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## CARBAMAZEPINE AND OTHER ANTI-EPILEPTIC DRUGS IN THE AQUATIC ENVIRONMENT

### KARBAMAZEPINA I INNE LEKI O DZIAŁANIU PRZECIWPADACZKOWYM W ŚRODOWISKU WODNYM

#### Abstract

This paper is part of a series of publications discussing the prevalence of pharmaceuticals in the aquatic environment and the effectiveness of their removal and degradation during wastewater treatment processes. The paper discusses the problem of the presence of carbamazepine and other anti-epileptic drugs. The authors reviewed the basic characteristic parameters of these compounds, and based on the analysed literature data, the problem of anti-epileptic drugs, mainly carbamazepine, in the aquatic environment. Carbamazepine appears to be exceptionally persistent at municipal wastewater treatment plants as has been confirmed by current studies on its elimination and degradation, as well as reports on its presence in surface water, groundwater and even drinking water. The latest studies demonstrated highly effective removal of carbamazepine during oxidation processes. The application of these methods in real life situations should enable the effective protection of the aquatic environment.

*Keywords: carbamazepine, anti-epileptic drugs, wastewater, surface water, groundwater*

#### Streszczenie

Artykuł jest częścią serii publikacji obejmujących zagadnienia występowania farmaceutyków w środowisku wodnym oraz skuteczności ich eliminacji i degradacji w procesach oczyszczania ścieków i uzdatniania wody. Praca przedstawia zagadnienia dotyczące karbamazepiny i innych leków przeciwpadaczkowych. Podano podstawowe parametry charakterystyczne dla opisywanych związków i w oparciu o dane literaturowe przybliżono problem, jakim jest występowanie leków przeciwpadaczkowych, a zwłaszcza karbamazepiny w środowisku wodnym. Karbamazepina okazuje się być farmaceutykiem wyjątkowo trwałym w warunkach oczyszczania ścieków miejskich, co potwierdzają dotychczasowe wyniki badań nad jej eliminacją i degradacją, a także doniesienia o obecności tego związku w wodach powierzchniowych, podziemnych, a nawet wodzie przeznaczonej do spożycia. Najnowsze badania wykorzystujące procesy utleniania wykazują bardzo wysoką skuteczność w eliminacji karbamazepiny, co stanowi dobry prognostyk w odniesieniu do ochrony środowiska wodnego.

*Słowa kluczowe: karbamazepina, leki przeciwpadaczkowe, ścieki, wody powierzchniowe, wody podziemne*

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## 1. Introduction

The aim of the study is to present issues concerning the presence of anti-epileptic compounds (in particular, carbamazepine) in wastewater as well as in surface water, groundwater and drinking water. Pharmaceuticals and specimens used by humans are usually converted into hydrophilic forms in the liver and only in this form are the metabolites excreted by the kidneys; this is the major path of drug removal from the human body. However, compounds that are not absorbed from the gastrointestinal tract or that are easily soluble electrolytes may leave the body unchanged [2]. These are discharged to the sewer system, and are then transported to municipal wastewater treatment plants where, at least in theory, compounds that may pollute the environment (i.e. drugs) are removed from wastewater. The actual removal efficiency of some specific pharmaceuticals is very low and sometimes close to zero (e.g. carbamazepine).

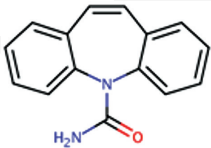
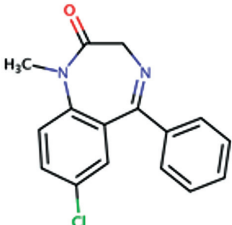
Since pharmaceuticals are not effectively removed from wastewater, they are discharged with the plant effluent into rivers (receivers), from where they may penetrate to groundwater or be taken up by the water treatment plants. Prior to 2007, more than 90 different pharmaceuticals had been identified all over the world – they were found in seas, lakes, rivers, groundwater, sediments and soils [3]. Although concentrations of these compounds found in rivers or drinking water are very low in comparison to the threshold concentrations that show negative effects on aquatic organisms, this does not relieve us from the obligation to produce drinking water of a high quality, free from pharmaceuticals.

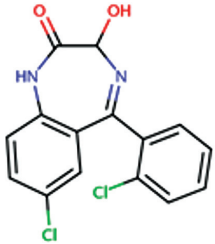
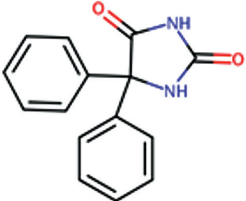
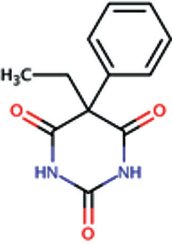
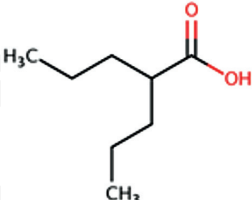
## 2. Characteristics of anti-epileptic drugs

Anti-epileptic pharmaceuticals have been used mainly in the treatment of epilepsy. This neurological disorder occurs when too many neurons become excited in the central nervous system. The most common and most widely used anti-epileptic drug is carbamazepine.

Table 1

Characteristics of selected anticonvulsants [30–35]

Name	Formula	Structure	CAS	Half-life	Excretion
Carbamazepine	$C_{15}H_{12}N_2O$		298-46-4	12–65 h	72% urine 28% faeces
Diazepam	$C_{16}H_{13}ClN_2O$		439-14-5	24–120 h	urine

Lorazepam	$C_{15}H_{10}Cl_2N_2O_2$		846-49-1	2–19 h	91% urine 9% faeces
Phenytoin	$C_{15}H_{12}N_2O_2$		57-41-0	7–42 h	urine
Phenobarbital	$C_{12}H_{12}N_2O_3$		50-06-6	53–118 h	urine faeces
Valproic acid	$C_8H_{16}O_2$		99-66-1	9–16 h	30-50% urine

Despite its widespread use, the research points out some negative effects this compound has on the human body – these include a lowered content of leukocytes and platelets in the blood and the risk of fetal distress. It has also been known that carbamazepine is toxic for some algae, bacteria, invertebrates and fish [5]. Other agents of this group are diazepam, lorazepam, phenobarbital, valproate and carbamazepine – these are included on the WHO Model List of Essential Medicines [36]. Table 1 presents some important information on anti-epileptic drugs.

### 3. The presence of pharmaceuticals in the environment

Potential sources of pharmaceuticals in the environment are presented in Fig. 1 [24].

Since anti-epileptic drugs are used in the treatment of epilepsy and anxiety, hospital and household wastewater are their main sources in the environment; through them, the drugs

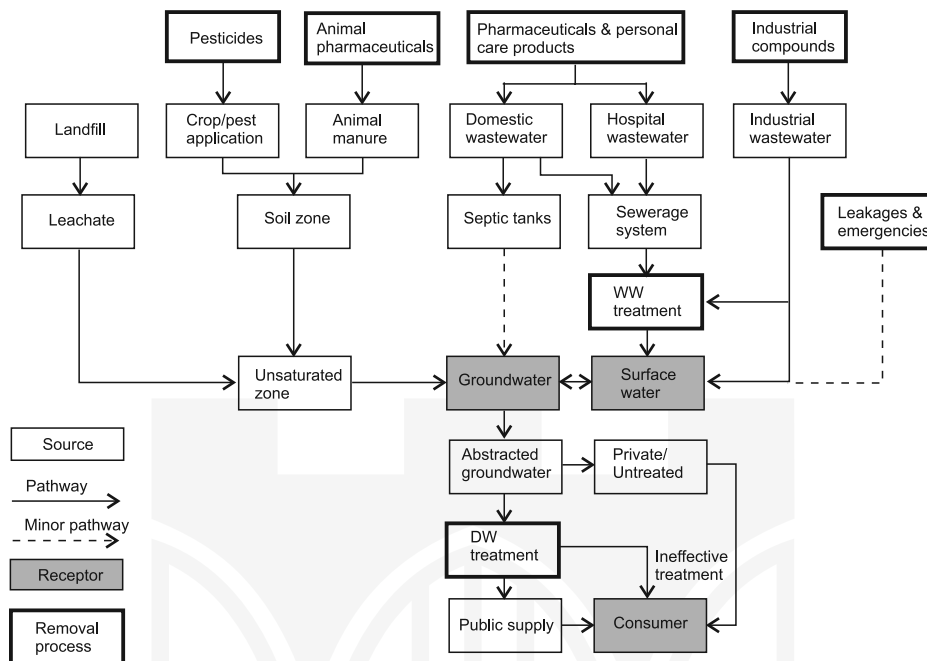


Fig. 1. Sources and pathways of pharmaceutical pollution in water and soil

are transported to the wastewater treatment plants. Studies in Belgium on the detection of, for example, carbamazepine (CBZ) and diazepam (DIA) in raw wastewater, showed that their concentrations were 227–1028 ng/l and 1–9 ng/l, respectively. The analysis was conducted using the technique of reversed-phase liquid chromatography coupled with tandem mass spectrometry (LC–MS/MS) [25]. Diazepam was also found in raw wastewater at 4 Chinese wastewater treatment plants - its concentrations ranged from 3 to 16 ng/l [22]. The analysis conducted in raw wastewater in Italy [26] showed the following concentrations of pharmaceuticals: CBZ = 0.30–1.17 mg/l, DIA = 0.002–0.010 mg/l and lorazepam = 0.17–0.25 mg/l. Based on these reports, it can be concluded that among the antiepileptic drugs, it is carbamazepine that appears in the wastewater in the highest concentrations.

Studies on the degradation efficiency of numerous pharmaceuticals [7] demonstrated that there was a minimal degradation of carbamazepine during anaerobic digestion. The process parameters such as temperature and sludge retention time (SRT) had no impact on its efficiency. Additionally, wastewater treatment with conventional activated sludge (CAS) and a membrane bioreactor (MBR) showed very poor removal of CBZ from wastewater: it was 5% for CAS and 4.4% for a MBR [27]. Poor removal of carbamazepine was also confirmed by analysis of its concentrations in the effluent from different wastewater treatment plants: 0.18–17.3 mg/l in Spain [5], 1.1 mg/l in Greece [12] and 3.4 mg/l in Norway [13].

The above conclusion means that wastewater which carries CBZ, is discharged to the receiving waters causing their contamination. Tests conducted on river water downstream from the effluent discharge [8], showed up to 330 ng/l of CBZ in a sample

taken 35.7 kilometers downstream from the discharge point. Other publications stated that the average CBZ concentrations in natural waters were: in Great Britain – 251 ng/l (max 684 ng/l) [19], in Italy – 345 ng/l [16] and even up to 1110 ng/l in the national park of Spain [5]. CBZ is not adsorbable on soil [11]; therefore, its presence in surface water may lead to its further penetration to groundwater. Also, for this reason, the utilisation of sludge from wastewater treatment plants contaminated with CBZ can lead to groundwater pollution and the accumulation of this drug in plants.

There have been reports on the presence of carbamazepine in groundwater in Germany (Halle, 2–83 ng/l [18], Leipzig about 90 ng/l [17] and also much higher concentrations of 900 ng/l [21], and even 2325 ng/l [15]), France 10.4 ng/l [28] and the US – up to 420 ng/l [15]. However, CBZ may be present in the environment, not only in its parent form but also as metabolites, which are found in groundwater at concentrations ranging from 0.9 to 39.9 ng/l [4, 9, 14].

The concentrations of pharmaceuticals found in surface water and groundwater are sometimes several orders of magnitude lower than threshold concentrations which show negative effects on aquatic organisms. However, it cannot be clearly stated that such low concentrations do not pose any hazards to living organisms when subjected to long-term exposure. Currently, there are no reliable studies confirming whether pharmaceuticals, even at low concentrations, may or may not have any effects on the human body. If water at the water treatment plants contains pharmacologically active compounds, including carbamazepine, one should effectively eliminate these compounds as a preventive measure.

Despite the use of advanced water treatment methods, there have been cases when carbamazepine was detected in drinking water. A study conducted in Japan showed CBZ concentrations of 12–25 ng/l [23]. An extremely high concentration of CBZ in drinking water (over 600 ng/l) was reported in Canada; the authors attributed it to an exceptional stability of this compound [10]. On the other hand, studies carried out in Spain confirmed the reduction of CBZ concentrations below the acceptable detection limits (0.03 ng/l) thus demonstrating that carbamazepine may be effectively removed at the water treatment plant [1].

#### **4. Removal and degradation**

Taking into account the fact that wastewater from hospitals and households are the greatest sources of anticonvulsants, some appropriate methods of the elimination or degradation of these compounds should be considered. In the case of hospital wastewater, some kind of pre-treatment before discharge into the sewage system could reduce the levels of these compounds that reach wastewater treatment plants. However, for household sewage, that option is not possible since it would be difficult to employ such a pretreatment unit in every home.

Investigations on using an additional ozone stage, prior to the anaerobic digestion of sewage sludge [6], has not shown a significant improvement in the degradation efficiency of the studied pharmaceuticals (including diazepam). However, in the case of carbamazepine, 60% degradation in thermophilic conditions was observed; anaerobic digestion that was

not preceded by ozonation was ineffective. Additionally, membrane processes, including nanofiltration, which shows only a small retention of CBZ [20], are ineffective in the removal of carbamazepine from the wastewater treatment plant effluent. Currently, research is conducted on the use of ferrate (VI) for the degradation of pharmaceuticals, including carbamazepine [29]. The results confirmed the successful degradation of CBZ depending on the initial concentrations and pH; for a concentration of 100 µg/l, 45% removal was observed at pH = 6 and 99% removal at pH = 9; for a concentration of 10 µg/l, removal of up to 99% was observed, regardless of pH. As part of the work, the authors also identified carbamazepine oxidation products, which in the case of using this method on a large scale would allow for monitoring and controlling the process efficiency.

## 5. Conclusions

- Pharmaceuticals are becoming an increasingly serious problem with regard to the protection of the aquatic environment and its living organisms;
- The presence of anti-epileptic drugs, particularly carbamazepine, was detected in effluents from wastewater treatment plants and natural waters around the world;
- Low removal efficiency of these compounds from wastewater contributes to the pollution of the water environment, particularly surface and groundwater;
- There are no conclusive results confirming the effects (or their lack) of prolonged exposure of organisms to low concentrations of carbamazepine;
- Solutions are being developed that help to achieve a significant reduction and degradation of carbamazepine and other pharmaceuticals; these should be implemented at full scale as these solutions are promising.

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