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Evaluation of the DBP formation potential of biocides and identification of knowledge gaps in environmental risk assessment

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Abstract

Disinfectants and preservatives used as biocides may contain or release active substances (a.s.) that can form by-products with the surrounding matrices during their application which may be released into the environment. Over the past 40 years, several hundred of these so-called disinfection by-products (DBPs) have been detected after applications of biocides used for disinfection. Due to intensive research and further development of analytical capabilities, many new DBP classes, such as iodinated DBPs (I-DBPs), halonitromethanes (HNMs), haloacetamides (HaAms), or halomethanesulfonic acids were detected worldwide in various matrices and applications. Due to the possible hazards and risks for humans and the environment, frequently occurring DBP classes, such as trihalomethanes (THM), haloacetic acids (HAA) and nitrosamines (NDMA), have already been included in many legislations and given limit values. In the European Union, biocides are assessed under the Biocidal Products Regulation 528/2012 (BPR) regarding their efficacy, potential hazards, and risks to human health and the environment. However, the available guidance for the environmental risk assessment (ERA) of DBPs remains vague. To identify knowledge gaps and to further develop the assessment scheme for the ERA of DBPs, a literature search on the multiple uses of biocides and their formation potential of DBPs was performed and the existing process for ERA was evaluated. The results show knowledge gaps on the formation of DBP in non-aqueous systems and DBP formation by non-halogen-based biocidal active substances. Based on the literature research on biocides, a possible proposal of grouping a.s. to consider their DBP formation potential is presented to simplify future ERAs. However, this also requires further research. Until then, a pragmatic approach considering the DBPs formation potential of the active substances and the identified knowledge gaps need to be established for the environmental risk assessment of DBPs in the EU.

Keywords EU biocidal products regulation, BPR guidance volume V, Disinfection by-product, DBPs, Environmental risk assessment, Biocidal product types, Biocide, Disinfectant, Preservative

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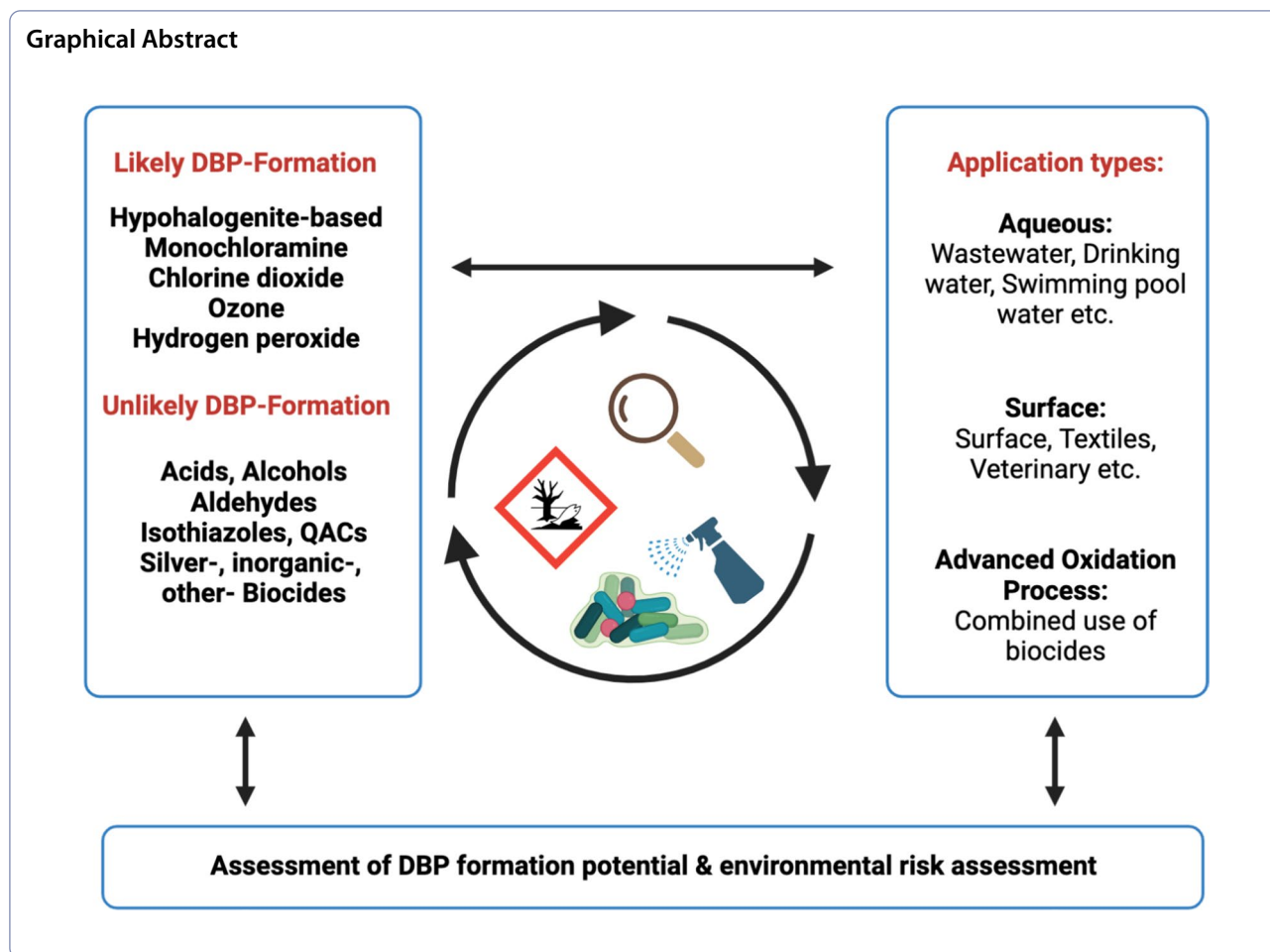
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Background

The use of biocides against harmful organisms is an effective way to reduce and eliminate these organisms. Their use can be essential, especially in the control of infection and disease control, such as disinfection of water. In the European Union, Regulation (EU) No 528/2012 of the European Parliament and the Council of 22 May 2012 concerning the making available on the market and use of biocidal products (Biocidal Products Regulation, BPR) defines a biocide as a substance or preparation containing one or more active substances intended to destroy, deter, render harmless, prevent the action of or otherwise exert a controlling effect on harmful organisms [1]. It classifies biocidal products into 22 different product types (PT) grouped into four main groups. These main groups are disinfectants, preservatives, pest control and other biocidal products. Each PT has a specific description and application; for example, the "human hygiene" PT 1 includes biocidal products used for human hygiene purposes, applied on or in contact with human skin or scalps for the primary purpose of disinfecting the skin or scalp.

The BPR is based on the precautionary principle. The aim of the BPR is the identification, evaluation and prevention or at least decrease of adverse effects and risks on humans and the environment caused by biocidal active substances and products. An environmental risk assessment (ERA) is conducted for the respective active substance and the corresponding biocidal products to assess potential impacts on the environment. This assessment requires information on substance release patterns, fate, and behavior in the environment. An authorization will be granted only if the biocidal product, as well as its residues, has no unacceptable effects on the environment (BPR Article 19 (1), (iv)). In this case, the term residue refers to a substance present "in or on products of plant or animal origin, water resources, drinking water, food, feed or elsewhere in the environment and resulting from the use of a biocidal product, including such a substance's metabolites, breakdown or reaction products." (Article 3 (1) (h)) [2]. Some of the biocidal a.s. used as a disinfectant in the product types (PT) 1–5 as well as preservatives in PT 11 and 12 tend to react quickly with the organic

matter present during the application and with each other, forming so-called disinfection by-products (DBPs). Therefore, based on the definition of residues, DBPs also need to be considered for an adequate risk assessment. This represents a major challenge because the type and the number of formed DBPs depend strongly on the application conditions. Hence, predicting the type and environmental concentration of the DBPs, as an important part of the risk assessment, is difficult, if not impossible. For the evaluation of DBPs under the BPR, a specific "Guidance on Disinfection By-Products" [2] was developed by the European Member States and ECHA and published in 2017. However, the ERA section of it is only focussing on the use of halogenated substances, as well as on PTs 2 (disinfectants and algacides, not intended for direct application to humans or animals), 11 (preservatives for liquid-cooling and processing systems) and 12 (slimicides). In addition, detailed technical guidance is still missing for the implementation of an ERA of DBPs for those application types covered by it. Therefore, information and data submitted by the applicants during a. s. approval or product authorization can be interpreted differently by individual EU Member States making a harmonized ERA of DBPs currently questionable. One reason is that there is no detailed step-by-step process or "test scenario" in the current version for different PTs to demonstrate DBP formation potential; only a general three-step process for determining DBP formation risk is explained. Hence, the risk for environment may be evaluated differently by member states. Thus, the precautionary principle and the level of protection in the EU Member States are defined differently, which may also hamper the mutual recognition of product authorizations between member states.

To identify possibilities for further development of the guidance, the following study discusses the DBP formation potential by the biocidal a.s. in PTs 1-5, 11 and 12. Based on these findings, it summarizes the occurrence of DBPs in the literature and proposes a possible grouping of biocidal a.s. based on their DBP formation potential. The three-step approach on DBP-assessment contained in the current Guidance on Disinfection By-Products was reviewed in detail, and its advantages and disadvantages were compiled and discussed considering the literature results on DBPs and a.s. regarding the formation and ERA of DBPs. Supplemental approaches based on the results were suggested to improve the guidance.

Methods

Evaluation of literature on DBPs [Step 1]

Since there is no uniform definition for the term "disinfection by-product" given neither in BPR nor the current Guidance on Disinfection By-Products regarding when

a by-product is considered a disinfection by-product, a working definition had to be established for the literature review. In the literature, disinfection by-products are often referred to as by-products from the reaction of biocides/disinfectants with organic/inorganic matrix. This definition is mainly based on aqueous applications [3]. The place and time of formation (during the application phase, after application, or at a later point in time) have not yet been further considered and defined in the literature. According to that, DBPs were defined as by-products that are formed directly during the application of the biocide. Further transformation or degradation of the biocide is beyond the scope of the BPR guidance on disinfection by-products. This study also considers only the application or use phase of the respective biocidal active substance/product. The production, formulation and disposal phases are not considered further either. The main part of the literature search on DBPs was conducted from 2013 to April 2019, including selected publications from before 2013 through references in newer literature. To support the findings from this main literature search, also review articles from 2019 to 2023 were taken into account. Both searches were done in the database Web of Science using the search terms „disinfection by-product*“ or „disinfection by product*“.

For the time period of 2013 to 2019, of almost 3000 search results, 154 were selected as relevant by screening titles and abstracts (Fig. 1). The 154 publications were selected manually to cover a wide range of formulation types (gaseous, liquid, solid), biocides (oxidizing/non-oxidizing biocides), matrices (aqueous/non-aqueous), as well as types of DBPs (non-halogenated/halogenated). If there was no specific reference to a biocidal active substance used in the experiment, the literature results were also discarded, e.g., novel AOP processes or multi-stage disinfection, which do not specifically appear as biocidal active substances in the ECHA database. This was necessary due to the regulatory context of our study. Studies where the experimental conditions, such as pH, temperature, biocide concentration, organic matrix, etc., were not evident were also not included. Studying the selected literature, 272 unique DBPs were identified, 186 of them being halogenated and 86 being non-halogenated [1.1]. The detailed literature review results were compiled (see Additional file 1; Sheet: Halogenated_DBPs; Nonhalogenated DBPs), including primary DBP data such as name, molecular structure, molecular formula and CAS No., formation conditions, name and CAS No. of applied biocide and treated matrix. The number of publications analyzing a specific DBP is recorded in Additional file 2: Table S1. To verify the consistency of identified knowledge gaps, recent review articles from 2019 to July 2023 were analyzed by searching the database Web of Science.

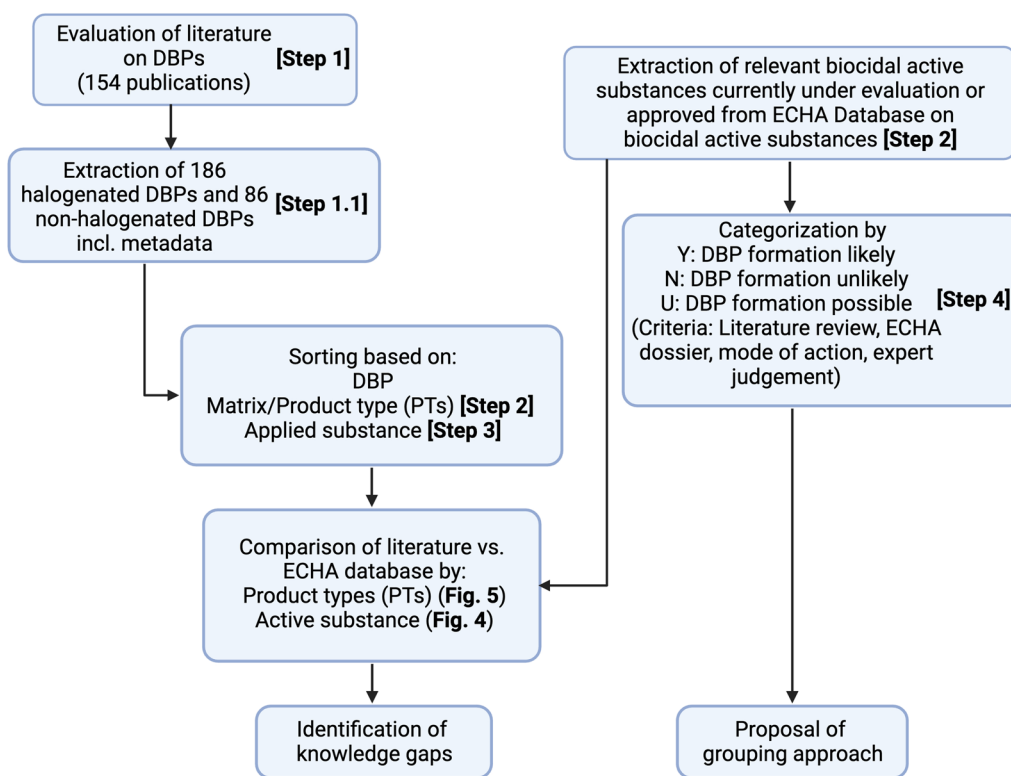


Fig. 1 Overview of the methodological approach

This search gave 330 results for review articles for the search terms "disinfection by-product" and "disinfection by product".

Allocation of test matrices from literature and biocidal a.s. to PTs [Step 2]

The matrices investigated in literature (see Additional file 1) were manually assigned to the biocidal PTs (Additional file 2: Table S2). Since not all literature studies represented natural environmental conditions, but

laboratory studies were also included, these were evaluated more closely and only assigned to a PT if realistic experimental conditions were provided. The laboratory studies included matrices such as artificial solutions like humic acid (HA), artificial seawater and algal organic material. If the experimental conditions were assumed unrealistic, the matrices were assigned to the "Other" category.

Using the ECHA database of biocidal active substances (access in November 2022, see Additional file 3), a list of

Table 1 Overview of approved biocidal a.s. or being under evaluation in the product type (PTs) in the ECHA database (as of November 2022)

Product type	Number of active substances under evaluation or approved
PT01 Human hygiene	26
PT02 Disinfectants and algaecides not intended for direct application to humans or animals	96
PT03 Veterinary hygiene	50
PT04 Food and feed area	68
PT05 Drinking water	28
PT11 Preservatives for liquid-cooling and processing systems	65
PT12 Slimicides	45
Sum	378

Table 2 Reactive molecules/a.s. and related number of findings in literature and ECHA database

Reactive molecule/a.s.	Number of biocidal a.s. (ECHA database)	Number of DBP related to reactive molecule in literature
Hypochlorite	60	632
QACs	56	0
Chlorine dioxide	30	71
Others	29	56
Acids	27	0
Hydrogen peroxide	42	27
Silver	21	0
Alcohols	22	0
Hypobromite	22	23
Inorganic	13	0
Isothiazolinone	13	0
Aldehyde	26	0
MITC	1	0
Monochloramine	10	205
Iodine	6	0
Ozone	4	140
Sum	382	1154

all biocidal active substances belonging to PTs 1–5, 11 and 12 was created [4]. All active substances that were approved or under assessment were further considered. Active substances that were no longer supported, had cancelled applications or were not approved were not considered as products containing the respective a.s. will disappear from the European market sooner or later [4]. Following this step, the number of active substances for each PT was summed up, and a total of 382 active substance/PT-combinations were considered for the evaluation (Table 1).

Categorization of biocidal a.s. based on reactive molecules [Step 3]

As literature data often did not specify exactly which regulatory-defined biocidal a.s. was used to generate the DBP analyzed in the experiments, it was not possible within the study to directly link biocidal a.s. specified in the ECHA database to the DBPs from the literature. Literature data mainly focused on the reactive molecules driving the reactions (e.g., chlorination). To specify which DBP might result from using a biocidal a.s. from the ECHA database, a categorization system was developed that categorized the biocidal a.s. in a system of reactive molecules that suited the results from the literature. This categorization system assigned the results of the literature search and the ECHA database to categories of reactive molecules (Table 2). The number of DBPs also includes multiple findings of the corresponding

unique 272 DBPs found. As an example, chloroform was observed several times in different studies and was therefore counted several times.

Criteria for the likeliness of DBP formation and categorization of active substances [Step 4]

An approach for assessing the DBP forming potential was developed for the respective biocidal a.s., and they were analyzed regarding their potential to form DBPs based on these criteria. The assessments of whether an active substance would generate DBPs during use were defined based on our literature research (publication, ECHA dossiers), their chemical structure and expert judgment. The criteria to classify the a.s. based on their chemical structure or “expert judgment” were only used if the literature or the ECHA dossier did not reveal any concrete information on DBP formation.

The chemical structure of a biocidal active substance (a.s.) can be used to categorize it into two main groups: halogenated (class 1) and non-halogenated substances (class 2):

- Halogenated a.s.: Have a high potential of DBP formation due to their high reactivity (see literature).
- Non-halogenated a.s.: More diverse in terms of their chemical structures. Non-halogenated a.s. include highly reactive oxidizing substances like ozone and peroxides.

For the categorization according to chemical structure, characteristic groups in the structural formula of the biocide were used, e.g., the hydroxyl group for the alcohols. Often, the assignment according to these characteristic molecular groups also corresponded to the type of disinfection mentioned in literature results, such as chlorine in the structure of the a.s. and chlorination as disinfection type.

The expert judgment was necessary because, e.g., substances like bromoacetic acid can act both as an acid, but also as an alkylating reagent. Since no literature on the use of bromoacetic acid as a disinfectant and DBP formation could be found and the ECHA dossier proposed the hydrolysis of bromoacetic acid in water to the bromide ion, it was included in the acid category. The reasoning is that the acid group here was considered to have a greater role as a biocidal effect than the releasing bromide ion.

Based on the assessments, an assignment was made into one of three groups: Y=DBP-formation likely; N=DBP-formation not likely, and U=DBP-formation possible. If DBP formation was described in the literature or ECHA dossier and could be additionally proven by chemical structure, or expert judgment, a DBP formation potential was expected (Y); if no evidence for DBP formation could be found in the literature or ECHA dossier, the a.s. was classified as non-DBP forming (N). If possible DBP formation of a.s. categories cannot be excluded due to their chemical structure, but no data was available, the last category was chosen (U).

Results and discussion

Literature review on DBPs

DBPs found in the literature search were discussed according to the number of studies found (see Additional file 1). A characterization of non-halogenated and halogenated DBP classes was carried out. According to the number of findings ($n=860$), among the halogenated DBPs, the group of trihalomethanes (26%) followed by haloacetic acids (18%) > haloacetonitriles (15%) were most frequently mentioned in the literature. The classes oxohalides (2%) and chloramines (1%) were also included in the consideration because they are partially regulated and constituted of only a few representatives. The DBP classes of haloacetamides, haloacetaldehydes and halonitromethanes together also accounted for 13% of the findings but were not discussed further because most of the literature focused only on drinking water, swimming pool water and the findings consisted of many different representative substances compared to the chloramines or oxohalides. Among the non-halogenated DBP classes, nitrosamines were the most frequent, followed by the aldehydes. Besides the mentioned DBP classes, further DBPs could

be found in literature that could not be assigned to any class. In the following, these DBP classes and their occurrence in the environment are explained in more detail based on the literature research.

Halogenated DBPs

Trihalomethanes (THM)

Trihalomethanes, which belong to the first DBP class discovered [5], form the group with the most findings. Trihalomethanes have the molecular formula CHX_3 , where the X represents any halogen (Br, Cl, I). It should be noted that only the four frequently regulated THM—chloroform, dibromochloromethane, bromodichloromethane and bromoform—have the most detections and not all trihalomethanes. The group of these 4 substances is called THM(4) and is often produced in greater quantities than other THM [6]. In addition to many drinking water and swimming pool water regulations [7, 8], THM(4) is also listed in the EU “Guidance on Disinfection By-Products” [2] as well as the GESAMP list for ballast water treatment [9]. Representatives of THM have already been detected in various matrices, including drinking water [10–18], swimming pool water (indoor [19–28], outdoor [29–32], air [33–35]), surface water [36–43], groundwater [39, 44–46], wastewater [47–51], ballast water [52–59] and food [60–68].

Haloacetic acids (HAA)

Haloacetic acids consist of the molecular formula CX_3COOH , where X is replaced by a halogen (Br, Cl, I) or hydrogen. HAA belong to the second largest DBP group, which are also regulated as sum parameters either as HAA(5) or HAA(9) in many drinking water and swimming pool water regulations [7, 8]. HAA(5) includes monochloroacetic acid (MCAA), monobromoacetic acid (MBAA), dichloroacetic acid (DCAA), dibromoacetic acid (DBAA) and trichloroacetic acid (TCAA). Bromochloroacetic acid (BCAA), dibromochloroacetic acid (DBCBA), dichlorobromoacetic acid (DCBAA) and tribromoacetic acid (TBAA) are added to be grouped as HAA(9). HAA have already been detected in drinking water [10, 13–15, 36, 77], swimming pool water [27, 29–31, 75, 78, 79], surface water [40, 56, 80] and food [60–62]. In contrast to THM, HAA are polar, non-volatile DBPs and are formed preferentially under acidic conditions. HAA can often degrade at high temperatures and serve as precursor substances for THM [81]. Within the EU, this group of DBPs is listed with individual representatives in the EU “Guidance on Disinfection By-Products” and the GESAMP list for ballast water treatment [9], but not in the drinking water and swimming pool water

regulations. Bromoacetic acid is also an approved biocidal a.s. in PT 4 (disinfectants for food and feed areas).

Haloacetonitriles (HAN)

Haloacetonitriles are the third largest group of DBP classes, and also here, a varying frequency of findings for the individual representatives can be seen. Haloacetonitriles consist of the basic structure of a nitrile ($R-C\equiv N$), where the R is a carbon that may be substituted with up to three halogens. HAN are formed by chlorinating free amino acids [69], proteinaceous materials, and combined amino acids bound to humic structures [69, 70] and were detected in various matrices of drinking water [10–12, 36, 71–73], swimming pool water [27, 30, 31, 74–76] and food process water [66]. Dichloroacetonitrile and dibromoacetonitrile account for over half of the findings and are regulated in many drinking and swimming pool water regulations [7, 8]. Bromochloroacetonitrile and trichloroacetonitrile have a similar frequency and are also considered in the WHO and EPA guidelines for drinking and swimming pool water [7, 8], but no limit values have been set yet. Bromochloroacetonitrile has been included in the EU “Guidance on Disinfection By-Products” [2] and the GESAMP list for ballast water treatment [9], but no limit values have been set.

Oxohalides

Other regulated halogenated DBPs are inorganic anions such as bromate or the oxohalides chlorite and chlorate. Due to its high carcinogenicity, bromate is regulated in drinking water, swimming pool water and wastewater treatment [7, 82, 83]. Oxohalides have already been found in swimming pool water [84–86], drinking water [87], wastewater [87], seawater [88] and food [89]. They are DBPs that result from disinfection with chlorine-releasing biocides or chlorine dioxide. They are also regulated in drinking and swimming pool water due to their toxic effect on human blood cells [7, 8]. They are also listed in the EU “Guidance on Disinfection By-Products” and the GESAMP list for ballast water treatment [2, 9]. Chlorate could also be formed as a by-product using chlorine, chlorine dioxide or hypochlorite for the disinfection of many fruits and vegetables [89].

Chloramines

Chloramines also form a subgroup of the halogenated DBP class and consist of the three representatives: mono-, di-, and trichloramine and are formed during the chlorination of nitrogenous compounds. The group of chloramines belongs to very volatile DBPs and, similar to trihalomethanes, can spread not only through water, but also mainly through the air as an exposure pathway [90]. Chloramines can be found in various matrices, including

swimming pool water [91], wastewater [92] and drinking water [93]. They are also regulated as individual representatives or sum parameters in swimming pool water and are listed in the EU “Guidance on Disinfection By-Products” [2], and the GESAMP list for ballast water treatment [9].

Non-halogenated DBPs

Note: Non-halogenated DBPs are not considered so far in the EU “Guidance on Disinfection By-Products” [2].

Nitrosamines

Nitrosamines form the largest group of the non-halogenated DBP classes and account for 80 findings out of 299, with NDMA alone accounting for 19. NDMA is considered the most toxic of the nitrosamines and is strictly regulated under drinking water and wastewater directives [7, 8, 83]. Nitrosamines have also been detected in swimming pool water [94, 95], drinking water [96], wastewater [97] and wash water used in food production [66]. Nitrosamines are not yet included in the EU “Guidance on Disinfection By-Products” or the GESAMP list for ballast water treatment [2, 9]. In toxicological studies, NDMA has been shown to cause liver, lung, and renal cancer due to its potential binding to DNA [98].

Aldehydes

Aldehydes form the second largest group with 64 findings of the non-halogenated DBP classes. Aldehydes are known for their high toxicity and carcinogenicity and have been reported in many matrices such as swimming pool water [23], drinking water [10, 14, 99], lake water [100], wastewater [101], ballast water [102], and wash water in food production [103].

Categorization of biocidal a.s.

Categorization

For the categorization, the biocidal a.s. that are under approval or already approved in the EU were first divided into two main groups: halogenated and non-halogenated a.s.. Halogenated a.s. were further assigned into five groups represented by the corresponding reactive molecule: hypochlorite, hypobromite, iodine, monochloramine and chlorine dioxide. Where appropriate, a sub-categorization into organic, inorganic and in situ representatives of a reactive molecule was performed. The chlorine dioxide group shows that the categorization by chemical structure requires compromises. Although chlorine acts as a halogen-releasing biocide, chlorine dioxide reacts mainly as an oxidant [104, 105].

The leading group of non-halogenated a.s. is much more diverse concerning the included chemical structures responsible for the biocidal activity. The highly

Table 3 Categorization of biocidal a.s. of the ECHA database according to their chemical structure

Categories	Subcategories	Biocidal a.s.	DBP formation likely? Y: Yes; N: No; U: Possible	Number of biocidal a.s.
Halogenated a.s.				
Hypochlorite	Organic	Chloramine B (127-52-6), tosylchloramide sodium (Chloramine T, 127-65-1), Symclosene (87-90-1), sodium dichloroisocyanurate dihydrate (51580-86-0), BCDMH (32718-18-6), BCMEH (89415-87-2)	Y	24
	Inorganic	Calcium hypochlorite (7778-54-3), sodium hypochlorite (7681-52-9), Chlorine (7782-50-5)	Y	24
	In-situ	Active chlorine from electrolysis (7782-50-5), hypochlorous acid (7782-50-5), sodium bromide (7726-95-6), sodium N-chlorosulfamate (7782-50-5), ambient water (7782-50-5), magnesium chloride hexahydrate (7782-50-5), sodium chloride (7782-50-5)	Y	12
Hypobromite	Organic	BCDMH (32718-18-6), Reaction products of 5,5-dimethylhydantoin, 5-ethyl-5-methylhydantoin with bromine and chlorine (DCDMH) (118-52-5)	Y	4
	Inorganic	Active bromine is generated from bromine chloride, sodium bromide and calcium hypochlorite, sodium bromide and sodium hypochlorite, and Bromide activated chloramine (BAC) generated from ammonium bromide and sodium hypochlorite	Y	9
	In-situ	Bromide activated chloramine (BAC) (12124-97-9), bromine chloride (7726-95-6), ambient water (7782-50-5), magnesium chloride & potassium chloride (7782-50-5), sodium bromide	Y	9
Iodine		Polyvinylpyrrolidone iodine (25655-41-8), Iodine (7553-56-2)	N/U	6
Monochloramine		Monochloramine (10599-90-3) various from ammonium carbamate, ammonium chloride, ammonium hydroxide, ammonium sulfate, ammonia with chlorine source	Y	10
Chlorine dioxide		Chlorine dioxide (10049-04-4) generated from sodium chlorite by electrolysis or the presence of sodium chlorate and hydrogen peroxide and strong acid or sodium chlorite and sodium bisulfate or sodium chlorite by acidification or sodium persulfate by acidification or sodium chlorite by oxidation, Chlorine dioxide generated from tetrachloroacoxide complex (TCDO, 9204776-2) by acidification (92047-76-2)	Y	30
Non-halogenated a.s.				
Ozone		Ozone generated from oxygen (10028-15-6)	Y	4
Hydrogen peroxide	In-situ	Hydrogen peroxide (7722-84-1), Peracetic acid (79-21-0) from 1,3-diacetyloxypropan-2-yl acetate with hydrogen peroxide (79-21-0), tetraacetyloxyethylenediamine (TAED) with hydrogen peroxide (79-21-0), 6-(phthalimido)peroxyhexanoic acid (PAP) (128275-31-0), tetraacetyloxyethylenediamine and hydrogen peroxide, Hydrogen peroxide from peracetic acid and peroxyoctanoic acid, MMPP (84,665-66-7), sodium percarbonate (7722-84-1), Performic acid generated from formic acid and hydrogen peroxide	Y	23
	Organic	Performic acid (107-32-4), Peroxyoctanoic acid (33734-57-5), Magnesium monoperoxyphthalate hexahydrate (MMPP) (84665-66-7), Peracetic acid (79-21-0)	Y	9
	Inorganic	Disodium peroxodisulphate/Sodium persulphate (7775-27-1), Calcium dihydroxide (1305-62-0), Calcium magnesium tetrahydroxide (39445-23-3), Pentapotassium bis(peroxymonosulphate) bis(sulphate) (70693-62-8), Dialuminium chloride pentahydroxide (12042-91-0)	Y	10
Aldehyde	Organic	Glutaral (Glutaraldehyde) (111-30-8), Glyoxal (107-22-2), Acrolein (107-02-8), Formaldehyde (50-00-0)	U	9
	In-situ	α,α'-trimethyl-1,3,5-triazine-1,3,5,2H,4H,6H)-trithanol (HHT) (25254-50-6), Reaction products of paraformaldehyde and 2-hydroxypropylamine (ratio 1:1) and ratio (3:2) (25254-50-6), Bronopol (52-51-7), (ethylenedioxy)dimethanol (Reaction products of ethylene glycol with paraformaldehyde (EGForm)) (3586-55-8), Methenamine 3-chloroallylochloride (CTAC) (4080-31-3), Tetrahydro-1,3,4,6-tetraakis(hydroxymethyl)imidazo[4,5-d]imidazole-2,5 (1H,3H)-dione (TMAD) (5395-50-6)	U	17
MITC		Methylene dithiocyanate (1,6317-18-6)	U	1
Alcohols		2-Phenoxyethanol (122-99-6), Ethanol (64-17-5), Propan-2-ol (67-63-0), Propan-1-ol (71-23-8), DCP (3380-30-1), Chlorocresol (59-50-7), Biphenyl-2-ol (90-43-7), Sodium 2-biphenylate (132-27-4), Chlorofene (120-32-1)	N	22
Acids		Nonanoic acid (112-05-0), Octanoic acid (124-07-2), Decanoic acid (33-48-5), L-(+)-lactic acid (79-33-4), Glycolic acid (79-14-1), D-gluconic acid (18472-51-0), Formic acid (64-18-6), Benzoic acid (65-85-0), Salicylic acid (69-72-7), Citric acid (77-92-9), Glucoprotamin (164907-72-6), Hydrochloric acid, Bromoacetic acid (79-08-3)	N	27

Table 3 (continued)

Categories	Subcategories	Biocidal a.s.	DBP formation likely? Y: Yes; N: No; U: Possible	Number of biocidal a.s.
Inorganic		Calcium oxide (1305-78-8), Calcium magnesium oxide (37247-91-9), Copper (7440-50-8), Copper sulphate pentahydrate (7758-99-8), Sulphur dioxide (7446-09-5), Reaction products of aluminum trihydroxide and hydrochloric acid and aluminum and water,	U	13
		BIT (2634-33-5), OIT (26530-20-1), MIT (2682-20-4), CMIT (55965-84-9), DCOIT (64359-81-5), TCMTB (21564-17-0)	N	13
Isothiazolinone		ADBAC/BKC (C12-16) (68424-85-1), ADBAC (C12-18) (68391-01-5), (ADEBAC (C12-C14)) (85409-23-0/85409-22-9), Amines-C10-16-alkyldimethyl, N-oxides (70592-80-2), DDAC (C8-C10) (68424-95-3), DDAC (7173-51-5), Ampholyt 20 (139734-65-9),	N	56
	QACs	Bardap 26 (94667-33-1), Dodecylguanidine monohydrochloride (13590-97-1), PQ Polymer (25988-97-0), Quaternary ammonium compounds, benzyl-C12-18-alkyldimethyl, salts with 1,2-benzisothiazol-3(2H)-one 1,1-dioxide (68989-01-5), Reaction mass of N,N-didecyl-N-(2-hydroxyethyl)-N-methylammonium propionate and N,N-didecyl-N-(2-(2-hydroxyethoxy)ethyl)-N-methylammonium propionate and N,N-didecyl-N-(2-(2-hydroxyethoxy)ethyl)-N-methyl ammonium propionate, polyhexamethylene biguanide hydrochloride with a mean number-average molecular weight (Mn) of 1415 and a mean polydispersity (PD) of 4.7 (PHMB(1415:4.7)), (1802181-67-4),		
Silver		Silver (7440-22-4), Silver zeolite 130328-20-0, Silver copper zeolite 130328-19-7, Silver chloride, Silver sodium hydrogen zirconium phosphate (265647-11-8), Silver borophosphate glass (308069-39-8), Silver nitrate (7761-88-8), Silver phosphate glass (308069-39-8), Silver zinc zeolite (130328-20-0) Silver nanomaterial (7440-22-4), titaniumdioxide with silver (79-21-0)	N	21
	Others	Sodium dimethyldithiocarbamate (128-04-1), pyriithione zinc (13463-41-7), PHMB (27083-27-8), TCMTB (21564-17-0), Diamine (2372-82-9), PDI (27083-27-8), Pyridine-2-thiol 1-oxide (3811-73-2), Cyanamide (420-04-2), THPS (55566-30-8), Chlorcresol (59-50-7), Ethylen oxide (75-21-8), meta sodium (137-42-8), methylene dithiocyanate (1:6317-18-6), dodecylguanidine monohydrochloride (13590-97-1), Willaertia subsp. Magna, C2c.Maky, Bacillus amyloliquefaciens strain 15B06, Free radicals generated in situ from ambient air or water, N-(3-aminopropyl)-N-dodecylpropane-1,3-diamine (2372-82-9), chlorhexidine digluconate (18472-51-0), Monolinuron (1746-81-2), 1-[2-(allyloxy)-2-(2,4-dichlorophenyl)ethyl]-1H-imidazole (35554-44-0)	U	29

reactive oxidizing substances like ozone and peroxides and seven other groups with specific chemical structures accounting for the biocidal reactivity are included. In the last group, called “others”, all the a.s. not fitting into any other of the groups are included. The DBP formation potential of the non-halogenated a.s. differs depending on the reactive molecule. It is estimated to be fairly high for ozone and peroxides and moderate to low for the other groups of non-halogenated a.s. If necessary, some a.s. were assigned to more than one group (e.g., BCDMH). The categorization is summarized in Table 3.

Halogen-based biocides

Halogen-releasing biocides

All halogen-releasing biocides have the same mode of action: they serve as a source of chlorine, bromine, or both. After the release of the halogen, the hypohalogenic acid of the respective halogen (HOCl, HOBr or HOI) is formed in the presence of water (Fig. 2). Hypohalogenic acids (HOCl, HOBr, HOI) and their hypohalogenites (OCl^- , OBr^- , OI^-) have a high oxidation potential and, thus, the possibility to inactivate microorganisms. Chlorine is the most widely used disinfectant for controlling harmful microorganisms due to its high efficiency, low cost and residual disinfection effect. Chlorine can also form halogenated DBPs such as aldehydes [106] or nitrosamines [96]. Chlorination of water is associated with an increased health risk of bladder cancer [107] and the US EPA Stage 2 guideline assumes a lifetime cancer risk from chlorinated water of one per thousand persons [108]. Bromine-releasing biocides are often generated by bromine-containing substances such as BCDMH or by using a strong oxidizer, which causes bromide to be oxidized to hypobromite [86]. Bromine-based disinfections can only be used without light; otherwise, the remaining bromine is degraded. An advantage of bromine-based biocides in terms of usability is that they degrade more slowly than hypochlorous acid at high temperatures due to their lower vapor pressure, which is why they are specifically used in higher temperatures such as spas [6]. Chlorine cyanurates can release chlorine slower by releasing chlorine only after the existing chlorine has been consumed or diluted. A major advantage concerning their scope of application is the low degradation rates

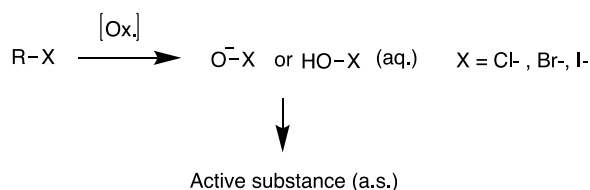


Fig. 2 Reaction mechanism of chlorine-, bromine- and iodine-releasing biocides in an aqueous matrix

of chlorinated cyanurates compared to hypohalogenated acids [86]. All classes of DBP were detected in studies on the DBP formation of HOCl and HOBr [109]. For the iodine-based biocides such as polyvinylpyrrolidone iodine (25254-50-6) and iodine (7553-56-2), no DBPs are known to occur during application. Nevertheless, in the presence of oxidizing agents, iodide can be oxidized to hypoiodous acid and form I-DBPs [110].

Chlorine dioxide

Chlorine dioxide is a yellowish gas often produced in situ at the point of use. It is not considered a chlorine disinfectant, as it acts differently without producing residual chlorine through conversion to chlorite and chlorate ions that remain in the solution [111]. In water, it remains a dissolved gas and does not hydrolyze or form hypochlorous acid. With the reaction of electron-rich molecules, it can form chlorite via a radical mechanism, which can decompose to chloride or chlorates. Chlorine dioxide is effective over a wide pH range, unlike chloramines or hypochlorite/hypobromite. The amount of chlorite and chlorate formed increases with higher concentrations and times of action. A direct THM formation by chlorine dioxide could not yet be determined. Nevertheless, in studies in the presence of a matrix, halogenated DBPs could be detected [112]. Apart from the formation of chlorates and chlorites, further studies are needed on forming direct DBPs when used in the food industry [113].

Inorganic chloramines

Inorganic chloramines consist mainly of three representatives: monochloramine (NH_2Cl), dichloramine (NHCl_2) and trichloramine (NCl_3) (Fig. 3). Chloramines are often produced by hypochlorous acid (HOCl) and a nitrogenous source such as ammonium. The ratio of chlorine to nitrogen and the pH-value is decisive for the amount and the species of chloramines formed. At neutral to alkaline pH, monochloramine is the dominant species. Chloramines have a lower oxidation potential than hypohalogenic acids and are relevant due to their high longevity [114]. Dichloramines (NHCl_2) and trichloramine (NCl_3) are unstable compounds, so only monochloramine is

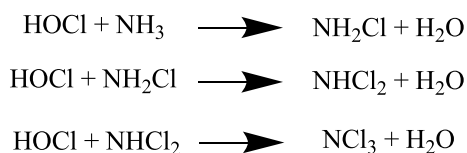


Fig. 3 Formation of chloramines based on the reaction of ammonia with hypochlorite

produced and used in practice. Disinfection of aqueous matrices by chloramines can lead to the formation of THMs, HAAs, N-DBPs, chloral hydrates, cyanogen compounds, nitrates, nitrites, organic chloramines and haloketones [115, 116]. The formation of nitrosamines during chloramination is one of the main disadvantages of this disinfection method [117, 118].

Non-halogen-based biocides

Ozone

Ozone has a very high oxidation potential and thus acts as a strong oxidizing agent [119]. Ozone can be produced by oxygen using UV light and electrical discharge (Fig. 4). Nowadays, ozone is only generated through discharge. Ozone can react as both a nucleophile and an electrophile. Ozone has no residual disinfection effect like chlorine and has the disadvantage of oxidizing bromide to bromate [120]. Ozone is often used in low concentrations for trace contaminant elimination and as a disinfectant in drinking water treatment. Even though ozone does not produce halogenated DBPs, downstream ozonation increases THM and HAA [121]. Carboxylic acids could be detected in comparison in six times higher concentration than other DBP classes after ozonation of drinking water [122].

Peroxide-group-based biocides

Among the peroxide-based biocides, hydrogen peroxide is the most relied upon and has the most applications [123]. In general, they contain a peroxy group ($-O-O-$) in their structure. Hydrogen peroxide and other hydroperoxide-based biocides develop their oxidizing effect using hydroxyl radicals (OH) and have a greater oxidizing potential than chlorine or chlorine dioxide. Despite this, high amounts of peroxides are required for disinfection compared to halogenated biocides. As with chlorine dioxide, although no direct formation of halogenated DBPs was observed, halogenated DBPs were indeed detected in the presence of the matrix [68, 124]. In a study on washing lettuce with peracetic acid, halogenated by-products were also found [68]. An advantage of peroxide-based biocides is their decomposition into the harmless degradation products of water and oxygen, which are not dangerous. An advantage of organic peroxides is that they produce hydrogen peroxide only in

contact with water and therefore do not produce residues or gasses. Peroxides are often used with other disinfection techniques such as silver, ozone, QACs or UV.

Aldehydes and formaldehyde releasers

The class of aldehydes contains the characteristic terminal carbonyl group (CHO). They are also formed as endogenous intermediates in biological metabolism and occur in the environment. So far, no studies on the formation of DBPs by aldehydes are known, and the formation potential is estimated to be low due to their chemical reactivity. They are highly effective broad-spectrum disinfectants and can be used in gaseous and volatile forms [125]. In addition, they are effective at high organic loads and are non-corrosive. The most prominent two representatives, formaldehyde and glutaraldehyde, are also volatile and toxic to humans. Aldehydes also belong to the DBPs, which are formed when oxidizing biocides such as ozone are used. Aldehydes can denature proteins and thus damage them [126]. Their mode of action has not been fully elucidated but is thought to consist of cross-linking proteins, DNA or RNA. Formaldehyde-releasing biocides can also have carcinogenic effects and have been declared as such since 2015 on the recommendation of the ECHA at a total concentration higher than 0.1% of possible formable formaldehyde [127].

Quaternary ammonium compounds (QACs)

Quaternary ammonium compounds all have the following structure: $NR_4^+X^-$ (R: organic residue; X: anion, e.g., chloride, hydroxide, bromide). Their mode of action is due to a cytoplasmic effect leading to cell death. It has been shown that they are preferentially found in wastewater and sediments, where they are generally largely biodegraded [128]. Despite degradability, they can also be found in surface water [129], soils and sediment [130, 131]. Besides the direct toxicity of QACs, they can form nitrosamines [132], primarily by reaction with chloramines. In a study on the disinfection of polycarbonate surfaces with diluted disinfectant solutions of QACs, chemical damage to the surface due to a change in the molecular structure was confirmed [133]. A direct formation of DBPs during using QACs is not known in the literature.

Isothiazolinones biocides

Isothiazolinones consist of a five-membered ring based on the structure of cyclopentane. The group of isothiazolinones has been banned by the EU in many applications due to the potential toxicity to cells and possible carcinogenicity hazard to humans and is expected to be replaced in the future [134]. Stability studies showed that

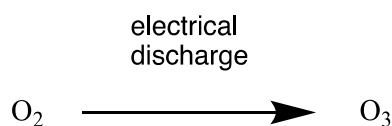


Fig. 4 General mechanism for the generation of ozone

the degradation of isothiazolinones has greater environmental relevance than the direct formation of DBPs. In the presence of an aqueous environment and nucleophiles, ring opening occurs, which can lead to a variety of transformation products (CaCl₂, loss of Cl and S, N-methylmalonamic acid, malonamic, malonic, acetic, and formic acids, 5-chloro-2-methyl-4-isothiazolin-1-oxide, N-methylglyoxylamide, ethylene glycol, and urea) but also to mineralization (CO₂) [135]. It is believed that for some isothiazolinones, the degradation products have higher toxicity than the biocide. No direct DBP formation by isothiazolinones has been studied or found in the literature.

Alcohol- and acid-based biocides

Alcohols all have in common that they contain a hydroxy group (-OH) in their structure; alcohol-based disinfectants have a wide range of applications, such as hand disinfection, surface disinfection, food disinfection and many more [136, 137]. Carboxylic acids have the characteristic carboxyl group (-COOH) and can exist in protonated or deprotonated forms. Due to their high rapid antimicrobial activity, ease of application and low cost, both alcohols and acids are very popular [138]. The formation of DBPs is also not known in the literature to occur using alcohols and acids as disinfectants.

Silver-, inorganic-based and other biocides

Many biocidal active substances, such as silver-containing biocides, are only represented with a few a.s./PT-combinations in the ECHA database. Most are not persistent, degraded to non-toxic products or partially mineralized [8]. For example, magnesium-based biocides (calcium magnesium oxide) are converted into their respective ionic components, which are part of the

existing chemical cycles [139, 140]. In terms of silver-based biocides, the active species is often a silver cation (Ag⁺) which is released and is not suspected of forming DBPs [141]. Even though the mechanisms behind disinfection by silver ions are not fully understood, it is assumed that they do not produce toxic DBPs [142]. Biocides that have a high chemical reactivity and are categorized in “others” as well are, e.g., sulfur dioxide, ethylene oxide and free radicals (generated in situ from ambient air or water). Those a.s. categorized in the category “others” show various reactivities, and their DBP formation potential would have to be investigated individually. In the ECHA dossiers on biocides in the category “others”, studies on behavior in different compartments such as air, water or soil are included, but the focus here is not on DBP formation and in some cases, data are very old or incomplete. No literature studies on these a.s. were found during our search.

Comparison of findings from literature to ECHA database

DBPs found in the literature are summarized within the categories of reactive molecules in Fig. 5 and can also be seen in Table 2. For halogenated DBPs, $n=860$ entries, and for non-halogenated DBPs, $n=294$ entries were considered. In literature, the largest proportion of DBPs can be attributed to hypochlorite-based biocides, with more than 55% [$n=1154$] making them responsible for the largest fraction of DBPs detected. It can be seen that a large part of the other reactive molecules still needs to be investigated in more detail concerning their potential to form DBPs. Therefore, the share of reactive molecules does not necessarily relate to the potency of DBP formation of the respective reactive molecule, but also relates to study design preferences in research.

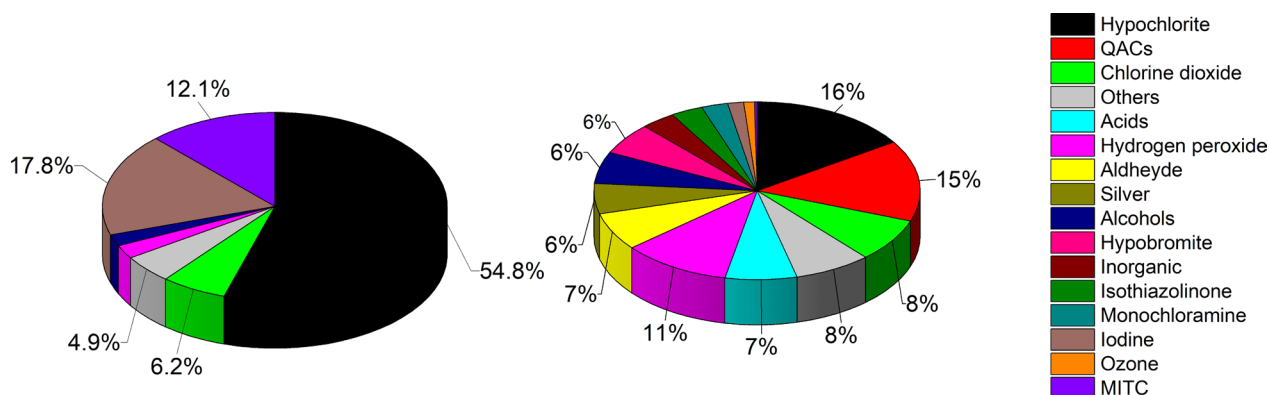


Fig. 5 Fraction of categories of reactive molecules studied in DBP literature ($n=1154$ findings, left) and the fraction of those categories in the ECHA database ($n=382$ active substance/PT-combinations)

Looking at the shares of a.s. in the ECHA database, hypochlorite alone as a reactive molecule account for 16% of the active substance/PT-combinations [$n=382$], being the reactive molecule with the most a.s. in all investigated PTs. Summing the proportions of the potentially non-DBP-forming biocide categories (QACs, acids, alcohols, isothiazolinones, aldehydes, MITC, iodine-, silver-, inorganic-, other-biocides), the result is 46% of all a.s. considered in the relevant PTs. However, it has to be kept in mind that the number of a.s. that are approved or under approval does not necessarily reflect the highest amounts of a.s. used on the market.

Overall, it can be shown that for most of the biocidal a.s. in the ECHA database, information on their DBP formation potential is not yet available in literature. For some major groups (hypochlorite-based biocides, monochloramines, chlorine dioxide), many studies on DBP formation are already available. But even if these groups of biocidal a.s. are represented in the literature, it does not mean that all PTs are also represented regarding their DBP formation.

Application matrices: aqueous-based vs. non-aqueous-based applications

The amount of water present during disinfection use is another relevant factor for DBP formation, and common disinfection uses can be divided into two cases. In the first case, the disinfection occurs in an aqueous solution. All substances reacting with each other or influencing the reaction process are dissolved in water over the entire disinfection use. This is, for example, the case in drinking water (PT5), preservatives for liquid-cooling and processing systems (PT11) and swimming pool water (PT2). In the second case, the amount of water is much more limited in the disinfection of surfaces (PT2) or the food industry (PT4). These disinfection uses will usually not occur without water, as residual water will be present on the treated surface and the a.s. formulation will mainly include water. However, the reacting substances responsible for DBP formation will not necessarily be in solution and thus might be unavailable for reaction over the entire disinfection use. The DBP formation may be influenced by the solubility of the different components of the matrix, both the organic components being the source for DBPs and inorganic components (e.g., bromide or iodide) influencing the reaction process [143]. In addition to its function as a solvent, water also affects the reactivity of numerous functional groups by protonating or deprotonating them. These effects may differ in a mixture with limited water amount. Consequently,

compared to the same reaction mixture in an aqueous solution, alternative reaction may occur in a non-aqueous setting, leading to divergent results concerning the resulting DBPs. No studies investigating DBP formation under conditions of surface disinfection could be identified in the literature [3]. In a recently published review of the use of ozone for disinfection during the Covid crisis, it was found that masks could become damaged by repeated disinfection with ozone and that the polymer bonds could be degraded. Also, ozone is suspected to promote oxidative destruction of natural rubber or plastic surfaces and unsaturated organic compounds [144, 145]. The authors did not perform further investigations on DBPs. In addition, all literature studies were assessed regarding the matrices used in the experiments to match literature data with the possible uses. If possible, the investigated matrices were assigned to application types (Additional file 3: Table S2). These application types were assigned to the product types PT to compare registrations in the ECHA database and the generally studied PTs in our literature search. Laboratory studies, which used artificial matrices as a basis, were not considered in this compilation since they cannot be related to realistic use scenarios of PTs.

It can be seen that only a very specific part of the possible uses is covered in the literature (Fig. 6, bottom). Drinking water (PT 5) is one of the most well-studied matrices due to the diversity of different studies concerning DBP formation, which is why many field studies can already be referred to here and legal limit values have already been established [146]. In addition, PT 2 plays a significant role and is also well-studied in terms of DBPs, with a proportion of almost 46% of all findings. However, these studies focus on swimming pool water and some other types of water disinfection. Important to mention is that PT 2 also includes different application types, such as surface disinfection, textile disinfection, aquariums, air conditioning systems, walls, floors and air, which still need to be investigated for DBPs in the literature (Fig. 6, bottom) Another product type accounting for 18% of all a.s./PT-combinations in the ECHA database and, to a minimal extent, also present in the literature search is PT 4, which covers disinfection in the food and feed sector. Studies such as that of Cardador et al. [60, 64, 147] and Bao Loan et al. [62] have investigated washing solutions and the food treated with chlorine that is used in the disinfection processes (cheese [60, 61, 147], vegetables [148]) juices and soft drinks [149], meat, fish).

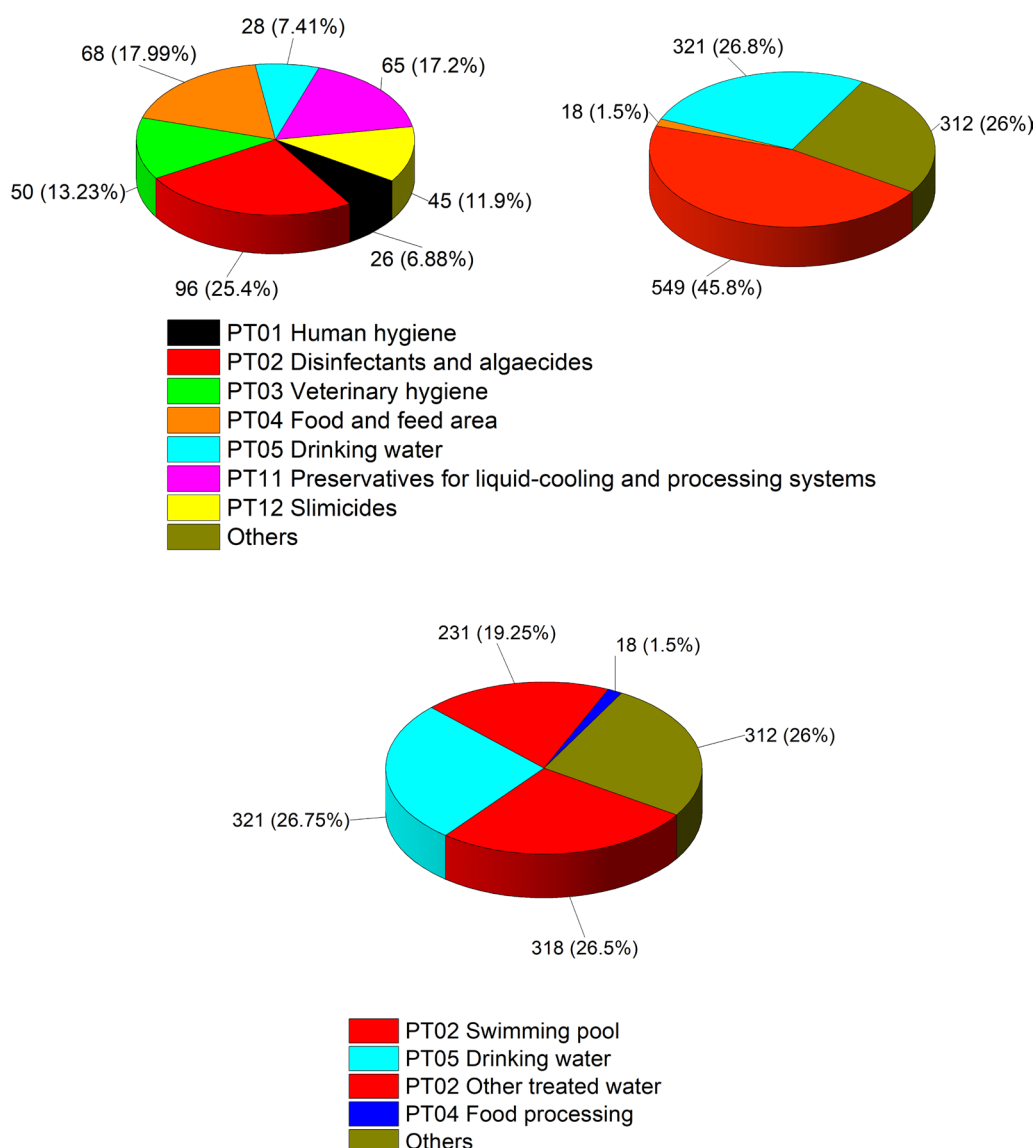


Fig. 6 Number of biocidal a.s. per PT in the ECHA database (left; access November 2022) and the number of studies investigating the PTs (right) and detailed investigated application types in the literature (bottom)

It should be noted, however, that only aqueous matrices were investigated for DBP formation and not solids or surfaces. Disinfectants or disinfecting solutions are often used in the food industry for sanitizing, washing, blanching, cooling and transporting the final product. It would be important to conduct further studies in all PTs with little or no water-containing matrices, as the conditions (contact time, temperature, concentration, pH, DOC/COD load, etc.) defined as key parameters in the BPR guidance can be quite different. An example is the disinfection of post-harvest foodstuffs in washing plants where contact times of 1–5 min are achieved. A review article on the application of silver-based nanomaterials showed that in contrast to classical disinfection, such as

chlorine, additional parameters, such as the morphology of the nanosilver and the scaffold material, must be taken into account [142]. In the disinfection of drinking water/swimming pool water, chlorine remains in the water for several hours [150]. Several studies have shown that the use of disinfectants can have an impact on essential nutrient components such as vitamins and secondary plant compounds [151]. The authors did not do any research on the possible formation of DBPs. A recent review article on the use of ozone also reported negative changes in color, odor, firmness, weight, and texture in fruits and vegetables [152]. Despite this, there is a high need for research in the study of processing fresh-cut vegetables using biocides. The insufficient availability of

data regarding DBP residues in fresh-cut products poses a significant challenge when it comes to a comprehensive assessment of the associated food safety risk [153].

PT 1 (Human hygiene) and 3 (Veterinary hygiene) have yet to be investigated concerning DBP formation and thus represent a major unexplored field of research. An example is using disinfectants in the veterinary area, e.g., potable water supplies, medical equipment disinfection, rubber mannequin, syringes, needles, blood- or body-fluid spill, environmental surfaces, laundry, dental therapy and medical waste [154]. In addition, a.s. are used in human hygiene, e.g., hand or scalp disinfection, and body and oral hygiene. Many of these applications have mainly organic matrices, such as amino acids in the blood plasma. DBP formation thus does not seem unlikely. Among the results from the literature search, several studies on essential amino acids have shown that some can react with hypochlorite. In past studies, a wide variety of DBPs have already been demonstrated in the chlorination of peptides in the water of the seven essential amino acids such as leucine [106, 155, 156], isoleucine [106, 156], histidine [157], lysine [158], methionine [159], threonine [160, 161], phenylalanine [106, 156], tryptophan, and valine [106, 156, 158].

The analysis of review articles from 2019 to 2023 showed that they mainly were related to aqueous applications such as (such as (drinking water [162–164], wastewater [165, 166], washing water, fruit vegetables or health effects [163, 167], advanced oxidation processes [168–171]). The results of the search in the review articles did not reveal any further findings on DBP formation in other application types (surface, steel disinfection, etc.) or by non-oxidizing biocides tested concerning DBPs.

Consideration of use volumes of the active substances on DBP formation volumes

To assess potential risks by DBPs, information on their amounts potentially released to the environment would be needed. The preliminary information necessary to evaluate would be the total use amount of the respective DBP-forming biocidal a.s. This data needs to include the volumes of biocidal a.s. used in each particular PT or even better, a specific use, as both the number of DBPs formed and the amount entering the environment will, besides the applied volume, depend on the PT or the particular use. However, this data is not available. COWI performed the best comprehensive data compilation for the European market on behalf of the European Commission [5]. The industry submitted the information within the notification procedure following the entry into force of the Biocidal Product Directive 98/8/EC. The evaluated data originate from the time period 1998–2001; therefore, conclusions for the present situation must be

regarded with care. Nevertheless, some results are consistent with the current situation or are at least expected to be reasonably similar.

The information misses important details, as only the overall tonnage per PT is given, without detailed volumes of biocidal a.s. used within particular PTs, due to confidentiality reasons. The total annual volume of sales of biocidal a.s. (production and imports) in the EU was estimated to be about 400,000 tones. The majority of nearly 90% of those amounts were produced or imported in PTs 1–5, 11 and 12. Most relevant was the production/import in PT2, accounting for 50.4% of the volume, followed by PT 5 and 11, accounting for >12% each. The actual amount is expected to be higher due to the entry of eastern European countries into the EU in 2004 and 2007.

Although generally no volumes for single substances were given, the sum of used sodium hypochlorite, chlorine and hydrogen peroxide, the three substances with the highest production volumes, was stated to be approximately 54% across all PTs. As the a.s. are used in the relevant PTs 1–5 and 11–12, it can be assumed that about half of the amounts of biocidal a.s. produced or imported are proven to generate DBPs potentially. For well-founded decisions on the relevance of a risk assessment for DBPs, a much more detailed data source on the use of biocidal active substances would be necessary.

Current approaches and challenges to ERA for DBPs in the regulation

The current BPR “Guidance on Disinfection By-Products” [2] provides a general approach for the environmental risk assessment of DBPs. The risk assessment includes three steps, which are required, to underpin the absence of unacceptable effects:

- An initial worst-case risk assessment for a set of known marker DBPs, using aPEC (predicted environmental concentration)/PNEC (predicted no effect concentration) approach assuming 100% conversion of the biocidal active substance;
- Chemical assessments in which (changes in) group parameters (e.g., AOX (adsorbable organic halogens)) are determined;
- A refined risk assessment for known marker DBPs, appended with a whole effluent testing (WET)-approach to cover unknown DBPs.

The current BPR guidance correctly describes the potential complexity when dealing with DBPs, but the proposed approach is challenging and although it needs much effort from authorities and industry parties, it is questionable whether DBPs are considered adequately. Furthermore, due to the generic character

Table 4 Discussion of the 3-stepped approach of the BPR “Guidance on Disinfection By-Products” (ECHA, 2017 [2])

Concepts	Step 1 “Worst-case”-calculation (PEC/PNEC)	Step 2 Group parameter approach (AOX, TOC)	Step 3 Whole effluent testing (WET)
Approach	100% conversion of a.s. into known “marker” DBPs	Formation of DBPs correlates with the increase of group parameters (TOC, AOX)	Whole effluent testing to cover known and unknown DBPs
Pros	<ul style="list-style-type: none"> • No complicated choice of relevant DBPs • Relatively simple calculation • Consideration of the “worst-case scenario” for known DBPs 	<ul style="list-style-type: none"> • Not expensive & elaborate as no single substance analysis is necessary 	<ul style="list-style-type: none"> • Consideration of unknown DBPs • Consideration of mixture toxicity • Existing established procedures for aqueous matrices ([172, 173])
Cons	<ul style="list-style-type: none"> • Suitable only for known DBPs, unknown DBPs not considered • “Marker” DBPs maybe represent only a small fraction • Limited monitoring data (bias) lead to bias of DBPs considered as marker DBPs • High number of DBPs (PEC/PNEC) compared to a group parameter such as AOX • Own risk assessment (effect data, exposure assessment) for each DBP may be necessary • Overestimation of exposure due to 100% conversion to one DBP (“which is not reasonable for most/some cases) 	<ul style="list-style-type: none"> • Unclear if group parameters correlate with DBP formation (identity, number) quantitatively • Trigger threshold unclear (depending on PTs, matrices, etc.) • Group parameters not directly correlated with environmental risk, unclear how to incorporate in ERA 	<ul style="list-style-type: none"> • No specific determination of ecotoxicity of single DBPs • Correlation of ecotoxicity with single DBPs difficult • DBPs responsible for ecotoxicity remain unidentified • Representativeness of the samples is questionable, high number of measurements necessary • Only established for aqueous samples • Selection of harmonized bioassays necessary • Not established for continuous processes • Unclear how it relates to exposure assessment
Conclusions	<ul style="list-style-type: none"> • High workload for risk assessments for all marker DBPs and PTs and application types, considering the key parameters • Limited explanatory power • Applicability of the guidance and experimental suggestions for implementation in non-aqueous PT (PTs 1, 2, 3, 4) is missing (requires further guidance) • Focus of the guidance is only on halogenated DBPs, with no consideration of non-halogenated DBPs • No detailed recommendations and guidance in the case of conflicting data on the different steps • No guidance on how to perform a risk assessment for chemicals, which are a.s. and DBPs simultaneously 		

* Steps need not necessarily be performed in consecutive order, but should all be considered for a complete environmental risk assessment

of the existing guidance and the lack of detailed instructions and requirements, a consistent interpretation by all competent authorities is questionable (Table 4). Consequently, a harmonized scientific-based ERA of DBPs is currently not possible, which may also hamper the mutual recognition of product authorization between member states.

To offer a practical approach to simplifying the current three-step process, based on our findings, a grouping of the a.s. and an allocation of DBPs to these groups can be discussed. This allocation of DBPs is based on the reactive molecule related to an a.s. (see Table 3) and independent of the PT, which facilitates the DBP allocation by disregarding the complexity of application types within the PTs. This approach could help to simplify the assessment of disinfectants/preservatives and their DBP formation potential. Moreover, the approach can be combined with the current guidance, i.e., as a supplement to the initial worst-case approach in the first step.

As an example, for the category of hydrogen peroxide, some a.s. of the 42 a.s. associated with this category could be initially tested for their DBP formation potential. In

the next step, if DBPs are formed, these DBPs would be considered as relevant DBPs/DBP classes for all future a.s. approvals in this a.s. category. At the moment, without this grouping approach, all hydrogen peroxides-based a.s. would need to be tested individually regarding formed DBPs, i.e., for each a.s. the potentially formed DBPs have to be identified, and marker DBPs defined. An exemplary schematic diagram of the proposed grouping approach in comparison to the current approach is shown in Fig. 7.

However, it has to be kept in mind that it was not possible until now to define a worst-case scenario for DBP formation as this is a complex reaction system influenced by various parameters. The definition of worst-case applications would thus not be possible at the moment. Similarly, the effort for biocides grouped in the category “Others” remains the same. As DBP formation and the quantity depend on PT/application type, consideration of DBP risks via a grouping of a.s. may not represent the environmental worst-case. Also, the initial selection of a.s. for DBP formation determination would have to be done as representative as possible.

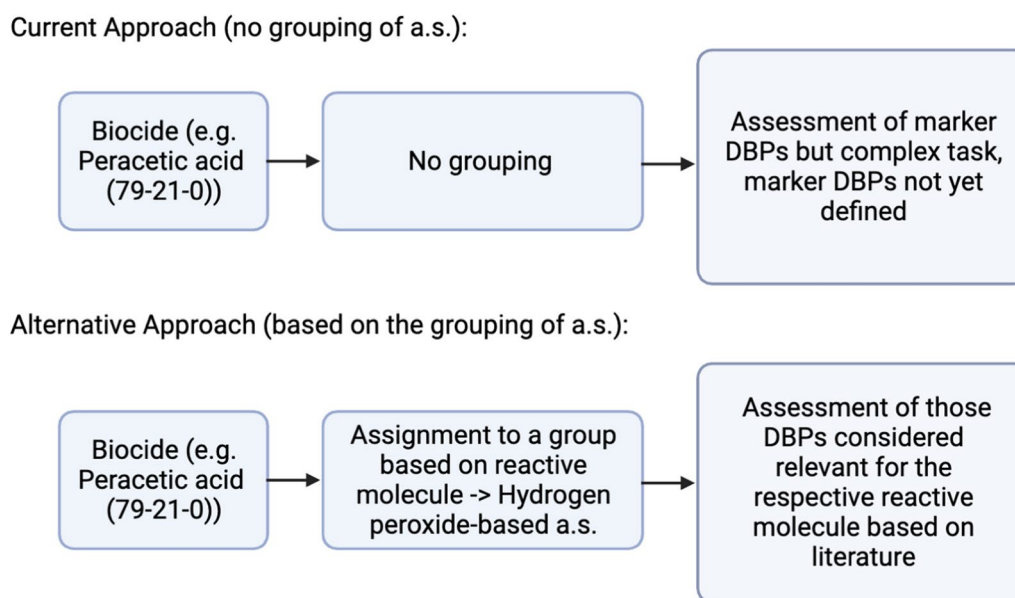


Fig. 7 Simplified schematic workflow diagram between alternative approach by grouping a.s. and the current approach in the EU Biocide Guidance

Conclusion

The literature, as summarized here, shows that there is still a lack of knowledge on DBPs and their impact on the environment. A strict differentiation between the definition of DBPs and transformation products is necessary, this should be included in the EU “Guidance on Disinfection By-Products”. Based on the results of the present study DBPs should be considered as by-products that are formed during the use phase.

Based on the types of applications, DBP classes and biocidal a.s. used, it can also be seen that the focus of the literature to date has been on the disinfection of aqueous matrices and applications such as drinking water, wastewater, swimming pool water, or process water in the food industry. For this reason, environmental conditions defined as key parameters in the current Guidance on Disinfection By-Products are based primarily on aqueous application types. In the future, other major application types, such as surface disinfections used to disinfect and sanitize surfaces such as floors, furniture, washrooms, tiles, walls, instruments, and clothes, should also be investigated regarding the DBP formation potential and environmental risk. These non-aqueous application types could have unknown DBPs or a different distribution of DBP classes formed during disinfection, resulting in the need to modify or to extend the prioritization of Guidance on Disinfection By-Products.

Also, there is a strong bias in literature towards biocidal a.s. acting through chlorination compared to other reactive molecules. The proposed categorization of biocidal

a.s. concerning their DBP formation potential could lead to considerable relief in terms of future ERA as many biocidal a.s. might not require a DBP assessment due to their missing formation potential. From the grouping of a.s., whether an a.s. is likely or unlikely to be classified as a DBP former, it follows that more stringent or extended criteria (e.g., by exact determination of the mode of action, oxidation potential, and halogenation potential) may be necessary for classification as a DBP former.

Furthermore, more ecotoxicity studies are required to identify emerging DBP classes of concern for the environment and sort out irrelevant DBPs. To determine the ecotoxicity as well as the fate and distribution of DBPs and a.s., experiences from computational simulation studies could also be used as a first approach. In addition, updated data on the production quantities and consumption of a.s., capable of forming DBP, would be necessary.

The idea of a grouping of a.s. with regard to DBP formation potential is challenging, and more research was identified that needs to be addressed before the guidance can be improved. Several findings from this research could contribute to this discussion and improvement. Until then, a pragmatic approach taking into account the DBPs formation potential of the active substances and the identified knowledge gaps need to be established for the environmental risk assessment of DBPs in the EU.

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s12302-023-00781-w>.

Additional file 1. Summary of the DBP literature search.

Additional file 2. Table S1. Number of publications considering the respective DBPs. **Table S2.** Overview of the number of different DBPs by product types (PTs) and investigated matrix.

Additional file 3. Entries from the ECHA database.

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Author contributions

MU: conceptualization, investigation, methodology, formal analysis, writing—original draft, writing—review and editing. MH: investigation, data curation, writing—original draft, writing—review and editing. SH: investigation, data curation, writing—original draft, writing—review and editing. SW: investigation, data curation, writing—original draft, writing—review and editing. AK-B: investigation, data curation, writing—original draft, writing—review and editing. VL: resources, supervision, conceptualization. TW: resources, supervision.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article and its supplementary information files. The authors declare that data supporting the findings of this study are available within the references given in the article and its supplementary information files.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors have no competing interests to declare that are relevant to the content of this article.

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