

An assessment of the potential toxicity of transformation products arising from the direct photolysis of psychotropic drugs: Decontamination vs. toxicity increase

Davide Vione*

Department of Chemistry, University of Turin, Via Pietro Giuria 5, 10125 Torino, Italy

Abstract: Background: Psychotropic drugs are contaminants of emerging concern, and some of them are also very toxic to aquatic organisms. Photodegradation is a major removal pathway for these compounds in sunlit surface waters. Psychotropic drugs are known to generate transformation products (TPs) upon direct photolysis, and the environmental impact of these TPs should be assessed. Methods: The software ECOSAR was used to assess acute and chronic toxicity of the compounds towards fish, crustaceans, and algae. Results: The TPs were often less toxic than their parent molecules, and in silico evidence of a toxicity increase was obtained in around 10% of the cases. However, comparison with available experimental data for carbamazepine suggests that the formation of just one or few toxic TPs should trigger concern, because of the potential to increase the overall toxicity of the irradiated mixture. Conclusions: The direct photolysis appears to often produce decontamination, but there are several cases where formation of at least one more toxic TP should raise concern. For the drugs considered here, it is the case of alprazolam, carbamazepine and diazepam, and also of desipramine because of the formation of mutagenic acridine.

Key words: photodegradation; sunlit surface waters; photochemical self-decontamination; photosensitisation; direct photolysis; contaminants of emerging concern (CECs).

Citation: Vione D. An assessment of the potential toxicity of transformation products arising from the direct photolysis of psychotropic drugs: Decontamination vs. toxicity increase. *Environmental Chemistry and Safety*, 2026, 2, 9600013. <https://doi.org/10.26599/ECS.2026.9600013>

1. Introduction

The so-called contaminants of emerging concern (CECs) are chemicals that usually occur at trace levels in natural waters, but they have the potential to harm aquatic organisms and, potentially, also human health even at such low concentration values. CECs include pesticides, pharmaceuticals, personal care products including sunscreens, household chemicals, fragrances, as well as industrial chemicals. Agricultural or urban soil runoff, aquaculture activities, recreation (e.g., swimming in the case of sunscreens) and, most of all, wastewater discharge (both urban and industrial) are the main routes of CECs to the aquatic environment. In the case of wastewater, the main issue is that the current treatment plants (WWTPs) are unable to completely remove CECs from the water flow [1-4]. The biological treatment is currently the main barrier against CECs, but many of them are biorecalcitrant and rather water-soluble. For these reasons, many CECs are insufficiently biodegraded by activated sludge or equivalent biotreatment, and the extent of partitioning on biosolids would not be enough to effectively remove these compounds, even in the absence of biodegradation, when biosolids are separated from the

water phase [5]. For these reasons, after wastewater discharge, CECs often end up in surface waters and groundwater, where biodegradation is usually at least as difficult as it is in WWTPs [6,7].

In the case of sunlit surface waters, photodegradation is a major route by which CECs are attenuated. The photodegradation process typically entails two main pathways, namely direct photolysis and indirect photochemistry. In the case of the direct photolysis, CECs absorb sunlight and get transformed as a consequence. As far as indirect photochemistry is concerned, sunlight is absorbed by natural compounds called photosensitizers, the main ones in surface waters being nitrate, nitrite, as well as the chromophoric dissolved organic matter (CDOM) [8-12]. The absorption of sunlight by nitrate and nitrite yields the hydroxyl radical ($\cdot\text{OH}$), which can oxidize inorganic carbon species (most notably, HCO_3^- and CO_3^{2-}) to produce the carbonate radical, $\text{CO}_3^{\cdot-}$. In contrast, sunlight absorption by CDOM yields $\cdot\text{OH}$ plus the excited triplet states ($^3\text{CDOM}^*$, which can oxidize CO_3^{2-} to $\text{CO}_3^{\cdot-}$), as well as singlet oxygen, $^1\text{O}_2$ ($^3\text{CDOM}^* + \text{O}_2 \rightarrow \text{CDOM} + ^1\text{O}_2$). The transient species (also named photochemically produced reactive intermediates or PPRIs) $\cdot\text{OH}$, $\text{CO}_3^{\cdot-}$, $^3\text{CDOM}^*$, and $^1\text{O}_2$ are all involved in indirect photochemical processes that cause the degradation of CECs [13-17].

CEC degradation, either direct or indirect, is not the end of the story, however. Indeed, the primary contaminant is photochemically transformed into a variety of transformation products (TPs), which can be harmless, about as toxic as the parent CEC, or even more toxic. In some cases, new hazard endpoints

Correspondence to: Vione D, davide.vione@unito.it

Received: December 15, 2025; Revised: January 29, 2026; Accepted: February 17, 2026

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might also appear in TPs as compared to the parent compound (e.g., mutagenicity) [18,19]. Among the many CECs that occur in surface waters, psychotropic drugs represent an emerging class of contaminants of widespread and increasing occurrence. These compounds are often toxic to aquatic organisms, but their aromatic rings allow for sunlight absorption. This issue enables direct photolysis processes, which are often major transformation routes for psychotropic drugs in sunlit surface waters [20].

An in-silico toxicity assessment has been carried out for a number of psychoactive substances detected at the inlet and at the outlet of a WWTP, including several metabolites, but these compounds would likely arise from human or microbial metabolism and not specifically from the direct photolysis process [21]. A comprehensive, in silico toxicity screening has been carried out for the photolysis products of the antipsychotic drug asenapine, showing that most of them would be about as toxic as the parent molecule [22]. These findings raise concern, by showing that photolysis might not achieve effective decontamination of this and possibly also other psychoactive drugs. An even more concerning finding is related to the direct photolysis of carbamazepine, with actual toxicity measurements showing that the irradiated mixtures were more toxic than the parent compound [23]. Experimental toxicity data on crustaceans (*Daphnia magna*) are also available for the UV/H₂O₂ treatment of mixtures containing carbamazepine [24], and they suggest that carbamazepine degradation might result into detoxification. However, the test was conducted with non-environmental UV-C radiation, and the UV/H₂O₂ methodology mainly relies on the photochemical production of [•]OH rather than the direct photolysis. Overall, it appears that incomplete knowledge is currently available of the environmental effects of the photolysis TPs of psychoactive drugs. The known TPs arising from the direct photolysis of a range of psychotropic drugs have been listed in a literature review [25], but no systematic assessment is available to date concerning their effects on the natural environment and, most notably, on freshwater organisms.

To fill in this knowledge gap, this work had the goal of assessing the acute and chronic toxicity of the known TPs arising from the direct photolysis of several psychotropic drugs (anti-epileptic, anti-depressive, as well as anti-psychotic). Toxicity was assessed towards representative freshwater organisms (fish, crustaceans –daphnid– and algae) with the use of the ECOSAR software, which applies a quantitative structure-activity relationship approach to the assessment of acute and chronic toxicity of organic chemicals [26]. The results give insight into the role of the direct photolysis in the detoxification of psychotropic drugs, or in the production of TPs of peculiar concern.

2. Methods

The chemical structures of the TPs deriving from the direct photolysis of several psychotropic drugs (antidepressants, antiepileptics, and antipsychotics) were obtained from a review paper on the subject [25]. On this basis, the acute and chronic toxicity (LD₅₀, EC₅₀, and ChV values) of each TP was assessed by means of the ECOSAR software developed by USEPA, considering representative freshwater organisms belonging to different trophic levels (fish, daphnid, and algae) [26].

ECOSAR requires as input the molecular formula of a chemical and gives as output the following toxicity endpoints: (1) the lethal dose 50 (LD₅₀) for fish and crustaceans (daphnid), which is the compound concentration that is expected to kill 50% of the test organisms; (2) the effective concentration 50 (EC₅₀), which is the concentration value that causes 50% inhibition of algal growth, as well as (3) the chronic value ChV, which is the geometric mean between the no-observed effect concentration and the lowest observed effect concentration for each kind of test organism (fish, daphnid, or algae). Because the more toxic a compound is, the lower is the concentration value at which it exerts its effects, the most toxic compounds are those showing the lowest LD₅₀, EC₅₀, and ChV values. Coherently, an increase in toxicity is indicated by a decrease in the above values, when passing from the parent compound to the known TPs.

As recommended by ECOSAR developers [26], a decrease in toxicity was assumed to be significant when a TP showed a toxicity value that was an order of magnitude higher than the corresponding value of the parent compound. The reason is that ECOSAR is based on a quantitative structure-activity relationship that has unavoidable uncertainties. For the same reason, the reverse (a decrease of the relevant values by an order of magnitude) was applied for the toxicity increase. In all the other cases, the toxicity of the TP was considered to be comparable to that of the parent drug.

A further limitation that is inherent to the present approach is that it only considers toxicity, either acute or chronic, thereby neglecting other important effects such as mutagenicity or carcinogenicity. A warning is here provided in the presence of TPs that have known such effects, but these are not systematically taken into account. It should also be remarked that TPs usually occur at lower environmental concentrations than their parent drug, thus the formation of one or even several toxic TPs could take place even in the framework of an overall decontamination. In such a scenario, the parent drug could generate more toxic TPs but at very low levels, and the overall toxicity of the mixture would decrease. However, this seems not to be the case for the available experimental data concerning the photolysis of carbamazepine [22], where the toxicity of the irradiated mixture increased despite the fact that TPs were detected at much lower concentrations than their parent drug. Moreover, the identification of TPs is still mostly a qualitative work, with few indications about actual concentration values [25]. Therefore, it would not be easy to identify a scenario where detoxification is operational despite the formation of toxic compounds. In this framework, the best use of the ECOSAR results would be to trigger a concern whenever a TP appears to be more toxic than its parent drug.

3. Results and Discussion

The psychotropic drugs assessed in this work belong to the classes of antiepileptics (alprazolam, carbamazepine, diazepam, and midazolam), antidepressants (bupropion, citalopram, desipramine, fluoxetine, fluvoxamine, imipramine, mianserin, paroxetine, and venlafaxine), as well as antipsychotics (amisulpride, chlorpromazine, and zotepine). The meaning of the table entries is as follows: LD₅₀(F) = LD₅₀ for fish; LD₅₀(D) = LD₅₀ for daphnid; EC₅₀(A) = EC₅₀ for algae; ChV(F) = chronic value (ChV) for fish; ChV(D) = ChV for daphnid; ChV(A)

= ChV for algae.

Like many anti-epileptic drugs considered here, alprazolam has a seven-atom ring with two nitrogens [25]. Alprazolam is quite toxic to aquatic organisms, and its chronic toxicity towards fish is particularly remarkable (see Table 1). The direct photolysis of alprazolam involves in part chlorine loss (TP1) or 7-atom ring fragmentation (TP2), with a toxicity decrease that would, however, not be significant enough. In contrast, ring contraction/rearrangement with the formation of a 6-atom aromatic ring, together with chlorine retention, gives a compound (TP3) that is more toxic (for daphnid) than the parent drug.

Amisulpride has a sulfa moiety, and in most cases its direct photolysis does not result in extensive changes in the molecular structure (Table 2) [25]. Therefore, loss of hydrogen atoms or of lateral chains, as well as ring oxidation basically

leave the overall structure unmodified. Unsurprisingly, the resulting intermediates show similar toxicity as the parent compound. In particular, both amisulpride and TP51-3 show peculiar chronic toxicity towards crustaceans. In contrast, TP4 is the result of a 5-atom ring loss that would cause detoxification (for fish).

Bupropion is quite toxic towards all the considered organisms (Table 3). It undergoes extensive transformation upon direct photolysis, in one case through ring closure (transformation of an open aliphatic chain into an alicyclic ring) [25] that preserves the overall toxicity (TP1). In the other case (TP2), fragmentation of the lateral chain would result into detoxification as far as all organisms are concerned.

Carbamazepine, an anti-epileptic drug (Table 4), is the psychotropic pharmaceutical that is most often found in surface waters, and one of the most concentrated pharmaceuticals over-

Table 1. Toxicity endpoint values [mg L^{-1}] ($\text{LD}_{50}(\text{F}) = \text{LD}_{50}$ for fish; $\text{LD}_{50}(\text{D}) = \text{LD}_{50}$ for daphnid; $\text{EC}_{50}(\text{A}) = \text{EC}_{50}$ for algae; $\text{ChV}(\text{F}) =$ chronic value for fish; $\text{ChV}(\text{D}) = \text{ChV}$ for daphnid; $\text{ChV}(\text{A}) = \text{ChV}$ for algae), commercial drug names, structure, and TPs of the anti-epileptic drug alprazolam. Compared to the parent drug, the TPs have: ■ comparable toxicity, or ▲ higher toxicity (for daphnid).

Alprazolam	Common Names	Structure
$\text{LD}_{50}(\text{F})$ 2.50 $\text{ChV}(\text{F})$ 0.018 $\text{LD}_{50}(\text{D})$ 2.85 $\text{ChV}(\text{D})$ 0.141 $\text{EC}_{50}(\text{A})$ 1.06 $\text{ChV}(\text{A})$ 1.01	Farmapram, Xanax	
 $\text{LD}_{50}(\text{F})$ 7.52 $\text{ChV}(\text{F})$ 0.038 $\text{LD}_{50}(\text{D})$ 4.64 $\text{ChV}(\text{D})$ 0.314 $\text{EC}_{50}(\text{A})$ 2.12 $\text{ChV}(\text{A})$ 1.944		
		 $\text{LD}_{50}(\text{F})$ 1.90 $\text{ChV}(\text{F})$ 0.093 $\text{LD}_{50}(\text{D})$ 0.79 $\text{ChV}(\text{D})$ 0.015 $\text{EC}_{50}(\text{A})$ 1.90 $\text{ChV}(\text{A})$ 1.01

Table 2. Toxicity endpoint values [mg L^{-1}], commercial drug names, structure, and TPs of the anti-psychotic drug amisulpride. Compared to the parent drug, the TPs have: ▼ lower toxicity (for fish), or ■ comparable toxicity.

Amisulpride	Common Names	Structure
$\text{LD}_{50}(\text{F})$ 218 $\text{ChV}(\text{F})$ 0.48 $\text{LD}_{50}(\text{D})$ 2.69 $\text{ChV}(\text{D})$ 0.082 $\text{EC}_{50}(\text{A})$ 6.83 $\text{ChV}(\text{A})$ 1.14	Barhemsys	
 $\text{LD}_{50}(\text{F})$ 622 $\text{ChV}(\text{F})$ 0.93 $\text{LD}_{50}(\text{D})$ 2.53 $\text{ChV}(\text{D})$ 0.12 $\text{EC}_{50}(\text{A})$ 9.28 $\text{ChV}(\text{A})$ 1.45		 $\text{LD}_{50}(\text{F})$ 249 $\text{ChV}(\text{F})$ 0.52 $\text{LD}_{50}(\text{D})$ 2.68 $\text{ChV}(\text{D})$ 0.086 $\text{EC}_{50}(\text{A})$ 7.12 $\text{ChV}(\text{A})$ 1.03
		 $\text{LD}_{50}(\text{F})$ 780 $\text{ChV}(\text{F})$ 1.12 $\text{LD}_{50}(\text{D})$ 2.86 $\text{ChV}(\text{D})$ 0.14 $\text{LD}_{50}(\text{A})$ 10.86 $\text{ChV}(\text{A})$ 1.68
 $\text{LD}_{50}(\text{F})$ 3690 $\text{ChV}(\text{F})$ 2.72 $\text{LD}_{50}(\text{D})$ 1.97 $\text{ChV}(\text{D})$ 0.22 $\text{EC}_{50}(\text{A})$ 14.2 $\text{ChV}(\text{A})$ 1.96		

Table 3. Toxicity endpoint values [mg L⁻¹], commercial drug names, structure, and TPs of the anti-depressive drug bupropion. Compared to the parent drug, the TPs have: ▼ lower toxicity (for all organisms), or ■ comparable toxicity.

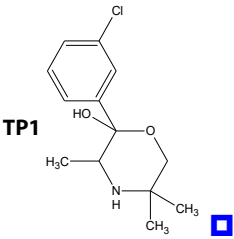
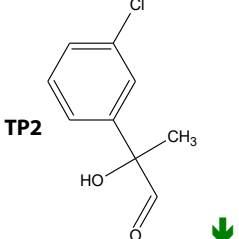
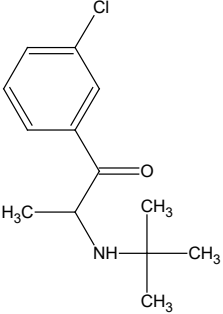
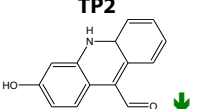
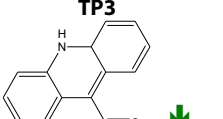
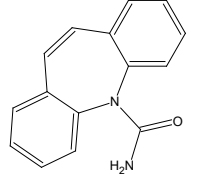
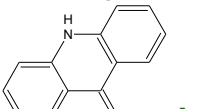
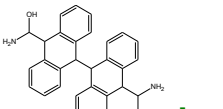
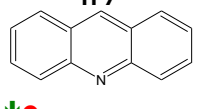
Bupropion	Common Names	Structure
LD ₅₀ (F) 2.79 ChV(F) 0.084 LD ₅₀ (D) 0.41 ChV(D) 0.042 EC ₅₀ (A) 0.22 ChV(A) 0.086 	Wellbutrin, Zyban 	
LD ₅₀ (F) 8.39 ChV(F) 0.32 LD ₅₀ (D) 1.15 ChV(D) 0.11 LD ₅₀ (A) 0.72 ChV(A) 0.26 ■	LD ₅₀ (F) 30.2 ChV(F) 6.69 LD ₅₀ (D) 30.0 ChV(D) 0.28 EC ₅₀ (A) 16.0 ChV(A) 5.45 ▼	

Table 4. Toxicity endpoint values [mg L⁻¹], commercial drug names, structure, and TPs of the anti-epileptic drug carbamazepine. Compared to the parent drug, the TPs have: ▼ lower toxicity; ▲ higher toxicity (for fish), or ▼ ● lower toxicity (for algae), but the compound is mutagenic.

Carbamazepine	Common Names	Structure
LD ₅₀ (F) 41.3 ChV(F) 0.90 LD ₅₀ (D) 14.9 ChV(D) 1.17 EC ₅₀ (A) 0.26 ChV(A) 0.13 	Zentiva, Tegretol 	
LD ₅₀ (F) 14.9 ChV(F) 2.36 LD ₅₀ (D) 13.8 ChV(D) 2.62 EC ₅₀ (A) 37.9 ChV(A) 13.3 ▼	LD ₅₀ (F) 5.08 ChV(F) 0.58 LD ₅₀ (D) 5.75 ChV(D) 0.96 EC ₅₀ (A) 10.3 ChV(A) 4.35 ▼	LD ₅₀ (F) 3.39 ChV(F) 0.34 LD ₅₀ (D) 3.27 ChV(D) 0.58 EC ₅₀ (A) 6.31 ChV(A) 2.86 ▲
		
LD ₅₀ (F) 308 ChV(F) 29.1 LD ₅₀ (D) 170 ChV(D) 15.3 EC ₅₀ (A) 112 ChV(A) 27.5 ▼	LD ₅₀ (F) 177 ChV(F) 12.2 LD ₅₀ (D) 20.0 ChV(D) 1.56 EC ₅₀ (A) 18.4 ChV(A) 5.86 ▼	LD ₅₀ (F) 9.63 ChV(F) 1.09 LD ₅₀ (D) 6.17 ChV(D) 0.84 EC ₅₀ (A) 7.61 ChV(A) 2.61 ▼ ●

all in the water environment [27]. Although extensively used in clinical practice, carbamazepine is definitely not as popular as typical over-the-counter drugs such as ibuprofen, paracetamol, or diclofenac. Still, the biorecalcitrance of carbamazepine is deeply involved into its environmental occurrence. Indeed, carbamazepine is widely excreted as a glucuronic acid conjugate in addition to the original drug. In WWTPs, activated-sludge bacteria leave the parent drug unmodified while detaching the glucuronate moiety from the conjugate.

As a result, carbamazepine is often found at higher concentrations at the WWTP outlets than at the inlets, the additional amount being generated inside the WWTP upon conjugate breaking. The poor biodegradation of the parent drug accounts for its poor removal, also taking into account the fact that carbamazepine is not hydrophobic enough to undergo important partitioning on biosolids. As a consequence, carba-

mazepine is largely left in the water phase and it is one of the pharmaceutical compounds that are most often detected in rivers or lakes, at relatively high concentration values compared to the other CECs [27]. Due to slow degradation, carbamazepine (together with the artificial sweetener acesulfame K) is a very good indicator of wastewater dilution. In other words, by comparing the contaminant concentration values at the WWTP outlet and downstream in the river, after complete mixing between wastewater and river water, one can determine how many times has wastewater been diluted by river water [28].

The 7-atom ring and the lateral chain are the carbamazepine moieties that undergo the most transformation upon direct photolysis. In several cases, formation of less toxic TPs would be the result (TP1 and TP6 for fish and algae, TP2, TP3, and TP7 for algae, and TP5 for all organisms). However,

TP4 would show an increase in toxicity (towards fish) compared to carbamazepine. Interestingly, there is experimental evidence that the direct photolysis of carbamazepine causes a toxicity increase of the irradiated mixtures compared to the parent compound [23]. While it is very possible that a toxic TP escapes detection, the comparison between the scenarios suggested by ECOSAR results and by actual experiments indicates that the occurrence of a single more toxic TP can be a matter of concern and should trigger an alarm.

Moreover, care should be taken towards the occurrence of TPs with acridine-like structures, where the 7-atom ring has been transformed into an aromatic, 6-atom one. First of all, acridine-9-carboxyaldehyde (TP4) is peculiarly toxic towards fish. Moreover, acridine itself (TP7) is less acutely or chronically toxic than carbamazepine towards algae, but it is a well-known mutagen. Therefore, the hazard class of the parent compound (toxicity) is modified in the case of acridine, which might be potentially carcinogenic [29].

Chlorpromazine has a 3-ring aromatic structure with heteroatoms (Table 5) that is very little transformed in the direct photolysis process [25]. Apparently, what makes the difference between equally or less toxic TPs is the retention (or lack of it) of the chlorine atom linked to the aromatic ring. The TPs that lost the Cl group, replaced by OH (TP1, TP2), turned out to

be less toxic than the parent chlorpromazine. In particular, TP1 would be less toxic for fish and possibly algae (in the latter case, ratios between toxicity values are very near an order of magnitude, thus just on the verge of significance), while TP2 would be less toxic towards all organisms. In contrast, TP3 retained the Cl atom and would be about as toxic as the parent compound.

Citalopram (Table 6) is quite toxic towards crustaceans. Its direct photolysis mainly results into a modification of the tertiary amine group [25], but this change in structure does not seem to be important enough to modify toxicity of TPs significantly, compared to the parent drug.

Dezipramine (Table 7) has a structure that somewhat resembles carbamazepine, with a 7-atom ring that contains a nitrogen atom. That ring undergoes contraction as its main phototransformation pathway, producing two acridine-like structures [25] that are less acutely or chronically toxic than the parent compound towards all organisms. However, in a similar way as already observed for carbamazepine, the combination of ring contraction with loss of the lateral chain yields mutagenic acridine (TP1) among the detected TPs. That event would totally modify the environmental impact of the reacted mixture, from short- or middle-term to long-lasting effects.

Diazepam (Table 8) is an anti-epileptic drug with a 7-

Table 5. Toxicity endpoint values [mg L^{-1}], commercial drug names, structure, and TPs of the anti-psychotic drug chlorpromazine. Compared to the parent drug, the TPs have: ▼ lower toxicity, or ■ comparable toxicity.

Chlorpromazine	Common Names	Structure
LD ₅₀ (F) 1.68 ChV(F) 0.042 LD ₅₀ (D) 0.265 ChV(D) 0.028 EC ₅₀ (A) 0.126 ChV(A) 0.051	Thorazine, Largactil	
TP1 LD ₅₀ (F) 13.8 ChV(F) 0.57 LD ₅₀ (D) 1.84 ChV(D) 0.168 EC ₅₀ (A) 1.22 ChV(A) 0.439	TP2 LD ₅₀ (F) 128 ChV(F) 8.91 LD ₅₀ (D) 14.5 ChV(D) 1.12 EC ₅₀ (A) 13.4 ChV(A) 4.25	TP3 LD ₅₀ (F) 5.66 ChV(F) 0.19 LD ₅₀ (D) 0.81 ChV(D) 0.080 EC ₅₀ (A) 0.46 ChV(A) 0.18

Table 6. Toxicity endpoint values [mg L^{-1}], commercial drug names, structure, and TPs of the anti-depressive drug citalopram. Compared to the parent drug, the TPs have ■ comparable toxicity.

Citalopram	Common Names	Structure
LD ₅₀ (F) 4.47 ChV(F) 0.14 LD ₅₀ (D) 0.65 ChV(D) 0.065 EC ₅₀ (A) 0.36 ChV(A) 0.138	Elopram, Feliximir, Kaidor, Ricap, Verisan	
TP1 LD ₅₀ (F) 15.0 ChV(F) 0.62 LD ₅₀ (D) 1.99 ChV(D) 0.18 EC ₅₀ (A) 1.32 ChV(A) 0.48	TP2 LD ₅₀ (F) 5.88 ChV(F) 0.20 LD ₅₀ (D) 0.84 ChV(D) 0.082 EC ₅₀ (A) 0.49 ChV(A) 0.18	 LD ₅₀ (F) 5.88 ChV(F) 0.20 LD ₅₀ (D) 0.84 ChV(D) 0.082 EC ₅₀ (A) 0.49 ChV(A) 0.18

Table 7. Toxicity endpoint values [mg L⁻¹], commercial drug names, structure, and TPs of the anti-depressive drug dezipramine. Compared to the parent drug, the TPs have: ▼ lower toxicity, or ▼ lower toxicity, but the compound is mutagenic.

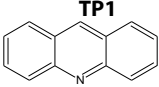
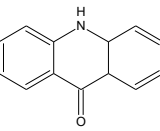
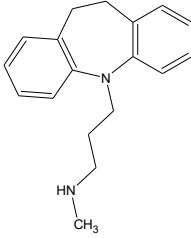
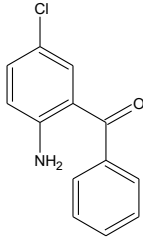
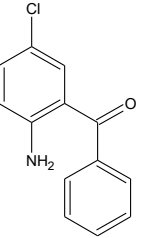
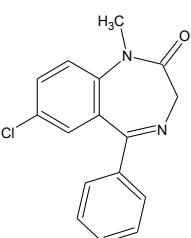
Dezipramine	Common Names	Structure
LD ₅₀ (F) 0.743 ChV(F) 0.016 LD ₅₀ (D) 0.123 ChV(D) 0.014 EC ₅₀ (A) 0.053 ChV(A) 0.022  LD ₅₀ (F) 9.63 ChV(F) 1.09 LD ₅₀ (D) 6.18 ChV(D) 0.845 EC ₅₀ (A) 7.61 ChV(A) 2.61	Norpramin, Pertofrane  LD ₅₀ (F) 308 ChV(F) 29.1 LD ₅₀ (D) 170 ChV(D) 15.3 EC ₅₀ (F) 112 ChV(A) 27.5	

Table 8. Toxicity endpoint values [mg L⁻¹], commercial drug names, structure, and TPs of the anti-epileptic drug diazepam. Compared to the parent drug, the TPs have ▲ higher toxicity (for daphnid).

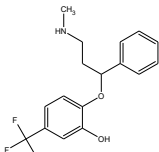
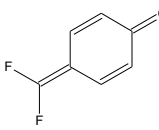
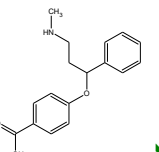
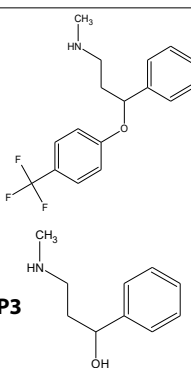
Diazepam	Common Names	Structure
LD ₅₀ (F) 26.9 ChV(F) 0.070 LD ₅₀ (D) 21.4 ChV(D) 1.91 EC ₅₀ (A) 1.98 ChV(A) 1.24  LD ₅₀ (F) 1.99 ChV(F) 0.25 LD ₅₀ (D) 1.39 ChV(D) 0.24 EC ₅₀ (A) 2.42 ChV(A) 1.00	Valium, Ansiolin, Noan  LD ₅₀ (F) 9.77 ChV(F) 0.23 LD ₅₀ (D) 1.82 ChV(D) 0.40 EC ₅₀ (A) 4.84 ChV(A) 2.75	

atom ring that contains two nitrogen atoms [25]. Such a ring undergoes fragmentation upon diazepam direct photolysis. The TPs thus generated show increased toxicity for crustaceans. It is possible that some of the toxic effects are linked

to the benzophenone-like structure of the two TPs, which might be linked with cellular oxidative stress or even phototoxicity [30].

Fluoxetine is quite toxic, especially towards algae (Table 9).

Table 9. Toxicity endpoint values [mg L⁻¹], commercial drug names, structure, and TPs of the anti-depressive drug fluoxetine. Compared to the parent drug, the TPs have: ▼ lower toxicity, or ■ comparable toxicity.

Fluoxetine	Common Names	Structure
LD ₅₀ (F) 1.08 ChV(F) 0.025 LD ₅₀ (D) 0.17 ChV(D) 0.019 EC ₅₀ (A) 0.079 ChV(A) 0.033  LD ₅₀ (F) 1.27 ChV(F) 0.033 LD ₅₀ (D) 0.36 ChV(D) 0.035 EC ₅₀ (A) 0.18 ChV(A) 0.072 	Fluoxeren, Prozac  LD ₅₀ (F) 9.18 ChV(F) 1.06 LD ₅₀ (D) 6.02 ChV(D) 0.72 EC ₅₀ (A) 4.22 ChV(A) 1.60 LD ₅₀ (F) 429 ChV(F) 39.2 LD ₅₀ (D) 230 ChV(D) 19.1 EC ₅₀ (A) 134 ChV(A) 31.0	 LD ₅₀ (F) 149 ChV(F) 12.4 LD ₅₀ (D) 15.7 ChV(D) 1.15 EC ₅₀ (A) 16.4 ChV(A) 5.00

It is possible that the toxicity of fluoxetine is linked in some way to its CF₃ moiety, the retention of which in TP1 produces similar toxicity as the parent compound. In contrast, the transformation of CF₃ leads to detoxification (TP2-TP4). A similar issue holds for fluvoxamine (Table 10), in which case the only known TP is an isomer [25] that shows similar toxicity as the parent drug.

The anti-depressive drug imipramine (Table 11) is another compound with carbamazepine-like structure. Ring

contraction does not appear to take place in this case [25], which would be good news from the point of view of the effects of the products (no acridine-like compounds among the detected TPs). Conversely, ring oxidation, fragmentation or total loss of the lateral chain would all result into detoxification. The latter would be more marked for TP2 and TP3 compared to TP1, which retained the dimethylamine group of imipramine.

Mianserin (Table 12) has a 7-atom ring that occurs in a

Table 10. Toxicity endpoint values [mg L⁻¹], commercial drug names, structure, and TPs of the anti-depressive drug fluvoxamine. Compared to the parent drug, the TP has: ■comparable toxicity.

Fluvoxamine	Common Names	Structure
LD ₅₀ (F) 11.8 ChV(F) 0.47 LD ₅₀ (D) 1.60 ChV(D) 0.15 EC ₅₀ (A) 1.03 ChV(A) 0.37	Maveral, Dumirox, Fevarin	
LD ₅₀ (F) 11.8 ChV(F) 0.47 LD ₅₀ (D) 1.60 ChV(D) 0.15 EC ₅₀ (A) 1.03 ChV(A) 0.37		

Table 11. Toxicity endpoint values [mg L⁻¹], commercial drug names, structure, and TPs of the anti-depressive drug imipramine. Compared to the parent drug, the TPs have: ▼lower toxicity.

Imipramine	Common Names	Structure
LD ₅₀ (F) 0.141 ChV(F) 0.0020 LD ₅₀ (D) 0.027 ChV(D) 0.0030 EC ₅₀ (A) 0.0089 ChV(A) 0.0041	Tofranil	
LD ₅₀ (F) 1.15 ChV(F) 0.027 LD ₅₀ (D) 0.185 ChV(D) 0.020 EC ₅₀ (A) 0.085 ChV(A) 0.035	TP1	
LD ₅₀ (F) 4.31 ChV(F) 0.515 LD ₅₀ (D) 2.90 ChV(D) 0.455 EC ₅₀ (A) 4.38 ChV(A) 1.68	TP2	
LD ₅₀ (F) 2.25 ChV(F) 0.275 LD ₅₀ (D) 1.54 ChV(D) 0.256 EC ₅₀ (A) 2.52 ChV(A) 1.01	TP3	

Table 12. Toxicity endpoint values [mg L⁻¹], commercial drug names, structure, and TPs of the anti-depressive drug mianserin. Compared to the parent drug, the TPs have: ■comparable toxicity.

Mianserin	Common Names	Structure
LD ₅₀ (F) 6.61 ChV(F) 0.239 LD ₅₀ (D) 0.921 ChV(D) 0.088 EC ₅₀ (A) 0.557 ChV(A) 0.207	Lantanon	
LD ₅₀ (F) 24.6 ChV(F) 1.19 LD ₅₀ (D) 3.12 ChV(D) 0.272 EC ₅₀ (A) 2.28 ChV(A) 0.792	TP1	
LD ₅₀ (F) 8.61 ChV(F) 0.335 LD ₅₀ (D) 1.17 ChV(D) 0.109 LD ₅₀ (A) 0.744 ChV(A) 0.272	TP2	

fused-ring configuration [25]. The overall, multi-ring structure is not extensively modified by direct photolysis and the two detected TPs, arising from ring hydroxylation or loss of a methyl group, would have comparable toxicity as the parent compound.

Midazolam (Table 13) also has a fused-ring configuration, but photodegradation follows a different route than mianserin in terms of structural modifications between parent drug and the only known TP [25]. In the case of midazolam as well, however, changes are not deep enough to significantly modify toxicity when compared with the parent compound.

Paroxetine (Table 14) is quite toxic towards all organisms, but it undergoes extensive molecular fragmentation [25] that results into decreased toxicity for both known TPs. In particular, TP1 would be less toxic towards all organisms; in the case of TP2, which has a fused-ring structure, the decrease in toxicity would be significant for fish only.

Venlafaxine (Table 15) mainly undergoes hydroxylations at different positions [25]. The outcome would be either a non-significant variation in toxicity (TP1, TP3, TP4, TP7, TP8), or a significant detoxification: towards algae for TP2, fish and algae for TP5, and all organisms for TP6.

Zotepine (Table 16) has only one known TP, deriving from CH₃ loss from a tertiary amine moiety [25]. As observed previously for mianserin and citalopram, methyl loss from the

amine group would not be sufficient to modify toxicity to a significant extent.

Overall, from the current assessment it appears that detoxification would be more common than an increase in toxicity for the considered psychotropic drugs. In particular, out of the 47 TPs that underwent toxicity assessment, approximately 50% appeared to be less toxic than their parent contaminant, while another ~40% had comparable toxicity. In contrast, only about 10% of the TPs were more toxic than the parent drug. However, when comparing predictions with available experimental data in the case of carbamazepine, it appears that the formation of one TP with higher toxicity may be enough, to increase the toxicity of the irradiated mixture above that of the parent drug.

Two indications can thus be derived from the data obtained in this work: (i) from a merely statistical point of view, a TP arising from direct photolysis is more likely to be less toxic than more toxic, compared to the parent psychotropic drug; (ii) however, the formation of a single TP that is predicted to be more toxic than the parent compound should trigger an alarm, which of course requires experimental confirmation to check for the possibility of a carbamazepine-like scenario. From this point of view, among the psychotropic drugs considered in this work, those arising the most concern would be alprazolam, carbamazepine, and diazepam. Moreover,

Table 13. Toxicity endpoint values [mg L⁻¹], commercial drug names, structure, and TPs of the anti-epileptic drug midazolam. Compared to the parent drug, the TP has: ■comparable toxicity.

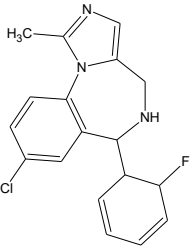
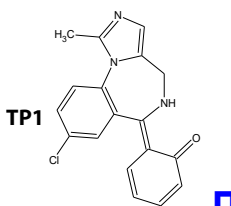
Midazolam	Common Names	Structure
LD ₅₀ (F) 3.15 ChV(F) 0.091 LD ₅₀ (D) 0.473 ChV(D) 0.049 EC ₅₀ (A) 0.248 ChV(A) 0.097	Ipnovel, Talentum	
 TP1 ■	LD ₅₀ (F) 6.30 ChV(F) 0.215 LD ₅₀ (D) 0.895 ChV(D) 0.087 EC ₅₀ (A) 0.522 ChV(A) 0.197	

Table 14. Toxicity endpoint values [mg L⁻¹], commercial drug names, structure, and TPs of the anti-depressive drug paroxetine. Compared to the parent drug, the TPs have: ▼lower toxicity.

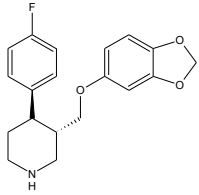
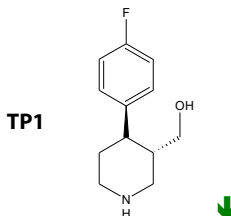
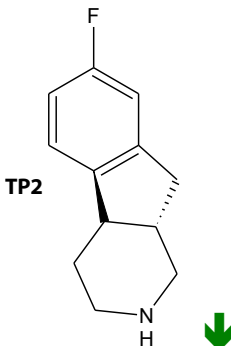
Paroxetine	Common Names	Structure
LD ₅₀ (F) 0.996 ChV(F) 0.022 LD ₅₀ (D) 0.163 ChV(D) 0.018 EC ₅₀ (A) 0.072 ChV(A) 0.030	DaparoX, Dropaxin, Eutimil, Sereupin, Seroxat, Stiliden	
 TP1 ▼	 TP2 ▼	
LD ₅₀ (F) 41.7 ChV(F) 2.45 LD ₅₀ (D) 4.96 ChV(D) 0.406 EC ₅₀ (A) 4.11 ChV(A) 1.36	LD ₅₀ (F) 7.59 ChV(F) 0.305 LD ₅₀ (D) 1.02 ChV(D) 0.094 EC ₅₀ (A) 0.663 ChV(A) 0.240	

Table 15. Toxicity endpoint values [mg L⁻¹], commercial drug names, structure, and TPs of the anti-depressive drug venlafaxine. Compared to the parent drug, the TPs have: ▼ lower toxicity, or ■ comparable toxicity.

Venlafaxine	Common Names	Structure
LD ₅₀ (F) 7.68 ChV(F) 0.28 LD ₅₀ (D) 1.06 ChV(D) 0.10 EC ₅₀ (A) 0.65 ChV(A) 0.24	Efexor, Zarelis	
TP2 LD ₅₀ (F) 19.1 ChV(F) 1.12 LD ₅₀ (D) 1.93 ChV(D) 0.66 EC ₅₀ (A) 7.55 ChV(A) 1.38	TP3 LD ₅₀ (F) 4.95 ChV(F) 0.19 LD ₅₀ (D) 0.93 ChV(D) 0.14 EC ₅₀ (A) 1.65 ChV(A) 0.42	TP4 LD ₅₀ (F) 14.6 ChV(F) 0.80 LD ₅₀ (D) 1.61 ChV(D) 0.49 EC ₅₀ (A) 5.62 ChV(A) 1.08
TP5 LD ₅₀ (F) 106 ChV(F) 11.8 LD ₅₀ (D) 4.39 ChV(D) 0.47 EC ₅₀ (A) 53.7 ChV(A) 5.87	TP6 LD ₅₀ (F) 63.4 ChV(F) 5.90 LD ₅₀ (D) 3.34 ChV(D) 2.62 EC ₅₀ (A) 30.0 ChV(A) 3.76	TP7 LD ₅₀ (F) 14.0 ChV(F) 0.84 LD ₅₀ (D) 1.36 ChV(D) 0.48 EC ₅₀ (A) 5.59 ChV(A) 1.00
		TP1 LD ₅₀ (F) 40.3 ChV(F) 2.17 LD ₅₀ (D) 4.93 ChV(D) 0.41 EC ₅₀ (A) 3.86 ChV(A) 1.31
		TP8 LD ₅₀ (F) 0.88 ChV(F) 0.12 LD ₅₀ (D) 2.17 ChV(D) 0.41 EC ₅₀ (A) 2.58 ChV(A) 0.46

Table 16. Toxicity endpoint values [mg L⁻¹], commercial drug names, structure, and TPs of the anti-psychotic drug zotepine. Compared to the parent drug, the TP has: ■ comparable toxicity.

Zotepine	Common Names	Structure
LD ₅₀ (F) 1.80 ChV(F) 0.045 LD ₅₀ (D) 0.283 ChV(D) 0.030 EC ₅₀ (A) 0.135 ChV(A) 0.055	Lodopin, Zoleptil	
TP1 	LD ₅₀ (F) 2.38 ChV(F) 0.065 LD ₅₀ (D) 0.364 ChV(D) 0.038 EC ₅₀ (A) 0.183 ChV(A) 0.073	

dezipramine should be added to the list as well, because of the formation of mutagenic acridine. From this point of view, carbamazepine is doubly concerning because of the formation of both toxic and mutagenic TPs.

A further issue is that some TPs are hydroxyderivatives that might potentially be formed upon reaction between their parent compounds and $\cdot\text{OH}$ (indirect photochemistry). In a majority of circumstances, they would be less toxic than the parent compound: it is the case of carbamazepine (TP1), chlorpromazine (TP1 and TP2), and venlafaxine (TP2, TP5, TP6). In fewer cases, toxicity would be comparable to that of the parent drug (TP1 of fluoxetine, TP1 and TP4 of venlafaxine). On this basis, it could be tentatively hypothesized that the $\cdot\text{OH}$ reaction may have more detoxification potential compared to the direct photolysis.

4. Conclusion

This survey suggests that the direct photolysis of psy-

chotropic drugs would often produce TPs that are less toxic than their parent compound. The formation of more toxic TPs would be definitely less common, but this consideration would not be enough to avoid concerns. The case of carbamazepine, for which experimental data about the toxicity of irradiated mixtures is available, suggests that the formation of a more toxic TP could be sufficient to produce irradiated mixtures with increased toxicity compared to the initial drug. Therefore, the results of this work could be used for a prioritization of drugs for subsequent studies. Priority should be given to compounds, for which even one TP is predicted to be more toxic than the parent drug. When this approach is applied to the current results, particular concern would be raised by the anti-epileptic drugs alprazolam, carbamazepine, and diazepam. The anti-depressant drug dezipramine should be added to the list as well, due to the formation of mutagenic acridine among the TPs. Interestingly, all the mentioned drugs have a heterocyclic 7-atom ring, and the TPs of concern (more

toxic or mutagenic) derive from ring rearrangement or fragmentation.

Acknowledgments

This study was funded by the European Union - NextGenerationEU, in the framework of the GRINS -Growing Resilient, INclusive and Sustainable project (GRINS PE00000018-CUP D13C22002160001). The views and opinions expressed are solely those of the author and do not necessarily reflect those of the European Union, nor can the European Union be held responsible for them.

Conflicts of Interest

The author declares that there are no conflicts of interest in this work. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

Data Availability

All data needed to support the conclusions in the paper are presented in the manuscript. Additional data related to this paper may be requested from the corresponding author.

Ethical Approval

Not applicable.

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