Carbamazepine in water and wastewater treatment plants

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Carbamazepine (CBZ) is one of the most frequently used drugs for the medical treatment of epilepsy and bipolar disorder, being a mood stabilizer. It is metabolized in the liver and excreted mainly as hydroxylated and conjugated metabolite and only around 5% as an unchanged drug.

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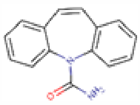
1. Carbamazepine Usage and Physicochemical Characteristics

CBZ is one of the most frequently used drugs for the medical treatment of epilepsy and bipolar disorder, being a mood stabilizer [1]. It is metabolized in the liver and excreted mainly as hydroxylated and conjugated metabolite and only around 5% as an unchanged drug [2]. The formula, structure, identifier (i.e., CAS number) and the main physicochemical characteristics of CBZ are summarized in **Table 1**.

Table 1. Main CBZ physicochemical characteristics.

CAS n.	Formula	Structure	Molecular Weight	pK_a	Log K_{OW}	K_H	S
298-46-4	$C_{15}H_{12}N_2O$		236.274 g/mol	2.3 [3] 13.9 [4]	2.45 [5]	2.24×10^{10} atm·m^3/mol [6] P	0.0005 mol/L [5] at 18 mg/L and 25 °C [4]

CAS n.: Chemical Abstracts Service number; Formula: Chemical formula; pKa: log of acid dissociation constant; Log K_{ow}: log of octanol-water partition coefficient; KH: Henry's law constant; S: water solubility; P: predicted value.

CBZ is not considered a volatile compound and it is characterized by a value of the octanol-water partitioning coefficient below 3 which entails that it is moderately hydrophobic; it is also considered soluble in water based on the available values of the solubility. Moreover, in the aquatic environment and most of the water and wastewater treatment processes, CBZ is present as a non-ionized form, since its pK_a is far from neutral, which is the usual pH condition for these treatments [7]. All these characteristics proved that CBZ is refractory to the traditional water and wastewater treatment processes and particularly to biological processes, as reported by several authors [8][9][10][11]. As a consequence, it is usually found in the effluent of the treatment plants and then in the surface water bodies where it is frequently released. The NORMAN Network database, which includes 20 countries and 25,359 samples, shows that the frequency of detection in this environmental matrix is about 73% [5]. The frequent occurrence of CBZ in the aquatic environment represents a relevant and concerning matter since this substance has adverse toxicological effects [1]. Indeed, CBZ is classified as a toxic compound concerning marine and surface water compartments, being the lowest predicted no-effect concentration (PNEC) below 0.1 µg/L in both compartments (0.005 µg/L and 0.05 µg/L, respectively) according to the criteria proposed by NORMAN Prioritization framework for emerging substances and the REACH regulation [5][12]. Thus, CBZ represents a risk for the environment, but also for human health when surface water is used as a source for drinking water production.

2. Wastewater Treatment Plants (WWTPs)

Frequency of detection (Fd) is the parameter of relevance when evaluating the pollution of water by a contaminant that describes the steadiness of its occurrence. For CBZ, its frequency of detection is often significantly high, defining pollution not randomly but consistently present in wastewater influent and effluent. On this account indeed, Loos et al. (2013) reported a frequency of detection of 90% in WWTPs effluent sampled across the EU [13]; Di Marcantonio et al. (2020) found an Fd of 96% and 91% in the influent and effluent, respectively [8]. According to Thiebault et al. (2017), Suebdi et al. (2015), Tran and Gin (2017) and Rivera-Jaimes et al. (2018), 100% Fd was recorded in both influent and effluent [11][14][15][16]. **Table 2** lists the average concentrations at which CBZ was found across the world in the influent and effluent of wastewater treatment plants: even if the values are often in the range of ng/L, there are also exceptions with concentrations reaching the order of magnitude of µg/L.

Table 2. CBZ concentration (ng/L) mean and range in WWTPs worldwide, considering raw wastewater (RWW) and treated wastewater (TWW).

Location	n° WWTPs	RWW (Mean/*Median*)	RWW Range	TWW (Mean/*Median*)	TWW Range	Ref.
China	5×	45	24–72	34	24–49	[17]
China		17	n.a.	18	n.a.	[18]
China		14	10–20	16	13–21	[19]
USA	2× *	193	61–588	289	91–731	[15]
USA	5×	115	34–350	21	<LOQ-62	[20]
Canada	5×	757	n.a.	713	n.a.	[21]
Mexico	*	214	85–380	285	165–476	[16]
Singapore	*	*323*	323–339	313	262–336	[11]
Spain		<LOQ	n.a.	97	n.a.	[22]

Location	n° WWTPs	RWW (Mean/*Median*)	RWW Range	TWW (Mean/*Median*)	TWW Range	Ref.
Spain	(WWTP1) *	166	69–283	102	29–198	[23]
	(WWTP2) *	172		140		
Spain	4× *	422	70–970	100	60–150	[24]
Turkey	5× *	19	<LOQ-95	5	<LOQ-75	[25]
Italy		570	n.a.	370	n.a.	[26]
Italy	76×	209	<LOQ-1381	193	<LOQ-890	[8]
Italy		140	n.a.	179	n.a.	[27]
Switzerland		256	n.a.	251	n.a.	[27]
Czech Republic		460	210–710	510	220–730	[28]
France		215	51–937	163	5–357	[14]
Germany		1536	246–815	1614	1020–2309	[29]
Germany	6×	*1900*	1500–2100	2000	1800–2200	[30]
Portugal	2×	*470*	440–500	520	500–540	[30]
Portugal	2×	*95*	47–226	117	62.7–245	[31]
African countries	(review)		117–6145		64–1438	[32]
India		1642	22–8200	393	88–900	[33]

Data shown are either reported as such in the articles or calculated with the data available (*). The data reported in Italic are medians. When needed, WebPlotDigitizer was used to gain data from graphs.

Regarding time-related patterns for CBZ pollution of wastewaters, seasonality is usually excluded, being CBZ a substance not linked to seasonal illness; moreover, daily patterns have not been detected [34]. However, some studies report that drier seasons exerted an influence on the CBZ concentration detected at WWTPs due to lower dilution, particularly in the case of combined sewers [1].

The behavior of CBZ in WWTPs has been well addressed in the reviews by Couto et al. (2019) [34] and Krzeminski et al. (2019) [35], along with other contaminants of emerging concern (CECs). WWTPs are not (yet) designed to remove CECs, which are hence often discharged in the receiving water body through the treated effluent [34]. Particularly, CBZ seems quite refractory to biological treatments [22][35]; furthermore, it is also not expected to adsorb greatly on solids (medium-low octanol-water partition coefficient) [34] and therefore these can explain the poor removal in WWTPs [10]. The removal reported for CBZ is often even negative, due to recombination processes of precursors, accumulation within the plant, release by solids and sampling strategies that do not consider the plant Hydraulic Retention Time (HRT) [8][11][34][36]. Regarding the influence of the WWTP layout, an interesting study is the one conducted by Di Marcantonio et al. (2020) [8], where 76 WWTPs were analyzed for 2.5 years. According to the results, CBZ showed very low removal efficiencies (lower than 50%), the lowest being recorded for layouts comprising secondary treatments alone, slightly improving where primary or tertiary treatments were also included. Indeed, the review by Yang et al. (2017) and that of Hai et al. (2018) also confirmed the scarce removal by the secondary treatment, regardless of the system used (Conventional Activated Sludge, membrane bioreactor, others) [1][37].

3. Drinking Water Treatment Plants (DWTPs)

Indeed, CBZ is detected at the influent of DWTPs, as shown in **Table 3**, as in the effluents.

Table 3. CBZ concentration (ng/L) mean and maximum and Fd (%) in DWTPs worldwide.

Location	n° DWTPs	Water Source	RW			TW			Ref.
			Fd	Mean/*Median*	Max	Fd	Mean/*Median*	Max	
Canada	17×	GW/SW	50	*3*	749	25	*0.21*	601	[38]
Canada	5× *	SW	68	3.1	7.2	65.6	1.92	3.6	[39]
USA		SW	13	1.4	1.6	13	0.3	0.4	[40]
USA	31× *	GW/SW	37	6.1	17.9	27	3.6	6.9	[41]
USA	29×	GW/SW	56	*15.9*	35.7	8	*17.75*	26.5	[42]
Japan	6× *	GW/SW	39	7.3	100	13	1.9	25	[43]
Korea	5×	SW	100	7.7	21.1	5	0.67	0.67	[44]
Korea		SW	92	10.3	46.4	13	1.7	17.7	[45]
China		SW	100	1.33–1.82		100	0.37–1.15		[46]
China		SW	100	0.8	1.01	13	n.a.	0.65	[47]
Sweden	90×	GW/SW	41.5	0.95	n.a.	35	0.95	n.a.	[48]

Location	n° DWTPs	Water Source	RW			TW			Ref.
			Fd	Mean/*Median*	Max	Fd	Mean/*Median*	Max	
Sweden	7× *	SW	100	10.48	13.44	28.5	2.91	11.32	[49]
Spain	*	SW	92	153	245	8.3	0.02	0.09	[50]
Spain	*	GW	100	*84.5*	167	89	1.1	5.7	[51]
Italy	3× *	SW	66.6	13.8	34.57	41.7	0.2	1.20	[52]
Portugal		GW/SW	96	3.3	16.8	69	1.8	13.5	[53]

Data shown are either reported as such in the articles or calculated with the data available (*). Fd: frequency of detection (%), GW: groundwater, n.a.: not available, RW: raw water, SW: surface water, TW: treated water. Values in italics are medians; when needed, WebPlotDigitizer was used to gain data from graphs.

The frequency of detection (%) is often quite high and not necessarily decreasing between influent and effluent of the water treatment plant, highlighting the persistence of the compound. The Fd median value, considering the studies reported in **Table 3**, for raw water is 80%, whereas for treated water it is 25%. The concentration in the effluent is usually lower, confirming at least a partial effect of the water treatment units. The concentrations reported by worldwide example studies in **Table 3** shows quite a variability: in raw water, the range spans from almost zero to hundreds of ng/L, whereas in treated water it is reduced to tens of ng/L. However, the presence of CBZ at the effluent of DWTPs is common in different countries and plant layouts. In general, treatments for the removal of colloids and solids are indeed not deemed to be effective against CBZ due to its characteristics, while improved outcomes might be linked to chemical oxidation processes such as ozonation, adsorptive process by granular activated carbon (GAC) and membrane filtration [34].

Simazaki et al. (2015) found that the average removal of CBZ by plants that included ozonation and activated carbon was of 97 ± 2%, whereas the removal was reduced to 62 ± 49% where such processes were not applied [43]. The importance of the oxidation steps in the removal of CBZ is also underlined by Kim et al. (2020) [44]. Pulicharla et al. (2021) found instead the removal of CBZ to be as low as 0–40% even in DWTPs with a layout that included inter-ozonation, activated carbon and sand filtration [39].

High removal efficiencies were also recorded for DWTPs employing Granular Activated Carbon (GAC) and Biological Activated Carbon (BAC) in Italy [52], even though concentration was not always reduced to below the limit of quantification (LOQ). The high removal of CBZ by nanofiltration/reverse osmosis (NF/RO) was instead witnessed by Radjenović et al. (2008) [51] and Al-rifai et al. (2011) [54].

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