Trends in Environmental Analytical Chemistry 32 (2021) e00148

Contents lists available at ScienceDirect

Trends in Environmental Analytical Chemistry

journal homepage: www.elsevier.com/locate/treac

A step forward in the detection of byproducts of anthropogenic organic micropollutants in chlorinated water

Cristina Postigo [a,b,*], Rubén Gil-Solsona [a], María Fernanda Herrera-Batista [a], Pablo Gago-Ferrero [a], Nikiforos Alygizakis [c,d], Lutz Ahrens [b], Karin Wiberg [b]

[a] Water, Environmental, and Food Chemistry Unit (ENFOCHEM), Department of Environmental Chemistry, Institute of Environmental Assessment and Water Research (IDAEA-CSIC), Jordi Girona 18-26, 08034, Barcelona, Spain
[b] Department of Aquatic Sciences and Assessment, Swedish University of Agricultural Sciences (SLU), Box 7050, SE-750 07, Uppsala, Sweden
[c] Environmental Institute, Okružná 784/42, Koš, 97241, Slovakia
[d] Laboratory of Analytical Chemistry, Department of Chemistry, National and Kapodistrian University of Athens, Greece

ARTICLE INFO

Keywords:
Chlorination byproducts
Suspect screening
Water disinfection
High-resolution mass spectrometry
Reclaimed water

ABSTRACT

Contaminants of emerging concern (CECs) are widespread in the water cycle. Their levels in disinfected waters are usually low, as they may transform into CEC disinfection byproducts (DBPs) during disinfection processes or partially removed in previous water treatment steps. The occurrence of CEC DBPs in real waters has been scarcely addressed, although their presence may be of relevance in water circular economy scenarios, and thus deserves further study in water regeneration systems. In this work, a database of CEC DBPs (n=1338) after chlorination was generated and is ready to use in future screening studies to assess the relevance of these chemicals in contaminat mixtures. Moreover, the transformation of CECs during chlorination, their main reaction pathways with chlorine, and current knowledge gaps were critically reviewed.

1. Introduction

The pollution of environmental waters with organic pollutants of anthropogenic origin is a topic that has attracted the attention of the scientific community since the second half of the 20th century. Advances in analytical instrumentation have allowed the determination of trace concentrations (ranging from pg/L to μg/L level) of a wide variety of anthropogenic organic contaminants of emerging concern (CECs) in the aquatic environment. CECs include unregulated pollutants, such as pharmaceuticals, hormones, detergents, personal care products (UV filters, parabens, biocides), industrial additives, artificial sweeteners, illicit drugs, per- and polyfluoroalkyl substances (PFASs), brominated and organophosphate flame retardants, algal toxins, microplastics, plasticizers, nanomaterials, siloxanes, and a wide range of plant protection products [1,2]. Their presence in water may result in negative effects in wildlife and eventually in humans, e.g., endocrine-disrupting effects, antibiotic resistance, neurotoxic and/or genotoxic effects [2,3].

One of the main sources of CECs into the aquatic environment is domestic wastewater (untreated and treated) [4,5]. Other relevant CEC sources are industrial effluents and spills (from oil refineries, pulp and paper mills, or chemical industries), landfill leachates, and agricultural runoff [2,6]. Although CEC levels in pollution sources are diluted when reaching natural water bodies and may be further reduced by natural photo- and biodegradation processes [7,8], their presence in source waters used to produce drinking water has been repeatedly reported [9–12]. Some CECs can even move through the drinking water treatment trains and can be present, although at very low concentrations, in the finished drinking water [9,13–15].

Due to the large diversity of CECs, targeting all of them along the environmental and urban water cycles represents a huge analytical challenge. This task becomes even more difficult when all potential transformation products (TPs) of CECs have to be considered. TPs form after photo- and biotransformation reactions occurring in nature or biological wastewater treatment [16,17]. Some TPs have been reported to be more toxic than their parent compounds [18–24]. Recalcitrant CECs and TPs also transform during disinfection processes [25], resulting in the formation of disinfection byproducts (DBPs) [25,26]. While concentrations of CECs in disinfected water are usually too low to rise any health concern [17], the occurrence and potential effects of their DBPs still merits investigation. Most CEC DBPs have been identified in

* Corresponding author at: Water, Environmental, and Food Chemistry Unit (ENFOCHEM), Department of Environmental Chemistry, Institute of Environmental Assessment and Water Research (IDAEA-CSIC), Jordi Girona 18-26, 08034, Barcelona, Spain.
E-mail address: cprqam@cid.csic.es (C. Postigo).

https://doi.org/10.1016/j.teac.2021.e00148
Received 21 July 2021; Received in revised form 3 September 2021; Accepted 4 October 2021
Available online 12 October 2021

controlled laboratory studies [23,27–32] and their potential formation in real scenarios remains still largely unexplored.

Although water disinfection, and in particular chlorination, is widely applied for drinking water production, it is also becoming very relevant to ensure the microbiological safety of wastewater reuse in the transition to a water circular economy. Reclaimed water is mostly used as a non-potable water source for irrigation of crops and gardens, flushing toilets, cleaning streets, cooling industrial processes, recharging aquifers, and restoring environmental water levels [33]. Very few direct potable reuse projects are currently running in the world, while indirect potable reuse and *de facto* reuse are very extended worldwide [34]. Overall, water reuse will increase in the future in locations affected by severe water scarcity episodes due to climate change, as without any doubt, reclaimed water is a very valuable water resource. However, the chlorination of treated wastewater, usually rich in ammonia, results in the formation of chloramines [35], reactive towards organic matter and strongly linked to the generation of the human carcinogens nitrosamines. Moreover, this practice has been proven to change the dissolve organic matter fingerprint of water [36] and has the potential to form and release CEC DBPs into the environment. Thus, research to ensure the quality of reclaimed water and minimize its potential negative effects is needed.

The increased availability of bench-top high-resolution mass spectrometers in research laboratories in recent years has enabled the identification of many new DBPs in disinfected water [37]. However, there is still a large fraction of the halogenated material formed during water chlorination that remains unknown [38], and this fraction may be even larger in chlorinated wastewater that in drinking water, as most research in this field has been conducted in the latter. Non-target screening of disinfected waters using high-resolution mass spectrometry (HRMS) will contribute to further uncover the unknown DBPs, and particularly, relevant CEC DBPs that may potentially form during the disinfection processes. Numerous non-target screening workflows and approaches are currently available in the literature for the identification and prioritization of CECs in water [39–44]. Many of them are based on the application of extensive pre-defined lists of suspect CECs and broad compound databases (PubChem or ChemSpider) [15,44–46]. Suspect lists containing tens, and even thousands, of CECs are accessible for suspect screening at the NORMAN database system (https://www.norman-network.com/nds/) as well as in other open access repositories (e.g., Zenodo). However, there are no specific pre-defined lists for CEC DBPs.

This manuscript aimed at generating a compound database for the rapid screening of CEC DBPs in chlorinated water. Consequently, insights into the work conducted so far in this field are provided, and the main knowledge gaps are highlighted. Moreover, the main reaction pathways that CECs undergo during water chlorination are summarized.

2. State of the art and knowledge gaps on CEC DBP research

Most research studies on CEC DBPs focused on pharmaceuticals and personal care products (PCPs) (Fig. 1), followed by industrial chemicals and pesticides/biocides.

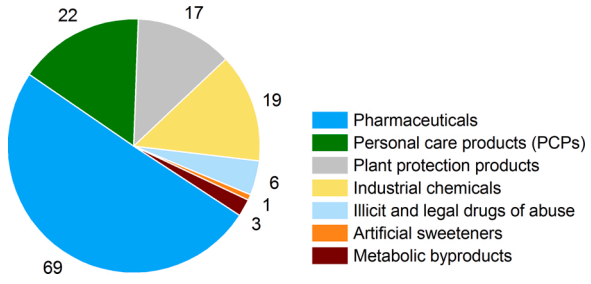


Fig. 1. CEC classes explored for its reactivity with chlorine in the peer-reviewed literature (n = 137). The numbers indicate the chemicals included in each CEC class.

The current knowledge on CEC DBPs has been mainly gained from batch-scale chlorination experiments under controlled conditions. From these studies, the reaction kinetics and CEC half-life are usually obtained. In addition, the reaction pathways between chlorine and the selected CEC are usually proposed based on the TPs identified in the solutions.

Batch-scale chlorination experiments are usually conducted with individual CECs at controlled pH values in pure water (Milli-Q grade, HPLC-grade, or deionized water) to avoid matrix interferences during DBP analysis [31,47–52]. CEC:chlorine ratios used in these experiments ranged between 1:1000 and 1:10 (on a molar or concentration basis), being the lowest ratios similar to those employed in drinking water treatment plants [47,49,53–55]. These ratios allow calculating pseudo-first-order reaction constants because chlorine is present in great excess and its concentration is maintained constant compared to the CECs. DBP identification experiments are conducted with CEC concentrations (from μg/L to mg/L) higher than those found in the environment to facilitate TP discovery and also avoid the enrichment step otherwise required for their detection [27,47–50,53,56,57].

Operational parameters such as the chlorine dose or pH were found to have profound effects on the reaction kinetics in most cases [51,52,58–61]. The pH effect depends on the CEC, but also the initial chlorine dose. Reaction rates usually increased with decreasing pH [23,31,47,59,61,62]. This may be attributed to the higher prevalence of hypochlorous acid (HOCl) over hypochlorite ions (OCl^-) at lower pH values (pK_a = 7.5), being the former usually more reactive than the latter for most CECs [63]. However, the dominant CEC species in solution at a specific pH is also determinant for the degradation kinetics. For instance, in the case of cocaine, the neutral form is more reactive with chlorine than the protonated one (pK_a = 8.6) and its increased ester hydrolysis at lower pH values results in lower cocaine half-lives at lower pH values [47]. In the case of phenolic chemicals like benzophenone-type UV filters or 11-Nor-9-carboxy-Δ^9-tetrahydrocannabinol (THC-COOH) the high electron density of the phenolate ion that forms as the pH increases results in faster reaction kinetics at higher pH values [64,65]. A bell-shape pH-rate profile has been reported for other phenolic compounds like bisphenol A (BPA), tetrabromo-BPA (TBBPA), bisphenol S (BPS), and triclosan, with increasing rates up to pH values of 7–8 and then decreasing rates as the water pH is further increased [48,51,52].

As for the chlorine dose, CEC reaction gets usually faster as the initial chlorine dose and hence, the chlorine:CEC ratio is increased [22,54,60,61]. The presence of inorganic ions such as bromide and iodide in the water may shift the formation of chlorine-containing DBPs to bromine- and iodine-containing DBPs [54,66]. The mechanism behind is the generation of strong halogenating agents, *viz.*, hypobromous acid (HOBr) and hypoiodous acid (HOI)) after the oxidation of bromide and iodide by free available chlorine. Moreover, the presence of bromide has been reported to increase the degradation rate of some CECs [62,67].

Chlorine quenchers like ascorbic acid [68–71], sodium sulfite [72,73], sodium thiosulfate [74–76], or ammonium chloride [77,78] are commonly added to the water samples to stop the oxidation reactions and avoid the formation of additional DBPs during sample treatment and storage. However, this practice may affect the stability of the CEC DBPs formed. Degradation of the monochlorinated derivatives of cocaine [79] and desnitro-imidacloprid [80] occurred in the presence of ascorbic acid and sodium sulfite, respectively [80]. The chlorinated amines formed during chlorination of amine-containing pharmaceuticals can be converted back to the parent compound after reaction with sodium thiosulfate [81]. Quenching the chlorination reaction could be avoided if the analysis of the samples for CEC DBP identification can be conducted immediately to avoid further transformation of the chemical species in solution, and procedural blanks are done with ultrapure water using the same chlorination conditions. The latter is in any case recommended to rule out the formation of artifacts during sample treatment and analysis.

One of the main limitations of the existing studies in this field is that

the majority of the CEC DBP identifications reported are tentative (at different levels of confidence), i.e., the molecular structures of newly discovered CEC DBPs were confirmed with the analysis of pure standards only on a few occasions [23,49,56,82]. Another crucial limitation of most of the studies is that the environmental occurrence of the CEC DBPs identified was not investigated. Some authors fortified real waters with the selected CEC and conducted chlorination reactions to confirm the formation of the identified DBPs in real waters. DBPs found in chlorinated CEC-fortified tap water and wastewater were generally in good agreement with those observed in ultrapure water [31,32,61]. However, the formation of these compounds in real waters containing CECs at environmental concentrations has been scarcely addressed.

Likewise, reaction kinetics were mainly investigated in pure water, and thus the effects of other components in real waters that may compete for chlorine and slow down some of the reactions were not evaluated. As for the reaction kinetics, the majority of the studies performed consider HOCl as the only active oxidant in the chlorine solution. However, there is also evidence that the low concentrations of Cl_2O and Cl_2 (relative to HOCl) in the chlorine solution can play an important role in CEC degradation [83,84]. Thus, the widely reported apparent rate constants used to measure the reactivity of CECs during chlorination ($(K_{app}=K_{obs}/[FAC]_0$), where $[FAC]_0$ is the initial free active chlorine concentration) should be interpreted with caution, as they may over- or under-predict reaction rates. Furthermore, it is extremely difficult to compare the reactivity of various CECs towards chlorine because it depends on the conditions at which the chlorination reaction is conducted (i.e., CEC:chlorine ratio, initial chlorine dose, temperature, pH, bromine content, and water type such as pure water or fortified surface water).

3. Analytical strategies for CEC DBP identification

Because CECs are typically highly polar molecules and some of them have relatively high molecular weight (600−1000 Da) (e.g., algal toxins or macrolide antibiotics), most of their DBPs are also likely to be very polar and thus, amenable to liquid chromatography coupled to mass spectrometry (LC–MS) analysis. Hence, LC–MS interfaced with electrospray ionization is commonly used to discover CEC DBPs. The electrospray interface is capable of obtaining gas-phase ions from a wider range of molecules without fragmenting them (including thermally unstable molecules) as compared to electron ionization (commonly used with gas chromatography coupled to mass spectrometry (GC–MS)), which aids in molecule identification. GC coupled to MS or electron capture detection has been employed to identify or detect semi-volatile and volatile DBPs, including final products e.g., THMs and HAAs [54,77,85–87]. Identification of non-volatile DBPs by GC–MS requires sample extract derivatization, for instance with N-methyl-N-(*tert*-butyldimethylsilyl)-trifluoroacetamide (MTBSTFA) as in the case of triclosan and its chlorination DBPs [51], or N,O-bis (trimethylsilyl)-trifluoroacetamide (BSTFA), as in the case of paraben [88] and acetaminophen DBPs [89]

HRMS analyzers (time of flight (ToF) and Orbitrap) have been increasingly used in recent years as they provide empirical formula information for unknown DBPs [1]. However, chlorination byproducts were also identified using mass spectrometers equipped with low-resolution analyzers such as, quadrupole or ion trap, or a combination of them, such as triple quadrupole (QqQ) or quadrupole-linear ion trap (Q-LIT) [51,55]. These identifications were based on the nominal mass of the parent and fragment ions, the evaluation of the isotopic patterns, and the rationalization of the fragmentation pattern observed.

For the analysis of CEC DBPs by LC-HRMS, the water samples were typically directly injected into the system [28,47,52,55,56,59,69]. This is the reason why many experiments for DBP identification were generally conducted with pure water fortified at a high CEC concentration. The analysis of CEC DBPs in real samples usually involved a solid phase extraction (SPE) step to remove matrix interferences and/or pre-concentrate the analytes [76,79,90–92]. SPE or liquid-liquid extraction of the water samples was required for their GC–MS analysis [54,75]. Column chromatography fractionation on C18 silica gel was also used to isolate nicotine DBPs for their identification by GC–MS and nuclear magnetic resonance [73], and discover bisphenol-A DBPs by LC-HRMS [76].

For DBP analysis by LC–MS, using either high- or low-resolution instruments, a full scan MS experiment was first run over a selected mass to charge (*m/z*) range, and then product ion scans at different collision energies were registered for the *m/z* features of interest. This can be done within the same run, by applying a data-dependent analysis (DDA) scan mode, or in sequential runs. In DDA mode, different criteria were established to select the ions of interest, such as an intensity threshold or an *m/z* difference of 2 ± 0.2 Da to identify chlorine isotope clusters [55]. Exclusion times of several seconds (e.g., up to 15 s [55]) were applied to favor the selection of a wide variety of ions.

Peaks were prioritized from HRMS full MS scan data using specific software that helps in removing background signals, resolving co-eluting interferences, and recognizing and grouping isotopic patterns [31,60]. Peak or feature prioritization was done following different approaches: statistical significance of the peak intensity change between control (non-chlorinated) and treated (chlorinated) samples, evaluation of the time trends throughout the experiments, etc. [93]. Feature identification was based on fragment rationalization of the MS2 spectra obtained or the use of suspect lists of potential DBPs that may form. These suspect lists were developed after a literature search of the specific CEC TPs identified in degradation studies and using *in silico* prediction tools (i.e., the Eawag-BBD database Pathway Prediction system http://eawag-bbd.ethz.ch/predict/ or BioTransformer http://biotransformer.ca/) [23].

To identify bromine-containing DBPs formed during the chlorination of bromine-containing CECs, e.g., for TBPA, a precursor ion scan (PIS) approach was used [92]. Herein, those ions that produced bromine (*m/z* 79 and 81) as a fragment were monitored. Same approach (PIS of *m/z* 126.9), already used to identify iodine-containing DBPs in disinfected water [94], could be also applied to investigate DBPs from iodine-containing CECs.

4. Main reaction pathways of CECs with chlorine

While some CECs (e.g., amphetamine and methamphetamine, benzophenone-type UV filters with two phenolic hydroxyl groups, BPA [22,55,76]) disappear within seconds or few minutes in the presence of chlorine, longer contact times (up to several hours) are needed for the complete removal of other CECs (e.g., 3,4-methylenedioxyamphetamine (MDA), 3,4-methylenedioxy ethylamphetamine (MDEA), 3,4-methylenedioxymethamphetamine (MDMA) [55]). The CECs with the longest half-life or slowest rate constant are likely to be found also in disinfected waters. In addition to the chemical nature of the CEC, DBP formation and stability in water has been reported to depend on the chlorination conditions (e.g., CEC:chlorine ratio) [31,60].

Chlorine reacts with CECs mainly through electrophilic attack, although oxidation reactions and addition reactions on unsaturated bonds are also possible. Specifically, halogenation occurs in aromatic rings containing activating (donor) groups such as hydroxyl- or amino-groups that increase the electronic density of carbon atoms at the *ortho*- and *para*-positions. Primary CEC DBPs generated by the aforementioned reactions may further transform via bond cleavage and/or coupling reactions between two DBPs [63,99]. Chlorination rarely leads to mineralization of CECs [73,75,95,96], being small molecular weight DBPs such as trihalomethanes, haloacetic acids, haloacetonitriles, and haloacetamides identified as final DBPs [31,77,97,98].

Chlorine reactivity is usually limited to specific molecule moieties, in particular, reduced sulfur moieties, amines, or activated aromatic systems [63]. Overall, reactivity decreases in the order sulfur moieties > primary and secondary amine > phenols, tertiary amine > > other aromatics, carbonyls, and amides [63].

The following subsections describe the reaction pathways of specific CECs with chlorine. CEC selection was based on the current available

peer-reviewed literature, their relevance as environmental contaminants and the provision of a wide array of chemical structures in the present review.

4.1. Drugs of abuse and psychoactive drugs

Chlorine attack to the tertiary amine of cocaine results in N-dealkylation, halogenation, and to a minor extent, amide formation [47]. The main DBPs reported are norcocaine, norbenzoylecgonine (after benzoylecgonine formation due to ester hydrolysis of cocaine), monochlorinated derivatives of cocaine, and *N*-formylnorcocaine [47,79].

Addition, substitution, and oxidation reactions in the pyrrolidine moiety of nicotine occur after the attack of HOCl/OCl^- on its nitrogen atom that acquires a positive charge [73]. As a result, oxidation DBPs, like cotinine, nicotinic acid, nornicotine, nicotyrine, and myosmine, as well as chlorinated DBPs, like 5-chloro-nicotyrine and 5-chloro myosmine are formed.

In the case of the cannabis biomarker THC-COOH, chlorine attacks at the *para*- and/or *ortho*-positions of its phenolic group [65]. As for the stimulants, MDEA, MDA, and MDMA, electrophilic aromatic substitution occurs at the *meta*-position of their benzene ring after the corresponding amide side-chain cleavage [55].

During the chlorination of the benzodiazepines diazepam and oxazepam, the main site of chlorine attack is the C3 of the 1,4-diazepine structure. In the case of diazepam, oxygen transfer results in the formation of 7-chloro-1-methyl-5-phenyl-1,3-dihydro-2H-1,4-benzodiazepine-2,3-dione as the main DBP. As regards oxazepam, rearrangement of its molecular structure is induced by abstraction of one proton, resulting in the contraction of the diazepine ring and formation of 6-chloro-4-phenyl-2(1 H)-quinazolinone [100,101]. Quinazoline derivatives are also formed during diazepam and nordazepam chlorination. Benzophenone derivatives, formed after the opening of the 1, 4-diazepine ring, are identified as the final minor byproducts of benzodiazepine chlorination [101].

One of the most abundant chlorination DBPs of the antidepressant citalopram is desmethylcitalopram, a known human metabolite, formed after transformation of the tertiary amine group into a secondary amine [102]. This compound may further oxidize via oxygen transfer, firstly at the furan ring, and then at the secondary amine. The N-oxide derivative was found to be very stable in the solution.

Chlorination of methadone results in the formation of 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP), a known methadone human metabolite, and four other DBPs. They formed after intramolecular cyclization, dehydrogenation, oxidation, and chlorination. Following similar reaction pathways, EDDP is further transformed into three additional DBPs [103].

4.2. Antibiotics

Transformation of antibiotics during chlorination results in DBPs that still keep bacterial growth inhibitory properties, and thus they may also play a relevant role in the selection of antibiotic-resistant microorganisms in the environment [104,105].

Various transformation pathways were identified during the chlorination of sulfonamide antibiotics [50,57] (Fig. 2). They include chlorine substitution, S-C bond cleavage, S-N hydrolysis, desulfonation, hydroxylation/oxidation, and conjugation reactions. Chlorine substitution, S-N hydrolysis, and desulfonation DBPs are common to all. However, chlorine substitution proceeds in different ways, depending on the molecule. N-chlorination of the aniline moiety occurs in the case of

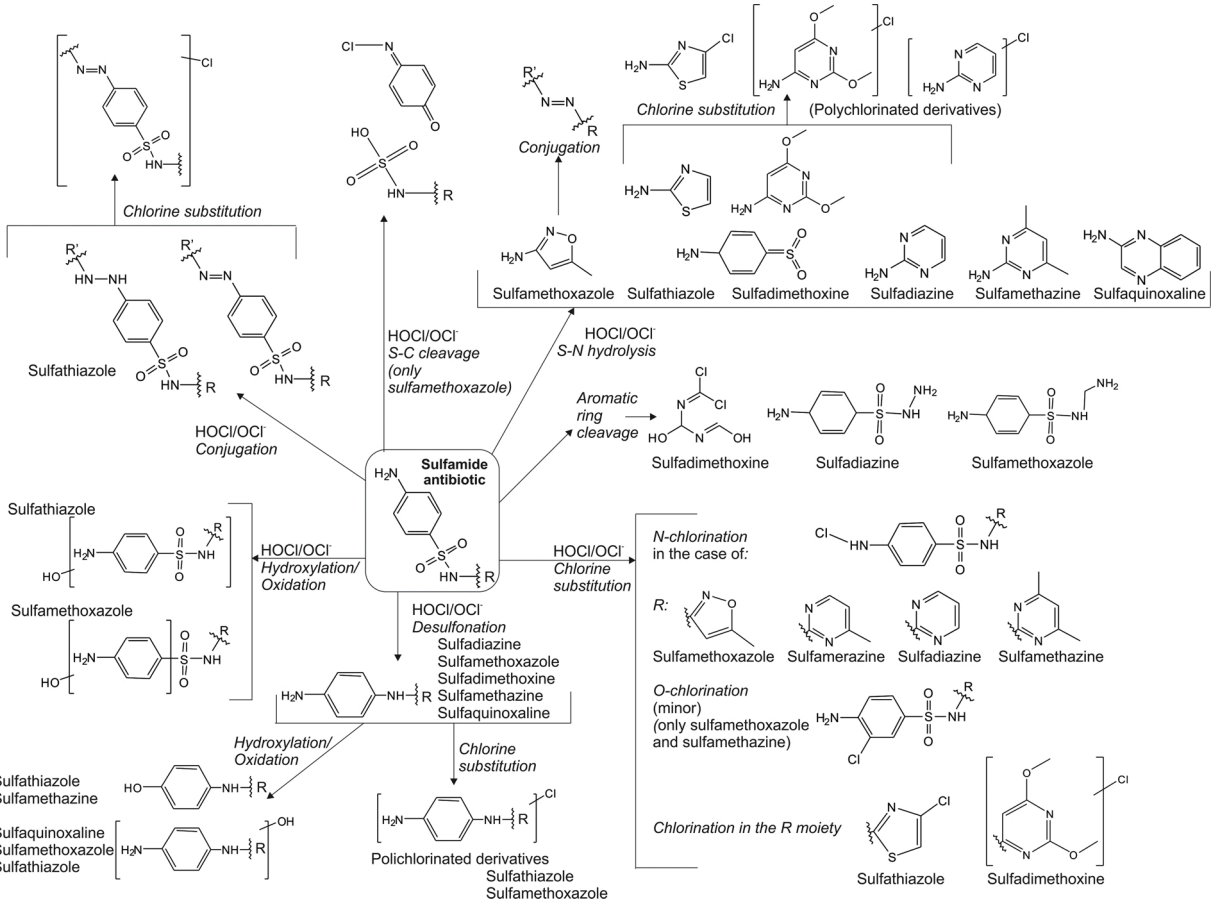


Fig. 2. Transformation pathways of sulfonamide antibiotics in the presence of chlorine (adapted from [50,57,68,77,98,144]).

sulfamethoxazole [57], sulfamethazine [50], sulfamerazine, and sulfadiazine [68], while chlorine substitution takes place in the thiazole moiety in the case of sulfathiazole, or in the dimethoxypyrimidine moiety for sulfadimethoxine [57]. The remaining reaction pathways are compound-dependent. For instance, S-C cleavage DBPs were only produced by sulfamethoxazole. The presence of a strongly electrophilic carbon center α- to the sulfonyl or sulfonamide group is essential for this reaction to occur [77].

The transformation of tetracycline antibiotics in the presence of chlorine mainly leads to chlorine and hydroxyl substituted DBPs without any substantial ring cleavage [106]. Particularly, in the case of doxycycline, DBPs formed after a double demethylation, sequential chlorination at the *para*- and *ortho*-positions of the hydroxyl group of the phenol aromatic ring, and N-chlorination of the amide [107].

As regards fluoroquinolone antibiotics, chlorine attacks firstly the piperazine ring of the molecule, while the quinolone moiety is unreactive [108,109]. This is why flumequine, a fluoroquinolone that lacks the piperazine ring, does not apparently react with chlorine. Flumequine indeed transforms only after the attack of reactive species derived from the chlorination of other fluoroquinolones (i.e., levofloxacin or enrofloxacin) to its quinolone moiety [108,109]. Ciprofloxacin, with a secondary amine in the piperazine ring, rapidly transforms into an N-chloro derivative that further undergoes piperazine ring cleavage. In contrast, enrofloxacin, with a tertiary amine in the piperazine ring, slowly reacts with chlorine to form a highly reactive chlorammonium intermediate that catalyzes its halogenation or that of other species in solution (e.g., halodecarboxylation in the case of flumequine) [109]. Similar findings regarding chlorine reactivity were observed also in the case of norfloxacin (a fluoroquinolone with a secondary amine) and ofloxacin and levofloxacin (fluoroquinolones with a tertiary amine) [108,110]. After piperazine ring cleavage during ciprofloxacin chlorination, the molecule further oxidizes to form a 7-amino-8-chloro-derivative of the fluoroquinolone moiety, that is likely to retain the antibiotic activity of ciprofloxacin. This conclusion was reach after finding it in a bioactive fraction of a bioactive sample using an effect-directed analysis approach [104].

Chlorine also reacts rapidly with the secondary amine of chloramphenicol forming an N-chloro derivative. DBPs may also generate from electrophilic substitution reactions on its aromatic ring. These substitution reactions also occur in a DBP formed after amide cleavage. Dichloroacetonitrile, dichloroacetamide, and chloroform are the ultimate products of C-C cleavage, oxidation, and substitution reactions [74].

In the case of trimethoprim, chlorine reactivity is governed by its 2,4-diamino-5-methylpyrimidinyl moiety. Although no substantial degradation into small DBPs was observed, chlorine- and hydroxyl-substituted isomeric products were identified [111].

The cephalosporin cefazolin reacts with chlorine via oxidation of its thioether-sulfur to form sulfoxide and di-sulfoxide derivatives. Then, the electrophilic substitution of the α-hydrogen to the amide bond with chlorine may also occur in sulfoxide derivatives [112].

4.3. Other pharmaceuticals

Active aromatic systems are usually the target of chlorine attack. For instance, chlorination (or bromination, if bromine is present in the solution) of salbutamol [60] and acetaminophen [113] occurs at the *ortho*-position of the phenolic group. In the case of propranolol [60], chlorination takes place in the naphthalene ring, while in the case of atenolol, it happens at the benzene ring after hydrolysis of its amide group to yield carboxylic acid [60]. Acetaminophen may also transform into the toxic 1,4-benzoquinone and *N*-acetyl-*p*-benzoquinone imine [113]. Additional transformation pathways of the aforementioned β-blockers/β-agonists include hydroxylation and dealkylations.

The transformation of the non-steroidal anti-inflammatory drug diclofenac in the presence of chlorine proceeds through hydroxylation of the molecule, and subsequent oxidation of the phenolic hydroxyl group, decarboxylation of the parent compound, and chlorine electrophilic substitution in the non-chlorinated aromatic ring [66]. In the presence of bromide and iodide, similar transformation pathways result in the generation of decarboxylated, brominated or iodinated DBPs. Hydroxylated derivatives were found only when bromide was present in solution. In naproxen-containing solutions, chlorine substitution mainly occurs at the C7 position of the naphthalene ring of naproxen to form ((2S)-2-(5-chloro-6-methoxy-2-naphthyl)-propionic acid). Thirteen additional DBPs are further formed after demethylation, decarboxylation, hydroxylation, and dehydrogenation reactions [114].

The pyrazolone-type analgesics/antipyretics phenazone and propyphenazone convert into their halogenated derivatives after attack in their pyrazolone ring. These DBPs were further transformed via hydroxylation and dealkylation [32,75]. The reaction of chlorine with another pyrazolone drug, aminopyrine, occurs through pyrazolone ring cleavage, hydroxylation, dehydrogenation, and halogenation [87].

Chlorine reacts with fenamic acids (i.e., mefenamic acid, tolfenamic acid, and clofenamic acid) through single or double chlorine electrophilic substitution in their aromatic ring (at the *ortho*- and *para*-positions of the amino moiety). Moreover, N-chloro derivatives, hydroxyl-derivatives, and oxidized-derivatives result from the attack on the nitrogen, oxidation reactions, and nucleophilic substitution at the aromatic ring, respectively [30].

The transformation of carbamazepine during chlorination has been extensively investigated [49,59,82,115,116] (Fig. 3). N-chlorination and epoxidation of carbamazepine are two initial, competitive processes that result in two key intermediates: N-chloramide-carbamazepine (favored at high pH values) and 10,11-epoxide-carbamazepine [116]. Both species are highly reactive, and HOCl/OCl- mediated transformations result in different chlorinated and hydroxylated derivatives. Eventually, iminostilbene and acridine are formed, which may further oxidize to oxoiminostilbene and 9-formylacridine, and 9(10)-H-acridone, respectively. In the case of oxcarbazepine, a keto analog of carbamazepine, chlorine sequentially replaces the hydrogens at the α-carbon to the carbonyl group [91]. The hydrolysis of mono- and dichlorinated derivatives of oxcarbazepine results in the formation of 1-(2-benzaldehyde)-(1H, 3 H)-quinazoline-2,4-dione, that accumulates in the solution at the end of the reaction time. The amide moiety is not reactive to chlorine [91].

While some iodinated X-ray contrast media like iopromide, iohexol, iomeprol, and diatrizoate are recalcitrant to chlorine oxidation, iopamidol is readily transformed in the presence of chlorine [61]. Two main DBPs (DBP705 and DBP777) are initially formed and serve as precursors of the other DBPs observed. DBP777 forms by inversion of a side chain while DBP705 forms by cleavage of that side-chain; however, the mechanism is not fully understood yet. Iopamidol is a source of toxic iodo-DBPs (iodoacids and iodo-trihalomethanes) during chlorination. In the presence of chlorine, iodine is released from the molecule and thus, is available in the solution to be incorporated into the natural organic matter [117].

Glucocorticoid DBPs that generate during chlorination are bioactive substances [118]. Chlorine reacts with prednisone to form 9-chloro--prednisone (major DBP), Δ1-adrenosterone, a hydroxyprednisone derivative, and a chlorinated Δ1-adrenosterone derivative. Prednisone itself is a chlorination DBP of prednisolone, cortisone, and cortisol. In the case of prednisolone, 11β-hydroxyboldione forms after cleavage of the side chain at C17. Moreover, chlorinated prednisone, chlorinated prednisolone, Δ1-adrenosterone, and its chlorinated derivative are also generated at high chlorine:prednisolone ratios. Chlorination of cortisone also results in two chlorinated prednisone derivatives, a hydroxylated cortisone derivative, adrenosterone, and Δ1-adrenosterone. Cortisone itself is also a DBP of cortisol chlorination, in addition to two chlorinated prednisolone derivatives. The reaction of chlorine with dexamethasone produces 11-keto-dexamethasone and 17-oxo-dexamethasone at high chlorine:dexamethasone ratios [118].

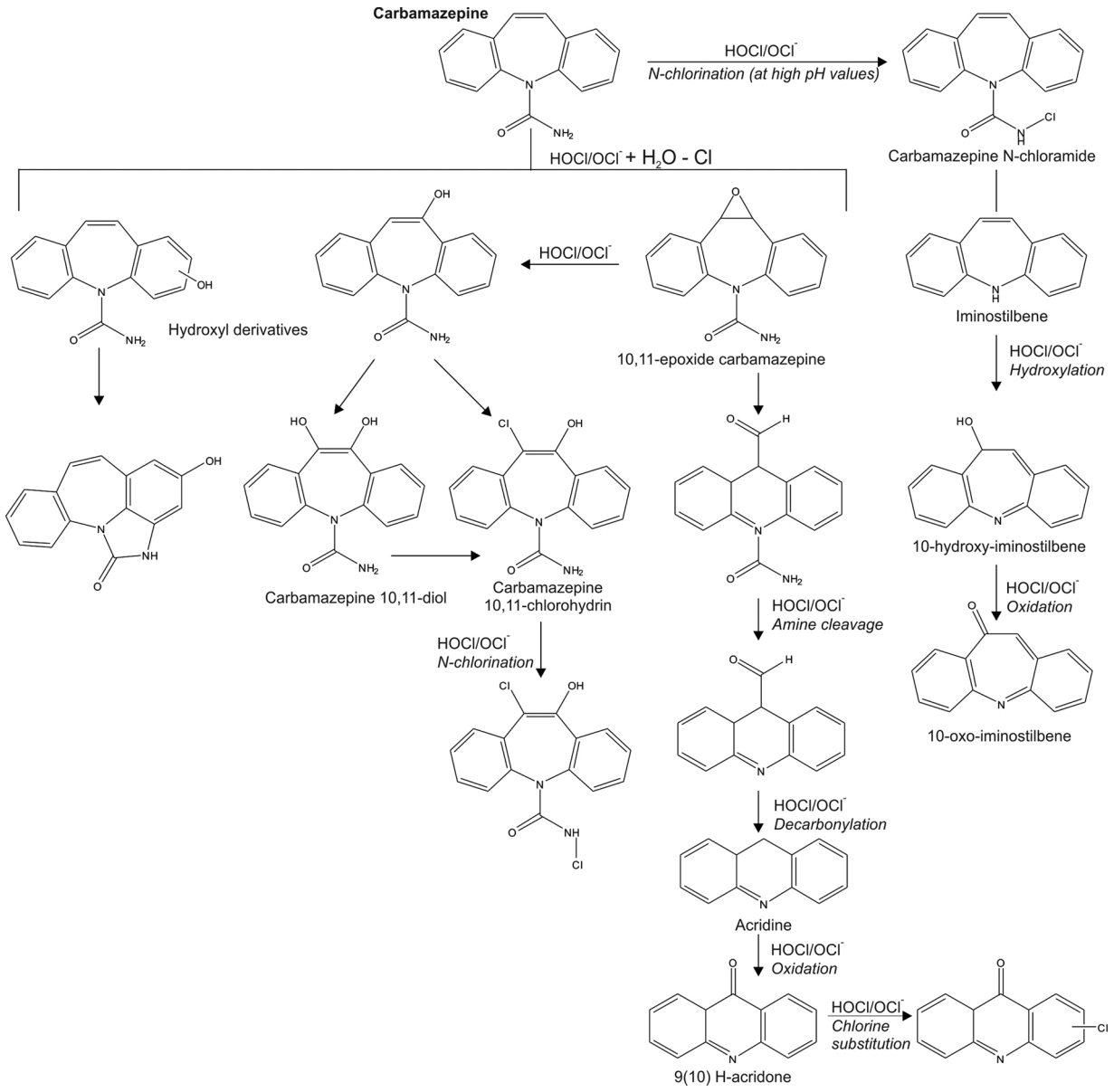


Fig. 3. Carbamazepine transformation pathways in the presence of chlorine (adapted from [49,59,116]).

Chlorine attacks mainly the phenol ring of 17α-ethinylestradiol via electrophilic substitution to form monohalogenated derivatives and eventually dihalogenated derivatives. These secondary DBPs are further transformed into products with a destroyed phenolic moiety [119].

The reactivity of vinca alkaloids (anticancer drugs) with chlorine has been also investigated. Vincristine is more stable in the presence of chlorine than vinblastine, vinorelbine and its metabolite 4-O-deacetyl vinorelbine that are quickly degraded. While vincristine DBPs result only from oxidation reactions (deacetylation in the vindoline moiety, epoxide formation in the catharantine moiety, O-demethylation, or dehydration reactions), the other three drugs also present chlorinated derivatives formed through electrophilic substitution of the parent drugs or their oxidized DBPs [69].

Tamoxifen is recalcitrant to chlorination and thus no DBPs form during the disinfection process. However, its main metabolites 4-hydroxy-tamoxifen and 4-hydroxy-N-desmethyl-tamoxifen are very reactive to chlorine. This is attributed to the presence of a hydroxyl group at the phenyl ring that acts as a strongly activating group towards electrophilic aromatic substitution. Chlorination of tamoxifen metabolites results in the formation of several mono-chlorinated, di-chlorinated, and hydroxylated derivatives. The reactivity of their amine moiety is lower than that of their phenolic ring and therefore, no N-chlorinated compounds are generated [28].

The antidiabetic metformin transforms into a dehydro-1,2,4-triazol-amine derivative and a chloro-organic nitrile, being the latter much more stable than the former [120].

Chlorination of the antiacid cimetidine results in cimetidine sulfoxide, 4-hydroxymethyl-5-methyl-1H-imidazole, 4-chloro-5-methyl-1H-imidazole, and a product proposed to be either a β- or δ-sultam. While the formation of cimetidine sulfoxide is a consequence of common chlorination transformation pathways, the last three DBPs are generated via less common C-C bond cleavage and intramolecular nucleophilic substitution reactions [63].

4.4. Personal care products

Electrophilic aromatic substitution is the main transformation pathway identified for benzophenone-type UV-filters, most likely at the *ortho*- and *para*-carbons to the hydroxyl group, and results in mono-, di- and tri-halogenated derivatives. Those benzophenone-type UV-filters

without an electron-donating phenolic hydroxyl group (e.g., octocrylene, benzhydrol, benzophenone, benzoylbiphenyl, and 4-methoxybenzophenone) are recalcitrant to chlorine [22,54]. In contrast, those with two phenolic hydroxyl groups (e.g., 2,4-dihydroxybenzophenone (BP1), 2,2′-dihydroxy-4,4′-dimethoxybenzophenone (BP6), 2,2′-dihydroxy-4-methoxybenzophenone (BP8 or dioxybenzone)) are completely transformed in seconds. A general transformation pattern for benzophenone-type UV filters during chlorination is observed (Fig. 4). After initial electrophilic substitution, Baeyer-Villiger oxidation converts the biphenyl ketones into the corresponding phenyl esters that may undergo nucleophilic hydrolysis and result in the corresponding phenolic and benzoic acid analogs. The formation of one chlorobenzoquinone and four phenyl benzoquinones is also observed after cleavage and subsequent transformation of the phenyl esters [121]. Additional DBPs may also form after decarboxylation and subsequent chlorination or cyclization of the phenyl esters. In the latter case, polycyclic aromatic hydrocarbons are formed [121]. Furthermore, ring cleavage may eventually also occur [22,121]. In the specific case of 2-hydroxy-4-methoxy-5-sulfonic acid-benzophenone (BP4), the formation of chlorine-containing acetic acids as final DBPs is also reported [122]. BP4 and presumably other benzophenone-type UV filters present photochemical activity, and thus, they may generate indirect photodegradation reactions in the solution [38]. Highly toxic BP4 iodinated derivatives are formed when iodide is present in water after electrophilic substitution with HOI and subsequent oxidation and hydrolysis [123]. Bromoform is pointed as a stable DBP formed during chlorination of UV filters, in particular oxybenzone and dioxybenzone, in seawater [54].

Chlorine reacts with the antimicrobial preservatives parabens via electrophilic aromatic substitution at the *ortho*-position, since the *para*-position is already occupied by the ester group [29,124]. As a result, monohalogenated and dihalogenated derivatives are formed. Halogen substitution in the *meta*- position of the phenolic moiety does not occur, since tri-halogenated derivatives were not identified in any study. Dihalogenated species are then expected to further react with chlorine via electron transfer mechanisms to form quinones or products with the phenolic ring opened [29].

In the case of the antimicrobial triclosan, chlorination of the phenolic ring and cleavage of the ether bond are identified as the main transformation pathways [51,125]. Triclosan DBPs include (chlorophenoxy)-phenols, 2,4-dichlorophenol, 2,4,6-trichlorophenol, and chloroform.

4.5. Industrial contaminants

The phenolic rings of BPA are the target of HOCl, HOBr (if bromide is present in the solution) [76], or HOI (if iodide is present in the solution) [58] that via electrophilic attack generate polyhalogenated compounds (Fig. 5). The iodine incorporation rate seems to be lower than that of bromine or chlorine. While only mono- and dihalogenated species with only one I atom form, up to four Br or Cl atoms could be incorporated in the BPA molecule. After a first halogenation that may occur at the *ortho*-position to the phenolic group, monohalogenated derivatives convert rapidly into dihalogenated compounds. This second halogenation occurs preferentially on the halogenated phenolic ring. These dihalogenated congeners may be halogenated for a third and even fourth time at the other phenolic ring. Tetrahalogenated BPA derivatives may cleave between the isopropyl moiety and the phenol to give trihalogenated phenols and 2-(3,5-dihalogen-4-hydroxyphenyl)-propan-2-ol. The cleavage products may again recombine resulting in tetrahalogenated phenoxy-phenol structures (Fig. 5). The methylation of 2-(3,5-dihalogen-4-hydroxyphenyl)-propan-2-ol species was also observed,

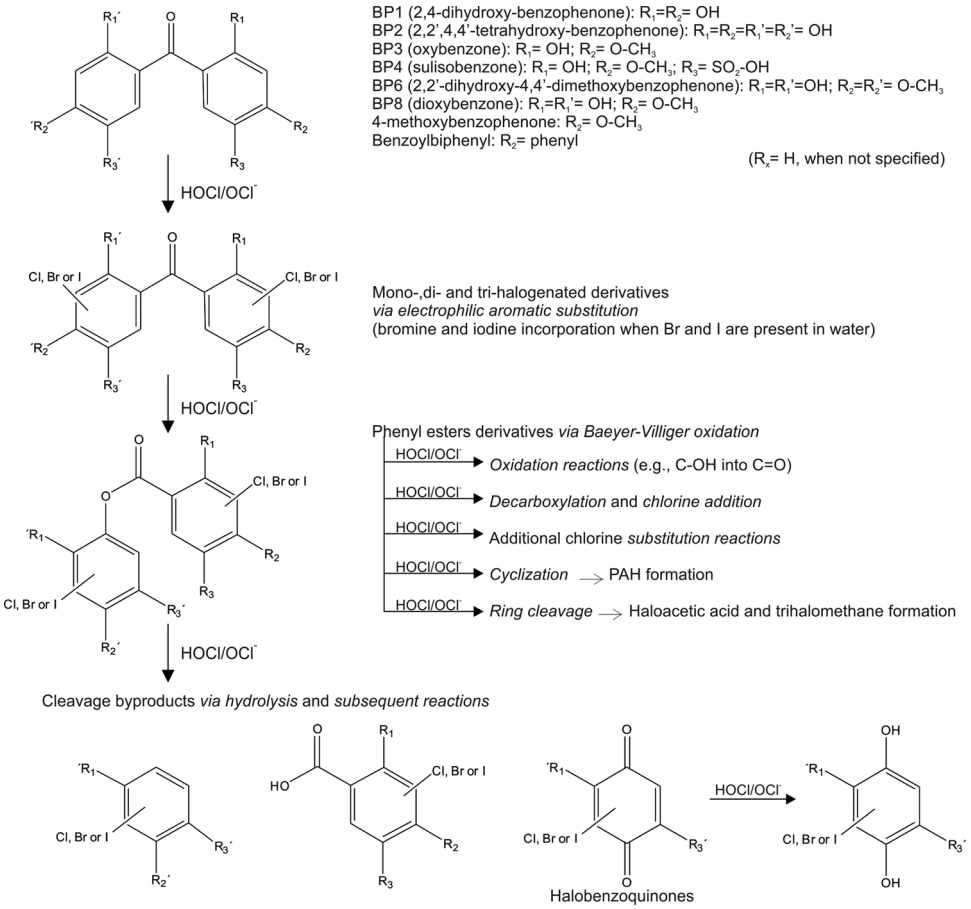


Fig. 4. General scheme summarizing the main transformation pathways of benzophenone UV-filters during chlorination (adapted from [27,54,67,121,123,145]).

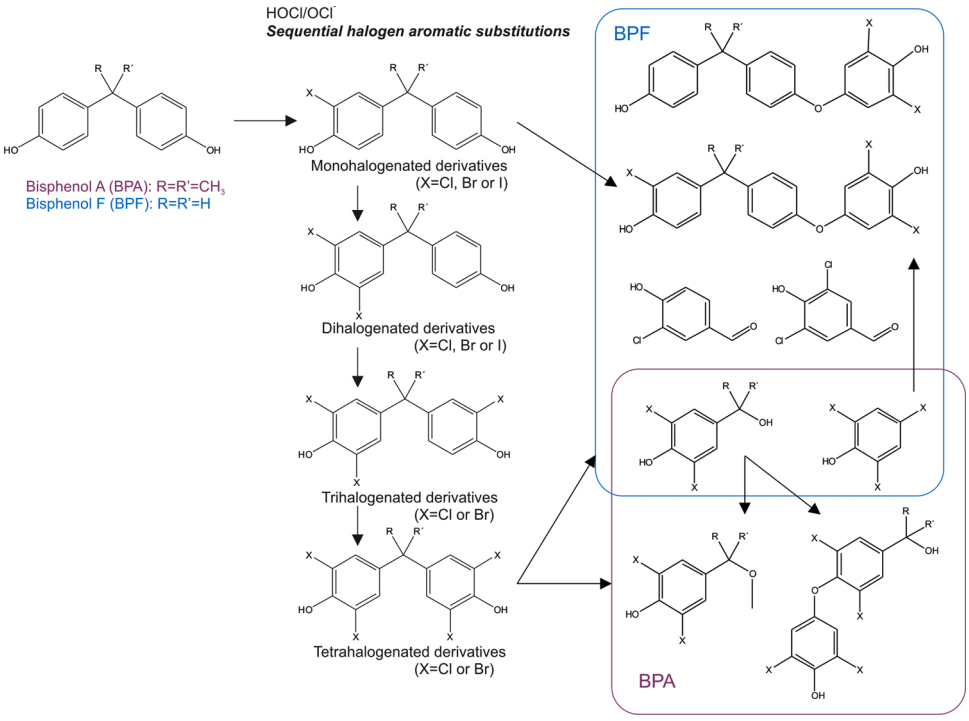


Fig. 5. Bisphenol A (BA) and bisphenol F (BPF) transformation pathways in the presence of chlorine (adapted from [58,76,92]).

although no plausible mechanism has been proposed for this reaction yet. All BPA DBPs completely decompose after 2 h of chlorination into small DBPs like trihalomethanes or trihaloacetic acids.

The substituents in the phenol ring affect chlorination kinetics [58]. For instance, while BPA contains two activated phenol rings (by *para*--alkyl substitution), 2,4-dichlorophenol contains two deactivating chloro-substituents that stabilize the phenolate form and slowdown its reaction toward electrophiles.

BPS, one of the main alternatives to BPA use, is transformed in the presence of chlorine by two main pathways [48]. Like BPA, after sequential chlorine electrophilic substitution, different mono- and polychlorinated derivatives of BPS form. In parallel, electron transfer can also oxidize the phenol moiety. This may result in the cleavage of the BPS molecule and formation of 4-hydroxybenzenesulfonic acid (BSA) and 4-chlorophenol, or coupling reactions that form various polymeric products or dimers. BSA may be further attacked by chlorine electrophilic substitution. The presence of humic acids in the solution inhibits the degradation of BPS via electron transfer.

As reported for BPA and BPS, electrophilic aromatic substitution is the main transformation pathway of bisphenol F (BPF) in the presence of chlorine, which results in the formation of polychlorinated derivatives of BPF [92]. The formation of highly substituted species is enhanced at high chlorine:BPF ratios. The concentration of these species in the solution decreases as the chlorination reaction proceeds. The oxidation of the methylene connecting the two phenolic rings forms polyphenolic compounds.

Chlorine can also transform phenolic compounds via electron transfer, as reported for TBBPA [52]. The transformation of TBBPA involves in the first place the formation of TBBPA phenoxy radical. Then, this radical and especially, secondary intermediates like the 2,6-dibromo-4-isopropylphenol carbocation and 2,6-dibromo-phenol carbocation, formed after β-scission, undergo substitution (bromination and exchange of bromine for chlorine), dimerization, and oxidation reactions. Brominated halobenzoquinones (Br-HBQs) are pointed out as final DBPs in the TBBPA oxidative transformation pathway. Halobenzoquinones are unstable in chlorinated water and transform into their corresponding and more stable halo-hydroxyl-benzoquinones (OH-HBQs) [126].

Benzothiazole (BTH) and 1-H-benzotriazole are quite recalcitrant to chlorination. In contrast, 2-amino-benzothiazole (2-amino-BTH) reacts completely within less than 5 min [23]. Chlorination of 2-amino-BTH solutions results in four DBPs, formed after chlorine and hydroxyl addition in its benzene moiety: amino-6-chloro-BTH, 2-amino-5, 6-dichloro-BTH, 6-chloro-5-hydroxy-BTH, and 2-amino-5,6-di-hydroxy-BTH. The reaction of chlorine with 1-hydroxy-benzotriazole generates the recalcitrant 1-H-benzotriazole. Chlorination and oxidation reactions at the benzene ring of 5,6-dimethyl-1-H-benzotriazole (also known as xylyltriazole) result in the formation of 4-chloro-xylyltriazole, 4-hydroxy-xylyltriazole, 4,7-dihydroxy-xylyltriazole, and 5-methyl-benzotriazole-6-carbaldehyde.

Four main types of reactions during the chlorination of the two rubber and polymer related chemicals 1,3-di-o-tolylguanidine (DTG) and 1,3-diphenylguanidine (DPG) occur: molecule cleavage via ipso-chlorination to produce monophenylguanidine derivatives, halogenation of the aromatic ring, hydroxylation, and intramolecular cyclization [56].

4.6. *Artificial sweeteners*

In the presence of chlorine, the thiazine ring of acesulfame opens, which produces N-chlorinated sulfamic acids as major DBPs. Besides, known small molecular weight DBPs such as haloacetic acids and haloacetamides are formed [31].

Other artificial sweeteners viz., saccharin, cyclamate and sucralose are recalcitrant to chlorination [127,128].

4.7. *Plant protection products*

The neonicotinoid insecticides imidacloprid and thiamethoxam are recalcitrant to chlorination, at least at time scales relevant to water treatment and/or distribution [129]. In contrast, clothianidin can be extensively transformed in less than 2 h. Chlorine addition, most likely at the secondary amine of the imidazole moiety of imidacloprid, results in desnitro-imidacloprid and imidacloprid-urea, two byproducts formed

by microbial and abiotic processes [80]. In the case of desnitro-imidacloprid, sequential chlorination may occur at the same location after the formation of the corresponding imino tautomer. The chlorinated form of imidacloprid-urea is also one major product found during imidacloprid chlorination, in addition to chlorinated imidacloprid. The alkaline hydrolysis of thiamethoxam (at pH 10) results in two byproducts: THX-H 248 (after hydrolysis of the nitro-imine group into a ketone) and THX-H 237 (after ring-opening with hydroxide attack at the imine carbon). The latter reacts with chlorine via chlorine addition at the secondary amide group without the electron-withdrawing nitro substituent. THX-H 237 also forms during clothianidin chlorination, in addition to two other major products generated after the loss of the nitro group and formation of the ketone, and chlorination of the remaining secondary amide [80].

Chlorination of the β-triketone herbicides tembotrione and sulcotrione initially occurs at the α-carbon of the carbonyl functional groups. Then, the cyclohexanedione ring cleavage occurs. Additional and sequential chlorine attacks at the same carbon produce tri-chlorinated derivatives and the release of glutaric acid. The hydrolysis of these DBPs results in benzoic acid derivatives and chloroform. Oxidative decarboxylation of benzoic acid derivatives results in the formation of the corresponding phenols. An additional DBP forms by intramolecular cyclization after dichlorination at the α-carbon [97].

The fungicides azoxystrobin, difenoconazole, iprovalicarb, metalaxyl-M, procymidone and triadimenol do not transform after 1 h contact with chlorine. In contrast, fenhexamid, cyprodinil, and pyrimethanil exhibit high transformation rates [70]. The most reactive fungicide, fenhexamid, transforms through electrophilic halogenation at the chloro-phenol moiety, and release this moiety from the molecule. Cyprodinil and pyrimethanil, due to their similarity, follow equal reaction pathways. Their DBPs form after electrophilic halogenation in either the benzene or the pyrimidine ring, hydroxylation followed by electrophilic halogenation at the benzene ring, and intramolecular cyclization due to the loss of hydrogen.

Chlorine attacks phenylurea hebicides (e.g., N-phenylurea, dichlorophenyl-urea, monuron, metoxuron, etc.) at both N atoms of the phenyl urea moiety, resulting in N-chlorinated products, and via electrophilic chlorination at *ortho*- and *para*-positions of the phenylurea aromatic group [130].

The *s*-triazine herbicides prometryn, terbutryn, and ametryn are also highly reactive in the presence of chlorine (completely transformed within 1 h of contact time) and form very stable DBPs. In all cases, sequential oxidation of the molecules to form the sulfoxide and sulfone derivatives occurs. Additional DBPs are formed after chlorination of the sulfoxide form and further oxidation of the sulfone into an alcohol, after loos of the methyl sulfone moiety [131].

5. A compound database of CEC DBPs in chlorinated water for suspect screening

A pre-defined list of CEC DBPs that may form during water chlorination was built based on the studies published in the peer-reviewed literature. It contains 1483 entries in total, which include 137 CECs (Table S1), the DBPs formed from these CECs during chlorination reactions, and additional small-molecular weight DBPs detected in chlorinated waters. DBPs formed after combined UV/HOCl or ClO_2 disinfection were also included for some CECs.

Most of the CEC DBPs compiled in the database are amenable to LC–MS analysis (91 % of the entries). The remaining CEC DBPs are either predicted or amenable to GC–MS analysis (small and semi-polar molecules capable of volatilizing in the injection port). Thus, the list is meant to be preferably used with LC-HRMS acquired data using electrospray ionization. Up to 59 % of the LC–MS-detected features are ionizable under positive electrospray mode, while 40 % are ionizable under negative electrospray mode, and roughly 1% under both ionization modes. The preferable analysis mode is specified for each entry in the database.

In addition to the exact *m/z* of the ions expected to be produced during MS analysis, and their elemental composition, unequivocal identifiers were provided for each entry such as the simplified molecular input line entry specification (SMILES), or the IUPAC standard international chemical identifier (InChI) and InChIKey (a hashed version of the standard InChI). However, for some of the entries, these identifiers were tentatively assigned, because the structure of the CEC DBP is not yet confirmed and several positional isomers are possible. This is also specified for each case in the database.

When available, fragments observed during MS^2 fragmentation of the parent ions were also registered to provide additional identification points. The measured mass of the *m/z* fragment ions was provided instead of their theoretical mass.

This database is available for use at the NORMAN Suspect List Exchange as CHLORINE_TPS (https://www.norman-network.com/?q=suspect-list-exchange). An automated search of the exact masses contained therein within the full-scan HRMS data acquired would lead to identify potential DBP candidates in the water samples. This could be done with self-developed or commercial software or directly through the NORMAN Digital Sample Freezing Platform [132]. Besides the mass accuracy of the molecular ion, additional proofs of identity could be obtained by manually comparing the fragments observed in the MS^2 data with those listed in the database for each compound and generating a retention time index for which the candidate SMILES, also provided in the database, is required [133].

6. Presence of CEC DBPs in environmental waters

Many studies have proven the formation of the CEC-DBPs detected in laboratory-scale experiments in environmental waters by fortifying real samples with the target CEC and subsequent chlorination. Only very few studies have explored the occurrence of these chemicals in real waters. This has been done by developing specific methods for target CEC DBPs [53,55,91,126,134] or after application of suspect screening approaches [79,90,121,134,135]. The CEC DBPs detected in unmodified water samples are reviewed below.

A chlorinated derivative of the antidpressant duloxetine formed after chlorination of the naphthalene ring was detected in the effluent of a WWTP of Lisbon with a treatment train based on clarification, biofiltration and UV/chlorine disinfection. The *in silico* predicted ecotoxicity of this TP to different organisms (fish LC_{50} 96 h, D magna LC_{50} 48 h, green algae EC_{50} 96 h, and *T. pyriformis* IGC_{50}) was at least two-fold higher than that of the parent compound [71].

3-chloro-BP4 was the only BP4 DBP found in the water of two swimming pools in Beijing. The estimated concentration of 3-chloro-BP4 was similar or three times higher than that of the parent compound [136]. BP1 and two chlorinated byproducts (monohalogenated and dihalogenated derivatives) were found also in swimming pool water [121]. These findings are of concern as these DBPs may further react with chlorine and convert into halobenzoquinones.

Halo-hydroxyl-benzoquinones are stable halobenzoquinone DBPs commonly found in drinking water distribution networks. They are twofold less toxic than the parent compounds, but still more toxic than regulated DBPs such as trihalomethanes and haloacetic acids [126].

Four diazepam DBPs, formed after cleavage of the diazepinone ring, were detected in drinking water samples from Beijing. Three of them presented a relatively high detection frequency (30–66 %) and maximum concentrations of 4 ng/L, while the remaining DBP was detected only in 14 % of the 80 investigated samples and quantified at a maximum concentration of 0.37 ng/L [53].

Effluent samples from a WWTP that uses chlorine as tertiary treatment showed the presence of citalopram and two DBPs, desmethylcitalopram and an N-oxide derivative, which are also human metabolites. Citalopram DBPs were estimated to occur at concentrations 10 times lower than the parent compound, and were not found in influent water.

However, their formation during the biological treatment cannot be discarded [102].

Li et al. [91] identified the major byproducts detected in laboratory-scale experiments of oxcarbazepine chlorination, except acridine, in tap water samples. Dihydroxy-carbamazepine was detected in all samples at concentration levels below 15 ng/L. 1-(2-benzaldehyde)-(1H, 3 H)-quinazoline-2,4-dione, an oxidized form of it, and a DBP resulting from the loss of the $CONH_2$ lateral chain, ring oxidation and intramolecular cyclisation were found in three out of the five investigated tap water samples at an average estimated concentration of 10 ng/L [91].

After suspect screening, neviparine DBPs were detected in a surface water system impacted by WWTPs that use chlorination. Although their national prevalence was exceptionally low since nevaparine was found in trace amounts in surface waters collected from all the major rivers and lakes in South Africa [135].

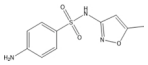
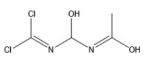
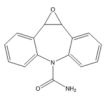
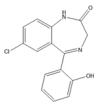
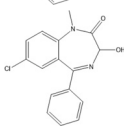
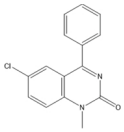
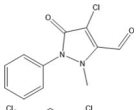
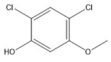
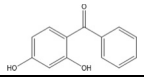
Monochlorinated and dichlorinated derivatives of the cytotoxic drug methotrexate were detected in one of the three hospital effluent samples investigated by Yin et al. [137].

A dichlorinated derivative of omeprazole, together with various hydrolysis byproducts of this drug, was tentatively detected in influent and effluent WWTP samples and surface water samples; despite the parent compound was not present in any of them [137]. Due to its low concentrations, its detection required the monitoring of selected reaction transitions, more sensitive than full scan HRMS.

(3-chlorobenzo)-1,3-dioxole and 3-chlorocatecol were observed to form in water containing MDA and MDMA, respectively, during the potabilization train. While the MDA DBP and its parent compound and MDMA were not found in the effluent samples, which suggest the removal of these compounds during treatment, the MDMA DBP was observed after final chlorination. Estimated concentration of 3-chlorocatecol in the DWTP effluent ranged from 0.5 to 5.8 ng/L [55].

Effluents from ten wastewater treatment facilities in southern California (US) disinfected with chloramine and/or chlorine prior their discharge to the ocean presented concentrations of dibrominated salicylic acid up to 208 ng/L and dichlorinated salicylic acid up to 192 ng/L [138]. Monohalogenated and the chloro-bromo derivatives were also frequently present in the effluent waters investigated, but at lower

Table 1
CECs and CEC DBPs found in reclaimed water with a suspect approach using the CEC DBPs database.

CODE	t_R*	Exact monoisotopic mass	Formula	Tentative compound		Parent compound	Confidence level**	Proofs of identity
1	1.55	161.9866 [M-H]	$C_4H_5NO_4S$	6-methyl-1,2,3-oxathiazin-4(3 H)-one 2,2-dioxide		Acesulfame	2	Mass accuracy, plausible t_R, 3 fragments
2	4.10	254.0594 [M+H]	$C_{10}H_{11}N_3O_3S$	4-amino-N-(5-methylisoxazol-3-yl) benzenesulfonamide (Sulfamethoxazole)		–	2	Mass accuracy, plausible t_R, 3 fragments
3	3.97	184.9879 [M+H]	$C_4H_6Cl_2N_2O_2$	(E)-N-(((dichloromethylene)amino) (hydroxy)methyl)acetimidic acid		Sulfamethoxin	2	Mass accuracy, plausible t_R, 1 fragments
4	4.50	280.1077 [M+H]	$C_{15}H_{14}N_2O_3$	–		Carbamazepine	3	Mass accuracy, plausible t_R, 1 fragments
5	5.37	253.0972 [M+H]	$C_{15}H_{12}N_2O_2$	1a,10b-dihydro-6H-dibenzo[b,f]oxireno [2,3-d]azepine-6-carboxamide (Carbamazepine epoxide)		Carbamazepine	2	Mass accuracy, plausible t_R, 5 fragments
6	5.37	274.0440 [M+H]	$C_{14}H_{11}NO$	acridine-10(9 H)-carbaldehyde		Carbamazepine	2	Mass accuracy, plausible t_R, 2 fragments
7	7.16	287.0582 [M+H]	$C_{15}H_{11}ClN_2O_2$	7-chloro-5-(2-hydroxyphenyl)-1,3-dihydro-2H-benzo[e][1,4]diazepin-2-one		Diazepam	2	Mass accuracy, plausible t_R, 2 fragments
8	7.34	301.0739 [M+H]	$C_{16}H_{13}ClN_2O_2$	7-chloro-3-hydroxy-1-methyl-5-phenyl-1,3-dihydro-2H-benzo[e][1,4]diazepin-2-one		Diazepam	2	Mass accuracy, plausible t_R, 2 fragments
9	7.44	271.0633 [M+H]	$C_{15}H_{11}N_2OCl$	6-chloro-1-methyl-4-phenylquinazolin-2 (1 H)-one		Diazepam	2	Mass accuracy, plausible t_R, 2 fragments
10	5.31	237.0426 [M+H]	$C_{11}H_9ClN_2O_2$	4-chloro-2-methyl-5-oxo-1-phenyl-2,5-dihydro-1H-pyrazole-3-carbaldehyde		Phenazone	2	Mass accuracy, plausible t_R, 2 fragments
11	5.56	190.9672 [M-H]	$C_7H_6Cl_2O_2$	2,4-dichloro-5-methoxyphenol		BP6	2	Mass accuracy, plausible t_R, 1 fragments
12	4.53	213.0557 [M-H]	$C_{13}H_{10}O_3$	(2,4-dihydroxyphenyl)(phenyl) methanone (BP1)		BP3	2	Mass accuracy, plausible t_R, 1 fragments

* t_R: retention time.
** According to Schymanski's confidence scale [143].

concentrations. The total concentration of the halogenated derivatives of salicylic acid was usually equal or higher than the concentration measured for salicylic acid itself. Additional CEC DBPs measured in the effluent waters sampled are chlorogemfibrozil (up to 56 ng/L), bromogemfibrozil (up to 8 ng/L), chloronaproxen (up to 23 ng/L), bromonaproxen (up to 132 ng/L), chlorodiclofenac (up to 29 ng/L), chloro-4-tert-octylphenol (up to 19 ng/L), chloro-4-nonylphenol (up to 115 ng/L), dichloro-4-nonylphenol (up to 19 ng/L), bromo-4-nonylphenol (up to 39 ng/L), and dibromo-4-nonylphenol (up to 372 ng/L) [138]. The highest concentrations were found in the effluents from plants employing only secondary treatment.

A preliminary study that applied the CEC DBP database to reveal these type of compounds in reclaimed water revealed the tentative presence of 12 compounds, listed in Table 1 in the chlorinated effluent of two WWTPs at the Northeastern coast of Spain. Two out of the 12 tentatively identified compounds were not chlorination byproducts but organic micropollutants (e.g., 1: acesulfame and 2: sulfamethoxazole). Compounds 3, 4, and 5 may result from the transformation of carbamazepine, while compounds 6, 7, and 8 may form after diazepam transformation. Note that compound 9 (a diazepam DBP) was also reported to occur in 30 % of the Beiging tap water samples investigated (n = 80) by Zhang et al. [53]. Compound 10 was reported to form after chlorination of phenazone, while compounds 11 and 12 (BP1) correspond to transformation byproducts of BP6 and BP3, respectively. However, since compound 11 is a halogenated derivative of BP6 and its presence is much higher in the secondary treatment effluent than in the tertiary treatment effluent, it is more likely that this compound forms after biotransformation of an unknown chlorinated aromatic compound. All CEC DBPs detected, except compounds 3 and 10, were already present in the effluent of the secondary treatment, most likely due to the biodegradation of the aforementioned CECs. Indeed, many of them have been reported as biodegradation byproducts in the peer-reviewed literature [139–142]. Thus, compounds 3 and 10 were exclusively formed after disinfection. Details on the type of samples analyzed, sample treatment and analysis for suspect analysis, and data treatment are provided in Text S1 as supporting information, as well as further discussion on the data obtained.

7. Conclusions and future perspectives

Laboratory scale experiments have provided evidence on the wide spectrum of chemicals that may form after chlorination of a specific CEC. Indeed, this type of experiments is key to uncover CEC DBPs. However, the relevance of these compounds in water is still unknown, because their occurrence at environmental concentrations in real waters has been scarcely addressed. This is of uttermost importance in water circular economy scenarios that base water recycling schemes in chlorine-base disinfectants, as CEC DBPs will be continuously released into the environment through the different uses of reclaimed water. The released CEC DBPs can be stable, or further transform into small molecular weight DBPs, such as trihalomethanes and haloacetic acids, and eventually be mineralized.

This work provides tools for the rapid screening of CEC DBPs in disinfected water and disentangle the complexity of the DBP mixtures. On the one hand, it delivers a list generated for suspect screening of these compounds in water using mostly LC-HRMS. This list is ready-to-use for any study dealing with the determination of DBPs and can be easily updated with newly discovered CEC DBPs. On the other hand, the main chlorination transformation pathways of CECs reviewed in this manuscript may serve to predict the formation of DBPs of other CECs containing similar reactive moieties and thereby, expanding the list of suspect DBPs for specific CECs. The main limitation of the suspect screening approach is the low levels at which these chemicals may be present in water. Thus, water concentration is required before HRMS analysis. For this, generic-purpose sorbents or a combination of different SPE sorbents is recommended to retain the highest number of chemicals.

Ideally, the identity and presence of these compounds in water needs to be confirmed and quantified, respectively, using pure analytical standards. However, these are not commercially available for most CEC DBPs. To advance non-target and suspect screening of these chemicals in water, it is necessary to develop generic and fast (semi-)quantitative workflows for the correct assessment of the risk that the presence of CEC DBPs may pose to exposed organisms. Despite the low level reported for some CEC DBPs in environmental waters, their presence should not be considered harmless, because CEC DBPs may be more toxic than the corresponding parent compounds or may have a relevant role in the toxicity of the chemical mixture. Novel analytical approaches such as effect-based analysis can be applied to identify the toxic or bioactive CEC DBPs formed during water disinfection.

It is important to highlight that chlorination is only one of the various disinfection methods currently used to disinfect water. Indeed, ozonation and UV disinfection are widely spread for water reclamation, either alone or prior to chlorine application. Thus, the list here provided do not cover the complexity of DBP mixtures in water recycling systems, since CEC DBPS are water treatment-specific.

Declaration of Competing Interest

The authors declare that they have not known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

CP acknowledges support from Fundación General del CSIC through the ComFuturo Programme (2nd edition). This work was supported by the Government of Catalonia (Consolidated Research Groups 2017 SGR 01404), and the "Agencia Estatal de Investigación" from the Spanish Ministry of Science and Innovation (MEDISTRAES III, PID2019-110212RB-C22) and the IDAEA-CSIC, a Centre of Excellence Severo Ochoa (CEX2018-000794-S). CP acknowledges support from the Swedish University of Agricultural Sciences through the August T Larsson Guest Researcher Programme. We would also like to acknowledge the personnel from the WWTPs that kindly assisted in water sample collection.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.teac.2021.e00148.

References

[1] S.D. Richardson, S.Y. Kimura, Water analysis: emerging contaminants and current issues, Anal. Chem. 92 (2020) 473–505, https://doi.org/10.1021/acs.analchem.9b05269.
[2] R.P. Schwarzenbach, B.I. Escher, K. Fenner, T.B. Hofstetter, C.A. Johnson, U. Von Gunten, B. Wehrli, The challenge of micropollutants in aquatic systems, Science (80-.) 313 (2006) 1072–1077, https://doi.org/10.1126/science.1127291.
[3] J.O. Tijani, O.O. Fatoba, O.O. Babajide, L.F. Petrik, Pharmaceuticals, endocrine disruptors, personal care products, nanomaterials and perfluorinated pollutants: a review, Environ. Chem. Lett. 14 (2016) 27–49, https://doi.org/10.1007/s10311-015-0537-z.
[4] M. Sörengård, H. Campos-Pereira, M. Ullberg, F.Y. Lai, O. Golovko, L. Ahrens, Mass loads, source apportionment, and risk estimation of organic micropollutants from hospital and municipal wastewater in recipient catchments, Chemosphere 234 (2019) 931–941, https://doi.org/10.1016/j.chemosphere.2019.06.041.
[5] C. Postigo, M.J. López de Alda, D. Barceló, Drugs of abuse and their metabolites in the Ebro River basin: occurrence in sewage and surface water, sewage treatment plants removal efficiency, and collective drug usage estimation, Environ. Int. 36 (2010), https://doi.org/10.1016/j.envint.2009.10.004.
[6] D.J. Fairbairn, M.E. Karpuzcu, W.A. Arnold, B.L. Barber, E.F. Kaufenberg, W. C. Koskinen, P.J. Novak, P.J. Rice, D.L. Swackhamer, Sources and transport of contaminants of emerging concern: a two-year study of occurrence and spatiotemporal variation in a mixed land use watershed, Sci. Total Environ. 551–552 (2016) 605–613, https://doi.org/10.1016/j.scitotenv.2016.02.056.
[7] E. Koumaki, D. Mamais, C. Noutsopoulos, M.-C. Nika, A.A. Bletsou, N. S. Thomaidis, A. Eftaxias, G. Stratogianni, Degradation of emerging contaminants

from water under natural sunlight: the effect of season, pH, humic acids and nitrate and identification of photodegradation by-products, Chemosphere 138 (2015) 675–681, https://doi.org/10.1016/j.chemosphere.2015.07.033.
[8] X. Sanchez-Vila, E. Vàzquez-Suñé, P. Rodríguez-Escales, A. Jurado, A. Folch, A. Carles-Brangarí, J. Carrera, D. Fernàndez-Garcia, Emerging organic contaminants in aquifers: sources, transport, fate, and attenuation, Handb. Environ. Chem. 46 (2016) 47–75, https://doi.org/10.1007/698_2015_5010.
[9] S. Kleywegt, V. Pileggi, P. Yang, C. Hao, X. Zhao, C. Rocks, S. Thach, P. Cheung, B. Whitehead, Pharmaceuticals, hormones and bisphenol A in untreated source and finished drinking water in Ontario, Canada - Occurrence and treatment efficiency, Sci. Total Environ. 409 (2011) 1481–1488, https://doi.org/10.1016/j.scitotenv.2011.01.010.
[10] A. Pal, Y. He, M. Jekel, M. Reinhard, K.Y.H. Gin, Emerging contaminants of public health significance as water quality indicator compounds in the urban water cycle, Environ. Int. 71 (2014) 46–62, https://doi.org/10.1016/j.envint.2014.05.025.
[11] Q. Gao, K.M. Blum, P. Gago-Ferrero, K. Wiberg, L. Ahrens, P.L. Andersson, Impact of on-site wastewater infiltration systems on organic contaminants in groundwater and recipient waters, Sci. Total Environ. 651 (2019) 1670–1679, https://doi.org/10.1016/j.scitotenv.2018.10.016.
[12] A.-L. Rehrl, O. Golovko, L. Ahrens, S. Köhler, Spatial and seasonal trends of organic micropollutants in Sweden's most important drinking water reservoir, Chemosphere 249 (2020), https://doi.org/10.1016/j.chemosphere.2020.126168.
[13] S.Y. Wee, D.E.M. Haron, A.Z. Aris, F.M. Yusoff, S.M. Praveena, Active pharmaceutical ingredients in Malaysian drinking water: consumption, exposure, and human health risk, Environ. Geochem. Health (2020), https://doi.org/10.1007/s10653-020-00565-8.
[14] R. Tröger, S.J. Köhler, V. Franke, O. Bergstedt, K. Wiberg, A case study of organic micropollutants in a major Swedish water source – removal efficiency in seven drinking water treatment plants and influence of operational age of granulated active carbon filters, Sci. Total Environ. 706 (2020), https://doi.org/10.1016/j.scitotenv.2019.135680.
[15] R. Tröger, H. Ren, D. Yin, C. Postigo, P.D. Nguyen, C. Baduel, O. Golovko, F. Been, H. Joerss, M.R. Boleda, S. Polesello, M. Roncoroni, S. Taniyasu, F. Menger, L. Ahrens, F. Yin Lai, K. Wiberg, What's in the water? – target and suspect screening of contaminants of emerging concern in raw water and drinking water from Europe and Asia, Water Res. 198 (2021), https://doi.org/10.1016/j.watres.2021.117099.
[16] P.Y. Nguyen, G. Carvalho, M.A.M. Reis, A. Oehmen, A review of the biotransformations of priority pharmaceuticals in biological wastewater treatment processes, Water Res. 188 (2021), 116446, https://doi.org/10.1016/j.watres.2020.116446.
[17] S. Yan, W. Song, Photo-transformation of pharmaceutically active compounds in the aqueous environment: a review, Environ. Sci. Process. Impacts 16 (2014) 697–720, https://doi.org/10.1039/C3EM00502J.
[18] W.C. Cory, A.M. Welch, J.N. Ramirez, L.C. Rein, Naproxen and its phototransformation products: persistence and ecotoxicity to toad tadpoles (Anaxyrus terrestris), individually and in mixtures, Environ. Toxicol. Chem. 38 (2019) 2008–2019, https://doi.org/10.1002/etc.4514.
[19] A.R. Ribeiro, B. Sures, T.C. Schmidt, Cephalosporin antibiotics in the aquatic environment: a critical review of occurrence, fate, ecotoxicity and removal technologies, Environ. Pollut. 241 (2018) 1153–1166, https://doi.org/10.1016/j.envpol.2018.06.040.
[20] J. Li, L.-Y. Ma, L.-S. Li, L. Xu, Photodegradation kinetics, transformation, and toxicity prediction of ketoprofen, carprofen, and diclofenac acid in aqueous solutions, Environ. Toxicol. Chem. 36 (2017) 3232–3239, https://doi.org/10.1002/etc.3915.
[21] A. Majumder, B. Gupta, A.K. Gupta, Pharmaceutically active compounds in aqueous environment: a status, toxicity and insights of remediation, Environ. Res. 176 (2019), https://doi.org/10.1016/j.envres.2019.108542.
[22] J. Li, L. yun Ma, L. Xu, Transformation of benzophenone-type UV filters by chlorine: kinetics, products identification and toxicity assessments, J. Hazard. Mater. 311 (2016) 263–272, https://doi.org/10.1016/j.jhazmat.2016.02.059.
[23] M.C. Nika, A.A. Bletsou, E. Koumaki, C. Noutsopoulos, D. Mamais, A.S. Stasinakis, N.S. Thomaidis, Chlorination of benzothiazoles and benzotriazoles and transformation products identification by LC-HR-MS/MS, J. Hazard. Mater. 323 (2017) 400–413, https://doi.org/10.1016/j.jhazmat.2016.03.035.
[24] V.G. Beretsou, A.K. Psoma, P. Gago-Ferrero, R. Aalizadeh, K. Fenner, N. S. Thomaidis, Identification of biotransformation products of citalopram formed in activated sludge, Water Res. 103 (2016) 205–214, https://doi.org/10.1016/j.watres.2016.07.029.
[25] C. Postigo, S.D. Richardson, Transformation of pharmaceuticals during oxidation/disinfection processes in drinking water treatment, J. Hazard. Mater. 279 (2014) 461–475, https://doi.org/10.1016/j.jhazmat.2014.07.029.
[26] F.D.L. Leusch, P.A. Neale, F. Busetti, M. Card, A. Humpage, J.D. Orbell, H. F. Ridgway, M.B. Stewart, J.P. van de Merwe, B.I. Escher, Transformation of endocrine disrupting chemicals, pharmaceutical and personal care products during drinking water disinfection, Sci. Total Environ. 657 (2019) 1480–1490, https://doi.org/10.1016/j.scitotenv.2018.12.106.
[27] J. Li, L.-Y.L. yun Ma, L.L. Xu, Transformation of benzophenone-type UV filters by chlorine: kinetics, products identification and toxicity assessments, J. Hazard. Mater. 311 (2016) 263–272, https://doi.org/10.1016/j.jhazmat.2016.02.059.
[28] N. Negreira, J. Regueiro, M. López de Alda, D. Barceló, Transformation of tamoxifen and its major metabolites during water chlorination: identification and in silico toxicity assessment of their disinfection byproducts, Water Res. 85 (2015) 199–207, https://doi.org/10.1016/j.watres.2015.08.036.
[29] H. Yoom, J. Shin, J. Ra, H. Son, D. Ryu, C. Kim, Y. Lee, Transformation of methylparaben during water chlorination: effects of bromide and dissolved organic matter on reaction kinetics and transformation pathways, Sci. Total Environ. 634 (2018) 677–686, https://doi.org/10.1016/j.scitotenv.2018.03.330.
[30] L. Ma, J. Li, L. Xu, Aqueous chlorination of fenamic acids: kinetic study, transformation products identification and toxicity prediction, Chemosphere 175 (2017) 114–122, https://doi.org/10.1016/j.chemosphere.2017.02.045.
[31] A.J. Li, P. Wu, J.C.-F. Law, C.-H. Chow, C. Postigo, Y. Guo, K.S.-Y. Leung, Transformation of acesulfame in chlorination: kinetics study, identification of byproducts, and toxicity assessment, Water Res. 117 (2017) 157–166, https://doi.org/10.1016/j.watres.2017.03.053.
[32] R. Rodil, J.B. Quintana, R. Cela, Transformation of phenazone-type drugs during chlorination, Water Res. 46 (2012) 2457–2468, https://doi.org/10.1016/j.watres.2012.02.018.
[33] Mediterranean wastewater reuse working group (MED WWR WG), Mediterranean Wastewater Reuse Report, 2007. https://ec.europa.eu/environment/water/water-urbanwaste/info/pdf/final_report.pdf.
[34] C.E. Scruggs, C.B. Pratesi, J.R. Fleck, Direct potable water reuse in five arid inland communities: an analysis of factors influencing public acceptance, J. Environ. Plan. Manag. 63 (2020) 1470–1500, https://doi.org/10.1080/09640568.2019.1671815.
[35] J. Sanchís, W. Gernjak, A. Munné, N. Catalán, M. Petrovic, M.J. Farré, Fate of N-nitrosodimethylamine and its precursors during a wastewater reuse trial in the Llobregat River (Spain), J. Hazard. Mater. (2020), 124346, https://doi.org/10.1016/j.jhazmat.2020.124346.
[36] J. Sanchís, M. Petrović, M.J. Farré, Emission of (chlorinated) reclaimed water into a Mediterranean River and its related effects to the dissolved organic matter fingerprint, Sci. Total Environ. 760 (2021), 143881, https://doi.org/10.1016/j.scitotenv.2020.143881.
[37] C. Postigo, S.D. Richardson, Non-target screening and novel methods based on mass spectrometry detection for identification of unknown disinfection byproducts, in: T. Manasfi, J.-L. Boudenne (Eds.), Anal. Form. Toxic. Disinfect. Byprod. Drink. Water, Compr. Anal. Chem. Ser., Elsevier, 2021, pp. 1–29, https://doi.org/10.1016/bs.coac.2021.01.001.
[38] X.-F. Li, W.A. Mitch, Drinking water disinfection byproducts (DBPs) and human health effects: multidisciplinary challenges and opportunities, Environ. Sci. Technol. 52 (2018) 1681–1689, https://doi.org/10.1021/acs.est.7b05440.
[39] A.M. Brunner, M.M.L. Dingemans, K.A. Baken, A.P. van Wezel, Prioritizing anthropogenic chemicals in drinking water and sources through combined use of mass spectrometry and ToxCast toxicity data, J. Hazard. Mater. 364 (2019) 332–338, https://doi.org/10.1016/j.jhazmat.2018.10.044.
[40] Z. Tian, K.T. Peter, A.D. Gipe, H. Zhao, F. Hou, D.A. Wark, T. Khangaonkar, E. P. Kolodziej, C.A. James, Suspect and nontarget screening for contaminants of emerging concern in an urban estuary, Environ. Sci. Technol. 54 (2020) 889–901, https://doi.org/10.1021/acs.est.9b06126.
[41] P.A. Lara-Martín, A.C. Chiaia-Hernández, M. Biel-Maeso, R.M. Baena-Nogueras, J. Hollender, Tracing urban wastewater contaminants into the Atlantic Ocean by nontarget screening, Environ. Sci. Technol. 54 (2020) 3996–4005, https://doi.org/10.1021/acs.est.9b06114.
[42] T. Köppe, K.S. Jewell, C. Dietrich, A. Wick, T.A. Ternes, Application of a non-target workflow for the identification of specific contaminants using the example of the Nidda river basin, Water Res. 178 (2020), https://doi.org/10.1016/j.watres.2020.115703.
[43] L.-M. Beckers, W. Brack, J.P. Dann, M. Krauss, E. Müller, T. Schulze, Unraveling longitudinal pollution patterns of organic micropollutants in a river by non-target screening and cluster analysis, Sci. Total Environ. 727 (2020), https://doi.org/10.1016/j.scitotenv.2020.138388.
[44] F. Menger, L. Ahrens, K. Wiberg, P. Gago-Ferrero, Suspect screening based on market data of polar halogenated micropollutants in river water affected by wastewater, J. Hazard. Mater. 401 (2021), https://doi.org/10.1016/j.jhazmat.2020.123377.
[45] A.B. Martínez-Piernas, P. Plaza-Bolaños, A. Agüera, Assessment of the presence of transformation products of pharmaceuticals in agricultural environments irrigated with reclaimed water by wide-scope LC-QTOF-MS suspect screening, J. Hazard. Mater. 412 (2021), https://doi.org/10.1016/j.jhazmat.2021.125080.
[46] M. Čelić, A. Jaén-Gil, S. Briceño-Guevara, S. Rodríguez-Mozaz, M. Gros, M. Petrović, Extended suspect screening to identify contaminants of emerging concern in riverine and coastal ecosystems and assessment of environmental risks, J. Hazard. Mater. 404 (2021), https://doi.org/10.1016/j.jhazmat.2020.124102.
[47] I. González-Mariño, J.B. Quintana, I. Rodríguez, N. Sánchez-Méndez, R. Cela, Transformation of cocaine during water chlorination, Anal. Bioanal. Chem. 404 (2012) 3135–3144, https://doi.org/10.1007/s00216-012-6428-2.
[48] Y. Gao, J. Jiang, Y. Zhou, S.Y. Pang, J. Ma, C. Jiang, Y. Yang, Z. song Huang, J. Gu, Q. Guo, J. Bin Duan, J. Li, Chlorination of bisphenol S: kinetics, products, and effect of humic acid, Water Res. 131 (2018) 208–217, https://doi.org/10.1016/j.watres.2017.12.049.
[49] Y. Han, M. Ma, N. Li, R. Hou, C. Huang, Y. Oda, Z. Wang, Chlorination, chloramination and ozonation of carbamazepine enhance cytotoxicity and genotoxicity: multi-endpoint evaluation and identification of its genotoxic transformation products, J. Hazard. Mater. 342 (2018) 679–688, https://doi.org/10.1016/j.jhazmat.2017.08.076.
[50] Y. Yang, J. Shi, Y. Yang, J. Yin, J. Zhang, B. Shao, Transformation of sulfamethazine during the chlorination disinfection process: transformation, kinetics, and toxicology assessment, J. Environ. Sci. (China) 76 (2019) 48–56, https://doi.org/10.1016/j.jes.2018.03.024.

[51] P. Canosa, S. Morales, I. Rodríguez, E. Rubí, R. Cela, M. Gómez, Aquatic degradation of triclosan and formation of toxic chlorophenols in presence of low concentrations of free chlorine, Anal. Bioanal. Chem. 383 (2005) 1119–1126, https://doi.org/10.1007/s00216-005-0116-4.

[52] Y. Gao, S.Y. Pang, J. Jiang, J. Ma, Y. Zhou, J. Li, L.H. Wang, X.T. Lu, L.P. Yuan, Transformation of flame retardant tetrabromobisphenol a by aqueous chlorine and the effect of humic acid, Environ. Sci. Technol. 50 (2016) 9608–9618, https://doi.org/10.1021/acs.est.6b02844.

[53] X. Zhang, Y. Yang, J. Zhang, Y. Yang, F. Shen, J. Shen, B. Shao, Determination of emerging chlorinated byproducts of diazepam in drinking water, Chemosphere 218 (2019) 223–231, https://doi.org/10.1016/j.chemosphere.2018.11.076.

[54] T. Manasfi, B. Coulomb, S. Ravier, J.L. Boudenne, Degradation of organic UV filters in chlorinated seawater swimming pools: transformation pathways and bromoform formation, Environ. Sci. Technol. 51 (2017) 13580–13591, https://doi.org/10.1021/acs.est.7b02624.

[55] M. Huerta-Fontela, O. Pineda, F. Ventura, M.T. Galceran, New chlorinated amphetamine-type-stimulants disinfection-by-products formed during drinking water treatment, Water Res. 46 (2012) 3304–3314, https://doi.org/10.1016/j.watres.2012.03.029.

[56] B.J.B.J. Sieira, R. Montes, A. Touffet, R. Rodil, R. Cela, H. Gallard, J.B.J. B. Quintana, Chlorination and bromination of 1,3-diphenylguanidine and 1,3-di-o-tolylguanidine: kinetics, transformation products and toxicity assessment, J. Hazard. Mater. 385 (2020), 121590, https://doi.org/10.1016/j.jhazmat.2019.121590.

[57] M. Wang, D.E. Helbling, A non-target approach to identify disinfection byproducts of structurally similar sulfonamide antibiotics, Water Res. 102 (2016) 241–251, https://doi.org/10.1016/j.watres.2016.06.042.

[58] P.J. Vikesland, E.M. Fiss, K.R. Wigginton, K. McNeill, W.A. Arnold, Halogenation of bisphenol-A, triclosan, and phenols in chlorinated waters containing iodide, Environ. Sci. Technol. 47 (2013) 6764–6772, https://doi.org/10.1021/es304927j.

[59] M. Soufan, M. Deborde, A. Delmont, B. Legube, Aqueous chlorination of carbamazepine: kinetic study and transformation product identification, Water Res. 47 (2013) 5076–5087, https://doi.org/10.1016/j.watres.2013.05.047.

[60] J.B. Quintana, R. Rodil, R. Cela, Reaction of β-blockers and β-agonist pharmaceuticals with aqueous chlorine. Investigation of kinetics and by-products by liquid chromatography quadrupole time-of-flight mass spectrometry, Anal. Bioanal. Chem. 403 (2012) 2385–2395, https://doi.org/10.1007/s00216-011-5707-7.

[61] F.M. Wendel, C. Lütke Eversloh, E.J. Machek, S.E. Duirk, M.J. Plewa, S. D. Richardson, T.A. Ternes, Transformation of iopamidol during chlorination, Environ. Sci. Technol. 48 (2014) 12689–12697, https://doi.org/10.1021/es503609s.

[62] J.B. Quintana, R. Rodil, P. López-Mahía, S. Muniategui-Lorenzo, D. Prada-Rodríguez, Investigating the chlorination of acidic pharmaceuticals and by-product formation aided by an experimental design methodology, Water Res. 44 (2010) 243–255, https://doi.org/10.1016/j.watres.2009.09.018.

[63] M. Deborde, U. von Gunten, Reactions of chlorine with inorganic and organic compounds during water treatment-kinetics and mechanisms: a critical review, Water Res. 42 (2008) 13–51, https://doi.org/10.1016/j.watres.2007.07.025.

[64] S. Zhou, Y. Xia, T. Li, T. Yao, Z. Shi, S. Zhu, Degradation of carbamazepine by UV/chlorine advanced oxidation process and formation of disinfection by-products, Environ. Sci. Pollut. Res. (2016), https://doi.org/10.1007/s11356-016-6823-x.

[65] I. González-Mariño, I. Rodríguez, J.B. Quintana, R. Cela, Investigation of the transformation of 11-nor-9-carboxy-δ9-tetrahydrocannabinol during water chlorination by liquid chromatography-quadrupole-time-of-flight-mass spectrometry, J. Hazard. Mater. 261 (2013) 628–636, https://doi.org/10.1016/j.jhazmat.2013.08.006.

[66] H. Dong, Z. Qiang, X. Yuan, A. Luo, Effects of bromide and iodide on the chlorination of diclofenac: accelerated chlorination and enhanced formation of disinfection by-products, Sep. Purif. Technol. 193 (2018) 415–420, https://doi.org/10.1016/j.seppur.2017.09.068.

[67] N. Negreira, P. Canosa, I. Rodríguez, M. Ramil, E. Rubí, R. Cela, Study of some UV filters stability in chlorinated water and identification of halogenated by-products by gas chromatography-mass spectrometry, J. Chromatogr. A 1178 (2008) 206–214, https://doi.org/10.1016/j.chroma.2007.11.057.

[68] V. de J. Gaffney, V.V. Cardoso, M.J. Benoliel, C.M.M. Almeida, Chlorination and oxidation of sulfonamides by free chlorine: identification and behaviour of reaction products by UPLC-MS/MS, J. Environ. Manage. 166 (2016) 466–477, https://doi.org/10.1016/j.jenvman.2015.10.048.

[69] N. Negreira, J. Regueiro, M. López de Alda, D. Barceló, Reactivity of vinca alkaloids during water chlorination processes: identification of their disinfection by-products by high-resolution quadrupole-Orbitrap mass spectrometry, Sci. Total Environ. 544 (2016) 635–644, https://doi.org/10.1016/j.scitotenv.2015.12.005.

[70] T. Rodríguez-Cabo, M. Paganini, I. Carpinteiro, L. Fontenla, I. Rodríguez, M. C. Pietrogrande, R. Cela, Liquid chromatography time-of-flight mass spectrometry evaluation of fungicides reactivity in free chlorine containing water samples, J. Mass Spectrom. 48 (2013) 216–226, https://doi.org/10.1002/jms.3151.

[71] R.A. Osawa, A.P. Carvalho, O.C. Monteiro, M.C. Oliveira, M.H. Florêncio, Degradation of duloxetine: identification of transformation products by UHPLC-ESI(+)-HRMS/MS, in silico toxicity and wastewater analysis, J. Environ. Sci. 82 (2019) 113–123, https://doi.org/10.1016/j.jes.2019.02.025.

[72] Q. Chai, S. Zhang, X. Wang, H. Yang, Y.F. Xie, Effect of bromide on the transformation and genotoxicity of octyl-dimethyl-p-aminobenzoic acid during chlorination, J. Hazard. Mater. 324 (2017) 626–633, https://doi.org/10.1016/j.jhazmat.2016.11.035.

[73] A. Zarrelli, M. DellaGreca, A. Parolisi, M.R. Iesce, F. Cermola, F. Temussi, M. Isidori, M. Lavorgna, M. Passananti, L. Previtera, Chemical fate and genotoxic risk associated with hypochlorite treatment of nicotine, Sci. Total Environ. 426 (2012) 132–138, https://doi.org/10.1016/j.scitotenv.2012.03.047.

[74] Y. Zhang, Y. Shao, N. Gao, Y. Gao, W. Chu, S. Li, Y. Wang, S. Xu, Kinetics and by-products formation of chloramphenicol (CAP) using chlorination and photocatalytic oxidation, Chem. Eng. J. 333 (2018) 85–91, https://doi.org/10.1016/j.cej.2017.09.094.

[75] M.Q. Cai, L. Feng, J. Jiang, F. Qi, L.Q. Zhang, Reaction kinetics and transformation of antipyrine chlorination with free chlorine, Water Res. 47 (2013) 2830–2842, https://doi.org/10.1016/j.watres.2013.02.047.

[76] M. Bourgin, E. Bichon, J.P. Antignac, F. Monteau, G. Leroy, L. Barritaud, M. Chachignon, V. Ingrand, P. Roche, B. Le Bizec, Chlorination of bisphenol A: non-targeted screening for the identification of transformation products and assessment of estrogenicity in generated water, Chemosphere 93 (2013) 2814–2822, https://doi.org/10.1016/j.chemosphere.2013.09.080.

[77] M.C. Dodd, C.H. Huang, Transformation of the antibacterial agent sulfamethoxazole in reactions with chlorine: kinetics, mechanisms, and pathways, Environ. Sci. Technol. 38 (2004) 5607–5615, https://doi.org/10.1021/es035225z.

[78] J.M. Buth, W.A. Arnold, K. Mcneill, Unexpected products and reaction mechanisms of the aqueous chlorination of cimetidine, Environ. Sci. Technol. 41 (2007) 6228–6233, https://doi.org/10.1021/es070606o.

[79] L. Bijlsma, C. Boix, W.M.A. Niessen, M. Ibáñez, J.V. Sancho, F. Hernández, Investigation of degradation products of cocaine and benzoylecgonine in the aquatic environment, Sci. Total Environ. 443 (2013) 200–208, https://doi.org/10.1016/j.scitotenv.2012.11.006.

[80] K.L. Klarich Wong, D.T. Webb, M.R. Nagorzanski, D.W. Kolpin, M.L. Hladik, D. M. Cwiertny, G.H. Lefevre, Chlorinated byproducts of neonicotinoids and their metabolites: an unrecognized human exposure potential? Environ. Sci. Technol. Lett. 6 (2019) 98–105, https://doi.org/10.1021/acs.estlett.8b00706.

[81] K.E. Pinkston, D.L. Sedlak, Transformation of aromatic ether- and amine-containing pharmaceuticals during chlorine disinfection, Environ. Sci. Technol. 38 (2004) 4019–4025, https://doi.org/10.1021/es035368l.

[82] Y. Pan, S.S. Cheng, X. Yang, J. Ren, J. Fang, C. Shang, W. Song, L. Lian, X. Zhang, UV/chlorine treatment of carbamazepine: transformation products and their formation kinetics, Water Res. 116 (2017) 254–265, https://doi.org/10.1016/j.watres.2017.03.033.

[83] J.D. Sivey, A.L. Roberts, Assessing the reactivity of free chlorine constituents Cl 2, Cl 2O, and HOCl toward aromatic ethers, Environ. Sci. Technol. 46 (2012) 2141–2147, https://doi.org/10.1021/es203094z.

[84] J.D. Sivey, C.E. McCullough, A.L. Roberts, Chlorine monoxide (Cl2O) and molecular chlorine (Cl2) as active chlorinating agents in reaction of dimethenamid with aqueous free chlorine, Environ. Sci. Technol. 44 (2010) 3357–3362, https://doi.org/10.1021/es9038903.

[85] G.M. Shaydullina, N.A. Sinikova, A.T. Lebedev, Reaction of ortho-methoxybenzoic acid with the water disinfecting agents ozone, chlorine and sodium hypochlorite, Environ. Chem. Lett. 3 (2005) 1–5, https://doi.org/10.1007/s10311-005-0103-1.

[86] C. Wang, M. Bavcon Kralj, B. Košmrlj, J. Yao, S. Košenina, O.V. Polyakova, V. B. Artaev, A.T. Lebedev, P. Trebše, Stability and removal of selected avobenzone's chlorination products, Chemosphere 182 (2017) 238–244, https://doi.org/10.1016/j.chemosphere.2017.04.125.

[87] M.Q. Cai, L. Feng, L.Q. Zhang, Transformation of aminopyrine in the presence of free available chlorine: kinetics, products, and reaction pathways, Chemosphere 171 (2017) 625–634, https://doi.org/10.1016/j.chemosphere.2016.12.033.

[88] Q. Mao, F. Ji, W. Wang, Q. Wang, Z. Hu, S. Yuan, Chlorination of parabens: reaction kinetics and transformation product identification, Environ. Sci. Pollut. Res. 23 (2016) 23081–23091, https://doi.org/10.1007/s11356-016-7499-y.

[89] F. Cao, M. Zhang, S. Yuan, J. Feng, Q. Wang, W. Wang, Z. Hu, Transformation of acetaminophen during water chlorination treatment: kinetics and transformation products identification, Environ. Sci. Pollut. Res. 23 (2016) 12303–12311, https://doi.org/10.1007/s11356-016-6341-x.

[90] C. Boix, M. Ibáñez, L. Bijlsma, J.V. Sancho, F. Hernández, Investigation of cannabis biomarkers and transformation products in waters by liquid chromatography coupled to time of flight and triple quadrupole mass spectrometry, Chemosphere 99 (2014) 64–71, https://doi.org/10.1016/j.chemosphere.2013.10.007.

[91] Z. Li, H. Fenet, E. Gomez, S. Chiron, Transformation of the antiepileptic drug oxcarbazepine upon different water disinfection processes, Water Res. 45 (2011) 1587–1596, https://doi.org/10.1016/j.watres.2010.11.038.

[92] S. Zheng, J. chen Shi, J. ying Hu, W. xin Hu, J. Zhang, B. Shao, Chlorination of bisphenol F and the estrogenic and peroxisome proliferator-activated receptor gamma effects of its disinfection byproducts, Water Res. 107 (2016) 1–10, https://doi.org/10.1016/j.watres.2016.10.048.

[93] F. Menger, P. Gago-Ferrero, K. Wiberg, L. Ahrens, Wide-scope screening of polar contaminants of concern in water: a critical review of liquid chromatography-high resolution mass spectrometry-based strategies, Trends Environ. Anal. Chem. 28 (2020), e00102, https://doi.org/10.1016/j.teac.2020.e00102.

[94] M. Yang, X. Zhang, Q. Liang, B. Yang, Application of (LC/)MS/MS precursor ion scan for evaluating the occurrence, formation and control of polar halogenated DBPs in disinfected waters: a review, Water Res. 158 (2019) 322–337, https://doi.org/10.1016/j.watres.2019.04.033.

[95] W. Fu, B. Li, J. Yang, H. Yi, L. Chai, X. Li, New insights into the chlorination of sulfonamide: smiles-type rearrangement, desulfation, and product toxicity, Chem. Eng. J. 331 (2018) 785–793, https://doi.org/10.1016/j.cej.2017.09.024.
[96] H. Wang, C. Hu, L. Liu, X. Xing, Interaction of ciprofloxacin chlorination products with bacteria in drinking water distribution systems, J. Hazard. Mater. 339 (2017) 174–181, https://doi.org/10.1016/j.jhazmat.2017.06.033.
[97] A. Tawk, M. Deborde, J. Labanowski, H. Gallard, Chlorination of the β-triketone herbicides tembotrione and sulcotrione: kinetic and mechanistic study, transformation products identification and toxicity, Water Res. 76 (2015) 132–142, https://doi.org/10.1016/j.watres.2015.02.060.
[98] F. Dong, C. Li, J. Crittenden, T. Zhang, Q. Lin, G. He, W. Zhang, J. Luo, Sulfadiazine destruction by chlorination in a pilot-scale water distribution system: kinetics, pathway, and bacterial community structure, J. Hazard. Mater. 366 (2019) 88–97, https://doi.org/10.1016/j.jhazmat.2018.11.096.
[99] J.B. Quintana, R. Rodil, I. Rodríguez, Transformation products of emerging contaminants upon reaction with conventional water disinfection oxidants, Transform. Prod. Emerg. Contam. Environ. (2014) 123–160, https://doi.org/10.1002/9781118339558.ch04.
[100] B. Yang, C. Xu, R.S. Kookana, M. Williams, J. Du, G. Ying, F. Gu, Aqueous chlorination of benzodiazepines diazepam and oxazepam: kinetics, transformation products and reaction pathways, Chem. Eng. J. 354 (2018) 1100–1109, https://doi.org/10.1016/j.cej.2018.08.082.
[101] I. Carpinteiro, R. Rodil, J.B. Quintana, R. Cela, Reaction of diazepam and related benzodiazepines with chlorine. Kinetics, transformation products and in-silico toxicological assessment, Water Res. 120 (2017) 280–289, https://doi.org/10.1016/j.watres.2017.04.063.
[102] R.A. Osawa, A.P. Carvalho, O.C. Monteiro, M.C. Oliveira, M.H. Florêncio, Transformation products of citalopram: identification, wastewater analysis and in silico toxicological assessment, Chemosphere 217 (2019) 858–868, https://doi.org/10.1016/j.chemosphere.2018.11.027.
[103] I. González-Mariño, J.B. Quintana, I. Rodríguez, M. Cores, R. Cela, Transformation of methadone and its main human metabolite, 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP), during water chlorination, Water Res. 68 (2015) 759–770, https://doi.org/10.1016/j.watres.2014.10.058.
[104] A. Jaén-Gil, M.-J. Farré, A. Sànchez-Melsió, A. Serra-Compte, D. Barceló, S. Rodríguez-Mozaz, Effect-based identification of hazardous antibiotic transformation products after water chlorination, Environ. Sci. Technol. 54 (2020) 9062–9073, https://doi.org/10.1021/acs.est.0c00944.
[105] N.L. Kennedy Neth, C.M. Carlin, O.S. Keen, Emerging investigator series: transformation of common antibiotics during water disinfection with chlorine and formation of antibacterially active products, Environ. Sci. Water Res. Technol. 5 (2019) 1222–1233, https://doi.org/10.1039/c9ew00182d.
[106] P. Wang, Y.L. He, C.H. Huang, Reactions of tetracycline antibiotics with chlorine dioxide and free chlorine, Water Res. 45 (2011) 1838–1846, https://doi.org/10.1016/j.watres.2010.11.039.
[107] N.L. Kennedy Neth, C.M. Carlin, O.S. Keen, Doxycycline transformation and emergence of antibacterially active products during water disinfection with chlorine, Environ. Sci. Water Res. Technol. 3 (2017) 1086–1094, https://doi.org/10.1039/c7ew00215g.
[108] N.H. El Najjar, M. Deborde, R. Journel, N.K. Vel Leitner, Aqueous chlorination of levofloxacin: kinetic and mechanistic study, transformation product identification and toxicity, Water Res. 47 (2013) 121–129, https://doi.org/10.1016/j.watres.2012.09.035.
[109] M.C. Dodd, A.D. Shah, U. Von Gunten, C.H. Huang, Interactions of fluoroquinolone antibacterial agents with aqueous chlorine: reaction kinetics, mechanisms, and transformation pathways, Environ. Sci. Technol. 39 (2005) 7065–7076, https://doi.org/10.1021/es050054e.
[110] X. Wang, Y. Li, R. Li, H. Yang, B. Zhou, X. Wang, Y. Xie, Comparison of chlorination behaviors between norfloxacin and ofloxacin: reaction kinetics, oxidation products and reaction pathways, Chemosphere 215 (2019) 124–132, https://doi.org/10.1016/j.chemosphere.2018.09.100.
[111] M.C. Dodd, C.H. Huang, Aqueous chlorination of the antibacterial agent trimethoprim: reaction kinetics and pathways, Water Res. 41 (2007) 647–655, https://doi.org/10.1016/j.watres.2006.10.029.
[112] L. Li, D. Wei, G. Wei, Y. Du, Transformation of cefazolin during chlorination process: products, mechanism and genotoxicity assessment, J. Hazard. Mater. 262 (2013) 48–54, https://doi.org/10.1016/j.jhazmat.2013.08.029.
[113] M. Bedner, W.A. MacCrehan, Transformation of acetaminophen by chlorination produces the toxicants 1,4-benzoquinone and N-acetyl-p-benzoquinone imine, Environ. Sci. Technol. 40 (2006) 516–522, https://doi.org/10.1021/es0509073.
[114] E. Du, J. Li, S. Zhou, L. Zheng, X. Fan, Transformation of naproxen during the chlorination process: products identification and quantum chemistry validation, Chemosphere 211 (2018) 1007–1017, https://doi.org/10.1016/j.chemosphere.2018.08.036.
[115] W.L. Wang, Q.Y. Wu, Y. Du, N. Huang, H.Y. Hu, Elimination of chlorine-refractory carbamazepine by breakpoint chlorination: reactive species and oxidation byproducts, Water Res. 129 (2018) 115–122, https://doi.org/10.1016/j.watres.2017.11.016.
[116] Tana Tandarić, Valerije Vrček, Davor Šakić, A quantum chemical study of HOCl-induced transformations of carbamazepine, Org. Biomol. Chem. 14 (2016) 10866–10874, https://doi.org/10.1039/C6OB02166B.
[117] C. Postigo, D.M.D.M. Demarini, M.D.M.D. Armstrong, H.K.H.K. Liberatore, K. Lamann, S.Y.S.Y. Kimura, A.A.A. Cuthbertson, S.H.S.H. Warren, S.D.S. D. Richardson, T. McDonald, Y.M. Sey, N.O.B. Ackerson, S.E. Duirk, J.E.J. E. Simmons, Chlorination of source water containing iodinated X-ray contrast media: mutagenicity and identification of new iodinated disinfection byproducts, Environ. Sci. Technol. 52 (2018) 13047–13056, https://doi.org/10.1021/acs.est.8b04625.
[118] N.C. Pflug, A. Kupsco, E.P. Kolodziej, D. Schlenk, L.M. Teesch, J.B. Gloer, D. M. Cwiertny, Formation of bioactive transformation products during glucocorticoid chlorination, Environ. Sci. Water Res. Technol. 3 (2017) 450–461, https://doi.org/10.1039/c7ew00033b.
[119] Y. Lee, U. Von Gunten, Transformation of 17a-ethinylestradiol during water chlorination: effects of bromide on kinetics, products, and transformation pathways, Environ. Sci. Technol. 43 (2009) 480–487, https://doi.org/10.1021/es8023989.
[120] D. Armbruster, O. Happel, M. Scheurer, K. Harms, T.C. Schmidt, H.J. Brauch, Emerging nitrogenous disinfection byproducts: transformation of the antidiabetic drug metformin during chlorine disinfection of water, Water Res. 79 (2015) 104–118, https://doi.org/10.1016/j.watres.2015.04.020.
[121] X. Sun, D. Wei, W. Liu, J. Geng, J. Liu, Y. Du, Formation of novel disinfection by-products chlorinated benzoquinone, phenyl benzoquinones and polycyclic aromatic hydrocarbons during chlorination treatment on UV filter 2,4-dihydroxybenzophenone in swimming pool water, J. Hazard. Mater. 367 (2019) 725–733, https://doi.org/10.1016/j.jhazmat.2019.01.008.
[122] J. Lu, P. Yang, W. Dong, Y. Ji, Q. Huang, Enhanced formation of chlorinated disinfection byproducts in the UV/chlorine process in the presence of benzophenone-4, Chem. Eng. J. 351 (2018) 304–311, https://doi.org/10.1016/j.cej.2018.06.089.
[123] F. Yang, D. Wei, M. Xiao, X. Sun, Q. Guo, Y. Liu, Y. Du, The chlorination transformation characteristics of benzophenone-4 in the presence of iodide ions, J. Environ. Sci. 58 (2017) 93–101, https://doi.org/10.1016/j.jes.2017.04.023.
[124] W.L. Chen, J.Y. Cheng, X.Q. Lin, Systematic screening and identification of the chlorinated transformation products of aromatic pharmaceuticals and personal care products using high-resolution mass spectrometry, Sci. Total Environ. 637–638 (2018) 253–263, https://doi.org/10.1016/j.scitotenv.2018.05.011.
[125] E.M. Fiss, K.L. Rule, P.J. Vikesland, Formation of chloroform and other chlorinated byproducts by chlorination of triclosan-containing antibacterial products, Environ. Sci. Technol. 41 (2007) 2387–2394, https://doi.org/10.1021/es062227l.
[126] W. Wang, Y. Qian, J. Li, B. Moe, R. Huang, H. Zhang, S.E. Hrudey, X.F.X.-F. Li, Analytical and toxicity characterization of halo-hydroxyl-benzoquinones as stable halobenzoquinone disinfection byproducts in treated water, Anal. Chem. 86 (2014) 4982–4988, https://doi.org/10.1021/ac5007238.
[127] M. Scheurer, F.R. Storck, H.-J. Brauch, F.T. Lange, Performance of conventional multi-barrier drinking water treatment plants for the removal of four artificial sweeteners, Water Res. 44 (2010) 3573–3584, https://doi.org/10.1016/j.watres.2010.04.005.
[128] L. Soh, K.A. Connors, B.W. Brooks, J. Zimmerman, Fate of sucralose through environmental and water treatment processes and impact on plant Indicator species, Environ. Sci. Technol. 45 (2011) 1363–1369, https://doi.org/10.1021/es102719d.
[129] K.L. Klarich, N.C. Pflug, E.M. DeWald, M.L. Hladik, D.W. Kolpin, D.M. Cwiertny, G.H. LeFevre, Occurrence of neonicotinoid insecticides in finished drinking water and fate during drinking water treatment, Environ. Sci. Technol. Lett. 4 (2017) 168–173, https://doi.org/10.1021/acs.estlett.7b00081.
[130] S. Chusaksri, S. Sutthivaiyakit, D.L. Sedlak, P. Sutthivaiyakit, Reactions of phenylurea compounds with aqueous chlorine: implications for herbicide transformation during drinking water disinfection, J. Hazard. Mater. 209–210 (2012) 484–491, https://doi.org/10.1016/j.jhazmat.2012.01.063.
[131] R. Brix, N. Bahi, M.J. Lopez de Alda, M. Farré, J.-M. Fernandez, D. Barceló, Identification of disinfection by-products of selected triazines in drinking water by LC-Q-ToF-MS/MS and evaluation of their toxicity, J. Mass Spectrom. 44 (2009) 330–337, https://doi.org/10.1002/jms.1509.
[132] N.A. Alygizakis, P. Oswald, N.S. Thomaidis, E.L. Schymanski, R. Aalizadeh, T. Schulze, M. Oswaldova, J. Slobodnik, NORMAN digital sample freezing platform: a European virtual platform to exchange liquid chromatography high resolution-mass spectrometry data and screen suspects in “digitally frozen” environmental samples, TrAC Trends Anal. Chem. 115 (2019) 129–137, https://doi.org/10.1016/j.trac.2019.04.008.
[133] R. Aalizadeh, N.A. Alygizakis, E.L. Schymanski, M. Krauss, T. Schulze, M. Ibáñez, A.D. McEachran, A. Chao, A.J. Williams, P. Gago-Ferrero, A. Covaci, C. Moschet, T.M. Young, J. Hollender, J. Slobodnik, N.S. Thomaidis, Development and application of liquid chromatographic retention time indices in HRMS-based suspect and nontarget screening, Anal. Chem. 93 (2021) 11601–11611, https://doi.org/10.1021/acs.analchem.1c02348.
[134] C. Boix, M. Ibáñez, J.V. Sancho, W.M.A. Niessen, F. Hernández, Investigating the presence of omeprazole in waters by liquid chromatography coupled to low and high resolution mass spectrometry: degradation experiments, J. Mass Spectrom. 48 (2013) 1091–1100, https://doi.org/10.1002/jms.3260.
[135] T.P. Wood, A.E. Basson, C. Duvenage, E.R. Rohwer, The chlorination behaviour and environmental fate of the antiretroviral drug nevirapine in South African surface water, Water Res. 104 (2016) 349–360, https://doi.org/10.1016/j.watres.2016.08.038.
[136] M. Xiao, D. Wei, J. Yin, G. Wei, Y. Du, Transformation mechanism of benzophenone-4 in free chlorine promoted chlorination disinfection, Water Res. 47 (2013) 6223–6233, https://doi.org/10.1016/j.watres.2013.07.043.
[137] J. Yin, Y. Niu, B. Shao, Products of methotrexate during chlorination, J. Environ. Sci. 55 (2017) 100–108, https://doi.org/10.1016/j.jes.2016.06.024.
[138] D.N. Bulloch, E.D. Nelson, S.A. Carr, C.R. Wissman, J.L. Armstrong, D. Schlenk, C. K. Larive, Occurrence of halogenated transformation products of selected pharmaceuticals and personal care products in secondary and tertiary treated

wastewaters from Southern California, Environ. Sci. Technol. 49 (2015) 2044–2051, https://doi.org/10.1021/es504565n.
[139] F. Mao, Y. He, K.Y.-H. Gin, Occurrence and fate of benzophenone-type UV filters in aquatic environments: a review, Environ. Sci. Water Res. Technol. 5 (2019) 209–223, https://doi.org/10.1039/C8EW00539G.
[140] J. Li, L. Dodgen, Q. Ye, J. Gan, Degradation kinetics and metabolites of carbamazepine in soil, Environ. Sci. Technol. 47 (2013) 3678–3684, https://doi.org/10.1021/es304944c.
[141] T. Kosjek, S. Perko, M. Zupanc, M.Z. Hren, T.L. Dragičević, D. Žigon, B. Kompare, E. Heath, Environmental occurrence, fate and transformation of benzodiazepines in water treatment, Water Res. 46 (2012) 355–368, https://doi.org/10.1016/j.watres.2011.10.056.
[142] V. Martínez-Hernández, R. Meffe, C. Kohfahl, I. de Bustamante, Investigating natural attenuation of pharmaceuticals through unsaturated column tests, Chemosphere 177 (2017) 292–302, https://doi.org/10.1016/j.chemosphere.2017.03.021.
[143] E.L. Schymanski, J. Jeon, R. Gulde, K. Fenner, M. Ruff, H.P. Singer, J. Hollender, Identifying small molecules via high resolution mass spectrometry: communicating confidence, Environ. Sci. Technol. 48 (2014) 2097–2098, https://doi.org/10.1021/es5002105.
[144] R. Nassar, S. Mokh, A. Rifai, F. Chamas, M. Hoteit, M. Al Iskandarani, Transformation of sulfaquinoxaline by chlorine and UV light in water: kinetics and by-product identification, Environ. Sci. Pollut. Res. 25 (2018) 34863–34872, https://doi.org/10.1007/s11356-017-0814-4.
[145] W. Wang, Y. Qian, J.M. Boyd, M. Wu, S.E. Hrudey, X.-F. Li, Halobenzoquinones in swimming pool waters and their formation from personal care products, Environ. Sci. Technol. 47 (2013) 3275–3282, https://doi.org/10.1021/es304938x.