

# TRANSFORMATION PRODUCTS OF MICROPOLLUTANTS IN THE AQUATIC ENVIRONMENT: HIGHLY PREVALENT BUT COMMONLY OVERLOOKED

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## Summary

The presence of synthetic chemicals in the environment can affect both ecosystems and human health. In particular, the increasing contamination of the aquatic environment by complex mixtures of anthropogenic trace substances has become a major global concern. Once released into the environment, these compounds can undergo diverse transformation processes to form a wide range of transformation products (TPs), which are commonly unknown. Transformation inevitably alters the pattern of contamination and exposure, as new substances are formed with frequently different physicochemical properties, environmental behavior and toxicity in comparison to their precursor compounds. For instance, TPs can exhibit significantly greater persistence and mobility in the aquatic environment, posing a threat to both aquatic ecosystems and drinking water resources. Therefore, TPs need to be considered in the risk assessment and authorization process of chemicals. However, due to a combination of predictive, analytical, and regulatory challenges, TPs currently remain largely unrecognized and unregulated. By addressing these challenges, this thesis comprehensively characterizes the entry paths, occurrence, fate, and (eco)toxicological relevance of selected TPs in the aquatic system in Germany. These TPs have been largely overlooked in environmental studies and aquatic monitoring programs for decades, despite their precursors being produced and used in large quantities on a global scale.

The highly persistent and mobile substance **trifluoroacetate** (TFA) has garnered significant attention in recent years due to its diverse sources, widespread occurrence in the aquatic environment, and the lack of economically viable options to remove TFA from contaminated waters. One of the most frequently discussed diffuse sources is the formation of TFA in the atmosphere through the oxidation of volatile precursors and its subsequent scavenging from the atmosphere by wet deposition. Despite the previously reported occurrence of TFA in precipitation, the lack of recent and comprehensive data has severely limited the understanding of the significance of wet deposition as a source of TFA to the (aquatic) environment. Thus, in the present work, a nationwide field monitoring campaign covering all precipitation events over a one-year sampling period was conducted at eight sites across Germany. Samples were analyzed for TFA using ion exchange chromatography (IC) coupled to negative-ion electrospray tandem mass spectrometry (ESI-MS/MS). Of the analyzed samples, 16% exhibited TFA concentrations  $\geq 1 \mu\text{g/L}$ . The precipitation-weighted average TFA concentration of  $0.34 \mu\text{g/L}$  highlighted that wet deposition alone is responsible for approximately 0.3 to  $0.4 \mu\text{g/L}$  of TFA in surface waters in Germany. The annual wet deposition fluxes ranged from 91 to  $400 \mu\text{g/m}^2$ , with the highest fluxes observed in densely populated regions. The annual wet deposition of TFA for Germany during the observation period was estimated to be 68 t. The sampling revealed a pronounced seasonality, with the highest concentrations and wet deposition fluxes of TFA observed in summer. Pearson correlation analyses indicated that the transformation of TFA precursors in the troposphere is enhanced in summer due to

elevated concentrations of photochemically generated oxidants, primarily  $\cdot\text{OH}$ , which ultimately results in increased atmospheric TFA deposition. Overall, the study provided the first published data on TFA in precipitation in Germany since 1995/96. The derived data serves as a benchmark for future studies. In addition, it allows for the establishment of mass balances and can be used to develop models to predict the loads of TFA entering the aquatic environment from multiple sources.

The lack of robust historical data on the wet deposition fluxes of TFA also impeded long-term trend analyses. Specifically, a postulated increase in atmospheric formation and deposition of TFA due to substantial emission increases of numerous volatile TFA precursors in recent decades remained unquantified. To address this knowledge gap, archived plant samples were analyzed to evaluate the long-term temporal trends in the atmospheric deposition of TFA in Germany. A robust and highly sensitive analytical method for TFA in plant matrices was developed and validated. The method encompassed a three-step sequential extraction procedure followed by the analysis of the diluted sample extracts using IC-ESI-MS/MS. Subsequently, archived leaf samples of various tree species and sampling sites from the German Environmental Specimen Bank (observation period: 1989–2020) were analyzed for TFA. Statistical analysis revealed significant ( $p < 0.05$ ) positive trends in TFA concentrations in plant leaves, which is likely the result of both phytoaccumulation and increasing emissions of gaseous TFA precursors over the observation period. The concentrations increased by factors of up to 12 from 1989 to 2020. The highest concentrations (up to  $\sim 1,000 \mu\text{g}/\text{kg}$  dry weight) were found in Lombardy poplar leaves. Overall, the study presents the first trend analysis of TFA in biota and raises awareness of the escalating atmospheric deposition of TFA over the past three decades.

**Sulfamate** has previously been identified as a TP of the artificial sweeteners cyclamate and acesulfame in wastewater and drinking water treatment. The preliminary results indicated that sulfamate concentrations in wastewater treatment plant (WWTP) effluent are substantially higher than those of other wastewater-borne contaminants. However, despite its high global production and usage, no information was available on the sources, occurrence, and environmental significance of sulfamate in the aquatic system in Germany. To close this knowledge gap, a quantitative monitoring approach of different urban water cycle compartments was conducted. Target analysis based on IC-ESI-MS/MS revealed exceptionally high concentrations of sulfamate in wastewater (up to  $1,900 \mu\text{g}/\text{L}$ ), surface water (up to  $580 \mu\text{g}/\text{L}$ ), and finished drinking water (up to  $140 \mu\text{g}/\text{L}$ ) in Germany. Considering the limited data on short-term ecotoxicity, approximately 30% of the sulfamate concentrations detected in groundwater and surface water samples exceeded the derived predicted no-effect concentration (PNEC) of sulfamate. Therefore, the potential impact of sulfamate on the aquatic ecosystem in Germany cannot be excluded. Municipal WWTP effluent was identified as the primary source of sulfamate for the aquatic system, as its concentrations correlated positively ( $r > 0.77$ ) with the municipal wastewater tracer carbamazepine in samples from different waterbodies. Ozonation and activated

sludge experiments demonstrated that sulfamate can be formed through chemical and biological degradation of various precursors containing a sulfonamide group. Nevertheless, the transformation of precursors to sulfamate in WWTPs and receiving waters was found to be quantitatively insignificant, due to the substantial direct use of sulfamic acid as a descaling agent in domestic and industrial applications. Laboratory batch experiments, in conjunction with the findings from the sampling conducted at full-scale waterworks, demonstrated that the commonly applied drinking water treatment techniques, including ozonation and activated carbon filtration, are largely ineffective in removing sulfamate. Bank filtration was identified as the only option to efficiently eliminate sulfamate from contaminated raw water resources (removal: 62% to 99%). Overall, the study presents the first comprehensive analysis of sulfamate in the urban water cycle and suggests that there may be other high production volume inorganic chemicals that are currently overlooked in environmental studies and monitoring programs.

Despite **pantoprazole (PPZ)** being one of the most widely prescribed human pharmaceuticals globally, consistently low concentrations of this proton-pump inhibitor in environmental water samples have been documented. This can be attributed to the extensive metabolism of PPZ within the human body, with only minor amounts of the parent compound being excreted. Since environmental monitoring and risk assessment for regulatory purposes focus on the parent substances of pharmaceuticals, it was assumed that the current environmental exposure associated with the use of PPZ is considerably underestimated. In the presented thesis, 4'-O-demethyl-PPZ sulfide (M1) was identified as the most relevant PPZ metabolite for environmental analysis. This was achieved by applying reversed-phase high-performance liquid chromatography (RP-HPLC) coupled to high-resolution mass spectrometry (HRMS) to urine samples of a PPZ user, as well as to municipal wastewater. M1, which had not been investigated in previous monitoring studies, was found to be ubiquitous in WWTP influent and effluent (max.: 3 µg/L, detection frequency: 100%) as well as in surface water (max.: 1.2 µg/L; detection frequency: 97%) in Germany. Its average surface water concentration was approximately 30 times higher than that of the parent compound PPZ. Moreover, quantitative structure-toxicity relationship (QSTR) modeling indicated a lower preliminary freshwater PNEC for M1 (4.8 µg/L) compared to PPZ (28 µg/L). The analysis of archived suspended particulate matter (SPM) samples from the Rhine at Koblenz revealed that the concentrations of M1 increased significantly from 2005 to 2015 and were positively correlated with the prescription volume of PPZ. Conventional biological wastewater treatment was found to be insufficient to remove M1 (average removal: 22%). Laboratory-scale experiments and the analysis of samples taken after different treatment steps of an advanced full-scale WWTP demonstrated that post-treatment with activated carbon as well as ozonation can significantly improve the removal of M1 and PPZ during wastewater treatment, thereby reducing their release to the aquatic environment. During ozonation, a rapid oxidation of M1 was observed, accompanied by the formation of several ozonation products, which were proposed for the first time. The identity of the main ozonation TPs of M1 was

confirmed through the synthesis of reference compounds. Their detection in samples collected after the ozonation step of a full-scale WWTP demonstrated the transferability of the laboratory-scale ozonation experiments. M1 was found to be sufficiently removed from contaminated source waters (max. raw water concentration: 0.25 µg/L) by bank filtration under different redox conditions (removal  $\geq$  80 %) and by other commonly applied purification processes in drinking water production. In summary, this study revealed that the environmental exposure and risk associated with the use of PPZ have been previously underestimated, which likely extends to other human pharmaceuticals. Therefore, these findings call for more sophisticated approaches to environmental monitoring and risk assessment of pharmaceuticals that take TPs into account.

This thesis provides an in-depth understanding of the entry paths, occurrence, fate, and environmental significance of selected TPs in the aquatic system in Germany. It significantly advances our understanding of the introduction of TFA into the water cycle, by characterizing the source of wet deposition and elucidating long-term temporal trends of atmospherically deposited TFA. Additionally, the thesis gives comprehensive insights into the formation, behavior, removability, and potential (eco)toxicological risks of sulfamate, PPZ and its TPs. The thesis addresses key challenges in assessing and integrating TPs into chemical management and presents solutions to overcome these challenges. Finally, it highlights the urgent need for increased focus on TPs in research, aquatic monitoring, and regulation to safeguard the environment and human health.

## Zusammenfassung

Das Vorkommen synthetischer Chemikalien in der Umwelt kann sowohl Ökosysteme als auch die menschliche Gesundheit beeinträchtigen. Insbesondere die zunehmende Belastung der aquatischen Umwelt durch komplexe Mischungen anthropogener Spurenstoffe gibt Anlass zur Sorge. Nach ihrer Freisetzung in die Umwelt können diese Verbindungen verschiedene Transformationsprozesse durchlaufen und eine Vielzahl von Transformationsprodukten (TPs) bilden, die weitgehend unbekannt sind. Die Transformation verändert unweigerlich das Kontaminations- und Expositionsmuster, da neue Stoffe gebildet werden, die sich häufig in ihren physikalisch-chemischen Eigenschaften, ihrem Umweltverhalten und ihrer Toxizität von ihren Vorläuferverbindungen unterscheiden. So können TPs beispielsweise eine deutlich höhere Persistenz und Mobilität in der aquatischen Umwelt aufweisen, was sowohl für aquatische Ökosysteme als auch für Trinkwasserressourcen eine potenzielle Gefährdung darstellt. Daher müssen TPs bei der Risikobewertung und Zulassung von Chemikalien berücksichtigt werden. Aufgrund einer Kombination von prädiktiven, analytischen und regulatorischen Herausforderungen bleiben TPs derzeit jedoch weitgehend unerkannt und unreguliert. Um diesen Herausforderungen zu begegnen, werden in dieser Arbeit die Eintragspfade, das Vorkommen, der Verbleib und die (öko)toxikologische Relevanz ausgewählter TPs im aquatischen System in Deutschland umfassend charakterisiert. Diese TPs blieben jahrzehntelang in Umweltstudien und aquatischen Monitoringprogrammen weitestgehend unberücksichtigt, obwohl ihre Vorläufersubstanzen weltweit in großen Mengen produziert und verwendet werden.

Die sehr persistente und mobile Substanz **Trifluoracetat (TFA)** hat in den letzten Jahren aufgrund ihrer vielfältigen Quellen, ihrer weiten Verbreitung in der aquatischen Umwelt und des Mangels an wirtschaftlich vertretbaren Möglichkeiten zur Entfernung von TFA aus kontaminierten Wasserkörpern große Aufmerksamkeit erregt. Eine der am häufigsten diskutierten diffusen Quellen ist die Bildung von TFA in der Atmosphäre durch die Oxidation gasförmiger Vorläufersubstanzen und die anschließende Auswaschung von TFA aus der Atmosphäre durch nasse Deposition. Obgleich das Vorkommen von TFA im Niederschlag bekannt ist, besteht nach wie vor ein eingeschränktes Verständnis hinsichtlich der Relevanz der nassen Deposition als Quelle für TFA in der (aquatischen) Umwelt. Dies ist insbesondere auf eine unzureichende Datenbasis zurückzuführen. Daher wurde in dieser Arbeit eine bundesweite Monitoring-Kampagne an acht Standorten in Deutschland durchgeführt, die alle Niederschlagsereignisse während eines einjährigen Beobachtungszeitraums umfasste. Die Proben wurden mittels Ionenaustauschchromatographie (IC) gekoppelt mit negativer Elektrospray-Ionisation-Tandem-Massenspektrometrie (ESI-MS/MS) auf TFA untersucht. 16 % der Proben wiesen TFA-Konzentrationen  $\geq 1 \mu\text{g/L}$  auf. Die niederschlagsgewichtete mittlere TFA-Konzentration betrug  $0,34 \mu\text{g/L}$ . Dies verdeutlicht, dass allein die nasse Deposition für etwa  $0,3$  bis  $0,4 \mu\text{g/L}$  an TFA in Oberflächengewässern in Deutschland verantwortlich ist.

Die jährliche nasse Deposition lag zwischen 91 und 400  $\mu\text{g}/\text{m}^2$ , wobei die höchsten Werte in dicht besiedelten Regionen beobachtet wurden. Die jährliche nasse Deposition von TFA in Deutschland während des Beobachtungszeitraums wurde auf 68 t geschätzt. Die Probenahmen zeigten eine ausgeprägte Saisonalität, wobei die höchsten TFA-Konzentrationen und -Depositionen im Sommer beobachtet wurden. Pearson-Korrelationsanalysen deuteten darauf hin, dass die Umwandlung von TFA-Vorläufern in der Troposphäre im Sommer durch erhöhte Konzentrationen photochemisch erzeugter Oxidationsmittel, insbesondere  $\cdot\text{OH}$ , verstärkt wird, was letztlich zu einer erhöhten atmosphärischen TFA-Deposition führt. Insgesamt liefert die Studie die ersten publizierten Daten zu TFA im Niederschlag in Deutschland seit 1995/96. Die gewonnenen Daten und Erkenntnisse dienen als Referenzpunkt für zukünftige Studien. Darüber hinaus ermöglichen sie die Erstellung von Massenbilanzen und können für die Entwicklung von Modellen zur Vorhersage von TFA-Frachten, die aus verschiedenen Quellen in die aquatische Umwelt gelangen, verwendet werden.

Das Fehlen zuverlässiger historischer Daten über die nasse Deposition von TFA erschwerte auch die Analyse langfristiger Trends. So konnte die postulierte Zunahme der atmosphärischen Bildung und Deposition von TFA infolge des starken Anstiegs der Emissionen zahlreicher gasförmiger TFA-Vorläufersubstanzen in den letzten Jahrzehnten nicht quantifiziert werden. Um diese Wissenslücke zu schließen, wurden archivierte Pflanzenproben analysiert, um langfristige zeitliche Trends der atmosphärischen Deposition von TFA in Deutschland zu bestimmen. Eine robuste und hochempfindliche Analyseverfahren für TFA in Pflanzenmatrices wurde entwickelt und validiert. Die Methode bestand aus einer dreistufigen sequenziellen Extraktion und der Analyse der verdünnten Probenextrakte mittels IC-ESI-MS/MS. Anschließend wurden archivierte Blattproben verschiedener Baumarten und Probenahmestellen aus der Umweltprobenbank des Bundes (Beobachtungszeitraum: 1989–2020) auf TFA untersucht. Die statistische Analyse ergab einen signifikanten ( $p < 0,05$ ) positiven Anstieg der TFA-Konzentrationen in Blättern, der vermutlich das Ergebnis sowohl von Phytoakkumulation als auch von erhöhten Emissionen gasförmiger TFA-Vorläufersubstanzen innerhalb des Beobachtungszeitraums ist. Die Konzentrationen stiegen zwischen 1989 und 2020 um einen Faktor von bis zu 12 an, wobei die höchsten Konzentrationen (bis zu  $\sim 1.000 \mu\text{g}/\text{kg}$  Trockengewicht) in den Blättern der Schwarz-Pappel gefunden wurden. Insgesamt stellt die Studie die erste Trendanalyse von TFA in Biota dar und macht auf die starke Zunahme der atmosphärischen Deposition von TFA in den letzten drei Jahrzehnten aufmerksam.

**Sulfamat** wurde in der Vergangenheit als TP der künstlichen Süßstoffe Cyclamat und Acesulfam in der Abwasser- und Trinkwasseraufbereitung identifiziert. Die vorläufigen Ergebnisse wiesen darauf hin, dass die Sulfamatgehalte im Abwasser kommunaler Kläranlagen wesentlich höher sind als die anderer abwasserbürtiger Schadstoffe. Trotz der weltweit hohen Produktion und Verwendung von Sulfamat waren jedoch keine Informationen über die Quellen, das Vorkommen und die toxikologische Bedeutung von

Sulfamat in deutschen Gewässern verfügbar. Um diese Wissenslücke zu schließen, wurde ein quantitatives Monitoring verschiedener Kompartimente des urbanen Wasserkreislaufs durchgeführt. Die Analyse mittels IC-ESI-MS/MS offenbarte außergewöhnlich hohe Gehalte von Sulfamat in Abwasser (bis zu 1.900 µg/L), Oberflächenwasser (bis zu 580 µg/L) und Trinkwasser (bis zu 140 µg/L) in Deutschland. In Anbetracht der begrenzten ökotoxikologischer Daten überstiegen etwa 30 % der in Grundwasser- und Oberflächenwasserproben nachgewiesenen Sulfamatkonzentrationen die abgeleitete PNEC-Konzentration (PNEC: abgeschätzte Nicht-Effekt-Konzentration) von Sulfamat. Daher können potenzielle Effekte von Sulfamat auf das aquatische Ökosystem abwasserbeeinflusster Gewässer in Deutschland nicht ausgeschlossen werden. Kommunale Kläranlagenabwässer wurden als Hauptquelle von Sulfamat für das aquatische System identifiziert, da ihre Konzentrationen positiv ( $r > 0,77$ ) mit dem kommunalen Abwassertracer Carbamazepin in Proben aus verschiedenen Wasserkörpern korrelierten. Ozonungs- und Belebtschlammversuche bestätigten, dass Sulfamat beim chemischen und biologischen Abbau verschiedener Vorläufersubstanzen, die eine Sulfonamidgruppe enthalten, gebildet werden kann. Die Umwandlung von Vorläufersubstanzen zu Sulfamat in Kläranlagen und Gewässern stellte sich jedoch als quantitativ unbedeutend heraus, was auf die direkte Verwendung von Sulfamidsäure als Entkalkungsmittel in Haushalt und Industrie zurückzuführen ist. Laborversuche in Verbindung mit den Ergebnissen von Probenahmen in Wasserwerken zeigten, dass die meisten üblicherweise eingesetzten Trinkwasseraufbereitungstechniken, einschließlich Ozonung und Aktivkohlefiltration, nicht in der Lage sind, Sulfamat zu entfernen. Die Uferfiltration erwies sich als einzige Möglichkeit, Sulfamat effizient aus kontaminierten Rohwasserressourcen zu entfernen (Entfernung: 62 % bis 99 %). Insgesamt stellt die Studie die erste umfassende Analyse von Sulfamat im urbanen Wasserkreislauf dar und deutet darauf hin, dass möglicherweise weitere anorganische Chemikalien mit hohen Produktionsvolumina existieren, die derzeit in Umweltstudien und Überwachungsprogrammen übersehen werden.

Obwohl **Pantoprazol (PPZ)** eines der weltweit am häufigsten verschriebenen Humanarzneimittel ist, wurden in Gewässern nur sehr geringe Konzentrationen dieses Protonenpumpenhemmers nachgewiesen. Dies ist darauf zurückzuführen, dass PPZ im menschlichen Körper in hohem Maße metabolisiert wird und nur geringe Mengen der Ausgangsverbindung ausgeschieden werden. Da sich das Umweltmonitoring und die Risikobewertung für regulatorische Zwecke auf die Muttersubstanzen von Arzneimittelwirkstoffen konzentrieren, wurde angenommen, dass die derzeitige aus der Verwendung von PPZ resultierende Umweltexposition erheblich unterschätzt wird. In der vorliegenden Arbeit wurde 4'-O-Demethyl-PPZ-Sulfid (M1) als der für Umweltstudien relevanteste PPZ-Metabolit identifiziert. Dies wurde durch die Analyse von Urinproben eines PPZ-Konsumenten und Abwasserproben mittels Umkehrphasen-Hochleistungsflüssigkeitschromatographie (RP-HPLC) in Verbindung mit hochauflösender Massenspektrometrie (HRMS) erreicht. M1, das bisher in Studien keine Berücksichtigung

fand, war sowohl im Zu- und Ablauf der Kläranlage (max.: 3 µg/L, Nachweishäufigkeit: 100 %) als auch in Oberflächengewässern (max.: 1,2 µg/L, Nachweishäufigkeit: 97 %) in Deutschland weit verbreitet. Die mittlere Konzentration in Oberflächengewässern war etwa 30-mal höher als die der Ausgangsverbindung PPZ. Darüber hinaus ergab die Modellierung mittels quantitativer Struktur-Toxizitäts-Beziehung (QSTR) einen niedrigeren vorläufigen Süßwasser-PNEC für M1 (4,8 µg/L) im Vergleich zu PPZ (28 µg/L). Die Analyse von archivierten Schwebstoffproben aus dem Rhein bei Koblenz offenbarten, dass die Konzentrationen von M1 zwischen 2005 und 2015 deutlich angestiegen sind und positiv mit der Menge an PPZ korrelierten. Die konventionelle biologische Abwasserbehandlung erwies sich als unzureichend, um M1 ausreichend zu entfernen (durchschnittliche Entfernung: 22%). Laborexperimente und die Analyse von Proben nach verschiedenen Reinigungsstufen einer Kläranlage zeigten, dass die Behandlung mit Aktivkohle und die Ozonung die Elimination von M1 und PPZ deutlich verbessern und damit deren Freisetzung in die aquatische Umwelt reduzieren können. Während der Ozonung wurde eine schnelle Oxidation von M1, aber auch die Bildung mehrerer bisher nicht beschriebener Ozonungsprodukte beobachtet. Die Identität der wichtigsten Ozonungsprodukte wurde durch die Synthese von Referenzsubstanzen bestätigt. Ihr Nachweis in Proben, die nach der Ozonung in einer großtechnischen Kläranlage genommen wurden, bestätigte die Übertragbarkeit der Ergebnisse des Laborversuchs. Ferner konnte gezeigt werden, dass M1 durch Uferfiltration unter verschiedenen Redoxbedingungen (Entfernung  $\geq 80\%$ ) und andere üblichen Trinkwasseraufbereitungsverfahren aus kontaminiertem Rohwasser (max. Konzentration: 0,25 µg/L) entfernt werden kann. Zusammenfassend konnte gezeigt werden, dass die aus der PPZ-Applikation resultierende Umweltexposition erheblich unterschätzt wird. Dies dürfte auch für andere Humanarzneimittel zutreffen. Für das Umweltmonitoring und die Risikobewertung von Arzneimitteln sind daher Ansätze erforderlich, die neben der Muttersubstanz auch TPs berücksichtigen.

Diese Dissertation liefert eine umfassende Untersuchung der Eintragspfade, des Vorkommens, des Verbleibs sowie der Umweltrelevanz ausgewählter TPs im aquatischen System in Deutschland. Die Arbeit trägt wesentlich zum Verständnis des Eintrags von TFA in den Wasserkreislauf bei, indem sie die Quelle der nassen Deposition charakterisiert und langfristige zeitliche Trends des atmosphärisch deponierten TFA aufzeigt. Darüber hinaus liefert sie belastbare Erkenntnisse über die Bildung, das Verhalten, die Entfernbarkeit und die potenziellen (öko)toxikologischen Risiken von Sulfamat, PPZ und dessen TPs. Es werden die wichtigsten Herausforderungen bei der Bewertung und Integration von TPs in das Chemikalienmanagement aufgezeigt und Lösungsansätze zu deren Bewältigung präsentiert. Die Dissertation verdeutlicht, dass eine stärkere Berücksichtigung von TPs in der Forschung, der Gewässerüberwachung sowie der Regulatorik erforderlich ist, um den Schutz der Umwelt und der menschlichen Gesundheit zu gewährleisten.

# 1 General Introduction

## 1.1 Background

Presently, over 350,000 chemicals and mixtures of chemicals have been registered for production and use (Wang et al., 2020b). Many of these compounds designed to offer improvements in household, agriculture, industry or medical treatment can enter, disperse and persist in various environmental compartments. In particular, the contamination of the aquatic environment by anthropogenic trace substances – commonly referred to as micropollutants – has become a growing concern of global relevance (Bhatt et al., 2022; Kong et al., 2015; Ternes, 2007).

Although they generally occur at low concentrations (typically in the nanograms to micrograms per liter), the increasing contamination of aquatic systems with micropollutants is considered one of the major environmental problems facing humanity (Schwarzenbach et al., 2006). Health risks are commonly attributed to an often lifelong, sometimes even multigenerational exposure of organisms to specific substances (Yang et al., 2022) as well as combination effects of compound mixtures (Shao et al., 2019).

Once released into the environment, micropollutants are subject to degradation. However, the degradation of a micropollutant generally does not lead to its rapid and complete mineralization, i.e. its conversion to inorganic molecules and ions. Instead, numerous and frequently unknown transformation products (TPs) may be formed. Thus, transformation intrinsically alters the contamination and exposure pattern as new substances are released with often vastly different physicochemical properties and environmental behavior in comparison to the original compound. For instance, TPs can be much more persistent and mobile than their associated precursor (parent) compounds, implying a higher likelihood for long-lasting and widespread detrimental effects (Albers et al., 2023; Cousins et al., 2019; Zahn et al., 2019). Moreover, environmental concentrations of TPs are frequently exceeding those of their precursors (Buttiglieri et al., 2009; Funke et al., 2015; Kolpin et al., 2000). Although toxicity is only rarely increased as a result of the induced structural changes, multiple studies have demonstrated that certain TPs can be as toxic or even more toxic than their precursors (e.g., Han et al., 2019; Wang and Lin, 2012). Therefore, TPs need to be considered in the risk assessment and authorization process of chemicals to safeguard the environment and human health. However, due to a combination of predictive, analytical, and regulatory challenges, TPs remain largely unrecognized and unregulated.

This thesis aims in attaining an in-depth understanding of the entry pathways, occurrence, fate, and (eco)toxicological risk of selected TPs in the aquatic system. The three TPs under investigation, **trifluoroacetate**, **sulfamate**, and **4'-O-demethyl-pantoprazole sulfide** share a common feature: despite their precursors being produced and utilized in **substantial quantities** on a global scale, they have been **largely overlooked** in environmental studies and monitoring programs for decades.

## 1.2 Sources and Pathways of TPs in the Aquatic Environment

### 1.2.1 Overview

At present, about one-third of the Earth's geographically and temporally accessible runoff is withdrawn for agricultural, industrial, and domestic purposes (FAO, 2021).<sup>1</sup> Most of these activities result in the pollution of water resources by a broad spectrum of micropollutants<sup>2</sup> including pharmaceuticals, personal care products, pesticides, surfactants, hormones, flame retardants, artificial sweeteners, corrosion inhibitors, and many others.

Micropollutants can enter the aquatic system via both point and diffuse sources. Important point sources include municipal wastewater treatment plant (WWTP) discharges and combined sewer overflows, commercial and industrial effluents (e.g., hospitals, manufacturing plants), and waste disposal sites (e.g., landfills, industrial surface impoundments, agricultural waste lagoons). Diffuse sources occur over broader geographical scales and involve urban runoff, sewage system leakages, managed aquifer recharge using reclaimed water, atmospheric deposition and the leaching from soils treated with agrochemicals, biosolids, and animal wastes (Boxall, 2009).

Once in the environment, micropollutants can be transported between several environmental compartments. The distribution of a micropollutant depends on numerous factors and processes such as its partitioning behavior (e.g., sorption affinity to sludge, soil, and sediment), environmental factors (e.g., meteorology, hydrology, biogeography), and land use (Boxall, 2009). Either directly or indirectly, surface waters are a major receiving media for micropollutants. Contamination of groundwater bodies can occur through infiltration or groundwater-surface water interaction (Lambropoulou and Nollet, 2014).

Along the path of distribution and transformation of precursors, a wide range of TPs can be formed. As such, transformation processes represent the sources of TPs (**Figure 1.1**). Since the formation of a TPs is inevitably connected to the release and presence of precursor, TPs and their precursors often coexist in the aquatic environment (Brezina et al., 2017; Gracia-Lor et al., 2014; Scheurer et al., 2012b). However, given that TPs may have different physicochemical properties in comparison to their associated precursors, the temporal and spatial scales of their exposure can vary substantially. For instance, TPs of pesticides are frequently found in groundwater bodies, while their precursors may be absent or less abundant in groundwater. This can be explained by the lower sorption tendency and higher persistence of many pesticide TPs, leading to a high leaching potential and mobility in the unsaturated and saturated zone (Buttiglieri et al., 2009; Kiefer et al., 2019; Menger et al., 2021).

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<sup>1</sup> Runoff was defined as the sum of surface runoff, storm interflow, and groundwater runoff. Earth's geographically and temporally accessible runoff: 12,500 km<sup>3</sup>/a (Postel et al., 1996).

<sup>2</sup> In the present work, the term *micropollutants* encompasses transformation products (TPs) and their precursor compounds.

The transformation that a given compound undergoes at various stages of its life cycle is controlled by its structural affinity for specific transformation processes and the environmental conditions it is exposed to as a result of its entry paths and transport behavior. Many contaminants are transformed by a combination of processes that proceed at different rates and may produce different TPs.

The transformation of micropollutants in the environment involves biotic and abiotic processes. As these processes are also actively used for micropollutant removal in engineered systems, the formation of TPs is not restricted to natural environments but also extends to technical water treatment.

## 1.2.2 Biotic formation of TPs in the Environment and in Water Treatment

### Biotransformation of micropollutants by microorganisms

Biotransformation (biodegradation) is the breakdown of molecules by microorganisms, such as bacteria and fungi, which enables the continuous recycling of biologically essential elements within the Earth's biogeochemical cycle. It is generally recognized as the mass-wise most dominant degradation route for many micropollutants in wastewater treatment (Desiante et al., 2022) and in surface waters (Coll Mora et al., 2020).

The biotransformation of micropollutants can be divided into enzyme-catalyzed metabolic and co-metabolic reactions. Through metabolic reactions, compounds are metabolized by microbes as a source for energy and nutrients. When biotransformation occurs alongside the metabolic transformation of a primary substrate (e.g., natural organic matter) and does not provide a significant source of energy or nutrients to microorganisms, the process is referred to as co-metabolism. Direct metabolism of micropollutants as growth substrates results in the enrichment of specialized microorganisms and often takes place at higher concentrations (Benner et al., 2013; Dionisi, 2014), when easier to use nutrient sources are scarce. If the concentration of natural growth substrate is several magnitudes higher than of the xenobiotic (e.g., in raw wastewater), it is assumed that biotransformation of these substances is mainly co-metabolic (Clara et al., 2005).

During the decomposition of substances in water, dissolved and bound oxygen is consumed, resulting in shifts in the redox system, which essentially determines the nature and extent of microbial degradation processes. In the redox reactions, the available organic substances represent the electron donors, while reducible water constituents ( $O_2$ ,  $NO_3^-$ ,  $NO_2^-$ ,  $SO_4^{2-}$ ) and solid phases ( $Fe^{3+}$  and  $Mn^{4+}$  oxides and hydroxides) serve as electron acceptors (Hägglom et al., 2000). Under aerobic conditions, microorganisms mostly use molecular oxygen as the electron acceptor to accelerate the biodegradation process. Aerobic conditions are often considered more effective for the removal of a wide variety of organic contaminants, although certain micropollutants have shown to be eliminated more efficiently under anaerobic conditions (Liu et al., 2013; Storck et al., 2012), which are frequent in certain environmental compartments such as sediments (Bradley et al., 2001; Sánchez-Andrea et al., 2011) and aquifers (Knoll et al., 2020).

Biological wastewater treatment typically consists of aerobic and anaerobic stages for the removal of organic compounds and organically bound nitrogen. Due to the higher biological activity in the aerobic stage, removal efficiencies of organic compounds, including micropollutants, are generally higher in aerobic environments than under anaerobic conditions (Falås et al., 2016). However, an enhanced biological removal when applying a combination of different redox conditions and substrate concentrations has been found for certain micropollutants (Di Marcantonio et al., 2020; Falås et al., 2016). Similarly, several organic micropollutants present in treated wastewater have been found to be biodegraded during bank filtration and soil-aquifer treatments, which are often characterized by low substrate availability and sequential redox transitions along the soil and aquifer passage (Amy and Drewes, 2007; Regnery et al., 2016). Since many microorganisms can only develop within a narrow range of redox potentials, the degradation of parent compounds and thus the formation of TPs is dependent on the presence of respective redox states.

### **Biotransformation of micropollutants by vertebras**

This category includes TPs of xenobiotics, such as pharmaceuticals, pesticides, and food additives, that have been produced in humans and other vertebra as a result of metabolism (metabolites). These TPs are formed through enzyme-mediated chemical processes which convert non or poorly excretable substances into readily extractable substances. Phase I metabolism consists of oxidation, reduction or hydrolysis reactions and aims to convert lipophilic substances into more hydrophilic molecules by introducing or unmasking polar functional groups, such as amino ( $-NH_2$ ), hydroxyl ( $-OH$ ), and carboxyl ( $-COOH$ ) groups, thereby creating primary metabolites that are accessible to subsequent biotransformation steps. Phase II metabolism involves conjugation by coupling the parent compound, if polar groups are already present, or phase I metabolites to a polar endogenous molecule, such as glucuronic acid, sulfuric acid, acetic acid, and amino acids. Finally, the water-soluble conjugates are removed from the cell by transport proteins and excreted via the renal or bile route (Hodgson, 2012; Khetan and Collins, 2007; Wermuth, 2003).

Generally, these reactions are beneficial for the organism as they prevent the accumulation of lipophilic and potentially harmful exogenous chemicals within the body. However, in certain cases, they might transform a substance into a more reactive form, a phenomenon known as bioactivation or toxication (Gupta, 2018). For pharmaceuticals and pesticides which act as prodrugs (e.g., metamizole, ramipril) and propesticides (e.g., indoxacarb, pinoxaden), the *in vivo* enzymatic and/or chemical transformation of an inactive parent compound into a biologically active TP is explicitly wanted – often for the purpose of improved bioavailability and selectivity – and is part of their intended mode of action (Jeschke, 2016; Rautio et al., 2018).

### 1.2.3 Abiotic formation of TPs in the Environment and in Water Treatment

Abiotic transformation processes are due to chemical reactions that are not catalyzed by enzyme systems. They include chemical hydrolysis, oxidation–reduction, and photochemical reactions.

Hydrolysis is the reaction of a water-soluble compound with water, leading to the cleavage of certain moieties. One part of the parent compound gains the  $H^+$  ion of the water molecule, while the other part gains the  $OH^-$  ion. Since water is a ubiquitous reactant in the aquatic environment and hydrolyzable groups (e.g., amides, anhydrides, esters, carbamates, and imides) are present in many synthetic substances (Tebes-Stevens et al., 2017), hydrolysis is recognized as an important transformation process for dissolved organic micropollutants in water (Jiang et al., 2010; Katagi, 2002; Zhong et al., 2022). Hydrolysis of many micropollutants has been found to occur at slower rates at neutral pH, whereas it is faster under basic and acidic conditions (Białk-Bielińska et al., 2012; Mitchell et al., 2015; Su et al., 2016). Furthermore, the pattern of formed TPs can also be strongly pH-dependent (Hirte et al., 2016).

Oxidation is the chemical process in which a chemical entity loses electrons to an oxidizing agent (oxidant) and is thereby oxidized. Analogously, reduction is the process by which a chemical entity gains electrons from a reducing agent (reductant) and is thereby reduced. In the aquatic environment, redox processes play an essential role in metabolic processes, the mobilization and sequestration of metals, and the transformation of organic and inorganic compounds. Although the conditions leading to oxidation or reduction of compounds are created by living organisms, the redox reactions in natural systems, including soils, sediments, rivers, lakes, and aquifers, may proceed without further mediation by organisms (Mohatt et al., 2011; Tratnyek et al., 2011).

Photodegradation is a major transformation process of organic compounds in the atmosphere, on soil surfaces and in the surface layer of water bodies. For instance, photodegradation is regarded as a major degradation pathway for the non-steroidal anti-inflammatory drug diclofenac in water bodies (Poiger et al., 2001; Zhang et al., 2017). Photochemical reactions can be divided into direct and indirect photolysis. In direct photolysis, a molecule absorbs photons, which leads to its break-up (Carlson et al., 2015; Mathon et al., 2021). In indirect photolysis, degradation occurs via the reaction of the compound with a reactive species generated by photosensitizers, the latter having the ability to absorb radiation to reach an excited state. Important photosensitizers within the aquatic system are chromophoric dissolved organic matter (CDOM), nitrate and nitrite (Vinge et al., 2020). Irradiated CDOM yields excited triplet state chromophoric dissolved organic matter ( $^3CDOM^*$ ), singlet oxygen ( $^1O_2$ ), and hydroxyl radicals ( $\cdot OH$ ) (al Housari et al., 2010; Canonica et al., 2006; Coelho et al., 2011). Nitrate and nitrite absorb light to produce  $\cdot OH$  and other reactive oxygen and nitrogen species (Mack and Bolton, 1999).

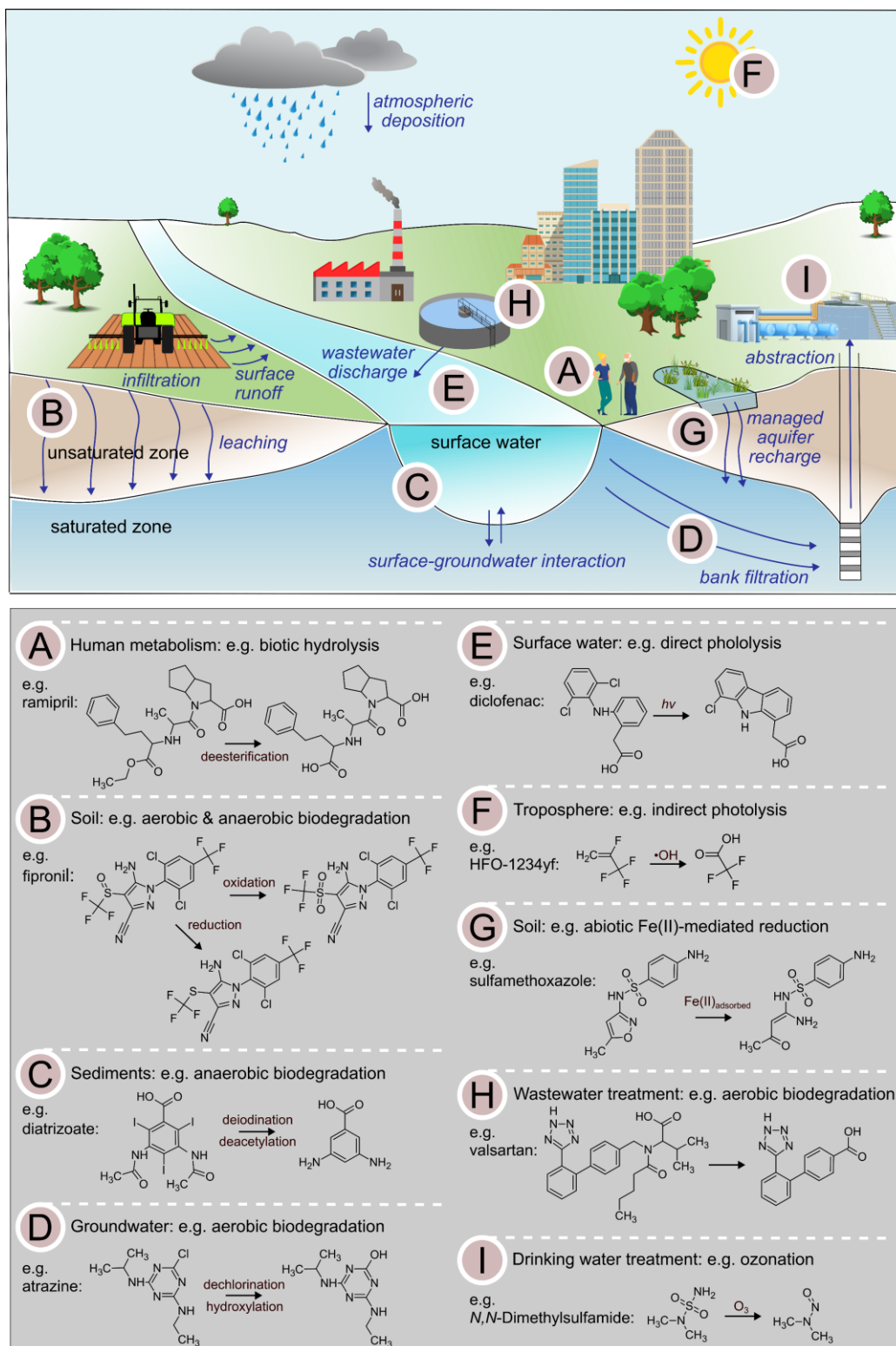
Oxidants such as ozone ( $O_3$ ), nitrate radicals ( $NO_3\cdot$ ), and  $\cdot OH$  also determine the ability of the atmosphere to process organic and inorganic pollutants. Tropospheric  $O_3$  is mainly produced by photochemical reactions of anthropogenic and naturally emitted volatile

organic compounds (VOCs) and nitrogen oxides (NO<sub>x</sub>) (Li et al., 2023). The NO<sub>3</sub><sup>•</sup> is predominantly derived from the oxidation of NO<sub>2</sub> by O<sub>3</sub> and only occurs in the nighttime due to its rapid photolysis in sunlight and its reaction with NO (Khan et al., 2015). The primary source of tropospheric <sup>•</sup>OH involves the photolysis of O<sub>3</sub> by solar ultraviolet (UV) radiation, in which the generated excited singlet oxygen atom reacts with water to form <sup>•</sup>OH (Chua et al., 2023). <sup>•</sup>OH is the most important cleansing agent of the lower atmosphere, providing the main sink for many greenhouse gases, such as methane and hydrofluorocarbons (HFCs) (Thompson et al., 2024).

Oxidation processes including ozonation, chlorination and advanced oxidation techniques (AOPs) are commonly used in water treatment for enhanced micropollutant removal and disinfection purposes. In ozonation, micropollutants react with either O<sub>3</sub> or <sup>•</sup>OH, resulting in the oxidative degradation of the precursor compound (Sonntag and von Gunten, 2012). O<sub>3</sub> is a selective oxidant and predominantly reacts with electron-rich organic moieties, notably activated aromatic compounds (phenols, anilines, and polycyclic aromatics), olefins, and deprotonated amines. <sup>•</sup>OH, on the other hand, is a non-selective oxidant showing diffusion-limited reactivity with almost all organic moieties, even C–H bonds. Hence, hydroxyl radicals transform various types of micropollutants with similar efficiency (Lee and von Gunten, 2010).

AOPs are characterized by the deliberate generation of highly reactive oxidants in diverse reaction systems. AOPs are primarily based on the *in situ* generation of <sup>•</sup>OH, but also encompass processes using other oxidizing species, such as sulfate or chlorine radicals (Bolton et al., 1996, 2001). The <sup>•</sup>OH-based non-photochemical AOPs include the generation of <sup>•</sup>OH in the absence of light either by ozonation or by reacting ferrous ion (Fe<sup>2+</sup>) and hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>) in acidic medium (i.e., Fenton reaction). In ozonation, OH radicals are produced by carrying out the reaction at elevated pH, by combining ozonation with H<sub>2</sub>O<sub>2</sub>, or by conducting the ozonation in the presence of a catalyst. In photochemical AOPs, UV radiation is used along with H<sub>2</sub>O<sub>2</sub>, O<sub>3</sub>, and Fe<sup>+2</sup> to generate <sup>•</sup>OH (Miklos et al., 2018; Sharma et al., 2018).

Conventional ozonation and AOPs can remove a wide variety of micropollutants (Kanakaraju et al., 2018; Malakootian et al., 2020; Pereira et al., 2012). Therefore, they provide an effective and non-selective attenuation option for biologically recalcitrant micropollutants present in aqueous media. However, oxidative treatments can also act as sources for potentially hazardous disinfection byproducts (DBPs) from inorganic precursors and naturally organic matter (NOM). Prominent examples of DBPs include the formation of the suspected human carcinogen bromate during ozonation (von Gunten, 2003) and the formation of halogenated DBPs during chlorination (Mazhar et al., 2020). Moreover, since oxidative treatments usually do not achieve complete mineralization, the oxidation of micropollutants can lead to the formation of hazardous TPs (Andrzejewski et al., 2008; Parker et al., 2017; Wang and Wang, 2021). In consequence, biologically-active post-treatment, mainly sand filtration or biological activated carbon (BAC) filtration, is commonly applied after ozonation to eliminate readily biodegradable and potentially harmful ozonation products (Brunner et al., 2019; Reungoat et al., 2012).



**Figure 1.1.** Examples of micropollutant transformation processes in different compartments including selected TPs from the transformation reactions. Intermediates are not shown. References: A: Meisel et al. (1994); B: Singh et al. (2021); C: Redeker et al. (2014); D: Arar et al. (2023); E: Kovacic et al. (2016); F: Hurley et al. (2008); G: Mohatt et al. (2011); H: Nödler et al. (2013); I: Schmidt and Brauch (2008).

### 1.3 Implications of TPs for Environmental and Human Health

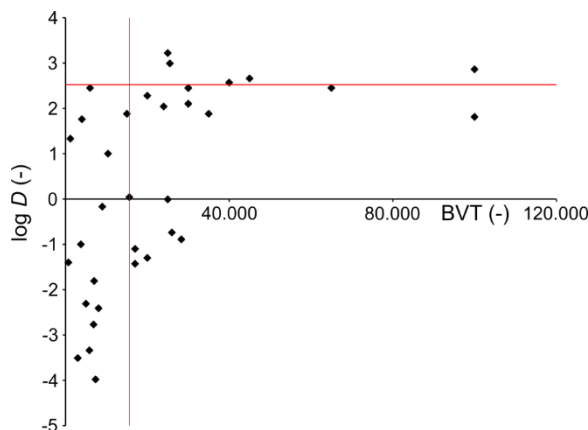
The environmental and human health risk of chemicals is a function of hazard and exposure. The effect of a biologically active compound is typically the result of the interaction between a particular moiety of the molecule and a receptor. If the biologically active moiety (toxophore) remains intact during transformation, it is likely that the TP shares the identical mode of action and therefore has similar toxicity as the precursor compound. This means that the quantitative reduction in concentration of a chemical is an inadequate surrogate for characterizing its environmental fate and ecological risk (Cwiertny et al., 2014). Thus, chemicals cannot be viewed in isolation from their TPs and the effects from parent compounds and their TPs must be considered in an additive manner (Boxall, 2009). Transformation processes may also result in the formation of TPs with even higher toxicity (Han et al., 2019; Tian et al., 2021; Wang et al., 2020a; Wang and Lin, 2012). For instance, Schmidt and Brauch (2008) showed that *N,N*-dimethylsulfamide, a metabolite of the fungicides tolylfluanid and dichlofluanid, acts as a precursor for the carcinogenic *N*-nitrosodimethylamine (NDMA), which can be formed during the ozonation of *N,N*-dimethylsulfamide contaminated raw waters.

Moreover, synergistic effects of compound mixtures – although previous studies have indicated that they are rare – can enhance overall toxicity (Martin, 2023). TPs may also exhibit unexpected effects towards non-target organisms or contribute to overall mixture toxicity through nonspecific intercalation of chemicals in biological membranes (i.e., baseline toxicity) (Escher et al., 2002), even if the specific activity of the parent compound has already vanished (Neuwoehner et al., 2010).

In addition to changes in toxicity, transformation often results in the formation of substances with lower molecular weight, increased polarity, and higher water solubility. As a result, TPs often exhibit much higher mobility, and sometimes higher persistence, in the environment compared to their precursors (e.g., Kiefer et al., 2019). TPs that are persistent in the environment and mobile in the aquatic environment are of particular concern because these intrinsic substance properties facilitate their rapid and widespread distribution as well as their accumulation in the water cycle (Hale et al., 2020; Hale et al., 2022; Neuwald et al., 2022).

Furthermore, many commonly applied near-natural (e.g., bank filtration) and technical water treatment processes have been found to be inappropriate to remove many persistent and mobile substances, even when advanced treatment methods, such as ozonation and activated carbon filtration, are applied (Gollong et al., 2022; Scheurer et al., 2016; Scheurer et al., 2017; Tang and Mao, 2023). For instance, based on the results of a standardized test for the removal of organic micropollutants with activated carbon, it was found that all of the tested substances with a  $\log D \leq 2.5$  at pH 8 could not be economically removed from contaminated water using activated carbon filtration (Nödler et al., 2018). In this test, removal of a substance is considered economic, if after 15,000 bed volumes treated (BVT), the concentration of the substance in the effluent does not exceed 10% of the concentration in the influent (i.e.,  $c/c_0 \leq 10\%$ ) (Happel et al., 2009). This

illustrates the generally low affinity of polar micropollutants for adsorption onto activated carbon, resulting in a poor efficiency of activated carbon filtration in removing these substances from contaminated raw waters.



**Figure 1.6.** Bed volumes treated (BVT) at  $c/c_0 = 10\%$  and  $\log D$  (calculated with ACD/pKa/logP GALAS model; ACD/Percepta) at pH 8 of various micropollutants. Vertical red line: 15,000 BVT, representing 30 m<sup>3</sup> of treated water per kg of activated carbon. Horizontal red line:  $\log D$  2.5. The  $\log D$  is a pH-dependent measure of lipophilicity. The lower the value, the more hydrophilic the compound.

Several studies have shown higher bioaccumulation potential of TPs in comparison to their parent compounds (Andrzejczyk et al., 2020; Arnnok et al., 2017; Fu et al., 2020). One example is the antibacterial and antifungal agent triclosan, which undergoes partial biotransformation under aerobic conditions to the more lipophilic methyl-triclosan during wastewater treatment and after land application of biosolids (Chen et al., 2011; Lozano et al., 2013). Recent studies have also highlighted the importance of bioaccumulation of ionic and ionizable chemicals, which differs from the traditional concept of bioaccumulation of non-polar substances, which is primarily driven by phospholipid partitioning. For example, the accumulation and elimination of per- and polyfluoroalkyl substances (PFAS) in animals and humans was found to be largely due to interactions of PFAS with proteins, including organic anion transporters, fatty acid binding proteins, and serum proteins such as albumin (Bangma et al., 2022). Similarly, pharmaceutical TPs with low affinity for membrane lipids have been shown to bind strongly to blood proteins (Kowalska et al., 2021; Maculewicz et al., 2022). Certain TPs, after being taken up through carrier-protein mediated active processes or mass flow/diffusion driven passive processes, were found to be highly accumulative in vascular plants (e.g., trifluoroacetate; see: Lan et al., 2020; Zhang et al., 2019a). This could result in chronic dietary exposure of animals and humans to these compounds.

In summary, transformation processes can affect both the environmental exposure to compounds and their toxicity. Consequently, TPs need to be included in the process of risk assessment and authorization of chemicals. However, TPs are still severely underrepresented in environmental and human health assessments and therefore remain largely unrecognized and unregulated. This can be attributed to a combination of predictive, analytical, and regulatory challenges, which are characterized in the following.

## 1.4 Predictive Challenges

In-depth investigations of degradation pathways, syntheses of the identified TPs, environmental monitoring, and (eco)toxicity testing are key elements in the environmental and human risk assessments of chemicals. However, given the vast quantity of synthetic precursor compounds and the even higher number of potential TPs arising from them, such efforts are only viable for selected case studies. To minimize financial and temporal expenses, computational tools and simple screening tests are commonly applied. They aim to identify and prioritize TPs needing further experimental investigation as estimates of their exposure and effects indicate that they are likely to contribute to the overall risk of a chemical (Escher and Fenner, 2011; Gassmann, 2021; Johannessen and Parnis, 2021). Tiered approaches allow for the gradual identification of the exposure and toxicity of TPs (Kern et al., 2010; Michel et al., 2022). For example, tier I could encompass literature data, conservative estimations of exposure assessed based on an estimation of the used amount and *in silico* methods to identify TPs that might be toxic, while tier II provides a further assessment of positive candidates at tier I. For instance, Melin et al. (2020) recently presented a hierarchization methodology to rank pesticides and to select metabolites to be monitored in the urban water cycle by combining data on the use (sale and type of use), toxicity, and environmental fate of the parent compounds.

Several *in silico* tools for predicting reaction pathways and TP formation have been developed. Most existing tools focus on biotransformation as the key degradation pathway, such as *enviPath* (Wicker et al., 2016) and *BioTransformer* (Djombou-Feunang et al., 2019). Predictive approaches covering abiotic transformation processes, such as the reaction of ozone with organic compounds in aqueous solution (Lee et al., 2017), are less common. Knowledge-based approaches take expert knowledge on the basis of sets of transformation rules into account while machine learning approaches estimate probability on the basis of empirical data (Wicker et al., 2010).

The toxicity of a substance is often predicted based on its physicochemical properties such as partitioning coefficients and environmental half-lives. *In silico* methods based on (quantitative) structure-activity relationship ((Q)SAR) modeling as well as read-across extrapolations are used to estimate the toxicological effects of TPs with insufficient experimental data (Anagnostopoulou et al., 2022; Escher and Fenner, 2011; Freeling et al., 2019; Neuwoehner et al., 2010). In read-across, reference points or points of departure for hazard characterization of untested substances are derived from the available experimental data for structurally related compounds, which are assumed to share a similar mode of action (Benfenati et al., 2019). For instance, Löffler et al. (2023) evaluated the structural similarity between TPs and their respective antimicrobial parent compounds using 2D and 3D measures. Above a certain structural similarity threshold, a similar mode of action was assumed, and the toxicity endpoints of the respective parent compound were used for risk assessment purposes.

In recent years, omics-based techniques have been increasingly applied in toxicology to characterize and quantify the molecular and biochemical changes in cells, tissues, and

organisms when being exposed to chemicals. Omics approaches can measure effects across a range of biological pathways simultaneously, allowing for high-throughput toxicity screening. Moreover, they can be used to investigate the mode of action (MOA) of a chemical and allow for the characterization of dose-response relationships and the evaluation of joint effects of environmental mixtures (Buesen et al., 2017; Sauer et al., 2017; Zhang et al., 2023).

It is important to note that prediction tools require high-quality training data for structurally diverse chemicals. However, findable, accessible, interoperable, and reusable (FAIR) data about TPs and pathways are still scarce (Palm et al., 2023). This becomes also apparent by the minor fraction (0.006%) of TPs ( $n = 6,860$ ) within the current PubChem database of 118 million individual compounds (PubChem, 2024).

## 1.5 Analytical Challenges

The elucidation of degradation pathways as well as the identification and quantification of TPs in environmental samples requires the use of advanced analytical protocols and methods. High-performance liquid chromatography (HPLC) coupled to electrospray ionization (ESI) tandem mass spectrometry (MS/MS) has become one of the preferred techniques for the quantitative analysis of a broad suite of compounds in aqueous samples as well as in extracts of soils, sediments, biota, and other environmental matrices. Due to their often polar and ionic nature, TPs are commonly not amenable to prevalent sample preparation techniques such as solid-phase extraction (SPE) as well as gas chromatography (GC) and reversed-phase (RP) HPLC analysis. As a result, other techniques have been applied for the enrichment and chromatographic separation of hydrophilic neutral analytes and charged compounds. For instance, vacuum-assisted evaporative concentration has been used as a non-selective sample pretreatment method of non-volatile and polar substances in aqueous samples (Köke et al., 2018; Mechelke et al., 2019; Schorr et al., 2023). Another technique to enhance the range of compounds that can be enriched in water samples involves the combination of SPE materials with different retention mechanisms (Huntscha et al., 2012; Köke et al., 2018; Zahn et al., 2016).

Ion chromatography (IC) has been successfully employed for trace analysis of charged substances in aqueous samples (Bruzzoniti et al., 2019; Egede Frøkjær et al., 2023; Scheurer et al., 2017; Scheurer et al., 2022; Schorr et al., 2023). Other chromatographic techniques with proven applicability for polar substances include hydrophilic interaction liquid chromatography (HILIC) (Bieber et al., 2017; Neuwald et al., 2021; Tisler and Zwiener, 2018), supercritical fluid chromatography (SFC) (Bieber et al., 2017; Neuwald et al., 2021; Tisler et al., 2022), and mixed-mode liquid chromatography (MMLC) (Montes et al., 2019).

For many years, triple quadrupole instruments operated in multiple reaction monitoring (MRM) mode and coupled to GC and HPLC have been the standard for the targeted quantification of a wide array of compounds in environmental samples. However, target analysis is limited to the tracking of a preselected portion of chemicals present in a sample

and requires reference standards for identification and quantification. Since TPs of micropollutants are commonly unknown and/or reference materials of TPs are often lacking, non-targeted analysis (NTA) and suspect screening using high resolution mass (HRMS) analyzers find increasing application. By providing high mass resolution and accuracy measurements, HRMS can be used to distinguish between compounds with the same nominal mass. HRMS systems, such as time-of-flight (TOF)- and Orbitrap-based mass spectrometry instruments, are coupled to quadrupoles and ion traps to add MS/MS or MS<sup>n</sup> capabilities to obtain mass spectra of multiple product ions. Subsequently, the chromatographic (retention time) and mass spectrometric (e.g., MS/MS fragmentation, isotope pattern) information is evaluated with the aid of post-acquisition data processing, mining tools, and mass spectral databases, such as MassBank ([www.massbank.eu](http://www.massbank.eu)), for tentative identification of suspects' hits. The identification of unknowns then allows for the elucidation of the biological and chemical transformations of the micropollutants (Boix et al., 2013; Christophoridis et al., 2016; Creusot et al., 2024; Funke et al., 2016; Man et al., 2023; Weizel et al., 2020).

Orthogonal analytical approaches are frequently used for the unequivocal structural elucidation of TPs. Nuclear magnetic resonance (NMR) is one option for a complementary technique for the identification and confirmation of TP structures (Krakkó et al., 2022; Tekle-Röttering et al., 2020; Zhang et al., 2019b). NMR is a non-invasive method based on the re-orientation of certain atomic nuclei with non-zero nuclear spins in an external magnetic field and the fact that NMR spectra are unique or highly characteristic to individual compounds and functional groups. Due to its comparatively low sensitivity, NMR is typically not applicable to samples with low analyte concentrations. Consequently, sample pretreatment is often necessary for the isolation of sufficient analyte quantities (Prasse et al., 2011; van Leerdam et al., 2014; Wick et al., 2011).

## 1.6 Regulatory Challenges

The majority of TPs still remain unrecognized and unregulated in current national and supranational chemical assessments, including those conducted in the EU, in the USA, and in China (Zahn et al., 2024). **Table 1.1** lists the five main European chemical registration frameworks and their risk assessments. While the fundamentals of the chemical risk assessments for these substance groups are similar, the terminologies, environmental protection goals, requirements for environmental fate and effect studies, and the consideration of TPs can differ substantially (**Table 1.1**). For instance, the determination of the mobility of pesticide TPs (e.g., through lysimeter experiments) is a key element in the EU risk assessment of active substances in plant protection products. For industrial chemicals registered under the EU REACH regulation, TP identification is also required. However, in practice, there are only a limited number of cases where TPs have been identified. Arp and Hale (2022) found experimental half-life data from simulation degradation test results for only 292 (2.2%) out of the considered 13,400 unique identifiable organic substances registered under REACH. This shows that TPs are commonly missed in the assessments.

Radioactive-labeled substances can be used to track TPs in degradation tests and are suggested in various guidelines. As such, simulation degradation studies for evaluating aerobic and anaerobic transformations of chemicals in soil (OECD 307) and in aquatic sediment systems (OECD 308) and the test to measure the time course of biodegradation of a test substance at low concentration in aerobic natural water (OECD, 2004) enable TP identification (OECD, 2002a, 2002b, 2004). However, due to the complexity of these simulation tests and to cut costs, weight-of-evidence persistency approaches (Redman et al., 2022) are commonly used instead, which do not provide information on TP formation (Zahn et al., 2024).

Differences in the European chemical registration frameworks can also lead to inconsistent assessment outcomes for similar chemicals. Moreover, some chemicals are registered under multiple frameworks due to their usage in multiple fields. As a consequence, harmonization of the EU chemical registration and aquatic risk assessment frameworks by introducing a “one-substance one-assessment (OSOA)” approach for chemicals (van Dijk et al., 2021) has been recently proposed by the European Commission (EC, 2023). As the implementation of the European Water Framework Directive (WFD), the Groundwater Directive (GWD) and Drinking Water Directive (DWD) is country-specific, differences in sample collection, analysis and data dissemination can further complicate chemical assessment across Europe. This issue has recently been exemplified by the different regulations on pesticides and their metabolites in European groundwater (Baran et al., 2022).

From a regulatory standpoint, a further complicating factor is that a single TP may have multiple sources (Nödler and Scheurer, 2019). For instance, 1*H*-1,2,4-triazole is a known metabolite of several triazole derivatives, which have been used as active ingredients in plant protection products (e.g., prothioconazole), biocides (e.g., tebuconazole) as well as in human and animal pharmaceuticals (e.g., fluconazole) (Hoog et al., 2018; Jørgensen and Heick, 2021). 1*H*-1,2,4-triazole is a common building-block in organic synthesis due to its stability and versatile biological activities. However, the high persistence of the substructure inevitably leads to the release of 1*H*-1,2,4-triazole from these precursors when they degrade. In addition, it also finds direct application in agriculture as a nitrification inhibitor (Zeeshan et al., 2023). Furthermore, monitoring studies have suggested significant direct industrial discharges of 1*H*-1,2,4-triazole from manufacturing or processing plants (Freeling and Fleig, 2023; Scheurer et al., 2016). With no evident quantitative data available concerning the relative distribution of TPs from all emission sources and with potentially different regulatory frameworks and jurisdictions coming into force, assigning the responsible legal authorities becomes particularly challenging. Moreover, the lack of understanding of individual contributions from different sources greatly hinders the implementation of effective measures to reduce the release of a substance into the (aquatic) environment.

**Table 1.1** Risk assessment approaches and requirements of different substance groups within the European Union. REACH: Registration, Evaluation, Authorisation and Restriction of Chemicals.

Substance group	Legislation	Guidance	Assessment Approach
<b>Industrial chemicals (REACH)</b>	Regulation (EC) No 1907/2006	European Chemicals Agency (ECHA) Guidance on Information Requirements and Chemical Safety Assessment  Guidance on Information Requirements and Chemical Safety Assessment, Part D: Framework for exposure assessment (ECHA, 2016)	Under REACH, the risk assessment must include an evaluation of the persistence, bioaccumulation, and toxicity (PBT) of the parent substance and its TPs. Registrants must provide information on TPs formed under environmental conditions.  <b>Environmental fate requirements:</b> <ul style="list-style-type: none"> <li>- Biodegradation studies: Standard tests (e.g., OECD 301, 302) are required to determine the biodegradability of the substance and its TPs.</li> <li>- Simulation studies: Studies in soil (OECD 307), sediment (OECD 308), and surface water (OECD 309) are required to understand the transformation and fate of TPs in different environmental compartments.</li> <li>- Identification and quantification: TPs must be identified and quantified in these studies, particularly if they are persistent or potentially harmful.</li> </ul> <b>Effects requirements:</b> <ul style="list-style-type: none"> <li>- Ecotoxicological tests: If TPs are present in significant quantities or suspected to be hazardous, additional ecotoxicological tests (e.g., aquatic toxicity, soil organism toxicity) must be conducted to assess their effects.</li> <li>- PBT Assessment: TPs must be assessed for PBT properties to determine their long-term environmental impact.</li> </ul>
<b>Plant protection products</b>	Regulation (EC) No 1107/2009	Guidelines on Active Substances and Plant Protection Products  Guidance document on the assessment of the relevance of metabolites in groundwater of substances regulated under regulation (EC) NO 1107/2009 (European Commission, 2021)	The environmental risk assessment involves evaluating both the active substances and their metabolites. Comprehensive studies on the fate and behavior of these substances are required.  <b>Environmental fate requirements:</b> <ul style="list-style-type: none"> <li>- Biodegradation studies: Studies on the metabolism of plant protection products in plants, soil, water, and air are required to identify TPs (e.g., OECD 307, 308, 309).</li> <li>- Field studies: Field dissipation studies may be required to confirm laboratory findings and understand the real-world behavior of TPs.</li> <li>- Kinetic Analysis: Determination of the degradation kinetics and pathways for both the parent compound and its TPs.</li> </ul> <b>Effects requirements:</b> <ul style="list-style-type: none"> <li>- Ecotoxicological tests: Additional toxicity tests on non-target organisms, including aquatic and terrestrial species, are required for significant TPs.</li> </ul>

Substance group	Legislation	Guidance	Assessment Approach
<b>Biocidal products</b>	Regulation (EU) No 528/2012	ECHA Guidance on Biocidal Products Regulation (ECHA, 2022)	<p>The environmental risk assessment involves studying the degradation and TPs of active substances.</p> <p><b>Environmental fate requirements:</b></p> <ul style="list-style-type: none"> <li>- Simulation studies: Required to assess the degradation of biocidal products in soil, water, and sediment (e.g., OECD 307, 308, 309).</li> <li>- Identification: Identification and quantification of TPs in these studies.</li> <li>- Degradation pathways: Understanding the complete degradation pathway and the formation of any persistent metabolites.</li> </ul> <p><b>Effects requirements:</b></p> <ul style="list-style-type: none"> <li>- Ecotoxicological tests: Conduct additional ecotoxicological tests for TPs, including acute and chronic toxicity tests on various environmental compartments.</li> </ul>
<b>Human and Veterinary Medicinal Products</b>	Directive 2001/83/EC (human medicines), Directive 2001/82/EC (veterinary medicines), Regulation (EC) No 726/2004	<p>European Medicines Agency (EMA) Guideline on Environmental Risk Assessment for Human Medicinal Products (EMA, 2024b)</p> <p>European Medicines Agency (EMA) Guidelines on Environmental Risk Assessment for Veterinary Medicinal Products (EMA, 2024a)</p>	<p>The environmental risk assessment includes evaluating the active ingredients and their TPs.</p> <p><b>Environmental fate requirements:</b></p> <ul style="list-style-type: none"> <li>- Biodegradation studies: Standard tests to assess the biodegradability of medicinal products and their TPs (e.g., OECD 301, 302).</li> <li>- Simulation studies: Simulation tests to understand the degradation of medicinal products in water and soil environments (e.g., OECD 308, 309).</li> <li>- TP analysis: Identification and quantification of TPs formed in the environment and during patient metabolism.</li> </ul> <p><b>Effects requirements:</b></p> <ul style="list-style-type: none"> <li>- Ecotoxicological tests: Required for major TPs that are persistent or potentially hazardous, including tests on aquatic organisms, soil organisms, and other relevant species. Alternatively, a total residue approach can be applied in which the environmental fate and toxicity of TPs is assumed to be covered by the parent compound. Predicted no effects concentration (PNEC) are compared to the total predicted exposure concentration (PEC).</li> </ul>

## 1.7 Overview of the TPs Investigated in this Thesis and Rationale for their Selection

### TP 1: Trifluoroacetate

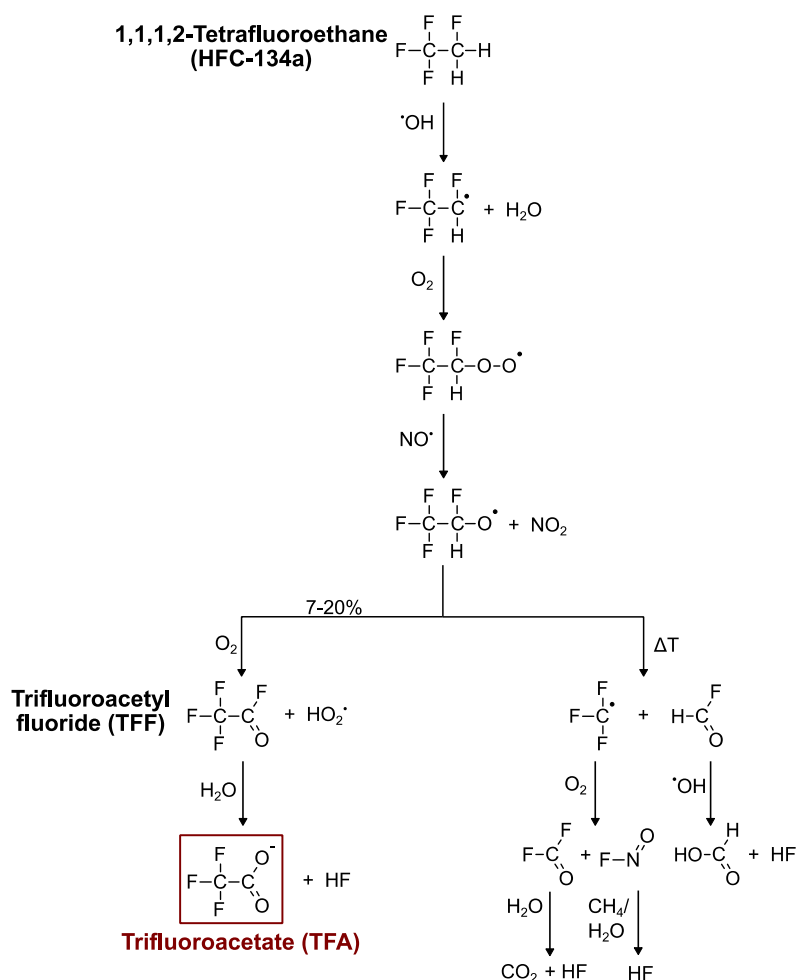
Trifluoroacetate (TFA)<sup>3</sup> is a highly persistent and mobile contaminant that has gained broad attention in recent years due to its widespread occurrence in the aquatic environment, expected accumulation in certain environmental compartments, and the absence of economically viable mitigation strategies to remove TFA from contaminated waters. TFA can be released into the aquatic environment by variety of anthropogenic sources. An important primary source (i.e., release of the compound itself) of TFA are discharges from industrial sites that produce or process TFA. Secondary sources (i.e., release of TFA from precursors) are highly diverse, since all compounds containing at least one carbon-bound trifluoromethyl moiety (C–CF<sub>3</sub>), including many pesticides and pharmaceuticals, are potential precursors of TFA. This is due to the exceptionally high (bio)chemical stability of the –CF<sub>3</sub> moiety, which results in the release of TFA as a quasi-terminal degradation product into the environment (Freeling and Björnsdotter, 2023).

One of the most frequently discussed secondary sources is the formation of TFA in the atmosphere through the oxidation of certain perfluoroalkyl-containing substances, including many hydrofluorocarbons (HFCs) and hydrofluoroolefins (HFOs). These were introduced as substitutes for ozone-depleting chlorofluorocarbons (CFCs) and find wide application as refrigerants, fire extinguishing agents, and physical blowing agents. The TFA formation yields of these fluorinated volatile precursors in the atmosphere can differ greatly from each other and depend on the formation of fluorinated intermediates that can further be converted to TFA (Behringer et al., 2021). **Figure 1.2** shows the degradation pathway of the currently most abundant HFC in the atmosphere, HFC-134a, yielding hydrogen fluoride (HF) and TFA as the final fluorinated TPs.

The atmospheric oxidation of HFC-134a is initiated by the reaction with  $\cdot\text{OH}$ . This abstraction reaction leads to the formation of the alkyl radical (CF<sub>3</sub>CFH $\cdot$ ), which adds molecular oxygen to yield the peroxy radical (CF<sub>3</sub>CFHO<sub>2</sub> $\cdot$ ). Further reaction with NO $\cdot$  results in the formation of the alkoxy radical (CF<sub>3</sub>CFHO $\cdot$ ). Two competing reaction pathways have been identified for CF<sub>3</sub>CFHO $\cdot$ . The larger fraction decomposes via C–C bond cleavage to form CF<sub>3</sub> $\cdot$  and HC(O)F, which are subsequently degraded to hydrogen fluoride (HF). The smaller fraction of 7–20% reacts with O<sub>2</sub> to form the intermediate trifluoroacetyl fluoride (TFF; CF<sub>3</sub>C(O)F). Hydrolysis of TFF in cloud water then leads to the formation of TFA (**Figure 1.2**). The rapid decomposition of CF<sub>3</sub>CFHO $\cdot$  limits the formation of TFF and hence the formation of TFA in the atmospheric degradation of HFC-134a (Wallington et al., 1996).

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<sup>3</sup> Due to its low pK<sub>a</sub> (0.23; Solomon et al. (2016)), trifluoroacetic acid (CF<sub>3</sub>C(O)OH) is present in the aquatic environment almost exclusively in its anionic form trifluoroacetate (CF<sub>3</sub>C(O)O $\cdot$ ). In the present work, the abbreviation TFA is used for both the acid and the anion.



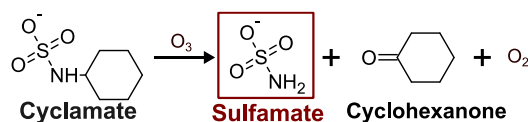
**Figure 1.2.** Atmospheric degradation pathway of HFC-134a via the fluorinated intermediate TFF to the terminal TPs hydrogen fluoride (HF) and trifluoroacetate (TFA) (Behringer et al., 2021; Wallington et al., 1996).

Prior research has proved that TFA is pervasive in precipitation. This is due to its formation in the atmosphere through the degradation of volatile fluorinated compounds and subsequent scavenging of TFA from the atmosphere, primarily through wet deposition. Most studies reporting the occurrence of TFA in precipitation were conducted from the mid-1990s to the early 2000s. For Germany, precipitation samples for the most recent published data on TFA were collected in 1995/1996. In addition, these studies included very limited numbers of samples, casting doubt on the representativeness of the derived data. Moreover, the emissions of numerous volatile TFA precursors have considerably increased over the last decades.

Due to the lack of current and comprehensive data on TFA in precipitation, the significance of wet deposition as a pathway for TFA to the environment in comparison to other known anthropogenic sources remained unknown and unquantified. This presents a major regulatory challenge for TFA. Moreover, as the underlying mechanisms governing the formation and environmental fate of TFA are still largely unknown, the predictive capabilities for TFA are currently limited. This predictive challenge becomes even more relevant considering the expected increase in the atmospheric formation and deposition of TFA in the coming years and decades due to rising global emissions of volatile TFA precursors (Behringer et al., 2021).

## TP 2: Sulfamate

Sulfamate<sup>4</sup> was identified for the first time by Scheurer et al. (2012a) as a major ozonation product of the artificial sweetener cyclamate. In laboratory experiments performed in both ultrapure and drinking water, cyclamate was found to undergo oxidation mainly at the carbon atom where the sulfonamide moiety is attached to the cyclohexyl ring (**Figure 1.3**).



**Figure 1.3.** Transformation reaction pathway for the ozonation of cyclamate leading to the major TPs sulfamate and cyclohexanone (Scheurer et al., 2012a).

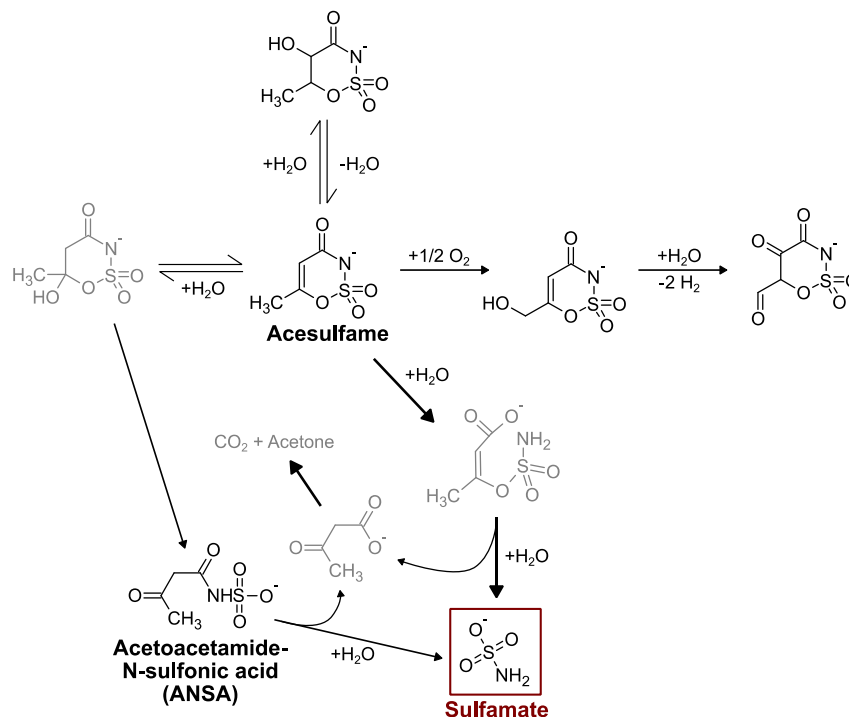
Sulfamate was also found to be the dominant TPs formed during the biodegradation of the artificial sweetener acesulfame (Castronovo et al., 2017) (**Figure 1.4**). In laboratory biodegradation experiments, a quantitative analysis of acesulfame and sulfamate revealed a closed mass balance and demonstrated that acesulfame was transformed almost entirely to sulfamate, indicating that the sulfonamide was stable and not hydrolyzed. In turn, the formation of sulfamate proved that both the sulfonic acid ester and the amide bond of acesulfame can be cleaved. Given that hydrolysis of the sulfonic ester would result in the formation of the TP acetoacetamide-N-sulfonic acid (ANSA), it was assumed that ANSA is a transient intermediate in the degradation pathway of acesulfame to sulfamate. Further experiments provided evidence that ANSA is a minor intermediate and that transformation of acesulfame to sulfamate proceeds via another pathway. The authors proposed that the amide moiety was hydrolyzed first, resulting in the formation of an alkyl sulfamate bearing a carboxylic group. However, they were unable to allocate one of the detected TPs to this proposed structure. Consequently, it was assumed that the alkyl sulfamate intermediate formed by the initial amide cleavage is short-lived and rapidly hydrolyses to yield the sulfamate and acetoacetic acid (Castronovo et al., 2017).

Based on these preliminary results, it was hypothesized that compounds containing a sulfonamide ( $\text{R}^1\text{-N-SO}_2\text{-R}^2$ ) moiety are potential precursors of sulfamate in the environment and during water treatment. In addition to these secondary sources, sulfamic acid is also employed as an acidic cleaning agent in both industrial and domestic applications. Despite the numerous sources, the presence and environmental significance of sulfamate in the urban water cycle in Germany have been unknown.

This can partly be attributed to several analytical challenges: Due to its ionic nature, sulfamate is not amenable to the prevalent GC and RP-HPLC based analytical methods and therefore requires alternative approaches for its detection and quantitation. The absence of commercially available isotopically labeled reference substances further hinders its incorporation into multi-residue methods applied in aquatic monitoring.

<sup>4</sup> Due to its low pKa (~1; Benson and Spillane (1980)), sulfamic acid ( $\text{H}_2\text{NSO}_3\text{H}$ ) occurs in its anionic form (sulfamate;  $\text{H}_2\text{NSO}_3^-$ ) in water under environmentally relevant conditions.

Moreover, non-target approaches often routinely exclude compounds with masses below 100 Da such as sulfamate. In addition, prioritization approaches in aquatic monitoring tend to focus on organic micropollutants and commonly exclude inorganic substances, which presents a major regulatory challenge for sulfamate.

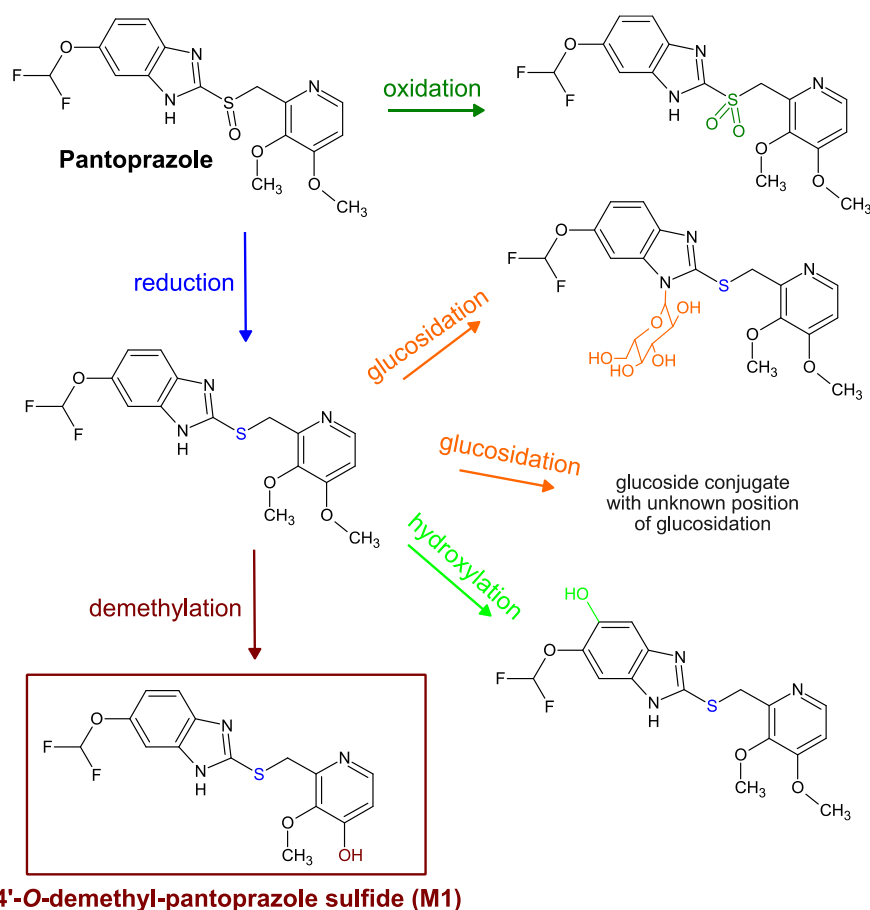


**Figure 1.4.** Proposed degradation pathway of acesulfame according to Castronovo et al. (2017). TPs confirmed by reference standards are printed in bold. Proposed intermediates which could not be detected are printed in grey.

### TP 3: 4'-O-demethyl-PPZ sulfide

Pantoprazole (PPZ) is considered the standard therapy for the treatment of various acid-related disorders and is one of the most prescribed human pharmaceuticals worldwide. PPZ is an acid-activated pro-drug which is extensively metabolized in the human body. Almost 80% of an oral or intravenous dose of PPZ is excreted as metabolites in the urine (Huber et al., 1996).

The metabolism of PPZ comprises a combination of phase I and phase II reactions. The main reactions that have been reported in mammals and a microbial model are the oxidation and reduction of the sulfinyl group, 4'-O-demethylation as well as sulfatation, glucuronidation and glucosidation of PPZ and its reduced/oxidized forms (Huber et al., 1995; Xie et al., 2005c; Xie et al., 2005b; Xie et al., 2005a). The metabolite addressed in the present thesis, 4'-O-demethyl-PPZ sulfide (M1), was identified in prior studies as the primary metabolite of the fungus *Cunninghamella blakesleeana* (Xie et al., 2005c) (**Figure 1.5**) as well as a major metabolite of PPZ in *Rattus norvegicus domestica* (Xie et al., 2005b). M1 has not been previously described as a human metabolite of PPZ.



**Figure 1.5.** Proposed metabolic pathways of pantoprazole by *Cunninghamella blakesleeana* as described by Xie et al. (2005c). After 96 h of incubation, approximately 93% of pantoprazole was metabolized to the six metabolites displayed.

Despite its extensive consumption worldwide, the concentrations of PPZ in environmental water samples documented in the scientific literature were surprisingly low. This can be attributed to the extensive metabolism of PPZ in the human body, with the parent compound being excreted in negligible quantities. Surprisingly, PPZ sulfide, PPZ sulfide- $\beta$ -D-glucuronide (+/-) and PPZ sulfone were the only PPZ metabolites included so far in an environmental study (Hernández et al., 2015), however, they were not detected in the sampled surface and wastewaters. These results suggest that the current environmental exposure associated with the application of PPZ is substantially underestimated.

The absence of environmental data on TPs of PPZ can be explained by the fact that the environmental health risk assessment of pharmaceuticals largely ignores transformation in regulatory authorization procedures. This represents a major regulatory challenge for PPZ. Moreover, the large number of PPZ metabolites described in the scientific literature, in combination with the paucity of comprehensive data on the identity, excretion fractions, and environmental fate of individual TPs of PPZ, has significantly impeded their prioritization and consideration in aquatic monitoring. This represents both a predictive and analytical challenge.

## 1.8 Objectives and Thesis Outline

To address critical gaps in current knowledge and to meet the imperative for a deeper understanding of TPs in the aquatic environment, this thesis pursued two main objectives. The **first objective** of this thesis was to provide a detailed characterization of the occurrence and fate of the selected TPs in the aquatic system in Germany.

The **second objective** was to emphasize the necessity for greater attention to be paid to TPs of precursors of different compound classes in research, chemical regulation, and chemical management to ensure the protection of the environment and human health.

The studies presented in **Chapter 2** and **Chapter 3** are designed to isolate and characterize the atmospheric deposition of **TFA**, which is a crucial step in improving the understanding of the various TFA contributions from all its emission sources and the underlying processes. **Chapter 4** and **Chapter 5** represent independent studies about **sulfamate** and **PPZ/4'-O-demethyl-PPZ sulfide**, respectively. These two studies pursue a more holistic approach by giving comprehensive insights into their formation, entry paths, environmental occurrence and behavior, removability during water treatment, and potential (eco)toxicological risks. The following sections describe the knowledge gaps and objectives of the individual chapters.

### Chapter 2: Wet deposition of trifluoroacetate

Due to the lack of current and comprehensive data on TFA in precipitation, the significance of wet deposition as a pathway for TFA to the environment remained unknown and unquantified. Consequently, our first study addressed this gap with the following tasks: to (i) determine the present occurrence of TFA in precipitation in Germany through a systematic and nationwide field monitoring initiative spanning the entirety of a year, to (ii) derive annual wet deposition mass fluxes of TFA, and to (iii) identify factors affecting the seasonal and spatial variations in the wet TFA deposition.

### Chapter 3: Long-term trends in the atmospheric deposition of trifluoroacetate

The production and emissions of numerous fluorinated CFC substitutes have increased significantly over the past decades. This increase in the emission of volatile TFA precursors was expected to be accompanied by an increase in the atmospheric formation and deposition of TFA. However, the lack of robust historical data on the wet deposition fluxes of TFA hindered trend analyses to test this hypothesis. To overcome this limitation, and with the process knowledge gained in the previous chapter, the task of the study was to analyze archived leaf samples of various tree species from the German Environmental Specimen Bank and use them as a biomonitoring tool for atmospherically deposited TFA. Hence, in our second study (i) an extraction method for plant matrices was developed and validated. Subsequently, archived plant samples were analyzed for TFA to evaluate the (ii) long-term temporal trends and (iii) spatial differences in the atmospheric deposition of TFA in Germany.

#### **Chapter 4: Sulfamate**

Despite the numerous household and industrial applications, there was no information on the sources, presence, and environmental significance of sulfamate in the urban water cycle in Germany. Consequently, our third study had the following tasks: to (i) elucidate the relevant sources and pathways of sulfamate into waterbodies in Germany by conducting a quantitative monitoring approach of different compartments of the urban water cycle and to (ii) assess the toxicological risk of sulfamate to aquatic organisms and human health. In addition, laboratory experiments were conducted to (iii) investigate the extent of sulfamate formation from potential precursors by biological degradation and ozonation in water treatment. Due to the physicochemical properties (inorganic compound, low molecular weight, ionic charge) of sulfamate, a specific focus was put on the (iv) evaluation of its removability during (drinking) water treatment.

#### **Chapter 5: Pantoprazole**

Numerous metabolites of PPZ have been reported in pharmacokinetic studies, but the data were inconclusive and did not allow for prioritization of PPZ metabolites for aquatic monitoring and risk assessment. Our fourth study addressed this gap with the following tasks: (i) Identification of the most relevant human metabolites of PPZ for environmental monitoring efforts by conducting HRMS analysis of urine samples of a PPZ consumer and wastewater samples. To (ii) evaluate the environmental occurrence and significance of the identified metabolites, comprehensive data on their presence in various compartments, including wastewater, surface water, bank filtrate, and finished drinking water in Germany, were collected. The environmental concentrations of target analytes in were then compared to the QSAR-derived freshwater predicted no-effect concentrations (PNECs). Furthermore, archived suspended particulate matter samples were analyzed to (iii) evaluate temporal concentration trends and potential correlation between PPZ usage and the occurrence of PPZ TPs in surface water. Finally, laboratory-scale ozonation and activated carbon adsorption experiments were carried out and compared to monitoring results obtained at a full-scale WWTP equipped with ozonation and activated carbon treatment to (iv) address recent developments and regulations in the field of advanced wastewater treatment and elucidate ozonation products of the most significant human metabolite of PPZ.

#### **Chapter 6: General Conclusions and Outlook**

This chapter presents a synthesis of the principal findings from a more general perspective, draws final conclusions and provides an outlook on further research needs.

## 6 General Conclusions and Outlook

The objective of attaining a more in-depth understanding of the entry paths, occurrence, and fate of selected TPs in the aquatic system was achieved through the combination of comprehensive sampling efforts with high temporal and spatial resolution, the development and application of sensitive methods for targeted and non-targeted chemical analyses, laboratory experiments, and statistical evaluations. The potential risk of the TPs towards aquatic organisms and human health was evaluated based on experimentally and computationally derived toxicological data.

### Trifluoroacetate

Water bodies integrate the signal of multiple sources of TFA, including atmospheric deposition, industrial discharges, municipal WWTP effluent, and runoff from agricultural land. As a result, the characterization and prioritization of the various TFA sources is particularly difficult, which presents both a predictive and regulatory challenge.

In our study, we successfully isolated and therefore characterized the previously unquantified source of wet deposition. This was achieved through a comprehensive year-long sampling effort at eight sites, providing the first published data on TFA in precipitation in Germany since 1995/96. We showed that wet deposition alone contributes approximately 0.3–0.4 µg/L of TFA in surface waters in Germany. Since the corresponding precipitation amounts of all samples were determined, we obtained exact information on the annual wet deposition flux of TFA at different sampling sites. We estimated that a total of 68 t/a of TFA were deposited in Germany during the study period.

Our sampling revealed a pronounced seasonality in the concentration and wet deposition flux of TFA, which was previously unknown. Pearson correlation analyses indicated that the transformation of TFA precursors in the troposphere is enhanced in summer due to elevated concentrations of photochemically generated oxidants, primarily  $\cdot\text{OH}$ , ultimately resulting in increased atmospheric TFA deposition. These periodic changes further suggested that the most significant proportion of TFA present in the atmosphere and in precipitation is the result of the atmospheric oxidation of volatile precursors. In turn, direct atmospheric TFA emissions, for example from fluoropolymer thermolysis, are likely to be a minor contributor. The highest annual TFA wet deposition fluxes were observed in densely populated regions in Germany. This aligns with previous research linking elevated TFA concentrations in surface waters and air to urbanized areas. Nevertheless, we found that the TFA concentration in Germany is generally more influenced by the time of a precipitation event within a year than by its location. Thus, it is highly advisable for future monitoring efforts to determine TFA concentrations and fluxes in precipitation over sufficiently long periods to derive representative data for a specific region.

The data set obtained can be used as a benchmark for future studies to establish mass balances, and to build models for the prediction of TFA loads entering the aquatic environment from multiple sources. The derived data and gained process understanding

have already been exploited in various subsequent studies, including the spatial analysis of the input pathways of TFA into the water cycle in Germany (Sturm et al., 2023), the evaluation of the influence of pesticide application as a source of TFA to groundwater bodies (Joerss et al., 2024), or the application of TFA as a novel hydrological tracer in the areas of surface-groundwater interaction, water dating, and water type characterization (Lange et al., 2024). Although the contamination of the environment with synthetic compounds is undesirable, the study by Lange et al. (2024) demonstrates that certain TPs can prove useful in various fields, for example to gain insight into (geo)hydrological processes, thus opening up new research opportunities.

The hypothesized increase in the atmospheric formation and deposition of TFA due to the increased emissions of volatile TFA precursors was validated in our second study. We showed that plant matrices can be an efficient biomonitoring tool to evaluate long-term changes in atmospherically deposited TFA and presented the first trend analysis of TFA in biota. To achieve this, a robust extraction method for the analysis of TFA in leaf samples was developed. After dilution, the sample extracts were directly analyzed using IC-MS/MS. This illustrates a substantial advantage of IC over other chromatographic techniques for the analysis of TFA and similar ionic substances, namely the direct injection of water samples containing any proportions of water-miscible organic solvents, such as methanol and acetonitrile, without compromising the chromatographic retention of the target analytes. Since no solvent-exchanges and other pretreatment steps were required, this also greatly reduced the likelihood of sample contamination, which represents a major challenge in the trace analysis of TFA. In addition, the use of volatile mobile phase additives eliminates the need for eluent suppression, allowing IC columns to be used directly in prevalent HPLC-systems. These points highlight the need for innovation and the consideration of alternative analytical approaches to overcome the challenges associated with many TPs.

The statistical analysis revealed a significant positive trend in the concentration of TFA in the studied leaf samples. The concentrations increased by factors of up to 12 in some species from 1989 to 2020. The highest concentrations (up to ~1,000 µg/kg dry weight) were observed in Lombardy poplar leaves. Further research is required to elucidate the influence of plant physiological and meteorological variables on the uptake and accumulation of TFA by vascular plants. Additionally, an enhanced understanding of the role of biomass loss on TFA accumulation by plants and the fate of TFA from decomposing plant litter is needed.

Due to its very hydrophilic nature, TFA is not expected to accumulate over time in animals and humans. However, increasing concentrations in plants could also lead to an increase in TFA levels in animals and humans. Human biomonitoring already shows widespread exposure to TFA. Our, yet unpublished results from a nationwide study outside of Europe revealed high urinary TFA concentrations in humans in the tens to hundreds of µg/L. This indicates that the dietary uptake of TFA is currently underestimated. It also demonstrates the need to rethink the traditional concept of bioaccumulation, which is predominantly based on the phospholipid partitioning of contaminants, thereby neglecting ionic

substances, such as TFA. Moreover, the ubiquitous presence of TFA along with its high concentrations in various environmental media, underscore the necessity for further research on the chronic toxicity of TFA to humans and the environment, which is currently lacking.

Finally, our study raised awareness of the significant increase in atmospheric deposition of TFA over the past three decades. Amendments to the Montreal Protocol and the European F-Gas Regulation have led to the phase-out of HFCs and the introduction of HFOs, the latter of which have lower global warming potentials (GWP) due to their shorter atmospheric lifetimes. However, HFOs generally exhibit higher molar TFA formation rates than their predecessors, which, in addition to increasing F-gas emissions, will further enhance global atmospheric TFA deposition. Behringer et al. (2021) estimated that TFA emissions from the atmospheric degradation of refrigerants and propellants released in Europe will rise exponentially from ~9,000 t in 2015 to ~40,000 t in 2030. Lately, Arp et al. (2024) have put forth the argument that TFA meets the criteria for a planetary boundary threat for novel entities (Persson et al., 2013). This is on account of the very high persistence of TFA and the increasing planetary-scale exposure to TFA from various sources, which could give rise to potential, irreversible disruptive impacts on vital Earth system processes. It is important to note that certain F-gases, due to their structure, do not form TFA and other perfluoroalkyl carboxylic acids (PFCAs) as atmospheric oxidation products. Therefore, future research should explore which F-gases possess the desired technical properties and are able to meet climate goals by having a low GWP, without contributing to the environmental burden of TFA and other PFCAs. These candidates could complement non-halogenated gases in various commercial and domestic applications.

### **Sulfamate**

The preliminary results of two previous studies indicated that the concentrations of sulfamate present in WWTP effluent are substantially higher than those of other wastewater-borne contaminants. Despite the numerous applications of sulfamic acid and its salts, information on the sources, occurrence, fate, and (eco)toxicological relevance of sulfamate in the urban water cycle in Germany was extremely limited. In our third study, we addressed this lack of knowledge.

A direct-injection IC-MS/MS method was employed for the quantification of sulfamate in aqueous samples. Strong ion suppression was observed in water samples with elevated mineral content. Since no suitable internal standard was commercially available, multiply isotopically labeled ( $^{15}\text{N}$ - $^{18}\text{O}_3$ ) sulfamate was synthesized and applied as an internal standard, thus compensating for matrix effects and allowing for robust quantification. This illustrates the critical need of (isotopically labeled) reference standards to overcome the analytical and regulatory challenges associated with TPs. Their accessibility could be improved by updating existing regulations that require registrants not only to publicly disclose the outcomes of their simulation degradation studies, but also to provide

reference standards for both the parent compounds and the identified TPs as part of the registration process (Zahn et al., 2024).

Our monitoring campaign revealed exceptionally high concentrations of sulfamate in wastewater (up to 1,900 µg/L), surface water (up to 580 µg/L) and finished drinking water (up to 140 µg/L) in Germany. Sampling of the Rhine at Koblenz over a three-week period showed an average sulfamate load of about 11 t per day, highlighting the much higher emissions of sulfamate to the aquatic environment compared to other commonly investigated micropollutants. For example, the average daily load of the pharmaceutical CBZ at the site during the same period was about 2,500 times lower. Considering the limited data on short-term ecotoxicity, about 30% of the presented sulfamate concentrations in groundwater and surface water samples exceeded the derived PNEC of sulfamate. Therefore, effects of sulfamate on the aquatic ecosystem of wastewater-impacted water bodies in Germany cannot be excluded.

Laboratory ozonation and activated sludge experiments confirmed that sulfamate can be formed through the chemical and biological degradation of a variety of compounds containing a sulfonamide ( $R^1-N-SO_2-R^2$ ) motif. However, the transformation of precursors to sulfamate in WWTPs and wastewater-impacted waterbodies was found to be quantitatively insignificant due to the direct and prevalent use of sulfamic acid in domestic and industrial applications. Municipal WWTP effluent was identified as the primary source of sulfamate in the urban water cycle, as its concentrations correlated positively with the municipal wastewater tracer CBZ in samples from different waterbodies. A notable deviation from the sulfamate-CBZ correlation was observed in a sample from the left bank of the Upper Rhine downstream a city hosting major industry, which suggested substantial industrial discharges of sulfamate into the Rhine at the location. This illustrates that the accompanying analysis of other micropollutants, which serve as source and process indicators, can be vital to identify, disentangle, and prioritize the contributions of individual TP sources.

The fact that only bank filtration was found to be effective for the removal of sulfamate emphasizes the importance of a multi-barrier approach in drinking water treatment. Furthermore, this demonstrates that to effectively reduce the prevalence of sulfamate and other highly mobile and persistent substances in the aquatic system, mitigation measures must be implemented throughout the entire life cycle of these substances. This necessitates a multi-faceted approach that goes beyond end-of-pipe technologies (i.e., water treatment) and encompasses strategies such as substance avoidance and production-integrated environmental protection. Sulfamic acid was recently selected as a priority substance within the stakeholder dialog “*Trace Substance Strategy of the German Federal Government*” ([www.dialog-spurenstoffstrategie.de](http://www.dialog-spurenstoffstrategie.de)). The objective is to initiate measures aimed at reducing the discharge of sulfamate into waterbodies by bringing together representatives of chemical manufacturers and formulators, wastewater and water associations, research organizations, and environmental associations.

Our study suggests that there are likely other high production volume inorganic chemicals that have been overlooked in environmental studies and monitoring programs. This is likely attributed to the fact that prioritization approaches tend to focus on organic micropollutants, and that highly polar analytes are not amenable to common routine RP-HPLC-based target methods. Non-target approaches to identify unknown substances using HRMS also primarily employ RP columns for chromatographic separation and commonly exclude compounds with masses below a specific threshold. These factors, regardless of being evoked by technical limitations or regulatory factors, ultimately lead to the discrimination of substances with specific inherent properties. This underscores the importance of a critical examination of chemical prioritization approaches and the necessity to align the scope of analytical methods and protocols with the requirements of fate and effect studies of chemicals as well as the overarching environmental protection goals.

### **Pantoprazole**

Despite its high consumption worldwide, the concentrations of PPZ in environmental water samples reported in the literature have been comparatively low. This was attributed to the fact that PPZ is extensively metabolized in the human body, with only small amounts of the parent compound being excreted. Numerous metabolites of PPZ have been reported, but the data were inconclusive and did not allow for prioritization of PPZ metabolites for aquatic monitoring and risk assessment.

By applying HRMS analysis to urine samples from a pantoprazole user and to wastewater influent and effluent, we identified 4'-O-demethyl-PPZ sulfide (M1) as the most relevant metabolite of PPZ. M1, which has not been investigated in previous monitoring studies, was found to be ubiquitously present in WWTP influents and effluents as well as in surface water bodies in Germany. The average concentration of M1 in surface water samples was 30 times higher than that of the parent compound PPZ. Moreover, QSTR modeling yielded a preliminary freshwater PNEC of M1 that was approximately six times lower than that of PPZ. While *in silico* methods such as QSTR can help to prioritize TPs, experimentally derived ecotoxicological data are needed to verify these predictions.

The target analysis of archived SPM samples from the Rhine revealed that the concentrations of M1 increased significantly from 2005 to 2015 and were positively correlated with the prescription volume of PPZ. This underlines the suitability of SPM analysis as a monitoring tool for aquatic micropollutants, including TPs. Temporally resolved environmental data are particularly valuable as they can uncover the impact of market changes, such as bans or the introduction of substitutes on the environmental burden of chemicals and allow for future predictions.

Laboratory-scale experiments and the analysis of samples after different treatment steps of a full-scale WWTP demonstrated that post-treatment with activated carbon as well as ozonation can significantly improve the removal of M1 and PPZ during wastewater treatment. This provides another example of the effectiveness of these techniques in

reducing the release of many biologically recalcitrant wastewater-borne contaminants into the aquatic environment. During ozonation, a rapid oxidation of M1 was observed, accompanied by the formation of several ozonation products, which were proposed for the first time. The ozonation products of M1 are not expected to be released in substantial amounts into receiving waters, as our findings suggested their removal in subsequent sand and biologically active granular activated carbon filtration. Nevertheless, the formation of stable and mobile ozonation products during water treatment represents a potential concern and must be considered.

In summary, our study confirmed that the environmental exposure and risk associated with the use of PPZ is currently underestimated. It is highly likely that the same applies to several other formerly or presently used pharmaceuticals. Our results show that the non-consideration of pharmacokinetics can lead to a significant misrepresentation and misjudgment of the environmental impact of pharmaceuticals. Therefore, the study calls for more sophisticated approaches to environmental monitoring and risk assessment of pharmaceuticals that not only take the parent compounds but also their TPs into account.

### **Overall conclusion**

This thesis complements existing knowledge by providing new insights into the entry paths, occurrence, fate, and (eco)toxicological risk of selected TPs that were found to be ubiquitous within the aquatic system in Germany. Moreover, this thesis presents ways to overcome several challenges hindering the consideration of TPs in environmental studies and regulation with the use of appropriate study designs and complementary research approaches. The results of the thesis provide strong arguments for decision makers and legislators to better integrate and harmonize TPs in chemical regulatory frameworks.

It is recommended that future studies adopt comprehensive approaches that also go beyond mere occurrence data. Instead, they should seek to elucidate the underlying mechanisms governing the formation and environmental fate of TPs. This is vital since high-quality field and laboratory data as well as an enhanced process understanding can decrease uncertainties in TP prediction, and, in turn, reduce the reliance on simulation degradation tests. Finally, the enhanced predictive capabilities may facilitate the effective consideration of TPs in the initial stages of chemical design and development, thus preventing the market entry of chemicals that form hazardous TPs in the first place. This would represent a fundamental step forward in the development of safe and sustainable chemicals.

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