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Review

Hazard and mode of action of disinfection by-products (DBPs) in water for human consumption: Evidences and research priorities

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ABSTRACT

Disinfection of water system is an essential strategy to protect human health from pathogens and prevent their regrowth during water distribution, but the reaction of disinfectant agents with organic matter can lead to the formation of disinfection by-products (DBPs). Given their widespread occurrence, potential human health impacts and (eco)toxicity associated with exposure to DBPs are of particular interest due to their potential carcinogenicity and vary non-carcinogenic effects, such as endocrine disruption. Understanding the public health implications of this emerging issue is crucial for societies and decision-makers, supporting more effective water safety plans. Here, we review the recent literature on the effects of DBPs presented in drinking water and treated swimming pools water, focusing particularly in unregulated compounds and the putative underlying mode of action, linking the available data with adverse health outcomes. Overall, the majority of studies highlight the limited knowledge in the understanding of the underlying mode of action of DBPs. Yet, available evidences indicate that different signaling pathways seem to be involved in the adverse outcomes associated with distinct DBPs classes. The main knowledge gaps in this field are also identified, and future research priorities discussed.

1. Introduction

Water treatment plant (WTP) is a crucial tool to promote safe and clean drinking water. However, during this complex treatment process the raw water can react with chemical agents forming disinfection by-products (DBPs). These chemical reactions have been mainly reported in two potential steps of water treatment, coagulation and disinfection. However, pre-oxidation technologies using oxidants such as sodium hypochlorite or ozone are also potential factors affecting DBPs formation (Li et al., 2017; Zheng et al., 2017).

The nature and quantity of DBPs formed depends on the physico-chemical properties of the raw water. The WTP operational conditions parameters are particularly important, including disinfectant dose, temperature, pH, contact time and coagulant agent used in the process. Environmental conditions, such as climate, and the specific characteristics of the distribution system are also relevant parameters (Plewa et al., 2017; Richardson, 2011; Richardson et al., 2015).

Humans are mostly exposed to water DBPs through direct ingestion of water, via inhalation and dermal absorption while showering, bathing and swimming in treated pools (Li et al., 2017; Richardson and Postigo, 2011).

In this work, we review the recent literature on the effects of DBPs present in drinking water and treated swimming pools, focusing in particular in unregulated compounds and the putative underlying mode of action, linking the available data with adverse health outcomes. The main knowledge gaps in this field are also identified, and future research priorities discussed.

1.1. Forcing agents of water DBPs formation

The main precursors of DBPs present in raw water can include natural organic compounds, such as humic and fulvic acids, and anthropogenic contaminants of emerging concern including endocrine disrupting chemicals (EDCs), non-steroidal anti-inflammatory drugs

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(NSAIDs), pharmaceutical and personal care products (PPCPs), pesticides and herbicides, cyanotoxins, textile dyes, hormones, surfactants and UV-filters (Postigo et al., 2017; Richardson et al., 2015). In recent years, special attention has been given to this emerging contaminants due to theirs widespread and daily use, reactivity as DBPs precursors and poorly characterized biological effects (Park et al., 2016; Postigo et al., 2017; Richardson et al., 2015).

Raw waters with lower aromatic natural organic matter content have been associated with the preferential way to generate iodinated DBPs (I-DBPs) such as I- THMs and I- HAAs (Dong et al., 2017; Nihemaiti et al., 2016). High levels of bromide in raw water is associated with the formation of bromate; source water with high algal or wastewater content (rich in nitrogen) has been associated with N- DBPs (Komaki and Plewa, 2017). However, the formation scenarios and many reaction pathways are still unclear due to the poorly characterized nature of precursors.

Popular disinfectants of drinking water include chlorine, chloramines, ozone, chlorine dioxide and ultraviolet light (UV) (Richardson et al., 2015). Chlorine is the most ubiquitous disinfectant used worldwide, applied alone or in combination with other disinfectants. The most common approach involves the use of chlorine-based disinfectants in combination with ozone in order to reduce the volume of some chlorine-based DBPs formed, such as THMs and HAAs. However, this combination results in the production of potential more reactive DBPs such as aldehydes, ketones, keto-aldehydes, carboxylic- acids, keto-acids, alcohols, among others. Disinfection with chloramines is usually associated with the formation of nitrogenated by-products such as nitrosamines (N-DBPs) (Kristiana et al., 2012). Even UV, considered as a clean technology, has the potential to produce aldehydes (Nikolaou et al., 1999; Richardson et al., 2015).

In addition to the nature of disinfectant agent, several physicochemical parameters are also important drivers for the formation of DBPs. The most relevant are pH and temperature, i.e., higher temperatures increases the amount of disinfectant used and the DBPs formed (Richardson et al., 2015). Basic pH promotes the formation of THMs but leads to the decrease of HAAs, haloacetamines and haloketones levels. In contrast, acidic pH increase the HAAs formation (Cortés and Marcos, 2018; Singer, 1995).

DBPs are also formed in disinfected swimming pools through reaction of the same chlorine-based disinfectants with precursors as urine, sweat, hair, sunscreens, lotions and personal care products (Yang et al., 2018). Chlorination is the most commonly used disinfection treatment in swimming pools. The higher formation of DBPs in swimming pools compared with drinking water is mainly associated with the high water temperature involved and the water recirculation. According to recent studies, the water of outdoor pools contained on average two times more DBPs, such as THMs (97,9 μg/L vs 67,7 μg/L) and HAAs (807,6 μg/L vs 412,9 μg/L) compared with indoor pools, during the same seasonal period (Cardador and Gallego, 2011; Simard et al., 2018). For outdoor pools, it is possible that the presence of higher levels of precursors requires the use of higher amounts of disinfectant and consequently higher levels of DBPs formed. Higher concentrations of DBPs such as total THMs (130 μg/L range vs 80 μg/L in average) were found in heated (26 °C) compared with non-heated (23 °C) outdoor pools (Simard et al., 2018). One of the most common DBPs in chlorinated swimming pools is trichloramine formed by reaction of nitrogenous compounds and chlorine (Villanueva and Cordier, 2015).

Coagulation is a commonly used process in water treatment to remove natural organic matter suspended in raw water. Recent studies suggested the importance of this treatment step in the production of some DBPs, namely N-DBPs, through the addition of coagulants such as chitosan or cationic polymers such as polyacrylamide (PAM) and polydiallydimethyl ammonium chloride (polyDADMAC) (Li et al., 2017; Nawrocki and Andrzejewski, 2011; Richardson and Postigo, 2011). The reaction mechanism of N-nitrosodimethylamine (N-DBP) formation is unclear but one possibility involves the amine group of PAM that can work as a precursor (Li et al., 2017).

Due to the complex processes of DBPs formation, their high diversity and complexity, this analysis is challenging (Table 1). However, understanding the public health implication of this issue is crucial for improving human health risk assessment and implementing effective water safety plans.

1.2. Water DBPs: legal context

Over the past twenty years, more than 600 DBPs have been identified in water but just 11, including THMs, HAAs, bromate and chlorite are currently regulated by USEPA under the stage I and II Disinfectants and DBPs Rules (USEPA, 2016b) (EPA, 2016). Still, it is estimated that over 50% of the halogenated material formed during chlorination are unknown and their toxicological risk poorly characterized. Importantly, several of these unregulated DBPs have been shown to be more genotoxic and cytotoxic than some regulated compounds. Unregulated and emerging DBPs includes different classes of compounds such as halomethanes, iodo-trihalomethanes, nitrosamines, halobenzoquinones among others (Table 1) (Plewa et al., 2017; Richardson et al., 2015).

On the EU legal context, the Drinking Water Directive 98/83/CE sets a maximum water concentration of 100 μg/L for most prevalent THMs (THM4 - sum of chloroform BDCM, DBCM and bromoform) (The Council of the European Union, 1998). In comparison with the regulation in United States, the maximum level for THMs in drinking water is set at 80 μg/L. Bromate are regulated in both the EU and US with the limit of 10 μg/L, chloride is regulated with the limit of 250 mg/L in EU and chlorite with 700 μg/L in US. In addition, only 5HAAs (sum of monochloro-, dichloro-, trichloro, monobromo-, and dibromoacetic acids) and chlorate are regulated in US with the limites of 60 μg/L and 700 μg/L, respectively. Regarding the unregulated and emerging families DBPs, Word Health Organization (WHO) included compounds such as *N*-nitrosodimethylamine (NDMA) (0,1 μg/L), dichloroacetonitrile (20 μg/L) and dibromoacetonitrile (70 μg/L) in the drinking water guidelines, reinforcing their potential toxicological effect to humans (WHO, 2017).

Considering disinfectants for swimming pools water (SPW), only THMs have been regulated in some European countries (Table 1). Based on DIN (national standards body for Germany) 19,643, the maximum contaminant level (MCL) of THMs, in Germany, is set at 20 μg/L. In fact, Germany is the country with the lowest parametric value comparing with other European countries such as Finland, where the MCL for THMs is 100 μg/L (WHO, 2000; Yang et al., 2018).

Given the limit information on the subject, it is crucial to improve risk assessment to support more effective regulatory limits and ensure the human health protection.

2. Exposure assessment and risk characterization of water DBPs

Given that DBPs are (semi-) volatile and skin permeable, the exposure pathways are numerous and include ingestion of water, inhalation and skin absorption while showering, bathing, swimming in treated pools, and hand dish-washing (Grellier et al., 2015; Richardson et al., 2015).

Toxicological studies, using cell cultures and animals, suggested potential genotoxicity, cytotoxicity, carcinogenicity, teratogenicity and endocrine disruption associated with the chronic exposure to DBPs, depending of the origin of water, disinfection procedure and disinfectant nature (Cortés and Marcos, 2018; Dong et al., 2017; Hanigan et al., 2017; Richardson et al., 2007) (Table 2). Neurotoxicity was also reported as a potential outcome based on bioassays. However only a few studies are available and therefore more knowledge is required (Guariglia Jr et al., 2011; Moser et al., 2004).

Epidemiological studies involving exposure to DBPs reported cancer and non-cancer outcomes, i.e., bladder, lung and colon cancer, birth defects, asthma and skin rashes. These outcomes were associated with

Table 1
Main classes of DBPs, average concentrations range and European legal context.
Modified from (Cortés and Marcos, 2018)

Main classes of DBPs.	Average concentration range (μg/L)	Regulated (EU)
HALONITROMETHANES	**	
Chloronitromethane, dichloronitromethane, trichloronitromethane (chloropicrin), bromonitromethane, dibromonitromethane, tribromonitromethane (bromopicrin), bromochloronitromethane, bromodichloronitromethane, dibromochloronitromethane		
HALOACETIC ACIDS AND OTHER HALOACIDS	*****	
Chloroacetic acid, Dichloroacetic acid, Trichloroacetic acid. Bromoacetic acid, Dibromoacetic acid, Tribromoacetic acid, Iodoacetic acid, Diiodoacetic acid, Triiodoacetic acid, Bromochloroacetic acid, Bromodichloroacetic acid, Bromoiodoacetic acid, Dibromochloroacetic acid, Chlorodibromoacetic acid		
TRIHALOMETHANES	******	DW; TSP
Chloroform, bromoform, dibromochloromethane, bromodichloromethane, dichloroiodomethane, bromochloroiodomethane, dibromoiodomethane, chlorodiiodomethane, bromodiiodomethane, iodoform, dichloromethane, bromochloromethane, chlorodibromomethane, dibromomethane		
OXYHALIDES		DW
Bromate (0.2–25.1), chlorate (up to 190), chlorite (up to 1100)		
HALOFURANONES	*	
mx, red-mx, ox-mx, emx, zmx, mucochloric acid, bmx-1, bmx-2, bmx-3, bemx-1, bemx-2, bemx-3		
HALOACETONITRILES	****	
chloroacetonitrile, dichloroacetonitrile, trichloroacetonitrile, bromoacetonitrile, dibromoacetonitrile, tribromoacetonitrile, bromochloroacetonitrile, bromodichloroacetonitrile, dibromochloroacetonitrile, iodoacetonitrile		
HALOKETONES	***	
Chloroacetones		
HALOAMIDES		
chloroacetamide, dichloroacetamide, trichloroacetamide, bromoacetamide, dibromoacetamide, tribromoacetamide, bromochloroacetamide, bromoiodoacetamide, bromodichloracetamide, dibromochloroacetamide, iodoacetamide, diiodoacetamide, chloroiodoacetamide		
HALOAMINES & OTHER AMINES	*****	
chloramines, nitrosamines (*N*-nitrosodimethylamine, *N*-nitrosodiphenylamine; N-nitrosopyroolidine; N-nitrosomorpholidine, N-nitrosopiperidine), heterocyclic amines		
ALDEHYDES	****	
formaldehyde, acetaldehyde, haloaldehydes, chloroacetaldehyde,haloacetaldehydes, dichloroacetaldehyde, bromochloroacetaldehyde, trichloroacetaldehyde (chloral hydrate), tribromoacetaldehyde		
OTHER DBPS: **Chloride**, quinones (benzoquinones), cyanogen halides, chlorophenols, aldoketoacids, carboxylic acids, haloacetates, halopyrroles, amoung others.		DW

Main groups and occurrence (μg/L) (average) *0,08-0,8; ** 0.1–10; ***10–60; **** 0,4–300; ***** 1–2500;****** 0,05–400 (Krasner et al., 2006; Richardson et al., 2007; Simard et al., 2018; Weinberg et al., 2002).
DW- Drinking Water; TSP- treated swimming pools. Individual regulated compounds are presented in bold.
Individual regulated compounds are presented in bold.

different contact routes such as respiratory, gastrointestinal tract and dermal contact. Most biological samples used in the former studies included blood, urine and exhaled bread (Allen et al., 2017; Cantor et al., 2010; Rahman et al., 2010; Tardiff et al., 2006; Villanueva and Cordier, 2015; Wright et al., 2017)

Vlaanderen et al. (2017) studied the association between the exposure to THMs (measured in exhaled breath) in swimming pools, and respiratory effects, such as asthma, using several biomarkers of immune response, i.e., interleukin-1rA, C-X-C motif chemokine 10, C-C motif chemokine 11, among others. The study suggested a positive association between short-term exposure to DBPs and the selected markers, namely cytokines and chemokines. Yet, a fully demonstration of the association between exposure to DBPs and this acute modification on immune response awaits further evidences as the potential influence of the physical activity in the quantification of immune markers in swimmers serum should be further clarified (Vlaanderen et al., 2017)

The most common adverse outcome reported in embryo development is cardiovascular defects (CVDs) with an association with a sum of 4 THMs (chloroform, BDCM, DBCM, and bromoform),THM4, although the association between the risk of CVDs and individual DBPs remains unclear (Richardson et al., 2007; Wright et al., 2017).

Considering cancer outcomes, positive association have been found for bladder cancer and THM4, HAAs and TCM (Table 2) (Grellier et al., 2015). It is important to highlight that some associations are not consistent across different epidemiological studies, given the complexity and diversity of this group of compounds. Some systematic reviews and meta-analysis dealing with cancers have been carried out but the evidence of association between humans DBPs exposure and cancer was not consistent to infer whether such association are causal (Grellier et al., 2015).

The potential genotoxic effects of DBPs, derived from in vitro studies, have been recent reviewed by Cortés and Marcos, (2018). Considering bacterial and mammalian based cell tests, the authors concluded that the potential genotoxic action of DBPs could be ranked, from the highest to the lowest, as iodinated-brominated-chlorinated DBPs. Considering DNA damage after chronic exposure to different target families of DBPs the rank order suggested was (from the higher to the lower): haloacetic acids > haloacetamines > haloacetonitriles > halonitromethanes followed by haloacetaldehydes > nitrosamines and finally trihalomethanes. Considering cell growth inhibition after chronic exposure, the higher inhibition was as follow: haloacetamides > haloacetaldehydes > halonitromethanes > haloacetic acids > haloacetonitriles > trihalomethanes > nitrosamines (Cortés and Marcos, 2018).

These recent studies in emerging DBPs, including halonitromethanes, iodo-trihalomethanes, iodo-acids, haloamides, halofuranones, haloacetonitriles, haloacetaldehydes, nitrosamines and halobenzoquinones, suggest they can display higher genotoxicity and cytotoxicity potential than those that are currently regulated such as trihalomethanes and haloacetic acids. Based on in vitro studies, iodoacetic acid (IAA) is one of the most genotoxic DBP identified, to date (Richardson et al., 2015, 2007; Wang et al., 2018).

In support of in vitro studies, several DBPs have been shown to be genotoxic, cytotoxic and carcinogenic in in vivo animal models, such as

zebrafish *Danio rerio* and *Daphnia magna* (Park et al., 2016; Teixidó et al., 2015; Zheng et al., 2017). According to the in vivo tests, families of DBPs such as acetamines and acetic acids are more genotoxic than acetonitriles and nitrosamines. Based on mammalian development studies, exposure to DBPs led to retarded fetal development, spermatotoxicity, delayed sexual maturation, changes in reproductive organs/placenta and skeletal effects (Tardiff et al., 2006; Wagner and Plewa, 2017; Wright et al., 2017). Recently, an association between DBPs and disruption of androgen signaling pathway was reported (Holmes et al., 2017). Based on this study, regulated and unregulated DBPs such as halobenzoquinones, haloacetonitriles, haloacids and halofuranones are able to binding to the androgen receptor as antagonist and subsequently altering gene transcription. Thus, some of these chemicals may disrupt normal endocrine function, mimicking or antagonizing endogenous hormones. However, the interaction of DBPs and nuclear receptors mediated signaling pathway (signaling and metabolic modules) needs further investigation (Holmes et al., 2017).

One of the main uncertainties relates on how the IC50 values derived for individual DBPs can be used to estimate the risk of complex mixtures. Since DBPs are present in waters as a complex mixture, studies with single compounds may not capture their potential synergistic, dose additive and antagonistic activity (Grellier et al., 2015).

One of the major knowledge gaps is related with the limit information available for many DBPs classes given that the majority of studies only address regulated DBPs such as THM4 and HAAs and only a few works have addressed emerging and unregulated DBPs, such as trichloromethane (TCM), bromodichloromethane (BDCM) and dibromochloromethane (DBCM) from BrTHMs class (Grellier et al., 2015). In addition, for the majority of DBPs, the underlying mechanism of action (MoA) is unknown and so more research on this topic is needed including the screening of additional adverse health effects.

3. Metabolism and putative mode of action (MoA) of water DBPs

According to the limit toxicological studies available concerning exposure to DBPs, modulation of several signaling pathways such as CYP2E1 gene, glutathione s-transferases GSTZ1 and GSTT1 have been associated with different adverse outcomes, such as bladder and lung cancers (Cantor et al., 2010; Grellier et al., 2015; Villanueva and Cordier, 2015) (Landi et al., 2003) and diseases at birth (Zhou et al., 2018) (Table 3).

Lung epithelial cells, in in vitro models, were exposed to THMs to assess DNA damaging ability, through changes in the activity of GSTT1 (a glutathione S-transferase). The results showed that BrTHMs (BDCM and TBM) were more rapidly metabolized through this GSTT1 route comparing with their corresponding non-brominated THMs (TCM and DCM). Nevertheless, additional polymorphisms of GSTT1 may influence the response of human cells to the genotoxic effects of the THMs. In consequence, further studies are needed to assess this potential carcinogenic risk of THMs exposure (Landi et al., 2003).

In another study, a positive association between long-term exposure to THMs and risk of bladder cancer in presence of GSTT1 and GSTZ1 polymorphisms was also shown. A genotype assays using cases with confirmed urothelial carcinoma, found a significant association between bladder cancer and GSTZ1 and GSTT1 polymorphisms, depending on THMs concentrations in drinking water. This is consistent with the hypothesis that these genes are involved in the adverse outcomes of THMs. However, more scientific evidence is required to support this association (Cantor et al., 2010; Villanueva and Cordier, 2015).

Recent studies conducted by Zhou et al. (2018) explored the association between CYP2E1 (gene rs2031920, rs3813867, and rs915906) and GSTZ1 (gene (rs7975) polymorphisms and adverse birth outcomes, through the exposure to selected THMs, namely BrTHM, and trichloroacetic acid (TCAA). Multivariate regression models were used to assess interactions between prenatal exposure to DBPs and newborns CYP2E1 and GSTZ1 polymorphisms expression in cord blood. Birth outcomes such as birth weight, birth length and gestational age were assessed. THMs were quantified in maternal blood and TCAA in maternal urine, including 426 pregnant women in a cohort study. The data were not consistent and given the sample sizes, the ability to effectively assess the effect was limited. The only potential interaction verified indicates that newborns with genetic variation of CYP2E1 gene rs2031920 could be correlated with the impact of prenatal BrTHM (sum of DBCM, BDCM and TBM) exposure on birth weight. Additional scientific evidence are needed in this case, but genetic susceptibility could play an important role, mediating the impacts of maternal exposure to DBPs on the birth outcomes (Zhou et al., 2018).

Nitrosamines metabolism and their potential carcinogenesis have also been suggested in association with human CYP2 family (Hanigan et al., 2017; WHO, 2002). According with this pathway, NDMA is metabolized by the CYP2E1, producing secondary metabolites: α-hidroxy-NDMA, subsequently metabolized in N-nitroso-methylamine and finally in Methyldiazonium ion. This final metabolite binds DNA forming DNA adducts causing cancer such as liver cancer, lung cancer and renal cancer (Godoy et al., 2002). However, for a correct definition of the MoA of NDMA and risk assessment all the exposure routes should be crossed. Concerning NDMA, human exposure may also include food, tobacco, among others (World Health Organization, 2004).

Other biomarkers have been screened such as the enzyme glyceraldehyde 3-phosphate dehydrogenase (GAPDH), that has been associated with exposure to DBPs and impairment, i.e., cytotoxy, genotoxy and neurotoxicity (Table 3). Similarly, changes on the nuclear enzyme Topoisomerase II has been associated with cellular mitosis and DNA stability (Komaki and Plewa, 2017; Pals et al., 2011).

Monohaloacetic acids (MonoHAAs) were linked with the generation of reactive oxygen species (ROS) due to the inhibition of GAPDH. This association may play an important role in neurodegenerative diseases such as Alzheimer's disease. The mechanism of action of MonoHAAs involves the DNA damage by alkylating the thiol group of the cysteine residue in the active site of GAPDH (Dad et al., 2013; Pals et al., 2011). Considering the monoHAAs DBPs family, the effects reported were higher in IAA followed by BAA and CAA. Despite the positive correlation, more studies are needed to clarify this MoA.

In addition, in the same acetic acids group of DBPs, it was recently proposed a putative interaction of IAA with catalase, also linked with the oxidative stress. According to Wang et al. (2018) the IAA binds the CAT through van der Waals and hydrogen bonding interactions in HIS 74 and TYR 357, that circles active sites. These interactions leads to changes in protein size and loss of protein skeletons (Wang et al., 2018).

Monohaloacetonitriles (monoHANs) were linked with the inhibition of decatenation activity of the enzyme topoisomerase II, in CHO cells, under acellular conditions. Topoisomerase is linked with cellular mitosis and DNA stability and replication. Komaki and Plewa, (2017) recently suggested that monoHANs leads the hyperploidy induction in cells, as a consequence of mitosis inhibition, by suppression of the topoisomerase decatenation activity. However, the model proposed was only partially supported (Table 3). Further investigations are needed to support the association between the hyperploidy verified with some monoHANS, namely chloroacetonitrile (CAN) and bromoacetonitrile (BAN), and tumorigenesis (Komaki and Plewa, 2017).

To evaluate oxidative damage, markers such as malondialdehyde (MDA) and 8- hydroxydeoxyguanosine (8-OHdG) were used (Du et al., 2013). Benzoquinones (HBQs) shown positive association with the production of intracellular ROS in T24 bladder cells though the measure of oxidative damage marker 8-OHdG. This association was concentration-dependent and suggested that DNA damage and protein carbonylation are involved in toxicity mechanism of this group of DBPs (Du et al., 2013).

Regarding endocrine disruption, nuclear receptors (NR) as androgen receptor (AR) was addressed (Holmes et al., 2017). In accordance, Halobenzoquinones and other DBPs classes such as haloacetonitriles,

Table 2
Summary of recent studies focusing mainly on the toxicological effects of emerging and unregulated DBPs.

DBP/Hazard agent	Water Matrix	DBPs concentrations tested/assessment	Endpoints Health outcome	Exposure assessment method/Model	Study reference
THM4; HAAs and TCM	Chlorinated water	PFs/SFs/RfDs exposure pathway dependent*	Cancer for bladder, rectum, colon, others unspecified cancers; Birth defects	Tap water and blood	Grellier et al., 2015 (review)
THMs, HAAs, formaldehyde and acetaldehyde	Chlorine and ozone	0.2, 0.5, 1.0 and 2.0 mg Cl2 L-1/24 h	Ecotoxicity of THMs, HAAs, and formaldehyde	*Daphnia magna* Exposure	Park et al., 2016
DBP9; DBCM; BDCM; DCAA;TCAA; HAA5; THM4; THMBr	Chlorinated water	n.d	Birth defects (CVDs)	Case control - levels in tap water compared with birth data	Wright et al., 2017
BDCM;BAM; 3-BPN; DBAA; DBAN; DCAN;DIAA; DCP; DCBQ; NDMA	Chemicals target	0.1 nM to 2 mM	Endocrine activity; disruption of endocrine system	ARBA - androgen receptor binding assay	Holmes et al., 2017
THMs	Clorinated pools	Medium increase after swimming: 0.7 to 2.3 for MET(Metabolic equivalents), and 1.4 to 7.1 μg/m^3 for exhaled total THM (sum of the four THM)	Gene expression and DNA methylation	Sampling blood; exhaled breath before and after swimming activity- blood gene expression	Salas et al., 2017
Haloaldehydes	Disinfected water using PFA-performic acid	0.8 mg/L; 0,6 mg/L; 1,5 mg/L PFA dose	Chromosomal mutation and DNA damage	Bacterial, plant, and human cells. Ames test (point mutation in Salmonella),the micronucleus (chromosomal damage) and Comet tests (primary DNA damage) on human hepatic cells (HepG2)	Ragazzo et al., 2017
Halomethanes; THM4;chlorinated, brominated and iodinated Haloacids; Haloacetonitriles: Haloaldehydes; Haloketones; Halonitromethanes; Haloamides	Chlorinated water	LOQ (Limit of quantification) 0,1–2.0 μg/L	Skin rashes	Sampling shower water in homes	Allen et al., 2017
Chloroacetamide; Bromoacetamide; Iodoacetamide; Chloroaceticacid; Bromoaceticacid; Iodoaceticacid; Chloroacetonitrile; Dichloroacetonitrile; Trichloroacetonitrile; Bromoacetonitrile; Dibromoacetonitrile; Iodoacetonitrile; *N*-Nitrosodimethylamine; *N*-Nitrosodiphenylamine; N-Nitrosomorpholine	Chorinated waste water	1–500 μM, compound depending	Mortality and morphology responses/Zebrafish larval behavior	Zebrafish embryos exposure	Hanigan et al., 2017
Trihalomethanes, Haloacetic acids, Haloacetaldehydes, Haloacetamides, Hydroxyfuranone, N-Nitrosamines, Halonitromethanes, N- Chloramines, Haloacetonitriles, Halobenzoquinones, Iodoacids classes: TCM,TBM,TIM, BDCM, DBCM, CDIM, BCIM, BDIM, DCIM, DBIM, CAA, BAA, IAA, DCAA, DBAA, DIAA, TCAA, TBAA, CDBAA, BCAA, BIAA, BDCAA,CAL,BAL, IAL, DCAL, DBAL,TCAL, TBAL, BCAL, DBCAL, BDCAL, CAcAm, BAcAm, IAcAm, DCAcAm,DBAcAm DIAcAm TCAcAm TBAcAm BCAcAm, BDCAcAm, BIAcAm,DBCAcAm, MX, MBA, MCA, NDMA, NDEA, NPIP, NPYR, NMOR, NDPhA, NMEA,TCNM, BNM, Cl-Glycine, Cl-Histamine, Cl-Ethanolamine, Cl-Lysine, Cl-NaAcetyl lysine, CAN,BAN, IAN,DCAN, DBAN, TCAN,2-CBQ, TriCBQ,TetraCBQ,2,5-DCBQ, 2,6-DCBQ, 2,5-DBBQ, 2,6-DBBQ, 2,3-DIBQ, Z3B3IPPA,Z3B3IPPA, E3B3IPPA, E3B2IPPA, E2I3MBDA	Chemical target	n.d	Genotoxicity: SCGE (single cell gel electrophoresis, comet assay) genetic endpoint	Mammalian cells	Cortés et al., 2018 (review)
NDEA	Chlorinated water	100, 150, 200, 250 and 300 mg/L	Mortality and morphology responses/Biochemical parameters	TK6 cells; zebrafish	Zheng et al., 2017

(*continued on next page*)

Table 2 (*continued*)

DBP/Hazard agent	Water Matrix	DBPs concentrations tested/assessment	Endpoints Health outcome	Exposure assessment method/Model	Study reference
Chloroform, Bromoform, BDCM, CDBM,DCA,TCA,DBA;TBA; BCA	Chemical target solutions	20–100 μg/mL	Endpoints such as growth, hatching success, malformations and lethality/ 76 h	Zebrafish	Teixidó et al., 2015

THM: Trihalomethanes; HAA: Holacetic acids; CF: Chloroform, BDCM: Bromodichloromethane, CDBM: chlorodibromomethane; DBCM: Dibromochloromethane; DCA: dichloroacetic acid; TBM: Bromoform; Br-THM: Brominated trihalomethanes; TCA trichloroacetic acid; DBA dibromoacetic acid, TBA tribromoacetic acid and BCA bromochloroacetic acid; TTHM: Total trihalomethanes; .BAM, 2-bromoacetamide; 3-BPN: 3-bromopropionitrile; DBP9: sum of chloroform, bromodichloromethane (BDCM), dibromochloromethane (DBCM), bromoform, monochloroacetic acid (MCAA), dichloroacetic acid (DCAA), trichloroacetic acid (TCAA), monobromoacetic acid (MBAA), and dibromoacetic acid (DBAA); DBAN: dibromoacetonitrile; DCAN: dichloroacetonitrile; DCBQ: 2,6-dichloro-1,4-benzoquinone; DCP- 2,3- dichloropropionamide; DIAA- diiodoacetic acid; HAA5, sum of MCAA, DCAA, TCAA, MBAA, and DBAA; THM4, sum of chloroform, BDCM, DBCM, and bromoform; THMBr, sum of BDCM, DBCM, and bromoform. TCM: trichloromethane, TBM: tribromomethane, TIM: triiodemethane, BDCM: bromodichloromethane, DBCM: dibromochloromethane, CDIM: chlorodiiodomethane, BCIM: bromochloroiodomethane, BDIM: bromodiiodomethane, DCIM: dichloroiodomethane, DBIM: dibromoiodomethane, CAA: chloroacetic acid, BAA: [bromoacetic acid, IAA: iodoacetic acid, DCAA: dichloroacetic acid, DBBA: dibromoacetic acid, DIAA: diiodoacetic acid, TCAA: trichloroacetic acid, TBAA: tribromoacetic acid, CDBAA: chlorodibromoacetic acid, BCAA: bromochloroacetic acid, BIAA: bromoiodoacetic acid, BDCAA: bromodichloroacetic acid, CAL: chloroacetaldehyde, BAL: bromoacetaldehyde, IAL: iodoacetaldehyde, DCAL: dichloroacetaldehyde, DBAL: dibromoacetaldehyde, TCAL: tri- chloroacetaldehyde, TBAL: tribromoacetaldehyde, BCAL: bromochloroacetaldehyde, DBCAL: dibromochloroacetaldehyde, CAcAm: chloroacetamide, BAcAm: bromoacetamide, IAcAm: iodoacetamide, DCAcAm: dichloroacetamide, DBAcAm: dibromoacetamide, DIAcAm: diiodoa- cetamide, TCAcAm: trichloroacetamide, TBAcAm: tribromoacetamide, BCAcAm: bromochloroacetamide, BDCAcAm: bromodichloroacetamide, BIAcAm: bro-moiodoacetamide, DBCAcAm: dibromochloroacetamide, MX: mutagen-X, MBA: mucobromic acid, MCA: mucochloric acid, NDMA: *N*-nitrosodimethylamine, NDEA: N-nitrosodiethylamine, NPIP: N-nitrosopiperidine, NPYR: N-nitrosopyrrolidine, NMOR: N-nitrosomorpholine, NDPhA: *N*-nitrosodiphenylamine, NMEA: *N*-nitrosomethylamine, TCNM: trichloronitromethane, BNM: bromonitromethane, CAN: chloroacetonitrile, BAN: bromoacetonitrile, IAN: iodoacetonitrile, DCAN: dichloroacetonitrile, DBAN: dibromoacetonitrile, TCAN: trichloroacetonitrile, 2-CBQ: 2-chlorobenzoquinone, triCBQ: trichloro-1-4-benzoquinone, tetraCBQ: tetrachloro-1,4-benzoquinone, 2,5-DCBQ: 2,5-dichloro-1,4-benzoquinone, 2,6-DCBQ: 2,5-dichloro-1,4-benzoquinone, 2,5-DBBQ: 2,5-dibromo-1,4- benzoquinone, 2,6-DBBQ: 2,6-dibromo-1,4-benzoquinone, 2,3-DIBQ: 2,3-di-iodo-1,4-benzoquinone, Z3B3IPPA: Z-3-bromo-3-iodopropenoic acid, E3B3IPPA: E-3-bromo-3-iodopropenoic acid, E3B2IPPA: E-3-bromo-2-iodopropenoic acid, E2I3MBDA: E-2-iodo-3-methylbutenedioic acid, NDEA: N-nitrosodiethylamine. * outcome metric- LECR; HI LECR = ΣLAEi × PF i.

haloacids and halofuranes were linked with endocrine disruption by binding to nuclear receptors as the AR, leading to changes in the transcription of target genes. This hypothesis was recently proposed by Holmes et al. (2017) testing 21 suspected and known DBPs (Table 3). According to this study, 14 of 21 DBPs were found to bind AR at IC50 values ranging from 1,86 mM for 2,3-dichloropropionamide (DCP) to 13,5 μM for 3,4,5,6- tretachloro-1,2-benzoquinone (TCBQ). Benzoquinones have shown higher affinity with AR, comparing with the other compounds tested, in accordance, the higher effect was found with TCBQ and DCBQ (2,6-dichloro-1,4-benzoquinone). Given the large number of NRs families in mammalians, future studies should address the modulation of additional NR by DBPs (Gutierrez-Mazariegos et al., 2015; Holmes et al., 2017; Santos et al., 2018; Santos and Castro, 2014).

More recently, epigenetic changes, histone modification, miRNA modulation and DNA methylation have been described as susceptible biomarkers (Vrijens et al., 2015; Salas et al., 2017; Tao et al., 2004). THMs and HAAs have been described to modulate DNA methylation and hypomethylation, which increases the mRNA expression of proto-oncogenes such as c-myc, c-jun (mice) and LINE-1 (human), linked with kidney and liver cancers, after long-term exposure (Pereira et al., 2001; Salas et al., 2017; Tao et al., 2004). The evidence in humans is still limited. Although, DNA methylation associated with changes in genetic elements, such as retrotransposons, seems to occur and folate metabolism seems to play a role in colorectal carcinogenesis, with folate deficiency associated with the increased formation of preneoplasic lesions in rodents, after exposure to DBPs (Geter et al., 2004; Villanueva and Cordier, 2015).

Hence, the use of epigenetics biomarkers and “omics” are expected to become important approaches to better understand the underlying molecular mechanisms and signature of disruption of DBPs.

Taken together, these results highlight the potential of DBPs to modulate many different signaling pathways potentially inducing adverse health effects. This is not surprising considering the large diversity of chemical structures. Hence, future studies should expand the screening to additional signaling pathways and untested DBPs. Scientific evidence in human effects of DBPs exposure in consumption water need to be more supported and specific exposure biomarkers should be taken in attention considering both genetics and lifestyle characteristics.

4. Conclusion and research priorities

According to Word Health Organization (WHO), the sixth goal for a sustainable development in accordance with Agenda 2030 is Water Quality (WHO, 2017). As a matter of fact, water safety and quality and sanitation are global priorities. Understanding the public health implications of chemical contamination of drinking water is important for societies, drinking water providers, risk assessors and their decision-makers due to their widespread occurrence and public health risks (Grellier et al., 2015).

The vast majority of the identified DBPs remains with unknown biological activities, which supports the need to understand how exposure to these compounds may impact the human health.

In summary, priority should be given to address the following knowledge gaps;

i) most available studies on DBPs health effects do not take in account individual characteristics, such as metabolic performance, genetics and lifestyle. Thus, these aspects should be integrated in the exposure assessments, considering also the MoA of individual and complex mixtures. Expanding the knowledge on the MoA of unregulated and poorly studied DBPs will improve risk assessment; ii) increase knowledge of new potential impacted signaling pathways and specific biomarkers should be identified to support a robust human health risk assessment. Ideally, adverse outcome pathways (APO) should be identified and characterized for target DBPs; iii) exposure

Table 3
Summary of recent studies addressing the putative mode of action of regulated and unregulated DBPs.

DBP/Hazard agent	Endpoints	Molecular Ligand	Model	Concentration of DBP/Treatment	Study reference
Monohaloacetic acids: IAA	Oxidative stress/cytotoxicity	Catalase (CAT, EC 1.11.1.6)- HIS 74 and TYR 357	Cell lines assay - mouse hepatocytes	(0, 1, 5, 10, 50, 100, 500, 1000, 2000, 400, 6000, 8000 mM) for 24 h	(Wang et al., 2018)
Monoacetonitriles: CAN and BAN	Hyperploidy induction/mitosis inhibition/disruption cell cycle (cell growth)	Topoisomerase II	CHO cells	0.3, 0.5 and 0.8 μg (nuclear protein)	(Komaki and Plewa, 2017)
halobenzoquinones, haloacetonitriles, haloacids, and halofuranones: (DCBQ), (DBAA), (CSA), (TCP), (DBAN), (MCA), (TCBQ), (4-NP), (MX), (NDMA), (2-CP), (BDCM), (TCAN), (BAM), (DCAN, (IAA), (3-BPN), (DIAA), (DBPN), (DCP)	Endocrine disruption	Androgen Receptor	ARBA, androgen receptor binding assay	0.1 nM to 2 mM	Holmes et al., 2017(Holmes et al., 2017)
Halobenzoquinones (HBQs): (DCBQ), (DCMBQ), (TCBQ), and (DBBQ)	Bladder cancer/oxidative stress	8-hydroxydeoxyguanosine (8-OHdG) and malondialdehyde (MDA) adducts of proteins	T24 bladder cancer cells	25, 50, 75, 100, 125, 150 μM; IC50 values are 95 μM for DCBQ, 110 μM for DCMBQ, 151 μM for TCBQ, and 142 μM for DBBQ/24 h exposure	(Du et al., 2013)
Monohaloacetic acids (monoHAAs): IAA; BAA; CAA	Mitochondrial stress and genomic DNA damage	Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) - cytosolic enzyme.	CHO cells	25 mM IAA, 60 mM BAA or 6 mM CAA for 4 h (Du et al., n.d.); IAA (10–50 μM), BAA (50–150 μM) or CAA (1–10 mM) 10 to 60 min (Pals et al., 2011)	(Du et al., n.d.); (Pals et al., 2011)
Thrihalomethanes: TCM;BDCM;DBCM, DCM and TBM	DNA damage	GSTT1 activity	Lung epithelial cells	10, 100, and 1000 μM	(Landi et al., 2003)
Thrihalomethanes and trichloroacetic acid: DBCM, BDCM, and TBM (BrTHMs) and TCM; TCAA	Birth outcomes	CYP2E1 (rs2031920, rs3813867, and rs915906) and GSTZ1 (rs7975) polymorphisms	Blood, urine and cord blood	Cohort study/The limit of detections (LOD) for blood BDCM, DBCM, TBM, and TCM were 0.45, 0.68, 2.00, and 1.95 ng/L/The LOD of TCAA in urine was 2.00 mg/L	(Zhou et al., 2018)

Iodoacetic acid (IAA); chloroacetonitrile (CAN); bromoacetonitrile (BAN); 2,6-dichloro-1,4-benzoquinone, (DCBQ), 2,6-dichloro-3-methyl-1,4-benzoquinone (DCMBQ); 2,3,6-trichloro-1,4-benzoquinone (TCBQ); 2,6-dibromobenzoquinone (DBBQ); 2,6-dichloro-1,4-benzoquinone (DCBQ), dibromoacetic acid (DBAA), chlorosuccinic acid (CSA), 2,4,6- trichlorophenol (TCP), dibromoacetonitrile (DBAN), mucochloric acid (MCA), 3,4,5,6 tetrachloro-1,2-benzoquinone (TCBQ), 4-n-nonylphenol (4-NP), 3-chloro-4-(dichloromethyl)-5-hydroxy-2(5H)-furanone (MX), N-nitrosodimethylamine (NDMA), 2-chlorophenol (2-CP), bromodichloromethane (BDCM), 2-bromopropionitrile (3-BPN), diiodoacetic acid (DIAA), 2,3- dibromopropionitrile (DBPN), 2,3- dichloropropionamide (DCP), trichloroacetonitrile (TCAN), 2- bromoacetamide (BAM), Dichloroacetonitrile (DCAN); bromodichloromethane (BDCM), dibromochloromethane (DBCM), bromoform(TBM), chloroform (TCM), dichloromethane (DCM) trichloroacetic acid (TCAA).

routes are still not sufficiently addressed particularly for unregulated DBPs; other possible exposure routes such as tobacco, food industry and occupational disinfected environments, should also be considered to improve risk evaluation; iv) treated drinking water shows a complex mixture of DBPs. It is essential to increase the knowledge on the toxicity of DBPs mixtures. Future research should focus in the development of sensitivity analytical methods to identify new DBPs and improve the accuracy of the dose-response relationship measurements; v) increase knowledge on toxicity ranks considering emerging classes of DBPs will help prioritizing which DBPs should go for more detailed studies; vi) further investigation is needed to address forcing agents, during WTP processes, i.e., how physicochemical parameters, such as temperature, pH, organic matter, pre-treatment and disinfectant agents and reactivity time, contribute to the formation of new DBPs, also including the reactions occurring during the distribution system, due to the residual disinfectant dose; vii) improve knowledge in filtration technologies after distribution system in order to minimized DPBs concentrations in consumption water; viii) conditions of lower rain-fall and high temperatures can contribute for increase formation of DBPs in drinking water due to the presence of more precursors (i.e., organic matter, toxins, etc.). This is particularly relevant considering the climate change scenarios which will hypothetically lead in some regions to alterations on the water cycle, temperature and extreme events. The importance of this association should be understood to improve the management of local water resources; ix) additional studies on treated swimming pools water are needed to improve exposure health assessment and effective parametric values.

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