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Byproduct Formation of Chlorination and Chlorine Dioxide Oxidation in Drinking Water Treatment

Their Formation Mechanisms and Health Effects

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Abstract

Increasing water scarcity caused by population growth, climate change, pollution from natural and anthropogenic sources, etc. is likely to impact the occurrence of water-associated infectious diseases. Nowadays, access to clean and safe water is a growing concern worldwide. Therefore, disinfection of drinking water is a vital step in public treatment systems as it ensures the removal of various contaminants, including pathogenic microorganisms (protozoa, viruses, bacteria, and intestinal parasites) that give rise to waterborne diseases. Nevertheless, undesirable disinfection byproducts (DBPs) are formed during disinfection as a result of reactions between chemical disinfectants and natural organic matter (NOM), and/or anthropogenic contaminants, and/or bromide/iodide that are present in the raw water. The chemical complexity and heterogeneity of matters in the raw water makes the characterization and the mechanism of DBPs formation quite difficult and ambiguous regardless of the previous hundreds of studies on DBPs generation. As chlorination is still the most economic and most often used disinfection method, and beside chlorination, the application of chlorine dioxide is becoming more widespread, this paper investigates the possible DBPs generated using chlorine and chlorine dioxide with highlighting their adverse health effects. It overviews the reactions of those disinfectants with inorganic and organic compounds. It is important to note that in order to better understand the performance of disinfectants in water treatment, further investigations on the mechanisms of them with inorganic and organic compounds found in water are critically needed.

Keywords

disinfection byproducts, chlorination, chlorine dioxide oxidation, health effect

1 Introduction

Nowadays, increasing water scarcity caused by population growth, climate change and pollution from natural and anthropogenic sources, etc. has strong impact on the occurrence of water-associated infectious diseases [1]. Access to clean and safe water presents a major challenge worldwide to avoid adverse human health effects and to support sustainable development of countries. According to the World Health Organization (WHO), waterborne diseases cause approximately more than 3.4 million deaths each year, making them the major contributor to disease and death around the world [2].

Hence, disinfection is a vital step in public drinking water systems [3] to provide safe drinking water by ensuring the removal of various contaminants, including pathogenic microorganisms (protozoa, viruses, bacteria, and intestinal parasites) that give rise to waterborne diseases.

Various technologies can be used for this purpose, and are classified as either physical (gamma radiation, X-rays, ultraviolet radiation, thermal sterilization, etc.) or chemical (heavy metals, acids or bases, halogens, ozone, permanganate, etc.). Chemical oxidation, the most commonly used form of disinfection treatment, has dramatically reduced waterborne infections since its introduction in the early 20th century [4].

Nevertheless, during disinfection, reactions take place between chemical disinfectants and natural organic matter (NOM), and/or anthropogenic contaminants, and/or

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bromide/iodide that are present in the raw water. And this leads to the formation of unwanted disinfection byproducts (DBPs) that are toxic to the aquatic environment and moreover cause adverse human health effects ranging from cancer induction to critical pregnancy issues [2].

Since the discovery of disinfection byproducts in drinking water in the 1970s, enormous research has been carried out to identify their types, understand their formation, and assess their health effects. Up to now, approximately 600 DBPs [5, 6] with a high chemical diversity have been identified, and only 18 DBPs of them have been regulated by the US Environmental Protection Agency, the European Union and the World Health Organization [7]. However, 74 DBPs classified as emerging pollutants [8].

The most extensively investigated classes are haloacetonitriles (HANs), trihalomethanes (THMs), halonitromethanes (HNMs), haloketones (HKTs), haloaldehydes (HALs), iodo-trihalomethanes (I-THMs), and haloacetic acids (HAAs) which are mostly generated from chlorination [9].

Several studies on the toxicology, genotoxicity, carcinogenicity, and mutagenicity of DBPs have revealed that DBPs are responsible for serious health complications, including bladder cancer, miscarriage, birth defects, etc. [8]. Furthermore, they are persistent, difficult to biodegrade and have the ability to accumulate in organisms. Many scientists believe that some unregulated DBPs are more cytotoxic and genotoxic than the regulated ones [10].

Additionally, many studies have shown that DBPs formation depends on dissolved organic matter (DOM) content (i.e., concentrations of dissolved organic carbon [DOC] and dissolved organic nitrogen [DON]), the presence of bromide ions, and disinfection conditions (i.e., type of oxidant, dosage of oxidant, reaction time, pH of water) [11].

Although chlorine is still the most preferred and widely used disinfectant in water treatment, the formation of large amounts of disinfection byproducts (DBPs) has raised serious concerns due to their potential toxicity to human health [12]. Chlorine dioxide (ClO_2) has therefore been used as an alternative disinfectant to chlorine due to its low production of regulated halogenated DBPs, especially THMs [13].

Furthermore, ClO_2 exhibits stable oxidizing and disinfecting power with little hydrolysis over a wide pH range from pH 2.0 to 10.0, making ClO_2 more practical than chlorine in treating high pH water [14]. However, ClO_2 reacts actively with naturally occurring organic and inorganic matter and yields chlorite (ClO_2^-) and chlorate (ClO_3^-), chloride (Cl^-) and limited halogenated DBPs [14, 15].

This study is an overview of the byproducts, which are formed when chlorine or chlorine dioxide disinfection/oxidation is applied. It focuses on their occurrence, their reactions with organic and inorganic matters, the legislative framework for DBPs, and their health effects. It shows that knowing the mechanism of DBPs generation is as important as their identification. As better understanding of the formation of disinfectant in water treatment will help in striking the balance between eliminating the risk of pathogen contamination and avoiding the exposure to disinfection byproducts.

2 Regulation of disinfection byproducts in the European Union (EU) and in Hungary

2.1 EU regulations

In Europe, the directive 2000/60/EC [16] of the European Parliament and the Council is the most important and highly developed branch of water legislation to date. This directive, commonly known as the "water framework directive" (WFD), is complemented by other legislation regulating specific aspects of water use, including the drinking water directive (DWD).

In 1980, the European Economic Community (EEC) implemented its first drinking water directive (80/778/EEC) [17] where 60 microbiological, organoleptic, and physical-chemical parameters were regulated under certain limits. Disinfection byproducts were not yet regulated under this standard [18].

In order to preserve the high quality of water, the EU commission tends to propose regular updates by adding new and emerging compounds to the list of criteria for determining water safety. These changes are mostly based on the latest scientific knowledge and recommendations of the World Health Organization (WHO).

The 98/83/EC Directive [19] was the first replacement of the "old" Drinking Water Directive 80/778/EEC [17] and was published in 1998 with an implementation period of five years (December 25, 2003). This directive introduced new, stricter minimum requirements for the quality of potable water. Disinfection byproducts such as total trihalomethanes and bromate were added for the first time.

On January 12, 2021, a new Drinking Water Directive (EU Directive 2020/2184) [20] entered into force, and EU countries, including Hungary, will have two years to implement the new legislation into national law. This new directive renovated the 24-years old 98/83/EC [19], which introduces the obligation for member states to improve or maintain access to safe water intended for human consumption for all Europeans. The revision of this

long-standing drinking water Directive was the upshot of the first-ever successful European Citizens' initiative, "Right2Water" [21] that reclaimed the EU to provide universal and safe access to water and sanitation. The new directive gives stricter limit values for several components and adds new components for which the quality of drinking water has not previously been regulated [22]. As the understanding of the harmful effects that disinfection byproducts can cause on human health, more byproducts are regulated in this directive. These byproducts include chlorate ion, chlorite ion, and haloacetic acids (HAAs).

Hence, in order to respect the new enforceable standards and to ensure the safety of drinking water, technological improvements, which must be preceded by appropriate research, are required.

2.2 Hungarian regulations

In Hungary, drinking water quality standards regulated only one chlorination byproduct: the maximum allowable chloroform concentration was 30 µg/l, but other byproducts were not regulated (Hungarian Standard MSZ 450-1:1989) [23, 24].

From 2001 a governmental decree regulated the quality of drinking water in Hungary (Governmental Decree No. 201/2001 (X.25.)) [25]. In this decree the limits and parametric values were mostly based on the 98/83 EU Directives [19] and WHO guidelines, however in case of some compounds the Hungarian regulation was stricter (e.g., THMs (50 µg/l), chlorite (0.2 mg/l)).

Recently a new governmental decree was published about the disinfection byproducts (Fig. 1 [18, 26]) (Governmental Decree No. 5/2023. (I. 12.)) [27], which is based on the 2020/2184 EU Directive [20]. Among other parameters, two DBPs appear as new compounds in the regulation (these two compounds were not regulated in Hungary before): chlorate (0.25 mg/l) and HAAs (60 µg/l), meanwhile the maximum allowable chlorite concentration increased to 0.25 mg/l.

3 Natural organic matter: organic precursors for DBPs production

During the past decades, many observations indicate a significant increase in NOM concentration levels in water sources due to global warming, changes in soil acidification, increased drought severity, more intense rain events, etc. [28].

In general, NOMs are present in water sources through biological activities, mainly algal and microbial, or are introduced to the water body via drainage within watersheds, including substances generated during the breakdown of terrestrial organisms and from human activities.

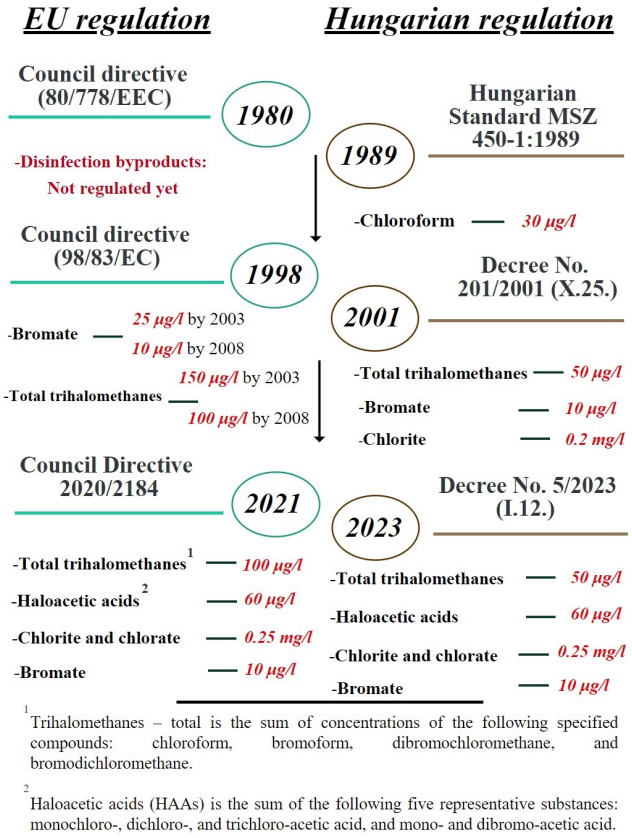


Fig. 1 Timeline of the introducing of disinfection byproducts into the EU and Hungarian directive, based on [18, 26]

Therefore, NOM is omnipresent in all natural water sources and even in soil and sediments [29].

In drinking water treatment, the presence of NOMs affects the efficiency of some treatment processes and, consequently, the safety of drinking water [30]. NOM can also contribute to biological regrowth in the distribution system and impart a yellowish tinge to water, which impacts its aesthetic quality (color, taste, and odor) [30]. Additionally, NOM is considered a major precursor for the formation of DBPs. Therefore, to address the generation of DBPs, researchers have suggested reducing the levels of NOM in source water [29]. To ensure their removal, various methods based on chemical or biological technologies are implemented during water treatment. Some of them are as follows: coagulation/flocculation followed by clarification, granular activated carbon (GAC) filtration, nanofiltration, advanced oxidation processes (AOPs) utilizing O_3, UV, H_2O_2/UV, H_2O_2/O_3 and UV/O_3, etc. [29]. Nevertheless, more advanced techniques that are environmentally sustainable and cost-effective are sought to replace those methods that are often associated with high operational costs. Microfiltration has been identified as a promising technology that can achieve NOM removal by utilizing a two-stage process [31].

Chemistry of natural organic matter

The influence of soil, climate, and hydrologic conditions on the biological activity in the environment leads to the production of a large variety of NOM with complex chemical properties that differ from one water body to another. This complexity makes its control in water treatment processes very challenging.

The aquatic NOM is classified as hydrophilic fractions (carbohydrates, proteins/amino acids, or carboxylic acids) or hydrophobic fractions (humic acid and fulvic acids) (Fig. 2) [32].

In river and lake waters, humic and fulvic acids make about 50% to 90% of the total dissolved organic carbon (DOC), both of which react actively with chlorine. Hydrophilic acids (up to 30%), carbohydrates (10%), simple carboxylic acids (5%), and protein/amino acids (5%), are among the other DOC components (Fig. 3) [32].

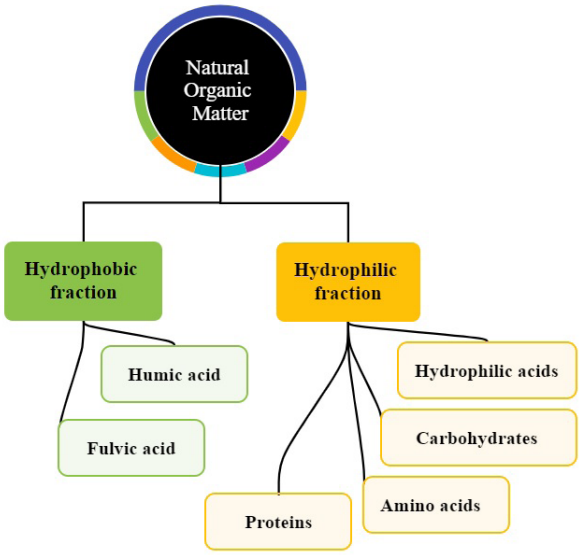


Fig. 2 Composition of natural organic matter in water

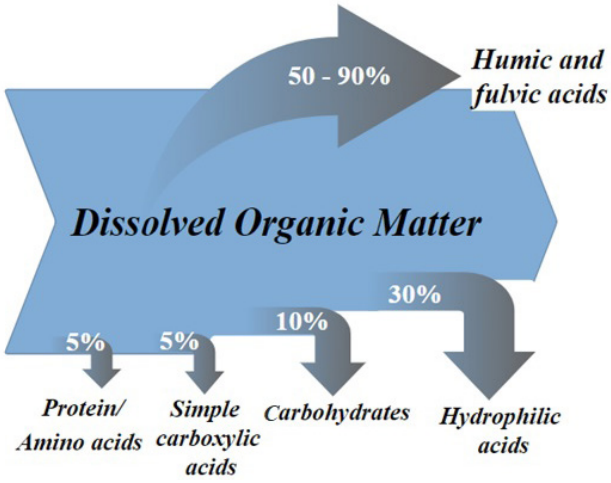


Fig. 3 Components of total dissolved organic matter, based on [32]

As already mentioned, NOM may affect the performance of unit processes:

- Humic substances can impact coagulation's efficiency and increase the turbidity of water by entering into permanent bonds with colloidal particles giving them a hydrophilic character [33].
- Hydrophilic fractions can cause biological regrowth in the distribution system.

Compared to the hydrophilic fraction, the hydrophobic fraction of NOM has been well characterized and is easier to remove by coagulation. Therefore, the relationship between the production of DBPs and hydrophilic fractions is not fully understood [34].

4 Chlorine

Chlorine was introduced to the water treatment process as a disinfectant in the early 20th century [35]. Nowadays, it is still the most widely used disinfectant worldwide [36] as it is considered the most economical and easily usable method for disinfecting water [37].

Chlorine belongs to the halogen family, and it is never found uncombined in nature. Thus, the disinfection of water by chlorine can be accomplished by using the following forms of chlorine:

- liquefied chlorine gas,
- sodium hypochlorite solution or calcium hypochlorite granules, and
- onsite chlorine generators [12].

However, the complex reaction between free residual chlorine (Cl_2) and naturally occurring organic matter (NOM) or/and bromide leads to the production of a great variety of chlorination byproducts (CBPs), particularly halogenated organic products or brominated byproducts.

4.1 Forms of chlorine and chlorination byproducts

4.1.1 Chlorine gas

When added to the water, Cl_2 reacts with H_2O and forms hypochlorous acid (HOCl) or hypochlorite ion (OCl^-) and chloride ion (Cl^-) according to Eq. (1) [38]:

$$Cl_2 + H_2O \rightleftharpoons HOCl + Cl^- + H^+ . \quad (1)$$

An equilibrium reaction occurs between the weak hypochlorous acid (HOCl) and its conjugate base, hypochlorite (OCl^-). This reaction is mainly controlled by pH:

$$HOCl + H_2O \rightleftharpoons OCl^- + H_3O^+ \quad (2)$$

(pK_a = 7.5 at 25 °C).

At low pH (generally < 5), HOCl is predominant in the water, yet at higher pH (> 9) OCl^- is the predominant species [39]. Hypochlorous acid is more effective in disinfecting water, as it has much faster reaction rates than hypochlorite. Therefore, chlorination is most effective at a slightly acidic pH (pH < 7.0).

4.1.2 Sodium hypochlorite/Calcium hypochlorite

Sodium hypochlorite (NaClO) also known as bleach, is a very strong yet unstable oxidant. It has been utilized since the 18th century.

When sodium hypochlorite (NaClO) is added to water, it reacts with H_2O to produce hypochlorous acid (HOCl) and sodium hydroxide (NaOH) according to Eq. (3):

$$NaClO + H_2O \rightleftharpoons HOCl + NaOH\,. \tag{3}$$

Calcium hypochlorite ($Ca(ClO)_2$) contains 20 to 70% of active chlorine and it has greater stability than sodium hypochlorite. However, it is extremely corrosive and can catch fire when it comes into contact with certain acidic substances [40].

When added to the water, calcium hypochlorite ($Ca(ClO)_2$) reacts with H_2O and forms hypochlorous acid (HOCl) and calcium hydroxide (Ca(OH)) according to Eq. (4):

$$Ca(ClO)_2 + 2H_2O \rightleftharpoons 2HOCl + Ca(OH)_2\,. \tag{4}$$

Free chlorine species include HOCl, OCl^-, Cl_2, H_2OCl^+, and Cl^+ react with organic compounds following one of three main mechanisms: addition, oxidation, or substitution [41].

4.1.3 Chlorination byproducts

A variety of undesirable halogenated organic compounds are formed when chlorine reacts with natural organic compounds. THMs, HAAs, chlorophenols, chloral hydrate, and HANs are some of these unwanted byproducts (Fig. 4 [42]). However, the majority of chlorinated organics in drinking water has yet to be fully characterized.

The largest groups commonly present in chlorinated water are THMs, followed by HAAs [43]. Although they typically occur at lower concentrations than THMs and HAAs, nitrogen DBP (N-DBP) groups, including HANs are far from being insignificant, as they exhibit high cytotoxicity and genotoxicity [44].

Moreover, the decay of sodium hypochlorite solutions during its storage and at certain conditions produces chlorate and chloride in two ways:

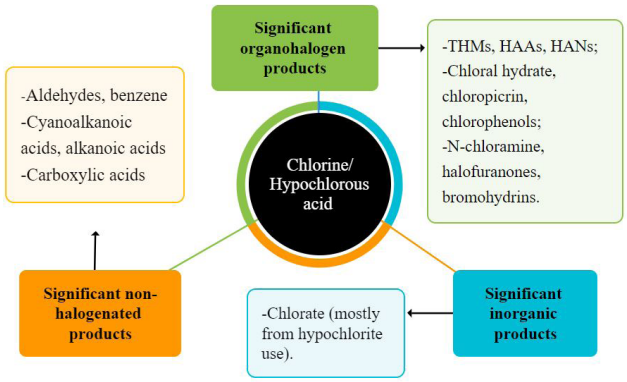


Fig. 4 Clorination byproducts present in disinfected waters by chlorine, based on [42]

1. In one way, the self-decomposition generates oxygen (O_2) and chloride (Cl^-) according to Eq. (5):

$$2OCl^- \rightleftharpoons O_2 + 2Cl^-\,. \tag{5}$$

2. In the other hand, as an intermediate steady-state species, ClO_2^- is formed and acts as an intermediate between chlorate ion and hypochlorite [45, 46]. Equation (6) is a fast reaction, while Eq. (7) is a slow reaction:

$$2ClO^- \rightleftharpoons ClO_2^- + Cl^- \tag{6}$$

$$ClO^- + ClO_2^- \rightleftharpoons ClO_3^- + Cl^-\,. \tag{7}$$

4.2 Reactions with the natural organic matter

Some researchers report that the primary precursor of chlorinated DBPs (e.g., THMs, HAAs, trihaloacetic acids (THAA), dihaloacetic acids (DHAA), HANs) formation is the hydrophobic fraction, when bromide ions are not present in water [47–49]. Nevertheless, hydrophilic carbon may also play an essential role in DBPs production especially in waters with a low fraction of hydrophobic NOM. Furthermore, in the presence of bromide ions (Br^-), HOBr is formed when chlorine reacts with bromide ion, and the hydrophilic fractions react actively with HOBr and produce brominated THMs [50].

4.2.1 Hydrophobic fractions

Humic and fulvic acids react strongly with chlorine [49]. Humic acids consume more chlorine and are the major organic precursors for THMs and HAAs including chloroform, trichloroacetic acid and dichloroacetic acid, while HANs formation is not influenced by the presence of humic acids [32, 51].

4.2.2 Hydrophilic fractions (carbohydrates, proteins/ amino acids, or carboxylic acids)

The hydrophilic fraction of natural organic matter is mainly composed of aliphatic carbon and nitrogenous compounds, as well as lower molecular weight proteins, carbohydrates, and amino acids, etc. [52].

This fraction is generally biodegradable in nature, so it is present at low concentration in water [53].

Carbohydrates and carboxylic acids have limited reactivity to chlorine. Thus, organochlorine compounds are not formed. However, β-dicarbonyl acids, when present in the hydrophilic fraction of natural waters, can serve as a significant precursor to the formation of THMs and other disinfection byproducts, such as dichloroacetic acid (DCAA) and dibromoacetic acid (DBAA), during chlorination [54].

Nevertheless, hydrophilic acids, including citric acid and amino acids, can react with chlorine and generate chloroform [55] and other byproducts such as *N*-mono- or *N*,*N*-dichlorinated derivatives that contribute to the total synthesis of hydrogen chloride.

According to some researchers, HANs are formed when amino acids present in raw waters react with chlorine [56].

Amino acids, which constitute a small fraction of NOM, have been detected in raw surface water sources where algae levels are significant. They can be found either in the free form or combined. Amino acids can generate a number of different DBPs after chlorination including *N*-chloroamino acids [3, 57], *N*-chloropeptides [58, 59], halonitroalkanes, halonitriles and haloamides [56], aldehydes and *N*-chloraldimines [60].

A study conducted by Hong et al. [61] demonstrated a positive correlation between THM formation and the aromaticity of amino acids, as indicated by their SUV254 values. Aromatic amino acids, such as tryptophan and tyrosine, were found to produce significantly higher levels of THMs compared to non-aromatic amino acids. These results suggest that SUV254 (is defined as the UV absorbance of a water sample at a given wavelength (254 nanometers) normalized for DOC concentration), a well-known indicator of the aromatic fraction of DOC [62, 63], may be an effective tool to predict THM production derived from amino acids. Additionally, the findings align with Hureiki et al.'s [64] investigation, which revealed that tryptophan and tyrosine exhibited higher THM formation potential than other amino acids.

The formation of HAAs was observed to be particularly reactive to chlorine when amino acids containing active ring structures, such as OH- and nitrogen-substituted rings, were present [61].

Interestingly, aspartic acid and asparagine, which lack reactive ring structures, also demonstrated elevated HAA production levels. Furthermore, four amino acids, namely histidine, phenylalanine, tyrosine, and tryptophan, demonstrated significantly higher ratios of trichloroacetic acid (TCfAA) to DCAA when compared to other amino acids.

Moreover, Nguyen et al. [65] demonstrated that amino acids and aromatic proteins found in organic carbon derived from algae are likely significant precursors for the formation of HAAs.

DHAAs, THMs and THAA

According to Hua and Reckhow [49] hydrophilic fractions of NOM act as the major precursor for DHAAs and THMs formation. Contrary, precursors to THAA are more hydrophobic in nature.

THMs and HAAs

In finished drinking water, where hydrophilic fractions of NOM tend to be dominant, greater yields of THMs are obtained compared to HAAs yields. This has led some researchers to conclude that hydrophilic fractions of NOM are more significant precursors of THMs than HAAs [47, 66].

According to some other researchers, the hydrophilic fraction yields more HAAs in comparison to THMs than the comparable hydrophobic fraction [48, 67]. This aligns with Hong et al.'s [61] findings, which showed that amino acids produced higher levels of HAAs than THMs when chlorinated.

Studies have repeatedly shown that when the hydrophobic fraction constitutes a greater proportion of the NOM the formation of both THM and HAA is greater as opposed to when the hydrophilic fraction predominates [47].

4.3 Reactions in the presence of bromide ion

Many studies show that the presence of Br^- in source waters shifts DBP categories to brominated species. Thus, it is considered the main inorganic precursor for brominated DBPs production, particularly brominated THMs and HANs [51, 68].

Furthermore, its presence in source water greatly affects the chlorinated byproducts yield and provokes the rise of THMs and HANs formation. Its presence, on the other hand, has no effect on HAAs production [51].

Bromide species react readily with the hydrophilic fraction of NOM compared to chlorine species. However, it is less reactive with the hydrophobic fraction [47, 69].

During disinfection, the bromide ion is easily oxidized by the free chlorine (hypochlorous acid) and leads to the

formation of active bromine (hypobromous acid, HOBr and hypobromite ion, OBr^-) which reacts with NOM faster than hypochlorous acid to form brominated byproducts [70]. Halogenated intermediates are also formed when active bromine and chlorine species interact with organic matter.

4.4 Health effects of chlorinated byproducts

4.4.1 THMs

Humans can be exposed to THMs through different ways, whether directly from drinking water or as through the volatilization of DBPs during cooking, bathing, showering, etc. [8].

Cytotoxicity

The halogen's aptitude as a leaving group determines the degree of cytotoxicity of byproducts. According to that, bromoform is the most cytotoxic THMs, followed by chloroform and then bromodichloromethane [44].

Genotoxicity

Chloroform, the most investigated THM, was generally not mutagenic or genotoxic. However, other THMs including brominated THMs have been proven to cause genomic DNA damage in CHO cells according to some mutagenic experiments, and they are bromoform, bromodichloromethane, and chlorodibromomethane, in that order of highest to lowest mutagenic potency [71, 72].

Carcinogenicity

Several studies have found that all four THMs are carcinogenic in rodents [8, 73] posing a risk to humans and aquatic life.

Chloroform was listed along with bromodichloromethane, by the International Agency for Research and Cancer (IARC), as possibly carcinogenic to humans and is known as Group 2B carcinogen compound [8].

Several studies demonstrated that chloroform and bromodichloromethane are carcinogenic in both mouse and rats and induced tumors at multiple organ sites. At doses that result in cytotoxicity, chloroform has caused kidney and renal tumors in male rats and liver tumors in male and female mice. Bromodichloromethane induced renal and liver tumors in the mouse, and renal and intestinal tumors in the rat.

According to IARC, those two THMs and dibromochloromethane are classified as 2B, possibly carcinogenic to humans. Dibromochloromethane can impact negativity human's nervous system, liver, and kidneys (Fig. 5 [74]).

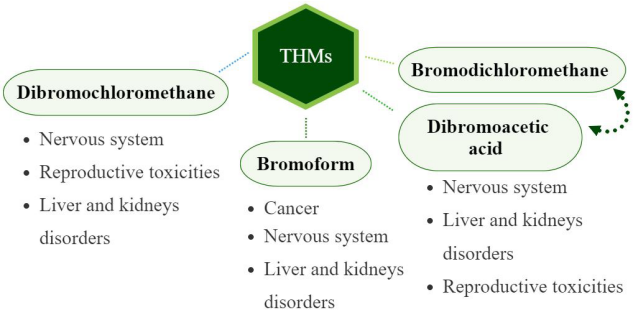


Fig. 5 Toxicological effects of THMs, based on [74]

In addition, bromoform [75] and chlorodibromomethane [76] induced liver and intestinal tumors in the rat and liver tumors in the mouse, respectively. They were found to be group 3 by IARC, which is not classifiable as to their human carcinogenicity.

4.4.2 HAAs

Cytotoxicity

Several studies have demonstrated that the level of toxicity depends significantly on the number and type of halogen atoms associated with the haloacetic acids [73, 77]. In most cases, mono-halogenated haloacetic acids have been shown to be more cytotoxic than di- or tri-halogenated equivalents.

Both dichloroacetic acid and trichloroacetic acid mostly harm the liver, according to toxicological studies conducted by the United States Environmental Protection Agency (US EPA) [78]. Additionally, dichloroacetic acid can also be neurotoxic.

Genotoxicity

In several experiments, it was discovered that bromoacetic acid, dibromoacetic acid, chloroacetic acid, and tribro-moacetic acid were mutagenic in bacteria and caused mammalian cells' genomic DNA damage [77, 79]. The mono-halogenated haloacetic acids were found to be more genotoxic than their di- or tri-halogenated equivalents, according to some observations [73]. Moreover, the brominated HAAs were more genotoxic than the chlorinated HAAs.

Carcinogenicity

Out of the five regulated HAAs, three of them (dibromoacetic acid, dichloroacetic acid, and trichloroacetic acid) are found to be carcinogenic. Some researchers have demonstrated that those HAAs have induced liver tumors (Fig. 6 [74]) in male mice, with dibromoacetic acid causing leukemia and abdominal cavity mesothelioma in rats, and liver and lung tumors in mice.

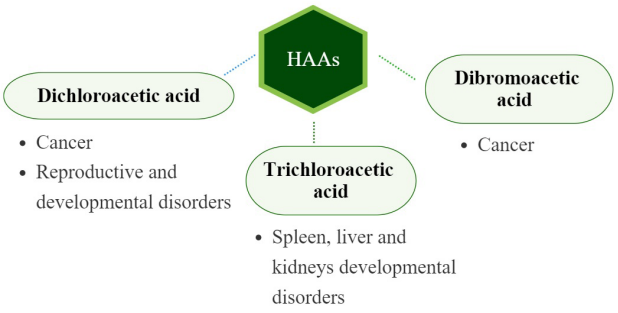


Fig. 6 Toxicological effects of HAAs, based on [74]

Dichloroacetic acid, trichloroacetic acid, bromo-chloroacetic acid, and dibromoacetic acid are classified as 2B Group of potential carcinogens according to IARC [80].

Gopal et al. [81] show that dichloroacetic acid can also cause liver, kidney, spleen, and developmental effect.

Several research has shown that brominated THMs including bromodichloromethane, chlorodibromomethane, and bromoform and brominated HAAs are frequently more genotoxic, cytotoxic, or carcinogenic thus, more hazardous to human health than their chlorinated analogues [8]. Hence, brominated DBPs have attracted significant attention [82].

4.4.3 HANs

N-DBPs particularly, HANs, HNMs, and haloacetamides have been found to be far more cytotoxic and genotoxic than THMs and HAAs according to studies in mammalian cells even at low concentrations [44].

HANs are an unregulated class of N-DBPs. Previous studies have shown that certain HANs, including bromoacetonitrile (BAN), chloroacetonitrile (CAN), dibromoacetonitrile (DBAN), dichloroacetonitrile (DCAN), trichloroacetonitrile (TCAN), and bromochloroacetonitrile (BCAN), are toxic [82].

Cytotoxicity

Multiple studies have shown that the five HANs are cytotoxic and are ranked BAN > DBAN > CAN > TCAN > DCAN from highest to lowest cytotoxicity [83].

Genotoxicity

HANs induced considerable DNA damage, with CAN and DCAN being more genotoxic than TCAN, BAN, and DBAN [83].

Compared to the carbonaceous DPSs (C-DBPs: e.g., trihalomethanes (THMs), haloacetic acids (HAAs)) and N-DBPs, HANs is found to be more genotoxic, and they cause DNA strand breaks in human lymphoblastic cells and Hela S3 cells [84].

Carcinogenicity

HANs have been identified as extremely carcinogenic nitrogen DBPs (N-DBPs). DBAN, BCAN, and CAN, in particular, caused dermal tumors in mice in the following order: BCAN > DBAN > CAN [83, 85].

- Generally, when mpared to their equivalent unsubstituted analogues, the brominated, di-, and tri-halogenated HANs are often more toxic [86].
- The three common groups are ranked from highest to lowest toxicity in the flollowing order [87]: HANs > HAAs > THMs.

5 Chlorine dioxide

Chlorine dioxide was first introduced as a water disinfectant in the United States in 1944. Then, it was utilized in Poland for the first time in the 1950s, but it wasn't until 1992 that this method of disinfection became significantly popular [32].

Chlorine dioxide (ClO_2) has gained great interest for several years and has become a better alternative disinfectant to chlorine because of its strong ability to prevent biofilm formation in drinking water distribution systems [88]. Chlorine dioxide is a strong and selective oxidant that is around 2.5 times more efficient than chlorine gas.

5.1 Chlorine dioxide disproportionation chemistry

Between pH values of 2 and 10.5, chlorine dioxide has been discovered to be relatively stable [89].

Rav-Acha et al. [90] and Werdehoff and Singer [91] demonstrated that at pH level under 2, the reduction of ClO_2 to Cl^- can occur in two stages and chlorate can be formed. This can be understood through the following steps:

$$4ClO_2 + 4H^+ + 4e^- \rightarrow 4HClO_2 \quad (8)$$

$$4HClO_2 \rightarrow 2ClO_2 + ClO_3^- + Cl^- + 2H^+ + H_2O\,. \quad (9)$$

Nevertheless, at pH 7, only the reduction of chlorine dioxide, which results in the generation of chlorite will occur:

$$ClO_2 + 1e^- \rightarrow ClO_2^- \quad (10)$$

$$ClO_2^- + 4H^+ + 4e^- \rightarrow Cl^- + 2H_2O\,. \quad (11)$$

However, in an alkaline medium, specifically at pH greater than 9 or 10, the auto-decomposition of chlorine dioxide will disproportionately produce chlorate and chlorite ions as illustrated in Eq. (12) [92]:

$$2ClO_2 + 2OH^- \rightarrow ClO_2^- + ClO_3^- + H_2O\,. \quad (12)$$

Additionally, when water treated with chlorine dioxide is exposed to light, chlorate and chlorite ions can be formed from the photodecomposition of ClO_2 [93].

Furthermore, when ClO_2 is generated onsite by combining chlorite or chlorate salts with strong acids (e.g., H_2SO_4, HCl) or oxidants (e.g., Cl_2, HOCl, H_2O_2), some unreacted reactants (e.g., chlorite or chlorate) may remain in the ClO_2 solution or certain side-reaction products (e.g., Cl_2) may form [14, 94].

Chlorite can be also generated when ClO_2 oxidizes some inorganic matter present in the raw water (e.g., Fe^{2+}, Mn^{2+}).

5.2 Byproducts of chlorine dioxide oxidation

ClO_2 reacts actively with naturally occurring organic and inorganic matter and produces 60% to 70% of ClO_2^- and ClO_3^- (0–30%), Cl^- and other components [14, 15].

A 24-hour experiment of Wajon et al. [95] shows that the range of ClO_2^- conversions from humic compounds is 48% to 67%, with a median of 62%. Additionally, Cl^-, the second most common reduced product, was produced from 18.1–30.0% of the consumed ClO_2 (median of 23.1%). However, only 4.8% of ClO_2 was converted to ClO_3^- and 2.5% total organic chlorine.

Those byproducts are formed according to the following reactions [92]:

$$ClO_2 + e^- (NOM) \rightarrow ClO_2^- \quad (13)$$

$$3ClO^- \rightarrow 2Cl^- + ClO_3^- . \quad (14)$$

Chlorite is accordingly the major formed byproduct which was found to cause oxidative stress [96, 97]. Although, chlorate is a minor product and induces little oxidative stress, it has shown evidence of carcinogenicity in rats, however it is not concluded yet to cause cancer to human. This results in a WHO guideline value of 0.7 mg/l for chlorite and chlorate. In the EU, ClO_2^- has currently stricter guideline value of 0.25 mg/l and ClO_3^- has recently been added as a new component and is regulated at 0.25 mg/l (Fig. 7) [98].

When used, it typically produces low or non-detectable levels of chlorine containing DBPs. ClO_2 solution generated in drinking water treatment facilities can carry certain quantities of free chlorine including HOCl, OCl^-, and Cl_2. Free chlorine reacts with NOMs and form low level of halogenated byproducts including THMs and HAAs [38, 99]. Although the highest amounts of haloacetic acids are produced after the use of chlorine disinfectant, a lower amount of dichloroacetic acid, bromochloroacetic acid and dibromoacetic acids can be formed after chlorine dioxide treatment of raw waters [100]. Numerous observations have demonstrated that HANs (DBAN) can also be produced after treatment with chlorine dioxide [101].

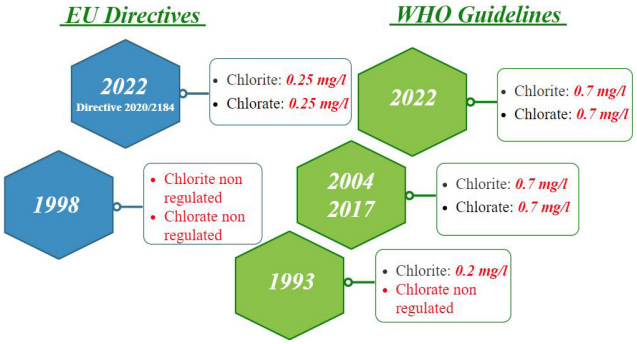


Fig. 7 History of guideline development of chlorite and chlorate

To sum up, mostly inorganic byproducts: chlorite and chlorate have been found as DBPs in water treatment from ClO_2 oxidation, the organic byproducts (acids, aldehydes, alcohols) and chlorinated byproducts (THMs, HAAs and HANs) have been found only in very low concentrations [102–104].

5.3 Reactions with the main organic precursor: natural organic matter

Chlorine dioxide is the only disinfectant that can produce chlorite. ClO_2 is reduced to the chlorite anion while reacting with organic compounds and acts as a one-electron acceptor [14]. Consequently, ClO_2 is a selective oxidant whose reactivity tends to favor organic compounds containing a lone pair of electrons or π electrons (e.g., tertiary amines, phenols and aniline).

The level of dissolved organic matter in the water is strongly correlated with chlorite concentration [91]. Unlike chlorite, the concentration of chlorate is not influenced by the level of organic matter dissolved in water.

However, pH of the water can affect the reactivity of certain precursors towards ClO_2, it also influences the kinetics of side-reactions involving in inorganic byproducts (i.e., ClO_2^-, ClO_3^- and HOCl). The pH conditions also alter the side reactions that occur during ClO_2 oxidation [105, 106].

5.3.1 Hydrophobic fractions

According to Świetlik et al. [107], ClO_2 preferentially interacts with hydrophobic parts of humic substances. And this reaction can generate some organic byproducts and inorganic byproducts.

At high pH, polyphenolics, which are mostly abundant in humic substances [108], act as the main electron-donating

groups in the reduction of ClO_2 resulting in the generation of significant amounts of DBPs (Scheme 1) [14]. By one-electron transfer, the oxidation of phenols by ClO_2 molecule forms a phenoxyl radical and chlorite in the first step. Thereafter, the reduction of another ClO_2 molecule produces HOCl and mainly benzoquinone (quinones) [109].

According to Wajon et al. [95] benzoquinone is considered as the major and only oxidation product of phenols when the molar ratio of ClO_2 to phenol is more than 3. However, when the molar ratio of ClO_2 to phenol is less than 1, chlorinated phenols are also found along with benzoquinone.

Further breakdown of benzoquinone may take place in the presence of significant amounts of ClO_2, resulting in the creation of ring cleavage products and low ClO_2^- yields with excess ClO_2 [110].

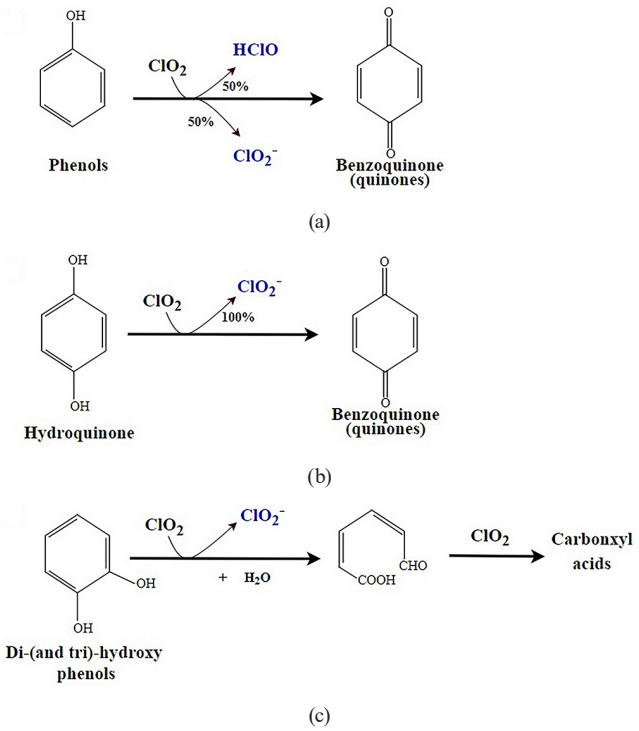
Chloramine and HOBr can be formed with insignificant concentration in the presence of HOCl [14].

40% to 60% of chlorite is generated upon mono-hydroxy phenols oxidation by ClO_2 [110]. The oxidation of hydroquinone produces benzoquinone and yields theoretically 100% of ClO_2^- of the ClO_2 consumed and no HOCl is formed. In addition, ClO_2^- yields of 100 percent for the reaction of ClO_2 with di- or tri-hydroxy phenols [110].

Unless additional treatment is applied, the concentration of ClO_2^- in drinking water remains the same.

Di- and tri-hydroxy phenols (e.g., resorcinol and phloroglucinol) and para-substituted mono-hydroxy phenols (e.g., p-cresol) ring cleavage is likely to occur together with the formation of carboxylic acids (e.g., oxalic and maleic acids) during ClO_2 oxidation.

It is important to note that ClO_2^- generated from humic substances is influenced by the ClO_2 dose, pH and varied with different reaction intervals. However, pH effect on ClO_2^- yields is negligible [110].



Scheme 1 Simplified reactions of ClO_2 oxidation of some phenolic compounds: (a) phenol; (b) hydroquinone; (c) catechol, adapted from [14]

5.3.2 Hydrophilic fractions (carbohydrates, proteins/amino acids, or carboxylic acids)

At pH 6, ClO_2 appears to be unreactive with many amino acids and *N*-chloro derivatives cannot be formed [111, 112]. However, it reacts actively with cysteine, tyrosine, and tryptophan [113], but slowly with histidine, proline, alanine, glycine and hydroxyproline. Although amino acids are a common form of primary amine, the amino group is inert toward ClO_2.

Cysteine-based amino acids or peptides, which are common thiol-containing moieties present in source waters, are oxidized by ClO_2 resulting in the production of RS• radical and chlorite [14]. Under neutral or slightly acidic conditions, cysteine can convert ClO_2^- to Cl^- [114]. Moreover, other compounds with high nucleophilicity including cystine and glutathione can further reduce ClO_2^- to Cl^-.

In a two-step reaction, tryptophan reacts rapidly with two ClO_2 to produce radical cation species ($Trp^{\bullet+}$) and ClO_2 in the first step and Trp-OClO adduct in the second. Trp-OClO adduct may react with water to produce a number of stable compounds, including *N*-formylkynurenine (NFK), and can also decompose to produce HOCl.

The overall tryptophan reacts with ClO_2 is as following [113]:

$$\text{Tryptophan} + 2ClO_2 + H_2O \rightarrow \text{NFK} + ClO_2^- + HOCl + H^+ . \quad (15)$$

Tyrosine (Tyr) is one kind of elementary amino acids which is typical nitrogenous organic compounds.

It should be noted that little is known about how the reaction parameters (such as ClO_2 dosage, pH, and reaction duration etc.) affect ClO_2 yields during ClO_2 oxidation of organic moieties and ClO_2^- generation is dependent on the distribution of functional groups [110].

5.4 Reaction of chlorine dioxide with inorganic compounds

Many inorganic compounds present in natural waters can be oxidized by ClO_2. At pH 7.0, ClO_2 interacts rapidly and at apparent second-order reaction rate constants with I^- (iodide), CN^- (cyanide), NO_2^-, SO_3^{2-} (sulfites), Fe^{2+}

(iron (II)), Mn^{2+} (manganese (II)), arsenic (III), but slowly reacts with ammonia (NH_4^+) and Br^- [101, 115].

However, with high concentrations of ClO_2 and in intense sunlight, ClO_2 can react with bromide ions and produce hypobromite and bromate [38].

Sulfide (S^{2-}) mainly reacts with ClO_2 to generate ClO_2^- at low concentration, and ClO_2^- is further reduced with the increase of concentration. In alkaline solution and via rapid one-electron transfer ClO_2 oxidizes Mn^{2+} (Eq. (16)) and Fe^{2+}, which leads to the formation of chlorite [116, 117].

$$Mn^{2+} + 2ClO_2 + 4OH^- \rightarrow MnO_2 + 2ClO_2^- + 2H_2O \quad (16)$$

In acidic solution pH < 7, chloride is formed after the oxidation of Mn^{2+} and Fe^{2+} by ClO_2 [109].

$$5Mn^{2+} + 2ClO_2 + 6H_2O \rightarrow 5MnO_2 + 12H^+ + 2Cl^- \quad (17)$$

$$5Fe^{2+} + ClO_2 + 4H^+ \rightarrow 5Fe^{3+} + Cl^- + 2H_2O \quad (18)$$

Regarding chlorate, it mostly originates from ClO_2 generators and ClO_2 creates relatively little ClO_3^- directly [118]. Chlorate can also be present naturally in the raw water sources.

5.5 Health effects of chlorine dioxide byproducts

Most of the limited studies about adverse health effects of chlorite and chlorate have been conducted on animals and few of them on humans. Consequently, data on humans is still ambiguous.

5.5.1 Chlorite

Toxicology

It has been demonstrated by Heubner and Jung [119] that chlorites can oxidize hemoglobin to methemoglobin in rats (in vitro and in vivo) and in humans (in vitro) [120] and even much faster than chlorate. Therefore, exposure to a high level of chlorite induces an increase in methemoglobin concentrations in the blood, which lowers oxygen's capacity to bind to hemoglobin.

Afterward, Heffernan et al. [121] and Abdel-Rahman et al. [122] reported that exposing to approximately 50 mg\l of chlorite has caused a reduction of erythrocyte glutathione levels and has produced methemoglobinemia in cats and rats. Yet, at 10 mg ClO_2^-/l no effect was seen.

Furthermore, chlorite can cause neurodevelopmental defects in animals during critical stages of neurodevelopment. It consequently affects brain growth, decreases locomotor and exploratory behavior, and alters auditory startle response. However, it is yet to be proven whether similar chlorite-induced neurodevelopmental effects might occur in human [123].

Several experiments show even more hematological alterations in animals exposed to chlorite.

Moore and Calabrese's [124] investigation on the hematotoxicity of chlorite in mice, showed that exposure to 100 ppm resulted in drastic increases in mean corpuscular volume, osmotic fragility, and glucose-6-phosphate activity. However, no other changes in hematologic parameters were seen.

Another study by Bercz et al. [97] on the hematologic and serum clinical chemistry parameters in African green monkeys revealed that exposure to 200 mg/l can cause erythema and ulceration of the oral mucosa, mucous nasal discharge, and avoidance of drinking water. And exposure to 58.4 mg/kg-day of chlorite resulted in erythrocyte and hemoglobin levels.

Nevertheless, no changes were detectable in hematologic clinical chemistry (erythrocyte, total and differential leukocyte, and reticulocyte counts, hemoglobin levels, hematocrit, osmotic fragility, and methemoglobin levels) or serum clinical chemistry (creatinine, blood urea nitrogen, alkaline phosphatase, lactate dehydrogenase, and alanine and aspartate aminotransferase) parameters.

Rats exposed to 10 mg/l of ClO_2^- in drinking water for 3 months, experienced considerable increases in 3H-thymidine incorporation, implying an increased turnover of intestinal epithelium [122].

More recent studies have shown that chlorite can result in different reproductive and developmental effects in animals (including neurodevelopmental endpoints, delays in sexual development, skeletal anomalies and reduced liver, spleen or body weight at birth) [125, 126].

Studies conducted on human volunteers for up to 12 weeks did not show significant effects on blood parameters at the maximum amount examined, 36 g/kg body weight per day [126].

Genotoxicity

The genotoxicity of chlorite in humans has not been documented anywhere yet. However, it has been evaluated in a number of in vitro and in vivo tests. In in vitro experiments, chlorite caused chromosomal abnormalities in Chinese hamster fibroblast cells and reversal mutations in *S. typhimurium* [127].

In contrary, in an in vivo essay Meier et al. [85] found no chromosomal abnormalities in either the mouse micronucleus test or a cytogenetic assay in mouse bone marrow

cells following gavage dosing with chlorite. However, when chlorite was injected intraperitoneally (7.5–60 mg/kg), the 27-micronucleus test in mice produced positive findings [128].

Carcinogenicity

Dermal carcinogenicity studies by Kurokawa et al. [129] have shown that chlorite did not result in increased tumor incidence. In two other investigations using mice and rats, it was confirmed that chlorite revealed no signs of being carcinogenic [130, 131]. However, these studies lack adequate evidence on chlorite's carcinogenic risk in humans. Therefore, chlorite is categorized as Group D, not classifiable as to human carcinogenicity [132].

Chlorite can also cause irritation in the mouth, esophagus, or stomach or birth defects [34].

5.5.2 Chlorate

Toxicology

Similar to chlorite, chlorate can oxidize hemoglobin to form methemoglobin yet after a brief lag period [118] Therefore, exposure to high chlorate concentration has caused methemoglobinemia with blood destruction in mice [133]. In addition, ClO_3^- induced persistent drops in red cell glutathione concentrations with continued treatment at 10 and 100 mg/l [122].

Chlorate is therefore assumed to be a potentially dangerous chemical [134, 135] confirmed that chlorate can harm young children's neurological systems and induce anemia. Nevertheless, since there is inadequate toxicological evidence, the IARC has not categorized chlorate.

And just like chlorite, studies conducted on human volunteers for up to 12 weeks did not show significant effects on blood parameters at the maximum amount examined, 36 g/kg body weight per day [126].

Genotoxicity

Meier et al. [85] experiment in mouse bone marrow cells, shows no chromosomal abnormalities in either the micronucleus test or a cytogenetic assay.

Carcinogenicity

There have been no investigations on the carcinogenic risk of chlorate alone. In rats, sodium and potassium chlorate were tested for their ability to produce kidney tumors. The presence of sodium chlorate in drinking water increased the incidence of kidney tumors, however the impact was not statistically significant due to the limited number of animals utilized [136].

In addition, chlorate has the ability to alter thyroid function by inhibiting the sodium iodide symporter (NIS) protein, which is in charge of controlling the quantity of iodine in the thyroid. This could have potential implications both for thyroid hyperplasia and cancer [137, 138].

5.5.3 Quinones

Quinones's metabolites may conjugate with glutathione and cysteine, and act as carcinogens leading to damage to certain cells (e.g., liver, bladder and kidney) [139, 140] Furthermore, quinones can be highly cytotoxic and potentially genotoxic, inducing aneuploidy in human cells [141].

According to several in vitro cytotoxicity tests, halogenated benzoquinones can cause greater cytotoxicity and/or developmental toxicity than the majority of the regulated DBPs [141].

6 Hungarian drinking water disinfection practice, current issues

In Hungary, for drinking water disinfection, mostly chlorination is applied (either in the form of chlorine gas or sodium hypochlorite), and in recent years the application of chlorine dioxide has become more and more widespread. Ozonation is mostly used in surface water treatment plants. In addition to chemical disinfection methods, UV radiation is frequently used, particularly after biological drinking water treatment technologies.

According to Hungarian practice, chlorination is applied not only as a final disinfectant, but it is also used for pre- or intermediate oxidation in order to convert ammonium ions to chloramines. This technology is called breakpoint chlorination, and it is a widely applied method for ammonium ion removal in Hungary. This technology usually requires the use of chlorine doses that are an order of magnitude higher than in the case of post-chlorination; therefore, chlorinated byproducts might form in high concentrations, and granular activated carbon has to be installed for the removal of them.

In cases of unfavorable raw water quality (e.g., high organic content and high ammonium concentration), it can be quite challenging to keep the THM concentration under the Hungarian limit (50 μg/l) in the finished water. Another issue is that huge percentage of these technologies use sodium hypochlorite instead of chlorine gas (due to safety considerations), and chlorate appears in the concentrated sodium hypochlorite solutions, especially if they are stored for a longer period of time during the summer. It might be difficult for these water treatment plants to meet the 0.25 mg/l chlorate concentration set by the

EU Directive 2020/2184 [20] and the new Hungarian Governmental Decree (Governmental Decree 5/2023. (I. 12.)) [142] in the treated water.

7 Conclusions

Chlorination and chlorine dioxide oxidation are among the most used methods for drinking water disinfection around the world. Chlorination is mostly used because it is inexpensive and easy to use, and chlorine dioxide is widely utilized as an alternative to chlorine because it tremendously reduces the formation of halogenated DBPs.

The complex reaction between free residual chlorine and NOM or/and bromide leads to the production of a great variety of CBPs which has yet to be fully characterized.

THMs, HAAs, chlorophenols, chloral hydrate, and HANs are some of these undesirable byproducts. However, the largest groups commonly present in chlorinated water are THMs, followed by HAAs and HANs. These components' possible health impact is widely documented.

THMs including brominated THMs have been proven to cause genomic DNA damage in CHO cells. Chloroform, bromodichloromethane and dibromochloromethane were listed, by the IARC, as possibly carcinogenic to humans and is known as Group 2B carcinogen compound.

The carcinogenicity of HAAs is also under investigation, dichloroacetic acid, trichloroacetic acid, bromo-chloroacetic acid, and dibromoacetic acid are classified as 2B Group of potential carcinogens according to IARC. Both dichloroacetic acid and trichloroacetic acid mostly harm the liver. Additionally, dichloroacetic acid can also be neurotoxic. Bromoacetic acid, dibromoacetic acid, chloroacetic acid and tribromoacetic acid were mutagenic in bacteria and caused mammalian cells' genomic DNA damage.

It is important to note that several research has shown that brominated THMs and brominated HAAs are frequently more genotoxic, cytotoxic, or carcinogenic thus, more hazardous to human health than their chlorinated analogues.

HANs as well have been identified as extremely carcinogenic N-DBPs and they can induce considerable DNA damage.

ClO_2 reacts actively with naturally occurring organic and inorganic matter and produces ClO_2^- and ClO_3^-, oxidized byproducts (acids, aldehydes, and alcohols), and several chlorinated organic byproducts. Chronic exposure to chlorate and chlorite can cause anemia and damage the nervous system in young children, but they are not classified by IARC because of insufficient toxicological data.

Further studies are needed for improving the understanding of the reactions between disinfectants and the complex organic matters. Human health effect of chlorine dioxide byproducts needs to be deeply investigated.

With better understanding of the toxic potential of most emerging DBPs, more and more byproducts have been regulated on regional and national level. It is rather challenging for the water utility operators to provide drinking water with good microbiological quality meanwhile not to exceed the maximum allowable concentration values for the regulated byproducts.

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