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A critical review on the pathways of carbamazepine transformation products in oxidative wastewater treatment processes

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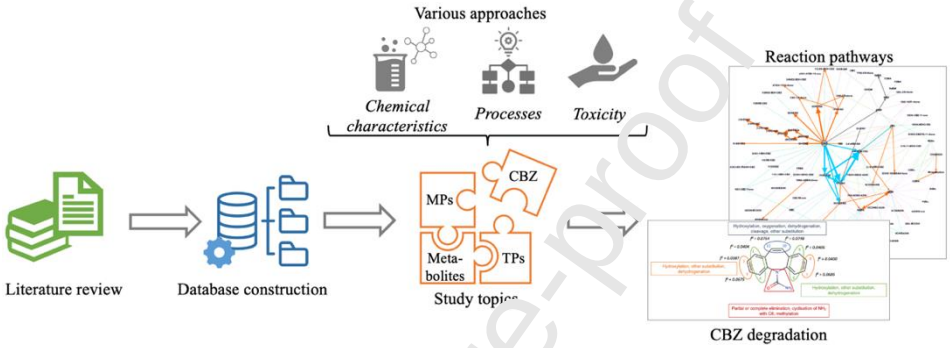
Graphic abstract



Abstract

Carbamazepine (CBZ) is an anticonvulsant drug, released in domestic and hospital wastewater, and one of the drugs most commonly detected in surface water. Conventional secondary processes do a very poor job of removing it (< 25%), but its concentrations are significantly reduced by polishing oxidation processes. However, there are still many unknowns regarding the transformation products generated and their fate. This review first presents the journey of CBZ and its transformation products (TPs) in wastewater, from human consumption to discharge in water bodies. It then goes on to detail the diversity of mechanisms responsible for CBZ degradation and the generation of multiple TPs, laying the emphasis on the different types of advanced oxidation processes (AOP). 135 TPs were reported and a map describing their formation/degradation pathways was drawn up. This work highlights the wide range of physicochemical properties and toxicity effects of TPs on aquatic organisms and provides information about TPs of interest for future research. Finally, this review concludes on the importance of quantifying TPs and of determining kinetic characteristics to produce more accurate reaction schemes and computer-based fate predictions.

Keywords: carbamazepine, transformation products, wastewater treatment, oxidation processes, micropollutant

1. Introduction

Organic micropollutants (MPs) are any natural or anthropogenic substances with potential or recognized hazardous effects on aquatic health occurring at low concentrations (e.g. from 1 ng to 1 µg per liter in water) (DG ENV European Commission, 2022; Dubey et al., 2021). The wide range of anthropogenic organic molecules includes, but is not limited to, pharmaceuticals and personal care products (PPCPs), hormones, surfactants and industrial chemicals. As shown in figure 1, they are generated by massive use in households, the industry and the health sector, and their main entry point into water bodies is through wastewater treatment plants (WWTPs) (Luo et al., 2014; Rogowska et al., 2020). Of particular concern are PPCPs (e.g. analgesics, antibiotics, psychiatric drugs, β-blockers), some of which are mentioned in Order 814.201.231 (2016) of the DETEC (Swiss Federal Department of the environment, transports, energy and communication) concerning verification of the treatment rate achieved owing to the measures taken to eliminate organic trace compounds in wastewater treatment plants (DETEC, 2016), and in the proposal for a revised Urban Wastewater Treatment Directive (DG ENV European Commission, 2022). In the last decades, a change in lifestyle worldwide due to modernization has led to a massive use of pharmaceuticals, and multiple studies have quantified them in WWTP effluents, surface water and drinking water (Feitosa-Felizzola & Chiron, 2009; Zhang et al., 2008).

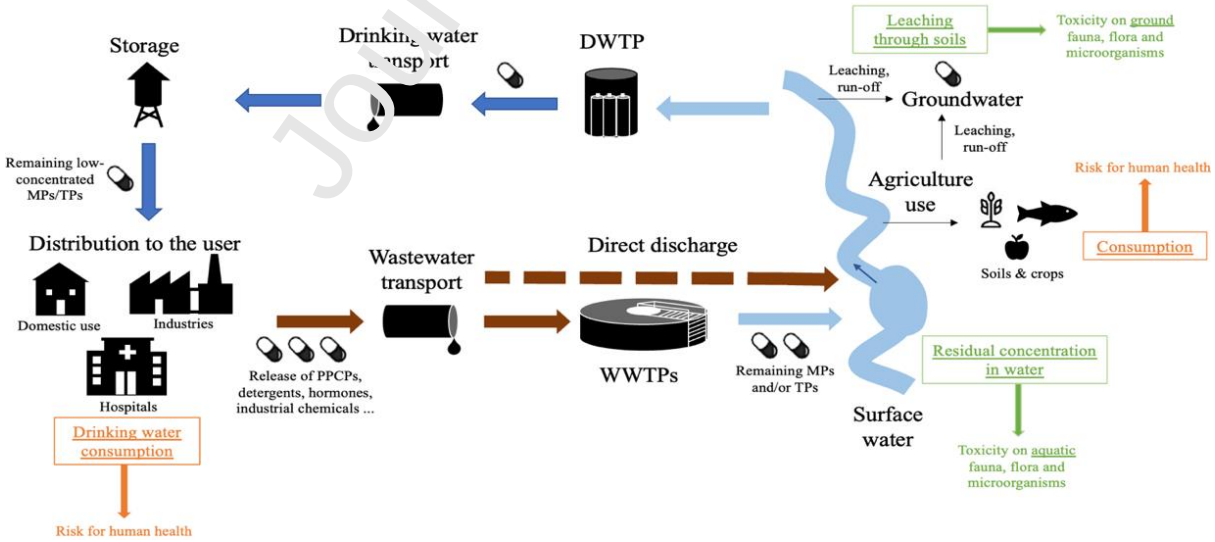


Figure 1: Chemicals in the urban water cycle (sewage and drinking water), and associated risks (based on Compagni et al., (2020)). DWTP = drinking water treatment plant, WWTP = wastewater treatment plant, PPCPs = pharmaceuticals and personal care products, MPs = Micropollutants, TPs = Transformation products

Furthermore, PPCPs are molecules designed to display specific biophysicochemical properties, some of which may be harmful to aquatic ecosystems (Caliman & Gavrilescu, 2009; Cizmas et al., 2015; Evgenidou et al., 2015).

Among PPCPs, carbamazepine (5H-dibenzo[b,f]azepine-5-carboxamide, CBZ) is a well-known marker of human activity in water bodies. It is an anticonvulsant mainly used in the treatment of epilepsy – prescribed at daily dose of 1 g (WHO Collaborating Centre for Drugs Statistic Methodology, 2021) – and bipolar disorder (Capodaglio et al., 2018; Hai et al., 2018). It also displays a remarkable chemical stability (INERIS : Normes de qualités environnementales, 2012; Zhang et al., 2008). The removal efficiency in conventional biological WWTPs is indeed poor, of less than 30% (Clara et al., 2004; Kim et al., 2014; Song et al., 2020). CBZ is therefore a pharmaceutical that is systematically quantified in different water matrices, especially in urban wastewater where it is found at concentrations of around 0.5 to 2 µg/L (Brezina et al., 2017). Exposure to CBZ has critical effects on aquatic species, such as mortality, reproductive or growth inhibition, developmental effects or morphological changes (Hai et al., 2018; Kaushik et al., 2016). Chemical oxidation or adsorption processes are often proposed as curative solutions to remove CBZ before effluents are discharged into the environment (Figure S1, supplementary data). Little is known however about the structure, properties and fate of the resulting transformation products (TPs) generated during oxidation processes. In addition, several studies have reported that TPs might be even more toxic to aquatic life than their parent compound (Ali et al., 2018; Wang et al., 2022; Xu et al., 2021). CBZ is consequently a molecule of primary interest.

A number of reviews have been published about the occurrence and removal of micropollutants in wastewater (Evgenidou et al., 2015, Capodaglio et al. 2018, Dubey et al. 2021, Feijoo et al., 2023), and a few about transformation product generation by one wastewater treatment process (Bonnot et al., 2022; Donner et al., 2013). Therefore, in our review, we tell the entire story of CBZ, from ingestion by patients to the TPs toxicity, covering metabolites generation by human organism, TPs generation by various oxidative processes and chemical characteristics and toxicity of TPs. Hence, this paper presents the various transformation products generated when carbamazepine is eliminated from water using different oxidative wastewater treatment processes. It compiles information from different disciplines (chemistry, processes, ecotoxicity) to provide a thorough and critical overview. We identified the main formation pathways, classified the transformation products and pathways, took toxicity into

account, and identified knowledge gaps in terms of TPs. This work covers the emission of TPs (human consumption and metabolization), their release in water bodies, and their transformation in water treatment processes.

2. Materials and methods

2.1 Keywords used for the literature review

The keywords used to run searches on original papers and review research on databases such as Elsevier, ResearchGate and Pubmed were taken from the following list:

- Carbamazepine, micropollutant, xenobiotic, pharmaceuticals, PPCPs.
- Products, metabolites.
- Occurrence, quantification, toxicity.
- Reaction pathways, degradation, removal, processes, advanced oxidation processes, water treatment.

Based on these keywords, 97 papers published between 2000 and 2022 were selected. Among them, 39 concerned the TPs of CBZ.

2.2 Construction of the transformation products database

The physicochemical characteristics of CBZ and its TPs were determined using MarvinSketch [v22.13.0] developed by ChemAxon© Ltd (http://www.chemaxon.com). This software was used in particular to draw the chemical structure of TPs, to calculate molecular weights (MW), chemical formulas, polar surface areas (PSA) and van der Waals surface areas (WSA), and to predict pKa (T = 20°C), logD (pH = 7) and the H-bond donor/acceptor count.

2.3 Data processing

Figures and tables were created using RStudio interface [v2022.07.2] and R programing language – more specifically, the *ggplot* library from the *tidyverse* package – based on databases constructed from literature data. And the specific *formattable* package was used to create table 1. The graphical visualization of CBZ transformation pathways into TPs, as shown in Figure 10, was generated using Gephi software [v0.9.5] for drawing maps and networks.

For statistical analyses using box-and-whisker plots, a Student-t-test was run after verification of data normality by means of a Shapiro-Wilk test. Whenever normality was not demonstrated, a Wilcoxon-Mann-Whitney test was then carried out. Statistically significant values were defined as p-values of 0.05 (*).

When results were reported in several scientific papers, the list of the articles in which these results appeared is presented in the supplementary data.

In this review, the degradation of CBZ by human bodily functions and its byproducts are referred to as *metabolization* and *metabolites*, respectively. The term *transformation products* (TPs) is used specifically for CBZ degradation products in treatment processes or water bodies.

3. CBZ in water systems

3.1 Excretion of CBZ after consumption

Once ingested by a patient, CBZ reaches the liver and undergoes hepatic metabolism. In hepatocytes, the biotransformation system, responsible for xenobiotic metabolism, is mainly composed of cytochrome enzymes (Miao et al., 2005; Schaffner, 1975). These enzymes modify drugs by introducing hydrophilic groups such as –OH, $–NH_2$, or –COOH; this is known as phase I transformation (Celiz et al., 2009). CBZ is transformed by cytochrome P450 (CYP), which uses nicotinamide adenine dinucleotide (NADH) to induce hydroxylation. CYP 1A2 is the main contributor in the production of 2/3-OH-CBZ (Bernus et al., 1996; Schaffner, 1975). Hydroxylated CBZ is then transported to another liver cell site and undergoes glucose conjugation (phase II metabolism) resulting in glucuronide conjugates. During CBZ metabolization, other molecules may form such as CBZ-10,11-epoxide (EP-CBZ) by epoxidation of the double bond of the azepine group by CYP3A4 or CYP2C8 (Miao et al., 2005; Schaffner, 1975). EP-CBZ may then be hydrolyzed into 10,11-dihydro-10,11-dihydroxylated-CBZ (DH-diOH-CBZ) by a specific epoxide hydrolase (Bernus et al., 1996). Free radicals may also be generated, leading to other CBZ transformations. The main CBZ metabolites and their formation pathways are shown in figure 2.

2% of the CBZ ingested is then excreted via urine and 13% via feces. Where its metabolites are concerned, 72% are excreted via urine and 28% via feces (Bahlmann et al., 2014; Brezina et al., 2017). Among the CBZ metabolites, N-glucuronide conjugates were one of the most abundant in urine, compared to O-glucuronide conjugates. He et al. (2019) reported

the proportion of CBZ metabolites encountered, after excretion, in a wastewater influent – DH-diOH-CBZ: 50.9%; N- and O-glucuronides: 14.6%; 3OH-CBZ: 8.7%; 2OH-CBZ: 7.0%; EP-CBZ: 4.3% and 10OH-CBZ: 1.2% (He et al., 2019). Consequently, in order to accurately study the fate of CBZ in water, its metabolites should be taken into account in addition to its concentration (Jelic et al., 2015).

In biological WWTPs, some metabolites can partially retransform into CBZ by enzymatic and/or chemical transformation (Celiz et al., 2009). Cleavage of glucuronide-conjugates by *β*-glucuronidase produced by fecal bacteria was reported, with a 19% removal efficiency (He et al., 2019). Consequently, deconjugation could generate CBZ during wastewater treatment, and could be an explanation for its apparent persistence in WWTPs. CBZ metabolites and conjugates, as well as deconjugation reactions, should therefore be considered in order to correctly estimate the removal of CBZ, as well as its behavior and occurrence in water.

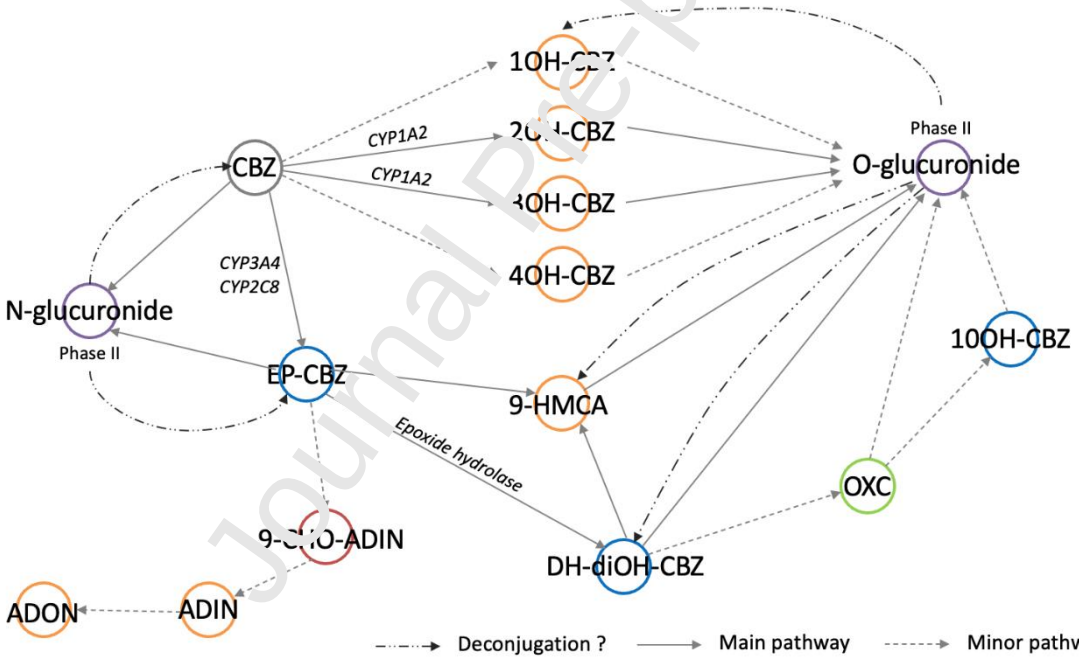


Figure 2: CBZ human metabolites and glucuronide conjugates formed by hepatic metabolism. The blue, pink, orange and green colors represent the primary drug, phase I, phase II metabolites and other molecules, respectively. 9-HMCA = 9-(Hydroxymethyl)-10-carbamoylacridan, ADIN = Acridine, ADON = acridone, OXC = oxcarbazepine. Based on Bernus et al. (1996), Miao et al. (2005), Bahlmann et al. (2014) and Mir-Tutusaus et al. (2021)

3.2 Concentrations of CBZ in the water matrix

Figure 3 displays the mean, minimum and maximum CBZ concentrations quantified in urban influents and effluents, in surface and ground water, and in drinking water (data from 17 papers from 2000 to 20/22).

The mean CBZ concentration in WWTP influents is 968 ng.L^{-1} (15 values), whereas the mean concentration in effluents from conventional WWTPs using the conventional activated sludge (CAS) process or a membrane bioreactor (MBR) is 740 ng.L^{-1} (19 values). There is consequently hardly any significant decrease in CBZ concentration during biological treatment. Among the papers considered for this study, some even show a slight increase in CBZ concentration in effluents compared to influents, such as Wick et al. (2009) or Brezina et al. (2017), with an increase of 80 ng.L^{-1} and 220 ng.L^{-1}, respectively (Brezina et al., 2017; Wick et al., 2009). Two hypotheses may explain this result: 1) the biological processes in the WWTP do not enable CBZ removal; or 2) biological matter in the WWTP causes a biological degradation of the CBZ that is offset by the production of CBZ by deconjugation of metabolites, leading to a neutral balance and resulting in a constant concentration in the process (Radjenović et al., 2009).

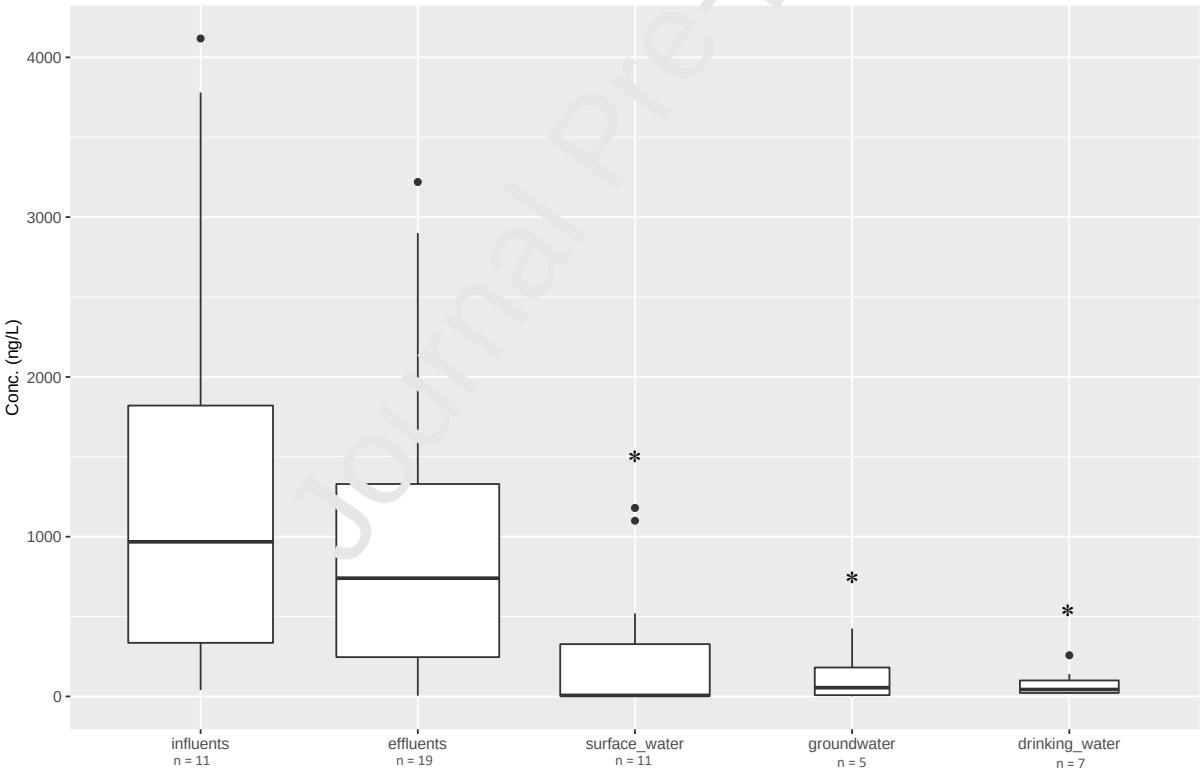


Figure 3: Box-and-whisker plots of CBZ concentrations indicating the mean, minimum, maximum, and upper and lower quartile concentrations in various water matrices (data from 17 papers, figure S4 supp. data). Statistical analyses were performed on datasets from different matrices, * $p < 0.05$.

The mean CBZ concentrations in surface water and groundwater are 272 $ng.L^{-1}$ (11 values) and 55 $ng.L^{-1}$ (11 values) respectively. This is significantly lower than the values found in effluents and can be explained by a dilution rate when effluents are discharged into rivers or adsorbed in soil during infiltration (Capodaglio et al., 2018).

The mean CBZ concentration in drinking water is 43 $ng.L^{-1}$ (7 values), ranging from 20 to 258 $ng.L^{-1}$ (Benotti et al., 2009; Mompelat et al., 2009). Wilkinson et al. (2022) recently reported a detection frequency of 78.5% in European drinking water (344 sample locations), and all continents are concerned except Antarctica (Wilkinson et al., 2022).

3.3 The main physicochemical characteristics of CBZ

Figure S2 in the supplementary data presents molecular physicochemical properties. CBZ, like most PPCP, is very little concerned by volatilization or stripping processes (Henry's law constant k_H of 1.09 x 10^{-5} $Pa.m^3.mol^{-1}$) which is why these mechanisms will not be described here (Capodaglio et al., 2018; Luo et al., 2014). LogD, the distribution coefficient, is a good descriptor for ionizable compounds since it is a measure of the pH-dependent solubility of all species. Thus, the Log D of CBZ is 2.77 (at pH 7), so it is considered as a moderate hydrophobic compound with a low ability to cross cellular membranes. Moreover, because CBZ is a non-ionized drug with a neutral pH (pKa >15), it has no adsorption affinities. Furthermore, the polar surface area (PSA) of CBZ, defined as the sum of the fractional contribution of all non-carbon atoms (nitrogen, oxygen or hydrogen), is 46.3 $Å^2$ suggesting that CBZ should be able to be adsorbed onto sludge (Ertl, 2008; Pajouhesh & Lenz, 2005; Patrick, 2002a, 2002b). To conclude, CBZ has a limited permeability and is non-ionized. However, due to its PSA and hydrophobicity, CBZ should partially escape the water phase by adsorption onto sludge. Consequently, CBZ removal by sorption is relatively inefficient (< 20% (Hai et al., 2018) and the distribution coefficient of CBZ between water and secondary sludge (K_d) is 1.2 $L.kg_{SS}^{-1}$ (Zhang et al., 2008).

The molecular characteristics of CBZ make it sensitive to oxidation processes. Indeed, CBZ has a number of possible chemical attack sites as detailed in Figure 4, which identifies the most probable reactions that can occur at each position. The primary reactive site of CBZ is the C10-C11 olefin double bond (Li et al., 2021). This π-bond has a low energy of (250 $kJ.mol^{-1}$) compared to σC-C bonds (350 $kJ.mol^{-1}$) meaning it is easily breakable (Jamart et al., 2015a) and both C10 and C11 atoms have the highest Fukui index (f^0 = 0.0754 and 0.0748,

respectively), showing that these positions are the most vulnerable to radical attacks (Xu et al., 2021). Indeed, unsaturated bonds have a high electron density, where easily accessible electrons are able to react with radicals. Carbons C1-3 and C7-9 from the two benzene rings are also quite reactive, even though their aromatic structures make them more resistant than the olefin bond due to electron sharing. In contrast, the carbamoyl group ($CONH_2$) is not at all reactive. The C-N and N-H bonds are indeed very difficult to break due to the presence of a primary amine (Jamart et al., 2015b). Radicals are therefore not likely to attack this site, except for a few transformations such as NH_2 methylation or C6-cyclization.

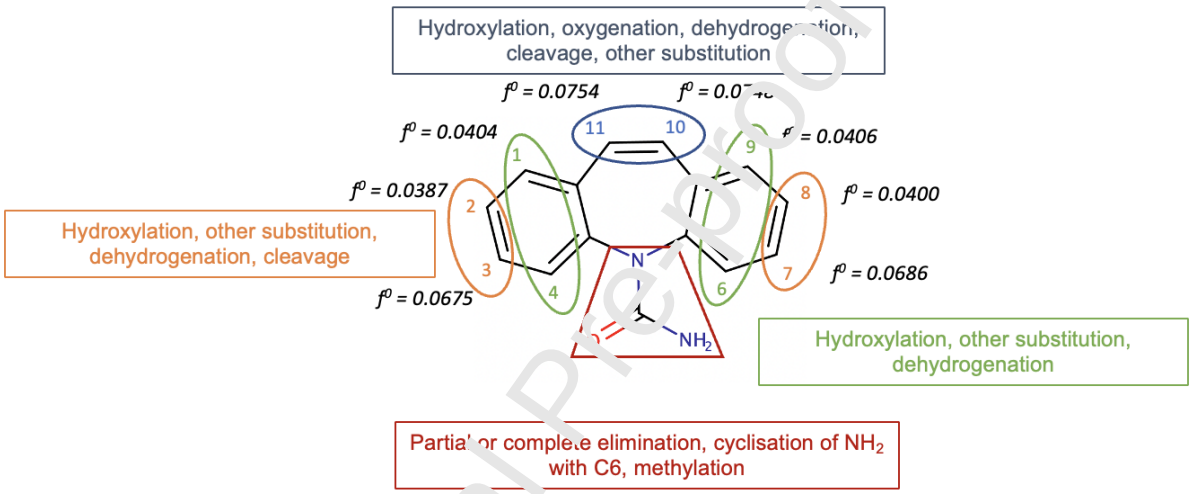


Figure 4: Main chemical attack sites, modification processes, and Fukui index f^0 (Xu et al., 2021) for CBZ

3.4 CBZ in different water treatment processes

In wastewater and drinking water treatment plants, different processes are used to produce water of a given quality. Secondary treatment consists of biological processes relying on microorganisms, in which products are transformed by cometabolism or enzymatic lysis and sorption on sludge (Pomiès et al., 2013; Speight, 2017). It seems unlikely that CBZ undergoes significant sorption and biotransformation (Clara et al., 2004; Kim et al., 2014; Radjenović et al., 2009) because the removal efficiency of CBZ using the conventional activated sludge (CAS) process, membrane bioreactors (MBR) or moving bed biofilm reactors (MBBR) is between 0 and 30%. The influence of a wide variety of experimental conditions (pH, temperatures, sludge and water characteristics, hydraulic retention time) could also explain the low removal efficiency of CBZ (Ergüder & Demirer, 2010; Luo et al., 2014; Radjenović et al., 2009).

Separation by means of membrane technologies (NF, RO) or degradation by advanced oxidation processes (AOP) have been widely investigated (Figure S3, supplementary data). CBZ retention by membrane is based on electrostatic or hydrophobic interactions, or size exclusion (Yadav et al., 2022). Some advanced oxidation processes (AOP) consist in selective attacks through the release of reactive oxygen (•OH, $^1O_2$, $SO_4^{\bullet-}$, HO_2•) or chlorine ($Cl^{\bullet}$, $Cl_2^{\bullet-}$, ClO•) species (Alharbi et al., 2017; Dai et al., 2012; Xie et al., 2022).

Others include Fenton and Fenton-like reactions, photocatalysis or photooxidation (H_2O_2, $S_2O_8^{2-}$, FeOCl, ClO^-). The most efficient AOPs for CBZ removal are TiO_2 photocatalysis (Franz et al., 2020) and Fenton reactions (Monsalvo et al., 2015; Sun et al., 2021) with removal efficiencies of 57-99% and 70-99%, respectively. Oxidation processes such as ozonation, chlorination and ultraviolet irradiation are also commonly known as being very efficient for removing CBZ (Andreozzi et al., 1999; Bourgin et al., 2017; Mathon et al., 2017; Yang et al., 2016). Ozonation in particular displayed a removal efficiency of 80% to 100%.

However, the higher the CBZ elimination rate, the higher the risk of formation of degradation products. Figure 5 presents the processes' ability to remove CBZ on the horizontal axis, the toxicity of the TPs and disinfection by-products (DBPs) generated on the vertical axis, and the upscaling abilities of the processes (colored dots) as determined in previous studies (Brienza & Katsoyiannis, 2017; Pei et al., 2019; Wenzel et al., 2008). Figure 5 is a schematic representation for operational purposes. Implementation of a simplified indictors for each studied criteria was thus necessary to compare various processes. TPs toxicity and CBZ removal ability were reviewed and normalized scores between 0 (highest toxicity and low removal) and 1 (low toxicity and high removal) were attributed for each process. Same procedure was implemented for upscaling ability using a color scale attributed for each score.

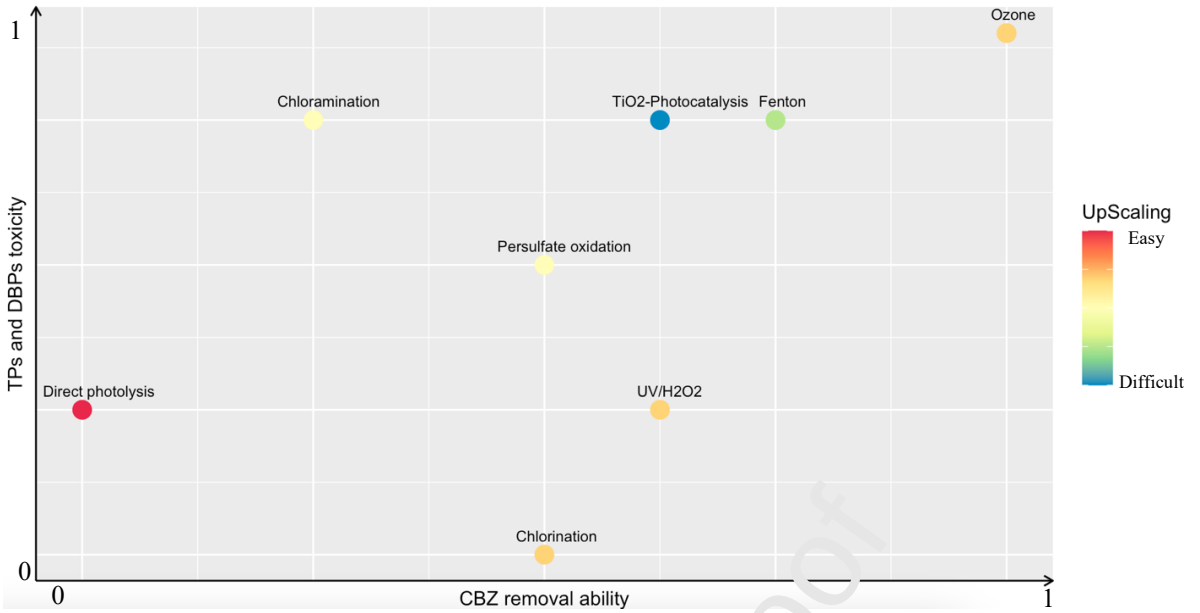


Figure 5: Comparison of different AOPs according to their CBZ removal ability, the toxicity of the synthesized transformation products (TPs) and disinfection by-products (DBPs), and their up-scaling abilities. These three criteria were sorted by attribution of a score from 0 (worst score) to 1 (best score). Based on Wenzel et al. (2008), Brienza et al. (2017) and Peter et al., (2019).

Transformation up to mineralization was never achieved, meaning that none of the processes exhibit both a high removal rate and an absence of TP/DBP production. In addition, chemical oxidation is non-specific and may target any of the sites of the CBZ structure. Consequently, several CBZ TPs are formed by AOP (O_3, H_2O_2, etc.) because the chemical oxidants generate smaller molecules or form other byproducts such as bromide (von Gunten, 2018).

New technologies such as TiO_2 photocatalysis, Fenton oxidation or chloramination, despite their higher operational costs or high TPs toxicity, are promising in terms of removal efficiencies of CBZ.

4. Transformation products of carbamazepine

4.1 Molecular transformation of CBZ leading to the production of TPs

There are two main CBZ degradation pathways (Figure 6). First, the attack of ozone on the olefin bond leads to a ring opening due to the Criegee mechanism followed by the formation of quinazoline after NH_2-C6 bonding (Somathilake et al., 2018). Three products 1-(2-benzaldehyde)-4-hydro-(1H,3H)-quinazoline-2-one (BQM), 1-(2-benzaldehyde)-(1H,3H)-quinazoline-2,4-dione (BQD) and 1-(2-benzoic acid)-(1H,3H)-quinazoline-2,4-dione (BaQD)

are therefore formed (Mcdowell et al., 2005). The second pathway involves either cleavage of the N5-$CONH_2$ bond, leading to the formation of iminostilbene (ISB), or hydroxylation/ oxygenation of the dibenzazepine, and more specially, the azepine ring. Bond cleavage then simplifies the structure of the molecule, rearranging it into three benzene rings in acridine (ADIN), acridone (ADON) or acridan (ADAN) analogues. These tricyclic structures can become quinazoline derivatives through the cleavage of one or two rings, thus joining up with route 1. Further simplification into aliphatic chains and mineralization is hardly ever achieved due to the low concentration and diversity of TPs.

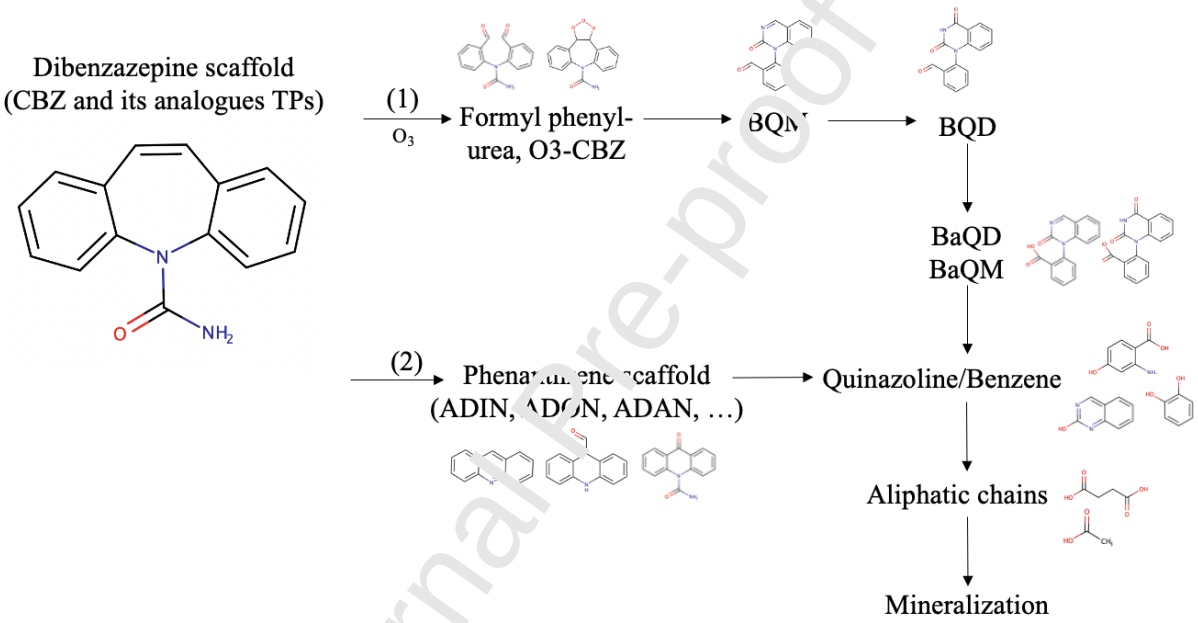


Figure 6: Two of the main degradation pathways from CBZ to mineralization (this study, based on a review of the literature). ADAN = acridan; ADIN = acridine; ADON = acridone; BQM = 1-(2-benzaldehyde)-4-hydro-(1H,3H)-quinazoline-2-one; BQD = 1-(2-benzaldehyde)-(1H,3H)-quinazoline-2,4-dione; BaQD = 1-(2-benzoic acid)-(1H,3H)-quinazoline-2,4-dione.

4.2 The main characteristics of transformation products

4.2-1 Molecular properties of TPs

So far, 135 TPs have been reported in previous works aiming to identify their chemical structures (Table S1, supplementary data). Since they can be formed through various processes, they are expected to display a wide variety of physicochemical characteristics (Figure 7). In order to discern specific behaviors, we separated the TPs into eight groups, based on the chemical scaffold of the molecule. For example, molecules with an iminostilbene core (CBZ analogs), a phenanthrene core (ADIN, ADAN or ADON analogs) or a quinazoline core, were

studied separately, and classified by level of degradation (from CBZ analogs to aliphatic acids, the TPs closest to mineralization). As we can see in Figure 7, the proportion of hydrophilic groups, H-bond donors and ionized molecules increases with the level of transformation. Their proportions increased (from CBZ analogs to aliphatic chains) from 70% to 100%, 47% to 100% and 12% to 100%, respectively. This is consistent with previous observations that radical attacks often result in the hydroxylation of other electrophilic addition reactions. Indeed, these functional groups (OH, $CONH_2$, COOH, NO_2) are well-known H-bond donor groups and, when added, increase the affinity of TPs for water. However, we noticed an exception in the case of ADIN and ADON analogs, which are mostly hydrophobic due to their tricyclic structure and their low substitution rate – 1 or 2 substituents only.

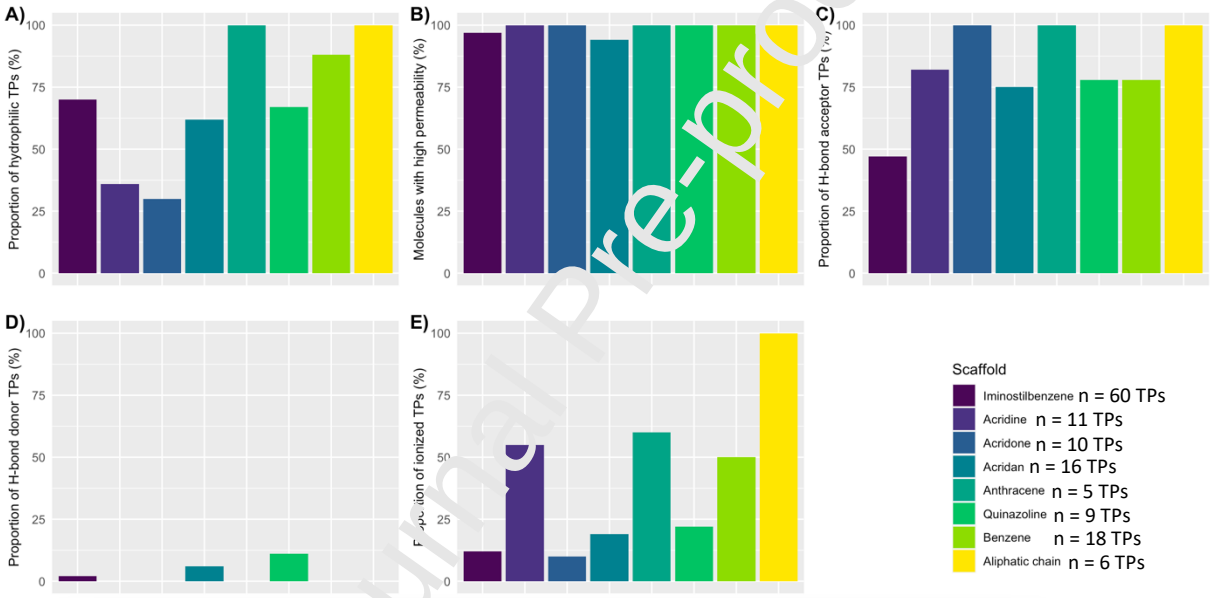


Figure 7: Physicochemical characteristics of the TPs of CBZ for each chemical scaffold. A) Hydrophilicity (number of molecules with LogD < 2.5), B) Permeability (number of molecules with PSA < 140 Å2), C) Number of molecules with a high H-bond acceptor count, D) Number of molecules with a high H-donor count, E) Number of charged molecules. Results are shown as the proportion of TPs for each characteristic. (Database constructed based on 39 research papers, figure S4 supp. data)

Furthermore, the level of degradation (more or less close to mineralization) also has an influence on the ionization state of the molecule. For example, the addition of the COOH functional group to TPs with an anthracene or benzene core and an aliphatic chain, will contribute to increasing the ionized proportion. Indeed, $COOH/COO^-$ has a pKa of less than 5.94 and is therefore present in its COO^- form in wastewater ($6 < pH < 8$). Similar observations were made for the tertiary amine of ADIN. NH_2/NH^+ has a pKa between 6.24 and 7.17, depending on the TP, and will therefore display its NH^+ form at the pH value usually measured in wastewater. Finally, almost all TPs have a PSA < 140 $Å^2$ and consequently have the capacity to permeate cells and be adsorbed onto cells.

4.2-2 Occurrence and concentrations of TPs in water matrices

Due to the wide range of metabolites excreted by the human organism and the TPs formed by water treatment processes, it is interesting to focus on the occurrence of TPs in different water matrices, from influents to surface water. No quantified data was found in the literature about TPs in groundwater so this subject is not addressed here.

Figure 8 presents the concentrations found in the literature for six TPs measured in WWTP influents, effluents and surface waters. First, it is worth noting that 5 of the TPs were found at concentrations lower than that of CBZ. Indeed, the mean concentration of 10OH-CBZ in influents was lower than 300 ng.L^{-1} and the mean concentrations of 2OH-CBZ, 3OH-CBZ, EP-CBZ and ADIN in influents were all lower than 80 ng.L^{-1}. Only DH-diOH-CBZ (Figure 8D) presented mean concentrations of 1,079 ng.L^{-1} in influents (n=9) and of 1,081 ng.L^{-1} in effluents (n=11), values higher than those of CBZ (968 ng.L^{-1} and 740 ng.L^{-1}, respectively). One explanation is that it is a final metabolite from phase I metabolism and is therefore a product of human excretion. Indeed, Bahlmann et al. (2014) estimated by meta-analysis that 32% of excreted CBZ metabolites are DH-diOH-CBZ. Furthermore, DH-diOH-CBZ is a human metabolite of oxcarbazepine, another anti-epileptic drug, which may also explain its high concentration compared to CBZ (Bahlmann et al., 2014).

No significant differences were observed between the concentrations of TPs such as EP-CBZ, DH-diOH-CBZ or 2/3/10OH-CBZ (all are human metabolites which explains their concentrations in influents) in conventional WWTP influents and effluents. These TPs are also important primary products of CBZ degradation, which is why, during water treatment, they may undergo further degradation, resulting in the formation of other TPs.

Few data concerning the occurrence of TPs in surface water were reported in the literature. It would appear however that the concentration of TPs decreases in surface water compared to effluents due to molecule dilution. Finally, it is also necessary to quantify TPs more extensively in various water matrices in order to allow a more in-depth data interpretation. Indeed, considerable amounts of TPs continue to be found in WWTP effluents (> 50 ng.L^{-1}) and research needs to urgently tackle the environmental scale and health issues they pose.

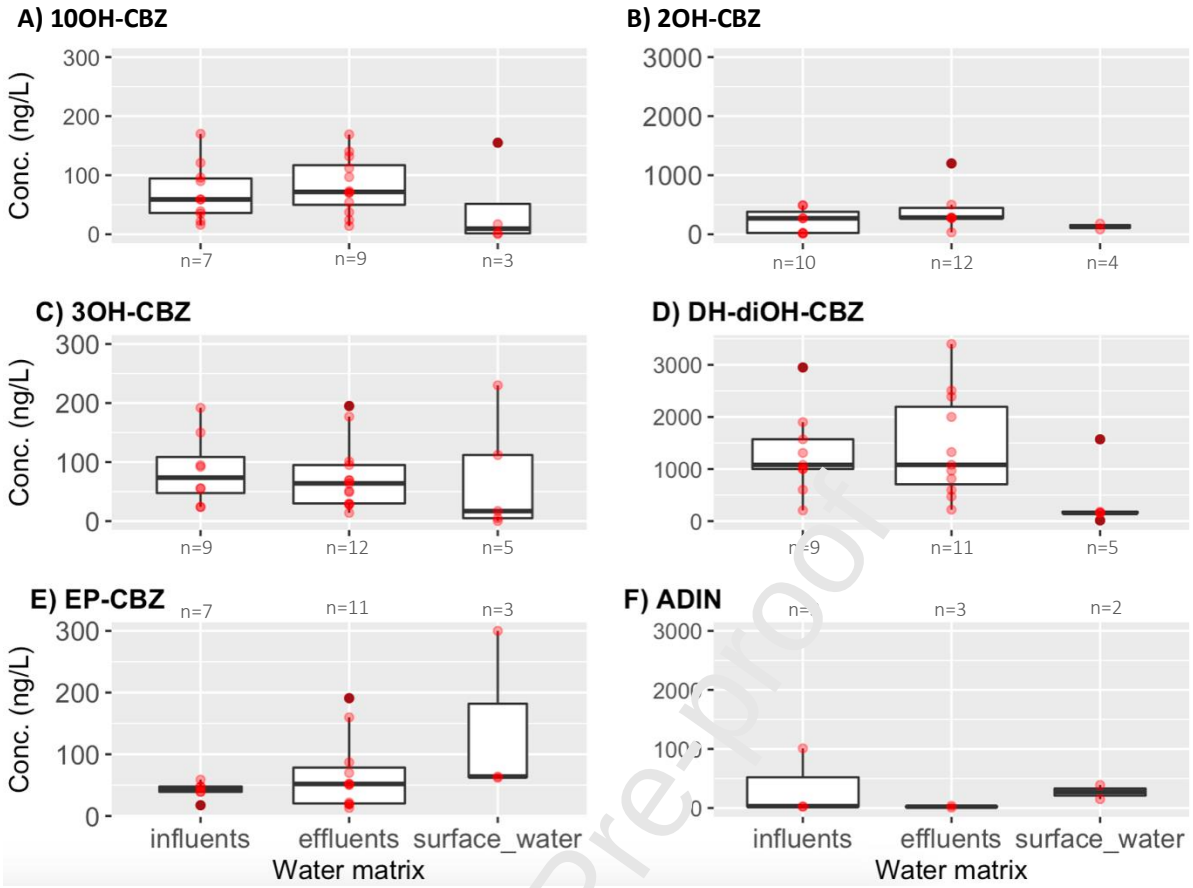


Figure 8: Box-and-whisker plots showing the quantification of a number of TPs from CBZ degradation in various water matrices; A) 10OH-CBZ, B) 2OH-CBZ, C) 3OH-CBZ, D) DH-diOH-CBZ, E) EP-CBZ, F) ADIN (Database constructed based on 8 research papers, figure S4 supp. data). No data were found for groundwater and drinking water)

4.2-3 TP toxicity

The acute and chronic toxicity values of 31 TPs were found in the literature (raw data, data obtained from ECOSAR predictions and from reviewed papers are presented in table S2 of the supplementary data) and classified into 4 environmental risk categories (Figure 9). Primary TPs (EP-CBZ, 10OH-CBZ, 9CHO-CBZ, BQM, etc.), intermediary TPs (ADIN, ADON, BQD, etc.) and final TPs (1,2,3,4-tetrahydroquinazoline-2,4-dione (QNL-2,4-dione), 2-[1-(2-carboxyphenyl)carbamoylamino] benzoic acid (CCBA), etc.) were studied. On average, 59% of TPs display acute aquatic toxicity, particularly toward green algae. Chronic toxicity evaluations show that 95% of TPs are toxic, with an average of 38% very toxic molecules. Comparing the toxicity results of TPs with those of CBZ, we estimated that 26% and 58% of TPs display acute and chronic toxicities, respectively, values much higher than those of CBZ.

Long-term exposure to TPs seems to have a greater effect than acute exposure, probably due to the accumulation and constant occurrence of TPs in water. In conclusion, long-term exposure to CBZ TPs has considerable hazardous consequences on aquatic life, although the toxicity mechanisms are not yet understood. Indeed, the toxicity of TPs can differ from that of CBZ due to their action mechanism (toxicodynamics) or the quantity present in the water matrix (toxicokinetics) (Evgenidou et al., 2015).

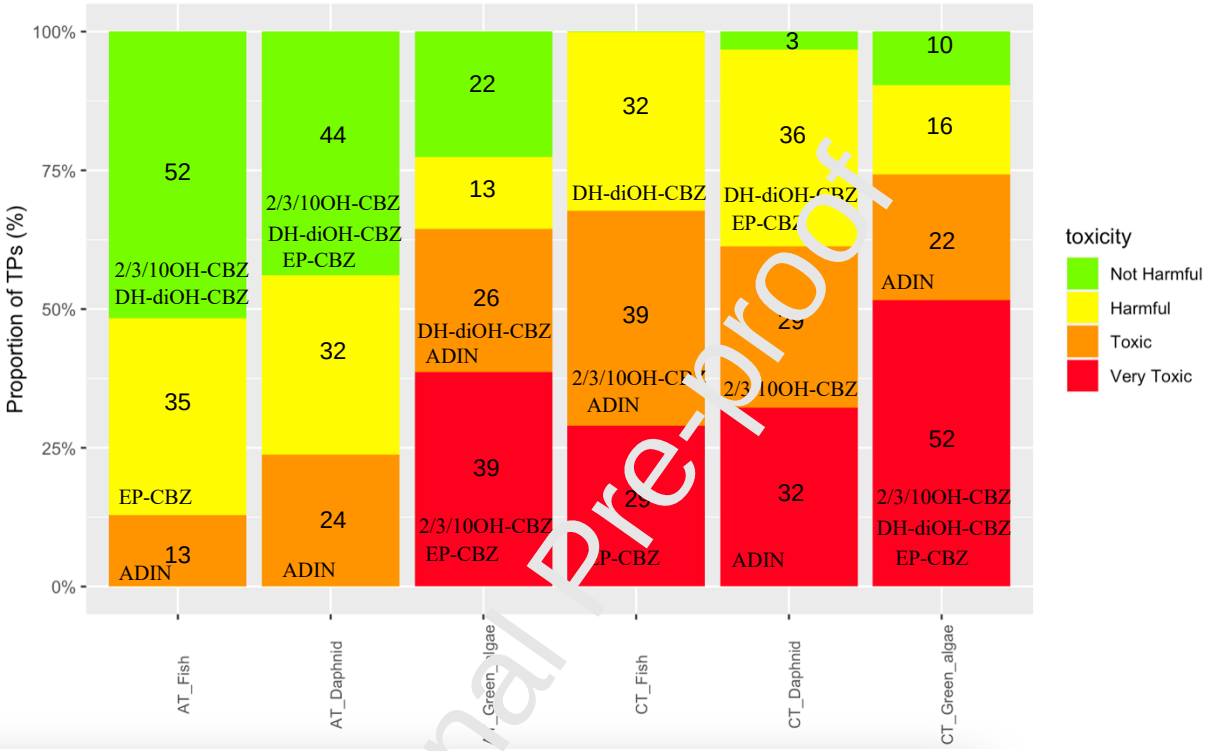


Figure 9: Proportions of TPs (31 TPs considered) in each toxicity category. Acute toxicity (AT) and Chronic toxicity (CT), predicted by ECOSAR software, in three different aquatic organisms (fish, daphnid, green algae). The TPs were classified as not harmful (> 100 $mg.L^{-1}$; green), harmful (10-100 $mg.L^{-1}$; yellow), toxic (1-10 $mg.L^{-1}$; orange) and very toxic (< 1 $mg.L^{-1}$; red) according to the Globally Harmonized System of Classification and Labeling of Chemicals (GHS). Results are shown in terms of the proportion of TPs in each toxicity category (Ali et al., 2018; Bu et al., 2018; Kråkström et al., 2020; Wang et al., 2022; Xu et al., 2021). TPs previously appearing in figure 8 are written in their corresponding toxicity category.

By comparing these toxicity results with those obtained in our previous analyses (Figures 6 and 7), we determined whether the toxicity of TPs is linked to their chemical structure. The most toxic TPs are ADIN, ISB, 2-[(2-formylphenyl)amino]benzaldehyde (FPAB), 9CHO-CBZ, EP-CBZ, 10OH-CBZ, 9CHO-ADAN, 1/2/10Cl-CBZ and BQM. No chemical scaffold in particular was identified as being responsible for toxicity. Indeed, most toxic compounds generally comprise CBZ derivatives (1/2/10Cl-CBZ, ISB, 10OH-CBZ, EP-CBZ), ADIN/ADAN analogues (ADIN, 9CHO-CBZ, 9CHO-ADAN), quinazoline (BQM) and benzene derivatives (FPAB). Moreover, it is interesting to note that, among the TPs quantified in different water matrices (Figure 8), only 3 displayed a significant level of toxicity (EP-CBZ, 10OH-CBZ and ADIN). It is however crucial to continue to further quantify TPs in water bodies, and efforts must focus on the more hazardous molecules.

4.3 Are CBZ reaction pathways and the TPs produced, process-dependent?

A detailed map of the degradation pathways of CBZ is presented in Figure 10 and includes 95 TPs and numerous chemical routes. It was created based on the data found in 34 papers addressing 6 types of oxidation processes used for water treatment. Blue and orange arrows represent the chemical reactions that are reported in all 6 oxidation processes (known as "common processes") or in several processes only (known as "multiple processes"), respectively. The other colors represent a particular process among: oxidation by reactive chlorine species (RClS) (7 papers) or reactive oxygen species (ROS) (11 papers), by ozone (4 papers), by persulfate (4 papers) or by a metal catalyst such as Fe (4 papers) or TiO_2 (4 papers). This representation makes it easy to differentiate primary TPs at the center of the map from final TPs on the outer layer of the circle.

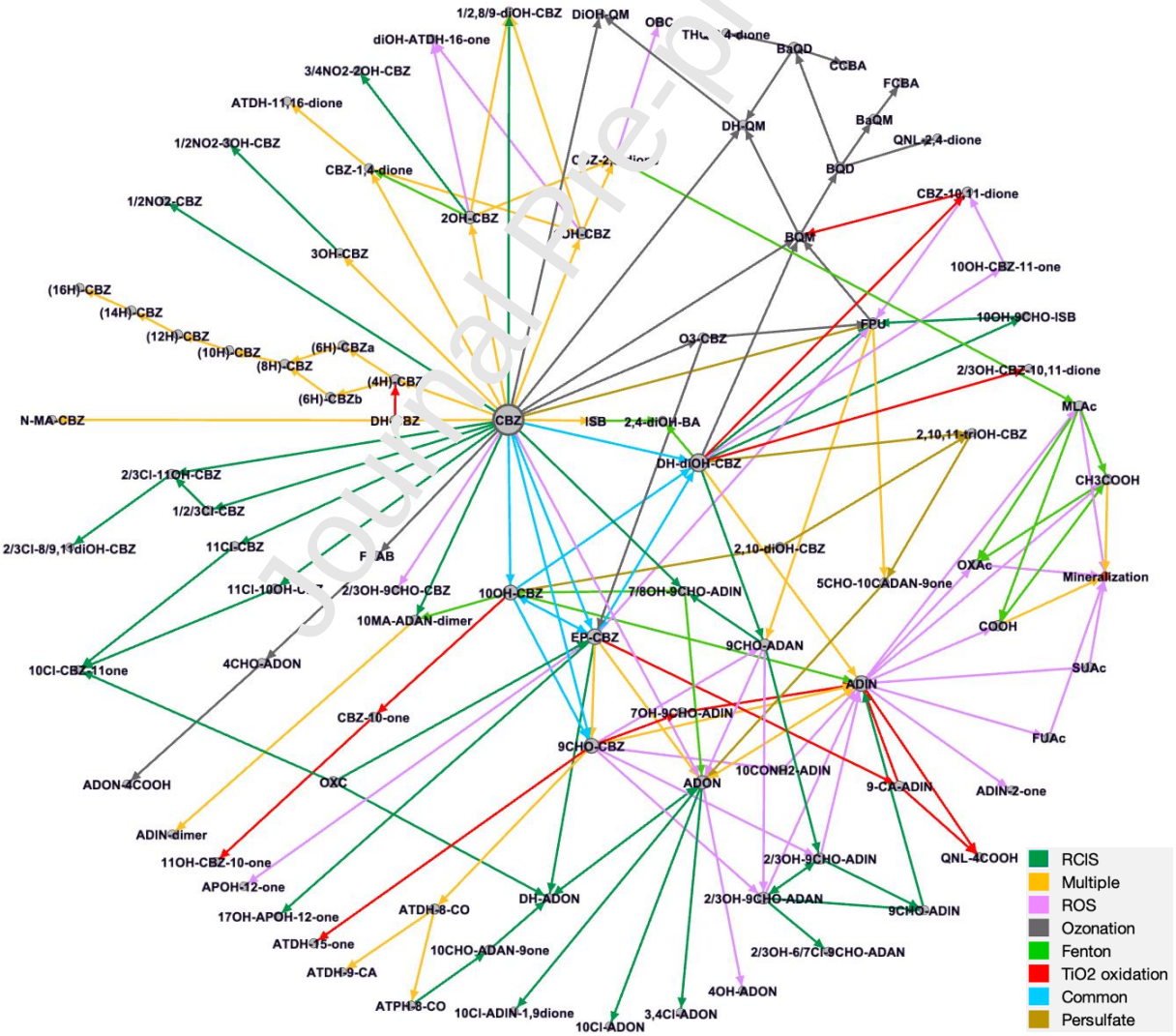


Figure 10: Map of CBZ degradation pathways leading to TP formation, classified by different processes. This figure takes into consideration both definitive and tentative structures. Chemical reactions are symbolized by directed arrows, which are colored differently according to the process. n = 34 papers: RClS (n=7); ROS (n=11); Ozonation (n= 4); Fenton (n=4); TiO2 oxidation (n=4); Persulfate (n=4), figure S4 supp. data.

The following paragraphs present the TPs and CBZ transformation pathways common to all oxidation processes (4-3-1), and those specific to each oxidation process (4-3-2 to 4-3-4).

4.3-1 TPs common to all six oxidation processes

Interestingly, four TPs were formed in all the 6 processes studied: carbamazepine-10,11-epoxide (EP-CBZ), 10,11-dihydro-10,11-dihydroxy-carbamazepine (DH-diOH-CBZ), 10-hydroxy-carbamazepine (10OH-CBZ) and carbamazepine-9-carboxaldehyde (9CHO-CBZ). They appear to be interconnected and were mentioned in a large number of research papers (n ≥ 10/34 papers). These four TPs are the result of an attack by radical species of the C10-C11 olefin double bond of CBZ. This is consistent with the fact that the π-bond is the primary reactive site. Indeed, many radicals such as Cl•, SO_4•- or •OH. and oxidants such as O_3, ClO_2, HOCl and $HFeO_4$, react quickly with electron donating groups (EDG) such as these carbon-carbon double bonds (Bourgin et al., 2017; Kråkström et al., 2020; Pan et al., 2017; Speight, 2018).

Several mechanisms lead to EP-CBZ formation. These include ozone attack, through the intermediary of molozonide-10,11-carbamazepine (O_3-CBZ) (Huerta-Fontela et al., 2011; Jamart et al., 2015a) or direct oxidation by radicals and oxidizing agents (Li et al., 2021; Pan et al., 2017). 9CHO-CBZ is formed from CBZ or 10OH-CBZ by a radical attack on the C10-C11 bond, followed by a rearrangement after opening of the azepine ring (Chiron et al., 2006; Jelic et al., 2013; Wang et al., 2022). 10OH-CBZ and DH-diOH-CBZ are formed by hydroxylation at the C10 and C11 positions. DH-diOH-CBZ can also result from EP-CBZ oxidation (Franz et al., 2020). Furthermore, after comparing these observations with previous toxicity analyses, it is interesting to highlight that, among the four TPs common to all processes, three are particularly toxic: EP-CBZ, 10OH-CBZ and 9CHO-CBZ (table S2, supplementary data). Until now, it had been impossible to link the chemical structures of the compounds to the processes that produce them.

Other TPs feature in the category “several processes”, such as 1/2/3OH-CBZ, CBZ-dione, ADIN, ADON, and DH-CBZ. ADIN and ADON are relatively stable intermediary products as few processes take degradation any further. These molecules then lead to the formation of many other TPs depending on the process used. This specific behavior of ADIN and ADON could be explained by their high hydrophobicity (LogD at pH 7 = 3.45 and 4.2, respectively). TPs from CBZ degradation were either generated by a single process, ozonation (e.g. BQM, BQD, BaQD), or produced by ROS attack (e.g. DH-diOH-CBZ, EP-CBZ, ADIN, etc.). Among these

TPs, several toxic molecules are produced by a number of processes including ozonation (e.g. BQM), Fenton (e.g. 2,4-diOH-BA), RClS (e.g. 1/2/10Cl-CBZ) or other ROS processes (e.g. 9CHO-ADAN). However, at this stage, it is difficult to classify WWTP processes according to the toxicity of their resulting CBZ TPs.

4.3-2 Oxidation by Reactive Oxygen Species (ROS)

Ozonation O_3 / ROS

The oxidation of CBZ by ozone (O_3) follows a distinct degradation pathway (pathway 1, Figure 6). The O_3 reacts directly through a selective reaction with carbon-carbon double bonds, aromatic rings, amines or thioethers groups. The olefin bond attack results in an opening of the CBZ ring, which produces TPs specific to this process, such as 1,1-bis(2-formylphenyl)urea (FPU), BQM, BaQD and other quinazoline derivatives. Moreover, O_3 generates hydroxyl radicals •OH (Kråkström et al., 2020; Lee et al., 2017) with a standard reduction potential of E_0 = 2.7-2.9 V (Table S3, supplementary data). This is higher than that of O_3 (E_0 = 2.06 V) and it promotes a faster, non-selective reaction on the different reactive sites of CBZ (Figure 4) by hydrogen abstraction, radical-radical reactions, electrophilic addition, and electron transfer (Kråkström et al., 2020; Mir-Tutusaus et al., 2021). There is consequently a wide range of TPs resulting from the attack of CBZ by hydroxyl radicals (Figure 10), reported throughout the literature: the main primary TPs are 1/2/3-hydroxy-carbamazepine (1OH-CBZ, 2OH-CBZ, 3OH-CBZ), 10,11-dihydrocarbamazepine (DH-CBZ), 4-hydro-carbamazepine (4H)-CBZ and the four TPs discussed previously. Intermediary TPs ADIN and ADON are also frequently identified in the literature (n = 10/34 papers).

Processes using metal catalysts and ROS

Fenton ($Fe(II)/H_2O_2$) and Fenton-like reactions ($Fe(III)/H_2O_2$) or photo-assisted Fenton reactions ($UV/H_2O_2/Fe(II)$ or $Fe(III)$) (Ali et al., 2018; Dai et al., 2012; Monsalvo et al., 2015) use hydrogen peroxide as an oxidant (H_2O_2) with water-soluble iron salts acting as a catalyst. The reaction can be UV-assisted to produce hydroxyl radicals •OH or other ROS (such as $O_2^{\bullet-}$, HO_2•), which will attack the CBZ. Furthermore, heterogeneous photocatalysis, using semiconductor oxides such as titanium dioxide (TiO_2), is also a promising solution for CBZ degradation. The TiO_2 particles can be shaped as a powder, mesh or nanotubes, for example, and are used for CBZ adsorption. TiO_2 activation by UV photocatalysis induces water oxidation

and dioxygen reduction, resulting in ROS. Interestingly, processes using metal catalysts (TiO_2 catalysis and Fenton) are responsible for specific reactions leading to the formation of small TPs, close to the mineralization stage, such as formic, acetic, oxalic, and malonic acids or quinoline-4-carboxylic acid (QNL-4COOH).

Figure 10 distinguishes ozonation, the Fenton reaction, TiO_2 photocatalysis and other ROS-based pathways since they are often studied separately in the literature. It is however important to specify that they are governed by the same ROS-based mechanism. Other examples of ROS-based processes include UV/H_2O_2, sunlight/H_2O_2, and UV/diketones. Where the transformation of CBZ into TPs is concerned, the differences between these processes lie in the degradation kinetics and the attack of different chemical sites on the CBZ molecule (Figure 4). Oxidation by ROS leads to the specific generation of a number of TPs, specifically formed from 9CHO-CBZ, ADIN or ADON, as well as succinic and fumaric acids (Figure 10).

4.3-3 Chlorination / reactive chlorine species RClS

Chlorine derivatives are frequently used in water disinfection processes and are now also the subject of research as a polishing treatment for MP removal (Pan et al., 2017; Suara & Bezares-Cruz, 2022; Xu et al., 2021; Yang et al., 2016). Indeed, reactive chlorine species, RClS, (Cl•, ClO•, Cl_2•$^-$, ClOH•$^-$) can be produced by UV activation of a number of oxidizing agents – Cl_2, ClO_2, HOCl, NaClO, NaCl, NH_2Cl, FeOCl – which react easily with EDG such as aromatic and phenolic groups and with organosulfur and secondary and tertiary amines (Pan et al., 2017). For this reason, they preferentially attack the tricyclic structure of CBZ. For example, Cl• and Cl_2•$^-$ display an elevated oxidation potential of E_0 = 2.47 V and 2.0 V, respectively; this is lower than that of the hydroxyl radical, but RClS are more selective (Xu et al., 2021).

A large number of TPs such as 1/2/3/11-chloro-carbamazepine (1/2/3/11Cl-CBZ) are consequently produced by the action of RClS. Since RClS are often coupled with ROS (due to the structure of the oxidizing agents containing oxygen atoms), some TPs may carry both chlorine and oxygen functions such as 11-chloro-10-hydroxy-carbamazepine (11Cl-10OH-CBZ) or 10-chloro-carbamazepine-11-one (10Cl-CBZ-11one). Furthermore, as the main TPs of CBZ, ADIN and ADON, are composed of aromatic groups, RClS are also able to attack them, resulting in the formation of chloro-derivatives: 3,4-dichloro-acridone (3,4Cl-ADON), 10-chloro-acridone (10Cl-ADON) or 10-chloro-acridine-1,9-dione (10Cl-ADIN-1,9-dione).

4.3-4 Persulfate oxidation / Sulfate radical $SO_4^{\bullet-}$

The sulfate radical $SO_4^{\bullet-}$ is produced by peroxymonosulfate (HSO_5^-) or peroxydisulfate ($S_2O_8^{2-}$) activation. It is a very strong oxidant (E_0 = 2.5-3.1 V, Table S3 supplementary data), which reacts easily with -OH, $-NH_2$ or -OR groups (Speight, 2018; Wu et al., 2019). Sulfate radicals can also react with the Cl- and organic matter present in the water matrix as well as with H_2O molecules to form ROS and RClS (Monteagudo et al., 2015; Wu et al., 2019). It is therefore difficult to distinguish TPs formed by sulfate radicals alone. Yet, whether the reaction is with ROS, RClS or $SO_4^{\bullet-}$, persulfate-based processes are responsible for the formation of numerous TPs. Interestingly, most TPs containing several hydroxyl groups were generated by persulfate oxidation processes (DH-diOH-CBZ, 2,10-diOH-CBZ, 2,10,11-triOH-CBZ).

Due to the complexity of CBZ degradation pathways and the wide range of TPs, it is difficult to predict which molecules will be generated during oxidation processes. This means that the risks they are likely to pose are also hard to anticipate. In this context, numerical tools could be of great interest for predicting degradation pathways.

5. Toward using numerical models to predict CBZ TPs

Looking at all the knowledge presented in this work, it stood out to us that understanding the generation mechanisms of TPs is crucial. To this aim, numerical models can help test different hypotheses of complex chemical reaction schemes. The objective here is to highlight current knowledge about the prediction by numerical tools of CBZ and TP generation, and the main issues faced.

Among the different types of numerical models, risk assessment models help target the chemical compounds to be considered when monitoring or conducting experimental studies on wastewater treatment plants, especially since there is no cutoff concentration (Delli Compagni et al., 2020). Quantitative Structure-Activity Relationship (QSAR) models provide information on the link between selected physicochemical parameters and toxicity (Voigt et al., 2021; Voigt & Jaeger, 2021). Fate models based on mass balance combined with stoichiometric and kinetic coefficients for individual mechanisms (e.g. sorption, volatilization, biodegradation, photolysis, etc.) predict the concentrations of MPs and TPs versus time in reactors (Plósz et al., 2013).

5.1 A need for a more relevant reaction scheme and more appropriate measurements

Table 1 presents the information found in the literature (10 papers) regarding the fate of CBZ and its TPs after undergoing oxidative processes. Only three papers (3/10) mentioned quantified TP concentrations (that is to say using standards during chemical analysis). They quantified 4, 1 and 4 TPs, among the 5, 9 and 24 TPs identified in each article respectively (De Laurentiis et al., 2012; König et al., 2016; Pan et al., 2017). All the other studies (7/10) reported peak areas for TPs, without providing any accurate quantification. It is reasonable to think that the lack of chemical standards can explain the low availability of TP concentration values. Mass balance calculations were carried out in one study only. Moreover, formation/degradation kinetic constants are never determined for TPs, whereas 7 out of 10 studies report a kinetic constant for the degradation of CBZ. This lack of information explains why the mechanism elucidation is still incomplete.

Table 1: Recent studies focusing on the identification and quantification, toxicity, kinetics, and mass balance of CBZ and TPs. The columns presenting the TPs' identification and quantification indicate the number of TP. The column "Reaction_pathway": 1 green = yes; 0 red = no. The kinetic constant column refers to the kinetics of CBZ degradation only. No values were found for the kinetic constants or stoichiometric parameters of CBZ TPs.

Reference	Process	TPs_identification	Reaction_pathway	TPs_quantification_concentration	Kinetic_constant	Mass_balance	Model	TPs_toxicity
De laurentiis et al., 2012	Photolyse	5	1	4	✔	✖	✔	✖
Jelic et al., 2013	TiO2 heterogeneous catalysis	7	1	0	✔	✖	✖	✔
Soufan et al., 2013	Chlorination (OHCl)	7	1	0	✔	✖	✖	✖
König et al., 2016	Catalytic hydrogenation	6	1	0	✖	✖	✖	✖
König et al., 2016	Electrochemical reduction	9	1	1	✖	✔	✖	✖
Pan et al., 2017	UV/Cl	24	1	4	✔	✖	✖	✔
Bu et al., 2018	UV/NH2Cl	11	1	0	✖	✖	✖	✔
Lu & Hu, 2019	UV/H2O2	6	1	0	✔	✖	✖	✔
Franz et al., 2020	TiO2 heterogeneous catalysis	17	1	0	✔	✖	✖	✖
Suara et al., 2022	UV/Cl	2	0	0	✖	✖	✖	✖
Wang et al., 2022	UV/NH2Cl	8	1	0	✔	✖	✖	✖

We noticed that the minimum data required (such as concentrations in the influent and sludge, kinetic constants and stoichiometric coefficients) were not frequently mentioned in the literature due to the limited amount of quantified experimental data for TPs. There is a lack of studies reporting quantified concentrations of TPs versus time. Mass balance is also hardly ever calculated (1 study/10) and yet it is the basis for predicting concentrations using a fate model. However, an issue of full mass balance calculations is the difficulty to perform the analysis of the particulate fraction. Indeed, for organic micropollutant quantification, it requires large sample volumes and the development of a specific analytical procedures (Becouze-Lareure et al., 2019). Several authors reported that the proportion of TPs quantified is low (<10%) compared to the quantity of degraded CBZ (Gulde et al., 2021; Plósz et al., 2013).

In addition, some papers reported three TPs that are often identified: EP-CBZ (7 studies/10), diOH-CBZ (6 studies/10) and ADIN (5 studies/10). These 3 TPs (non-quantified) should be added to models and more systematically quantified as they are encountered in most CBZ degradation processes (see part 4.3) and display a known toxicity (EP-CBZ and ADIN see part 4.2.3). Other TPs, such as 10OH-CBZ and 9CHO-CBZ are seldom studied and were mentioned in only 1 and 2 studies (/10) respectively. They should be studied more often since they are commonly found in all processes and also present a high level of toxicity. In other words, there is considerable room for progress in refining the reaction schemes considered in fate models. This gap requires determining the TPs that should be used in models to define the variables to be considered, and thereby improve the quantification capacity.

5.2 The main developments required to improve TP prediction models

Significant efforts and energy are still necessary to quantify the TPs of CBZ in order to predict their fate and thereby optimize the wastewater process. There are several analytical issues: the availability of analytical standards for all the TPs (commercial or synthesized) to be predicted, the development of suitable quantification limits for TPs (in the ng/L range), the development of specific preparation or quantification methods to analyze chemical structures different to those of CBZ (Celiz et al., 2009; Mathon et al., 2016), including a method to quantify TPs with hydrophobic properties ending up in solid matrices. This lack of analytical standards implies that future research on TPs should focus on definitive structures or on structure full elucidation rather than tentative structures that might not be accurate. In the medium term, the development of fate models will be supported by the characterization of TPs that are, as yet, unknown: non-target screening or isotopic methods are promising solutions to make progress in this direction.

Another area of progress would be to include information from different disciplines to predict chemical transformations, such as macroscopic equations from chemical properties (permeability, hydrophobicity, etc.) or microscopic characteristics (molecular orbital energy, Fukui index, and other quantum chemistry parameters). The determination of a quantum chemical method to calculate CBZ and TPs in the ozonation process is an encouraging example as shown by Lee et al. (2017). The EAWAG-BBD Pathway Prediction System (e.g.) (Gao et

al., 2009) used to predict plausible biodegradation pathways should also be further developed so that it can be applied in the context of oxidation processes.

Another issue of developing models is the incorporation of human metabolites as parent compounds, which lead to CBZ production by deconjugation and reverse reactions (see part 3.1). Their kinetic constants and stoichiometric coefficients still need to be determined before implementation in fate models. We also suggest developing a multi-approach generic model, applicable to various MPs in several processes, in order to predict TP concentrations. This would help in choosing the most relevant processes for MP and TP removal during wastewater treatment.

Conclusion

Carbamazepine (CBZ) and its transformation into TPs through several polishing oxidation processes such as ozonation, Fenton oxidation, UV and TiO_2 photocatalysis have been the focus of attention of several communities of researchers of different disciplines. Our thorough literature review counted at least 136 TPs generated by CBZ oxidation, through fast, non-selective radical reactions, including hydroxylation, oxygenation, dehydrogenation, cleavage or substitution. This work shows that TP generation is process-dependent, but 4 TPs are common to all polishing oxidation processes: carbamazepine-10,11-epoxide (EP-CBZ), 10,11-dihydro-10,11-dihydroxy-carbamazepine (DH-diOH-CBZ), 10-hydroxy-carbamazepine (10OH-CBZ) and carbamazepine-9-carboxaldehyde (9CHO-CBZ). Furthermore, 95% of the TPs studied display chronic toxicity toward aquatic organisms.

This review highlights the importance of conducting further works on the TPs generated during the oxidative treatment of CBZ. We suggest considering parent compounds, their human metabolites and their TPs to better characterize their fate in processes, and ultimately reduce discharges to the environment. Future requirements will be to quantify TP concentrations and parameters for computer-based fate predictions. Efforts in the future should focus on primary TPs such as EP-CBZ, DH-diOH-CBZ, 10OH-CBZ or 9CHO-CBZ because they are ubiquitous molecules with a certain level of toxicity. Furthermore, studies in real treatment conditions (e.g. full scale processes) are required for a better analysis of TPs generation. We also suggest developing a multi-approach generic model, applicable to various MPs in several processes, to predict TP concentrations. This would help us choose the most relevant processes for MP and TP removal during wastewater treatment.

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Credit authorship contribution statement

Jeanne Trognon: Conceptualization, Investigation, Writing - Original Draft, **Claire Albasi & Jean-Marc Choubert:** Validation, Supervision, Writing - Review & Editing

Highlights

- 135 transformation products were found in literature for oxidation of carbamazepine
- Their molecular structures, physico-chemical properties and toxicity are very diverse
- 95% of transformation products (TPs) display chronic toxicity on aquatic organisms
- 4 TPs were common to 6 processes, other are process-dependent
- Determining stoichiometric and kinetics parameters is urgent to predict TPs fate