Neele Puhlmann, Oliver Olsson, Klaus Kümmerer

Transformation products of sulfonamides in aquatic systems: Lessons learned from available environmental fate and behaviour data

Document type
Journal article | Author accepted manuscript / Postprint

This version is available at
https://doi.org/10.48548/pubdata-130

Citation details
Puhlmann, N., Olsson, O., & Kümmerer, K. (2022). Transformation products of sulfonamides in aquatic systems: Lessons learned from available environmental fate and behaviour data. *Science of the Total Environment*, 830, 154744. https://doi.org/10.1016/j.scitotenv.2022.154744
First published: 24.03.2022 by Elsevier

Transformation Products of Sulfonamides in Aquatic Systems: Lessons Learned from Available Environmental Fate and Behaviour Data

Neele Puhlmann[a], Oliver Olsson[a], Klaus Kümmerer[a,b]

[a]Institute of Sustainable Chemistry, Leuphana University of Lüneburg, Universitätsallee 1, 21335 Lüneburg, Germany

[b]Research and Education Hub, International Sustainable Chemistry Collaborative Center ISC_3

e-mail corresponding authors: klaus.kuemmerer@leuphana.de; oliver.olsson@leuphana.de

Highlights:

- **607 transformation products (TPs) of sulfonamides reported in 222 paper**
- **Data on occurrence, phys-chem, degradation, (eco)toxicity for 4%, 4%, 31%, 35%**
- **TP-mixtures can be more toxic than the single parent compounds**
- **Lack of data of high informative value by standard methods**
- **Mineralisation of TPs often unknown due to data gaps especially for individual TPs**

Abstract

Sulfonamides (SUAs) and their transformation products (TPs) contribute to environmental pollution. Importance of research on TPs' properties has been emphasised, e.g. allowing a comprehensive environmental risk assessment of their parent compounds. However, TPs' properties have been discussed in reviews on SUAs only marginally, if at all. For the first time, a scientific literature review aims to discuss the current state of knowledge on SUA-TPs including research gaps, and commonalities of SUA-TPs and TPs in general.

Literature on SUA-TPs was consulted systematically to collect data on occurrence, physicochemical properties, degradability, and (eco)toxicity. TPs of 14 SUAs were reviewed, and aspects applicable for TPs in general were identified to guide future handling of TPs as a complex category of compounds. The data of sulfamethoxazole (SMX), the main representative, was analysed in more detail to discuss insights on a chemical level.

Literature search resulted in 607 SUA-TPs reported in 222 publications. Only for 4%, 31%, and 35% of these TPs, data on occurrence in aquatic systems, on degradation, and (eco)toxicity, respectively, was found. Several mixtures of SUA-TPs were more ecotoxic than their parent compounds, e.g. 10 of 15 mixtures of SMX-TPs. Only few TPs were tested as single substance. Although several TPs could be eliminated experimentally, their mineralisation rate remained often unknown. Thus, further transformation to persistent TPs could not be ruled out. Standardised biodegradability tests of individual TPs would monitor their mineralisation rate, but are almost completely lacking. Reasons are likely poor availability of TPs, but also the focus on abiotic water treatment.

Data assessment demonstrated that data of high significance according to standard methods, e.g. OECD methods for chronic (eco)toxicity and ready biodegradability, is needed to assess environmental risks of prioritised TPs, but also to redesign their parent pharmaceutical for complete environmental mineralisation in a long-term (*Benign by Design*).

Keywords: Pharmaceutical, Treatment, Degradability, Ecotoxicity, Risk, Assessment

1. Introduction

The globally increasing use of pharmaceuticals comes along with ubiquitous and increasing pollution of the environment by their active ingredients (Wilkinson et al., 2022). As other active pharmaceutical ingredients (APIs), antibiotic sulfonamides (SUAs, effective against bacterial infections e.g. of the urinary tract) are excreted after human or veterinary administration either in their parent or metabolised form. They can enter the environment through effluents of wastewater treatment plants (WWTP), as a result of incomplete retention, through untreated wastewater, including stormwater overflow, or through the application of manure on soils of agriculture (Kümmerer et al., 2018; Tian et al., 2020). Contaminated manure is a relevant path of SUAs into the environment. With 544.1 tonnes of SUAs (active ingredient weight only) sold in 31 European countries in 2018, SUAs account for the third-largest amount of sales of veterinary antibiotics after tetracyclines and penicillins (European Medicines Agency, 2020). In recent years, the ubiquitous environmental occurrence of APIs, including SUAs, in the ng L^{-1} - µg L^{-1} range has been reviewed extensively (Charuaud et al., 2019; Fatta-Kassinos et al., 2011a; Felis et al., 2020). Transformation products (TPs) of APIs result from (bio)chemical transformation of APIs within the technical systems, such as WWTP, and in the environment after their release. TPs contribute to environmental pollution (Fatta-Kassinos et al., 2011b; Haddad et al., 2015; Klavarioti et al., 2009; Kümmerer et al., 2019). The occurrence of SUA-TPs is discussed in very few reviews only as an aside, e.g. with a focus on manure (Spielmeyer, 2018; Wohde et al., 2016).

SUAs and related TPs can affect the environment and human health, e.g. by influencing the composition of microbial communities (Cycoń et al., 2019), generation of antibiotic resistance (Baran et al., 2011; Ezzariai et al., 2018; Felis et al., 2020), or by phytotoxicity (Christou et al., 2018). However, properties of SUA-TPs are mostly unknown, if these TPs are known and identified at all (Kümmerer et al., 2019). Even more, adverse effects of known TPs and compound mixtures, including metabolites and TPs, are difficult to predict. This is not only due to a lack of reference standards but also due to a large number of endpoints to be investigated (Vasquez et al., 2014). As a reaction to this situation and the European Green Deal (European Commission, 2019), the EU has developed the "Strategic Approach to Pharmaceuticals in the Environment" recently (European Commission, 2020c). This strategy announces upcoming changes in the legislation of pharmaceuticals to tackle environmental pollution.

In the context of the removal of SUAs from sewage or the aquatic environment, considering only removal rates or half-lives of parent compounds (PC) is not sufficient: Information on TP formation and their environmental fate is required (Cycoń et al., 2019; Ezzariai et al., 2018; Spielmeyer, 2018). TPs of the main representative sulfamethoxazole (SMX), such as *N4*-acetyl-SMX, are often only mentioned in the context of environmental processes (Bílková et al., 2019; Felis et al., 2020) as well as within abiotic or biotic wastewater treatment (Charuaud et al., 2019; Tian et al., 2020; Wang and Wang, 2018). Pathways of a few SUAs based on several intermediates *via* different microorganisms were summarised (Chen and Xie, 2018; Wang and Wang, 2018). Among these bio-TPs are 3-amino-5-methylisoxazole, aniline, *N4*-hydroxy-SMX, and *N4*-acetyl-SMX (Chen and Xie, 2018). However, a comprehensive overview of TPs of diverse SUAs is missing, let alone their properties.

Although the importance of research on properties of the variety of TPs has been emphasised already in 2011 (Fatta-Kassinos et al., 2011b), the most outcome of the reviews found with information on properties of SUA-TPs was only general or based on assumptions since the SUA-TPs were not in focus (Charuaud et al., 2019; Ezzariai et al., 2018; Spielmeyer, 2018; Tian et al., 2020; Wang and Wang, 2018; Wohde et al., 2016). General statements were that chlorinated TPs may be toxic and that TPs containing the pharmacophore may be still active (Charuaud et al., 2019), whereas more polar *N4*-OH-sulfadiazine and TPs by cleavage of the heterocycle should be less active (Spielmeyer, 2018). There were no validations of these general statements and assumptions by (eco)toxicity studies of single TPs. However, if TPs are not considered, the fact that *N4*-acetylated SMX transfer back to SMX, for example, demonstrates the potential underestimation of the environmental effects of SUAs (Ezzariai et al., 2018; Wohde et al., 2016). Recent reviews paid more attention to transformation processes and toxic effects of SUA-TPs than before. Core element of provided information is the elimination of SUAs to support the development of water treatment technologies rather than data on SUA-TPs needed for their environmental risk assessment (Hu et al., 2022; Li et al., 2021).

Properties of SUA-TPs, including their environmental fate, have so far only been marginally discussed. This is the first time that a literature review aims to put the TPs instead of the PC in the spotlight. We discuss data that provide information on occurrence, degradability, and (eco)toxicity of SUA-TPs. Such data is needed for a comprehensive environmental risk assessment of SUAs. We aim to find common features and dissimilarities of SUA-TPs and identify knowledge gaps as guidance for future research. Aspects for TPs in general are of special interest in guiding the future handling of this complex category of compounds.

Considering these objectives, literature on SUA-TPs was searched systematically to collect data on their occurrence and properties. Although studies focused very often on the removal of the PCs only, secondary data on the behaviour of TPs could be obtained from such studies. All properties of reviewed TPs were included in our growing dataset together with information on their formation type (abiotic/biotic), structure, detection, and identification method, and the corresponding confidence level of the structure. The numbers of TPs in total, and for each SUA respectively, were determined to show the diversity and identify more or less studied SUAs. The proportion of TPs with data entries on occurrence and properties out of all collected TPs was extracted from the created dataset to identify knowledge gaps and further need for research. Data on the TPs of SMX (the most investigated SUA) was elucidated in more detail to understand their behaviour better, and based on this, to derive common ground for SUA-TPs.

2. Methods

2.1. Literature selection and description of publication pool

The literature was screened and selected systematically (Figure 1). Based on an initial literature search using also the *snowball* principle (Greenhalgh and Peacock, 2005), the following SUAs were selected: sulfachloropyridazine (SCP), sulfadimethoxine (SDM), sulfadiazine (SDZ), sulfaguanidine (SGU), sulfisoxazole (SIX), sulfamethoxypyridazine (SMP), sulfamerazine (SMR), sulfamethizole (SMT), sulfamethoxazole (SMX), sulfamethazine (SMZ, synonym sulfadimidine), sulfapyridine (SPY), sulfasalazine (SSZ) and sulfathiazole (STZ). The database Web of Science Core Collection was used to search for publications with the name of the selected SUA and "Degrad* OR Transformation" in the topic. Besides Web of Science, the database SciFinder was used for the systematic search of publications on SMX-TPs. References containing the two concepts "transformation products" and "sulfamethoxazole" closely associated with one another were selected for further screening. To cover a broader part of the literature and not to miss significant literature the *back-snowball* principle (Greenhalgh and Peacock, 2005) was applied.

The time frame (2000 till August 2021) was set based on an initial literature search regarding the development of research on TPs over time. The procedure and results of this first search can be found in section 1 of supplementary information. A number of search hits ≥ 70 were refined using the keyword "product". For the selection of suitable publications, the following excluding criteria were applied: The title is not within the subject; the abstract is not about identified TPs, but rather about the removal of SUAs or analytical method development; in the text, no TPs are mentioned (at least by giving molecular formula).

Thereafter, the pool of selected publications was described and evaluated by the following parameters: Number of publications…

a) …for each SUA,
b) …for different laboratory experiments of treatment processes (simulation of a treatment stage in waste water or potable water treatment plants (WTP)), or processes in the environment, abiotic or biotic) *vs.* monitoring in WTP or the environment,
c) …considering kinetics of TPs during the treatment process,
d) …considering mineralisation during the treatment process, e.g. by total organic carbon (TOC),
e) …for different detection and identification methods, and
f) …studying the (eco)toxicity of the mixture or individual TPs.

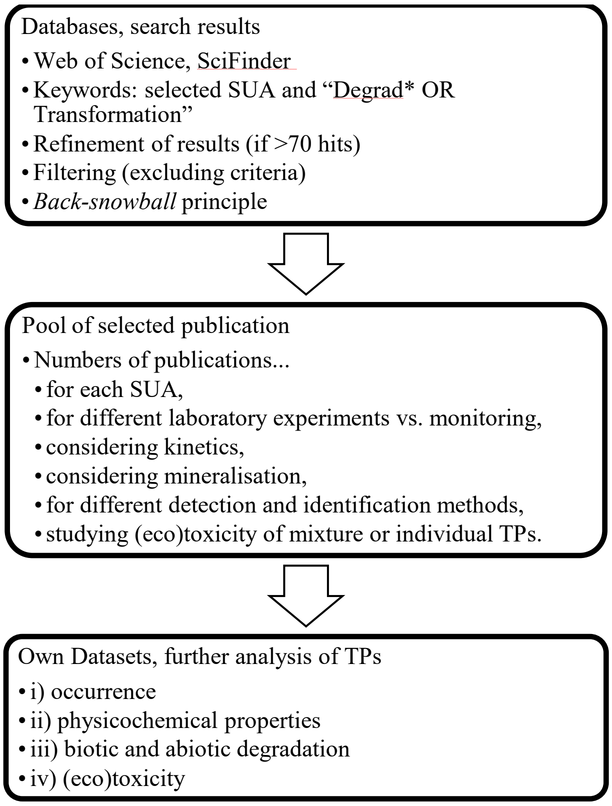


Figure 1: Workflow from literature databases to own datasets.

2.2. Creation of datasets and further analysis of TPs

Own datasets were created with information about TPs focussing on their i) occurrence in WTP or the environment, ii) physicochemical properties, iii) biotic and abiotic degradation and iv) (eco)toxicity (Figure 1). Thereby, the data was pre-assessed and grouped regarding the following procedure:

i) Data on the TP's occurrence in WTP, e.g. influent or effluent, or the environment, e.g. surface, ground, or spring water, was taken from literature if the method, including sampling and TP detection, was well described. Thereby, the information describing the sample was important for the datasets. Since reference standards are most often not available for TPs their use was no prerequisite. Therefore and because of an occurrence in low concentrations, other data than values for concentration, e.g. peak areas or the simple detection without any quantification, was also stored.

ii) Data on physicochemical properties *via* well-described calculation or experimental determination was collected. Among them were octanol-water partition coefficients expressed as logarithm (log P) and acid/base dissociation constants for the sulfonamide (*N1*) group (pK_{a2}). In natural waters, only the deprotonation of this NH-group in SO_2NH was relevant since the pK_{a1}-values for the *p*-amino (*N4*) group of SUAs are generally below pH 2 (Bonvin et al., 2013).

iii) To receive data for degradation, the kinetics of TPs during the degradation of the SUA, TP-mixtures, or the TP itself were surveyed concerning the concentration-time curve to evaluate the elimination kinetics. Thereby, data was collected in dependence on the type of degradation test, i.e. biotic or abiotic degradation according to a) standard methods, such as OECD, or other methods simulating b) the (advanced) water treatment or c) processes in the environment. The various test designs (e.g. regarding concentration of SUA, pH, oxygen, catalyst, treatment period), especially if not standardised, needed to be described in the study and saved together with the received data. Data on degradation based on *in silico* predictions was not part of the screened publications and thus not considered.

To evaluate the data entry/entries per TP, we have classified into “not eliminated”, “eliminated”, and “varying results” in dependence on the type of degradation test (6 types: a - c, biotic or abiotic each). TPs of the class “not eliminated” were not or partially eliminated (< 65%) until the end of the test period under the given conditions, whereas “eliminated” TPs were completely or almost completely eliminated (≥ 65%) within the test period under the given conditions. This classification was simple for TPs with a single data entry but less meaningful, compared to TPs with more than one data entry of similar elimination rate (within the same category for the type of degradation). Otherwise, i.e. when the data entries did not indicate similar elimination rate (e.g. due to different test conditions), data entries were classified as “varying results”.

iv) Data on (eco)toxicity was collected in dependence on the test approach, i.e. *in vitro* using TP-mixtures or the single substance or tested *in silico*. Thereby, the received data was saved together with the selected endpoint, e.g. growth inhibition of bacteria for ecotoxicity or mutagenicity for human toxicity. Combining test results on (eco)toxicity of TP-mixtures with kinetics for the TPs, such data could give hints for further *in silico* or *in vitro* testing of individual TPs.

2.3. Tools for in-depth evaluation of data on SMX-TPs

A more detailed study on SMX-TPs was conducted as representative for SUAs to derive generic conclusions. SMX was chosen because it was found to be the most investigated SUA, e.g. due to the highest number of publications and of TPs described in our publication pool. SMX-TPs were described in detail *via* post-processing. The data was evaluated as follows: The groups of data on the occurrences of SMX-

TPs in WTP and the environment were subclassified by sample types, e.g. WTP influent or effluent and surface water or groundwater. Data of these subgroups was reviewed.

As an extension of the classification into "not eliminated", "eliminated" and "varying results", the elimination rate of TPs with at least 3 data entries was assessed taking the test conditions into account to demonstrate the complexity of degradability due to its strong dependence on diverse biotic and abiotic test conditions. For this discussion, the mineralisation rate of the organic substances during the treatment was considered when available.

Data on (eco)toxicity (grouped by test approach, i.e. *in vitro* using TP-mixtures or the single substance, or *in silico*) was reviewed regarding different endpoints (initially without any exclusion of endpoints to get an overview). Where possible, TPs were classified as "toxic" and "not toxic" for a given endpoint. Thereby, (eco)toxicity was assessed in comparison to that of SMX. "Toxic" means similar or more toxic than SMX, and "not toxic" less toxic than SMX. In the case of different toxicities per TP, due to the dependence on different endpoints, the result of (eco)toxicity was classified as "depends". There, a closer evaluation was done.

3. Results

3.1. Selection and description of publications by their analytical methods (kinetic, mineralisation, and detection/identification)

In total, 222 publications were selected based on method 2.1 that has defined excluding criteria. Most of them correspond to SMX (88), SMZ (60), and SDZ (54), whereas only a few or no references were selected for SMP (5), SMT (5), SSZ (3), and SGU (1). A huge impact on the nature of data has the type of treatment of the PC. The focus in research providing information on TPs was on the abiotic advanced (waste)water treatment: 111 references, i.e. half of all selected publications. Especially the photocatalysis or (advanced) oxidation processes were studied to understand the removal of the PCs. The research extent of other categories (see method 2.1, lit b: simulation of biotic treatment stages in WTP, of abiotic or biotic processes in the environment, and monitoring in WTP or the environment) with around 25 references each was similar (Figure S3).

Kinetics of generation and possible elimination of TPs were reported in 80 publications. 41 references of these are dealing with the treatment and removal of SMX. Data on kinetics together with the degree of mineralisation can help to distinguish transient and persistent TPs. Mineralisation was investigated by 76 publications to characterise the efficiency of PC's treatment. Among them are 56 references, i.e. more than two-third, that correspond to experiments investigating advanced treatment (abiotic) in WTP, showing that improving abiotic treatment is the focus of research. In Table 1 the publications are classified by their test methods of mineralisation. Among 76 publications investigating mineralisation, 55 publications used the measurement of TOC. There are publications with combined methods. For example, 11 publications investigated kinetics of TOC in the treatment system together with kinetics of nitrite/nitrate and sulphate (N&S) to receive more information on mineralisation. The degree of mineralisation ranged from 0% to 100%, indicating that it strongly depends on test conditions. In general, drastic conditions (e.g. ozone concentration, catalysts) and a longer treatment period lead to a higher mineralisation rate. For example, 95% up to 100% mineralisation was reached in 11 studies mostly *via* electro-Fenton reaction (up to 400 mA, up to 8 h treatment) (e.g. Dirany et al., 2012; El-Ghenymy et al., 2013), or photocatalysis (up to 24 h treatment) (e.g. Fukahori and Fujiwara, 2015; Guo et al., 2013), and in one case even biotically using an isolated and acclimated SMX-degrading stain (*Acinetobacter* sp.) (Wang et al., 2018).

Table 1: Number of publications classified by their test methods of mineralisation.

Mineralisation	total	TOC	DOC	NPOC	N&S	N	^{14}C	^{13}C
total	**76**	**55**	**11**	**2**	**16**	**3**	**4**	**1**
TOC	**55**	42	1		11	1		
DOC	**11**	1	8		1	1		
NPOC	**2**			1	1			
N&S	**16**	11	1	1	3			
N	**3**	1	1			1		
^{14}C	**4**						4	
^{13}C	**1**							1

In 192 publications that deal with the TP formation and identification the data quality depends mainly on the sensitivity of detection and identification methods. Mass spectrometry (MS) plays a major role. Especially, tandem mass spectrometry (MS/MS) was most frequent (118 of 192 publications) used for the detection and identification of TPs. Others, such as the DAD-, UV- or conductivity detector play a minor role (Table 2). NMR, suitable for structure elucidation, was used rarely (10 publications), likely because it is very demanding (e.g. on amount of material).

In only 26 publications all detected TPs, and in further 31 publications, a part of TPs was identified by reference standard. This means that in 135 publications (70%) no reference standard was used. One reason is that TPs are often new compounds that cannot be bought and have to be synthesised (associated with high costs) which in turn needs a safe assessment of the molecular structure.

Table 2: Number of publications classified by detection or identification method. Abbreviation: tandem mass spectrometry (MS/MS), high-resolution mass spectrometry (HR-MS), mass spectrometry (MS), diode array detector (DAD), ultraviolet/visible light detector (UV), nuclear magnetic resonance spectroscopy (NMR).

Detection / Identification	total	MS/MS	HR-MS	MS	DAD	UV	Radio	Conductivity	NMR
total	**192**	**118**	**29**	**38**	**9**	**2**	**2**	**2**	**10**
MS/MS	**118**	110						2	6
HR-MS	**29**		27						2
MS	**38**			30	6				2
DAD	**9**			6	3				
UV	**2**					2			
Radio	**2**						2		
Conductivity	**2**	2						0	
NMR	**10**	6	2	2					0

The results indicate that data on TPs' (eco)toxicity is not very extensive, particularly for other SUAs than SMX. In around one-fourth of publications (59 publications) (eco)toxicity of TPs is discussed. Among these are 23 publications corresponding to SMX. Typical endpoints of *in vitro* testing were growth and/or luminescence inhibition against bacteria, such as *Vibrio fischeri* and *Escherichia coli* (28 bacteria test studies). It must be stressed that mainly mixtures of TPs (received from SUA treatment) were investigated (41/59 publications; entire distribution of (eco)toxicity tests given in Table S1), leading to low significance for a single TP. In mixtures, adverse effects are difficult to predict, due to the mutual influence of the components. Furthermore, the effect concentration relation is specific for each compound. Thus, even when the TP composition of tested mixture, including quantity ratios, is known, it cannot be concluded with certainty that the TP of the highest concentration is most or solely responsible for the toxic effect.

Summarising, we found that there is an imbalance between the extent of research on different SUAs with SMX as most investigated SUA. Reasons could be different medical consumption and therefore different expectations for the input into the environment associated with possible environmental risks, which result in prioritised research. SMX is the most prominent SUA antibiotic. For example, the combination of SMX and trimethoprim, in contrast to other SUAs, was among the antibiotics that contributed to 75% of the total oral antibiotic consumption in 16 out of 65 countries and areas in 2015 (World Health Organization, 2018). Analytical challenges play a further role. For example, most SUAs are water-soluble, except SSZ (Baran et al., 2011). This could be a reason for fewer publications on SSZ. A less scientific reason, but a typical phenomenon familiar to many researchers, is *me-too* research that builds on available knowledge, tools, and methods, including materials and chemicals.

Furthermore, most studies of our publication pool aimed to improve advanced treatment of SUAs, mostly through drastic conditions. It seems that the focus in research is on the development of treatment in WTP, less on environmental behaviour and assessment. However, costly advanced treatment cannot be the sole measure to avoid environmental micro pollution since only 80% of wastewater is treated at all (UN Water, 2017). Keeping the description of our publication pool in mind, the TP data described in the following can be analysed better.

3.2. Evaluation of data on TPs reported

The systematic literature research resulted in 607 reported SUA-TPs. The distribution of these TPs on corresponding PCs is shown in Figure 2. The number of TPs per SUA is linked to the number of studies on the respective SUA. Main representatives are TPs of SMX, SDZ, and SMZ with 124, 119, and 103 TPs, respectively, whereas TPs of SMT, SMP, and SGU are less represented with 15, 10, and 8 TPs, respectively.

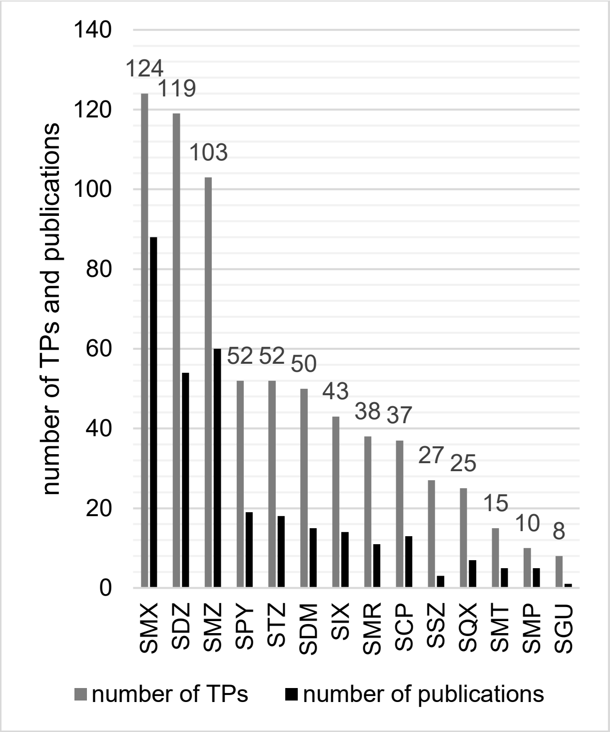


Figure 2: Number of TPs reported in the selected publications for each SUA of in total 607 SUA-TPs.

Chemical analysis and structure elucidation of TPs

Among the total of 598 TPs formed in degradation tests, there are 431 abiotic, 102 biotic, and 65 both, abiotic and biotic TPs. Furthermore, the SUA-TPs are classified according to their detection and identification method to support the assessment of the confidence in the proposed or elucidated structure. Figure 3 demonstrates that MS/MS is the most often applied detection method and reflects the foregoing publication description. Structures are proposed based on fragmentation patterns. High resolution MS techniques that detect the precision mass (monoisotopic mass with 4 decimal places) improve the determination of the formulas of the ions. However, without further elucidation e.g. *via* NMR spectroscopy the precise identification of isomers, for example, is almost impossible, if no reference standard is used to confirm the proposed structure (used for only 12% of 598 TPs (72/598)). Therefore, in many cases isomers cannot be discerned as the accurate position of the hydroxy group at the benzene ring, for example, remains unclear. Structures of only 4% (26/598) were elucidated by NMR. UV and DAD techniques are useful to observe kinetics of the PC and TPs. However, they are not suitable for TP structure elucidation; Reference standards are essential for TP identification: 6 TPs were detected using a UV or DAD method; All of them were identified with a standard.

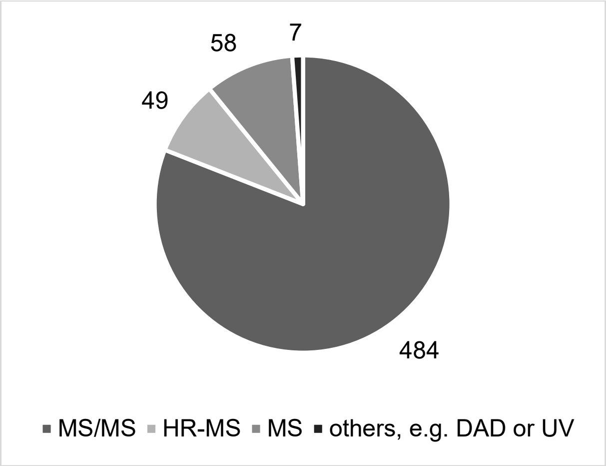


Figure 3: Number of TPs classified by their detection or identification method out of 598 SUA-TPs in total. In case of more than one data entry, the most sensitive method was considered. Abbreviation: tandem mass spectrometry (MS/MS), high resolution mass spectrometry (HR-MS), mass spectrometry (MS), diode array detector (DAD), ultraviolet/visible light detector (UV).

Datasets were created particularly to gather information on occurrence and properties of the described TPs. An overview of found data is given in Figure 4. Data entries regarding occurrence in WTP and/or the environment are made only for 23 TPs, i.e. nearly 4%, relating to 13 TPs with data for WTPs and environment, 4 TPs only for WTPs, and 6 TPs only for the environment.

Based on physicochemical properties of compounds, e.g. log P, their environmental fate and behaviour can be assessed. However, there is almost no data for selected TPs. Only for 21 TPs (4%), the log P (predicted or experimentally determined) was found in considered literature. Among them are 8 TPs, for which the log P is discussed together with the bioconcentration factor to make statements regarding their fates (Zhang et al., 2020).

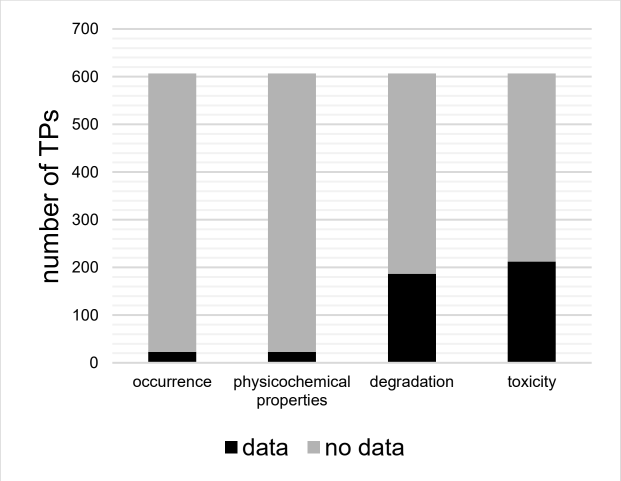


Figure 4: Overview of TPs with data entries regarding occurrence and properties.

Data on behaviour during abiotic or biotic degradation was extracted for 187 TPs. Data is based mainly on kinetics under given test conditions. Studies on degradability of individual TPs, taking their mineralisation rates also into account, are very rare. The data evaluation leads to classifying TPs into “eliminated”, “not eliminated” and “varying results” depending on type of degradation test (Figure 5). TPs with “varying results” are mainly TPs studied more often. Consequently, the results differ depending on test methods. This group demonstrates that a rough grouping of degradation tests is a simplification. It cannot reflect the wide range of test conditions during experimental tests simulating technical treatment processes or the environment. Furthermore, data according to standard test methods, e.g. OECD, with clearly defined conditions are very rare. There are data entries only for 21 and 5 TPs resulting from biotic and abiotic degradation, respectively. Additionally, among them, data of 10 TPs reflects biotic degradation of two TP-mixtures, that were both more biodegradable than their PCs (Gao et al., 2013; Sun et al., 2019). Such results are not very meaningful for a single TP as TP’s mineralisation remains unclear, and give only hints for further investigation.

Data on (eco)toxicity were found for 212 TPs (Figure 4). However, the data is based mainly on tests of TP-mixtures (data for 172 TPs). Thus, a clear indication of (eco)toxicity of individual TPs is hardly possible. Even data by *in silico* methods, where the substance does not have to be available, is rare (data for 68 TPs). Only for 17 TPs, data on (eco)toxicity from *in vitro* testing of the single compound was found.

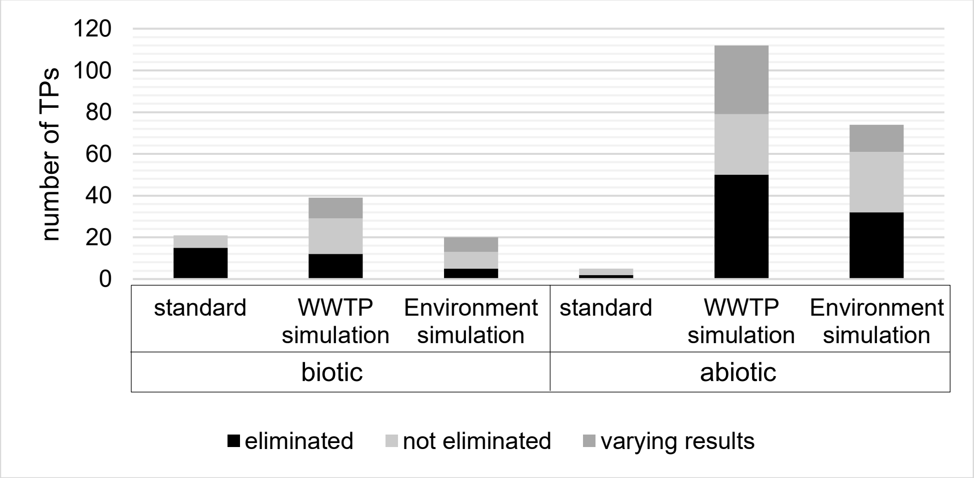


Figure 5: Number of TPs with data on degradation during different degradation tests with further classification, i.e. “not eliminated”, “eliminated” or “varying results” during degradation tests, mostly derived from kinetics. It depends strongly on the test conditions.

Summarising, more than 600 SUA-TPs were found in the reviewed literature. Most of them were detected and their structures proposed using MS/MS and HR-MS. Only a few SUA-TP structures were further elucidated by NMR, e.g. to distinguish isomers. The main reason is likely that the focus of most of reviewed studies was on the elimination of the SUA with TP detection in passing. Furthermore, TPs were present in low concentrations (as often several TPs are resulting from one PC) and would have required elaborate isolation for structure elucidation by NMR. This is in line with the findings of other authors: Non-targeted MS/MS and HR-MS would be suitable for a more sophisticated TP analysis. They are increasingly used (Chibwe et al., 2017; Hernandez et al., 2014; Wohde et al., 2016).

Data on occurrence and physicochemical properties of SUA-TPs are very rare. The evaluation of data on degradation shows that tests of environmental degradation according to standard methods, e.g. OECD, are underrepresented, although they would allow a more reliable and comparable assessment of degradability. Moreover, they provide a data basis to develop or improve *in silico* models. The (eco)toxicity entries are dominated by data on TP-mixtures. Data on single TPs are rare.

One of the reasons for these data gaps is likely that TPs in general are not intentionally formed for any use as it is for the PCs, and therefore not or hardly regulated by law. Even TPs from pesticides, which are subject to requirements for ecotoxicology in contrast to pharmaceuticals (European Union, 2009), are still neglected in current proposals for future risk assessment of pesticides (Schäfer et al., 2019). However, TPs are likely to get more attention, e.g. due to the European Green Deal and the follow-up EU strategies, e.g. for a toxic-free environment (European Commission, 2020a, 2020c, 2020b, 2020d). Associated with the aspect of unintentional formation, is the low commercial availability of TPs, complicating individual testing. Commissioning an elaborate synthesis would be related to high costs (Menz et al., 2017). This is seen as another reason for the data gaps.

3.3. In-depth evaluation of the data on SMX-TPs

The dataset evaluation revealed that SMX is the most investigated representative (88 publications). In total, 124 SMX-TPs were described in the analysed literature. Among them are constitutional isomers that are counted in our dataset as one TP if the detailed structure was not elucidated (e.g. position of a hydroxyl group at a benzene ring).

Detection *via* MS/MS accounts for the largest part of SMX-TPs (Table S3), analogous to all SUA-TPs. 22 of 118 TPs were identified using a reference standard. 9 of 118 TPs could be identified by NMR, four of them also by a reference standard: 3A5MI, *N4*-chloro-*p*-benzoquinone imine, desamino-SMX, and *p*-nitro-

SMX. Based on this evaluation regarding the detection and identification methods as well as on the comparison with literature data, the confidence level is set for the proposed or elucidated structures of the SMX-TPs (Table S3). For this purpose, the classification of Schymanski et al. (2014) is extended by level 3c and 3d: probable structure detected by MS/MS or single MS, respectively, but missing comparison with literature data (Table S2).

70% of described SMX-TPs (87/124) were formed under abiotic conditions, particularly *via* photolysis and photocatalysis. Among them are highly hydroxylated TPs and dimers. Further 13% (15/124) are formed also under biotic conditions, e.g. *p*-nitro-SMX (TP283c), 3-amino-5-methylisoxazole (3A5MI, TP-99) and *N4*-acetyl-SMX (Ac-SMX, TP295a). The large number of abiotic TPs (87 + 15 = 102) is the consequence of the publication pool with predominantly abiotic treatments of SMX, as shown above. The low-selective attack by ubiquitous OH-radicals during advanced oxidation and photolysis is another reason for the diversity of abiotic TPs. For example, in the abiotic treatment experiment from Hu et al. (2021), using photocatalysis, and Zhu et al. (2021), using electro-Fenton, 17 and 18 TPs, respectively, were detected just for one single PC. It must be stressed that there are 55 abiotic TPs that were described only within one study each. However, several degradation methods, e.g. photo(cata)lysis or oxidation by ozone or chlorine can also lead to the same products. The SMX-TPs 3A5MI (TP98b), *p*-nitro-SMX (TP283c), an X-OH-SMX isomer (OH at benzene, TP269b), the SMX isomer (TP253), sulfanilic acid (TP173b), and desamino-SMX (TP238b) are generated and detected by at least 10 different studies. Different test conditions regarding the kind of catalyst, initial concentration of SMX, and pH value, for example, can also result in the same TPs. For instance, the oxidation of SMX by Gao et al. (2014) using chlorine, permanganate, and ozone led to 7, 5, and 5 TPs each, and in total 11 different TPs. Thus, among them are identical TPs formed by different oxidants: 3A5MI, *p*-nitro-SMX, and an X-OH-SMX isomer (OH at benzene, TP269b) (Gao et al., 2014).

17% (21/124) were generated only under biotic conditions, e.g. *N4*-formyl-SMX, *N4*-pterin-SMX, and SMX-*N1*-Glucuronide. Most of them were described only within one study each. The distribution indicates a gap in research on biotic processes, whether in the environment or technical treatment. Nevertheless, even with increased research efforts, lower diversity of biotic TP would be expected, as specific enzymes lead to fewer biotic TP, in contrast to abiotic processes driven by highly reactive and therefore less selective OH-radicals.

3.3.1. Occurrence of SMX-TPs in WTP and the environment

Information about the occurrence of SMX-TPs in WTP and/or the environment is available for 10% of identified TPs (12/124) (Table 3). These are all TPs most often described (at least by 10 references), apart from the SMX isomer (TP253) and sulfanilic acid for which information on occurrence is missing in our dataset. Most data entries were collected for Ac-SMX with 22 data entries since it is also a well-investigated metabolite and appeared already in some reviews (Ezzariai et al., 2018; Fatta-Kassinos et al., 2011a; Felis et al., 2020; Wohde et al., 2016). *p*-Nitro-SMX, desamino-SMX, and SMX-glucuronide (SMX-Glu) are investigated in at least 4 studies, all others in only one study.

Table 3: Occurrence of SMX-TPs in WTP and the environment

	WTP Eff: effluent Inf: influent d: detected nd: not detected	**Reference**	**Environment** SW: surface water GW: groundwater SpW: spring water nd: not detected	**Reference**
3A5MI	after ozonation: d	Deeb et al., 2017	SW: nd	Deeb et al., 2017
desamino-SMX	1/7 Eff: d Inf and Eff: nd	Osorio et al., 2016 García-Galán et al., 2016; Mamo et al., 2018	SW: ng L^{-1} range GW: max. 8 ± 1 ng L^{-1} SpW (4/62): d	Brienza et al., 2017; Osorio et al., 2016 Brienza et al., 2017 Nödler et al., 2012
X-OH-SMX isomer	Inf and Eff: nd	Deeb et al., 2017	SW: nd	Deeb et al., 2017
***N4*-formyl-SMX**	8/9 Eff: d	Achermann et al., 2018		
***p*-nitro-SMX**	1/7 Inf, and 1/7 Eff: d Inf and Eff: nd	Osorio et al., 2016 García-Galán et al., 2016; Knopp et al., 2016; Mamo et al., 2018	SW: nd GW: 54 ± 5 ng L^{-1} SpW (6/62): d	Brienza et al., 2017; Osorio et al., 2016 Brienza et al., 2017 Nödler et al., 2012
***p*-nitroso-X-OH-SMX, COOH-SMX, or *p*-nitro-SMX**	after ozonation and after biological post-treatment: d	Deeb et al., 2017	SW: d	Deeb et al., 2017
6,7-(OH)$_2$-SMX, reduced	after ozonation and after biological post-treatment: d	Deeb et al., 2017	SW: nd	Deeb et al., 2017
Ac-SMX	numerous tests, recently reviewed	Felis et al., 2020	SW: max. 356 ± 30 ng L^{-1}, frequency 100% (n=14) GW: nd - 6.2 ng L^{-1}, with frequency 25% (n=21) GW: d GW: nd	Zha et al., 2017 Jurado et al., 2020 López-Serna et al., 2013 Archundia et al., 2017; Brienza et al., 2017
***N4*-HAc-SMX**	1/9 Inf, and 8/9 Eff: d	Achermann et al., 2018		
***N4*-pterin-SMX**	5/9 Eff: d	Achermann et al., 2018		
***N4*-PtO-SMX**	3/9 Inf, and 7/9 Eff: d	Achermann et al., 2018		
SMX-Glu	Eff: d	Archundia et al., 2017	SW: ng L^{-1} range GW: nd GW: 9.66 - 22.9 ng L^{-1}	Archundia et al., 2017; Brienza et al., 2017 Archundia et al., 2017; Brienza et al., 2017 López-Serna et al., 2013

The analysis of influent and effluent is a typical test setup for the investigation of samples from WTPs. Such an influent-effluent study was conducted by more than the half of analysed studies (12/20). Influent-effluent comparison enables conclusions regarding the fate of TPs. More specific is the test setup by Deeb et al. (2017): The sampling was before and after ozonation, at the effluent after biological treatment, and finally from surface water loaded by wastewater. For example, 3A5MI was detected after ozonation, however was not detected before ozonation as well as after biological-post-treatment and in the corresponding surface water (Deeb et al., 2017). Thus, 3A5MI can be formed through ozonation, but eliminated or retained during biological treatment. To understand the behaviour during sedimentation, the occurrence in the sewer (pre-wastewater) and influent WW was compared by Mamo et al. (2018). The initial concentration of Ac-SMX was reduced by more than 50%. Desamino-SMX and *p*-nitro-SMX could not be detected in sewer or influent WW (Mamo et al., 2018). A fate study with conventional activated sludge treatment *vs.* a membrane bioreactor is also suitable to conclude on properties, in this case on biodegradability, where absorption on sludge or the membrane cannot be ruled out (García-Galán et al., 2016).

Environmental samples were most often surface water. In many cases, the circumstances of the sampling site (e.g. distance to the entry of wastewater) are regarded for the interpretation of data in terms of amount and diversity of TPs. The highest concentrations of Ac-SMX were detected in three rivers in China impacted by WWTP with max. 356 ± 30 ng L^{-1} (Zha et al., 2017). In groundwater, Ac-SMX was detected from different districts in Catalonia (Spain), e.g. with max. 6.2 ng L^{-1} in groundwater impacted by effluents from WWTP entering the Besòs river (López-Serna et al., 2013). Desamino-SMX and *p*-nitro-SMX were detected in groundwater in concentrations of max. 8 ± 1 ng L^{-1} and 54 ± 5 ng L^{-1}, respectively, at a watershed in Bolivia with high impact of wastewater (Brienza et al., 2017). The occurrence of TPs in spring water was pointed out in one study with 4 and 6 positive results out of 62 samples for desamino-SMX and *p*-nitro-SMX, respectively (Nödler et al., 2012).

Summarising, the occurrence of 12 SMX-TPs was investigated. All of them, except X-OH-SMX isomers (TP269b), were found in WTP and/or the environment, even sometimes in groundwater. This indicates mobility in the aquatic environment and therefore high polarity and at least temporary stability. TPs in general tend to be more polar than their PC due to introduction of more polar groups (Chibwe et al., 2017), as is the case with investigated SMX-TPs of Table 3. If the concentration could be determined (i.e. the TP was available as an analytical standard), it was in the low ng L^{-1} range – typical for TPs in the environment (Fatta-Kassinos et al., 2011b; Kümmerer, 2010). No information about all the other SMX-TPs (112 TPs) is available in our dataset. The data gap for TPs of other SUAs is even larger. For TPs of pesticides, unlike pharmaceuticals, the data situation can be somewhat better since they are at least partially subject to an environmental risk assessment. For example, about 33% of 45 TPs (of six pesticides, potentially formed in the environment) have been already detected in the aquatic environment (Hensen et al., 2020).

3.3.2. Properties of SMX-TPs

3.3.2.1. Physicochemical properties

Log P and the pK_a are important substance properties that determine the fate in the environment as well as (eco)toxicity. However, only a few studies provided these substance properties (Bonvin et al., 2013; Majewsky et al., 2014; Nödler et al., 2012; Zha et al., 2017; Zhang et al., 2020). Log P and pK_{a2} of 17 TPs and 9 TPs, respectively, are given in Table 4. Achermann et al. (2018) found that bio-SMX-TPs such as *N4*-pterin-SMX and other pterin-conjugates occur mainly in the aqueous fraction (as findings on occurrence already suggested). Therefore, a lower log P is expected compared to SMX as is the case for hydroxylated SMX-TPs. Such compounds could be rather mobile in the aquatic environment compared to TPs with higher log P than SMX. TPs with higher log P, e.g. chlorinated or brominated SMX-TPs, might be more likely to bioaccumulate (Zhang et al., 2020). Majewsky et al. (2014) investigated the ecotoxicity of SMX-TPs about pK_{a2}. They concluded increased ecotoxicity with increased pK_{a2} using the EC_{50} for growth inhibition of *Vibrio fischeri* as endpoint (Majewsky et al., 2014).

Table 4: Log P and pK_{a2} of SMX-TPs reported in references. SMX is listed for comparison.

TP	log P	Reference	pK_{a2}	Reference
SMX	0.89	Zhang et al., 2020	5.89 ± 0.07	Bonvin et al., 2013
3A5MI	0.3[a]	Majewsky et al., 2014		
HSO_2-3A5MI	<0[d]	Zhang et al., 2020		
SAA	-0.25[a]	Majewsky et al., 2014		
sulfanilic acid	-2.04[a]	Majewsky et al., 2014		
desamino-SMX	1.34 ± 0.40[b]	Nödler et al., 2012	6.92 ± 0.5[b]	Nödler et al., 2012
***p*-OH-SMX**	0.67[a]	Majewsky et al., 2014	4.89, 5.97[a]	Majewsky et al., 2014
***p*-nitroso-SMX**	0.96[a]	Majewsky et al., 2014	4.71 ± 0.1,	Bonvin et al., 2013

			5.74^{a}	Majewsky et al., 2014
X-OH-SMX (at isoxazole)			not determined (rapidly converted to NO-SMX)	Bonvin et al., 2013
***N4*-OH-SMX**	0.53^{a}	Majewsky et al., 2014	4.51, 6.07^{a}	Majewsky et al., 2014
***p*-nitro-SMX**	1.22^{d}, 0.81^{a}, 1.27 ± 0.41^{b}	Zhang et al., 2020, Majewsky et al., 2014 Nödler et al., 2012	3.66 ± 0.01, 5.70^{a}, 5.65 ± 0.4^{b}	Bonvin et al., 2013, Majewsky et al., 2014, Nödler et al., 2012
6,7-$(OH)_2$-SMX, reduced	$<0^{d}$	Zhang et al., 2020		
X-Cl-SMX	1.13^{d}	Zhang et al., 2020		
Ac-SMX	0.86, 0.86^{c}, 0.18^{a}	Zha et al., 2017, Jurado et al., 2020, Majewsky et al., 2014	5.90, 5.07 ± 0.08, 5.88^{a}	Zha et al., 2017, Bonvin et al., 2013 Majewsky et al., 2014
***N4*-(HO-acetyl)-SMX**	-0.64^{a}	Majewsky et al., 2014	5.28, 5.88^{a}	Majewsky et al., 2014
Br-SMX (at benzene)	1.37^{d}	Zhang et al., 2020		
Br-Cl-SMX (at benzene)	2.02^{d}	Zhang et al., 2020		
Br-Br-SMX (at benzene)	2.26^{d}	Zhang et al., 2020		
SMX-Glu			no pK_{a2}	Bonvin et al., 2013
Dimer of SMX	2.93^{d}	Zhang et al., 2020		

[a]MarvinSketch, [b]SciFinder, [c]ChemAxon, [d]unknown software used for prediction; Computed values reported in literature without further information on accuracy.

Summarising, we found log P and pK_{a2} values only for a part of reviewed SMX-TPs, although physicochemical properties would be useful to dictate the behaviour of compounds in the environment. Physicochemical properties are already routinely predicted, e.g. log P within drug discovery due to time and cost savings (Lombardino and Lowe, 2004). Computational prediction, e.g. *via* ChemSpider or EpiSuite, can fill data gaps, but needs expertise and eventually an *in vitro* confirmation.

3.3.2.2. Degradability

Data about abiotic and biotic degradability were found for more than 50% of reported SMX-TPs (64/124), mainly extracted from kinetic studies considering concentration-time curves (kinetics of 47 TPs). Information for 48 (75%), 13 (20%), and 3 (5%) of these 64 TPs originates from abiotic, abiotic & biotic, and biotic tests, respectively.

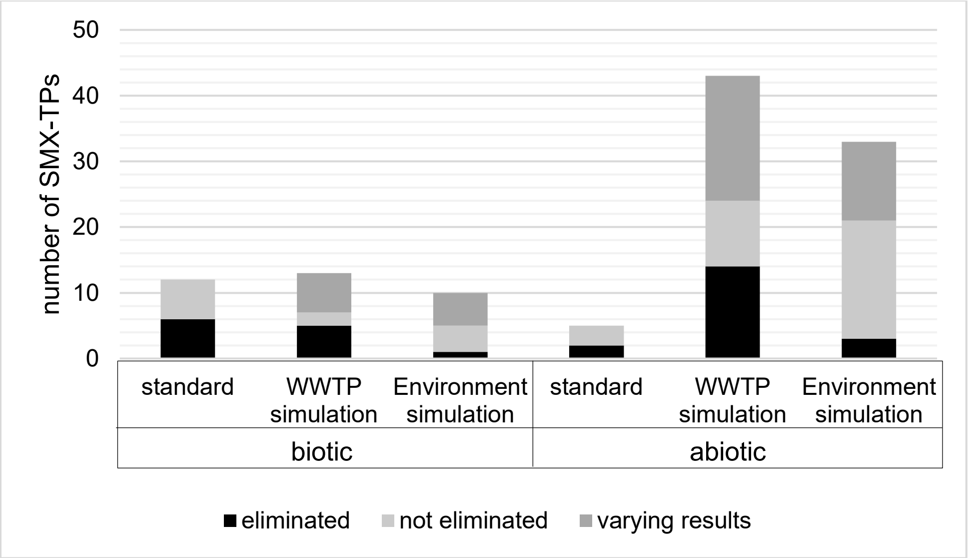


Figure 6: Number of SMX-TPs with data on degradation during different degradation tests with further classification, i.e. not eliminated or eliminated during degradation tests, mostly derived from kinetics. Different conditions of several tests lead to varying results.

The distribution of the classification for 64 SMX-TPs in dependence on type of degradation (standardised method, WTP or environmental simulation; biotic *vs.* abiotic) is nearly the same (Figure 6) as for all SUA-TPs (Figure 5). The lack of data according to standard methods is not that high as it is for the other SUA-TPs. However, the few data entries on biotic and abiotic degradation according to a standard method originate from two studies only, using OECD method 308 (modified water-sediment test setup) (Radke et al., 2009; Su et al., 2016). The comparison of rate constants for active and inactive sediments led to dissipation half-life (DT_{50}, all processes) and biodegradation half-life ($DegT_{50}$, biodegradation only) of TPs within a mixture after photolysis of SMX (Su et al., 2016), and of Ac-SMX and SMX-Glu (Radke et al., 2009). In the mixture, 3A5MI, *p*-nitro-SMX, the SMX isomer (TP253), and TP271c (SMX opened isoxazole ring) showed evidence of biodegradation (with DT_{50} of 39.7 d, 12.7 d, 7.6 d, and 2.4 d, respectively), whereas sulfanilic acid and 5-methylisoxazole-3-yl-sulfamate were eliminated abiotically (DT_{50} of 31 d and 74.9 d, respectively). Desamino-SMX and an X-OH-SMX isomer (OH at benzene ring) were recalcitrant (Su et al., 2016). Ac-SMX (DT_{50}: 8.5 d) and SMX-Glu (DT_{50}: 11.7 d) were removed from test system by biodegradation *via* sediment. Due to potential of back transformation into SMX under environmental conditions (Radke et al., 2009), they cannot be classified as biodegradable (Achermann et al., 2018). The fact that *N4*-acetyl-SUAs cleavage back into the PC was reviewed already (Ezzariai et al., 2018; Wohde et al., 2016). Back transformation was found in the selected literature also for *p*-nitro-SMX (Nödler et al., 2012; Su et al., 2016) and *p*-nitroso-SMX (Bonvin et al., 2013).

Data based on WTP and environment simulations is more complex since the fate of TPs depends strongly on the various test methods and conditions. Albeit diverse test conditions even within one type of degradation test (WTP or environment simulation, abiotic or biotic), there are 10 SMX-TPs with nearly all and at least 3 data entries of similar elimination rate: 6 TPs that were eliminated are listed in Table 5, and 4 TPs that were not eliminated are listed in Table 6. An eliminated TP may be a precursor of further degradation products. For example, the X-OH-SMX isomers were completely or at least almost completely eliminated within the test period. However, since PC's mineralisation was not complete as far as observed (Gómez-Ramos et al., 2011; Hu et al., 2007; Ioannidou et al., 2017), transformation to further, eventually persistent TPs cannot be ruled out.

Table 5: TPs that were eliminated in nearly all and at least 3 studies within one type of degradation test (WTP or environment simulation, abiotic or biotic). Simple conclusions are drawn in the last column.

TP	Degradation method	Result	Reference	Conclusion
***p*-aminophenol**	Microbacterium sp. strain BR1	transient metabolite, mineralisation unknown	Ricken et al., 2013	biodegradable in WTP simulations
	Microbacterium sp. strain BR1, TP treated individually	almost eliminated, mineralisation unknown	Ricken et al., 2015	
	electro-Fenton pre-treatment, activated sludge	total TOC removal after 2 weeks with activated sludge	Mansour et al., 2014	
formic acid, acetic acid, oxalic acid	well investigated compounds; an example for checking databases, e.g. ECHA, 2021			readily biodegradable
X-OH-SMX isomers (at benzene)	photocatalysis (TiO_2-SG, TiO_2-SG or Ce-ZnO, 5 - 8 h)	eliminated after max. 60 min, mineralisation unknown	Fabbri et al., 2019	predominantly eliminable in WTP simulations (abiotic), further TPs expected since mineralisation is not complete position of hydroxy group affects the elimination rate
	photocatalysis (TiO_2, pH 3, 1 h)	almost eliminated completely, mineralisation: 80% (DOC) of SMX	Hu et al., 2007	
	photocatalysis (H_2O_2, pH 6 or 9, H_2O_2 / NH_3, pH 9)	depends on conditions and OH-position: Isomer 270-1 was not eliminated (H_2O_2), isomer 270-2 degraded (H_2O_2 (only pH 9), H_2O_2 / NH_3) but not *via* H_2O_2 at pH 6), mineralisation unknown	Zhang et al., 2016	
	photocatalysis (WO_3-modified TiO_2)	eliminated, mineralisation: 28% (TOC) of SMX	Ioannidou et al., 2017	
	oxidation (ozone, 10 min)	eliminated almost completely, mineralisation: 0 - 25% (TOC) of SMX	Gómez-Ramos et al., 2011	
X-OH-SMX isomers (at isoxazole)	oxidation (Fe(VI))	eliminated, mineralisation unknown	Kim et al., 2015	eliminable in WTP simulations (abiotic), further TPs expected due to low or unknown mineralisation
	photocatalysis (TiO_2-SG, TiO_2-SG or Ce-ZnO, 5 - 8 h)	eliminated after max. 60 min, mineralisation unknown	Fabbri et al., 2019	
	photo-Fenton (H_2O_2, pH 3)	eliminated, mineralisation unknown	Hong et al., 2020	
	photocatalysis (WO_3-modified TiO_2)	eliminated, mineralisation: 28% (TOC) of SMX	Ioannidou et al., 2017	

Table 6: TPs that were not eliminated in nearly all and at least 3 studies of any category (WTP or environment simulation, abiotic or biotic). Conclusion is drawn in the last line.

TP	Degradation method	Result	Reference
3A5MI	photolysis (4 h)	not eliminable	Bonvin et al., 2013
	photolysis (1 week)	not eliminable	Gmurek et al., 2015
	photolysis (24 h)	not eliminable	Periša et al., 2013
	photolysis (30 min)	one of the most abundant and persistent intermediates	Trovó et al., 2009b
***p*-nitro-SMX**	photolysis (4 h) of *p*-nitro-SMX	photo-stable, environmental $t_{1/2}$: 337 ± 30 h, 1515 ± 135 h (summer, winter)	Bonvin et al., 2013
	photolysis (1 week)	not eliminable	Gmurek et al., 2015
	photolysis (nitrate-, nitrite-sensitised, 8 h)	not eliminable	Scholes et al., 2019
***p*-nitro-X-OH-SMX**	photolysis (4 h) of *p*-nitro-SMX	photo-stable	Bonvin et al., 2013
	photolysis (1 week)	not eliminable	Gmurek et al., 2015
	photolysis (nitrate-sensitised, 8 h)	not eliminable	Scholes et al., 2019
***p*-OH-X-nitro-SMX**	photolysis (4 h) of *p*-nitro-SMX	photo-stable	Bonvin et al., 2013
	photolysis (1 week)	not eliminable	Gmurek et al., 2015
	photolysis (nitrate-, nitrite-sensitised, 8 h)	not eliminable	Scholes et al., 2019
Conclusion: These TPs are expected to be photo-stable in the environment.			

In contrast to the presented 10 SMX-TPs with data entries of similar elimination (Table 5, Table 6), there are 5 SMX-TPs with at least 3 data entries of varying elimination rate: Ac-SMX, 6,7-$(OH)_2$-SMX, SAA, sulfanilic acid, and the SMX isomer. Examination of such data can be found in the supplementary information (section 5). Compared to other SMX-photo-TPs, sulfanilic acid, as well as 3A5MI, and the SMX isomer (TP253), are likely the most abundant and persistent TPs during photolysis (Guan et al., 2019; Trovó et al., 2009b).

Summarising, knowledge about degradability of TPs in the environment is crucial to understand their environmental fate. It is limited due to missing data from standardised methods, provided e.g. by OECD. Data from not standardised tests under very different conditions is less comparable since degradability as non-intrinsic property depends strongly on conditions, such as the kind of catalyst and light spectrum. This makes the evaluation of data of not standardised tests more difficult. Through comparison of several data entries per TP from different tests, we could at least tentatively conclude the degradation behaviour. For example, X-OH-SMX isomers were not detectable anymore after abiotic treatment (mainly photocatalysis, simulating conditions in WTP). However, they displayed persistence under biotic environmental conditions in the dark according to OECD method 308. The intact isoxazole ring of these isomers, (5-methylisoxazole-

3-yl) sulfamate, and desamino-SMX prevents their biotic transformation. Respectively, the TP271c, which is formed *via* ring-opening, biodegraded during the same study (Su et al., 2016). Biodegradation rates depend tremendously on the inoculum (density and diversity, i.e. source and concentration). An isolated and acclimated SMX-degrading stain (*Acinetobacter* sp.) can mineralise SMX almost completely (Wang et al., 2018). Compounds that are mineralised by a specialised inoculum would not necessarily mineralise in the environment, where the specialised strains are often out-competed in the complex bacterial composition. In contrast, conditions are set in WTP that favour nitrification, for example (Kassotaki et al., 2016). Furthermore, not-standardised data is of lower coverage and usability on the one hand and lower quality on the other since validity criteria are not defined. Methods such as OECD tests include criteria for a toxicity and a quality control. The endpoint for biodegradability is clearly defined. OECD method 301 F requires also a sterile control to distinguish abiotic from biotic processes (OECD 301 F). This also demonstrates the importance of laboratory methods as a complement to real-world methods for an understanding of complex processes by reducing the number of variables under standardised conditions.

3.3.2.3.**(Eco)toxicity**

Information on (eco)toxicity was found for more than half of selected SMX-TPs (64/124). The simplified classification of these SMX-TPs according to the test approach (i.e. tested as mixture, single substance *in vitro,* or *in silico*) is shown in Figure 7. Compared to Figure 4, the distribution is nearly the same for all SUA-TPs: The conclusions drawn already that the data based mainly on tests of TP-mixtures is valid for SMX-TPs, too.

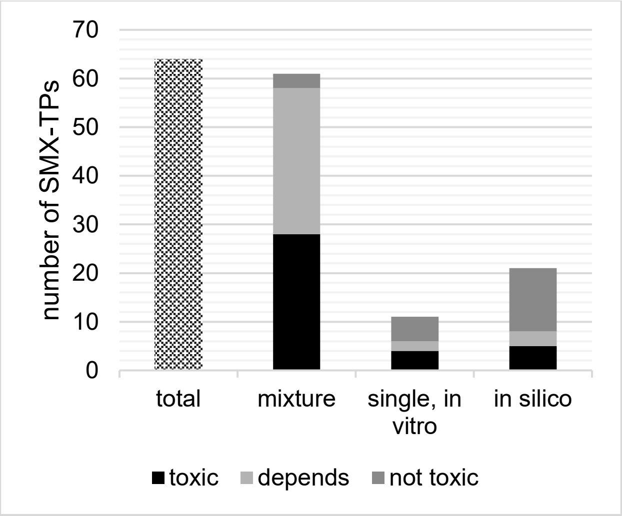


Figure 7: Number of SMX-TPs with data entries on (eco)toxicity, grouped by test approach (test of mixture, of single substances *in vitro* or *in silico*) subdivided according to the classification "toxic", "depends", and "not toxic". The result was classified as "depends" in the case of different (eco)toxicities per TP, due to the dependence on different endpoints.

Starting with tests of TP-mixtures, they are predominantly received after photo(cata)lysis or oxidation (e.g. by H_2O_2 or ozone). Data of TP-mixtures which is linked to nearly all TPs of the (eco)toxicity dataset (61/64) can be considered first hints. In many cases, TP-mixtures were more toxic than the PC related to the same endpoint (10 of 15 studies, e.g. by Gmurek et al. (2015), Qi et al. (2014), and Abellán et al. (2008)). Section 6 of the supplementary information provides further information on monitored endpoints of (eco)toxicity of SMX-TPs.

A typical procedure to gain first hints is the testing of mixtures along the treatment period of SUAs with changing compositions of compounds. Changes in toxicities for the samples along the treatment period can be linked to the concentration curves of these compounds, or in the case of unknown concentration, to relative changes of the intensity of the detection signal (typically as peak area). For example, when the (eco)toxicity was significantly reduced, TPs that are still present were considered possibly not toxic, e.g. TP201 ($C_6H_3NO_5S$) and 3A5MI, whereas TPs that were lost at the time of reduced (eco)toxicity could be toxic, e.g. desulfonated SMX or TP155 (Mirzaei et al., 2018). Thereby, the impact on reduced (eco)toxicity by the removal of the PC needs to be considered. Based on such a kinetic approach, potential toxic candidates should be further investigated as an individual compound *in vitro* (Trovó et al., 2009b) or at least *in silico* tests (Hong et al., 2020; Yang et al., 2017; Zhang et al., 2016).

In total, information about (eco)toxicity by *in silico*, *in vitro*, and both *in silico* and *in vitro* tests was found for 21, 7, and 4 TPs, respectively. Focus of data was on ecotoxicity, similar to studies on TP-mixtures. For example, acute and chronic ecotoxicity for fish, daphnia, and green algae was predicted using ECOSAR (Guan et al., 2019; Yang et al., 2017; Zhang et al., 2016), or growth inhibition of bacteria was investigated (Białk-Bielińska et al., 2017; Eguchi et al., 2004; Majewsky et al., 2014; Osorio et al., 2016).

More than half of investigated TPs (13/21) were predicted as less toxic than SMX. Among them are sulfanilic acid (Yang et al., 2017) and *N4*-acetyl-SMX (Jurado et al., 2020), which are also less ecotoxic according to *in vitro* daphnia and algae tests, e.g. using *Daphnia magna, Limnic green algae,* and *Lemna minor* (Białk-Bielińska et al., 2017; Eguchi et al., 2004; Grabarczyk et al., 2020; Trovó et al., 2009b). Although their chemical structures still include the pharmacophore they are also less toxic against *Vibrio fischeri* (Majewsky et al., 2014). Presumably, these TPs had lower binding affinity than SMX to inhibit the dihydropteroate synthase, central for the bacteriostatic effect, and did also not react *via* another mode of action.

5 TPs were predicted to be similar or more toxic for fish, daphnia, and green algae than SMX. Among them is *p*-nitro-SMX (Yang et al., 2017), which is also similar or more toxic as SMX to *Vibrio fischeri* and *Daphnia magna* according to *in vitro* tests (Majewsky et al., 2014; Osorio et al., 2016). Among them is also 3A5MI (Guan et al., 2019; Yang et al., 2017; Zhang et al., 2016), which is by contrast less toxic according to *in vitro* bacteria and daphnia tests (Majewsky et al., 2014; Trovó et al., 2009b). The prediction for 3A5MI contradicts the experimental result likely because 3A5MI was out of the applicability domains of the model. The class of anilines (unhindered) was used for prediction although the structure of 3A5MI does not belong to this class (Guan et al., 2019; Yang et al., 2017). Therefore, we consider only the *in vitro* result for 3A5MI, i.e. less toxic, for the dataset. In *in vitro* studies, additional 3 TPs, such as *p*-nitroso-SMX, showed similar or higher ecotoxicity compared to SMX (Majewsky et al., 2014; Osorio et al., 2016).

For 5 TPs (3 and 2 TPs from *in silico* and *in vitro* datasets, respectively) endpoints were very different. Therefore, they are classified as "depends". For example, desamino-SMX was found to be not harmful to *Daphnia magna* but harmful to *Vibrio fischeri* (Osorio et al., 2016).

Combination of *in silico* and *in vitro* test results for ecotoxicity (i.e. very few results for endpoints of human toxicity such as mutagenicity excluded) leads to an initial simplified statement for 24 TPs, displayed in Figure 8: More than half might be less ecotoxic than SMX (15/24), whereas almost one third is of similar or even higher ecotoxicity (7/24) compared to SMX: the SMX isomer (Yang et al., 2017; Zhang et al., 2016), SMX-dimer, OH-SMX-dimer (Yang et al., 2017), as well as *p*-OH-SMX, *p*-nitroso-SMX, *N4*-OH-SMX, and *p*-nitro-SMX. The study of the letter 4 TPs against *Vibrio fischeri* showed that structures without the *p*-amino group can also be bacteriostatic (Majewsky et al., 2014).

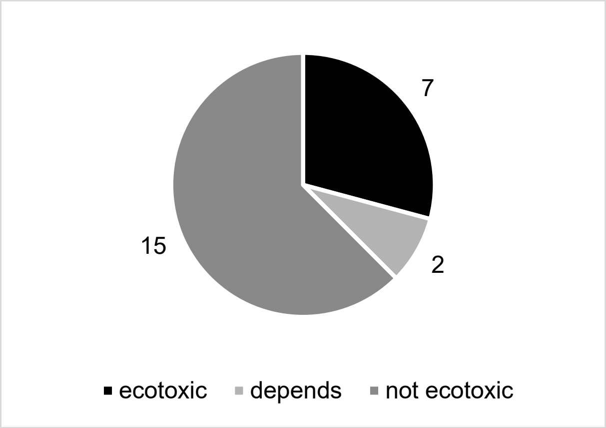


Figure 8: Number of TPs that displayed ecotoxic or not ecotoxic *via in vitro* and/or *in silico* tests. In total, data for 24 TPs was found. The result was classified as “depends” in the case of different ecotoxicity per TP, due to the dependence on different endpoints.

Summarising, the finding of toxic TP-mixtures demonstrates the need for further data on individual TPs to enable a comprehensive environmental risk assessment. However, experimental or computational data of individual TPs was found only for a quarter of SMX-TPs, despite the great advantage of *in silico* prediction not requiring elaborate synthesis of non-available TPs. On the other hand, *in silico* prediction has limitations. Fitting into the applicability domain and sufficient reliability are required for successful prediction (Lorenz et al., 2021) as discussed above for 3A5MI. Such information was missing in the publications of *in silico* data, although it would be essential to assess their validity. We could use *in vitro* data of the same endpoint to assess if/how often *in silico* predictions could be confirmed. However, there is not enough *in vitro* data to do this assessment. *In vitro* data on SMX-TPs is limited. Moreover, data entries belong to multiple endpoints, which are difficult to compare. Ecotoxicity alone as a single branch of toxicity depends very much on the endpoint, including the species. For example, SAA is classified as ecotoxic to plants and harmful to green algae (Białk-Bielińska et al., 2017), but less ecotoxic to *Vibrio fischeri* than SMX (Majewsky et al., 2014).

Possible reason for the identified gap of *in vitro* data – besides the aforementioned poor availability of TPs – is the diversity of TPs, which makes simultaneous detection and identification difficult. It might be impossible to select an ecotoxicity assay based on a specific mode of action, that is suitable for the diversity of TPs (Toolaram et al., 2014). Furthermore, ecotoxicity caused by another mode of action than that of the pharmaceutical should not be ruled out. For example, *in vitro* tests showed that TPs such as *p*-OH-SMX, *p*-nitro-, and *p*-nitroso-SMX with modified pharmacophore at the *p*-amino position can still be ecotoxic for bacteria.

Thus, a reasonable selection of methods is needed but difficult due to diverse TPs and multiple existing endpoints. Methods should be standardised to ensure comparability and quality as discussed already for degradation methods.

*3.3.3.*Common features and differences of SUA-TPs

SUA-TPs with common features based on the same mechanism of transformation are presented in Table 7. Thereby, it is differentiated between TPs that are identical for all SUAs ("non-specific TPs"), e.g. SAA, and TPs with different SUA-specific moieties (R) but identical transformed backbone of SUAs ("SUA-specific TPs"), e.g. desamino SUA. Common features that were frequently found are identified and highlighted in bold letters. Among them are the non-specific TPs SAA and sulfanilic acid (for 10 and 11 SUAs, respectively). Although SAA was found for almost all SUAs, the counterpart of the ε-bond cleavage (Figure 9) was less often detected, probably because of its reactivity or analytical challenges of a screening method. All observed bond cleavages are marked in Figure 9.

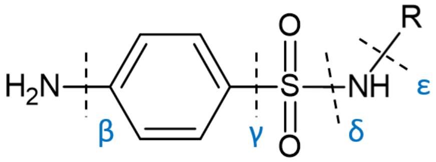


Figure 9: Bond cleavage in sulfonamides (adapted from Boreen et al. (2004)).

Among common SUA-specific TPs are *p*-nitroso- and *p*-nitro-SUA (for 10 SUAs each), and TPs formed *via* δ-bond cleavage, desulfonation, and hydroxylation especially at the aniline moiety (for all 14 SUAs each). In laboratory studies, hydroxylation as initial transformation step occurs very often *via* reactive OH-radicals formed in aqueous solutions under various conditions (e.g. oxidations), in contrast to more specific reactions, such as chlorination and glycosylation, that require the addition of further reactants and are less frequently studied. Thus, for all SUAs a hydroxylated SUA was described, while Cl- or glycosyl-SUAs were less often found. Additionally, the lack of typical biotic formyl-, glycosyl-, and pterin-TP for many SUAs confirms that biotic processes are less studied resulting in missing data for biotic degradation.

Desulfonation *via* Smiles rearrangement (γ-bond opening), which leads to an imine, was observed for six-membered SUAs during direct and indirect photolysis by Boreen et al. (2005) as a difference to five-membered SUAs (Boreen et al., 2004). Results of the literature search confirm Boreen et al.'s observation since TPs resulting from Smiles rearrangement were found only for six-membered SUAs, but not for five-membered SUAs. For five-membered SUAs, desulfonation leads to an amine. As an enhancement of the collected SUA-TPs, desulfonation *via* Smiles rearrangement (imine) can be expected also for 6-membered SMP (Figure 10). Thus, comparison of known TPs and identification of typical transformation mechanisms give guidance to define, search for and identify unknown but expected TPs. This would facilitate their detection and identification.

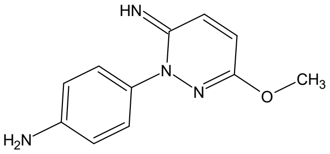
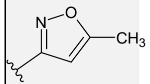
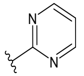
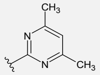
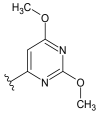
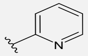
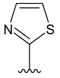
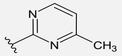
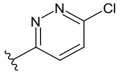
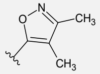
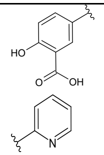
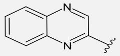
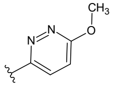
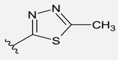
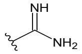


Figure 10: Desulfonated SMP (imine), expected for SMP as 6-membered SUA *via* Smiles rearrangement.

This approach, i.e. identifying expectable TPs based on general organic chemistry knowledge, has already been applied by Majewsky et al. (2015). A generic scheme was developed to predict possible TPs of SPY and SDZ. For this purpose, major transformation reactions, e.g. acetylation, hydroxylation, and desulfonation were identified. Before HPLC-QTOF screening, 5 corresponding product ions of each SUA were selected. The prediction of these product ions facilitated the tentative identification of numerous formerly unknown TPs: *p*-Nitro-SDZ, desamino-SPY, and *N4*-formyl-SPY were reported for the first time (Majewsky et al., 2015). However, even small structural changes can lead to different reactivities and therefore to different TPs. For example, Wang and Helbling (2016) observed the same reaction types for similar SUAs (SMX, STZ, SDM): chlorine substitution, δ-bond hydrolysis, and desulfonation, but γ-bond cleavage, oxidation/hydroxylation, and conjugation reactions were observed only for one or two SUAs. Therefore, laboratory testing is needed to confirm predicted TPs. For a reasonable laboratory effort, strategies are important to limit the number of TPs to the relevant ones (Hensen et al., 2020; Menz et al., 2017)

Table 7: TPs with common features, separated into non-specific and SUA-specific TPs for each SUA. The molar mass [g/mol] is given. TPs described for most SUAs are in bold type.

SUA M [g/mol]	**SMX** 253	**SDZ** 250	**SMZ** 278	**SDM** 310	**SPY** 249	**STZ** 255	**SMR** 264	**SCP** 285	**SIX** 267	**SSZ** 398	**SQX** 300	**SMP** 280	**SMT** 270	**SGU** 214
specific rest R														
non-specific TPs M [g/mol]	Hocks (✓) show for which SUAs the non-specific TPs were found in the literature.													
organic acids	✓	✓	✓			✓	✓	✓		✓	✓			
aniline (γ-bond cleavage) 93	✓	✓	✓	✓	✓	✓	✓							
p-benzoquinone imine 107	✓				✓								✓	
p-aminophenol 109	✓	✓	✓			✓	✓	✓	✓					
hydroquinone 110		✓	✓		✓		✓	✓						
benzenesulfonic acid 158	✓	✓				✓								
SAA (ε-bond cleavage) 172	✓	✓	✓	✓	✓	✓		✓	✓				✓	✓
sulfanilic acid (δ-bond cleavage) 173	✓	✓	✓	✓	✓	✓	✓	✓	✓			✓	✓	
SUA-specific TPs	Molar masses M [g/mol] show for which SUAs the SUA-specific TPs were found in the literature. M (TP) = M (SUA, see first row) -/+ M (common feature, see first column)													
specific rest R (ε-bond cleavage) -170		80	108					115						
NH_2R	**98**	**95**	**123**	**155**	**94**	**100**	**109**	**130**	**112**	**-149=**	**145**	**125**	**115**	**59**

(δ-bond cleavage) -155										**94**				
H(O)SO$_2$-NHR (γ-bond cleavage) -91 (-75)	162		187	235	174	180			189					
desulfonated SUA (Imine, I or Amine, A) -64	**189** (A)	**186** (I)	**214** (I, A)	**246** (I, A)	**185** (I, A)	**191** (A)	**200** (I, A)	**221** (I)	**203** (A)	**334** (I, A)	**236** (I, A)	**216** (A)	**206** (A)	**150** (I↔A)
desamino SUA (β-bond cleavage) -15	238	235	263	295	234					-149= 234				
4-*ipso*-OH-SUA +1	254	250	279	311	250	256	265			-149= 248			287 (incl. X-OH)	
***p*-nitroso-SUA +14**	**267**	**264**	**292**	**324**	**263**	**269**			**281**			**294**	**284**	**228**
X-OH-SUA +16	**269**	**266**	**294**	**326**	**265**	**271**	**280**	**301**	**283**	**-149= 265**	**316**	**296**	**286**	**230**
at aniline	**269**	**266**	**294**	**326**	**265**	**271**	**280**	**301**	**283**	**414**		**296**	**286**	**230**
at R	269	266	294	326	265	271			283		316			
N4-formyl-SUA +28	281	278	306		277	283					328			
***p*-nitro-SUA +30**	**283**	**280**	**308**	**340**		**285**	**294**	**315**	**297**		**330**		**300**	
X, Y-(OH)$_2$-SUA +32	285	282	310	342	281	287	296	317	299					
X-Cl-SUA +34	288		312	344		289					334			
N4-acetyl-SUA +42	295	292	320	352	291	297	306		309		342			
glycosyl-SUA +162	415	412	440		411	417								
pterin-SUA +175	428	425	453		424	430								
dimer of SUA 2*M(SUA) -2,-4	502	496	552	632, 648 (incl. X-OH, 2OH)		508			530	792			538	

4. Discussion of insights gained from the reviewed literature data

We have seen, that the diversity of TPs even within the group of SUAs and SMX as the main compound is tremendous: The dataset of SUA-TPs includes more than 600 different structures. However, data on their occurrence in the technosphere and the environment, degradability, and (eco)toxicity are scarce even for SMX, the most investigated SUA. Few data entries on occurrence suggest that SUA-TPs can be widespread in the environment, indicating this as a general feature. TPs are often more polar than respective PC. According to data of SMX-TPs, we expect SUA-TPs that have not been eliminated in WTP to be mobile in the aquatic environment at concentrations in the low ng L^{-1} range. Thus, they can often be considered persistent, mobile, and toxic (PMT) substances (Rüdel et al., 2020). To fill identified gaps of data on occurrence, tremendous laboratory work would be needed.

Only relevant TPs should be part of monitoring programs to reduce laboratory work, as discussed for TPs of pesticides (Escher et al., 2014; German Federal Environmental Agency, 2019; Hensen et al., 2020). An assessment scheme and criteria, as well as data, are needed to identify relevant TPs, i.e. TPs that might be ecotoxic and/or (very) persistent, and (very) mobile (Cousins et al., 2019). Compounds, especially small TPs such as organic acids, aniline, or sulfanilic acid, could be already registered in databases such as PubChem and SciFinder. In those cases, renewed investigation regarding their characteristics is not needed.

To assess, if TPs would be persistent or completely biodegradable in WTP or the environment, data from degradation tests of individual TPs, that investigate also their mineralisation, is needed. However, such data is almost completely absent for SUA-TPs. Most data on SUA-TPs was provided by elimination studies of their PC (simulation of WTP or environment). Data depend very much on different test conditions. Even though PC's mineralisation rate was monitored in many studies, the mineralisation rate of each formed and eliminated TP remained unknown. Eliminated TPs may further transform to persistent TPs, possibly ecotoxic. To assess ecotoxicity, data from significant testing of individual TPs is needed. However, such data is lacking for most SUA-TPs in reviewed literature. Many ecotoxicity tests were performed using mixtures of SUA-TPs. They indicated less or more ecotoxic TPs compared to the PC. Thus, for both degradability and ecotoxicity assessment, standardised testing of individual TPs is urgently needed to enable a comprehensive environmental risk assessment of the PC and the TPs themselves.

Poor commercial availability is a likely cause of data gaps. An approach to overcome the challenge of not buyable TPs (or being too expensive to synthesise) could be the use of *in silico* tools. TPs could be predicted using *in silico* models such as the EAWAG-BBD Pathway Prediction System (Fenner et al.), the photodegradation model META (Sedykh et al., 2001), and PathPred predicting enzyme-catalysed pathways (PathPred). Prediction can facilitate the detection of expected TPs. Properties of predicted structures (ideally analytically confirmed after abiotic or biotic generation) can be computed using (quantitative) structure-activity relationships ((Q)SARs) or other approaches, such as read-across. These tools are already well established for physicochemical parameters, such as pK_a, log P, and water solubility (Cumming et al., 2013; Lombardino and Lowe, 2004), but also toxicity such as mutagenicity (Ames). *In silico* models have limitations, e.g. regarding predictivity in general and applicability domain due to missing experimental data to develop/improve models (Lorenz et al., 2021). Therefore, extensive laboratory experiments to study the formation of TPs and further mechanisms cannot be circumvented for all substance classes. Furthermore, predictions for prioritised structures need to be confirmed by experimental tests (Hensen et al., 2020).

Another approach to overcome the challenge of not buyable TPs, and also limitations of *in silico* tools, would be the fast and simple generation of TPs, e.g. by photolysis, and subsequent biodegradability testing, teasing e.g. by OECD 301 D, OECD 308, or other standardised tests. OECD tests would be preferred as they are widespread and needed for the authorisation of chemicals and pharmaceuticals. This approach was done already by Rastogi et al. (2014, 2015a, 2015b) using β-blockers as an example and shortly after by Su et al. (2016) using SMX. Their studies have provided useful knowledge on TP-mixtures due to the use of standardised biodegradation tests. Then, TPs of interest need further individual investigation.

Similarly, ecotoxicity of TP-mixtures was tested in some reviewed studies to identify possible ecotoxic TPs for further investigation. For example, the formation of TP-mixtures in different matrices, e.g. distilled water *vs.* surface water, led to different TP compositions linked to different toxicities. Identified differences in composition could be used to derive potentially toxic TPs (Trovó et al., 2009a). Another example is a treatment study to improve the TOC removal, e.g. by using an appropriate catalyst. At the same time, ecotoxicity of the remaining TP-mixture was monitored and found to be reduced. In this way, TPs eliminated by improved test setup might be ecotoxic, whereas TPs that are still present in the mixture might not be ecotoxic (Mirzaei et al. 2018). These examples are comparable to experimental effect-driven approaches to determine the ecotoxicity of TPs, proposed already by Hensen et al. (2020) and Menz et al. (2017). According to an effect-driven approach, TP-mixtures along a degradation process (e.g. photodegradation) are screened to get first hints on ecotoxic TPs by the observation of effect changes compared to their kinetics. These TPs should be structural elucidated, isolated or synthesised, and then tested individually (Escher and Fenner, 2011). We want to highlight that finding no toxic mixture does not mean that compounds are not toxic as one PC often results in many TPs of different share, i.e. at lower concentrations. To illustrate, if there would be 10 TPs, the (eco)toxicity of one TP in the mixture needs to be 10-fold compared to the PC to reach the same toxic effect (simplifying that each TP has the same probability to be formed).

Besides the limitations of individual testing, the selection of endpoints can be challenging since ecotoxicity can be defined by many endpoints. The ecotoxicity standard within the environmental risk assessment of pharmaceuticals is the testing of chronic effects on algae, daphnia, and fish (European Commission, 2004; European Medicines Agency, 2018). As a result of taxa sensitivity comparison to reduce vertebrate testing, tests of antibiotics should focus on algae and cyanobacteria, whereas fish testing is unnecessary. For endocrine-active substances it would be the other way around: fish tests are necessary, whereas algae are not sensitive (Schwarz et al., 2021). Although there is this common practice of testing, ecotoxicity is still very complex. It can be tested and monitored on different levels (receptors, cells, organs, organisms, populations, ecosystems). There may be further, quite different environmental effects than currently known. Moreover, it might be impossible, as mentioned above, to select an ecotoxicity assay that is suitable for diverse TPs even if they stem from the same PC (Toolaram et al., 2014). Thus, multitude and diversity of TPs seem to be another big challenge of TP assessment, especially in terms of ecotoxicity.

Ultimately, the risk of any environmental effect posed by (potentially) ecotoxic TPs would be absent for those APIs that mineralise completely in the environment. No laborious testing would be needed.

Therefore, the concept *Benign by Design* (Kümmerer, 2007), based on the 10th principle of green chemistry *Design for Degradation* (Anastas and Warner, 1998), should be applied to the API discovery process to consider complete environmental degradability from the very beginning (Puhlmann et al., 2021). Further measures at the source to minimise emissions and levels of APIs and their TPs in the environment are improved prescribing practices, reduction of package sizes, and separate collection of household hazardous waste including pharmaceuticals (European Commission, 2020c).

5. Conclusion

The focus of this review was on fate and effects as well as properties of TPs, and their assessment including possible knowledge gaps. Pharmaceutical sulfonamides (SUAs) have been used as an illustrative group of substances as there are many similar PCs of high usage with many related publications, but also still many knowledge gaps.

This review indicates that further extensive research is needed to fill identified knowledge gaps: Despite many studies are dealing with SUA-TPs only a few data entries are available according to standardised tests related to environmental fate and toxicity. Thus, the environmental fate of most SUA-TPs is still unclear. Additionally, ecotoxicity data for the single TP is scarce, although potential ecotoxicity is indicated by many studies on TP-mixtures. The collected and systematised data together with future research can contribute to a comprehensive risk assessment of SUAs in the environment to avoid an underestimation of their environmental effects.

Based on findings for SUAs and data published for other pharmaceuticals and chemicals, some conclusions can be drawn that apply to TPs in general: There is a high number of compounds and an even higher number of TPs. Analysis of TPs is challenging, e.g. due to poor availability of TPs for testing, leading to large gaps of data, especially of high-quality data. Back transformation into the PC or further transformation to ecotoxic TPs poses a risk for the environment. Thus, complete elimination of the PC, e.g. in WTP, does not mean that no environmental pollution and related risks can occur, as elimination does not indicate complete mineralisation.

According to greener chemistry and pharmacy, measures should be taken to reduce or even avoid the input of chemicals and pharmaceuticals into the environment. The share of compounds whose input is unavoidable by essential use (e.g. excretion of APIs) should completely mineralise at the end of their life in the environment. In this context, data on TPs will be very important for future work on the redesign of SUAs for complete environmental mineralisation (*Benign by Design*): A TP that is pharmacologically active and also readily biodegradable in the environment would present a promising candidate for the redesign of pharmaceuticals including SUAs.

References

Abellán, M.N., Gebhardt, W., Schröder, H.F., 2008. Detection and identification of degradation products of sulfamethoxazole by means of LC/MS and -MSn after ozone treatment. Water Science and Technology: a Journal of the International Association on Water Pollution Research 58 (9), 1803–1812. doi:10.2166/wst.2008.539.

Achermann, S., Bianco, V., Mansfeldt, C.B., Vogler, B., Kolvenbach, B.A., Corvini, P.F.X., Fenner, K., 2018. Biotransformation of Sulfonamide Antibiotics in Activated Sludge: The Formation of Pterin-Conjugates Leads to Sustained Risk. Environmental Science & Technology 52 (11), 6265–6274. doi:10.1021/acs.est.7b06716.

Anastas, P.T., Warner, J.C. (Eds.), 1998. Green Chemistry: Theory and Practice. Oxford University Press, Oxford [England], New York.

Archundia, D., Duwig, C., Lehembre, F., Chiron, S., Morel, M.-C., Prado, B., Bourdat-Deschamps, M., Vince, E., Aviles, G.F., Martins, J.M.F., 2017. Antibiotic pollution in the Katari subcatchment of the Titicaca Lake: Major transformation products and occurrence of resistance genes. Science of The Total Environment 576, 671–682. doi:10.1016/j.scitotenv.2016.10.129.

Baran, W., Adamek, E., Ziemiańska, J., Sobczak, A., 2011. Effects of the presence of sulfonamides in the environment and their influence on human health. Journal of Hazardous Materials 196, 1–15. doi:10.1016/j.jhazmat.2011.08.082.

Białk-Bielińska, A., Caban, M., Pieczyńska, A., Stepnowski, P., Stolte, S., 2017. Mixture toxicity of six sulfonamides and their two transformation products to green algae Scenedesmus vacuolatus and duckweed Lemna minor. Chemosphere 173, 542–550. doi:10.1016/j.chemosphere.2017.01.035.

Bílková, Z., Malá, J., Hrich, K., 2019. Fate and behaviour of veterinary sulphonamides under denitrifying conditions. Science of The Total Environment 695, 133824. doi:10.1016/j.scitotenv.2019.133824.

Bonvin, F., Omlin, J., Rutler, R., Schweizer, W.B., Alaimo, P.J., Strathmann, T.J., McNeill, K., Kohn, T., 2013. Direct photolysis of human metabolites of the antibiotic sulfamethoxazole: evidence for abiotic back-transformation. Environmental Science & Technology 47 (13), 6746–6755. doi:10.1021/es303777k.

Boreen, A.L., Arnold, W.A., McNeill, K., 2004. Photochemical fate of sulfa drugs in the aquatic environment: sulfa drugs containing five-membered heterocyclic groups. Environmental Science & Technology 38 (14), 3933–3940. doi:10.1021/es0353053.

Boreen, A.L., Arnold, W.A., McNeill, K., 2005. Triplet-sensitized photodegradation of sulfa drugs containing six-membered heterocyclic groups: identification of an SO2 extrusion photoproduct. Environmental Science & Technology 39 (10), 3630–3638. doi:10.1021/es048331p.

Brienza, M., Duwig, C., Pérez, S., Chiron, S., 2017. 4-nitroso-sulfamethoxazole generation in soil under denitrifying conditions: Field observations versus laboratory results. Journal of Hazardous Materials 334, 185–192. doi:10.1016/j.jhazmat.2017.04.015.

Charuaud, L., Jarde, E., Jaffrezic, A., Thomas, M.-F., Le Bot, B., 2019. Veterinary pharmaceutical residues from natural water to tap water: Sales, occurrence and fate. Journal of Hazardous Materials 361, 169–186. doi:10.1016/j.jhazmat.2018.08.075.

Chen, J., Xie, S., 2018. Overview of sulfonamide biodegradation and the relevant pathways and microorganisms. Science of The Total Environment 640-641, 1465–1477. doi:10.1016/j.scitotenv.2018.06.016.

Chibwe, L., Titaley, I.A., Hoh, E., Simonich, S.L.M., 2017. Integrated Framework for Identifying Toxic Transformation Products in Complex Environmental Mixtures. Environmental Science & Technology Letters 4 (2), 32–43. doi:10.1021/acs.estlett.6b00455.

Christou, A., Michael, C., Fatta-Kassinos, D., Fotopoulos, V., 2018. Can the pharmaceutically active compounds released in agroecosystems be considered as emerging plant stressors? Environment International 114, 360–364. doi:10.1016/j.envint.2018.03.003.

Cousins, I.T., Ng, C.A., Wang, Z., Scheringer, M., 2019. Why is high persistence alone a major cause of concern? Environmental Science: Processes & Impacts 21 (5), 781–792. doi:10.1039/C8EM00515J.

Cumming, J.G., Davis, A.M., Muresan, S., Haeberlein, M., Chen, H., 2013. Chemical predictive modelling to improve compound quality. Nature Reviews Drug Discovery 12 (12), 948–962. doi:10.1038/nrd4128.

Cycoń, M., Mrozik, A., Piotrowska-Seget, Z., 2019. Antibiotics in the Soil Environment-Degradation and Their Impact on Microbial Activity and Diversity. Frontiers in Microbiology 10, 338. doi:10.3389/fmicb.2019.00338.

Deeb, A.A., Stephan, S., Schmitz, O.J., Schmidt, T.C., 2017. Suspect screening of micropollutants and their transformation products in advanced wastewater treatment. Science of The Total Environment 601-602, 1247–1253. doi:10.1016/j.scitotenv.2017.05.271.

Dirany, A., Sirés, I., Oturan, N., Ozcan, A., Oturan, M.A., 2012. Electrochemical treatment of the antibiotic sulfachloropyridazine: kinetics, reaction pathways, and toxicity evolution. Environmental Science & Technology 46 (7), 4074–4082. doi:10.1021/es204621q.

ECHA, 2021. Acetic acid: Biodegradation in water. <https://echa.europa.eu/de/registration-dossier/-/registered-dossier/15549/5/3/2> (retrieved 09.01.21).

Eguchi, K., Nagase, H., Ozawa, M., Endoh, Y.S., Goto, K., Hirata, K., Miyamoto, K., Yoshimura, H., 2004. Evaluation of antimicrobial agents for veterinary use in the ecotoxicity test using microalgae. Chemosphere 57 (11), 1733–1738. doi:10.1016/j.chemosphere.2004.07.017.

El-Ghenymy, A., Garrido, J.A., Rodríguez, R.M., Cabot, P.L., Centellas, F., Arias, C., Brillas, E., 2013. Degradation of sulfanilamide in acidic medium by anodic oxidation with a boron-doped diamond anode. Journal of Electroanalytical Chemistry 689, 149–157. doi:10.1016/j.jelechem.2012.11.013.

Escher, B., Tang, J., Busetti, F., Allard, S., Charrois, J., 2014. Micropollutants, mixtures and transformation products in recycled water: how much do we really know? <https://vuir.vu.edu.au/32062/1/Micropollutants,+mixtures+and+transformation+products-Final+Report+ver2+with+Appendices.pdf>.

Escher, B.I., Fenner, K., 2011. Recent Advances in Environmental Risk Assessment of Transformation Products. Environmental Science & Technology 45 (9), 3835–3847. doi:10.1021/es1030799.

European Commission, 2004. Art. 8 (3), Directive 2004/27/EC of the European Parliament and of the Council of 31 March 2004: amending Directive 2001/83/EC on the Community Code relating to Medicinal Products for Human Use. <https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32004L0027&from=EN> (retrieved 18.02.21).

European Commission, 2019. The European Green Deal. <https://ec.europa.eu/info/sites/default/files/european-green-deal-communication_en.pdf> (retrieved 21.12.21).

European Commission, 2020a. A new Circular Economy Action PlanFor a cleaner and more competitive Europe. <https://eur-lex.europa.eu/resource.html?uri=cellar:9903b325-6388-11ea-b735-01aa75ed71a1.0017.02/DOC_1&format=PDF> (retrieved 18.02.21).

European Commission, 2020b. Chemicals Strategy for Sustainability Towards a Toxic-Free Environment. <https://ec.europa.eu/environment/pdf/chemicals/2020/10/Strategy.pdf> (retrieved 18.02.21).

European Commission, 2020c. Pharmaceutical Strategy for Europe. <https://ec.europa.eu/commission/presscorner/detail/en/ip_20_2173> (retrieved 18.02.21).

European Commission, 2020d. Zero pollution action plan. <https://ec.europa.eu/environment/strategy/zero-pollution-action-plan_de#ecl-inpage-208> (retrieved 18.02.21).

European Medicines Agency, 2018. Draft guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00 Rev. 1). <https://www.ema.europa.eu/en/environmental-risk-assessment-medicinal-products-human-use> (retrieved 07.03.22).

European Medicines Agency, 2020. European Surveillance of Veterinary Antimicrobial Consumption, 'Sales of veterinary antimicrobial agents in 31 European countries in 2018', (EMA/24309/2020). <https://www.ema.europa.eu/en/documents/report/sales-veterinary-antimicrobial-agents-31-european-countries-2018-trends-2010-2018-tenth-esvac-report_en.pdf>.

European Union, 2009. EU Regulation (EC) No 1107/2009 of the European Parliament and of the Council of 21 October 2009 concerning the placing of plant protection products on the market and repealing Council Directives 79/117/EEC and 91/414/EEC, 2009.

Ezzariai, A., Hafidi, M., Khadra, A., Aemig, Q., El Fels, L., Barret, M., Merlina, G., Patureau, D., Pinelli, E., 2018. Human and veterinary antibiotics during composting of sludge or manure: Global perspectives on persistence, degradation, and resistance genes. Journal of Hazardous Materials 359, 465–481. doi:10.1016/j.jhazmat.2018.07.092.

Fabbri, D., López-Muñoz, M.J., Daniele, A., Medana, C., Calza, P., 2019. Photocatalytic abatement of emerging pollutants in pure water and wastewater effluent by TiO2 and Ce-ZnO: degradation kinetics and assessment of transformation products. Photochemical & Photobiological Sciences 18 (4), 845–852. doi:10.1039/C8PP00311D.

Fatta-Kassinos, D., Meric, S., Nikolaou, A., 2011a. Pharmaceutical residues in environmental waters and wastewater: current state of knowledge and future research. Analytical and Bioanalytical Chemistry 399 (1), 251–275. doi:10.1007/s00216-010-4300-9.

Fatta-Kassinos, D., Vasquez, M.I., Kümmerer, K., 2011b. Transformation products of pharmaceuticals in surface waters and wastewater formed during photolysis and advanced oxidation processes - degradation, elucidation of byproducts and assessment of their biological potency. Chemosphere 85 (5), 693–709. doi:10.1016/j.chemosphere.2011.06.082.

Felis, E., Kalka, J., Sochacki, A., Kowalska, K., Bajkacz, S., Harnisz, M., Korzeniewska, E., 2020. Antimicrobial pharmaceuticals in the aquatic environment - occurrence and environmental implications. European Journal of Pharmacology 866, 172813. doi:10.1016/j.ejphar.2019.172813.

Fenner, K., Wackett, L., Schmid, E. EAWAG-BBD Pathway Prediction System. <http://eawag-bbd.ethz.ch/predict/> (retrieved 09.08.21).

Fukahori, S., Fujiwara, T., 2015. Photocatalytic decomposition behavior and reaction pathway of sulfamethazine antibiotic using TiO2. Journal of Environmental Management 157, 103–110. doi:10.1016/j.jenvman.2015.04.002.

Gao, S., Zhao, Z., Xu, Y., Tian, J., Qi, H., Lin, W., Cui, F., 2014. Oxidation of sulfamethoxazole (SMX) by chlorine, ozone and permanganate--a comparative study. Journal of Hazardous Materials 274, 258–269. doi:10.1016/j.jhazmat.2014.04.024.

Gao, Y., Gao, N., Deng, Y., Gu, J., Gu, Y., Zhang, D., 2013. Factors affecting sonolytic degradation of sulfamethazine in water. Ultrasonics Sonochemistry 20 (6), 1401–1407. doi:10.1016/j.ultsonch.2013.04.007.

García-Galán, M.J., Petrovic, M., Rodríguez-Mozaz, S., Barceló, D., 2016. Multiresidue trace analysis of pharmaceuticals, their human metabolites and transformation products by fully automated on-line solid-phase extraction-liquid chromatography-tandem mass spectrometry. Talanta 158, 330–341. doi:10.1016/j.talanta.2016.05.061.

German Federal Environmental Agency, 2019. Recommendation list for the monitoring of metabolites of plant protection agents in German groundwater: German Federal Environmental Agency.

Gmurek, M., Horn, H., Majewsky, M., 2015. Phototransformation of sulfamethoxazole under simulated sunlight: Transformation products and their antibacterial activity toward Vibrio fischeri. Science of The Total Environment 538, 58–63. doi:10.1016/j.scitotenv.2015.08.014.

Gómez-Ramos, M.d.M., Mezcua, M., Agüera, A., Fernández-Alba, A.R., Gonzalo, S., Rodríguez, A., Rosal, R., 2011. Chemical and toxicological evolution of the antibiotic sulfamethoxazole under ozone treatment in water solution. Journal of Hazardous Materials 192 (1), 18–25. doi:10.1016/j.jhazmat.2011.04.072.

Grabarczyk, Ł., Mulkiewicz, E., Stolte, S., Puckowski, A., Pazda, M., Stepnowski, P., Białk-Bielińska, A., 2020. Ecotoxicity screening evaluation of selected pharmaceuticals and their transformation products towards various organisms. Environmental Science and Pollution Research International 27 (21), 26103–26114. doi:10.1007/s11356-020-08881-3.

Greenhalgh, T., Peacock, R., 2005. Effectiveness and efficiency of search methods in systematic reviews of complex evidence: audit of primary sources. BMJ (Clinical Research ed.) 331 (7524), 1064–1065. doi:10.1136/bmj.38636.593461.68.

Guan, C., Jiang, J., Pang, S., Ma, J., Chen, X., Lim, T.-T., 2019. Nonradical transformation of sulfamethoxazole by carbon nanotube activated peroxydisulfate: Kinetics, mechanism and product toxicity. Chemical Engineering Journal 378, 122147. doi:10.1016/j.cej.2019.122147.

Guo, C., Xu, J., Wang, S., Zhang, Y., He, Y., Li, X., 2013. Photodegradation of sulfamethazine in an aqueous solution by a bismuth molybdate photocatalyst. Catal. Sci. Technol. 3 (6), 1603. doi:10.1039/c3cy20811g.

Haddad, T., Baginska, E., Kümmerer, K., 2015. Transformation products of antibiotic and cytostatic drugs in the aquatic cycle that result from effluent treatment and abiotic/biotic reactions in the environment: An increasing challenge calling for higher emphasis on measures at the beginning of the pipe. Water Research 72, 75–126. doi:10.1016/j.watres.2014.12.042.

Hensen, B., Olsson, O., Kümmerer, K., 2020. A strategy for an initial assessment of the ecotoxicological effects of transformation products of pesticides in aquatic systems following a tiered approach. Environment International 137, 105533. doi:10.1016/j.envint.2020.105533.

Hernandez, F., Ibanez, M., Bade, R., Bijlsma, L., Sancho, J.V., 2014. Investigation of pharmaceuticals and illicit drugs in waters by liquid chromatography-high-resolution mass spectrometry. TRAC-Trends in Analytical Chemistry 63, 140–157. doi:10.1016/j.trac.2014.08.003.

Hong, M., Wang, Y., Lu, G., 2020. UV-Fenton degradation of diclofenac, sulpiride, sulfamethoxazole and sulfisomidine: Degradation mechanisms, transformation products, toxicity evolution and effect of real water matrix. Chemosphere 258, 127351. doi:10.1016/j.chemosphere.2020.127351.

Hu, J., Li, X., Liu, F., Fu, W., Lin, L., Li, B., 2022. Comparison of chemical and biological degradation of sulfonamides: Solving the mystery of sulfonamide transformation. Journal of Hazardous Materials 424, 127661. doi:10.1016/j.jhazmat.2021.127661.

Hu, L., Flanders, P.M., Miller, P.L., Strathmann, T.J., 2007. Oxidation of sulfamethoxazole and related antimicrobial agents by TiO2 photocatalysis. Water Research 41 (12), 2612–2626. doi:10.1016/j.watres.2007.02.026.

Hu, Z., Xie, X., Li, S., Song, M., Liang, G., Zhao, J., Wang, Z., 2021. Rational construct CQDs/BiOCOOH/uCN photocatalyst with excellent photocatalytic performance for degradation of sulfathiazole. Chemical Engineering Journal 404, 126541. doi:10.1016/j.cej.2020.126541.

Ioannidou, E., Frontistis, Z., Antonopoulou, M., Venieri, D., Konstantinou, I., Kondarides, D.I., Mantzavinos, D., 2017. Solar photocatalytic degradation of sulfamethoxazole over tungsten – Modified TiO 2. Chemical Engineering Journal 318, 143–152. doi:10.1016/j.cej.2016.06.012.

Jurado, A., Margareto, A., Pujades, E., Vázquez-Suñé, E., Diaz-Cruz, M.S., 2020. Fate and risk assessment of sulfonamides and metabolites in urban groundwater. Environmental Pollution (Barking, Essex : 1987) 267, 115480. doi:10.1016/j.envpol.2020.115480.

Kassotaki, E., Buttiglieri, G., Ferrando-Climent, L., Rodriguez-Roda, I., Pijuan, M., 2016. Enhanced sulfamethoxazole degradation through ammonia oxidizing bacteria co-metabolism and fate of transformation products. Water Research 94, 111–119. doi:10.1016/j.watres.2016.02.022.

Kim, C., Panditi, V.R., Gardinali, P.R., Varma, R.S., Kim, H., Sharma, V.K., 2015. Ferrate promoted oxidative cleavage of sulfonamides: Kinetics and product formation under acidic conditions. Chemical Engineering Journal 279, 307–316. doi:10.1016/j.cej.2015.04.139.

Klavarioti, M., Mantzavinos, D., Kassinos, D., 2009. Removal of residual pharmaceuticals from aqueous systems by advanced oxidation processes. Environment International 35 (2), 402–417. doi:10.1016/j.envint.2008.07.009.

Knopp, G., Prasse, C., Ternes, T.A., Cornel, P., 2016. Elimination of micropollutants and transformation products from a wastewater treatment plant effluent through pilot scale ozonation followed by various activated carbon and biological filters. Water Research 100, 580–592. doi:10.1016/j.watres.2016.04.069.

Kümmerer, K., 2007. Sustainable from the very beginning: rational design of molecules by life cycle engineering as an important approach for green pharmacy and green chemistry. Green Chem. 9 (8), 899–907. doi:10.1039/b618298b.

Kümmerer, K., 2010. Pharmaceuticals in the Environment. Annu. Rev. Environ. Resour. 35 (1), 57–75. doi:10.1146/annurev-environ-052809-161223.

Kümmerer, K., Dionysiou, D.D., Olsson, O., Fatta-Kassinos, D., 2018. A path to clean water. Science (New York, N.Y.) 361 (6399), 222–224. doi:10.1126/science.aau2405.

Kümmerer, K., Dionysiou, D.D., Olsson, O., Fatta-Kassinos, D., 2019. Reducing aquatic micropollutants - Increasing the focus on input prevention and integrated emission management. Science of The Total Environment 652, 836–850. doi:10.1016/j.scitotenv.2018.10.219.

Li, J., Zhao, L., Feng, M., Huang, C.-H., Sun, P., 2021. Abiotic transformation and ecotoxicity change of sulfonamide antibiotics in environmental and water treatment processes: A critical review. Water Research 202, 117463. doi:10.1016/j.watres.2021.117463.

Lombardino, J.G., Lowe, J.A., 2004. The role of the medicinal chemist in drug discovery--then and now. Nature Reviews. Drug Discovery 3 (10), 853–862. doi:10.1038/nrd1523.

López-Serna, R., Jurado, A., Vázquez-Suñé, E., Carrera, J., Petrović, M., Barceló, D., 2013. Occurrence of 95 pharmaceuticals and transformation products in urban groundwaters underlying the metropolis of Barcelona, Spain. Environmental Pollution (Barking, Essex : 1987) 174, 305–315. doi:10.1016/j.envpol.2012.11.022.

Lorenz, S., Amsel, A.-K., Puhlmann, N., Reich, M., Olsson, O., Kümmerer, K., 2021. Toward Application and Implementation of in Silico Tools and Workflows within Benign by Design Approaches. ACS Sustainable Chemistry & Engineering 9 (37), 12461–12475. doi:10.1021/acssuschemeng.1c03070.

Majewsky, M., Glauner, T., Horn, H., 2015. Systematic suspect screening and identification of sulfonamide antibiotic transformation products in the aquatic environment. Analytical and Bioanalytical Chemistry, 5707–5717. doi:10.1007/s00216-015-8748-5.

Majewsky, M., Wagner, D., Delay, M., Bräse, S., Yargeau, V., Horn, H., 2014. Antibacterial activity of sulfamethoxazole transformation products (TPs): general relevance for sulfonamide TPs modified at the para position. Chemical Research in Toxicology 27 (10), 1821–1828. doi:10.1021/tx500267x.

Mamo, J., García-Galán, M.J., Stefani, M., Rodríguez-Mozaz, S., Barceló, D., Monclús, H., Rodriguez-Roda, I., Comas, J., 2018. Fate of pharmaceuticals and their transformation products in integrated membrane systems for wastewater reclamation. Chemical Engineering Journal 331, 450–461. doi:10.1016/j.cej.2017.08.050.

Mansour, D., Fourcade, F., Huguet, S., Soutrel, I., Bellakhal, N., Dachraoui, M., Hauchard, D., Amrane, A., 2014. Improvement of the activated sludge treatment by its combination with electro Fenton for the mineralization of sulfamethazine. International Biodeterioration & Biodegradation 88, 29–36. doi:10.1016/j.ibiod.2013.11.016.

Menz, J., Toolaram, A.P., Rastogi, T., Leder, C., Olsson, O., Kümmerer, K., Schneider, M., 2017. Transformation products in the water cycle and the unsolved problem of their proactive assessment: A combined in vitro/in silico approach. Environment International 98, 171–180. doi:10.1016/j.envint.2016.11.003.

Mirzaei, A., Chen, Z., Haghighat, F., Yerushalmi, L., 2018. Hierarchical magnetic petal-like Fe3O4-ZnO@g-C3N4 for removal of sulfamethoxazole, suppression of photocorrosion, by-products identification and toxicity assessment. Chemosphere 205, 463–474. doi:10.1016/j.chemosphere.2018.04.102.

Nödler, K., Licha, T., Barbieri, M., Pérez, S., 2012. Evidence for the microbially mediated abiotic formation of reversible and non-reversible sulfamethoxazole transformation products during denitrification. Water Research 46 (7), 2131–2139. doi:10.1016/j.watres.2012.01.028.

Osorio, V., Sanchís, J., Abad, J.L., Ginebreda, A., Farré, M., Pérez, S., Barceló, D., 2016. Investigating the formation and toxicity of nitrogen transformation products of diclofenac and sulfamethoxazole in wastewater treatment plants. Journal of Hazardous Materials 309, 157–164. doi:10.1016/j.jhazmat.2016.02.013.

PathPred. PathPred: Pathway Prediction server. <https://www.genome.jp/tools/pathpred/>.

Periša, M., Babić, S., Škorić, I., Frömel, T., Knepper, T.P., 2013. Photodegradation of sulfonamides and their N 4-acetylated metabolites in water by simulated sunlight irradiation: kinetics and identification of photoproducts. Environ Sci Pollut Res 20 (12), 8934–8946. doi:10.1007/s11356-013-1836-1.

Puhlmann, N., Mols, R., Olsson, O., Slootweg, J.C., Kümmerer, K., 2021. Towards the design of active pharmaceutical ingredients mineralizing readily in the environment. Green Chem. 23 (14), 5006–5023. doi:10.1039/D1GC01048D.

Qi, C., Liu, X., Lin, C., Zhang, X., Ma, J., Tan, H., Ye, W., 2014. Degradation of sulfamethoxazole by microwave-activated persulfate: Kinetics, mechanism and acute toxicity. Chemical Engineering Journal 249, 6–14. doi:10.1016/j.cej.2014.03.086.

Radke, M., Lauwigi, C., Heinkele, G., Mürdter, T.E., Letzel, M., 2009. Fate of the antibiotic sulfamethoxazole and its two major human metabolites in a water sediment test. Environmental Science & Technology 43 (9), 3135–3141. doi:10.1021/es900300u.

Rastogi, T., Leder, C., Kümmerer, K., 2014. Designing green derivatives of β-blocker Metoprolol: a tiered approach for green and sustainable pharmacy and chemistry. Chemosphere 111, 493–499. doi:10.1016/j.chemosphere.2014.03.119.

Rastogi, T., Leder, C., Kümmerer, K., 2015a. A sustainable chemistry solution to the presence of pharmaceuticals and chemicals in the aquatic environment – the example of re-designing β-blocker Atenolol. RSC Adv 5 (1), 27–32. doi:10.1039/C4RA10294K.

Rastogi, T., Leder, C., Kümmerer, K., 2015b. Re-Designing of Existing Pharmaceuticals for Environmental Biodegradability: A Tiered Approach with β-Blocker Propranolol as an Example. Environmental Science & Technology 49 (19), 11756–11763. doi:10.1021/acs.est.5b03051.

Ricken, B., Corvini, P.F.X., Cichocka, D., Parisi, M., Lenz, M., Wyss, D., Martínez-Lavanchy, P.M., Müller, J.A., Shahgaldian, P., Tulli, L.G., Kohler, H.-P.E., Kolvenbach, B.A., 2013. Ipso-hydroxylation and subsequent fragmentation: a novel microbial strategy to eliminate sulfonamide antibiotics. Applied and Environmental Microbiology, 5550–5558. doi:10.1128/AEM.00911-13.

Ricken, B., Fellmann, O., Kohler, H.-P.E., Schäffer, A., Corvini, P.F.-X., Kolvenbach, B.A., 2015. Degradation of sulfonamide antibiotics by Microbacterium sp. strain BR1 - elucidating the downstream pathway. New Biotechnology, 710–715. doi:10.1016/j.nbt.2015.03.005.

Rüdel, H., Körner, W., Letzel, T., Neumann, M., Nödler, K., Reemtsma, T., 2020. Persistent, mobile and toxic substances in the environment: a spotlight on current research and regulatory activities. Environ Sci Eur 32 (1), 5. doi:10.1186/s12302-019-0286-x.

Schäfer, R.B., Liess, M., Altenburger, R., Filser, J., Hollert, H., Roß-Nickoll, M., Schäffer, A., Scheringer, M., 2019. Future pesticide risk assessment: narrowing the gap between intention and reality. Environ Sci Eur 31 (1), 21. doi:10.1186/s12302-019-0203-3.

Scholes, R.C., Prasse, C., Sedlak, D.L., 2019. The Role of Reactive Nitrogen Species in Sensitized Photolysis of Wastewater-Derived Trace Organic Contaminants. Environmental Science & Technology 53 (11), 6483–6491. doi:10.1021/acs.est.9b01386.

Schwarz, S., Gildemeister, D., Hein, A., Schröder, P., Bachmann, J., 2021. Environmental fate and effects assessment of human pharmaceuticals: lessons learnt from regulatory data. Environ Sci Eur 33 (1), 68. doi:10.1186/s12302-021-00503-0.

Schymanski, E.L., Jeon, J., Gulde, R., Fenner, K., Ruff, M., Singer, H.P., Hollender, J., 2014. Identifying Small Molecules via High Resolution Mass Spectrometry: Communicating Confidence. Environmental Science & Technology 48 (4), 2097–2098. doi:10.1021/es5002105.

Sedykh, A., Saiakhov, R., Klopman, G., 2001. META V. A model of photodegradation for the prediction of photoproducts of chemicals under natural-like conditions. Chemosphere 45, 971–981. doi:10.1016/S0045-6535(01)00007-8.

Spielmeyer, A., 2018. Occurrence and fate of antibiotics in manure during manure treatments: A short review. Sustainable Chemistry and Pharmacy 9, 76–86. doi:10.1016/j.scp.2018.06.004.

Su, T., Deng, H., Benskin, J.P., Radke, M., 2016. Biodegradation of sulfamethoxazole photo-transformation products in a water/sediment test. Chemosphere 148, 518–525. doi:10.1016/j.chemosphere.2016.01.049.

Sun, X., Feng, M., Dong, S., Qi, Y., Sun, L., Nesnas, N., Sharma, V.K., 2019. Removal of sulfachloropyridazine by ferrate(VI): Kinetics, reaction pathways, biodegradation, and toxicity evaluation. Chemical Engineering Journal 372, 742–751. doi:10.1016/j.cej.2019.04.121.

Tian, S., Zhang, C., Huang, D., Wang, R., Zeng, G., Yan, M., Xiong, W., Zhou, C., Cheng, M., Xue, W., Yang, Y., Wang, W., 2020. Recent progress in sustainable technologies for adsorptive and reactive removal of sulfonamides. Chemical Engineering Journal 389, 123423. doi:10.1016/j.cej.2019.123423.

Toolaram, A.P., Kümmerer, K., Schneider, M., 2014. Environmental risk assessment of anti-cancer drugs and their transformation products: A focus on their genotoxicity characterization-state of knowledge and short comings. Mutation Research. Reviews in Mutation Research. doi:10.1016/j.mrrev.2014.02.001.

Trovó, A.G., Nogueira, R.F.P., Agüera, A., Fernandez-Alba, A.R., Sirtori, C., Malato, S., 2009a. Degradation of sulfamethoxazole in water by solar photo-Fenton. Chemical and toxicological evaluation. Water Research 43 (16), 3922–3931. doi:10.1016/j.watres.2009.04.006.

Trovó, A.G., Nogueira, R.F.P., Agüera, A., Sirtori, C., Fernández-Alba, A.R., 2009b. Photodegradation of sulfamethoxazole in various aqueous media: persistence, toxicity and photoproducts assessment. Chemosphere 77 (10), 1292–1298. doi:10.1016/j.chemosphere.2009.09.065.

UN Water, 2017. Wastewater. The untapped resource report 2017, The United Nations World Water Development Report 2017. <http://www.unesco.org/new/en/natural-sciences/environment/water/wwap/wwdr/2017-wastewater-the-untapped-resource/> (retrieved 18.02.21).

Vasquez, M.I., Lambrianides, A., Schneider, M., Kümmerer, K., Fatta-Kassinos, D., 2014. Environmental side effects of pharmaceutical cocktails: What we know and what we should know. Journal of Hazardous Materials 279, 169–189. doi:10.1016/j.jhazmat.2014.06.069.

Wang, J., Wang, S., 2018. Microbial degradation of sulfamethoxazole in the environment. Applied Microbiology and Biotechnology 102 (8), 3573–3582. doi:10.1007/s00253-018-8845-4.

Wang, M., Helbling, D.E., 2016. A non-target approach to identify disinfection byproducts of structurally similar sulfonamide antibiotics. Water Research 102, 241–251. doi:10.1016/j.watres.2016.06.042.

Wang, S., Hu, Y., Wang, J., 2018. Biodegradation of typical pharmaceutical compounds by a novel strain Acinetobacter sp. Journal of Environmental Management 217, 240–246. doi:10.1016/j.jenvman.2018.03.096.

Wilkinson, J.L., Boxall, A.B.A., Kolpin, D.W., Leung, K.M.Y., La, i.R.W.S., Galbán-Malagón, C., Adell, A.D., Mondon, J., Metian, M., Marchant, R.A., Bouzas-Monroy, A., Cuni-Sanchez, A., Coors, A., Carriquiriborde Pedro, Rojo, M., Gordon, C., Cara, M., Moermond, M., Luarte, T., Petrosyan, V., Perikhanyan, Y., Mahon, C.S., McGurk, C.J., Hofmann, T., Kormoker, T., Iniguez, V., Guzman-Otazo, J., Tavares, J.L., Gildasio De Figueiredo, F., Razzolini, M.T.P., Dougnon, V., Gbaguidi, G., Traoré, O., Blais, J.M., Kimpe, L.E., Wong, M., Wong, D., Ntchantcho, R., Pizarro, J., Ying, G.-G., Chen, C.-E., Páez, M., Martínez-Lara, J., Otamonga, J.-P., Poté, J., Ifo, S.A., Wilson, P., Echeverría-Sáenz, S., Udikovic-Kolic, N., Milakovic, M., Fatta-Kassinos, D., Ioannou-Ttofa, L., Belušová, V., Vymazal, J., Cárdenas-Bustamante, M., Kassa, B.A., Garric, J., Chaumot, A., Gibba, P., Kunchulia, I., Seidensticker, S., Lyberatos, G., Halldórsson, H.P., Melling, M., Shashidhar, T., Lamba, M., Nastiti, A., Supriatin, A., Pourang, N., Abedini, A., Abdullah, O., Gharbia, S.S., Pilla, F., Chefetz, B., Topaz, T., Yao, Koffi, Marcellin, Aubakirova, B., Beisenova, R., Olaka, L., Mulu, J.K., Chatanga, P., Ntuli, V., Blama, N.T., Sherif, S., Aris, A.Z., Looi, L.J., Niang, M., Traore, S.T., Oldenkamp, R., Ogunbanwo, O., Ashfaq, M., Iqbal, M., Abdeen, Z., O’Dea, A., Morales-Saldaña, J.M., Custodio, M., La Cruz, H. de, Navarrete Ian, Carvalho, F., Gogra, A.B., Koroma, B.M., Cerkvenik-Flajs, V., Gombač, M., Thwala, M., Choi, K., Kang, H., Ladu, J.L.C., Rico, A., Amerasinghe, P., Sobek, A., Horlitz, G., Zenker, A.K., King, A.C., Jiang, J.-J., Kariuki, R., Tumbo, M., Tezel, U., Onay, T.T., Lejju, J.B., Vystavna, Y., Vergeles, Y., Heinzen, H., Pérez-Parada, A., Sims, D.B., Figy, M., Good, D., Teta, C., 2022. Pharmaceutical pollution of the world's rivers. Proceedings of the National Academy of Sciences 119 (8), e2113947119. doi:10.1073/pnas.2113947119.

Wohde, M., Berkner, S., Junker, T., Konradi, S., Schwarz, L., Düring, R.-A., 2016. Occurrence and transformation of veterinary pharmaceuticals and biocides in manure: a literature review. Environmental Sciences Europe 28 (1), 23. doi:10.1186/s12302-016-0091-8.

World Health Organization, 2018. WHO report on surveillance of antibiotic consumption: 2016-2018 early implementation. Licence: CC BY-NC-SA 3.0 IGO.

Yang, Y., Lu, X., Jiang, J., Ma, J., Liu, G., Cao, Y., Liu, W., Li, J., Pang, S., Kong, X., Luo, C., 2017. Degradation of sulfamethoxazole by UV, UV/H2O2 and UV/persulfate (PDS): Formation of oxidation products and effect of bicarbonate. Water Research 118, 196–207. doi:10.1016/j.watres.2017.03.054.

Zha, D., Li, Y., Wang, L., Yang, C., Lu, G., 2017. Occurrence and attenuation of pharmaceuticals and their transformation products in rivers impacted by sewage treatment plants. RSC Adv. 7 (65), 40905–40913. doi:10.1039/C7RA06852B.

Zhang, R., Yang, Y., Huang, C.-H., Li, N., Liu, H., Zhao, L., Sun, P., 2016. UV/H2O2 and UV/PDS Treatment of Trimethoprim and Sulfamethoxazole in Synthetic Human Urine: Transformation Products and Toxicity. Environmental Science & Technology 50 (5), 2573–2583. doi:10.1021/acs.est.5b05604.

Zhang, Y., Li, L., Pan, Z., Zhu, Y., Shao, Y., Wang, Y., Yu, K., 2020. Degradation of sulfamethoxazole by UV/persulfate in different water samples: Influential factors, transformation products and toxicity. Chemical Engineering Journal 379, 122354. doi:10.1016/j.cej.2019.122354.

Zhu, Y., Deng, F., Qiu, S., Ma, F., Zheng, Y., Lian, R., 2021. Enhanced electro-Fenton degradation of sulfonamides using the N, S co-doped cathode: Mechanism for H2O2 formation and pollutants decay. Journal of Hazardous Materials 403, 123950. doi:10.1016/j.jhazmat.2020.123950.