Disinfection as a Source of Diverse By-Products of Potential Health Concern

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It is well known that chlorine as hypochlorous acid or hypochlorite can function both as an oxidizing agent and a halogenating agent (Rice, 1987). Oxidation is probably the predominant chemical process occurring in chlorine's water and food contact applications, but the halogenated by-products have received the most attention. The chemistry and distribution of by-products produced differs somewhat with the pH of the solution as well as the composition of the precursor chemicals that are available for reaction.

Table 1 Relative characteristics of oxidants/disinfectants
(*from Rice and Gomez-Taylor, 1987)*

Oxidant	Disinfecting Efficiency	Oxidizing Efficiency	Halogenation Capability
Chlorine	**High**	**High**	**High**
Chlorine dioxide	**High**	**High**	**Low**
Monochloramine	**Low**	**Low**	**Low**
Ozone	**High**	**High**	**None (no bromide)**
Hydrogen peroxide	**Low**	**Moderate**	**None**
Bromine	**High**	**Moderate**	**High**
Iodine	**High**	**Low**	**Low**

There are numerous detailed assessments and reviews of the chemistry and toxicology of chlorine and by-products in water (EHC, 2000; WHO, 1996; WHO, 2004; Federal Register, 2006, Bull, 2006; Woo, 2002). The toxicology of numerous DBPs has been studied extensively for more than 30 years, however, the number of by-products is so large and their individual concentrations are so low that it is questionable whether there is value in examining many of them in detail. One study applied structure-activity techniques and genotoxicity data as a method for prescreening the DBPs in order to rank them in respect to carcinogenic potential from long term exposure (Woo et al, 2002). Of the 209 DBPs analyzed, only 20 were of priority concern with Moderate or High-Moderate rating. Four of those were structural analoges of MX, and five were haloalkanes that are likely controlled by regulations. The remaining eleven included halonitriles, haloketones, haloaldehyde, halonitroalkane and dialdehyde. This project only examined compounds for which some occurrence data existed. The Bull et al. (2006) report reported similar conclusions for these identified DBPs, but extended the work to compounds that were predicted to occur based on the chemistry of natural organic matter, but for which occurrence data had not been collected. This study identified haloquinones, nitrosamines, and organic N-chloramines as additional DBPs that should be of concern.

Disinfection by-products in drinking water and recycled water

Chlorination and chlorinated/brominated by-products are the most extensively studied chemicals produced from disinfectants and sanitizers in water. One reason is that compared to non-halogenated

compounds, they are more readily separated from water solutions for analysis due to their hydrophobicity.

The best indication of the complexity is probably best illustrated in Tables 2 and 3 by the numerous categories of halogenated by-products that have been detected in one or more studies (longer lists exist). Naturally occurring polyphenolic compounds are some of the most likely precursors for many of the products. The trihalomethanes of historical interest include chloroform, bromodichloromethane, dibromochloromethane and bromoform (Cotruvo, 1981; Cotruvo, 1982) but several other brominated/iodinated THMs have been detected at much lower frequencies and concentrations. Since that time numerous families and hundreds of individual halogenated disinfection by-products (DBPs) have been identified and quantified in chlorinated drinking water. Among these are halogenated acetic acids (HAAs), haloacetonitriles HANs), haloketones, halopicrins, halophenols, and halofuranones, in addition to non-halogenated oxidized products such as acids, aldehydes and ketones. As a group, the THMs and HAAs probably account for the largest portion of the identifiable DBPs in chlorinated drinking water (perhaps half in many cases).

Chlorine will oxidize bromide in water to HOBr, which is a more active halogenating agent than HOCl, so in the presence of bromide the analogous brominated and mixed halogenated by-products will be formed and probably predominate, e.g., in chlorinated desalinated water which often contains milligram amounts of bromide. In the presence of ammonia or organic amines hypochlorous acid will form N-chloro compounds such as mono- and dichloramine from ammonia, and monochloramine is used as a secondary disinfectant *vide infra*.

Several hundred individual DBPs have been identified at parts per billion to parts per trillion levels in drinking water. The aggregated total quantity of DBPs in a drinking water may range from a few micrograms per liter in very low organic carbon groundwater or membrane treated water, to perhaps a milligram per liter or more in some waters with high levels of NOM precursors, depending upon the chlorine dosage, quantity of NOM precursors, pH, temperature and contact time. In the presence of ammonia and amines, chloramines will rapidly form and they are poor halogenating and oxidizing agents, so the presence of ammonia will suppress the formation of many but not all of the halogenated and oxidized DBPs.

While many DBPs have been identified, there are good comprehensive quantitative data available for a few dozen in water supplies. Data from a recent study of 12 utilities using several disinfectants in the U.S. and Canada by the U.S. EPA (2004; also reported in Krasner *et al*, 2006) provided in Tables 2 and 3 is probably indicative of many water supplies. The disinfectants used varied among these utilities, with ozone (1 utility) and chlorine dioxide (4 utilities) employed in some utilities, but all systems employed chlorine or chloramines at some stage in the treatment. These data may differ slightly from those reported because the means represent the average of utility means, rather than an overall mean of all samples. Since the U.S. EPA survey included only 12 utilities, it probably does not reflect extreme occurrences of DBPs. Nevertheless, the variation of DBP concentrations among the 12 utilities ranges up to two orders of magnitude. It should not be assumed that the concentrations covary with one another in dependable patterns among water utilities or even within the same system in different seasons of the year (Wright *et al*., 2002; Bull *et al*, 2008).

A key consideration for potable reuse of wastewater is that many DBPs are of low molecular weight and some have low polarity and this has resulted in their appearance in the product waters after reverse osmosis and AOX treatment (Project Occurrence Database). DBPs are the only group of chemicals which occurred in the final product waters at concentrations that exceed 1 µg/L. Since many of these compounds are mutagenic, they fall into a category under the threshold of toxicological concern (TTC) methodology of chemicals that require chemical specific data to estimate risk.

Table 2. Disinfectant by-products in 12 drinking water utilities in U.S. and Canada[a]

Disinfectant By-Product	Number of utilities	Mean	Median	Range
Chloroform	12	16[b]	12	0.5-47
Bromodichloromethane	12	10	12	2.2-19
Dibromochloromethane	12	6.5	4.7	0.1-20.5
Bromoform	12	2.1	0.7	6.4
Dichloroiodomethane	12	1.1	0.45	0.08-1.5
Bromochloroiodomethane	12	0.4	0.3	0-2.5
Dibromoiodomethane	10	0.29	0	2.5
Chloroiodomethane	12	0.11	0	0-1.1
Bromodiiodomethane	12	0.03	0	0-0.4
Iodoform	12	0.04	0	0-0.4
Monochloroacetic acid	12	1.6	0	0-3.9
Monobromoacetic acid	12	0.3	0.27	0-1.0
Dichloroacetic acid	12	14	15	1.4-22
Bromochloroacetic acid	12	5.9	4.4	1.7-11
Dibromoacetic acid	12	3.4	1.2	0-12
Trichloroacetic acid	12	9.4	6.1	0.5-35
Bromodichloroacetic acid	12	4.6	5.5	0-9.4
Dibromochloroacetic acid	12	2.2	1.5	0-5.9
Tribromoacetic acid	12	0.12	0	0-0.9
Chloroacetonitrile	12	0.07	0.055	0-0.26
Bromoacetonitrile	12	0.005	0	0-0.04
Dichloroacetonitrile	12	1.4	1.2	0.1-4.1
Bromochloroacetonitrile	11	0.8	0.6	0-2.6
Dibromoacetonitrile	12	0.6	0.3	0-2.3
Trichloroacetonitrile	12	0.02	0	0-0.15
Bromodichloroacetonitrile	12	0	0	0-0.4
Dibromochloroacetonitrile	12	0.01	0	0-0.15
Tribromoacetonitrile	12	0	0	0
Dichloroacetaldehyde	12	2.2	1.7	0.4-11.1
Bromochloroacetaldehyde	12	0.5	0.32	0-1.3
Chloral hydrate	12	2.2	1.8	0.2-5.9
Tribromoacetaldehyde	12	0.19	0.04	0-0.93
Chloropropanone	12	0.22	0.11	0-1.1

1,1-Dichloropropanone	12	0.61	0.58	0.12-1.3
1,3-Dichloropropanone	12	0	0	0
1,1-Dibromopropanone	12	0.032	0	0-0.12
1,1,1-Trichloropropanone	12	1.3	1.4	0.03-3.6
1,1,3-Trichloropropanone	12	0.02	0.02	0-0.13
1-Bromo-1,1-dichloropropanone	12	0.24	0.2	0-0.95
1,1,1-Tribromopropanone	12	0	0	0
1,1,3-Tribromopropanone	12	0.005	0	0-0.033
1,1,3,3-Tetrachloropropanone	12	0.05	0	0-0.26
1,1,1,3-Tetrachloropropanone	12	0.08	0.07	0-0.13
1,1,3,3-Tetrabromopropanone	12	0.05	0	0-0.025
Chloronitromethane	12	0.04	0	0-0.16
Bromonitromethane	12	0.02	0	0-0.08
Dichloronitromethane	12	0.12	0.24	0-0.38
Bromodichloronitromethane	12	0.11	0	0-0.42
Dibromonitromethane	12	0.07	0	0-0.19
Chloropicrin	12	0.26	0.16	0.04-0.92
Bromodichloronitromethane	12	0.32	0.24	0-1.0
Dibromochloronitromethane	12	0.30	0.18	0-0.44
Bromopicrin	12	0.35	0	0-0.63

[a] Weinberg *et al.* 2002; Krasner *et al*. 2006
[b] Concentrations in µg/L

Table 3. Additional analyses of disinfection by-products and total organic halogen in a survey of 12 utilities in the U.S and Canada[a].

Disinfectant By-Product	Number of Utilities	Mean	Median	Range
Monochloroacetaldehyde	12	0.42[b]	0.22	0-1.3
Dichloroacetaldehyde	12	3.4	2.7	0.5-9.5
Bromochloroacetaldehyde	11	1.2	1.1	0.1-3.5
3,3-Dichloropropenoic acid	12	0.43	0.14	0-2.7
Bromochloromethylacetate	12	0.036	0	0-0.4
Monochloroacetamide	8	0.14	0	0-0.5
Monobromoacetamide	8	0.24	0	0-1.1
2,2-Dichloroacetamide	12	1.5	1.7	0-3.8
Dibromoacetamide	8	0.87	0.25	0-2.8
Trichloroacetamide	8	0.51	0.30	0-1.1
BMX-1[c]	10	0.034	0	0-0.13
BEMX-1	10	0.10	0	0-0.72
BMX-2	10	0.028	0	0-0.15
BEMX-2	10	0.12	0	0-0.81
BMX-3	10	0.004	0	0.04
BEMX-3	10	0.097	0	0-0.41

MX	12	0.11	0.020	0-0.18
Red-MX	2	0.033		0-0.29
EMX	12	0.013	0	0-0.10
ZMX	10	0.011	0	0-0.12
Ox-MX	10	0	0	0
Mucochloric acid (ring)	12	0.085	0.01	0-0.71
Mucochloric acid (open)	12	0.081	0.09	0-0.19
TOX	12	169[c]	182[c]	65-236[c]

[a] Weinberg et al. 2002; Krasner et al. 2006
[b] Concentrations in µg/L
[c] Abreviations: MX = 3-chloro-4-(dichloromethyl-5-hydroxy-2H(5H)-furanone; BMX-1 = 3-chloro—4-(bromochloromethyl-5-hydroxy-2(5H)-furanone; BMX-2 = 3-chloro-4-(dibromomethyl-5-hydroxy-2H(5H)-furanone; BMX-3 = 3-bromo-4-(dibromomethyl-5-hydroxy-2H(5H)-furanone; EMX =(E)-2-chloro-3-(dichloromethyl)-4-oxobutenoic acid;

BEMX-1, BEMX-2, BEMX-3 = corresponding brominated analogs of EMX.

N-Chloramines

N-Chloramines are produced from the chemical reactions between ammonia or amines and chlorine. The most common form is monochloramine ((CAS 10599-90-3). Chloroamines may be deliberately produced by combining the ammonia or amines with chlorine prior to contact with the medium to be disinfected or they may be spontaneously formed whenever chlorine is used if ammonia or amines are present in the medium. Wastewaters are heavily contaminated with nitrogenous chemicals from human waste products. In addition to inorganic N-chloramine, there are analogous organic N-chloramines. N-chlorodimethylamine is an example of an organic amine formed from dimethylamine. N-chloramines are labile so they will exchange halogens as well as transfer halogens to other amine or amide compounds with which they are in proximity.

N-chloramine chemistry
Because of its low oxidizing efficiency and low halogenation capability monochloramine has a lesser tendency to produce halogenated DBPs and oxidation products. Related chemicals are N-chloroamides that could be formed by reactions of chlorine with amides such as protein peptides. N-chloramine can react with secondary amines such as dimethylamine to produce dimethylhydrazine which can be oxidized in the presence of the chloramine to N,N-dimethylnitrosamine (Choi, 2002; Mitch, 2002).

Figure 1

$$NH_2Cl + (CH_3)_2NH \rightarrow (CH_3)_2\,N\text{-}NH_2$$

$$(CH_3)_2\,N\text{-}NH_2 + NH_2Cl/OCl^- \text{(Oxidation)} \rightarrow CH_3)_2N\text{-}N{=}O$$

Chloramine and organic chemical exposures

Human exposure to chloramines is primarily from consumption of chloraminated drinking water, which is regulated not to exceed 4 mg/l in the USA. At the default daily consumption level of drinking water, this could be as much as 6 to 8 mg/day.

Other DBPs of potential interest

There are some concerns about the focus on regulated by-products as being indicative of the hazards associated with disinfection by-products in general. Efforts to control some of these by-products are likely to reduce or produce or substantially increase the concentrations of some other by-products that are likely to be much more potent toxicologically. The chemistry and detection of numerous DBPs has been studied extensively for more than 30 years, however, the number of by-products is so large and their individual concentrations are so low that it is questionable whether there is value in examining many of the individual chemicals in detail. In an attempt to identify higher interest candidates one study applied structure-activity techniques and genotoxicity data as a method for prescreening of 209 DBPs in order to rank them in respect to carcinogenic potential from long term exposure (Woo *et al,* 2002). A subsequent structure activity study of novel by-product formation from substructures within NOM identified haloquinones and used QSAR and analogies with related compounds to identify several other by-products that could be of interest (Bull *et al*, 2006). Chemicals identified in this study included those identified by Woo (Woo *et al*, 2002), but provided an additional list of probable by-products. Those considered to be of most concern were a number of halogenated quinones, halogenated cyclopentenoic acid derivatives, halonitriles, and various N-chloramines. In addition nitrosamines (e.g., N,N-dimethylnitrosamine etc. are known to be formed in water containing N-chloramines and secondary amines.

MX-related chemicals

Another chemical family of interest that have been detected in ppt levels in chlorinated drinking water is the MX-related chemicals. MX (3-chloro-4-(dichloromethyl)-5-hydroxy-2-[5H]furanone) is the common name applied to one member of a group of halomethylhydroxyfuranones formed from oxidation, halogenation and ring cleavage of phenolic-type natural organics in the water. They are cyclic lactones or open chain carboxyl compounds and would not be highly volatile. These chemicals have been shown to be multitarget carcinogens in the rat, and they are strongly positive in the Ames chemical mutagenicity assay. Levels of MX in drinking water have been detected in the range of 3 to 310 parts per trillion with the 75th percentile concentration of 60 ppt (Krasner *et al*, 2006).

MX is the common name applied to a group of halomethylhydroxyfuranones probably formed from oxidation, halogenation and ring cleavage of phenolic-type natural organics in the water. They are cyclic lactones or open chain carboxyl compounds and would not be highly volatile. These chemicals have been shown to be multitarget carcinogens in the rat, and they are strongly positive in the Ames chemical mutagenicity assay. Three of the MX compounds were in the highest rank of High-Moderate concern; the remaining 17 were in the Moderate category. These halogenated MX compounds included chlorinated and brominated analogues (Woo et al, 2002). A bioassay was conducted in male and female Wistar rats at doses ranging from 0.4 mg/kg/day to 6.6 mg/kg/day (Komulainen *et al*, 1997). Tumors were found at all of the test doses. Levels of MX in drinking have been detected in the range of 3 to 67 parts per trillion. An estimated calculation of the risk from lifetime consumption of 2 litres of drinking water per day containing 67 ppt (the highest concentration detected at that time) yielded a hypothetical risk of 2

in 1,000,000 (Melnick *et al* , 1997). This is a low risk with respect to the WHO Guidelines for Drinking-water Quality which utilizes a reference value of 1 in 100,000. Also, the USEPA drinking water regulations are considered safe when falling in the hypothetical risk range of 1 in 10,000 to 1 in 1,000,000. However, there is also the possibility that small amounts of these chemicals are rapidly detoxified by thiols such as glutathione after ingestion.

There are some concerns about the focus on regulated by-products as being indicative of the hazards associated with disinfection by-products in general. Efforts to control some of these by-products are likely to reduce or produce or substantially increase the concentrations of some other by-products that are likely to be much more potent toxicologically. It has long been known that various phenolic precursors are intermediates in the formation of most of the THMs and HAAs. Excess chlorine results in cleavage of the phenolic ring to give rise to haloacids and THMs. If chloramine is utilized in place of free chlorine to reduce THMs and HAAs, there is a high likelihood that higher concentrations of halogenated quinones will be encountered than in the presence of free chlorine (Heasley *et al*., 2004; Bull *et al*., 2006). Moreover, N-chloramines can interact with other secondary amines in the water to form N-nitrosamines, usually in the parts per trillion range, but occasionally at ppb levels. The latter levels have been found primarily in wastewaters that contain unusually large amounts of ammonia and secondary amines as compared to typical drinking waters. However, the question of whether additional nitrosamines may be formed with certain alkaloids (e.g. 3-methylindole) that occur in surface waters should be explored. These by-products are likely to be of health concern if they occur in the ng/L range.

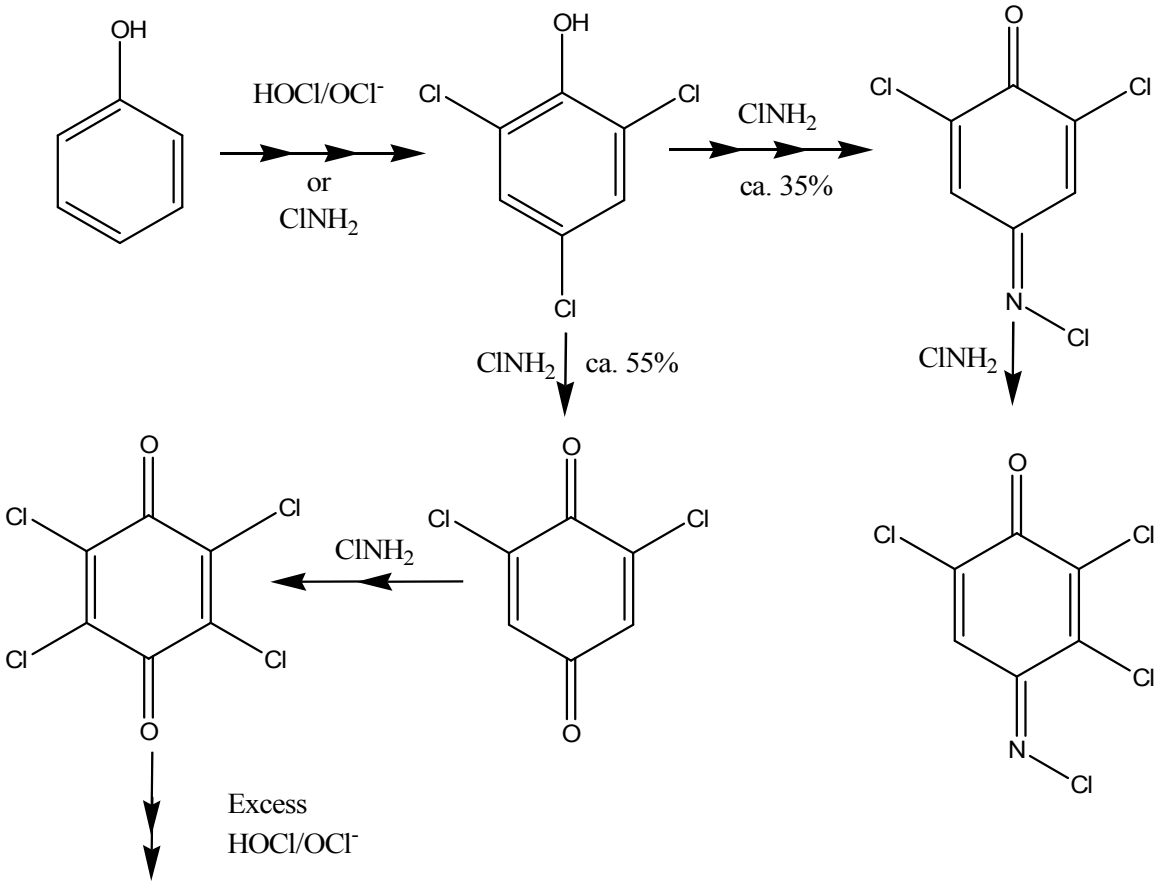
Finally, the hypochlorite in solution can disproportionate to form significant amounts of chlorate upon storage at warm temperatures for long periods of time. Therefore, hypochlorite solutions should be stored under temperate conditions and used reasonably soon after purchase and not stored for months.

Haloquinones

The formation of the major regulated by-products goes through a series of intermediates with various phenolic and other unidentified precursors that naturally occur in surface waters, but may not occur in many foods. It is important to recognize that changing from processes that utilize free chlorine to the use of chloramine has a high likelihood of preserving some of the intermediate species. Figure 2 illustrates the changes in products that would be expected by reactions with phenol treated with chloramine in place of free chlorine. A variety of quinone structures have been shown to occur with chloramine that will be destroyed by ring cleavage with free chlorine (Heasley *et al,* 2004). Treatment of the related phenol structures, m-cresol and resorcinol, are the principal sources of THMs in treated drinking water. It has long been known that various phenolic precursors are intermediates in the formation of most of the THMs and HAAs. Excess chlorine results in cleavage of the phenolic ring to give rise to haloacids and THMs. If chloramine is utilized in place of free chlorine to reduce THMs and HAAs, there is a high likelihood that higher concentrations of halogenated quinones will be encountered than in the presence of free chlorine (Heasley *et al*., 2004; Bull *et al*., 2006). Moreover, N-chloramines can interact with other secondary amines in the water to form N-nitrosamines, usually in the parts per trillion range, but occasionally at ppb levels. The latter levels have been found primarily in wastewaters that contain unusually large amounts of ammonia and secondary amines as compared to typical drinking waters. However, the question of whether additional nitrosamines may be formed with certain alkaloids

(e.g. 3-methylindole) that occur in surface waters should be explored. Because of their structures and functional mechanisms these by-products are likely to be of jnterest if they occur in the ng/L range.

Figure 2



Haloacids and aliphatic products

Finally, the hypochlorite in solution can disproportionate to form significant amounts of chlorate upon storage at warm temperatures for long periods of time. Therefore, hypochlorite solutions should be stored under temperate conditions and used reasonably soon after purchase and not stored for months.

Dissolved organic nitrogen

Nitrogen compounds are ubiquitous in water but often difficult to isolate and analyze so they have been mostly studied later in the evolution of DBP analyses. They are largely composed of degraded amino sugars, peptides and porphyrins but many other chemical forms can exist. It is logical to expect that recycled waters being derived from wastewaters would contain significant quantities of organic compounds derived from bacterial activity and indeed from the degradation of bacterial cells. Leenheer and Westerhoff have studied fractionation techniques involving

membrane dialysis, solvent extraction, and use of XAD resins. Among the fractions they isolated were colloids (amino sugars which are reflective of bacterial cell wall degradation), hydrophobic and amphiphilic neutrals (peptides) peptides, amino acids, and hydrophilic bases.

Many types of nitrogen compounds are biologically active so they are a mostly untapped reservoir of chemicals of interest. One group of particular interest includes the organic N-chloramines, that are readily formed by halide exchange with other N-chloramines, including monochloramine. This exchange could occur in water during processing or *in vivo* after ingestion.

Organic N-Chloramines

Organic N-chloramines have long been known to form in drinking water treated with chlorine or chloramine. They are largely regarded as a nuisance as they reduce disinfection by decreasing the available free chlorine. There has been little systematic work to characterize the forms of organic N-chloramine that are present in water beyond the formation of the N-chloramines of α-amino acids. The broad spectrum of more diverse organic nitrogen compounds that can occur in wastewater at relatively high concentrations indicates that it is necessary to better understand the nature of these by-products and their potential toxicological effects.

Organic N-chloramines produced from α-amino acids are generally more readily formed and they degrade more readily than compounds that either have no carboxyl group or if it is further removed from the amine group. While slower in formation, dichloramines are more readily formed with non-amino acid nitrogens at physiological pH and probably in drinking water (Nightingale et al., 2000). At the macromolecular level, exocyclic nitrogens of purine and pyrimidine bases react more readily to form N-chloramines, but over time the chlorine is transferred to cyclic nitrogens and these under radical decay and are responsible for damaging DNA (Hawkins and Davies, 2001; Hawkins and Davies, 2002). The same phenomenon has been demonstrated to occur in chlorinated wastewater (Bedner et al., 2004). Organic N-chloramines produced in plasma proteins have a half-life of approximately 2 hours, indicating they are sufficiently stable to survive to reach critical targets in vivo (Hawkins and Davies, 19990.

The toxicological properties of administered organic N-chloramines have only been studied with in vitro systems. In general, dichloramines are substantially more active than monochloramines (ca 30-fold) (Thomas et al., 1987). In part, this probably reflects decreased polarity of the compounds, but may reflect some differences in the specificity of reactions that occur with dichloramines vs. monochloramines. In a project being conducted with South Australia water, it appears that mutagenic activity is greater with those chloramines with the longest half-lives (e.g. N-chloroglycine among monochloramines and N-dichloroethanolamine).

More interesting properties of the organic N-chloramines are their involvement in modifying processes involved in the cell cycle. In particular, they have been shown to cause apoptosis in some systems (Englert and Schacter, 2002), but suppress apoptosis in others (Than et al., 2001). N-chloramines produced by phagocytic cells have been shown to be inhibitors of DNA repair (Pero et al., 1996) and monochloramine produces cell cycle arrest (Hosako et al., 2003). Modification of processes involved in cell cycle control are associated with the development of cancer in the intact animal.

Organic-N-chloramines that could occur in disinfected water are potentially quite diverse. As there are no in vivo data for these compounds (other than monochloramine, itself), in vivo

information of any orally administered organic N-chloramines is available. Some information is needed on selected chemicals to assess the probable risks associated with the class as a whole. The few compounds identified below were selected as likely to be representative of the type of organic N-chloramines that could be of greatest concern.

Disinfectant residues and DBPs
Chlorate (present in stored hypochlorite solutions)
Bromate (formed from ozonation of bromide, and a chlorine contaminant))

Quinone derivatives
2-chloro-1,4-dibenzoquinone
2,3-dichloro-1,4-dibenzoquinone
2,3,6-trichloro-1,4-dibenzoquinone
2,6-dichloro-3-methyl-1,4-benzoquinone
2,6-dichloro-1,4-benzoquinone-4-(N-chloro)imine
2,3,5,6-tetrachloro-1,4-dibenzoquinone (probably less toxic and/or carcinogenic than other members of the class)

Organic N-chloramines
N-chloroethanolamine
N-dichloroethanolamine
N-chloroglycine and other N- haloaminoacids
ε-N-chlorolysine and dichloro form on the same nitrogen. The α-N-chlorolysine of interest for comparison, because it is less likely to form the dichloramine at pHs used for formation of monochloramine

Nitrosamines
N-nitroso-N-dimethylamine
N-nitroso-N-diethylamine
N-nitrosomorpholine
N-nitroso-3-methylindole

MX-related compounds

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Chlorine Dioxide

Chlorine dioxide (ClO_2) (Lee, 2008) is an antimicrobial agent recognized for its disinfectant properties since the early 1900's. Chlorine dioxide is a greenish yellow gas at room temperature that is very soluble in water (EFSA, 2005). Chlorine dioxide is reduced in water generating chlorite ion; chlorite is reduced to chloride. In the absence of oxidizable substances and in the presence of alkali in water, chlorine dioxide is reduced, generating chlorite and chlorate.

Chlorine dioxide is a comparatively weak oxidizing agent, and has a lower oxidation potential than ozone, chlorine, or hypochlorous acid, thus it is more selective in its reactions. Typically, chlorine dioxide will react with compounds that have activated carbon bonds such as phenols, or with other active compounds such as sulfides, cyanides, and reduced iron and manganese compounds (Fukayama et al., 1986; SCVPH, 2003). Most importantly, chlorine dioxide is very specific in its reactivity, and enters into only a few side reactions compared to chlorine. Further, chlorine dioxide, if pure, does not chlorinate organic material and therefore does not form trihalomethanes (THMs) and other chlorinated by-products.

Chlorine dioxide in water and DBP chemistry have been described in an early review (Rice and Cotruvo, 1978). In the formation of reaction by-products in aqueous solution, aqueous chlorine dioxide can react with carbohydrates, lipids, amino acids, peptides and proteins (Fukayama et al., 1986; Rice and Gomez-Taylor, 1986). Chlorine dioxide in water acts primarily as an oxidant rather than chlorinating agent, and its redox potential in aqueous solution ($ClO_2 + e^- = ClO_2^-$, 1.15 V), is less than that of hypochlorous acid ($HClO + H^+ + 2e^- = Cl^- + H_2O$, 1.49 V). Therefore, chlorine dioxide is likely to be less reactive and produce fewer by-products than chlorine (Tsai et al., 1995).

Wastewaters can contain large amounts of bioorganic chemicals from food and animal waste. Chlorine dioxide can oxidize simple carbohydrates (e.g., glucose) to form carbonyl derivatives that are subsequently oxidized to carboxylic acids. Polysaccharides (e.g., cellulose) are also susceptible to oxidation, and may produce gluconic acid. However, some of these reactions require elevated temperatures ($> 80^oC$), and are not likely to occur in aqueous chlorine dioxide.

Some unsaturated fatty acids in lipids can react with chlorine dioxide, and produce a variety of compounds such as unsaturated ketones, chloroketones, chlorohydrins, dichloro-addition products, and epoxides (Rice and Cotruvo, 1978; Rice and Gomez-Taylor, 1986). In some instances chlorinated compounds might have occurred from chlorine dioxide that also contained some chlorine. Saturated aliphatic hydrocarbons are neither oxidized nor chlorinated by chlorine dioxide. In commercial poultry chiller water in the presence of chlorine or chlorine dioxide, 12 saturated and unsaturated aliphatic aldehydes having 5 to 11 carbons (pentanal, hexanal, heptanal, octanal, trans-2-octenal, nonanal, trans-2-nonenal, decanal, 2,2-nonadienal, trans-2-decenal, 2,4-decadienal and trans-2-undecenal) were detected by gas chromatography/mass spectroscopy (GC/MS) analysis, and hexanal and nonanal were the two major aldehydes detected (Tsai et al., 1987).

Chlorine dioxide is relatively inert toward individual amino acids, and reactions are pH-dependant (Tan et al., 1987). Chlorine dioxide oxidizes tryptophan to form indoxyl, isatine and indigo red (Fukayama et al., 1986). Tyrosine formed dopaquinone upon oxidation by chlorine dioxide. Sulfur-containing amino acids (cystine and methionine) produce bisulfoxide and

sulfonic acid derivatives (Rice and Gomez-Taylor, 1986). Reaction of aqueous chlorine dioxide with peptides and proteins is considered to be mainly due to interaction with individual amino acid moities in the peptides, but reaction by-products have not been identified.

Phenols and hydroquinones can be oxidized in the reaction with chlorine dioxide; *p*-benzoquinone and aromatic carboxylic acids are produced when chlorine dioxide is present in excess (Wajon et al., 1982). In the reaction with humic acid and other natural materials in raw water, pure chlorine dioxide does not produce THMs, but is reported to produce oxidation products (i.e., benzenepolycarboxylic acids, aliphatic dibasic acids, carboxyphenylgyloxylic acids, and aliphatic monobasic acids). Several derivatives of furan and dioxane also were identified in the reaction with humic acid and other natural materials (Rice and Gomez-Taylor, 1986).

More than 40 DBPs were detected in finished drinking water from a water plant using chlorine dioxide (Richardson et al, 1994). Multispectral identification techniques were employed but the products were not quantified. The predominant identified products were organic esters, acids and olefins, and only two aldehydes (benzaldehyde and ethylbenzaldehyde were detected. A few halogenated compounds were detected probably from some chlorine in the treatment process. Numerous aliphatic carboxylic acids were reported, including maleic acid/anhydride. It is possible that other aldehydes were formed and oxidized during treatment or processing, and also that some of the products were formed from precursors that were not ordinarily part of the natural organic matter (NOM) in the water.

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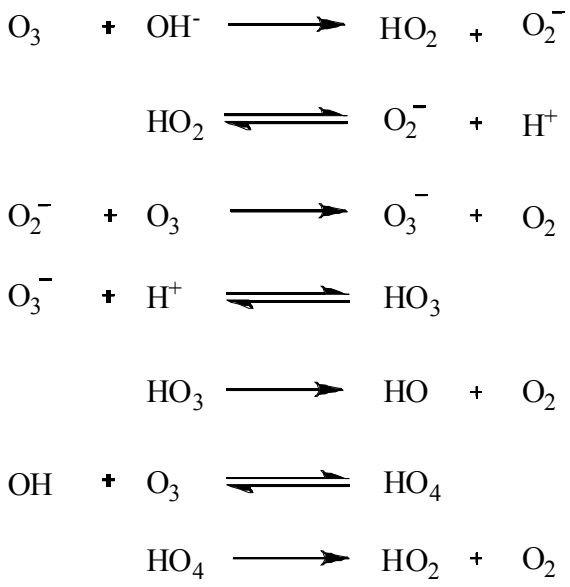
Ozone and peroxides

Ozone and hydrogen peroxide in are widely used as disinfectant (ozone), oxidant or as a source of peroxide radicals for chemical oxidation (Arvidison, 2008). UV light is used with both to generate free radicals.

Although the decomposition of gaseous ozone is relatively simple and produces only oxygen as a byproduct, the decomposition of ozone in the aqueous phase is far more complex; generating a large number of reactive species that can participate further in numerous side reactions or hastening its decomposition. In pure water, ozone decomposes by a radical chain reaction (Figure 3) by hydroxide and propagated by super oxide and hydroxyl radicals (Kirk-Othmer, 1996). Peroxides decompose to hydroxyl radicals with ultraviolet light as well as by the Fenton reaction (with Fe++) that engaged in free radical oxidation processes. Hydroxy radicals are the highest energy and most reactive species in water and can indiscriminately react with most organic chemicals and the rates are essentially diffusion controlled. If present in large > stoichiometric amounts they can produce mineralization of the organic carbon.

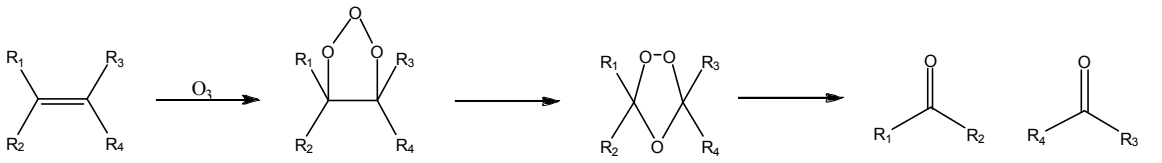
Ozone in water and its DBP chemistry have been described in an early review (Rice and Cotruvo, 1978). There is an extensive literature going back more than 60 years on the chemistry and mechanisms of reaction of ozone and active oxygen species with organic chemicals (e.g.,Criegee, 1938) More recently there is substantial data on the decomposition/disappearance of chemicals under ozonation and advanced oxidation water treatment conditions (e.g., AwwaRF, 2007). However, the identification of the intermediates and by-products produced under those conditions is much less developed. An early study of mutagenic effects of 28 model chemicals ozonated under extreme conditions and identification of some of the by-products was reported in 1977 (Cotruvo et al, 1977). Depending upon reaction conditions and chemical type some mutagens were formed and some became less mutagenic after ozonation (Cotruvo et al, 1977, Caulfield et al, 1979, Burleson, 1982). Due to its high oxidation potential, ozone reacts

Figure 3 One example of a proposed decomposition sequence.



with a large number of chemical types. For example, halogens, with the exception of fluorine, form hypohalite ions that, in the presence of excess ozone, are oxidized to halites (Rice and Cotruvo, 1978; Rice and Gomez-Taylor,1986; Kirk-Othmer, 1996). Metal ions such as Fe^{2+} and Mn^{2+} are converted to hydroxides ($Fe(OH)_3$) or metal oxides (MnO_2) (Kirk-Othmer, 1996). In addition, ozone reacts with most active organic substrates including, but not limited to, olefins, acetylenes, aromatics, C-H bonds, C=N, N=N, SI-H and Si-C bonds (Kirk-Othmer, 1996). Under extended reaction times and free radical conditions and high concentrations of ozone and peroxy compounds, hydrocarbons can be broken down (mineralized) into carbon dioxide and water (Rice and Gomez-Taylor, 1986). The most common and classical chemical transformation induced by ozone (Figure 4) is the cleavage of olefin double-bonds forming, depending on the location and substitution of the double bond, ketones or aldehydes (Criegee, 1938).

Figure 4



The reactivity of ozone depends greatly on the conditions employed during ozonation. For example, in solutions with pHs below 6 and at or below room temperatures, ozone reacts directly with organic molecules. Increasing the pH above 8, ozone decomposes to highly energetic hydroxyl radicals that react non-selectively with materials via electron transfer,

hydrogen abstraction, addition reaction, etc. Between pH 6 and 8, ozone can react by both pathways (Rice & Gomez-Taylor, 1986). Therefore, the conditions under which ozone is used as a disinfectant must be closely monitored and controlled to give the desired result.

Ozone will oxidize bromide to HOBr, and bromate in water. HOBr is an excellent brominating agent as evidenced by product distributions reacts with proteins peptides and amino acids producing brominated tyrosine (Tyr) and short lived N-brominated species such as bromamines and bromamides. Hawkins and Davies (2005) reported that greater than 40% of HOBr generated in the presence of bovine serum albumin (BSA) is converted to short lived bromamides and bromamines. Above 4 °C, these protein-derived N-bromo compounds decompose rapidly (either directly or through the formation of free radicals) by a number of pathways including oxidation of Tyr, formation of carbonyl functionalities in proteins, and rearrangement and fragmentation of proteins. Given the reactive nature of HOBr and the N-bromo compounds and the variation of the chemical composition of protein chains and their macromolecular configuration; small quantities of numerous compounds would be expected. However, specific compounds or classes of compounds were not identified in the literature.

Reactions with nucleophiles

Nucleophiles can be oxidized to oxycompounds as illustrated in Figure 5

$R_2S + O_3 \rightarrow R_2SO + O_2 \rightarrow + O_3 \rightarrow R_2SO_2 + O_2$

$R_3N + O_3 \rightarrow R_3N\rightarrow O + O_2$

$R_3P + O_3 \rightarrow R_3P\rightarrow O + O_2$

$R_3As + O_3 \rightarrow R_3As\rightarrow O + O_2$

$(RO)_3 + O_3 \rightarrow (RO)_3\text{-}PO_3 \rightarrow (RO)_3P\rightarrow O + O_2$

Sulfides are rapidly converted to sulfoxides and then sulfones. A well known example of this is the pesticide aldecarb which can be oxidized to aldecarb sulfoxide and aldecarb sulfone. The toxicology of aldecarb sulfoxide is similar to aldecarb, and the sulfone is somewhat less toxic, indicating that oxidation and decline of the measured concentration of a chemical does not necessarily equal detoxification. Tertiary amines, phosphines and arsenes are converted to the corresponding oxides. Those precursors are not probable water contaminants except for unique industrial discharges. Phosphites are converted to phosphates. Under non-acidic conditions, tertiary amines form the N-oxide (protonation in acidic solution would impede nucleophilic chemical activity). Primary and secondary amines are converted to several N-oxidized forms including organic nitro (nitrate) compounds and N-oxides (Oehlschlaeger, 1978), and possibly nitrosamines if the conditions are not acidic (Cotruvo et al, 1977). For example, isopropyl amine forms 2 –nitropropane and isopropylammonium nitrate.

Commercially, amine oxides are used as chemical intermediates, and long-chain alkylamine oxides are used as nonionic surfactants and foam stabilizers. They have high polarity close to that of quarternary ammonium salts which would indicate environmental mobility and resistance to removal by several technologies. Small amine oxides are hydrophilic, have high

water solubility and poor solubility in most organic solvents. Some examples are pyridine N-oxide and N-methylmorpholine N-oxide. Medicinal uses of N-oxides are increasing because they have stable free radical character and are paramagnetic(Soule, 2007). Some amine oxides of anti-cancer drugs are metabolized in oxygen-deficient cancer tissue to the active drug. Amine oxides are common metabolites of medications and psychoactive drugs so they are potentially present in wastewaters, would be difficult to analyze and could survive several types of treatment. Drug examples include nicotine, zolmitriptan and morphine.

Potential Chemical Residues
Common aldehydes (e.g., formaldehyde) and ketones
Common carboxylic acids
N-oxy compounds including amine oxides and nitrates
Possibly short lived active oxygen compounds
Bromate and brominated DBPs if bromide is present in water

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