doubles for every 2 mg/litre	Negative effect if ozone is used for hypochlorite oxidation Most likely no effect with hypochlorite	Decreases with increasing TOC; precursor content important Non-humic acid being less reactive with ozone
UVA ₂₅₄	Increase with increasing UV absorbance; precursor content important Aromaticity of TOC being more important	Increase with increasing UV absorbance; precursor content important Aromaticity of TOC being more important	Positive effect Ozone demand increases with UV (UV absorbance is mostly due to aromaticity and hydrophobic fraction)	Negative effect if ozone is used for hypochlorite oxidation Probable negative effect with hypochlorous acid	Decreases with increasing UV absorbance; precursor content important Humic acid being more reactive with ozone
Bromide	Shift towards brominated species	Shift towards brominated species	Independent of bromide at <0.25 mg/litre At >0.25 mg/litre, aldehydes can decrease due to ozone–bromide oxidation	Shift towards more toxic bromate in hypochlorite solutions	Bromide threshold Curvilinear increase and dependent upon ozone residual
Alkalinity	No discernible effect	No discernible effect	Slight positive effect	Unknown	Positive effect

Table 10 (Contd).

Variable	Impact on THMs	Impact on HAAs	Impact on aldehydes	Impact on chlorate/chlorite	Impact on bromate
Minimization strategies	TOC removal, minimizing chlorine residual, alternative disinfectants, pH control, minimizing contact time	TOC removal, minimizing chlorine residual, alternative disinfectants, pH control, minimizing contact time	pH control, TOC removal by coagulation, GAC, optimizing doses, contact time	Avoid hypochlorite dosing solution Minimize storage Properly tune generators Use freshly made solutions	pH depression, ammonia addition, radical scavengers, minimizing and optimizing ozone residual
Removal strategies	GAC, electron beam, air stripping	GAC, electron beam	Biofiltration, advanced oxidation, GAC, nanofilters	Ferrous sulfate, GAC, electron beam, UV irradiation, nanofilters	Ferrous sulfate, UV irradiation, high-energy electron beam, GAC

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2.11.1 Source control

Source control options involve controlling nutrient inputs to waters (e.g., algae growth control) (Hoehn et al., 1990) that are used as drinking-water sources, watershed management (e.g., constructing stormwater detention basins), saltwater intrusion control (e.g., development of structural or hydrodynamic barriers to control TOC and bromide), and using the concept known as aquifer storage and recovery (e.g., drawing water during seasons when the quality of the water is best) (Singer, 1994a).

2.11.2 Organohalogen by-products

Strategies for control of organohalogen by-products include removal of DBPs that are formed using technologies such as oxidation, aeration and carbon adsorption (Clark et al., 1994); and removal of precursors using treatment techniques such as conventional treatment, oxidation, membrane processes, carbon adsorption and biological degradation. For many organic compounds that are difficult to oxidize, such as chloroform, the kinetics of ozone oxidation are generally very slow but are faster if used in combination with UV irradiation. GAC adsorption and membrane filtration are relatively expensive processes; moreover, NOM removal by GAC cannot be accomplished to any significant degree in a filter/adsorber (i.e., GAC filter cap) mode but requires a separate post-filtration adsorber bed. The use of membranes requires pretreatment to prevent fouling, as well as processing of waste brine. The use of ozone in combination with biologically active GAC filters is a promising alternative to reduce DBP precursors.

2.11.3 Inorganic by-products

Properly designed and operated chlorine and chlorine dioxide generator systems can minimize some of the production of chlorate ion. Removal of chlorite and chlorate has been reported using reduction by Fe^{2+} or sulfite or by GAC (Voudrias et al., 1983; Lykins & Clark, 1988). GAC is seen as problematic because of chlorate production and a short bed life. A chemical process using an appropriate agent such as reduced iron (e.g., ferrous sulfate) appears to be a more promising approach (Kraft & van Eldick, 1989; Gordon et al., 1990).

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If bromate is present in treated water entering the coagulation process (i.e., formed during pre-ozonation), several options exist for its removal. An aqueous-phase reducing agent (e.g., Fe^{2+}) can be added at the rapid mix step. Powdered activated carbon can likewise be added as a solid-phase reductant to remove bromate and DBP precursors. Not all utilities contemplating ozone application intend to employ pre-ozonation. Rather, they may use intermediate ozonation prior to the filtration process; in this situation, removal of bromate by activated carbon is possible. This approach has potential relevance to integration of GAC columns into a process train or, more realistically, to retrofitting of rapid sand filters with GAC filters. For groundwaters that require no coagulation, bromate can be removed after ozonation using a GAC filter, UV irradiation or high-energy electron beam irradiation (Siddiqui et al., 1994, 1996a,b,c).

Brominated or bromochlorinated amines formed during the oxidation step of the process train using chlorine can potentially be removed using a suitable activated carbon before terminal chlorination. However, carbon that has an accumulation of surface oxides, which develop through reaction of amines, will have a diminished capacity to reduce halogenated amines to nitrogen. Organic amines can potentially be removed by activated carbon adsorption.

2.11.4 Organic by-products

There are some technologies for removing organic contaminants formed after chlorination and chloramination, a less viable option than minimizing their formation through DBP precursor removal or use of alternative disinfectants. Studies of ozone oxidation have shown that aromatic compounds, alkenes and certain pesticides (some of which have structural similarities to certain organic DBPs) are removed well by ozone treatment, but that alkanes are poorly removed. Also, removal efficiency improves for the alkenes and aromatic compounds with increasing ozone dosage and for some alkanes with increasing pH. For most compounds, the efficacy of ozone is not affected by the background water matrix if the ozone is used after coagulation. Andrews et al. (1996) showed that using hydrogen peroxide at 1.0 mg/litre in combination with UV effectively reduced or prevented the formation of aldehydes.

2.12 Models for predicting disinfectant by-product formation

The regulation of THMs and other halogenated DBPs has been complicated by findings that alternative disinfectants to free chlorine may also form by-products that are of potential health concern. Additional complicating factors impacting the regulation of DBPs have been the emergence of *Giardia* and *Cryptosporidium* as major water-borne pathogens.

In view of the finding that water chlorination produces DBPs, some of which are carcinogenic, mutagenic or possibly teratogenic, several countries have recently laid down standards for various DBP levels. This stimulated the search for mathematical models to describe or predict DBP formation in disinfected water and to evaluate the effectiveness of water treatment technologies designed to reduce DBP levels so as to comply with the standards. Most of these models are based on fitting mathematical equations to various empirical observations, rather than mechanistic and kinetic considerations. This is mainly due to the complexity of the reactions between organic precursors and disinfecting chemicals, which usually involve several parallel pathways leading to a great variety of products. The complexity of the DBP formation reactions also makes it difficult to develop universally applicable models for simulating DBP formation potential associated with disinfection of a diverse array of natural source waters. However, the analysis presented by many models suggests that many waters exhibit comparable general responses to changes in a given parameter (i.e., responses lending themselves to simulation by a particular mathematical functionality), although specific responses associated with individual waters may vary. The multiple regression models developed by many researchers represent a rational framework for modelling DBP formation in many sources. Another potential application is the modelling of DBP mixtures, e.g., predicting HAA levels from THM and water quality data.

2.12.1 Factors affecting disinfectant by-product formation and variables of interest in disinfectant by-product modelling

The information on the factors controlling DBP formation, which is available in the literature, is briefly summarized below.

The extent of formation of DBPs is dependent on several water quality parameters, such as TOC concentration, UVA_{254} , bromide concentration and temperature. It is also dependent on chlorination conditions, such as chlorine dose, pH, ammonia concentration and contact time. After the various statistically significant factors were identified, mathematical equations were developed to describe the formation of various DBPs. A least squares method was used to determine the optimum equation coefficients that best describe the experimental data. The optimum coefficients have been defined as those that produce a minimum residual error between the mathematical predictions and the experimental data.

2.12.2 Empirical models for disinfectant by-product formation

Numerous models for predicting THM formation through chlorination have been reported (Moore et al., 1979a; Kavanaugh et al., 1980; Engerholm & Amy, 1983; Urano et al., 1983; Amy et al., 1987, 1998; Morrow & Minear, 1987; AWWARF, 1991; Hutton & Chung, 1992). Of these, models reported by AWWARF (1991) and Amy et al. (1998) are more recent and were derived from a variety of natural source waters and more realistic treatment conditions. Not much information has been reported on the formation of other chlorination DBPs. Only Amy et al. (1998) summarized empirical models for THMs, HAAs and chloral hydrate. These chlorination by-product models can be used to assess both in-plant and distribution system formation of THMs, HAAs and chloral hydrate. Water quality conditions such as DOC, pH, temperature and bromide are needed as inputs to the models; such data then allow assessment of chlorination DBP formation as a function of reaction time:

DBP concentration (total THMs or THM species, total HAAs or HAA species, or chloral hydrate) =
f(TOC, bromide, chlorine, pH, temperature, time)

Relatively little is known about the kinetics of the formation of bromate and other DBPs during ozonation and the quantitative effects of water quality factors (temperature, pH, etc.); such an understanding is crucial for evaluating various bromate control strategies. Siddiqui & Amy (1993) and Amy et al. (1998) developed statistical relations to predict the concentrations of various ozone DBPs, including bromate, as a function of water treatment variables. Correlation matrix analysis

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has shown that ozone dose, dissolved ozone concentration, bromide concentration, pH and reaction time all have a positive influence on bromate formation. Von Gunten & Hoigne (1994) developed kinetic models for bromate formation.

Ozone, as a result of its strong oxidizing power, produces a variety of organic by-products, such as aldehydes and ketoacids, when used to treat natural source waters. These by-products — especially aldehydes — are highly biodegradable, and there is concern for regrowth of microorganisms following ozone treatment. They are also potentially hazardous and may produce increased amounts of chlorinated by-products upon chlorination. Siddiqui et al. (1997) developed a model to estimate the potential for total aldehyde formation in source waters upon ozonation.

2.12.3 Models for predicting disinfectant by-product precursor removal

It is recognized that chlorination will continue to be the most common disinfection process; hence, enhanced removal of DBP precursors present in raw sources represents a valuable option for reducing the potential for by-product formation. The removal of NOM can be achieved either by providing additional processes, such as GAC and nanofiltration, or by enhancing the existing coagulation, flocculation and sedimentation processes. Predictive models have been developed for assessing coagulation efficiency in removing NOM and reducing DBP precursor levels (AWWARF, 1991; Amy et al., 1998).

Coagulation can reduce DOC and DBP precursors but not bromide levels; hence, a greater proportion of brominated DBP species can potentially be produced in the finished water.

The effects of precursor removal by chemical coagulation can be assessed through the use of treated water models. One can either predict DBPs formed under a given degree of precursor removal or define the degree of precursor removal required to meet DBP regulations. The impact of bromide ion on meeting regulations can also be assessed. If one makes the assumption that precursor reactivity (i.e., DBP/DOC) does not change, one can also assess other precursor removal processes, such as GAC or membrane processes, through use of the raw/untreated

water models. Care should be exercised when using models to approximate post-chlorination DBPs following an ozonation step.

2.13 Summary

- The primary and most important role of drinking-water treatment is to remove or inactivate harmful microorganisms. Another role is to minimize the concentrations of disinfectants and DBPs without compromising in any way the removal or inactivation of pathogens.
- Drinking-water utility managers must be more knowledgeable about options to meet regulations. It is often more practical to use treatment methods that control the concentration of several contaminants than to modify treatment practices for each new standard that is promulgated.
- A thorough understanding of DBP formation would help the successful balancing of appropriate microbial inactivation with the minimization of DBPs. Water quality variables affect DBP formation and must be considered when developing a strategy to control DBPs with various disinfectants.
- The chemistry of chlorine and its by-products has been well studied, and ozone and its by-products have recently received much attention. Studies of chlorine dioxide and chloramines and their by-products are relatively few, although more work in these areas is now being undertaken.
- One of the simplest processes to minimize halogenated DBP formation is limiting the free chlorine contact time by using monochloramine to maintain a distribution system residual following primary disinfection by chlorine or ozone. Chloramines are an effective means of controlling DBPs. However, the growth of nitrifying bacteria (and related production of nitrite) is a potential problem in chloraminated water supplies.
- Various nitrogen-containing organic compounds may be present in source waters after chlorination and chloramination. Because of analytical complexities, very few detailed studies have been undertaken to

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determine the individual compounds present and their concentrations.

- Many factors between the source and the tap can influence the DBPs to which consumers are exposed. Although THMs and HAAs continue to form with increasing contact time, some other halogenated DBPs, such as HANs and halo ketones, form rapidly but then decay in the distribution system as a result of hydrolysis. This has major implications regarding exposure to these DBPs, depending upon their proximity to the treatment plant. For treated source waters, median levels of HAAs are often approximately one-half of the median THM levels.
- For low-bromide source waters, chloroform is normally the dominant THM species; DCA and TCA are the most prevalent HAA species; DCAN is the most prevalent HAN species; and 1,1,1-TCPN is the most prevalent of the two measured halo ketones. Very low levels of chloropicrin have been observed by various researchers; this compound appears to form slowly during the incubation period, with concentrations tending to level off at 40 h. For high-bromide waters, increased levels of brominated DBPs are observed.
- Chlorine dioxide is a strong oxidant that under certain conditions surpasses chlorine in its ability to destroy pathogenic organisms. When chlorine dioxide is prepared and administered without excess free chlorine, THMs and other chlorinated by-products are not produced, but inorganic by-products are formed.
- TOC levels have been found to be correlated with halogenated DBP formation. The nature of this relationship varies with the source. TOC removal can be used as a surrogate for the reduction of DBP formation.
- Although the presence of chloral hydrate and HANs in chlorinated samples may be attributed to precursors other than amino acids, the potential for amino acids to be present in natural sources is well documented. Surface waters, but not groundwaters, tend to contain amino acids. However, the removal of these precursors during conventional water treatment is not well understood.

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- The amount of chlorate that is present in delivered hypochlorite solutions depends on many factors. Freshly made hypochlorite solutions will contain less chlorate than hypochlorite that is stored without concern for temperature and pH. If a utility is using a single tank to store hypochlorite, it is likely that the level of chlorate is increasing in the tank. Thus, storage tanks should be periodically flushed and cleaned, and, if possible, the storage time should be reduced.
- Models have been developed that can be used to simulate the fate and movement of DBP precursors in distribution systems. The models can be designed as a planning tool for evaluating the impacts of source water management strategies and estimating DBP exposures. Some limitations of existing models include calibration with a limited database, application to only a specific water source or group of related sources, lack of terms to simulate important parameters, such as reaction time, and inadequate validation.

3. TOXICOLOGY OF DISINFECTANTS

In assessing the hazards associated with drinking-water disinfection, it is important not to neglect the disinfectants themselves. Adding disinfectant in excess of the demand has several practical benefits. First, it ensures that reaction of the disinfectant with DBP precursors (largely organic material and ammonia) does not shorten contact time to the point of ineffective disinfection. Second, residual disinfectant helps to prevent regrowth of organisms in the remaining portions of the treatment and distribution systems.

The result of this practice, however, is that one of the chemicals that is present in the finished water at the highest concentration is the disinfectant. In the present regulatory climate in many countries, chemicals that are introduced as direct additives to food would be subjected to a significant amount of toxicological screening before they could be used. Since the major disinfectants were introduced almost 100 years ago, they were subjected to much less thorough toxicological evaluations than would be required today. However, many of these data gaps have been addressed in the past decade.

3.1 Chlorine and hypochlorite

3.1.1 *General toxicological properties and information on dose-response in animals*

Chlorine gas has long been recognized as a lung irritant. This topic will not be reviewed in the present document, as it appears to be largely irrelevant to the small amounts of chlorine that are volatilized from chlorinated water in showers or other points of use in the household. In water treatment plants, however, there is a possibility of occupational exposures that could have severe sequelae. For information on these higher-level exposures, the interested reader is referred to a recent review by Das & Blanc (1993). The effects of chlorine gas that have been observed in humans will be discussed in section 3.1.3.

Sodium hypochlorite (NaOCl) or calcium hypochlorite (Ca(OCl)₂) solutions have also been utilized extensively in the disinfection of drinking-water. The stock solutions used for this

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purpose are highly caustic and are a clear concern for occupational exposures. The concentration required to produce irritation and decreased basal cell viability in the skin of guinea-pigs after an application period of 2 weeks was 0.5% sodium hypochlorite (Cotter et al., 1985). Reducing the concentration to 0.1% resulted in no effect on basal cell viability relative to control animals. Yarrington (1970) demonstrated that instillation of bleach into the oesophagus of dogs produced irritation. The minimal exposure that produced oesophageal burns was 10 ml of commercial bleach with a 5-min exposure. It should be noted that the highly alkaline pH (about pH 11) of sodium hypochlorite is not likely to be encountered in drinking-water.

There have been relatively few evaluations of the effects of chlorine or hypochlorite in drinking-water. The present review will focus on studies with treatment periods longer than 4 weeks where drinking-water was the primary route of exposure. Reference to earlier studies of shorter duration and less general applicability to a safety evaluation can be found in previous reviews (Bull, 1980, 1982a,b, 1992; Bull & Kopfler, 1991).

Daniel et al. (1990a) evaluated the toxicity of solutions of chlorine prepared by bubbling chlorine gas into distilled water and adjusting the pH to 9.4. The nominal concentrations of chlorine used were 0, 25, 100, 175 or 250 mg/litre in distilled water (approximately 0, 3, 10, 16 or 21 mg/kg of body weight per day). These solutions were provided as drinking-water to both male and female Sprague-Dawley rats (10 per sex per dose) for 90 days. No deaths occurred in any treatment group. However, there were statistically significant decreases in drinking-water consumption in females treated with 100 mg/litre and higher, probably due to decreased palatability. There were no consistent effects of chlorine treatment on organ to body weight ratios or clinical chemistry parameters. A no-observed-effect level (NOEL) of 10 mg/kg of body weight per day was identified by the authors based on reduced body weight gain. However, since this was associated with reduced palatability of the drinking-water, it is not considered to be a true toxicological end-point.

The study in rats was followed up with another study in B6C3F₁ mice (Daniel et al., 1991a). Male and female B6C3F₁ mice (10 per sex per group) were administered 12.5, 25, 50, 100 or 200 mg of chlorine per litre of drinking-water for 90 days (calculated mean daily doses

were 2.7, 5.1, 10.3, 19.8 or 34.4 mg/kg of body weight in males and 2.8, 5.8, 11.7, 21.2 or 39.2 mg/kg of body weight in females). Spleen and liver weights were depressed in males, but not in females, at the highest dose rates (100 and 200 mg/litre). There were no other consistent indications of target organ effects based on serum enzyme concentrations. No gross or microscopic lesions could be related to treatment with chlorine.

Several of the following studies utilized solutions of sodium hypochlorite as the treatment chemical. It is now known that such solutions can contain very high concentrations of chlorate within a short time of their preparation (Bolyard et al., 1993). The extent of this contamination has not been reported.

Hasegawa et al. (1986) examined the effects of much higher concentrations (0.025, 0.05, 0.1, 0.2 or 0.4%) of sodium hypochlorite (equivalent to 7, 14, 28, 55 and 111 mg/kg of body weight per day) administered in drinking-water to male and female F344 rats for 13 weeks. Twenty rats of each sex were assigned to each experimental group. Significant suppression of body weight (as a result of decreased consumption of water and food) occurred at 0.2% and above. The authors noted slight damage to the liver as indicated by increased levels of serum enzymes (not specified) at 0.2% and 0.4% sodium hypochlorite in both sexes. No evidence of treatment-related pathology was observed in this study or in a 2-year study in which males were subjected to 0.05% or 0.1% (13.5 or 27.7 mg/kg of body weight per day) and females to 0.1% or 0.2% (34 or 63 mg/kg of body weight per day) sodium hypochlorite. The extended exposures were conducted with 50 animals of each sex per treatment group. Analysis of dosing solutions was not reported.

In a 2-year bioassay, the National Toxicology Program (NTP) examined chlorine at 0, 70, 140 or 275 mg/litre (expressed as atomic chlorine, Cl) in drinking-water of F344 rats and B6C3F₁ mice (70 per sex per group) (NTP, 1992). These solutions were prepared from gaseous chlorine and neutralized to pH 9 by the addition of sodium hydroxide. Stability studies indicated that 85% of the initial target concentration remained after 3 days of preparation. Stock solutions (concentrations not specified) were prepared once weekly, and solutions for drinking were prepared 4 times weekly. Based on body weight and water consumption, doses in these studies were

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approximately 0, 4, 7 or 14 mg/kg of body weight per day for male rats; 0, 4, 8 or 14 mg/kg of body weight per day for female rats; 0, 7, 14 or 24 mg/kg of body weight per day for male mice; and 0, 8, 14 or 24 mg/kg of body weight per day for female mice. The only treatment-related non-tumour pathology was found to be a dilatation of renal tubules in male mice receiving 275 mg/litre for more than 66 weeks. No non-neoplastic lesions were observed in either male or female rats.

A number of immunological changes have been associated with the treatment of rodents with sodium hypochlorite in drinking-water. Water containing 25–30 mg of sodium hypochlorite per litre was found to reduce the mean number of peritoneal exudate cells recovered from female C57BL/6N mice after 2 weeks of treatment. This was, in turn, associated with a significant decrease in macrophage-mediated cytotoxicity to melanoma and fibrosarcoma cell lines (Fidler, 1977). The treatment period was increased to 4 weeks in a subsequent study, which demonstrated that 25 mg of sodium hypochlorite per litre decreased the ability of peritoneal macrophages to phagocytose ⁵¹Cr-labelled sheep red blood cells. Macrophages obtained from the mice treated with hypochlorite were found to be less effective in destroying B16-BL6 melanoma cells *in vitro*. Mice so treated were also found to have increased pulmonary metastasis of B16-BL6 cells when they were introduced by subcutaneous injection (Fidler et al., 1982).

Exon et al. (1987) examined the immunotoxicological effects of sodium hypochlorite at 5, 15 or 30 mg/litre (0.7, 2.1 or 4.2 mg/kg of body weight per day) in the drinking-water of male Sprague-Dawley rats (12 per dose) for 9 weeks. Delayed hypersensitivity reaction to bovine serum albumin was observed at the highest dose administered. Oxidative metabolism by adherent resident peritoneal cells was decreased at 15 and 30 mg/litre, and the prostaglandin E₂ levels of these cells were found to be significantly elevated. No effects on natural killer cell cytotoxicity, antibody responses, interleukin 2 production or phagocytic activity were observed. The effects on macrophage activity suggest that some impairment does occur at relatively low levels of sodium hypochlorite. As pointed out by the authors, these were relatively mild effects, the significance of which was unknown. It is not clear that these effects would be translated into a significant impairment of the immune response to a particular infectious agent. However, modification of macrophage function appears to be one of the most sensitive responses identified in studies

of chlorine or hypochlorite in experimental animals. A study in which female C57BL/6 mice were administered hypochlorite in their drinking-water (7.5, 15 or 30 mg of hypochlorite per litre) for 2 weeks showed no effects on the immune system as measured by spleen and thymus weight, plaque-forming cell response, haemagglutination titre and lymphocyte proliferation (French et al., 1998).

Altered liver lipid composition has been observed as a result of acute intragastric administration of sodium hypochlorite (5 ml of a 1% solution) to rats (Chang et al., 1981). These data do not provide a clear indication of whether these effects might give rise to pathology. The concentrations of hypochlorite utilized were much greater than those that would be encountered in drinking-water.

The effects of hypochlorous acid and hypochlorite on the skin have received relatively little attention despite the current interest in bathing as a significant source of chemical exposure from drinking-water. Robinson et al. (1986) examined the effects of both hypochlorite and hypochlorous acid solutions applied to the skin of the entire body of female Sencar mice except for the head. Exposures were to 1, 100, 300 or 1000 mg/litre as hypochlorous acid at pH 6.5 for 10 min on 4 consecutive days. Hypochlorite (formed by raising the pH to 8.5) was studied only at 1000 mg/litre. Significant increases in epidermal thickness and cell counts within the epidermal layer were observed at concentrations of hypochlorous acid (pH 6.5) of 300 mg/litre and above, but the thickness of the skin was not significantly different from that in animals at 100 mg/litre. The increases in skin thickness were associated with an epidermis whose thickness was increased to 4–6 cells as compared with the normal 1–2 cells seen in mice. The effects of hypochlorite were much less marked. Following a single application, the increased thickness of the skin observed in mice exposed to hypochlorous acid (i.e., pH 6.5) did not appear until 4 days after the treatment. This differed from hypochlorite, other disinfectants and the positive control, 12-*O*-tetradecanoylphorbol-13-acetate (TPA). In the latter cases, the maximal response was observed within 24–48 h after treatment. The hyperplastic response to hypochlorous acid required 12 days to return to normal. This study suggests a considerable margin of safety between the concentrations of chlorine required to produce hyperplasia and those that are found in drinking-water.

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The reactive nature of chlorine always raises questions of whether it is chlorine or a by-product that is responsible for any effect. Several studies have examined the formation of by-products in the gastrointestinal tract following the administration of chlorine. Invariably, these studies have involved the administration of chlorine or hypochlorite by gavage at very high concentrations relative to the amounts that would be encountered in chlorinated drinking-water. As a consequence, the by-products formed following gavage dosing of high concentrations may not be representative of the by-products that would be seen following the consumption of modest to moderate levels of chlorine in larger volumes of water. A particular issue is that the high organic carbon concentration relative to chlorine that would be encountered in the gastrointestinal tract when water is consumed at low concentrations should dissipate disinfectant before sufficient oxidative power would be present to break down substrates to small molecules. Despite these design flaws, the data do indicate that by-products are formed. The bulk of them remain as higher molecular weight products, which may have little toxicological importance.

Vogt et al. (1979) reported that chloroform could be measured in the blood, brain, liver, kidneys and fat of rats to which sodium hypochlorite was administered by gavage at doses of 20, 50 or 80 mg in 5 ml of water. Thus, the by-product chloroform can be formed by the reaction of chlorine with stomach contents.

Mink and co-workers (1983) pursued this observation and found that other by-products could be detected in the stomach contents and plasma of rats that had been administered sodium hypochlorite solutions neutralized to pH 7.9. In addition to chloroform, DCAN, DCA and TCA were detected in the stomach contents analysis. DCA and TCA were also detected in blood plasma.

The third group of compounds identified as by-products of chlorination in stomach contents of the rat are the organic *N*-chloramines (Scully et al., 1990). *N*-Chloroglycine, *N*-chloroleucine or *N*-chloroisoleucine and *N*-chlorophenylalanine were confirmed products of reactions with normal amino acids that would ordinarily be found in the gastrointestinal tract. *N*-Chlorovaline and *N*-chloroserine were also tentatively identified. Organic chloramines are reactive and could be responsible for toxic effects that may be attributed to chlorine in toxicological studies. The chlorine demand

of free amino acids in stomach contents was found to be only about 4% of the total. Consequently, this process may be substrate-limited at concentrations of chlorine found as residuals in drinking-water. However, use of higher concentrations of chlorine would also lead to breakdown of proteins present in the stomach fluid. Thus, as concentrations are increased to levels that would be used in animal studies, these products would be formed at a much higher concentration, similar to the phenomena noted with THM and HAA by-products.

3.1.2 Reproductive and developmental toxicity

In general, animal studies have demonstrated no reproductive or teratogenic effects of chlorine. Druckrey (1968) examined the effects of water chlorinated to a level of 100 mg/litre (approximately 10 mg/kg of body weight per day) in BDII rats for seven generations. No effects were observed on fertility, growth or survival.

A number of subsequent studies have studied the effects of chlorine or hypochlorite on more specific aspects of reproduction or development. Meier et al. (1985b) reported that oral administration of sodium hypochlorite (pH 8.5) prepared from chlorine gas and administered at 4 or 8 mg/kg of body weight per day for 5 weeks increased the incidence of sperm head abnormalities in B6C3F₁ mice (10 animals per group). The effect was not observed when the solutions were administered at pHs at which hypochlorous acid was the predominant species (pH 6.5). However, other studies have not been able to associate adverse reproductive outcomes with the administration of chlorine or sodium hypochlorite.

Carlton et al. (1986) found no evidence of sperm head abnormalities or adverse reproductive outcomes in Long-Evans rats. Male rats were treated for 56 days prior to mating and female rats from 14 days prior to mating through gestation. Each experimental group consisted of 11–12 males and 23–24 females. Solutions of chlorine were prepared at pH 8.5, so the study evaluated hypochlorite as the dominant form in the drinking-water. Doses were as high as 5 mg/kg of body weight per day.

3.1.3 Toxicity in humans

There have been significant human exposures to chlorine and hypochlorite solutions. Much of that experience is with inhalation of chlorine gas, which is known to be a strong respiratory irritant. Chlorine gas is also the largest single component involved in toxic release incidents. A third major source of exposure is solutions of sodium hypochlorite, usually marketed as bleach. Bleach is frequently involved in human poisonings. These exposures are not particularly relevant to exposures to chlorine or hypochlorite in drinking-water. Therefore, only a few case reports are identified that illustrate the types of problems that have been encountered. There was no attempt to make this review comprehensive.

The irritating effects of chlorine gas have been well documented because of its use as a chemical warfare agent during World War I (Das & Blanc, 1993). In a follow-up of survivors of gassing, it was concluded that there was no evidence of permanent lung damage; however, these studies clearly indicated that survivors had breath sounds that suggested bronchitis and limited chest and diaphragmatic movement, even emphysema. Most studies suggested that there were high incidences of acute respiratory disease and a lesser prevalence of chronic sequelae. Similar sequelae have been identified following exposure of humans to accidental releases of chlorine gas. In these more modern characterizations, the acute signs and symptoms included a high incidence of pulmonary oedema and severe bronchitis. These signs and symptoms are of generally short duration and resolve themselves over the course of about 1–4 weeks. However, chronic sequelae are observed in some individuals, depending in part upon the severity of the exposure. In such cases, a decrease in the forced expiratory volume is the most consistently reported clinical sign.

Two recent reports suggest that chronic sequelae to acute exposures to chlorine gas may be more prevalent than previously appreciated. Moore & Sherman (1991) reported on an individual who was previously asymptomatic and who developed chronic, recurrent asthma after exposure to chlorine gas in an enclosed place. Schwartz et al. (1990) followed 20 individuals who had been exposed to chlorine gas in a 1975 incident. The prevalence of low residual lung volume was increased during the follow-up period. Sixty-seven per cent of those tested were found to have residual volumes below 80%

of their predicted values. Five of 13 subjects tested for airway reactivity to methacholine were found to have a greater than 15% decline in forced expiratory volume.

Controlled studies have been conducted in healthy, non-smoking men exposed to chlorine gas at 1.5 and 2.9 mg/m³ (0.5 and 1.0 ppm) for 4 or 8 h (reviewed in Das & Blanc, 1993). Four hours of exposure to 2.9 mg/m³ (1.0 ppm) produced significant decreases in the forced expiratory volume. One individual who was found to be experiencing more difficulty than other subjects at this dose and who was later exposed to 1.5 mg/m³ (0.5 ppm) experienced a significant decrease in forced expiratory volume. While 1.5 mg/m³ (0.5 ppm) appears protective for most people, some more sensitive individuals may in fact have more significant responses to chlorine gas.

The effects of chronic exposure to chlorine gas have received only limited study. In one study of paper mill workers, a more rapid age-related decrease in lung volumes of workers exposed to chlorine relative to those exposed to sulfur dioxide was noted, but the trend was not statistically significant (Das & Blanc, 1993). Other studies failed to identify chronic sequelae.

There are frequent reports of human poisonings from bleach. Most often these exposures result from the mixing of bleach with acidic products or ammonia. Acidification converts hypochlorite to hypochlorous acid, which dissociates to chlorine gas, offgasses very rapidly from the solutions and presents an inhalation exposure (MMWR, 1991). Mixing bleach with ammonia results in the formation of monochloramine and dichloramine, both of which are effective respiratory irritants (MMWR, 1991).

Any potential effects of chlorine or hypochlorite in drinking-water are obscured by the fact that by-products inevitably coexist with the residual chlorine. One series of studies in which by-products formed were minimized by dissolving chlorine in distilled water attempted to identify effects of chlorine in drinking-water on humans. Chlorine in drinking-water was administered in a rising-dose tolerance study beginning with 0.1 mg/litre in two 500-ml portions and rising to a concentration of 24 mg/litre, equivalent to 0.34 mg/kg of body weight per day (Lubbers & Bianchine, 1984). No clinically important changes were observed. No findings of clinical importance

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were identified in a follow-up treatment with repeated dosing with 500-ml portions of a solution containing 5 mg of chlorine per litre for a 12-week period (Lubbers et al., 1984a).

Another study attempted to determine whether consumption of chlorinated drinking-water affected blood cholesterol levels (Wones et al., 1993a). The impetus for this study was a toxicological study in pigeons that suggested that chlorine raised blood cholesterol levels and modified serum thyroid levels (Revis et al., 1986a,b) and an epidemiological study that associated small increases in cholesterol of women with residence in communities having chlorinated water (Zeighami et al., 1990a,b; described in detail in section 5.2.2). A prior study (quoted in Wones et al., 1993a) was conducted that examined men who consumed water containing 2, 5 or 10 mg of chlorine per litre and found a small increase in serum cholesterol levels at the highest dose group. However, no control group was studied, so the changes could have been attributed to the change in diet imposed as part of the study protocol (Wones & Glueck, 1986). The longer-term study was composed of 30 men and 30 women who received a controlled diet for the duration of the study. The first 4 weeks represented an acclimatization period during which all subjects received distilled water. Half the subjects were assigned to a group that consumed 1.5 litres of water containing 20 mg of chlorine per litre for the following 4 weeks. At the end of each 4-week period, blood was analysed for cholesterol, triglycerides, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol or apolipoproteins A1, A2 and B. There were no significant effects. There was a slight trend towards lower thyroid hormone levels in men consuming chlorine, but this was not clinically significant (Wones et al., 1993a). These data suggest that observations obtained previously in pigeons could not be repeated under comparable conditions of chlorine consumption. It is notable that the animals utilized in the original pigeon study had consumed a modified diet (Revis et al., 1986a) that was deficient in calcium and other trace metals. A subsequent study failed to replicate the previous results in pigeons (Penn et al., 1990).

3.1.4 *Carcinogenicity and mutagenicity*

The International Agency for Research on Cancer (IARC) has evaluated the carcinogenicity of hypochlorite salts and concluded that there were no data available from studies in humans on their

carcinogenicity and inadequate evidence for their carcinogenicity in experimental animals. Hypochlorite salts were assigned to Group 3: the compounds are not classifiable as to their carcinogenicity to humans (IARC, 1991).

Several studies have shown that sodium hypochlorite produces mutagenic responses in bacterial systems and mammalian cells *in vitro*. However, there is no evidence of activity in mammalian test systems *in vivo*. It is not clear to what extent this is influenced by the formation of mutagenic by-products as a result of reactions with components of the incubation media. Wlodkowski & Rosenkranz (1975) used short-term exposures of *Salmonella typhimurium* strain TA1530 followed by ascorbic acid-induced decomposition to reduce the cytotoxic effects of hypochlorite. The investigators applied 0.14 : mol per tube and added ascorbic acid after intervals of 5, 10 and 15 min. At 5 min, a clear positive response was observed with minimal cytotoxicity. Significant responses were also observed in strain TA1535, but not in strain TA1538.

Rosenkranz (1973) and Rosenkranz et al. (1976) also demonstrated a positive mutagenic response in DNA polymerase A deficient *Escherichia coli* to 0.006 : mol of sodium hypochlorite. This response was unaffected by the addition of catalase, suggesting that the response was not related to the generation of hydrogen peroxide.

Matsuoka et al. (1979) reported that sodium hypochlorite at a concentration of 6.7 mmol/litre (0.5 mg/ml) produced chromosomal aberrations in Chinese hamster ovary (CHO) cells in the presence of S9 mix. This concentration was cytotoxic in the absence of S9. Some concern must be expressed about whether responses observed with such high and clearly cytotoxic concentrations in an *in vitro* system represent specific clastogenic effects. The authors report only one concentration tested with and without S9. It is probable that the positive response in the presence of S9, if it is a specific response, was a result of detoxifying hypochlorite. This protection could be non-specific as well, in that it may not have depended upon any catalytic activities present in the S9 fraction (i.e., the added protein may have acted as a reactive sink to dissipate excess hypochlorite). Consequently, it is difficult to use these data in interpreting the effects of chlorine or hypochlorite *in vivo*.

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Ishidate (1987) studied the induction of chromosomal aberrations in cultures of Chinese hamster CHL cells at sodium hypochlorite concentrations ranging from 125 to 500 : g/ml without exogenous metabolic activation and from 31 to 125 : g/ml with and without rat liver S9 mix. A clear increase in the number of cells with structural chromosomal aberrations was observed at 500 : g/ml without S9 mix, while the results obtained in the other series, showing weakly positive responses, were considered inconclusive.

Meier et al. (1985b) evaluated the ability of hypochlorite and hypochlorous acid to induce chromosomal damage or micronuclei in the bone marrow of CD-1 mice. The samples to be tested were generated by bubbling chlorine gas into water and then adjusting the pH to 6.5 (predominantly hypochlorous acid) or 8.5 (predominantly hypochlorite). The doses administered were 1.6, 4 or 8 mg/kg of body weight for 5 consecutive days. There was no evidence of increased micronuclei or chromosomal abnormalities in bone marrow cells. Significant positive responses were observed with positive control chemicals in both assays. As reported in section 3.1.2, these authors detected a positive response in the sperm head abnormality assay in mice treated at these same doses of hypochlorite in two separate experiments. This assay is used primarily as a mutagenicity assay rather than as an assay for reproductive toxicities. Hypochlorous acid had no effect in the sperm head abnormality assay.

Tests of the ability of hypochlorite to induce cancer in rodents were conducted in F344 rats by Hasegawa et al. (1986). Sodium hypochlorite concentrations of 0, 500 or 1000 mg/litre (males) and 0, 1000 or 2000 mg/litre (females) were administered in the drinking-water for 104 weeks (equivalent to 13.5 and 27.7 mg/kg of body weight per day for males and 34.3 and 63.2 mg/kg of body weight per day for females). There were 50 male and 50 female rats assigned to each experimental group. No tumours could be attributed to sodium hypochlorite administration.

NTP (1992) conducted a 2-year bioassay of chlorine in F344 rats and B6C3F₁ mice. The concentrations administered in drinking-water were 0, 70, 140 or 275 mg/litre, and there were 70 animals of each sex assigned to each group (approximately 0, 4, 8 or 14 mg/kg of body weight per day for rats and 0, 7, 14 or 24 mg/kg of body weight per

day for mice). There was an apparent positive trend in the induction of stromal polyps of the uterus of female mice treated with chlorine, but this was considered unlikely to be treatment-related because the incidence was below those observed in historical controls. In female rats, there was an increase in mononuclear cell leukaemia at both 140 and 275 mg/litre (8 and 14 mg/kg of body weight per day). However, the response was not considered treatment-related because it fell within the range of historical controls, there was no apparent dose-response, and there was no evidence for such an increase in male F344 rats.

A single study suggested that sodium hypochlorite could act as a promoter of skin tumours following initiation with 4-nitroquinoline-1-oxide in female ddN mice (Hayatsu et al., 1971). A solution of sodium hypochlorite that contained 10% effective concentrations of chlorine was utilized. Skin tumours were produced in 9 of 32 mice given 45 applications of sodium hypochlorite following initiation. Sodium hydroxide solutions were utilized as a control for the alkaline pH of sodium hypochlorite and produced no tumours. No tumours were observed with 60 applications of sodium hypochlorite solution in non-initiated mice. Pfeiffer (1978) conducted a much larger experiment that utilized 100 mice per group. This author found that a 1% sodium hypochlorite solution applied alternately with benzo[*a*]pyrene for 128 weeks was ineffective in producing skin tumours in female NMRI mice above those that had been initiated with benzo[*a*]pyrene alone at doses of 750 or 1500 : g. Pretreatment with the sodium hypochlorite solution before application of the benzo[*a*]pyrene actually reduced tumour yields at 128 weeks with doses of either 750 or 1500 : g of benzo[*a*]pyrene. Sodium hypochlorite used in a more traditional initiation/promotion study (i.e., sodium hypochlorite treatment following initiation with benzo[*a*]pyrene) produced a decrease in the tumour yield with the 750 : g dose of benzo[*a*]pyrene, but had no effect following 1500 : g. Thus, the ability of sodium hypochlorite to act as a tumour promoter may depend upon the initiator used, or the smaller experiment of Hayatsu et al. (1971) may simply be a false result.

As pointed out in section 3.1.1, application of solutions of hypochlorous acid to the skin of Sencar mice results in the development of hyperplasia. The concentrations required are considerably lower (300 mg/litre) (Robinson et al., 1986) than those used in the studies of either Hayatsu et al. (1971) or Pfeiffer (1978). Sodium hypochlorite

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was also effective at lower doses, but less so than equivalent concentrations of hypochlorous acid. These results suggest that these prior evaluations may have been conducted at too high a dose. There appear to be no reports on the effectiveness of hypochlorous acid as a tumour promoter, but the lack of activity at doses of less than 300 mg/litre would suggest that this is of no concern.

3.1.5 *Comparative pharmacokinetics and metabolism*

A series of pharmacokinetic studies using ³⁶Cl-labelled hypochlorous acid were conducted by Abdel-Rahman and co-workers (1983). These studies are of limited value because the form of ³⁶Cl could not be determined in various body compartments.

3.1.6 *Mode of action*

There are no specific toxicities of chlorine for which a mechanism needs to be proposed. It is a strong oxidizing agent, and it must be presumed that damage induced at high doses by either gaseous chlorine or solutions of hypochlorite is at least partially related to this property. In studies in which sodium hypochlorite is used without neutralization, a strong alkaline pH can also contribute to its effects. There is always the possibility that chlorine is inducing subtle effects by virtue of its reaction with organic compounds that are found in the stomach. Such reactions have been demonstrated, but there is no convincing evidence to date that any specific toxicity can be attributed to these by-products.

3.2 Chloramine

3.2.1 *General toxicological properties and information on dose-response in animals*

There have been relatively few evaluations of the toxic properties of chloramine in experimental animals. In large part this is because it is not marketed as a product but is created for disinfection purposes on-site and *in situ*. Chloramine is primarily used as a residual disinfectant in the distribution system. The final solution consists of mostly monochloramine, with traces of other chloramines, such as dichloramine. Chloramines, as a group, are generally recognized as potent respiratory irritants, because the formation of these compounds when household bleach and ammonia are mixed results in a number

of poisoning cases each year (MMWR, 1991). In spite of this, there has been no attempt to quantify dose-response relationships in animals.

Eaton et al. (1973) investigated concerns about chloramine-induced methaemoglobin formation in kidney patients dialysed with chloramine-containing water. This was done by examining the ability of relatively large volumes of tapwater to oxidize haemoglobin in dilute suspensions of red blood cells. This circumstance is reflective of dialysis, but not of the concentrated suspension of these cells *in vivo*. Nevertheless, the authors were able to show that methaemoglobin formation occurred in a dose-related manner when 1 volume of red blood cells (human) was suspended in 100 volumes of tapwater containing 1 mg of chloramine per litre or above. This effect was not produced by comparable concentrations of sodium hypochlorite. The ability to induce methaemoglobin formation was eliminated by treating the water by reverse osmosis followed by carbon filtration. Clearly, chloramine is capable of inducing methaemoglobinaemia at low concentrations when there is a large reservoir of chloramine. This is a decidedly different exposure pattern from that of normal humans and other mammals, as they consume small volumes of water relative to the volume of red blood cells that are exposed.

Moore et al. (1980a) studied alterations of blood parameters in male A/J mice treated with 0, 2.5, 25, 50, 100 or 200 mg of monochloramine per litre in carbonate/bicarbonate-buffered (pH 8.9) drinking-water. Twelve animals were assigned to each group, and treatments were maintained over a 30-day period. Consistent with the interpretation provided above, there were no treatment-related effects on osmotic fragility, methaemoglobin levels, haemoglobin concentrations, reticulocyte counts or a number of other derived parameters. Haematocrits of mice treated with 50, 100 or 200 mg/litre were actually higher than those observed in control mice. White blood cell counts were not altered in these animals.

Daniel et al. (1990a) conducted a more traditional 90-day study of monochloramine in Sprague-Dawley rats (10 animals per sex per dose). Treatment concentrations were 0, 25, 50, 100 or 200 mg/litre, corresponding to doses of 0, 1.8, 3.4, 5.8 or 9.0 mg/kg of body weight per day in males and 0, 2.6, 4.3, 7.7 or 12.1 mg/kg of body weight per day in females. Controls received carbonated, pH-adjusted drinking-water. A large number of haematological and clinical chemistry

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measures were included in the evaluation. Body weights were significantly depressed in both sexes at treatment concentrations in the 50–200 mg/litre range, but this appeared to be related to depressed water and food consumption. There were minor changes in organ to body weight ratios at the highest dose, but no evidence of treatment-related pathology was observed. Male rats were found to have decreased haematocrits at 100 mg/litre, and red blood cell counts were slightly depressed at 100 and 200 mg/litre. The authors concluded that monochloramine was more toxic than chlorine or chlorine dioxide. However, it must be noted that the changes in blood parameters were small and in themselves of no clinical significance. Other measures were not related to specific toxic reactions. Based on the decrease in organ and body weights observed in both sexes, the authors concluded that the no-observed-adverse-effect level (NOAEL) was 100 mg/litre, equivalent to 5.8 mg/kg of body weight per day.

The work in rats was followed up with a second study in B6C3F₁ mice (Daniel et al., 1991a). Male and female B6C3F₁ mice (10 per sex per group) were administered 0, 12.5, 25, 50, 100 or 200 mg of chloramine per litre of drinking-water for 90 days (calculated mean daily dose was 0, 2.5, 5.0, 8.6, 11.1 or 15.6 mg/kg of body weight for males and 0, 2.8, 5.3, 9.2, 12.9 or 15.8 mg/kg of body weight for females). Water consumption significantly decreased at 100 and 200 mg/litre in males and at 25–200 mg/litre in females. Weight gain was significantly depressed in both sexes at 100 and 200 mg/litre. Neutrophil concentrations in blood were significantly depressed in both male and female mice at the two highest doses, but other white blood cell counts were unaltered. Absolute and relative spleen and liver weights were depressed at both 100 and 200 mg/litre. No gross or microscopic evidence of target organ toxicity was observed that could be related to treatment. Based on decreased organ weights, weight gain, and food and water consumption, the authors concluded that the NOAEL was 50 mg/litre, equivalent to 8.6 mg/kg of body weight per day.

A 13-week study in which groups of 10 Sprague-Dawley rats were given drinking-water containing 200 mg of monochloramine per litre or buffered water as a control, *ad libitum* or restricted to the same consumption as the monochloramine group, was designed to resolve some of the outstanding toxicological questions. The results of this study indicated that the reduced body weight gain and the minor biochemical, haematological, immunological and histopathological

changes associated with exposure to 200 mg of monochloramine per litre (equivalent to 21.6 mg/kg of body weight per day) in drinking-water were largely related to reduced water and food consumption (Poon et al., 1997).

In a 9-week study, Exon et al. (1987) examined the ability of monochloramine to modify immunological parameters in male Sprague-Dawley rats (12 per dose) exposed to concentrations of 0, 9, 19 or 38 mg of monochloramine per litre, equivalent to 0, 1.3, 2.6 or 5.3 mg/kg of body weight per day. At the middle and highest dose, chloramine treatment was observed to increase prostaglandin E₂ synthesis by adherent resident peritoneal cells (which include macrophages) in response to lipopolysaccharide stimulation. No attempt was made to relate this finding to other indices of modified macrophage function. A small depression in spleen weights was observed at the highest dose. The implications of these data for immune function are not clear. Other measures of immune function did not reveal statistically significant changes with treatment. These included a decrease in antibody formation at the lowest and middle doses in response to keyhole limpet haemocyanin injection or delayed-type hypersensitivity reactions to bovine serum albumin injected into the footpad.

The effect of monochloramine on skin irritation was tested by immersing Sencar mice into water containing chloramine at concentrations ranging from 1 to 1000 mg/litre for 10 min a day (Robinson et al., 1986). Unlike hypochlorous acid (pH 6.5) or hypochlorite (pH 8.5), chloramine did not produce hyperplasia of the skin.

3.2.2 Reproductive and developmental toxicity

Studies in laboratory animals have indicated no reproductive or developmental effects associated with chloramine. Abdel-Rahman et al. (1982a) administered monochloramine to female Sprague-Dawley rats at concentrations of 0, 1, 10 or 100 mg/litre (0, 0.15, 1.5 or 15 mg/kg of body weight per day) for 2.5 months prior to breeding and through gestation. Only six animals were assigned to each treatment group. Reproductive performance was comparable between groups, and fetal weights were not adversely affected by treatment. Between 50 and 60 fetuses were available (male and female combined) for evaluation. There was no evidence of treatment-related skeletal or soft tissue anomalies.

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Carlton et al. (1986) examined the effects of monochloramine administered by gavage at doses of 0, 2.5, 5 or 10 mg/kg of body weight per day on the reproductive performance of Long-Evans rats. Males (12 per group) were treated from 56 days prior to and through mating, and females (24 per group) from 14 days prior to mating and throughout the mating period. No statistically significant effects on sperm morphology, concentration or motility were observed, nor were there any effects on fertility, viability, litter size, pup weights, day of eye opening or day of vaginal patency.

3.2.3 Toxicity in humans

The primary harmful effects of chloramine have been documented in humans poisoned by chloramine formed when household bleach was mixed with ammonia for use as a cleaning solution. Chloramine is a strong respiratory irritant. These effects were discussed in section 3.1.3.

Forty-eight men completed an 8-week protocol during which diet and other factors known to affect lipid metabolism were controlled. During the first 4 weeks of the protocol, all subjects consumed distilled water. During the second 4 weeks, one-third of the subjects were assigned randomly to drink 1.5 litres of water containing 0, 2 or 15 mg of monochloramine per litre each day. At 2 mg/litre, no significant changes were observed in total, HDL or LDL cholesterol, triglycerides or apolipoproteins A1, A2 or B. Parameters of thyroid function were unchanged. However, an increase in the level of apolipoprotein B was observed at 15 mg/litre (Wones et al., 1993b).

3.2.4 Carcinogenicity and mutagenicity

Shih & Lederberg (1976) first demonstrated that monochloramine induced mutation in a *Bacillus subtilis* reversion assay. The concentration range studied extended from 18 to 74 : mol/litre. A positive dose-response was observed through 56 : mol/litre, but 74 : mol/litre was cytotoxic. Repair-deficient mutants of *B. subtilis*, *rec3*, *recA* and *polyA5*, were consistently more sensitive to the cytotoxic effects of chloramine, while the *uvr* and *recB* mutants were not. The sensitivity of the *polyA5* mutants parallels the observations of Rosenkranz (1973) with sodium hypochlorite and suggests that DNA polymerase A is involved in the repair of DNA lesions produced by both chemicals. Thus, it is possible that a

common intermediate or mechanism is involved in the mutagenic effects of hypochlorite and chloramine.

A broader list of chloramines was tested by Thomas et al. (1987) in *Salmonella typhimurium* tester strains TA97a, TA100 and TA102. The chloramines tested included those that could be formed at low levels from natural substrates in drinking-water or in the stomach. TA100 was found to consistently be the most sensitive strain. The most potent mutagens were the lipophilic dichloramines formed with histamine, ethanolamine and putrescine. The corresponding monochloramines were less potent. The more hydrophilic chloramines, such as taurine-chloramine, had little activity. Monochloramine was active in the 50 : mol/litre range, remarkably consistent with the data of Shih & Lederberg (1976). Hypochlorous acid was inactive at all concentrations that were tested, up to and including concentrations that induced cytotoxicity.

Ashby and co-workers (1987) were unable to induce clastogenic effects in the mouse bone marrow micronucleus assay when chloramine was administered orally. They suggested that the *in vitro* clastogenic effects were probably attributable to non-specific cytotoxic effects that are secondary to the release of hypochlorite to the media.

Meier et al. (1985b) found that intraperitoneal administration of monochloramine to CD-1 mice at doses of up to 8 mg/kg of body weight was without significant effect on either micronuclei or chromosomal aberrations in the bone marrow. These data would appear to be consistent with the findings of Ashby et al. (1987).

Studies on the carcinogenicity of chloramine are limited to a single set of 2-year experiments conducted by the NTP (1992). Drinking-water containing 0, 50, 100 or 200 mg of chloramine per litre was provided to F344 rats and B6C3F₁ mice. Seventy animals of each species and of each sex within a species were assigned to each experimental and control group. Doses in rats were 0, 2.1, 4.8 or 8.7 mg/kg of body weight per day in males and 0, 2.8, 5.3 or 9.5 mg/kg of body weight per day in females; doses in mice were 0, 5.0, 8.9 or 15.9 mg/kg of body weight per day in males and 0, 4.9, 9.0 or 17.2 mg/kg of body weight per day in females. Of some interest was the finding that two renal cell adenomas were found in male B6C3F₁

mice treated with the high dose of chloramine. In addition, one renal adenoma was found in one male mouse treated with 100 mg/litre and in one female mouse treated with 200 mg/litre. While this tumour site is rare in both species, there was no real dose–response trend, nor were the differences between the control and treatment groups statistically significant. A second finding of some concern was an increase in the incidence of mononuclear cell leukaemia in F344 rats. This pathology was increased in rats treated with chloramine or hypochlorite, although the effects were not clearly dose-dependent. The incidence of mononuclear cell leukaemia was significantly greater than in concurrent controls and was elevated above the historical incidence as well. Nevertheless, these increases were not considered to be treatment-related. In part, this conclusion arose from the lack of a clear dose–response. It was also based on the fact that there was no comparable trend in male rats.

3.2.5 Comparative pharmacokinetics and metabolism

The pharmacokinetics of ^{36}Cl derived from monochloramine have been examined in male Sprague-Dawley rats (Abdel-Rahman et al., 1983). These data are difficult to interpret because the specific form of the label is not known.

3.3 Chlorine dioxide

3.3.1 General toxicological properties and information on dose–response in animals

Despite its use as a disinfectant, there have been very few general toxicological evaluations of chlorine dioxide, because most studies have focused on its major by-product, chlorite, which is considered in section 4.6. The present review will first focus on the limited characterization of chlorine dioxide’s general toxicology, then follow up with a discussion of its haematological and thyroid effects.

Some very cursory investigations of chlorine dioxide’s effects as a respiratory irritant were published by Haller & Northgraves (1955) in an article dealing with the general chemical properties of the compound. In essence, these data suggested that exposure to chlorine dioxide in air at a concentration of more than 420 mg/m³ (150 ppm) for

longer than 15 min was fatal to guinea-pigs. The total study involved six guinea-pigs.

Rats (3–5 per group) were exposed to chlorine dioxide in various concentrations (0.28–9520 mg/m³ [0.1–3400 ppm]) and for various periods (3 min–10 weeks). All the rats exposed daily to chlorine dioxide at 28 mg/m³ (10 ppm) died in less than 14 days. Purulent bronchitis and disseminated bronchopneumonia were found at necropsy. No such changes were demonstrable in rats exposed to approximately 0.28 mg/m³ (0.1 ppm) for about 10 weeks (Dalhamn, 1957).

The LC₅₀ of chlorine dioxide in rats (5 per sex per group) exposed by inhalation for 4 h was 90 mg/m³ (32 ppm) (Ineris, 1996).

Robinson et al. (1986) studied the ability of chlorine and alternative disinfectants to induce epidermal hyperplasia in the skin of Sencar mice. The thickness of the interfollicular epidermis was significantly increased by 10-min daily exposures to water containing up to 1000 mg of chlorine dioxide per litre for 4 days. The thickness of the epidermis was similar to that induced by an equivalent dose of hypochlorous acid. Unlike hypochlorous acid, however, there was no significant increase in skin thickness at concentrations of 300 mg/litre or less.

The study of Daniel et al. (1990a) was the first subchronic study that adhered to modern expectations of toxicological studies. These authors provided male and female Sprague-Dawley rats (10 per sex per treatment group) with 0, 25, 50, 100 or 200 mg of chlorine dioxide per litre of drinking-water for 90 days, equivalent to 0, 2, 4, 6 or 12 and 0, 2, 5, 8 or 15 mg/kg of body weight per day for males and females, respectively. Conventional measures of body weight, organ weights, a broad battery of clinical chemistry parameters and histopathological examinations were all included in the study design. Body and organ weights were significantly depressed at 200 mg/litre in both sexes. This appeared to be secondary to depressed water consumption, which is known to be tightly coupled to food consumption in rats. The only significant histopathological damage found was goblet cell hyperplasia and inflammation. This was observed at all doses of chlorine dioxide in both male and female rats. Presumably this inflammation occurs as a result of volatilization of

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chlorine dioxide from the water bottle. The amount of chlorine dioxide actually inhaled as a result of volatilization from the drinking-water containing the lowest dose of chlorine dioxide (25 mg/litre) must be extremely low. This suggests that there might be some concern for sensitive individuals showering with water containing chlorine dioxide.

The ability of chlorine dioxide to induce methaemoglobinaemia and haemolytic anaemia has received extensive study. Abdel-Rahman et al. (1980) found decreased red blood cell glutathione (GSH) concentrations and decreased osmotic fragility in Sprague-Dawley rats and white leghorn chickens given drinking-water containing chlorine dioxide concentrations of 1, 10, 100 and 1000 mg/litre for up to 4 months, but the changes were not consistently dose-related. However, the authors found that the morphology of red blood cells was modified (codocytes and echinocytes) in all dose groups, the severity increasing with increased treatment concentration. Methaemoglobin was not detected throughout these studies. However, there was no formal statistical evaluation of these results, and only four rats were assigned to each experimental group. Administration of acute doses of as little as 1 mg/kg of body weight by gavage decreased red blood cell GSH concentrations. This response was not increased as dose was increased to 4 mg/kg of body weight.

Abdel-Rahman and co-workers extended these observations to longer treatment periods in a subsequent publication (Abdel-Rahman et al., 1984a). Again, only four animals were assigned to each treatment group. At 7 and 9 months of treatment, red blood cells appeared to become resistant to osmotic shock at all treatment concentrations (1–1000 mg/litre). These data did not display a clear dose–response despite the large variation in the dose administered.

The study of Abdel-Rahman et al. (1984a) also reported changes in the incorporation of ³H-thymidine into the DNA of various organs. Incorporation was significantly inhibited in testes and apparently increased in the intestinal mucosa. The effect on apparent DNA synthesis was particularly marked in the testes at 100 mg/litre, amounting to about 60% inhibition. These data are difficult to interpret for several reasons. First, rats were sacrificed 8 h after being injected with ³H-thymidine. Ordinarily, sacrifices are made 30–60 min after injection because the blood is essentially depleted of ³H-thymidine in an hour. Thus, it is not possible to determine if the lowered amount of label is related to decreased synthesis or to

increased turnover of DNA. Second, the result was based on total counts in DNA, which makes it impossible to determine what cell type is affected or whether the change was associated with replicative or repair synthesis. Third, only four animals were used per experimental group.

In a rising-dose protocol study, Bercz et al. (1982) evaluated the effects of chlorine dioxide on African green monkeys. These animals were provided chlorine dioxide in drinking-water at concentrations of 0, 30, 100 or 200 mg/litre, corresponding to doses of 0, 3.5, 9.5 or 11 mg/kg of body weight per day. Each dose was maintained for 30–60 days. Animals showed signs of dehydration at the highest dose (11 mg/kg of body weight per day), so exposure at that dose was discontinued. No effect was observed on any haematological parameter, including methaemoglobinaemia. However, statistically significant depressions in serum thyroxine levels were observed when animals were dosed with chlorine dioxide at a concentration of 100 mg/litre. No effect had been observed in a prior exposure of the same animals to 30 mg/litre for 30 days. The NOAEL in this study was 3.5 mg/kg of body weight per day.

The effects of chlorine dioxide on thyroid function were followed up by Harrington et al. (1986). Thyroxine levels in African green monkeys administered drinking-water containing 100 mg of chlorine dioxide per litre (4.6 mg/kg of body weight per day) were again found to be depressed at 4 weeks of treatment, but rebounded to above-normal levels after 8 weeks of treatment. These investigators also found significantly depressed thyroxine levels in rats treated with 100 or 200 mg of chlorine dioxide per litre in drinking-water (equivalent to 14 and 28 mg/kg of body weight per day) for 8 weeks. This change was dose-related. Lower doses were not examined in the rat study. The authors indicated that the results were based on 12 determinations; it was not clear if these measurements were made on individual animals.

A set of *in vivo* and *in vitro* experiments was conducted in an attempt to explain the effects of chlorine dioxide on serum thyroid hormone concentrations. The authors demonstrated that chlorine dioxide oxidizes iodide to reactive iodine species that would bind to the stomach and oesophageal epithelium. Rat chow that was treated with chlorine dioxide at approximately 80 mg/litre was found to increase the binding of iodine to chow constituents. This activation of iodine resulted in retention of labelled iodine in the ileum and colon

and reduced uptake by the thyroid gland. Previous work demonstrated that chlorine dioxide was more effective than chlorine in activating iodide to a form that would covalently bind with a variety of natural foodstuffs (Bercz et al., 1986). Based on these observations, the authors concluded that the effects of chlorine dioxide were probably due to altered gastrointestinal absorption of iodide and reduced uptake into the thyroid gland.

3.3.2 *Reproductive and developmental toxicity*

A number of reproductive effects have been reported in studies with laboratory animals, but the relevance for humans of these findings remains uncertain. The reproductive effects of chlorine dioxide in Long-Evans rats were studied by Carlton et al. (1991). Chlorine dioxide was administered by gavage at doses of 2.5, 5 or 10 mg/kg of body weight per day to male rats (12 per group) for 56 days prior to and through mating and to female rats (24 per group) from 14 days prior to mating and through pregnancy. Fertility measures were not significantly different among the dose groups. There were no dose-related changes in sperm parameters (i.e., concentration, motility, progressive movement or morphology). Thyroid hormone levels were altered significantly, but not in a consistent pattern. The only significant difference was significantly depressed vaginal weights in female pups whose dams had been treated with 10 mg/kg of body weight per day.

An evaluation of the effects of chlorine dioxide on the fetal development of Sprague-Dawley rats was conducted by Suh et al. (1983). Chlorine dioxide was administered at 0, 1, 10 or 100 mg/litre (0, 0.1, 1 or 10 mg/kg of body weight per day) for 2.5 months prior to mating and throughout gestation. The total number of implants per dam was significantly reduced at the highest concentration of chlorine dioxide. The percentage of anomalous fetuses was increased in a dose-related manner, but the response was not statistically significant. These anomalies arose primarily as the percentage of abnormal or incomplete sternebrae in treated rats relative to controls. The lack of statistical significance was undoubtedly related to the relatively few female rats that were included in the study (6–8 females per treatment group). As a consequence, the results of this study must be considered inconclusive.

Orme et al. (1985) found that chlorine dioxide administered in the drinking-water of female Sprague-Dawley rats (13–16 per dose) at concentrations of 0, 2, 20 or 100 mg/litre (0, 1, 3 or 14 mg/kg of body weight per day) throughout pregnancy and through weaning decreased thyroxine levels in the serum of the pups at 100 mg/litre. This was associated with delayed development of exploratory behaviour in the pups away from their dams, and this, in turn, was probably due to an indirect effect on iodine uptake. In a second experiment, pups given 14 mg of chlorine dioxide per kg of body weight per day directly by gavage on postnatal days 5–20 showed significantly depressed activity and a decrease in serum thyroxine levels. Studies by the same group (Taylor & Pfohl, 1985) indicated that cerebellar and forebrain cell counts (based on DNA measurements) were depressed in 11-day-old pups that had been treated with chlorine dioxide at 14 mg/kg of body weight per day by gavage from 5 days of age. Cerebellar cell counts remained depressed in rats at 21 days, but forebrain counts were essentially the same as in controls. At 50–60 days of age, the locomotor activity (measured by wheel-running) of these animals was depressed relative to control animals.

The effects of chlorine dioxide on brain development were examined further by Toth et al. (1990). These authors administered chlorine dioxide by gavage at 14 mg/kg of body weight per day from postnatal day 1 to 20. Body weight was reduced, but cerebellar weight was unaltered at any age. Forebrain weight and protein content were reduced on postnatal days 21 and 35. DNA content was depressed on postnatal day 35, and the number of dendritic spines on cerebral cortical pyramidal cells was significantly reduced. No histopathological changes in the forebrain, cerebellum or brain stem were observed. There were no consistent changes in serum thyroxine or triiodothyronine levels in treated animals.

Collectively, these data suggest some effects of chlorine dioxide on brain development. In most studies, there are suggestions of modified thyroid function associated with these effects. It must be pointed out that the changes in thyroid hormone levels are modest, much less than are produced with classical antithyroid drugs such as propylthiouracil (Toth et al., 1990).

3.3.3 Toxicity in humans

The effects of chlorine dioxide were assessed in a two-phase study in 10 healthy male volunteers. The first study was a rising-dose tolerance study (Lubbers & Bianchine, 1984) in which doses of chlorine dioxide were increased from 0.1 to 24 mg/litre, administered in two 500-ml portions. The maximum dose for a 70-kg person was 0.34 mg/kg of body weight. The details of this study were described in section 3.1.3. Some small changes in a variety of clinical chemistry parameters were observed, but none was found to be outside the accepted range of normal. The second phase of the experiment involved the daily administration of a 500-ml portion of a solution containing 5 mg/litre to 10 healthy volunteers for a period of 12 weeks (Lubbers et al., 1984a). Again, measurement of a large battery of clinical chemistry parameters and routine physical examination failed to identify any effects of chlorine dioxide that fell outside of the normal range. Parameters yielding significant differences appeared to be primarily a result of parallel drift of values with the control group.

As with other disinfectants, it is important to recognize that chlorine dioxide is a potent respiratory irritant. No quantitative data can be used to construct a dose–response relationship for this effect.

3.3.4 Carcinogenicity and mutagenicity

The mutagenic or clastogenic effects of chlorine dioxide have received little attention. Ishidate et al. (1984) found chlorine dioxide to be positive in *Salmonella typhimurium* tester strain TA100. A linear dose–response was observed at concentrations between 2 and 20 : g per plate. Chlorine dioxide was ineffective as a clastogenic agent in a CHO system.

Meier et al. (1985b) evaluated the ability of chlorine dioxide to induce chromosomal aberrations and micronuclei in bone marrow of CD-1 mice or sperm head anomalies. Chlorine dioxide failed to produce such damage following gavage doses of up to 16 mg/kg of body weight for 5 days.

With the exception of a 1949 study by Haag (cited in TERA, 1998), which has serious limitations, no tests of the carcinogenic

activity of chlorine dioxide in experimental animals were identified in the scientific literature.

3.3.5 Comparative pharmacokinetics and metabolism

There are significant differences in the pharmacokinetics of ^{36}Cl obtained from different disinfectants. The absorption rate for ^{36}Cl -labelled chlorine dioxide was at least 10 times that observed with chlorine, chloramine or chloride. The relative amount of ^{36}Cl that is eliminated in the urine and faeces at 24 h has a distinct pattern from that observed with other disinfectants and sodium chloride. However, the terminal half-life of the ^{36}Cl appears similar for all disinfectants. These data suggest that the form of ^{36}Cl that is being absorbed differs chemically with the different disinfectants. In the case of chlorine dioxide, this is supported by the observation that measurable amounts of chlorite (about 3% of the original dose) are eliminated in the urine during the first 24 h, and chlorite comprises about 20% of the label present in blood 72 h after administration of the test dose (Abdel-Rahman et al., 1980). However, this higher absorption rate is not explained by the absorption rates of chlorite and chlorate, which are about one-tenth as rapid (Abdel-Rahman et al., 1982b). This suggests that some of the absorption could be as chlorine dioxide itself. On the surface, this hypothesis would seem to be incompatible with the high reactivity of this disinfectant. As with other disinfectants, the terminal elimination phases observed for ^{36}Cl from chlorine dioxide seem compatible with the hypothesis that the bulk of the elimination is as chloride ion.