

Article

A Comparative Study of Advanced Oxidation Processes for the Removal of the Antibiotic Sulfadoxine from Water—Transformation Products and Toxicity

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Abstract: Sulfonamides, including sulfadoxine (SDX), are widely used antibiotics, particularly for malaria treatment. However, their extensive use has led to environmental pollution, microbial resistance, and public health risks. Advanced Oxidation Processes (AOPs) offer promising methods to degrade such pollutants in water, though they may generate more toxic by-products. This study evaluates three AOPs with different hydroxyl radical generation principles: the Fenton reagent ($\text{H}_2\text{O}_2/\text{Fe}^{2+}$), hydrogen peroxide photolysis (UV-C/ H_2O_2), and heterogeneous photocatalysis (UV-A/ TiO_2). Heterogeneous photocatalysis showed superior performance, achieving 100% degradation and 77% mineralization under optimized conditions. Further analysis explored the effects of UV dose, catalyst concentration, and pH on process efficiency. The influence of water matrices, including Ultrapure Water (UW), Tap Water (TW), and Surface Water (SW) from the Aliakmonas River, was also examined. High-Resolution Mass Spectrometry identified 11 SDX transformation products formed during photocatalysis, with their formation mechanisms reported for the first time. An ecotoxicity assessment using ECOSAR software revealed insights into the potential environmental impact of these by-products.

Keywords: sulfadoxine; Fenton reaction; UV-C photolysis; heterogeneous photocatalysis; transformation products identification



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1. Introduction

Sulfonamides are a cornerstone within the class of antibiotics renowned for their efficacy in the treatment of various bacterial, viral, and parasitic infections. Chronic advances in organic synthesis have enabled the development of a variety of pharmaceutical agents in this class [1]. Consequently, sulfonamides exhibit remarkable selectivity in their mechanism of action by specifically modulating metabolic pathways that are critical for microbial survival. This specificity of their action emphasizes their therapeutic effect and places them on the top shelves of pharmaceutical products (PPs) [2,3].

Sulfadoxine (SDX) is a sulfonamide of central importance in the treatment of malaria, a disease known for its epidemic nature and devastating effects on people of all ages. SDX performs its therapeutic role by interfering with the synthesis of dihydropteroate

synthase (DHPS), a key metabolic enzyme in folic acid biosynthesis. This molecule plays a crucial role in facilitating the metabolism and transport of carbon units and is involved in a specific metabolic pathway in which methyl groups are converted into triphosphates during DNA synthesis [4,5]. Through this precise mechanism, SDX effectively stops an essential metabolic process of the pathogen and suppresses the spread of infection.

The phenomenon of bacterial adaptation and the development of drug resistance is a well-documented and worrying aspect of modern medicine. Bacterial species have shown the ability to evolve and develop defence mechanisms in response to prolonged exposure to pharmaceutical agents, posing significant challenges to the efficacy of future antimicrobial therapies [6–8]. Bacteria have shown amazing abilities to rapidly adapt to such environments. One example of this is the species of *Staphylococcus*, which has developed resistance to paracetamol in a remarkably short time—only 18 years after its first use [9]. This alarming trend illustrates the extent of the threat posed by the widespread presence of PPs in the environment.

Consequently, it is imperative to adopt comprehensive strategies aimed at mitigating the impact of pharmaceutical residues on the environment while addressing the challenges posed by antimicrobial resistance. The main pathways through which active pharmaceutical ingredients enter the environment include public and industrial sewage systems [10]. In response to the growing awareness of the environmental hazards posed by such residues, regulatory frameworks such as those in European legislation have been established to limit the release of these substances into aquatic ecosystems [6,11,12].

Conventional activated sludge treatment in wastewater treatment plants has been shown to be ineffective in removing a variety of PPs by biodegradation [13]. The need for tertiary technologies that effectively address the challenge of complete removal of PPs and other toxic organic micropollutants from wastewater to protect the aquatic environment and promote the potential reuse of treated effluents has led to the development of so-called Advanced Oxidation Processes (AOPs) [14–18]. AOPs involve the generation of highly reactive, non-selective hydroxyl radicals through the application of processes such as photolysis, ozonation, photocatalysis, or treatment with hydrogen peroxide. These hydroxyl radicals effectively oxidize and degrade a wide range of organic contaminants, including pharmaceuticals, leading to the generation of transformation products (TPs) [19,20].

Traditionally, the presence of TPs was not a cause for concern, as their potential impact on the environment was either unknown or ignored. However, recent research studies have highlighted the importance of TPs as emerging contaminants [12,21]. Unlike PPs, which have known and predictable pharmacological properties and environmental fate, TPs can have different chemical properties and toxicological profiles, posing new challenges for environmental risk assessment and management [22–25].

While the degradation of PPs is a key objective in wastewater treatment, it is therefore crucial to consider the fate and impact of TPs generated in such processes and to aim for higher levels of mineralization. Complete mineralization of organic constituents is often a challenging goal, mainly due to the inherent complexity of the chemicals involved and the practical constraints associated with the development of highly effective treatment systems [19,26–28]. In many cases, complete mineralization remains elusive due to various factors. These include the recalcitrant nature of certain pharmaceutical compounds that are not degraded under conventional treatment conditions.

This study addresses the challenge of pharmaceutical contamination, focusing on a distinctive member of the major group of sulfonamides. By investigating the matter holistically, the results offer a three-fold contribution to the field of wastewater treatment. First, by conducting a comprehensive and direct comparison of three widely used AOPs (Fenton, $\text{H}_2\text{O}_2/\text{UV-C}$, and heterogeneous photocatalysis— $\text{TiO}_2/\text{UV-A}$) and evaluating

their performance not only in terms of SDX removal, but also in mineralization levels, we identify the superior treatment method. Furthermore, we investigate the influence of key process parameters on the selected optimal AOP, along with the impact of different water matrices, providing practical guidance for its real-world implementation. Second, in an effort to decipher the degradation pathways of SDX, high-resolution mass spectrometry was employed in order to identify the TPs produced by the most effective AOP. A total of 11 TPs of SDX were documented, with 9 of them being reported for the first time, shedding light on the previously unexplored chemical transformations during the degradation process. Finally, beyond merely identifying TPs, we assess their potential toxicity using an *in silico* approach, using Quantitative Structure–Activity Relationship (QSAR) software known as ECOSAR. This integrated analytical and computational approach provides a crucial first step in evaluating the environmental risk associated with these previously unknown transformation products.

2. Materials and Methods

2.1. Material and Reagents

An analytical-grade standard (>95%) of sulfadoxine was supplied by Superlco, PA, USA. Ultrapure water (UW) ($18.2 \text{ M}\Omega \times \text{cm}$) from a purification system (MilliQ, Millipore, MA, USA) was used for all experiments with synthetic solutions. $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$ from Sigma-Aldrich, USA, was used for the Fenton experiments. TiO_2 Aeroxide®P25 nanoparticles (suspension, 75% anatase and 25% rutile, average primary particle size 21 nm, and a BET surface area $\sim 50 \text{ m}^2/\text{g}$) from Evonik Industries AG, Germany, were used for heterogeneous photocatalysis. H_2O_2 (30% *w/w*) was purchased from Merck, Germany. For the HPLC mobile phases, HPLC-grade water and methanol were supplied by Merck, Germany. H_2SO_4 (Fluka Chemie GmbH, Buchs, Switzerland) and NaOH (Merck, Darmstadt, Germany) buffers were used for the required pH adjustments.

Two other water types, Tap water (TW) and SW (Surface water), were used to study the water matrix effect. TW was natural well-water (serving CETH) that was filtered and chlorinated. SW was obtained from the Aliakmon River. Water quality parameters of feed water are summarized in Table S1.

2.2. AOPs Setups

Fenton reaction experiments were carried out in simple volumetric flasks of 250 mL at a stirring rate of 300 rpm. The solutions for these experiments contained H_2O_2 (20 mg/L), SDX (5 mg/L), and $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$ (2.6 mg/L) in UW water. The same concentration of H_2O_2 and SDX was used for the photolysis and photocatalysis experiments, in a laboratory setup that has been described in a previously published study [29], with the exception that membrane modules were not utilized in our study. The active volume of this setup (the volume of sample directly exposed to UV light) is 2.3 L and the stirring was set at 600 rpm. In addition, UV-C (TUV PL-L 24 W, 253.7 nm emission) and UV-A (Actinic BL PL-L 24 W, 365 nm emission) lamps were supplied by Phillips, Netherlands. A portable radiometer (RM-12, Elektronik GmbH, Germany) was employed to measure the light intensity. Catalase from bovine liver (Sigma-Aldrich, St. Louis, MI, USA) was used in all experiments with H_2O_2 to decompose the residual H_2O_2 and ensure its deactivation, a known ability of this reagent [30].

2.3. Instrumental Analysis

Sulfadoxine was determined using a CBM-20A HPLC (Shimadzu Europa GmbH, Duisburg, Germany) coupled to a Diode Array detector at 215 nm. A Shim-pack GIST C18 reverse-phase column, 5 μm , $150 \times 4.0 \text{ mm}$ (Shimadzu, Japan), was used for the

analysis. The mobile-phase composition was 60/40 *v/v* water/methanol, with a flow rate of 1 mL/min. The furnace temperature was set to 40 °C. The method's calibration range was 10–0.05 mg/L, and the Limit of Detection (LOD) was determined based on the signal-to-noise ratio (S/N) at a concentration of 0.2 mg/L. Prior to injection, all samples were filtered with 0.22 µm nylon syringe filters supplied by LabSolutions, Greece. For the heterogeneous photocatalysis experiments, samples were centrifuged for 10 min at 4500 rpm using a Heraeus Megafuge 16R centrifuge (Thermo Fisher Scientific, Germany) and filtered with 0.45 µm nylon syringe filters prior to 0.22 µm filtration.

A Q Exactive™ Focus Orbitrap LC-MS/MS (Thermo Fisher Scientific, Dreieich, Germany), equipped with a heated electrospray ionization source (H-ESI II), was used for separation and analysis of target compounds. For the LC separation, a Thermo Hypersil GOLD aQ column (50 mm × 2.1 mm, 1.9 µm particle size) was employed. Additional information regarding the mobile-phase and the Orbitrap mass analyser parameters are available in the previously published work of Anagnostopoulou et al. [20].

A TOC-5000A Analyser system (Shimadzu Europa GmbH, Duisburg, Germany) was used for the Total Organic Carbon (TOC) measurements. The LOD of the analysis was 0.1 mg/L. Prior to analysis, the samples were treated in the same way as for HPLC analysis.

A Liquid Chromatography system (CBM-20A, Shimadzu Europa GmbH, Duisburg, Germany) coupled with a Conductivity Detector (CDD-10A VP, Shimadzu Europa GmbH, Germany) was used to determine the ion content of the TW and SW samples. For cation determination, a method using 1 mL/min (isocratic flow) of 4.0 mM methane sulfonic acid (Supelco, PA, USA) with the corresponding column (Shodex™ IC YS-50, Shodex™, Japan) was used. For anion determination, a 0.8 mL/min (isocratic flow) 3.6 mM Sodium Carbonate (Supelco, PA, USA) method was used, with the appropriate column (IC SI-52 4E, Shodex™, Japan) coupled to an Anion Suppressor System (Xenoc™ Anion Membrane Suppressor, Shimadzu Europa GmbH, Duisburg, Germany).

The pH of the samples was measured using a digital pH-meter (InoLab 750, WTW), while the M-Alkalinity (CaCO₃) was determined similarly to previously published studies [31,32].

2.4. Toxicity Assessment

The ECOSAR v2.2 (Ecological Structure–Activity Relationships) software was employed to assess the toxicity of the TPs generated. This tool has already proven to be a valuable *in silico* method for predicting the potential acute and chronic toxicity of organic molecules across three trophic levels (fish, daphnids, and green algae). This tool uses a classification system based on the molecular structure of each compound and relies on mathematical correlations between the estimated toxicity values (mmol/L) and the predicted logK_{ow} values. The toxicity levels provided by the simulation tool ranged from 0.0 to 100 and categorized the substances as (i) very toxic (0.0–1.0), (ii) toxic (1–10), (iii) harmful (10–100), or (iv) non-toxic (>100). The approach of this analysis was based on a previously published study [20].

3. Results and Discussion

3.1. Screening of Different AOPs

3.1.1. Fenton Reagent

The Fenton reaction has been used as a treating process to degrade sulfonamides, as it generates hydroxyl radicals through the catalytic reaction between Fe²⁺ and H₂O₂ [33]. However, prior to the oxidation experiments with the Fenton reagent, reference tests needed to be performed in order to investigate the prospect of direct reaction between SDX and

H₂O₂. For these experiments, it was highly important to have H₂O₂ in excess, in order to ensure that there will be enough reagent for a potential full degradation of SDX.

Although H₂O₂ is a strong oxidizing agent, it was not effective in oxidizing SDX by itself, as negligible degradation of SDX was observed. In contrast, when Fe²⁺ was added to the solution, significant and rapid degradation of SDX occurred, with the contaminant being completely degraded in a remarkably short time frame of only 30 s (Figure 1). However, while the Fenton reaction demonstrated rapid removal of the contaminant, the overall mineralization efficiency of the process was modest, with TOC removal reaching a level of 28%. The pH of the treated solution is critical for Fenton AOPs to avoid the precipitation of iron as hydroxide [33,34]. In this case, the initial pH was within the acceptable range (pH 3) and no further adjustment needed to be taken.

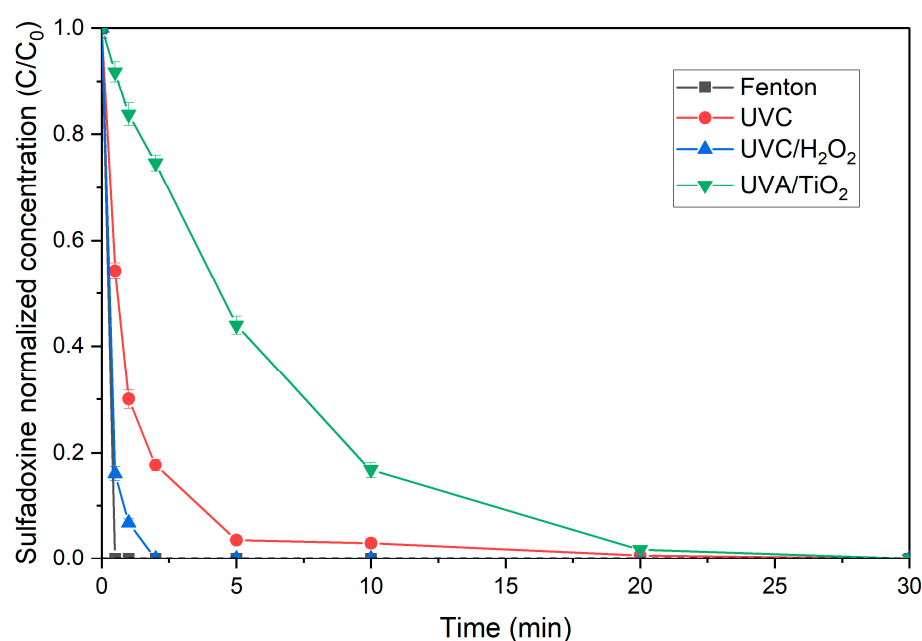


Figure 1. SDX degradation kinetics with Fenton, UV-C, UV-C/H₂O₂, and UV-A/TiO₂.

3.1.2. Photolysis Processes

UV-C radiation was employed for the direct photolysis of SDX. As the spectrum of SDX shows (Supplementary Materials, Figure S1), the molecule exhibits strong absorbance at the lamp's wavelength (253.7 nm). This is consistent with the literature, as the radiation in this wavelength range shows high efficiency in degrading organic contaminants with aromatic moieties [35–37]. Therefore, it was interesting to investigate the prospect of a photolytic UV-C degradation process. An SDX solution was exposed to a UV-C dose of 2.93 W/L per unit volume, under stirring and as depicted in Figure 1; SDX was completely degraded within 30 min of treatment, while the corresponding mineralization was about 41%.

Next, the additional generation of hydroxyl radicals through the UV-C photolysis of H₂O₂ [38] was assessed in SDX solutions. As expected, the addition of H₂O₂ accelerated the degradation of the contaminant and resulted in complete removal after only 2 min (Figure 1). Interestingly, despite the remarkable variance in efficiency observed in the degradation rate of SDX, the mineralization showed no significant improvement, and reached a plateau at a level of 42%. This can be explained by the rapid photolysis of H₂O₂ using UV-C radiation. Since the hydroxyl radicals have a half-life of 1 ns, and their main source is fully consumed at the early stages of the process, it is understandable that the mineralization rates cannot exceed the level of approx. 40%, as UV-C radiation can not further degrade the generated TPs, and the generation of oxidative radicals stops after the complete consumption of H₂O₂.

3.1.3. Heterogeneous Photocatalysis Processes

In heterogeneous photocatalysis, the hydroxyl radicals are generated through light-induced reactions of water molecules on the surface of a solid catalyst [39]. TiO_2 was the photocatalyst selected for the process, given its superior properties, in comparison to other materials. Specifically, TiO_2 is considered to be the most prominent catalyst for this type of AOP, as it combines chemical stability with enhanced photocatalytic activity, while it remains non-toxic and relatively cheap, as it is widely abundant [40].

Before evaluating the degradation of SDX, using a process with this principle of radical generation, it was important to perform a series of reference experiments to assess the adsorption of SDX molecules on TiO_2 nanoparticles and their potential degradation by UV-A irradiation. For the adsorption tests, 100 mg/L TiO_2 in suspension with SDX was left for 30 min in the dark and under stirring. To ensure the effective suspension of the catalyst, TiO_2 was diluted in 1 L of UW and left under stirring for at least 5 h, prior to being added to the spiked solution and diluted to a final volume of 2.3 L. The results showed 8% SDX removal, indicating low removal by adsorption. The type of TiO_2 that was employed has a point of zero charge (pH_{PZC}) of approximately 6.7 [32,41], while SDX has a pK_a of 6.17 [42]. Thus, the low levels of absorbance can be explained by the repulsive forces that develop, as both the pollutant and the catalyst are positively charged at the specific conditions (C). Similar to the adsorption tests, UV-A irradiation at 365 nm resulted in a moderate degradation of the compound (14%). This was expected based on the UV spectrum of the molecule (Supplementary Materials, Figure S1). It should be noted that the pH value of the initial solutions was approx. 5.2, and no further adjustments were made.

The photocatalytic experiments were performed next with 100 mg/L TiO_2 in suspension and a UV-A dose per unit volume of 4.26 W/L. As shown in Figure 1, despite the relatively slow degradation rate of this process compared to the other AOPs studied, SDX was completely removed after 30 min of operation, while the mineralization efficiency showed a considerable improvement, with a TOC removal of 54% being achieved.

The bar chart in Figure 2 provides a comparative analysis of the tested AOPs, focusing on their respective performance in terms of degradation and mineralization efficiency. These results highlight the effectiveness of heterogeneous photocatalysis as a promising approach for the combined SDX degradation/mineralization. Considering the presence of an aromatic and a heterocyclic ring in the target contaminant, heterogeneous photocatalysis was expected to outperform photolytic processes. These ring structures are known for their robustness and stability, making them typically difficult to degrade in the absence of photocatalysts [43–46]. Given the promising potential of heterogeneous photocatalysis, a further parametric investigation of this process was undertaken.

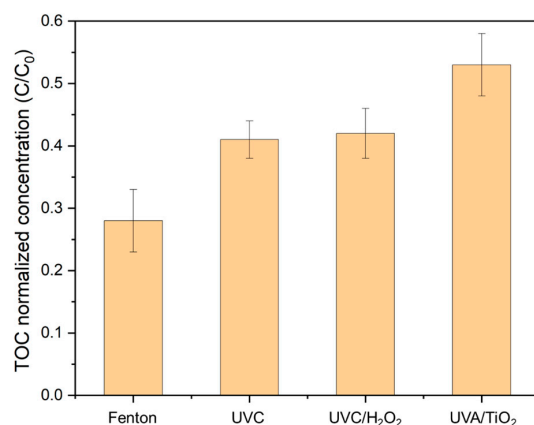


Figure 2. AOP degradation and mineralization performance.

3.2. Parametric Investigation of UV-A/TiO₂ Process

The parameters that can have a significant impact in a heterogeneous photocatalytic system are the UV dose, the catalyst concentration, and the pH. By systematically investigating these important operating variables at an extended process duration of a total of 60 min, we aimed to assess their effects on SDX degradation and mineralization, thus gaining valuable insights for optimizing the process for relevant environmental applications (removal of sulphonamides from water sources).

3.2.1. The Effect of UV-A Radiant Power per Volume Unit

A crucial parameter examined in this study was the UV-A light dose applied per liter of treated solution, as it significantly affects the performance of heterogeneous photocatalysis [31,32,47]. Four different values of radiant power per unit volume (or UV-A light doses) were tested: 2.13 W/L, 4.26 W/L, 6.39 W/L, and 8.52 W/L. Remarkably, only the case with the lowest radiant power failed to completely degrade all of the available SDX concentration within the specified time. To compare the efficiency of the remaining options, the percentage TOC removal was used as a criterion, under the condition of complete SDX removal within one hour of operation. At a UV-A light dose of 4.26 W/L, mineralization reached a level of 77%, while it seemed to stabilize at about 85% in the tests with higher light doses. To compare these results and determine the optimal conditions, the Electrical Energy per Order (EEO) value was calculated using Equation (1) [48]. The corresponding results are summarized in Table 1. Taking into consideration the factor of developing an energetically sustainable method and excluding the 2.13 W/L option due to incomplete SDX degradation, the UV-A dose of 4.26 W/L turns out to be the most efficient option used in all experiments discussed in the following sections.

$$EEO = \frac{\text{Energy (kW)} \times \text{Time (h)} / \text{Sample Volume (m}^3\text{)}}{\log \frac{TOC_0}{TOC_{60 \text{ min}}}} \left(\frac{\text{kWh}}{\text{m}^3} \right), \quad (1)$$

Table 1. UV-A radiant power per unit volume and experimental results, after 60 min.

Experiment No.	UV-A Light Dose (W/L)	TOC Removal (%)	EEO (kWh/m ³)
R 1	2.13	54 ± 3	30.8
R 2	4.26	77 ± 2	32.2
R 3	6.39	85 ± 4	35.7
R 4	8.52	87 ± 2	49.9

3.2.2. The Effect of Solution pH

As mentioned above, under certain pH conditions, different charges can be induced, leading to electrostatic interactions between the nanoparticles and the contaminants. These interactions are directly influenced by pH variations, which emphasizes the importance of investigating its effects on the overall efficiency of the process [49]. The type of TiO₂ that was employed has a point of zero charge (pH_{PZC}) of approximately 6.7 [32,41], while SDX has a pK_a of 6.17 [42]. Therefore, using concentrated H₂SO₄ and NaOH buffers, the pH of the solution was adjusted to approximately 3 and 8, while the pH of the solution without the addition of reagents was 5.2. SDX was completely degraded in all three cases, indicating the robustness of the heterogeneous photocatalytic process across a range of pH conditions. However, significant differences were observed in terms of mineralization efficiency. No difference was observed between the experiments at pH 3 and 5.2, with mineralization reaching 78 ± 3% and 77 ± 2%, respectively. Conversely, under alkaline conditions (pH 8), TOC removal was limited at 31%. Based on the PZC of the nanoparticles and the pK_a of the SDX molecule, electrostatic attraction should have been approximately

the same under all of the tested pH conditions. Thus, the potential lack of adsorption could not explain this change of mineralization efficiency. This indicates that under alkaline conditions, the transformation products that are generated exhibit significant robustness to further degradation, or exhibit significant alterations of pKa values compared to the parent compound.

3.2.3. The Effect of Catalyst Loading

In this study, the effect of TiO_2 load was also investigated by testing three different concentrations, 50 mg/L, 100 mg/L, and 300 mg/L. In all of the experiments, SDX was completely degraded, but slight variations were observed regarding the mineralization. Specifically, the experiments with 50 mg/L showed $60 \pm 2\%$ of mineralization, the ones with 100 mg/L of catalyst showed $77 \pm 2\%$ TOC removal, while in the experiments with 300 mg/L, the performance dropped again at $65 \pm 4\%$. These findings are in accordance with the literature, as previous studies on heterogeneous photocatalysis indicate that an increase in catalyst concentration leads to a proportional increase in active surface area, while excessive loads of suspended particles can hinder the penetration of photons into the reactor fluid and thus impede the photocatalytic reactions [31,32,50]. The concentration of 100 mg/L was found to be optimal and was used for the next experiments.

3.3. Investigation of Water Matrix Effect

The water matrix is a crucial parameter to consider when evaluating the performance of an AOP. TW and SW typically contain radical scavengers that can significantly reduce the rate of degradation (and mineralization). Inorganic anions such as Cl^- , NO_3^- , SO_4^{2-} , and CO_3^{2-} react with hydroxyl radicals and form less reactive oxidative species [50,51]. Additionally, these anions tend to adsorb on the catalyst's surface, reducing the active surface area available for the oxidation process [50,52]. Since the hydroxyl radicals are not selective oxidants, they can also react with organic compounds other than the target contaminants. This means that the presence of additional organic compounds (especially natural organics in SW) can act as scavengers and slow down the kinetics of SDX degradation and mineralization. Therefore, to realistically assess the performance of heterogeneous photocatalysis, we tested spiked samples of TW and SW. This approach allows a comprehensive evaluation of the photocatalytic process under conditions that are very similar to real environmental conditions.

The scavenging effects were evident in both the TW and SW matrices. As shown in Figure 3, the degradation kinetics of SDX were significantly decelerated in both real sample matrices, with the contaminant not fully degraded even after 60 min of processing. In addition, mineralization was very low at only 2% in TW and 6% in SW. It is important to note that the 6% mineralization in the SW sample refers not only to SDX, but also to the natural organic matter in the river.

Beyond the consumption of generated radicals by organic matter, due to their non-selective nature, the elevated ionic content of both TW and SW (Table S1) contributes to further scavenging of these radicals, hindering the overall degradation kinetics. Moreover, it is noteworthy that the pH value was higher than 7 in both TW and SW samples ($>\text{pH}_{\text{PZC}}$), indicating that the unfavorable electrostatic interactions between the catalyst nanoparticles and SDX were present in these samples too. This condition further diminishes the efficiency of heterogeneous photocatalysis, as shown by the degradation rates. Regarding these rates, the kinetic parameters of the UV-A/ TiO_2 system fit well to the first-order kinetic law in all of the tested water matrices (Table 2). These results provide a better understanding of the interference in heterogeneous photocatalysis caused by the radical scavengers present in

each water matrix. The respective kinetic diagrams for each water matrix can be found in the Supplementary Materials (Figure S2).

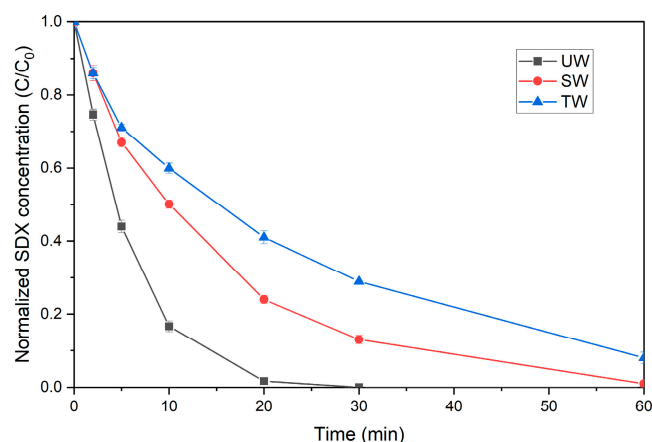


Figure 3. SDX-UV-A/TiO₂ kinetic analysis for UW, TW, and SW.

Table 2. Kinetic parameters of SDX degradation with heterogeneous photocatalysis, in UW, TW, and SW.

	k (min ^{−1})	R^2
UW	0.1972	0.9973
TW	0.0407	0.9969
SW	0.0757	0.9964

3.4. SDX Transformation Products

Samples taken at early time intervals of the photocatalytic experiments (within the first 10 min) were analysed by LC-HRMS to detect and identify both SDX and its transformation products. Previous studies have investigated some degradation pathways of SDX by photolytic and microbial treatment [53], but only two of the TPs produced by heterogeneous photocatalysis were included in their results. This indicates that different degradation mechanisms occur in a photocatalytic process leading to completely different intermediates.

Since SDX is a pollutant that has not been extensively studied, the fragmentation mechanisms (Figure 4) resulting from the MS2 spectra were taken into serious consideration in the prediction, identification, and interpretation of the detected TPs.

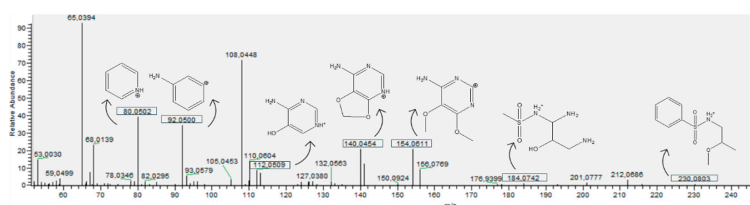


Figure 4. Main fragmentation pathway for SDX.

As shown in Figure 5, the 11 detected TPs can be formed by three distinct transformation mechanisms, bond cleavage, hydroxylation, and desulfonation. Among the identified TPs, TP156 and TP327 are the only previously reported ones [53], while the remaining ones were documented for the first time. The summary of TPs, their molecular formula, chemical structure, fragmentation pattern, and important MS data are summarized in the Supplementary Materials (Table S2). The proposed mechanisms for the formation of TPs are explained in detail as follows.

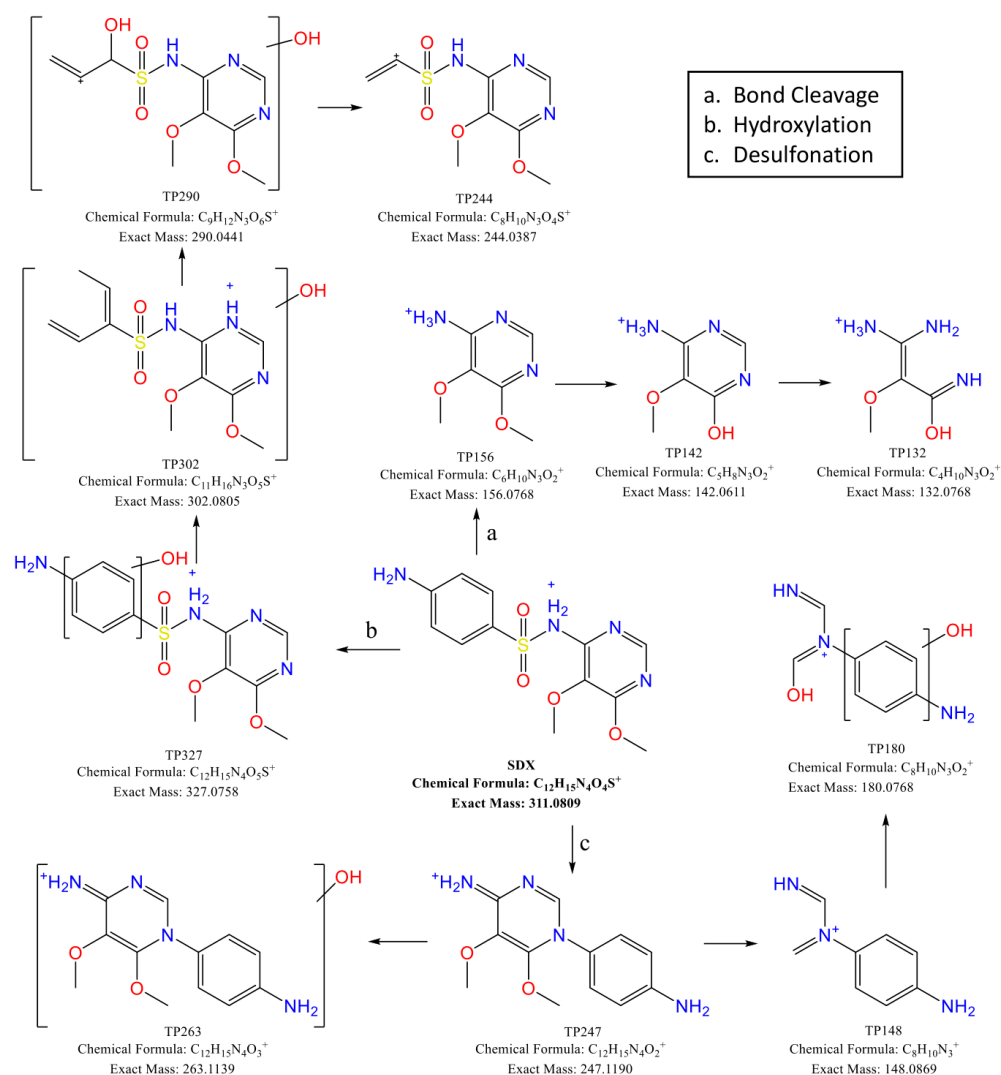


Figure 5. Proposed mechanisms for the formation of SDX TPs with heterogeneous photocatalysis. The mechanisms include: (a): bond cleavage, (b): hydroxylation, and (c): desulfonation.

3.4.1. Bond Cleavage

The transformation pathway of the bond cleavage mechanism takes place at the S-N bond and leads to TP156 ($C_6H_{10}N_3O_2^+$, $m/z = 156.0769$). As mentioned above, TP156 has already been reported, while the cleavage of the sulfonamide bond is a typical case, when it comes to this specific group of contaminants [53–55]. Successively, TP142 ($C_5H_8N_3O_2^+$, $m/z = 142.0612$) and TP132 ($C_4H_{10}N_3O_2^+$, $m/z = 132.0770$) are formed by bond cleavages in TP156. The fragmentation pattern of TP142 is not available, as its signal was too low to trigger fragmentation, but its identification is based on its parent molecule (TP156) and subsidiary molecule (TP132). This lack of fragmentation data can be attributed to the very low concentration of this molecule in the sample. TP132 provided fragments of very low mass, making it hard to accurately identify its exact structure, thus the proposed structure is just a suggestion.

3.4.2. Hydroxylation

Regarding this mechanism, all hydroxylated TPs that were detected and identified were mono-hydroxylated, meaning that a single hydroxyl group was attached to each parent molecule. There were four TPs involved in this pathway: TP327 ($C_{12}H_{15}N_4O_5S^+$, $m/z = 327.0758$), TP302 ($C_{11}H_{16}N_3O_5S^+$, $m/z = 302.0804$), TP290 ($C_{11}H_{16}N_3O_5S^+$, $m/z = 290.0438$), and TP244

($\text{C}_8\text{H}_{10}\text{N}_3\text{O}_4\text{S}^+$, $m/z = 244.0387$). The proposed structure of the molecule is based on the fragmentation pattern (Supplementary Materials, Table S2). However, the precise location of hydroxylation could not be determined.

3.4.3. Desulfonation

The TP247 ($\text{C}_{12}\text{H}_{15}\text{N}_4\text{O}_2^+$, $m/z = 247.1190$) is an important product in the SDX degradation pathway, as it acts as a parent molecule for other TPs. It is proposed that its formation is caused by the removal of the sulfate center and the connection of the benzene ring to a N of the diazine. This mechanism has already been reported before [54,56]. This pathway includes three additional TPs, TP263 ($\text{C}_{12}\text{H}_{15}\text{N}_4\text{O}_3^+$, $m/z = 263.1139$), TP180 ($\text{C}_8\text{H}_{10}\text{N}_3\text{O}_2^+$, $m/z = 180.0769$), and TP148 ($\text{C}_8\text{H}_{10}\text{N}_3^+$, $m/z = 148.0869$).

3.5. Evaluation of TP Time Profiles

In order to further understand the transformation mechanisms that take place during the heterogeneous photocatalysis process, it was essential to record the time profiles of the TPs. As most of these molecules are reported for the first time in the literature, analytical standards were not commercially available. Consequently, semi-quantification methods were necessary in order to monitor their abundance in the treated solutions. This approach relied on tracking and recording changes in peak areas over time. The major TPs of this study were the TP156, TP247, and TP302, as they act as parent compounds for the three distinct transformation pathways. Interestingly, the most dominant TPs had their highest peak area detected within the first 2 min of the process, and were not detected after 10 min. Their time profiles are visualized in Figure 6.

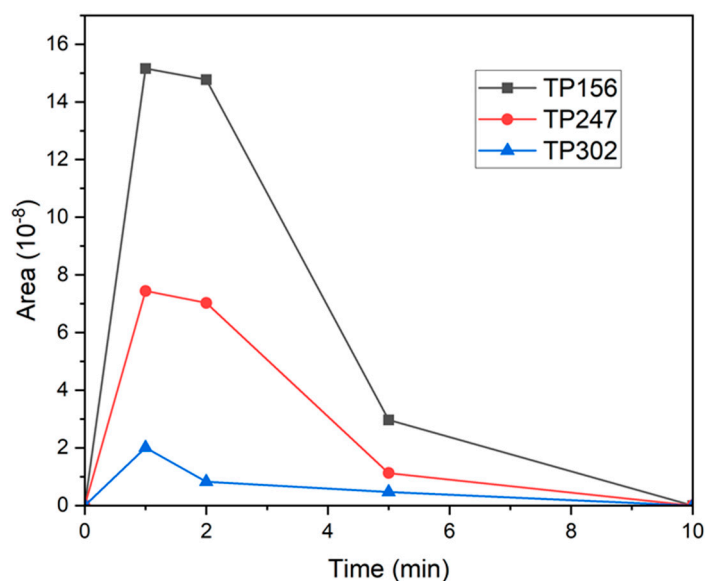


Figure 6. Time profiles of the dominant transformation products.

3.6. Assessment of TP Ecotoxicity (In Silico)

Given the emerging nature of TPs as pollutants, it is crucial to assess their ecotoxicity to understand their potential impact on aquatic ecosystems. The ECOSAR software was used for this purpose. The TP structures were entered into the system in the form of SMILES. Acute toxicity was assessed on the basis of LC50/EC50 values generated by the program, while chronic toxicity was assessed on the basis of ChV values. The results for three different aquatic organisms (Fish, Daphnide, and Green algae) were divided based on the toxicity criteria established by the European Union (No. 1272/2008/EC) [57], similar to a previously published study [20] (Figure 7). According to ECOSAR's QSAR models,

there is a mathematical relationship between the associated log of the estimated toxicity values (mmol/L), which indicate the concentration of a chemical at which a particular effect (such as 50% mortality) is observed. What is more, the $\log K_{ow}$ values were also predicted (EPI Suite KOWWIN prediction). Given that the toxicity levels were between 0.0 and 100, a drug may be categorized as (i) very toxic (toxicity between 0.0 and 1.0), (ii) toxic (toxicity between 1 and 10), (iii) harmful (toxicity between 10 and 100), or (iv) non-toxic (toxicity > 100).

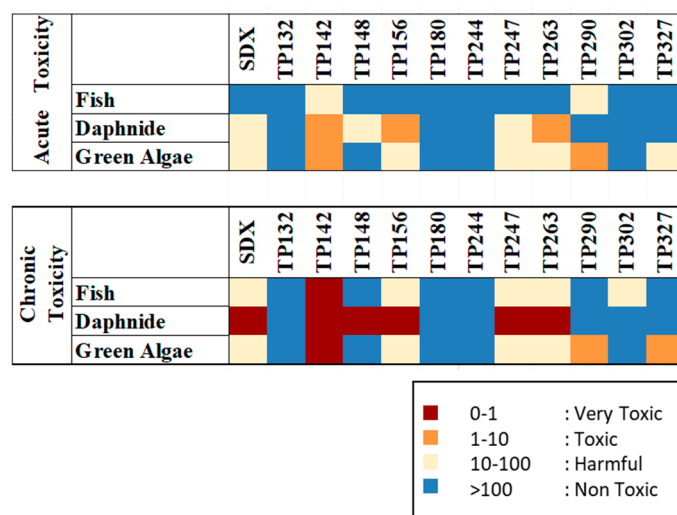


Figure 7. Toxicity assessment using in silico tool ECOSAR.

SDX is of particular concern due to its action as an aniline, as it has a mild short-term toxicity, but shows severe chronic toxicity in the case of Daphnia. When taking into consideration the distinct transformation pathways, some patterns can be observed. Cleaving the S-N bond of sulfonamides has been reported to lead to less toxic products [58]. In our case, TP156 seems to be slightly more toxic than its parent molecule, while the following product of this pathway, TP142, is the most toxic of the group, exhibiting strong long-term toxicity to all three organisms and short-term toxicity to Daphnia and green algae. The final product of this pathway, TP132, is considered as non-toxic. Interestingly, this indicates that the fragmentation of the heterocyclic ring can lead to drastically less toxic products [46]. The increased toxicity of TP142 is expected, as in cases of -NH₂-selective degradation processes, more toxic species are generated [46,59].

Interestingly, the dominant TP of the desulfonation pathway, TP247, exhibits equal toxicity with SDX, while its hydroxylated form, TP263, is slightly toxic in terms of acute toxicity towards Daphnide. Generally, TPs generated from desulfonation can be highly variable and unpredictable, as it is likely highly dependent on the specific structures of the heterocyclic and aniline rings [46,60]. The remaining TPs of this pathway, TP148 and TP180, are less toxic and non-toxic, respectively.

Finally, the hydroxylation pathway proved to be the less toxic one, with all of its TPs (TP327, TP302, TP290, and TP244) being less toxic than the parent compound, which seems to be generally the case with hydroxylation products [46,61].

4. Conclusions

This study addresses the critical issue of pharmaceutical contamination, focusing on SDX. A screening investigation of different AOPs is presented, where their efficacy in the degradation and mineralization of SDX in water is evaluated. Heterogeneous photocatalysis with UV-A/TiO₂, as expected, proved to be the most promising process,

reaching a mineralization efficiency of 77% under the optimal system configuration of 100 mg/L TiO₂, 4.26 W/L radiant power, and pH < 6. However, extensive scavenging effects were observed in water matrices containing inorganic ions and natural organic matter, resulting in lower kinetics and mineralization rate of SDX. In addition, 11 TPs were identified, 9 of which were reported for the first time, while efforts to elucidate their formation mechanisms (bond cleavage, hydroxylation, and desulfonation) shed light on the complex and unexplored degradation pathways of SDX. Finally, ecotoxicity analysis using ECOSAR software revealed that while the specific TPs are not expected to cause significant acute toxicity, chronic exposure may pose a challenge to aquatic organisms. This study offers a comprehensive assessment of SDX, an important emerging contaminant, and its TPs, in an effort to further understand the challenges associated with real-world scenarios of treating sulfonamide-contaminated water bodies.

Supplementary Materials: The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/app15020793/s1>. Table S1: Water quality parameters of the three water types used in this work; Table S2: Summary of TPs, their molecular formula, chemical structure, fragmentation pattern and important MS data. Figure S1: SDX absorbance spectrum; Figure S2: Different water matrix kinetics.

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