



Review

Carbamazepine as a Possible Anthropogenic Marker in Water: Occurrences, Toxicological Effects, Regulations and Removal by Wastewater Treatment Technologies

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Abstract: Carbamazepine (CBZ), a pharmaceutical compound, has been proposed as an anthropogenic marker to assess water quality due to its persistence in conventional treatment plants and widespread presence in water bodies. This paper presents a comprehensive literature review on sources and occurrences of CBZ in water bodies, as well as toxicological effects and regulations of the drug. Given the documented side effects of CBZ on the human body when taken medicinally, its careful monitoring in water is recommended. CBZ residues in drinking water may provide a pathway to embryos and infants via intrauterine exposure or breast-feeding, which may cause congenital malformations and/or neurodevelopmental problems over long term exposure. An in-depth technical assessment of the conventional and advanced treatment technologies revealed the inadequacy of the standalone technologies. Compared to conventional activated sludge and membrane bioreactor processes, effective removal of CBZ can be achieved by nanofiltration and reverse osmosis membranes. However, recent studies have revealed that harsh chemical cleaning, as required to mitigate membrane fouling, can often reduce the long-term removal efficiency. Furthermore, despite the efficient performance of activated carbon adsorption and advanced oxidation processes, a few challenges such as cost of chemicals and regeneration of activated carbon need to be carefully considered. The limitations of the individual technologies point to the advantages of combined and hybrid systems, namely, membrane bioreactor coupled with nanofiltration, adsorption or advanced oxidation process.

Keywords: advanced oxidation processes (AOPs); activated carbon adsorption; carbamazepine toxicity; conventional treatment processes; membrane technology; occurrence

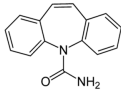
1. Introduction

The occurrence of pharmaceutically active compounds (PhACs) in environmental systems such as freshwater bodies has become a topic of growing concern over the last decade due to their

potential detrimental impacts on aquatic life and human health [1,2]. Because a large proportion of PhACs ends up in sewage via bodily excretion and indiscriminate disposal of unwanted/expired pharmaceuticals, disposal of untreated or ineffectively treated wastewater is considered a major source of their occurrence in environmental systems [3–6]. The need for effective removal of PhACs has resulted in the emergence of various advanced wastewater treatment technologies such as membrane technology and advanced oxidation processes [4].

The widespread occurrence of PhACs in wastewater and wastewater-impacted freshwater has triggered the establishment of water quality standards for their regular monitoring [5,7]. In this context, carbamazepine (CBZ) has been proposed as an anthropogenic marker of sewage contamination in freshwater bodies [8,9]. CBZ is an anticonvulsant and mood stabilizing drug used primarily in the treatment of epilepsy and bipolar disorder [10]. Table 1 summarizes the salient physicochemical properties of CBZ. CBZ is one of the most frequently detected pharmaceutical compounds in environmental systems [4,11]. It is ubiquitously present in raw wastewater in the high ng/L to low µg/L range and is only poorly removed by the conventional wastewater treatment plants (WWTP) [12,13]. Almost all the known advanced technologies have been tested for CBZ removal, however, none has appeared as a universal solution [14,15].

Table 1. Physicochemical and pharmacological properties of carbamazepine (modified after [16,17]).

Structure	
Formula	C ₁₅ H ₁₂ N ₂ O
CAS No.	298-46-4
Molecular Weight	236.2686 g·mol ^{−1}
Usage	Anticonvulsant/mood stabilizing drug
Water solubility	17.7 mg/L (25 °C)
Log P (octanol-water partition coefficient)	2.45
Log D at pH = 7 ^a	1.32
Henry's Law Constant	1.09 × 10 ^{−5} Pa·m ³ ·mol ^{−1} (25 °C)
Half-life (t _{1/2})	25–65 h
Excretion	72% absorbed and metabolized in liver, 28% excreted in feces
Metabolites in urine	CBZ, CBZ-epoxide, CBZ-diol, CBZ-acridan, 2-OH-CBZ, 3-OH-CBZ
Dosage	800–1200 mg/day
Other information	Autoinduction i.e., induces its own metabolism during continued intake

Note: ^a Log D is the logarithm of the distribution coefficient, which is the ratio of the sum of concentrations of all forms of the compound (ionised and unionised) in octanol and water at a given pH [3].

A number of interesting review papers have been published on the occurrences of micropollutants in environmental systems such as wastewater [18], surface water [4] and groundwater [5], as well as the performance of conventional treatment technologies for the removal of micropollutants [19–21]. The persistence of CBZ in conventional treatment processes leads to its widespread occurrence in water bodies. Thus, CBZ has been proposed as an anthropogenic marker to assess water treatment quality. CBZ removal by conventional WWTPs has been reviewed previously by Zhang et al. [16]. However, the efficacy of advanced treatment technologies has not been critically analyzed to date. In addition, toxicity of CBZ to aquatic species and human and relevant regulations have not been comprehensively reviewed.

In this paper, the occurrence of CBZ in wastewater and freshwater bodies (e.g., surface and groundwater) along with the associated influencing factors are systematically analyzed. In addition, the toxicological effects of CBZ on the aquatic ecosystem are critically discussed. Importantly, the factors governing the resistance of CBZ to the available wastewater treatment processes are elucidated, and the efficacy of advanced/emerging treatment processes is comprehensively discussed.

2. Occurrence in Aquatic Systems

Following consumption, up to 10% of CBZ is excreted from human body [4,22]. Recent studies have reported a few tens to several thousands of ng/L CBZ in municipal wastewater [22–24]. CBZ is poorly removed (typically less than 10%) by the conventional WWTPs [25–27]. Hence, treatment plant effluents are an important gateway for CBZ to enter surface and groundwater. Table 2 depicts the reported levels of occurrence of CBZ in WWTP effluent, surface water and groundwater. Generally, CBZ concentration has been reported to be higher in WWTP effluents as compared to surface water (Table 2) because dilution and natural attenuation can significantly reduce the concentration of pollutants [28]. CBZ is most likely to reach groundwater via bank infiltration of WWTP effluent [5,29]. In addition, seepage of landfill leachate and combined sewer overflows can contaminate groundwater [30]. In this section, the factors influencing the occurrence of PhACs including CBZ in raw wastewater, WWTP effluent and freshwater bodies are critically discussed.

Table 2. Occurrences of carbamazepine (CBZ) in municipal wastewater treatment plant (WWTP) effluent and freshwater.

Country	W WWTP Effluent		Surface Water	Groundwater
	No. of WWTPs *	Concentration (ng/L)	Concentration (ng/L)	Concentration (ng/L)
Canada	7	33–426 [a]	0.7–126 [b]	10–49 [c]
Germany	5	1075–6300 [d]	81–1100 [e]	1–100 [f]
Japan	20	81–86 [g]	0.1–34.7 [h]	1.64–97 [i]
South Korea	11	73–729 [j]	6–61 [k]	NA
Taiwan	4	290–960 [l]	0.5–120 [m]	NA
UK	3	152–4596 [n]	9–327 [o]	425–3600 [p]
USA	16	33–270 [q]	2–172 [r]	1.5–42 [s]

Notes: Data sources: [a] [31–34]; [b] [31,32,35]; [c] [36,37]; [d] [29,38–40]; [e] [38,40,41]; [f] [42,43]; [g] [44–46]; [h] [45, 47]; [i] [46,47]; [j] [48,49]; [k] [48–51]; [l] [52,53]; [m] [52]; [n] [54–56]; [o] [54,55,57,58]; [p] [30,59,60]; [q] [28,61–63]; [r] [61,63–65]; [s] [66,67]. * number of WWTPs surveyed for analyzing the concentration of CBZ; NA: not available.

2.1. Wastewater Treatment Plant Effluent

Since a number of factors can affect CBZ occurrence in wastewater, its concentration in WWTP effluent has been observed to be highly variable (30–6300 ng/L) (Table 2). The variation in WWTP effluent CBZ concentration (Tables 2 and 3) can be attributed to a number of factors such as CBZ production/consumption rate, environmental regulations, effectiveness of the WWTPs and the seasonal factors affecting WWTP performance [4,68,69].

Table 3. Seasonal variations in CBZ concentration along with its annual consumption rate.

Country	WWTP Effluent			Consumption Rate (tons/year)
	No. of WWTPs*	Concentration (ng/L)		
		Winter	Summer	
Australia	3	1480 [70]	NA	10 [16]
Austria	11	952 [71]	1337–1594 [3,71]	6 [16]
	11	1000 [72]	1500 [72]	
Canada	4	426 [32]	300 [33]	28 [16]
Finland	12	500 [6]	NA	4.8 [16]
	3	380–470 [73]	NA	
Germany	3	1900 [38]	2100 [40]	76 [16]
Korea	4	103–195 [48]	5–6 [48]	9.2 [48]
Switzerland	2	1000 [74]	950 [74]	4.1 [75]
	3	400–800 [26]	200–600 [26]	
UK	3 (Winter) 2 (Summer)	637–950 [56]	2499 [54]	40 [16]

Note: * Number of WWTPs surveyed for analyzing the concentration of CBZ in winter and summer; NA: not available.

Some studies have reported good correlation between CBZ concentration in wastewater with its production and consumption rate at the corresponding locations. For instance, Kasprzyk-Hordern et al. [22] and Choi et al. [48] studied the occurrence of PhACs such as carbamazepine, acetaminophen, sulfamethoxazole and codeine in wastewater from selected locations of UK and Korea, respectively. They observed that the concentration of pharmaceuticals in wastewater correlated well with their consumption rates in the respective countries [22,48]. By contrast, CBZ concentration in the WWTP effluent of Canada, Finland and Switzerland (Table 3) did not correlate well with CBZ consumption rates, indicating that there are other influencing factors.

PhAC occurrence in wastewater can be governed by, among other factors, their excretion rate after metabolism within human body. However, it is important to note that low excretion rate from human body does not necessarily lead to their detection in low concentration or frequency in water. For instance, excretion rate of CBZ and a few other PhACs such as ibuprofen, clofibric acid and gemfibrozil is generally low (1–10%), while excretion rates of up to 70% were reported for some PhACs such as atenolol and paracetamol [76,77]. However, as noted above, CBZ is detected in significantly high concentration in raw and treated wastewater because of its low removal by the natural attenuation process and by the WWTPs [4,78].

Seasonal variations that affect the flow pattern of wastewater in combined sewerage system can lead to the change in wastewater composition. In a study by Kasprzyk-Hordern et al. [22], an increase of up to two-folds in the concentration of PhACs including CBZ was observed during dry weather. Moreover, WWTP effluent CBZ concentration in some countries such as Australia [70], Switzerland [26,74] and USA [79] were reported to be consistently higher in winter than in summer (Table 3), which can also be attributed to drier weather conditions in winter [22,26].

2.2. Surface Water

The major source of CBZ in surface water is the disposal of WWTP effluent [80,81]. After its release to freshwater bodies, different natural attenuation processes such as photolysis, aerobic biodegradation, sorption onto sediments and dilution in surface water play an important role in reducing CBZ concentration [81,82]. However, in-stream attenuation rate varies depending on the physicochemical properties of the PhACs and the local environmental conditions. For instance, Kunkel and Radke [83] observed different attenuation rates for 10 pharmaceuticals including CBZ in river water, and this variation was generally attributed to the physicochemical properties of the compounds. Similarly, in a study that investigated the relationship between attenuation rate and physicochemical properties of 225 micropollutants [82], high attenuation rate was obtained for compounds having medium to low volatility ($-4 < \log K_{aw} < -2$) and significant hydrophilicity ($0 < \log K_{ow} < 4.5$). This is because these micropollutants are better exposed to in-stream biotic (e.g., biotransformation) and abiotic (e.g., photolysis) attenuation processes as compared to hydrophobic micropollutants that are adsorbed onto river sediments [84]. Since $\log K_{ow}$ value for CBZ falls between 0–4.5 [17,81], its concentration is expected to be reduced via in-stream attenuation processes [85].

Water dilution can reduce CBZ concentration in surface water. Indeed, higher concentrations of PhACs including CBZ was reported in surface water bodies during dry weather as compared to that observed in wet weather [86]. In a study by Wang et al. [87], CBZ concentration in surface water was lower in samples that were collected during summer than those collected during winter. This is probably because of the enhanced biodegradation rate due to higher temperature in summer [4,81]. Heavy rainfall can often cause increased leaching of PhACs from openly dumped municipal and hospital solid waste. Storm water runoff can lead these compounds to surface water, consequently increasing the concentration of PhACs in surface water [23,88].

Sorption onto river sediments has been reported to reduce the aqueous phase concentration of hydrophobic PhACs along the river segment. However, in this case, concentration of these pollutants is not significantly reduced by the in-stream biotic and abiotic attenuation processes [81,84,89]. In a study by Riml et al. [90], concentration of two PhACs, namely bezafibrate and metoprolol, was observed to

be mainly reduced by sorption onto sediments, while the role of biotransformation and photolysis was insignificant. Since it is a moderately hydrophobic compound ($\log K_{ow} = 2.45$), reduction in CBZ concentration has been attributed to photolysis and sorption [85,91].

Residues of CBZ are introduced into sea water via surface runoff and groundwater discharge [92]. Concentrations of CBZ in sea water are very low. Weigel et al. [93] detected CBZ in sea water at a concentration of 2 ng/L by using a method that comprised solid-phase extraction and GC/MS quantification with a detection limit of 0.1 and 0.7 ng/L. Although this value seems insignificant, the fact that CBZ is detectable in sea water indicates that it is an extremely persistent compound. Also interesting to note, is that residues of CBZ can accumulate in soil through seepage of irrigation water, and due to sewage sludge used as fertilizer [94,95]. A study conducted by the US Geological Survey found an average CBZ concentration of 41.6 ng/mg in the sediment of 44 rivers across the US [96].

2.3. Groundwater

Groundwater constitutes approximately 30% of the total freshwater resources in the world. Because 70% of the freshwater resources are frozen, groundwater represents 97% of freshwater available for human use [97]. Groundwater is the major source of freshwater for domestic and industrial use in many countries. PhACs can contaminate groundwater through different pathways such as percolation of landfill leachate, artificial recharge, percolation of storm water runoff and leakages from sewers and septic tanks [5]. Depending on the organic fraction of the soil, high attenuation of some PhACs such as hydrophobic compounds ($\log D > 3$) can occur in soil strata en route to groundwater [98,99]. Nevertheless, CBZ concentration in groundwater has been reported to be in the range of 1–100 ng/L in available studies from Canada, Germany, Japan and USA (Table 2). However, a higher concentration of CBZ (425 to 3600 ng/L) in groundwater was observed at a site in UK [30,59,60]. This is probably because CBZ concentration was also higher in WWTP effluents and surface water in that location (Tables 2 and 3). Indeed, Stuart et al. [30] reported that the occurrence of CBZ in groundwater is most likely to be derived from the bank infiltration of WWTP effluent or through surface water/groundwater interaction. Concentration of CBZ in groundwater may not be as high as in surface water but it is still an issue that should be addressed on a priority basis.

3. Toxicological Effects

CBZ is widely detected in water bodies, hence it is essential to evaluate its effects on the ecosystems. A number of studies have assessed the ecotoxicity of CBZ (Table 4). In an experiment conducted by Ying et al. [25], the respiratory quotient value for CBZ was 4.69, indicating potential risks to aquatic organisms. However, other experimental studies have shown that CBZ may not pose an immediate risk. For example, Ferrari et al. [100] studied the toxicological effects of CBZ on bacteria, algae, microcrustaceans and fish. It was observed to have a relatively limited acute ecotoxicity on the tested organisms.

Table 4. Effect of CBZ exposure on aquatic species under different exposure conditions.

Species	Critical Effects	Exposure Time	LC ₅₀ (mg/L)	EC ₅₀ (mg/L)	NOEC (mg/L)	LOEC (mg/L)	References
Water flea							
<i>Daphnia magna</i>	Mortality	2 days	111	-	-	-	[101]
<i>Chironomus dilutus</i>	Survival	10 days	47.3	10.2	-	-	[102]
<i>Hyalella azteca</i>	Growth	10 days	1.5	9.5	-	-	[102]
<i>Brachionus calyciflorus</i>	Reproduction inhibition	2 days	-	-	0.4	0.8	[100]
<i>Ceriodaphnia dubia</i>	Reproduction inhibition	7 days	-	-	0.025	0.1	[100]
<i>Daphnia magna</i>	Mobility inhibition	2 days	-	77.7	-	-	[100]
<i>Daphnia magna</i>	Immobilization	2 days	-	97.8	-	-	[103]
Bacteria							
<i>Aliivibrio fischeri</i>	Bioluminescence	30 min	-	64.2	-	-	[100]
<i>Vibrio fischeri</i>	Bioluminescence	5 min	-	87.4	-	-	[103]
Algae							
<i>Chlorella vulgaris</i>	Growth inhibition	24 h	-	110.9	-	-	[103]
<i>Desmodesmus subspicatus</i>	Inhibition of average growth rate	3 days	-	74	-	-	[104]
<i>Raphidocelis subcapitata</i>	Growth inhibition	4 days	-	89	>100	>100	[100]
Rainbow trout							
<i>Oncorhynchus mykiss</i>	Condition factor	42 days	-	-	-	2	[105]
<i>Oncorhynchus mykiss</i>	Antioxidant responses in muscle	42 days	-	-	-	0.001	[105]
<i>Oncorhynchus mykiss</i>	Changes in RNA-DNA ratio	42 days	-	-	-	2	[105]
Zebrafish							
<i>Danio rerio</i>	Developmental effects	3 days	>245	85.6	30.6	-	[106]
<i>Danio rerio</i>	Embryos and larvae mortality	10 days	-	-	25	50	[100]
Mycorrhizal fungus							
<i>Glomus intraradices</i>	Spore production	28 days	-	0.1	-	-	[107]
Duckweed							
<i>Lemna minor</i>	Inhibition of average growth rate	7 days	-	25.5	-	-	[104]
Cnidarian							
<i>Hydra attenuate</i>	Morphological changes	4 days	29.4	15.5	1	5	[108]

Notes: LC₅₀: lethal concentration to kill/inactivate 50% of population; EC₅₀: effective concentration that gives half-maximal response; NOEC: no-observed effect concentration; and LOEC: lowest-observed effect concentration. “-”: not available.

Possible human health effects of long-term exposure to different pharmaceuticals may include endocrine disruption, induction of antibiotic resistance in human pathogens, genotoxicity, carcinogenicity, allergic reactions, and reproductive and/or developmental effects [109,110]. Limited research has been conducted on the potential human health risks of long-term exposure to CBZ residues in water. Risk assessments conducted to date have generally shown that the trace concentrations of CBZ detected in drinking water does not pose an unacceptable health risk to humans [111]. However, careful monitoring must continue, given the documented side effects of CBZ on the human body when taken medicinally.

CBZ is the main cause of the Stevens–Johnson syndrome and its associated disease toxic epidermal necrolysis in Southeast Asian countries due to its intake medicinally [112]. These are two forms of a life-threatening skin condition with an overall mortality rate of 30%, in which cell death causes the epidermis to separate from the dermis [113]. Recent studies have also revealed that intrauterine exposure of CBZ is associated with spina bifida [114] and neuro developmental problems [115] of human embryo when gravidas were exposed to CBZ monotherapy. Atkinson et al. [116] also reported higher fetal losses and congenital malformation rates among women who were prescribed carbamazepine during pregnancy. Because the residue of CBZ in drinking water may provide a pathway to embryo and infant via intrauterine exposure or breast-feeding, the presence of CBZ in groundwater, and drinking water remains a significant concern warranting further systematic risk assessment studies.

4. Regulations

Strict regulations were introduced in the 1960s in many countries for pharmaceutical production [117]. For example, in Australia, the Therapeutic Goods Administration (TGA) undertakes assessments, similar to those of the US Food and Drug Administration (FDA), to “ensure that prescription and ‘over-the-counter’ medicines, medical devices, and related products, supplied in or exported from Australia, meet appropriate standards” [118].

Despite the release of a significant amount of PhACs into the environment, there is limited literature available on regulations for the presence of pharmaceuticals in water [117]. The regulatory framework set out for pharmaceuticals governs the quality and safety of use, rather than the health and environmental risks of long-term exposure to drinking water containing trace concentrations of pharmaceuticals. In the U.S., the FDA requires that an environmental assessment report be carried out when the expected concentration of the active ingredient of the pharmaceutical in the aquatic environment is equal to or higher than 1 µg/L. However, some state departments, such as the Minnesota Department of Health regulates that the CBZ concentration in drinking water must not exceed 40 µg/L [119]. Australian regulations require CBZ concentration in drinking water to be less than 100 µg/L [120]. In Europe, authorization for pharmaceutical production requires an environmental risk assessment [118]. In many countries, however, health risk-based standards and limit values for the presence of pharmaceuticals in drinking water have either not been set or are insufficient [111].

5. Biological Treatment Technologies for CBZ Removal

5.1. Activated Sludge Based Processes

Removal of PhACs by different biological treatment processes has been studied extensively [3,4]. In conventional activated sludge (CAS) processes, microorganisms generate energy by utilizing bulk organics present in wastewater as a primary source of food (also known as substrate). A part of this energy is used by the microorganisms for their cell growth and remaining energy is used for cell maintenance [121–123]. Since some PhACs such as antibiotics can be toxic to microorganisms and can inhibit their growth, an additional growth substrate (i.e., co-metabolism) is required to maintain microbial growth and diversity for adequate biodegradation [124,125].

The CAS process involves the application of microorganisms for the degradation of pollutants [16]. A membrane bioreactor (MBR) is an integration of the CAS process with an ultrafiltration (UF) or a microfiltration (MF) membrane for effective solid-liquid separation [3,126,127]. Removal of CBZ by CAS and MBR at different operating conditions such as hydraulic retention time (HRT), solids retention time (SRT) and initial concentration is presented in Table 5.

Table 5. CBZ removal by conventional activated sludge (CAS) and membrane bioreactor (MBR) under different operating conditions.

Process Type	Influent Concentration (ng/L)	SRT (days)	HRT (h)	Aerobic/Anoxic	Removal (%)	References
CAS	240	3	12	aerobic	negligible	[128]
	156	10	11.5	both	negligible	[126]
	350–1850	52–114	12.5–13.6	both	negligible	[71]
	350	2–20	1.5–20	both	negligible	[6]
	15–270	3.8–8.4	7.1–9.4	aerobic	negligible–80	[129]
	1000	10	7.3	both	negligible	[74]
	670–704	19	NA	aerobic	0	[130]
	10–20	11–15	9–17	both	negligible–25	[131]
MBR	200–600	15–25	16–24	aerobic	negligible	[132]
	240	infinite	14	aerobic	negligible	[128]
	156	>60	15	aerobic	negligible	[126]
	156	>60	7.2	aerobic	negligible	[126]
	704–1850	10–55	0.5–4	both	negligible	[71]
	1000	16	13	both	25	[74]
	704–1200	22	NA	both	negligible	[130]
	750,000	infinite	24	near-anoxic	68	[133]
	5	88	26	aerobic	40	[27]
	1400	70	24	aerobic	10	[134]

Notes: CAS: conventional activated sludge process; MBR: membrane bioreactor; SRT: solid retention time; HRT: hydraulic retention time; NA: not available.

In the CAS process, a settling tank is used to separate the treated water from the sludge. In MBR, this solid-liquid separation is performed by filtration via MF or UF membranes. Effective retention of the activated sludge by the membrane in MBR decouples SRT from HRT, thereby allowing the operation of the activated sludge based bioreactor at higher mixed liquor suspended solid concentration (MLSS) and longer SRT [135,136]. It has been reported in several studies that MBR provides better aqueous phase removal of moderately biodegradable PhACs as compared to the CAS process [126,137]. For example, removal of the nonsteroidal anti-inflammatory drug diclofenac by MBR was 56%, while its removal was 26% in CAS [138]. Similarly, MBR achieved up to 20% better removal of another nonsteroidal anti-inflammatory drug naproxen [126]. However, CBZ removal by both CAS and MBR has been reported to be poor and unstable (Table 5). Poor removal of CBZ can be attributed to its physicochemical properties such as molecular structure and hydrophilicity [71,134,139,140].

Sorption onto the activated sludge can increase the overall removal of PhACs. CAS and MBR are observed to achieve high removal (>80%) for hydrophobic PhACs ($\log D > 3$) but lower removal (typically < 20%) for hydrophilic PhACs [141,142]. Since CBZ is moderately hydrophobic, its removal via sorption onto activated sludge has been reported to range between 5 to 20% only [16,27]. This suggests that CBZ removal depends on its intrinsic biodegradability, which is governed by its molecular properties. In general, simple structured PhACs, especially without branched/multi chain groups, are readily degradable [134,143]. Moreover, PhACs containing an electron withdrawing functional group (EWG), such as carboxyl, halogen and amide, are resistant to biological treatment [134]. Indeed, CBZ contains an EWG (i.e., amide) that makes it resistant to biodegradation.

It is important to note that operating conditions such as SRT, HRT and MLSS concentration can also influence the removal of some PhACs by activated sludge [3,139]. However, because CBZ is a hardly biodegradable compound, available reports indicate limited influence of these parameters on CBZ removal. Zhang et al. [16] did not observe any CBZ removal by CAS even at an SRT of 100 days.

Similarly, Radjenovic et al. [128], observed no improvement in CBZ removal following the increase in the SRT of both CAS and MBR. By contrast, Wijekoon et al. [27] achieved 40% removal of CBZ in MBR at a SRT of 88 days. Notwithstanding the fact that the experimental conditions may have been different in these studies, the observations here suggest that the removal and fate of CBZ during biological treatment processes depend on multiple factors.

The effect of redox conditions or dissolved oxygen on the removal of PhACs in MBR has been reported in a few studies [144–146]. In a study by Suarez et al. [147], PhACs were classified based on their biodegradation potential under aerobic and anoxic conditions: they observed that readily degradable PhACs such as fluoxetine and ibuprofen were biodegradable under both anoxic and aerobic conditions, while a few such as roxithromycin, naproxen, diclofenac and erythromycin were persistent in anoxic conditions but highly biodegradable under aerobic conditions. However, hydrophilic PhACs including CBZ were resistant to biodegradation in both aerobic and anoxic conditions [147], and a negligible difference in CBZ removal by sequential anoxic–aerobic MBR versus conventional aerobic MBR was noted. Notably, however, Hai et al. [139] reported that near-anoxic conditions (DO = 0.5 mg/L) can be a favorable operating regime for CBZ removal. They explained that ‘sequential anoxic-aerobic’ and ‘continuous near-anoxic (DO = 0.5 mg/L)’ operation modes were different. In the former, oxygen transfer from the aerated compartments to the anoxic zone due to the sludge recirculation may influence the removal efficiency [139].

5.2. White-Rot Fungi and Their Extracellular Enzymes

White-rot fungi (WRF) can degrade a variety of recalcitrant pollutants (e.g., poly-aromatic hydrocarbons and PhACs) that are poorly degraded by bacteria-dominated activated sludge [148–152]. In presence of a readily degradable substrate, WRF produce one or more type of extracellular enzymes such as laccase and lignin peroxidases (LiP). These enzymes catalyze the degradation of recalcitrant pollutants over a wide range of pH [153,154]. In addition to the extracellular enzymes, Golan-Rozen et al. [155] observed that the intracellular enzyme viz cytochrome P450 plays a vital role in CBZ degradation by whole-cell WRF. They demonstrated that the degradation of CBZ reduced from 99% to approximately 15% when cytochrome P450 was inhibited [155]. Whole-cell WRF and their extracellular enzymes have been studied extensively for enhanced removal of PhACs as depicted in Table 6.

Table 6. Removal of CBZ by white-rot fungi and their extracellular enzymes.

Bioreactor Type	WRF Species/Enzyme Type	HRT (h)/Incubation Time (days)	Initial Concentration (ng/L)	Removal Efficiency (%)	References
Removal by whole-cell WRF					
Stirred tank (batch)	<i>Bjerkandera</i> sp. R1	14	1,000,000	99	[156]
Stirred tank (batch)	<i>B. adusta</i> (Laccase, LiP and MnP)	14	1,000,000	99	[156]
Stirred tank (batch)	<i>T. versicolor</i> (Laccase, LiP and MnP)	2	10,000	75	[157]
Stirred tank (batch)	<i>T. versicolor</i> (Laccase, LiP and MnP)	1	100,000	2	[158]
Stirred tank (batch)	<i>P. ostreatus</i> (Florida N001) (Laccase, MnP)	32	1000	50	[155]
Stirred tank (batch)	<i>P. ostreatus</i> (Florida F6) (Laccase, MnP)	32	1000	60	[155]
Stirred tank (batch)	<i>P. ostreatus</i> (PC9) (Laccase, MnP)	32	1000	99	[155]
Stirred tank ^a (continuous)	<i>P. chrysosporium</i> (MnP, LiP)	24	500,000	25–60	[159]
Fluidized bed ^a (continuous)	<i>T. versicolor</i> (Laccase, MnP, LiP)	72	200,000	95.6	[160]
Membrane bioreactor (continuous) ^a	<i>T. versicolor</i> (Laccase, MnP, LiP)	48	5000	20	[161]

Table 6. Cont.

Bioreactor Type	WRF Species/Enzyme Type	HRT (h)/Incubation Time (days)	Initial Concentration (ng/L)	Removal Efficiency (%)	References
Removal by extracellular enzymes					
Stirred tank (batch)	Laccase from <i>A. oryzae</i>	1	100,000	<5	[162]
Stirred tank (batch)	Laccase from <i>T. versicolor</i>	2	10,000	5	[157]
Stirred tank (batch)	LiP from <i>P. chrysosporium</i>	4	NA	10–15	[163]
Membrane bioreactor (continuous)	Laccase from <i>A. oryzae</i>	8	5000	<5	[162]
Membrane bioreactor (continuous)	Laccase from <i>A. oryzae</i>	8	5000	7	[164]

Notes: ^a Indicates fungal bioreactor operated under non-sterile conditions; NA: not available.

Depending on the fungal species, efficient removal of CBZ has been achieved by whole-cell WRF in sterile batch bioreactors (Table 6). Since WRF species produce different combinations of extracellular enzymes, their performance of CBZ degradation might be different. For instance, Rodarte-Morales et al. [156] observed that *Bjerkandera* sp. R1 and *Bjerkandera adusta* both achieved almost complete removal (99%) of CBZ at an initial concentration of 1 mg/L in a batch bioreactor over an incubation time of 14 days. On the other hand, *Trametes versicolor* was reported to achieve less than 5% removal when CBZ was incubated in a whole-cell batch bioreactor at an initial concentration of 0.1 mg/L and an incubation time of 24 h [158]. Difference in performance was not only observed in case of different WRF species but also in different strains of a WRF species. For instance, Golan-Rozen et al. [155] studied the removal of CBZ by three different strains of *Pleurotus ostreatus* under identical operating conditions. They observed that *P. ostreatus* (PC9) achieved 99% CBZ removal, while a moderate removal (50–60%) was achieved by other two strains, namely *P. ostreatus* (Florida N001) and *P. ostreatus* (Florida F6).

Extracellular enzymes produced by WRF species have been studied for the removal of PhACs including CBZ in both batch and continuous-flow enzymatic bioreactors (Table 6). Degradation of PhACs by extracellular enzymes such as laccase occurs due to the transfer of a single electron from the pollutant to the active sites of the enzyme. Similar to the activated sludge based treatment process, the extent of degradation by an enzyme also depends on the molecular properties of the PhACs. Since CBZ contains a recalcitrant EWG (i.e., amide), its degradation by extracellular enzymes has been reported to range only between 5–15% [157,162]. High removal of CBZ in whole-cell fungal bioreactor as compared to enzymatic membrane bioreactor was explained by Golan-Rozen et al. [155]. They observed that the intracellular enzyme viz cytochrome P450 plays a vital role in CBZ degradation by whole-cell WRF. They demonstrated that the degradation of CBZ reduced from 99% to approximately 15% when cytochrome P450 was inhibited [155].

Performance of WRF for PhAC removal has been predominantly assessed under sterile conditions to avoid bacterial contamination [158,165,166]. This is because bacterial contamination under non-sterile conditions can negatively affect the performance of whole-cell WRF [154,167]. Indeed, poor removal of CBZ has been reported in fungal bioreactors operated under non-sterile conditions as compared to sterile fungal bioreactors [168–170]. For instance, Nguyen et al. [161] reported only 5% CBZ removal in a whole-cell fungal membrane bioreactor. In another study, no CBZ removal was observed in a non-sterile fluidized bed fungal bioreactor during the treatment of hospital wastewater [171]. To avoid bacterial contamination, a number of strategies such as fungal biomass replacement/renovation and pre-treatment of wastewater have been proposed. These strategies have been reviewed by Asif et al. [154].

6. CBZ Removal by Advanced Physicochemical Treatment Technologies

6.1. Performance of Nanofiltration and Reverse Osmosis Membranes

Nanofiltration (NF) and reverse osmosis (RO) are pressure-driven membrane filtration technologies [172,173]. They utilize semi-permeable membranes to primarily target the removal of dissolved contaminants. Both NF and RO have been studied for the removal of PhACs from secondary treated wastewater and freshwater, producing excellent quality effluent [173–175]. Several studies have shown that both NF and RO membranes can effectively retain CBZ, with a typical removal efficiency of greater than 95% [176,177]. Table 7 illustrates representative examples of CBZ removal by NF/RO membranes under a wide range of operating conditions.

Table 7. CBZ removal from various water matrices by nanofiltration (NF) and reverse osmosis (RO) membranes under different operating conditions.

Membrane Type (Pore Size)	Configuration	Water Matrix	Initial CBZ Concentration (ng/L)	Applied Pressure (psi)	Removal (%)	References
NF (0.34 nm)	Flat-sheet	Groundwater	84.5	NA	>98	[176]
NF (0.27 nm)	Flat-sheet (tight)	MBR permeate	150	150	97.3 ± 0.6	[178]
NF (0.42 nm)	Flat-sheet (loose)	MBR permeate	150	75	71.2 ± 3.1	[178]
NF	Flat-sheet	WWTP effluent	500–850	4.35	6	[179]
NF	Flat-sheet	WWTP effluent	500–850	10	8	[179]
NF (0.84 nm)	Flat-sheet	Primary effluent	2000	72	74	[180]
NF	Spiral-wound	Hospital wastewater	1000	98	88	[181]
NF (0.84 nm)	Flat-sheet	Synthetic wastewater	750,000	261	80 ^a , 60 ^b	[182]
NF (0.68 nm)	Flat-sheet	Synthetic wastewater	750,000	261	95 ^a , 90 ^b	[182]
NF (0.84 nm)	Flat-sheet	Synthetic wastewater	750,000	986	70 ^a , 20 ^b	[183]
NF (0.84 nm)	Flat-sheet	Synthetic wastewater	750,000	261	80 ^a , 90 ^b	[184]
RO (0.34 nm)	Flat-sheet	Groundwater	84.5	NA	>98	[176]
RO	Flat-sheet	MBR permeate	150	250	91 ± 8.4	[178]
RO	Flat-sheet	MBR permeate	150	150	97.9 ± 1.5	[178]
RO	Flat-sheet	Primary effluent	1000	72	100	[180]
RO	Spiral-wound module	Hospital wastewater	1000	196	99	[181]

Notes: ^a Virgin membrane; ^b fouled membrane; NA: not available.

Conceptually, NF membranes can retain PhACs via following mechanisms: (i) sorption of a solute on the membrane surface; (ii) size exclusion i.e., the sieving property of the membrane; and (iii) charge repulsion. However, electrostatic interaction cannot contribute to CBZ removal by the charged NF membrane, since CBZ remains neutral over a wide range of pH [14]. Hence, the molecular weight cut-off (MWCO) of NF/RO membranes is an important parameter for CBZ removal. In a study by Bellona et al. [177], efficient retention of CBZ by the RO membrane was attributed to size exclusion mechanism because the molecular weight of CBZ (i.e., 236 g/mole) was greater than the MWCO of the RO membrane. In a study by Comerton et al. [178], a loose NF membrane (MWCO = 400 g/mole) and a tight NF (MWCO = 200 g/mole) achieved 7 and 67% CBZ removal, respectively, thus, exemplifying the role of membrane MWCO in CBZ removal. In another study by Nghiem & Hawkes [185], efficient rejection of CBZ was reported for the NF90 membrane (MWCO < 200 g/mole) as compared to the NF270 membrane (MWCO > 300 g/mole).

Membrane fouling can affect the rejection of PhACs by NF membranes due to change in membrane surface properties (Table 7). Notably, CBZ rejection by the NF membranes is governed by the type of foulants. For instance, CBZ rejection by the NF270 membrane was reduced by 5 and 10% due to fouling caused by humic acid and sodium alginate, respectively [186]. This reduction in CBZ removal can be attributed to its diffusion into permeate following its adsorption on the fouling layer formed on the membrane surface. A more dramatic reduction in CBZ rejection (by 50%) was reported when MBR permeate (comprising multiple foulant materials) was fed to the NF-filtration system [186,187]. In general, the combination of membrane fouling and scaling can affect pollutant removal more severely. Chemical cleaning is performed to clean fouled membranes. However, recurrent chemical

cleaning can affect membrane properties and, in turn, CBZ rejection. For example, significant reduction in CBZ rejection was observed due to cleaning the NF membrane by using caustic soda [184].

Natural organic matter (NOM) are ubiquitously present in surface water bodies. Since NF/RO processes are widely used for surface water treatment [188], the effectiveness of NF/RO for CBZ rejection in presence of NOM is vital. Comerton et al. [189] observed a statistically significant improvement in CBZ rejection during nanofiltration of pure water spiked with NOM. This is because CBZ, which is a moderately hydrophobic compound, can adsorb on NOM. However, a significant decrease in the rejection of CBZ was observed with concentration of the cations (calcium, magnesium, sodium) doubled. It has been hypothesized that increases in ionic strength and divalent cation concentration can cause conformational changes to NOM macromolecules. This may alter the presentation of sites for compound association leading to a reduction in NOM–compound complexation [189]. Therefore, the decrease in CBZ rejection in the natural waters with increase in cation concentration may be due to reduced association of CBZ with NOM.

6.2. Adsorption of CBZ by Activated Carbon

Activated carbons including granular activated carbon (GAC) and powdered activated carbon (PAC) are widely used as tertiary treatment processes primarily for color and odor removal from drinking water. GAC and PAC have also shown great potential for the removal of PhACs from secondary (i.e., biologically treated) wastewater [4,190,191]. Adsorption/removal of a pollutant by GAC/PAC is governed by the following mechanisms: (i) the electron donor–acceptor complex; (ii) the π – π dispersion interactions; (iii) hydrophobic interactions; and (iv) solvent effects that controls the solubility, reactivity and reaction kinetics [192,193]. The key properties of an adsorbent that can affect the efficacy of adsorption process include but are not limited to surface area, dose, surface chemistry and morphology, while water partitioning coefficient ($\log K_{ow}$), acid dissociation coefficient (pK_a), molecular structure and size of the pollutants can influence the extent of adsorption by GAC/PAC [194]. In previous studies, efficient removal of PhACs has been achieved by GAC having larger pore size, because it can effectively adsorb pollutants with different shapes and size. Moreover, it was noted that pore volume has more influence on the adsorption of PhACs than specific area, and larger pore volume can achieve higher removal efficiency [195,196]. Representative examples of CBZ removal by GAC/PAC from a variety of water matrix (e.g., surface water and MBR effluent) is provided in Table 8.

Table 8. Performance of granular activated carbon (GAC) and powdered activated carbon (PAC) for CBZ removal from various water matrices.

AC Type	Water Matrix	Initial CBZ concentration (ng/L)	Contact Time (min)	Removal (%)	References
GAC	Synthetic wastewater	1000	1440	99–80 ^a	[197]
	Ozonation effluent	36	–	88 ^b	[198]
	Groundwater	9	15	>75 ^c	[199]
	Surface water	25	–	99	[200]
	Disinfected surface water	600	1.5–3	79 ^d	[201]
	WWTP effluent	67	–	30 ^e	[202]
	GAC added to an activated sludge based bioreactor	22,000	1440	43 ^f	[203]
	WWTP effluent	4000	100	80 ^g	[204]
	WWTP effluent	30–100	130	>99	[190]
PAC	Surface water	78	300	95 ^h	[205]
	Surface water	78	300	36 ⁱ	[205]
	MBR permeate	1000	30	99.4 ^j	[206]
	Surface water	50	240	80	[207]
	WWTP effluent	30–100	20–40	95–100	[190]

Notes: ^a The specific throughput of CBZ in a carbon layer of 80 cm was 50 m³/kg when removal decreased to 80%; ^b the daily production of this drinking water treatment plant was 28,000 m³, and this removal was observed in winter; ^c the system comprised 20 granular activated filters (volume = 150 m³ each), experimental duration was 4 months; ^d the daily production of this drinking water treatment plant was 235,000 m³ (experimental duration = 3 weeks); ^e total GAC volume was 1900 m³; ^f the GAC concentration in the bioreactor was 1000 ppm, and experimental duration was 33 days; ^g the initial GAC concentration was 20 mg/L; ^h the PAC dose was 35 mg/L; ⁱ the PAC dose was 5 mg/L; and ^j the PAC dose was 10 g/L, “–”: not available.

Since CBZ is neutral at pH ranging from 0–14, its removal by activated carbon is governed by hydrophobic interaction that depends on water partitioning coefficient [4,17]. In a study Yu et al. [17], better adsorption of CBZ ($\log K_{ow} = 2.45$) by activated carbon as compared to naproxen ($\log K_{ow} = 3.18$) and 4-*n*-nonylphenol ($\log K_{ow} = 5.8$) was reported. Better adsorption of CBZ can be attributed to influence of pH on hydrophobicity of ionizable micropollutants [3]. Indeed, Yu et al. [17] demonstrated that activated carbon achieved better CBZ ($\log K_{ow} = 2.45$) removal as compared to naproxen because actual $\log K_{ow}$ value for naproxen was 0.89 at the operating pH (i.e., 6.4). On the other hand, 4-*n*-nonylphenol contains both hydrophobic and hydrophilic functional groups in its molecule. The hydrophilic groups of 4-*n*-nonylphenol can affect its adsorption by activated carbon [208,209]. Therefore, better adsorption of other micropollutants including CBZ as compared to 4-*n*-nonylphenol is possible [17].

Effectiveness of GAC/PAC was also investigated at pilot-scale plants treating secondary effluent. For instance, Ternes et al. [197] observed almost complete removal (>99%) of CBZ in a pilot-scale GAC plant. In another study, CBZ removal was 95% in pilot-scale GAC/PAC systems treating secondary effluent at an initial activated carbon dose of 30–100 mg/L [190]. GAC was observed to provide better removal of PhACs including CBZ as compared to two other water treatment processes, namely, ozonation and sand filtration [198].

Increasing activated carbon dose can improve CBZ removal. For instance, CBZ removal improved from 36 to 97% when the PAC dose was increased seven folds [205]. In a study by Nguyen et al. [210], instead of using PAC as a post-treatment, it was added directly to the mixed liquor of an MBR. In that study, CBZ removal improved from 50% to 90% following the increase in PAC dose to MBR from 0.1 to 0.5 g/L [210].

Compared to GAC, PAC has a larger surface area that can conceptually provide faster reaction kinetics and better removal efficiency. However, survey of the available literature suggests that both GAC and PAC are effective for CBZ removal (Table 8). Notably, to date the performance of PAC and GAC has been assessed in short term experiments [204,211]. Since saturation of binding sites reduces the removal of pollutants over time, research is required to investigate PAC/GAC regeneration aspects. Grover et al. [202] monitored the performance of a full-scale post-treatment GAC plant over a period of seven months. They observed that CBZ removal reduced over time, and GAC plant could only achieve 30% removal of CBZ during long term operation. In addition to the saturation of GAC binding sites, impurities such as humic substances can compete for GAC/PAC binding sites that may result in ineffective CBZ removal [4,202].

6.3. CBZ Degradation by Advanced Oxidation Processes

Due to the molecular properties of CBZ, conventional biological processes are not effective for its removal (see Section 5). On the other hand, despite the effective removal of CBZ by NF/RO membrane filtration and activated carbon adsorption (Tables 7 and 8), an additional step is required for the treatment of the produced concentrate. In this context it is noteworthy that advanced oxidation processes (AOP) may achieve effective degradation of CBZ (Table 9). Post treatment of biologically treated wastewater by AOPs may simultaneously achieve disinfection and PhAC removal [212].

Formation of hydroxyl radicals (OH^\bullet) are mainly responsible for the degradation of PhACs by AOPs, while formation of ozone radicals (O_3^\bullet) in ozonation process can also contribute to the degradation process [213,214]. Some PhACs such as naproxen are degraded by both OH^\bullet and O_3^\bullet radicals, while some are only susceptible to degradation by OH^\bullet radicals. CBZ, which is resistant to biological treatment, is effectively degraded by both OH^\bullet and O_3^\bullet radicals. For instance, Ternes et al. [197] reported almost complete removal (>99%) of CBZ (35–1000 ng/L) during ozonation process at an initial dose of 0.5 mg/L.

Table 9. Performance of various advanced oxidation processes (AOPs) for CBZ removal.

AOP Type	CBZ Initial Concentration (ng/L)	Operating Conditions	Removal (%)	References
Ozonation	1000	Dose = 0.5 mg/L Contact time = 20 min	>99	[197]
	35	Dose = 1–1.5 mg/L Contact time = 10 min	>97	[197]
	9	Dose = 0.2 mg/L Contact time = 15 min	>99	[199]
	8×10^5	Dose = 1 mg/L Contact time = 10 min	>99	[215]
	3.8	Dose = 1.5–2 mg/L Contact time = 20 min	80–99	[216]
	1.18×10^5	Dose = 0.1–2 mg/L Contact time = 10 h	80–99	[217]
	170	Dose = 0.8 mg/L Contact time = 24 min	100	[218]
	4.72×10^5	Dose = 1.5–4 mg/L Contact time = 20 min	>99	[219]
UV alone	5000	UV Wavelength = 254 nm Energy output = 83 W Irradiation time = 60 min	20	[220]
	NA	UV Wavelength = 200–280 nm Energy output = 120 W Irradiation time = NA	7	[221]
	1.5×10^7	UV Wavelength = 254 nm Energy output = 220 W Irradiation time = 2 h	16	[222]
	5×10^6	UV Wavelength = 254 nm Energy output = 400 W Irradiation time = 30 min	<5	[223]
	19–59	UV Wavelength = 254 nm Energy output = 10 W Irradiation time = 3 min	<10	[224]
UV/H ₂ O ₂	4.72×10^6	UV Wavelength = 254 nm Energy output = 83 W H ₂ O ₂ dose = 170 mg/L Irradiation time = 60 min	90	[187]
	210	UV Wavelength = 254 nm Energy output = 30 W H ₂ O ₂ dose = 2–20 mg/L Irradiation time = 20 min	14–74	[225]
	1000	UV Wavelength = 254 nm Energy output = 20 W H ₂ O ₂ dose = 5 mg/L Irradiation time = 15 min	60	[226]
	50,000	UV Wavelength = 254 nm Energy output = 83 W H ₂ O ₂ dose: 10–200 mg/L Irradiation time = 60 min	90–99	[220]

Table 9. Cont.

AOP Type	CBZ Initial Concentration (ng/L)	Operating Conditions	Removal (%)	References
UV/Cl ₂	19–59	UV Wavelength = 254 nm Energy output = 10 W H ₂ O ₂ dose = 5 mg/L Irradiation time = 3 min	20	[224]
	2.36 × 10 ⁵	UV Wavelength = 254 nm Energy output = 1000 W H ₂ O ₂ dose = 5 mg/L Irradiation time = NA	90	[227]
	1000	UV Wavelength = 254 nm Energy output = 80 W Cl ₂ dose = 1 mg/L Irradiation time = 20 min	55	[226]
	19–59	UV Wavelength = 254 nm Energy output = 10 W Cl ₂ dose = 5 mg/L Irradiation time = 1.5 min	30–60	[224]
	19–59	UV Wavelength = 254 nm Energy output = 10 W Cl ₂ dose = 3 mg/L Irradiation time = 3 min	50	[224]
	4 × 10 ⁶	UV Wavelength = 200–296 nm Energy output = 1000 W TiO ₂ dose = 100 mg/L Irradiation time = 9 min	99	[228]
UV/TiO ₂	5 × 10 ⁶	UV Wavelength = 254 nm Energy output = 250 W TiO ₂ dose = 20–500 mg/L Irradiation time = 30 min	80–98	[223]
	5 × 10 ⁶	UV Wavelength = 254 nm Energy output = 400 W TiO ₂ dose = 20–500 mg/L Irradiation time = 30 min	90–99	[223]
	5 × 10 ⁷	UV Wavelength = 254 nm Energy output = 400 W Fe ²⁺ dose = 5 mg/L Irradiation time = 15 min	>99	[229]
Photo-Fenton	1 × 10 ⁵	UV Wavelength = 200–296 nm Energy output = 30 W Fe ²⁺ dose = 5 mg/L Irradiation time = 1.5 h	95	[230]

Note: “NA”: not available.

Although UV photolysis alone has been observed to be ineffective for CBZ removal (0–20%) in a number of studies [220,231], removal can be significantly improved by adding H₂O₂ or a photocatalyst such as TiO₂ [214,220]. For instance, adding a single dose of H₂O₂ (5–15%) to UV photolysis process resulted in an enhanced CBZ removal of 60–75% [225,226]. In another study, H₂O₂-concentration dependent increase in CBZ removal by UV/H₂O₂ process was reported, and 99% removal was achieved at an initial H₂O₂ concentration of 120 mg/L [220]. CBZ removal can improve with increasing H₂O₂ concentration but it will reach a plateau beyond a threshold H₂O₂ concentration [220].

Fenton's reagent has been reported to efficiently oxidize (>99%) CBZ (Table 9). Notably, Fe⁺² based Fenton process achieved better CBZ removal than UV alone, UV/TiO₂ and UV/H₂O₂. However, the requirement of acidic conditions for Fenton's process is a considerable drawback for its practical application [232].

AOP are undoubtedly very efficient for the removal of CBZ but their practical applications are constrained by associated high cost of chemicals. Moreover, transformation products formed following the oxidation of PhACs including CBZ can be more toxic than the parent compound [220]. To overcome this issue, the use of biological filters or ACs can be a suitable option [233,234].

6.4. Combined/Hybrid Treatment Systems

A single treatment option may not be universally applicable, so a combined (sequential) or integrated treatment may be more effective for CBZ removal. Combined or hybrid treatment options are also conceptually beneficial, usually leading to improved treatment efficiencies [235–237]. Examples of possible combined/hybrid water treatment processes include membrane filtration followed by activated carbon, MBR followed by activated carbon, activated carbon adsorption followed by UV, integrated MBR-TiO₂ photocatalysis, and integrated MBR-PAC adsorption. A summary of CBZ removal by combined/hybrid treatment systems is presented in Table 10.

Table 10. CBZ removal by combined and integrated treatment systems.

Treatment Systems	CBZ Initial Concentration (ng/L)	Operating Conditions	Removal (%)	References
Integrated MBR-UV/TiO ₂	1×10^7	SRT = 60 d HRT = 50 h UV wavelength = 360 nm TiO ₂ dose = NA	up to 95	[238]
Integrated MBR-PAC	5000	SRT = infinite HRT = 24 h PAC dose = 0.1 g/L	50	[210]
Integrated MBR-PAC	5000	SRT = infinite HRT = 24 h PAC dose = 0.5 g/L	90	[210]
Integrated Gamma radiation-CAS (batch experiment)	1.7×10^7	Incubation time = 10 d Radiation dose = 800 Gy	>99	[239]
Integrated PAC-UF	3×10^5	PAC dose = 5–10 mg/L Contact time = 1.5 h	40	[240]
Integrated MBR-PAC	7.5×10^5	SRT = infinite HRT = 24 h PAC dose = 0.1 and 1 g/L	34 and 90	[211]
Integrated MBR-PAC	2×10^4	SRT = infinite HRT = 24 h PAC dose = 1 g/L	>99	[241]
Integrated MBR-PAC	390–1800	SRT = 20 d HRT = 24 h PAC dose = 1 g/L	99.4	[206]
Integrated CAS-GAC	2×10^4	SRT = NA HRT = NA GAC dose = 100–1000 mg/L	10–50	[203]
MBR followed by GAC	5000	SRT of MBR = infinite HRT of MBR = 24 h GAC contact time = 7 min	98	[242]
Ozonation followed by biological sand column	2.06	HRT of sand column = 5–6 d Ozone contact time = NA	80	[243]

Note: NA: not available.

Kleywegt et al. [244] investigated the removal of CBZ by GAC adsorption followed by UV photolysis that achieved effective removal of CBZ (93%). Serrano et al. [203] investigated the removal of PhACs including CBZ in a CAS process followed by GAC adsorption. They reported that adsorption onto activated carbon improved the overall removal of CBZ by as much as 40% [203]. Nguyen et al. [210] also reported an overall CBZ removal of 98% by an MBR followed by GAC adsorption. When a sequencing batch reactor coupled to an external microfiltration membrane was investigated by Serrano et al. [241], up to 93% CBZ removal was achieved following the addition

of a single dose (1 g/L) of PAC directly into the bioreactor. Likewise, the integrated MBR-PAC system was also reported to achieve 92% CBZ removal [211]. CBZ removal by MBR treatment followed by GAC filtration was investigated by Nguyen et al. [210]. While MBR alone showed a removal of less than 20%, MBR-GAC achieved an extremely efficient removal of 98% [210]. This result demonstrates that GAC post-treatment could significantly improve the removal of PhACs, which are resistant to degradation by the activated sludge.

Other integrated/hybrid technologies have also shown effective CBZ removal. AOPs cannot mineralize PhACs, however, it is important to note that the metabolites formed following the oxidation of CBZ have been reported to be readily mineralized by the activated sludge [245–247]. For instance, Hübner et al. [243] studied CBZ removal by combining ozonation with a sand column mimicking a soil aquifer treatment (SAT) systems. They observed that the degradation products of CBZ formed after ozonation were significantly mineralized (>80%) in the sand column at an HRT of 5–6 days [243]. In another study [239], a combination of gamma radiation and activated sludge based biological treatment achieved up to 79% CBZ mineralization. They reported that significant CBZ removal (>99%) was mainly achieved by gamma radiation at an initial dose of 800 Gy, while activated sludge was responsible for mineralization of CBZ [239]. In a study by Laera et al. [238], an integrated MBR-TiO₂/UV system achieved up to 95% CBZ removal from pharmaceutical industrial effluent, showing that the integration of biological and chemical oxidation processes can be an effective strategy for enhanced CBZ removal. Despite the efficacy of combined/integrated oxidation and biological processes for mineralization, the cost associated with the application of oxidation processes needs to be considered.

Carbamazepine has been consistently shown to be poorly removed by coagulation despite being a neutral compound [21,197,248–250]. However, a properly designed coagulation/flocculation unit can efficiently remove suspended solids and can thereby enhance the performance of a subsequent activated carbon adsorption unit by reducing competitive adsorption [151]. Coagulation pre-treatment has been found to significantly enhance carbamazepine removal efficiency by adsorption [197]. Because high concentrations of suspended or colloidal solids in the wastewater may impede the advanced oxidation processes, sufficient prior removal of these materials by a physicochemical treatment such as coagulation is required [251,252].

7. Fate and Metabolites of CBZ

CBZ transformation products following its metabolism in human body or following its degradation by different treatment processes have been reported (Figure 1). Figure 1 sheds light on different pathways of CBZ metabolism/degradation by AOPs, human liver, and microorganisms. Huerta-Fontela et al. [199] reported that CBZ degradation by ozonation occurs via a ring opening mechanism due to the attack of ozone on the non-aromatic carbon-carbon double bond of CBZ, forming the metabolite epoxy-carbamazepine. Compared to the CBZ degradation products reported by McDowell et al. [253] in UV photolysis (Figure 1), Vogna et al. [187] observed that the addition of H₂O₂ to UV photolysis yields different degradation products (Figure 1), indicating a difference in the degradation pathway of CBZ in presence of H₂O₂. In biological systems (such as human liver, fungus and activated sludge), CBZ degradation products usually contain the azepine structure (Figure 1).

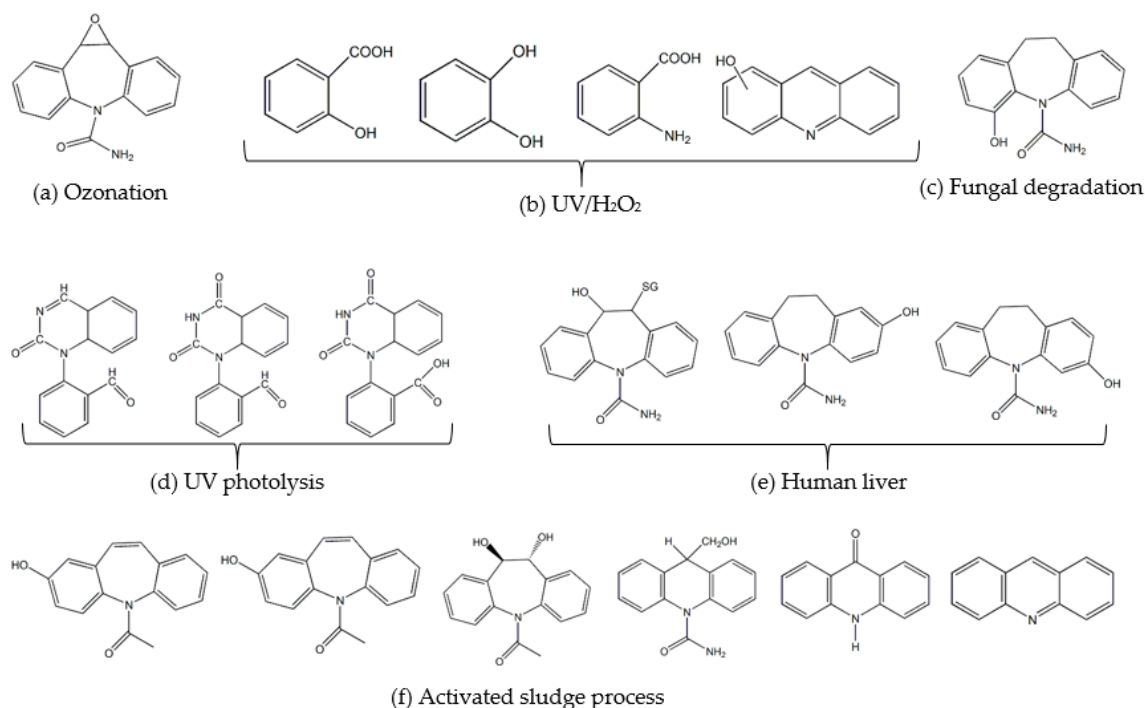


Figure 1. Metabolites/degradation products formed following CBZ degradation by (a) ozonation [199]; (b) UV/H₂O₂ [187]; (c) fungal degradation [254]; (d) UV photolysis [253]; (e) human liver [255]; (f) activated sludge process [256].

As depicted in Figure 1, several metabolites/degradation products have been reported for CBZ treatment by different processes. Toxicity of CBZ degradation products has been reported in a number of studies as summarized here. Based on the Yeast Estrogen Screen (YES) assay, Mohapatra et al. [257] reported that CBZ and its degradation products showed no estrogenic activity. In another study, Jelic et al. [160] investigated the toxicity of the media in a pulsed fluidized bed bioreactor containing whole-cell *T. versicolor* and CBZ at an initial concentration of 500 µg/L. The acute toxicity test (Microtox) showed the toxicity induced by CBZ was reduced from 95% to 24% after an incubation time of 10 days, suggesting that the degradation products were non-toxic [258]. Similarly, degradation products following the oxidation of CBZ by ozonation, UV and UV/H₂O₂ processes exhibited no genotoxic, cytotoxic or estrogenic effects [258]. CBZ metabolites including 10,11-dihydro-trans-10,11-dihydroxy-carbamazepine, acidone and acridine formed during CAS process [256] have also been reported to be non-toxic [258,259]. Although degradation products or metabolites of CBZ formed during CAS and AOPs are non-toxic, Bu et al. [255] reported that CBZ-2,3-arene (one oxide intermediate) is believed to cause idiosyncratic effect after CBZ consumption for medicinal purposes [255].

8. Conclusions and Outlook

Although its occurrence in freshwater may not pose an immediate threat to aquatic ecosystems or human health, effective removal of CBZ is still required for safe water reuse applications and drinking water treatment. Biological wastewater treatment processes such as conventional activated sludge and membrane bioreactor are not effective for CBZ removal due to its resistance to biodegradation. However, advanced wastewater treatment processes seem to be effective for efficient CBZ removal. For instance, CBZ removal by the reverse osmosis and nanofiltration membranes is above 90%. Similarly, post-treatment with granular and powdered activated carbon provides efficient CBZ removal ranging from 90–99%. However, membrane fouling in case of membrane technologies and regeneration of activated carbon are obstacles that warrant technical solutions. Depending on the type of fungal

species and operating condition, white-rot fungi can achieve almost complete removal of CBZ but bacterial contamination may affect the efficacy of fungal bioreactors during long term operations. Although advanced oxidation processes such as ozonation, UV/H₂O₂, UV/TiO₂ and Fenton processes are effective for CBZ removal, costs associated with the addition of chemicals, and separation of catalysts needs to be carefully considered. Finally, the literature to date suggests that degradation products formed following the degradation of CBZ by biological and chemical oxidation processes may not induce toxic effects on aquatic ecosystems.

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