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Assessing the environmental occurrence of the anthropogenic contaminant trifluoroacetic acid (TFA)

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Abstract

Trifluoroacetic acid (TFA) is a very persistent contaminant that has gained attention due to its multitude of anthropogenic sources, widespread occurrence in the environment, and expected accumulation in (semi-)closed drinking water cycles. Here, we summarize and assess the current knowledge on the anthropogenic sources of TFA to better understand the human-induced environmental TFA burden and highlight future research needs. Formation of TFA from the degradation of volatile precursors leads to diffuse and ubiquitous contamination of the environment. The analyses of ice core and archived leaf records have undoubtedly demonstrated that atmospheric depositions of TFA have increased considerably over the last decades in the Northern Hemisphere. Moreover, many point sources of TFA have been identified, which can lead to contamination hotspots posing a potential threat to human and environmental health. Also, unintentional formation of TFA during per- and polyfluoroalkyl substance (PFAS) remediation might become a major secondary source of TFA.

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Trifluoroacetic acid, Trifluoroacetate, Precursors, Trifluoromethyl group, PFAS.

Introduction

Compounds containing at least one carbon-bound trifluoromethyl moiety (C−CF_3) are potential precursors of the very persistent and very mobile (vPvM) substance trifluoroacetic acid (TFA; CF_3COOH)[1] (Figure 1), which belongs to the group of per- and polyfluoroalkyl substances (PFAS) under the Organisation for Economic Co-operation and Development (OECD) definition [1]. This is due to the exceptionally high (bio)chemical stability of the −CF_3 moiety, which results in the release of TFA as a quasi-terminal degradation product in the environment [2]. The −CF_3 group is a common constituent of many synthetic compounds [3], despite the fact that fluorine atoms are extremely rare in naturally occurring organic molecules. In the pharmaceutical and agrochemical industry, chemical design has long incorporated C−CF_3 moieties into molecules to enhance potency by promoting electrostatic interactions with targets, improving cell permeability and bioavailability as well as increased chemical and metabolic stability [4,5]. A current example is the antiviral medication nirmatrelvir/ritonavir (brand name: Paxlovid®) which has been granted use authorization or approval in several countries for the treatment of patients with mild-to-moderate coronavirus disease 2019 (COVID−19), who are at risk of progression to severe ailment [6]. Albeit the expected benefit of this medication for humankind, nirmatrelvir will potentially break down in the environment to form TFA [7]. When it comes to agrochemicals, around 40% of all fluorine-containing pesticides currently on the market contain a C−CF_3 moiety [8], and some of them have already been identified as precursors of TFA [3]. TFA is also a known degradation product of many fluorinated gases used in various applications, for instance, in refrigeration [9,10].

It has long been propagated that TFA is also naturally produced [2]. However, to date, research has not provided sufficient scientific evidence to support the existence of natural sources of TFA [11]. In contrast, there is mounting evidence from recent studies that large amounts of TFA are released into the environment by various anthropogenic sources and that the concentrations of TFA in certain environmental compartments have considerably increased over the last decades [12−15]. This is a matter of concern, as the exceptionally high persistence and mobility of TFA involves a higher likelihood for long-lasting and widespread detrimental effects [16,17]. Here, we compile and evaluate the current knowledge on the anthropogenic sources of TFA to give insights into the human-induced environmental TFA burden.

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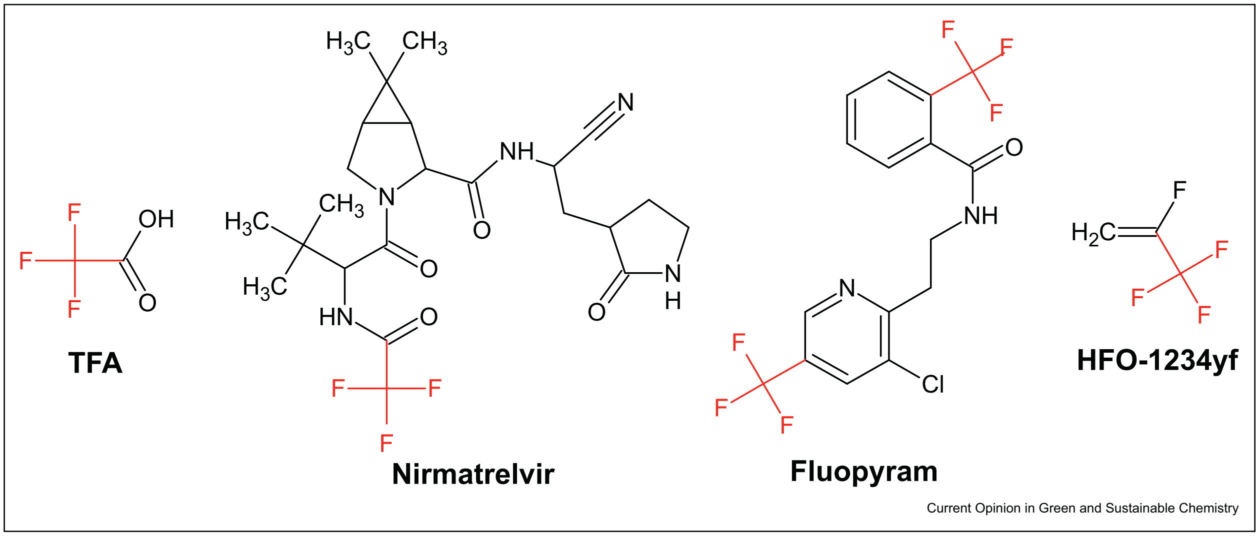
[1] Trifluoroacetic acid, being a strong acid, is present in the aquatic environment almost exclusively in its anionic form (trifluoroacetate; CF_3COO^-). In environmental studies, TFA is commonly used as an abbreviation for both the acid and the anion.

Figure 1



Examples for precursors of trifluoroacetic acid (TFA) through (bio)chemical degradation: the pharmaceutical nirmatrelvir, the pesticide fluopyram, and the refrigerant HFO-1234yf. The C-CF_3 moiety in each molecule is marked in red.

Primary and secondary point sources

Industrial sites

Industrial sites may serve as primary (direct release) and/or secondary (through degradation of precursor molecules) point sources of TFA [18]. TFA is widely used in organic synthesis as a solvent and catalyst. Moreover, TFA serves as the starting reagent for the preparation of building blocks employed in the synthesis of numerous fluorinated organic compounds [19]. During a screening of tap and surface waters in Southwest Germany in 2016/17, exceptionally high TFA levels of up to 140 μg/L were detected. Wastewater discharge from an industrial plant, specialized in the production and processing of TFA, was identified as the source of contamination and had a significant impact on surface and ground waters downstream [3]. Similar results were obtained in the Alz catchment in Bavaria, Germany, in which TFA concentrations increased approx. 40-fold from the upper Alz river (<0.5 μg/L) to downstream a fluorochemical plant (up to 22 μg/L) [3]. Concentrations of TFA in surface waters in Germany are generally much lower, as depicted by the median TFA concentration of 0.48 μg/L for surface water samples ($n = 43$) found in a different German study [20]. In fact, the surface water concentrations reported by Scheurer et al. are, to the best of our knowledge, the highest in the aquatic environment ever observed for TFA and show that direct industrial discharges of TFA can substantially increase the concentrations of receiving waters, even in great distance (>300 km) from the point of discharge [3]. Chen et al. studied the distribution of PFAS surrounding two fluorochemical manufacturing plants in Fuxin, China. TFA concentrations in outdoor settled dust and river water decreased exponentially as the distance increased from the plant providing further evidence for the direct release of TFA from such industries [21]. In a similar study conducted in China, concentrations of TFA in surface waters and soils in the vicinity of fluorochemical production plants were significantly higher than those in regions with minor industrial activity [18].

Municipal and industrial waste management

Municipal wastewater treatment plants (WWTPs) represent primary and secondary point sources of TFA for the aquatic environment. Research has shown that wastewater and wastewater-influenced waterbodies can bear a TFA formation potential through biotic or abiotic (e.g. ozonation [3] and photodegradation [22]) degradation. This can be explained by the presence of TFA precursors such as pharmaceuticals or biocides in the wastewater, and the fact that TFA itself cannot be removed by commonly applied water treatment processes [3,23]. However, it is unclear whether typical loads of precursors in municipal wastewater contribute significantly to the TFA balance of WWTPs. In the study by Scheuer et al., effluent concentrations were very similar to the respective inflow concentrations, and only one out of six WWTPs showed a significant increase in the TFA concentrations during the treatment process [3]. It can be assumed that the TFA concentration of treated wastewater is mainly determined by the concentration in the drinking water of the households connected to the respective sewage system. However, this might not be the case for municipal WWTPs with high fractions of industrial wastewater (e.g. from pharmaceutical or fluorochemical production facilities). Additional studies are needed to assess the role of WWTP effluent on TFA concentrations of receiving waterbodies.

Landfills are known to be significant sources of various emerging pollutants, including PFAS [24], and could potentially be relevant contributors to the environmental TFA burden. Although most studies on PFAS do not include TFA, one study in Sweden has reported high levels of TFA (up to 6.9 μg/L) in landfill leachate [25]. Landfills can constitute a primary and secondary source of TFA as a result of disposal of various consumer products, including pharmaceuticals and personal care products containing TFA precursors. Additional research is necessary to evaluate the role of landfills as a source of TFA contamination.

Fire protection and control

Firefighting training sites as well as military bases and airports are known point sources for PFAS [26]. In a study by Björnsdotter et al., elevated concentrations of TFA (up to 14 μg/L) were observed in water running out from a rock shelter equipped with sprinkler systems for fire protection [25]. Samples were also collected from five firefighting training sites with known or suspected use of aqueous film forming foams (AFFF); yet, TFA was only found at high concentration in the water connected to the rock shelter. Although high concentrations of most target PFAS were measured at this site, TFA did not correlate with PFAS that are typically associated with AFFF (e.g. perfluorooctane sulfonate and perfluorohexane sulfonate). Despite the lack of correlation with other PFAS typically found in AFFF, the discovery of such high concentrations of TFA in water running out from the rock shelter suggests that fire protection and control activities could be a relevant point source of TFA, either from its presence as a by-product in some AFFF formulations or from TFA precursors. Another explanation to the high concentrations of TFA in water connected to the rock shelter could be that fire protection agents other than AFFF have been applied there. For example, TFA is a degradation product of HFC-227ea that is used in fire suppression systems [27].

PFAS remediation

The growing focus on removing PFAS contamination from drinking water resources has produced various PFAS-disposing approaches. Recently, a promising novel method was published which showed that perfluoroalkyl carboxylic acids (PFCAs), a type of PFAS, can be mineralized under relatively mild conditions by a cascade of reactions in a dimethyl sulfoxide/water and sodium hydroxide mixture to form a series of nonfluorinated molecules and TFA [28]. Consequently, the degradation of PFAS by remediation technologies could become a major secondary source of TFA when such techniques find broad commercial application. This needs to be considered in the development and implementation of technical approaches for PFAS remediation in the future.

Secondary diffuse sources

Atmospheric deposition

TFA can be formed in the atmosphere through the oxidation of certain perfluoroalkyl-containing substances, such as hydrofluorocarbons (HFCs), hydrochlorofluorocarbons (HCFCs), hydrofluoroolefins (HFOs), and hydrochlorofluoroolefins (HCFOs), which were introduced as substitutes for ozone-depleting chlorofluorocarbons (CFCs) and find wide application as refrigerants, fire extinguishing agents, and physical blowing agents [29]. Another source of TFA is the thermolysis of fluoropolymer products, such as polytetrafluoroethylene (PTFE) during their use or incineration [30]. In addition, specific fluorinated inhalation anesthetics (e.g. isoflurane) as well as various fluorotelomer compounds (e.g. fluorotelomer alcohols, fluorotelomer iodides, and fluorotelomer acrylates), and perfluoroalkane sulfonamides can undergo atmospheric oxidation to produce TFA as well as other perfluorocarboxylic acids [31]. The molar yields of TFA as a degradation product from various precursor classes can differ greatly from each other. For example, Sulbaek Andersen et al. estimated a molar TFA yield during atmospheric oxidation of HCFOs-1233zd(E) of 2% [32], while for certain HCFCs (e.g. HCFC-124 [33]) and HFOs (e.g. HFO-1234yf [9]) molar TFA yields of 100% have been reported. The formation rates of intermediates that can be converted to TFA and the conversion rates of these intermediates to TFA are decisive for the TFA yield of a substance [29]. More experimentally derived data are needed, as substance-specific TFA yields are currently unavailable for the majority of potential TFA precursors.

Because of its low Henry's law constant and high water solubility, TFA is mainly scavenged from the atmosphere by wet deposition [34]. It can be expected that atmospheric deposition leads to a ubiquitous background contamination of the aquatic and terrestrial environment with TFA. For instance, TFA was found in 89% of the groundwater wells ($n = 247$) in Denmark in a screening study conducted by the Danish Environmental Protection Agency in 2021 (https://mst.dk/service/nyheder/nyhedsarkiv/2021/jan/nyt-stof-fundet-i-grundvandet/).

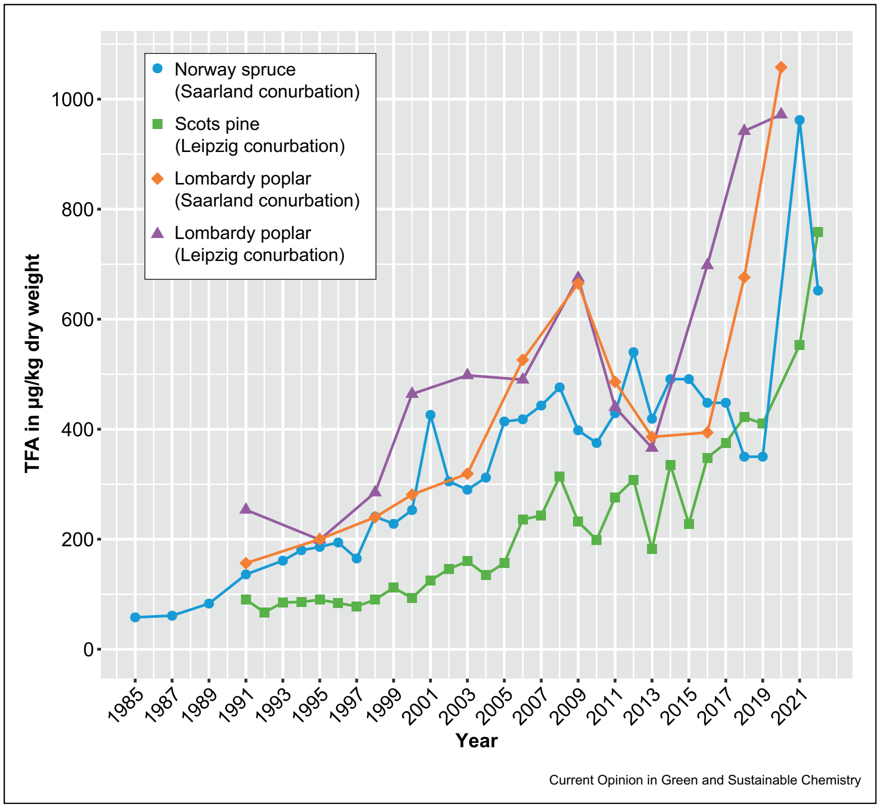
The importance of local point sources and diffuse atmospheric sources of TFA to a freshwater lake in Sweden was studied based on measured TFA input (surface water inflows, precipitation, and WWTP effluents), output (surface water outflows), and the TFA inventory of the lake. A relationship was observed between the input of TFA via streams and the catchment area of the stream, and it was suggested that atmospheric deposition of TFA (determined deposition flux (wet and dry) in 2018/19: 52 μg/(m^{2}a)) could explain a large fraction of the TFA input via streams [35].

As the production and consumption of numerous fluorinated CFC substitutes have considerably increased over the last decades, it was hypothesized that atmospheric formation and deposition of TFA have risen accordingly. Pickard et al. observed an increasing trend in the atmospheric deposition of TFA in two Arctic ice cores starting around 1990, when the Montreal Protocol was introduced to phase out ozone-depleting CFCs with substitutes that oxidize to form TFA. In their study, the deposition flux (wet and dry) increased from approx. 1.9 μg/(m^{2}a) in 1990 to approx. 20 μg/(m^{2}a)) in 2016 and correlated positively with the calculated TFA production rate of five major CFC replacements (HCFC-123, HCFC-124, HCFC-133a, HFC-134a, and HFC-227ea) [14]. TFA was measured in 1187 precipitation samples collected over the course of 12 consecutive months in 2018/19 at eight locations across Germany [12]. The precipitation-weighted average TFA concentration (0.335 μg/L; wet deposition flux: 190 μg/(m^2 a)) in this study was about four times higher than that reported in 1995/96 in Germany [36].

Furthermore, the monitoring by Freeling et al. revealed a pronounced seasonality of the TFA concentration and wet deposition flux of collected samples with maximum values in the summer and minimum values in the winter [12]. A similar seasonality of the flux of TFA has also been observed in precipitation in Sweden [35] as well as in surface snow collected in the Norwegian Arctic [37]. Wu et al. found that airborne TFA concentrations were always the highest between 12:00 am and 4:00 pm on five consecutive days in January 2013 in China [38]. The observed diurnal and seasonal changes of TFA in precipitation and air are likely caused by the varying atmospheric concentrations of photochemically generated oxidants, mainly hydroxyl radicals, which are responsible for the transformation of volatile TFA precursors in the troposphere.

Archived leaf samples of various tree species from the German Environmental Specimen Bank (observation period: 1985–2022) were analyzed for TFA to further investigate the temporal presence of TFA in the

Figure 2



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Temporal concentration trends of TFA in leaf samples from the sampling sites Saarland conurbation and Leipzig conurbation in Germany [13,39]. Note that additional species/sites were analyzed in the referenced studies, which are not displayed here.

terrestrial environment in Germany [13,39]. Figure 2 depicts the temporal concentration trends of TFA in leaf samples at two sampling sites in Germany. A statistically significant positive trend in the TFA concentration within the study period (approximately 2- to 5-fold change between 1995 and 2018) was found for most species/sites. The trend was attributed to bioaccumulation as well as increasing emissions of gaseous TFA precursors over the last three decades [13,39].

It can be assumed that the predominant source of TFA in the aforementioned sample matrices (precipitation, surface snow, ice cores, and terrestrial plants) was atmospheric deposition. Therefore, these results show an upsurge in the anthropogenic emissions of gaseous TFA precursors, leading to increasing atmospheric deposition of TFA in the Northern Hemisphere over the last three decades. It is expected that the atmospheric formation and deposition of TFA will greatly increase in the coming years due to rising global emissions of fluorinated refrigerants and also due to the switch to the latest generation of refrigerants, namely HFOs [29]. For instance, Holland et al. stated that the transition to HFO-1234yf from HFC-134a (assuming consumption is matched) would result in a 33-fold increase in the global atmospheric TFA burden, as the degradation of the former occurs with a higher rate and with a larger TFA yield [40]. Behringer et al. estimated that the TFA emissions resulting from the atmospheric degradation of TFA-forming HCFCs, HFCs, HFOs, and HCFOs released in Europe (EU-28) will increase exponentially from ∼9 kilotons in 2015 to ∼40 kilotons in 2030 [29]. Note that the earliest analyzed biota [13] and ice core [14] samples predate the introduction of HFCs in the early 1990s. Hence, TFA in samples pre-1990 is attributed to other sources, such as fluorotelomer and HCFC oxidation. HCFCs were introduced as a short-term replacement for CFCs but were ultimately scheduled to be phased out as well due to amendments made to the Montreal Protocol in the 1990s [29]. Moreover, recent modeling approaches showed that larger fractions of the measured total TFA deposition flux cannot solely be explained by HFC/HFO degradation [29,38]. Therefore, additional research is needed to identify and prioritize all relevant sources for airborne TFA.

Cahill determined the temporal change in TFA concentrations in surface waters in Northern California by resampling a transect that was originally sampled in 1998. The sampling locations were selected so that atmospheric deposition would be the dominant source of TFA. The results showed that TFA concentrations increased by an average of 6-fold over the intervening 23 years, with a median concentration of 0.18 μg/L (0.021–2.8 μg/L) [15]. TFA was also measured in urban surface waters, tap water, and snow in Beijing, China, in 2012. Compared with screening results of the same surface water sampling locations in 2002, a 17-fold increase from 0.023 to 0.098 μg/L to 0.34–0.83 μg/L was observed [41]. Unlike precipitation, surface waters integrate the signal of multiple sources of TFA, including wastewater treatment plant effluent or runoff from agricultural land, which makes source attribution difficult. Nevertheless, these studies demonstrate a substantial increase in the environmental burden of TFA in anthropogenically influenced terrestrial ecosystems within relatively short periods of time.

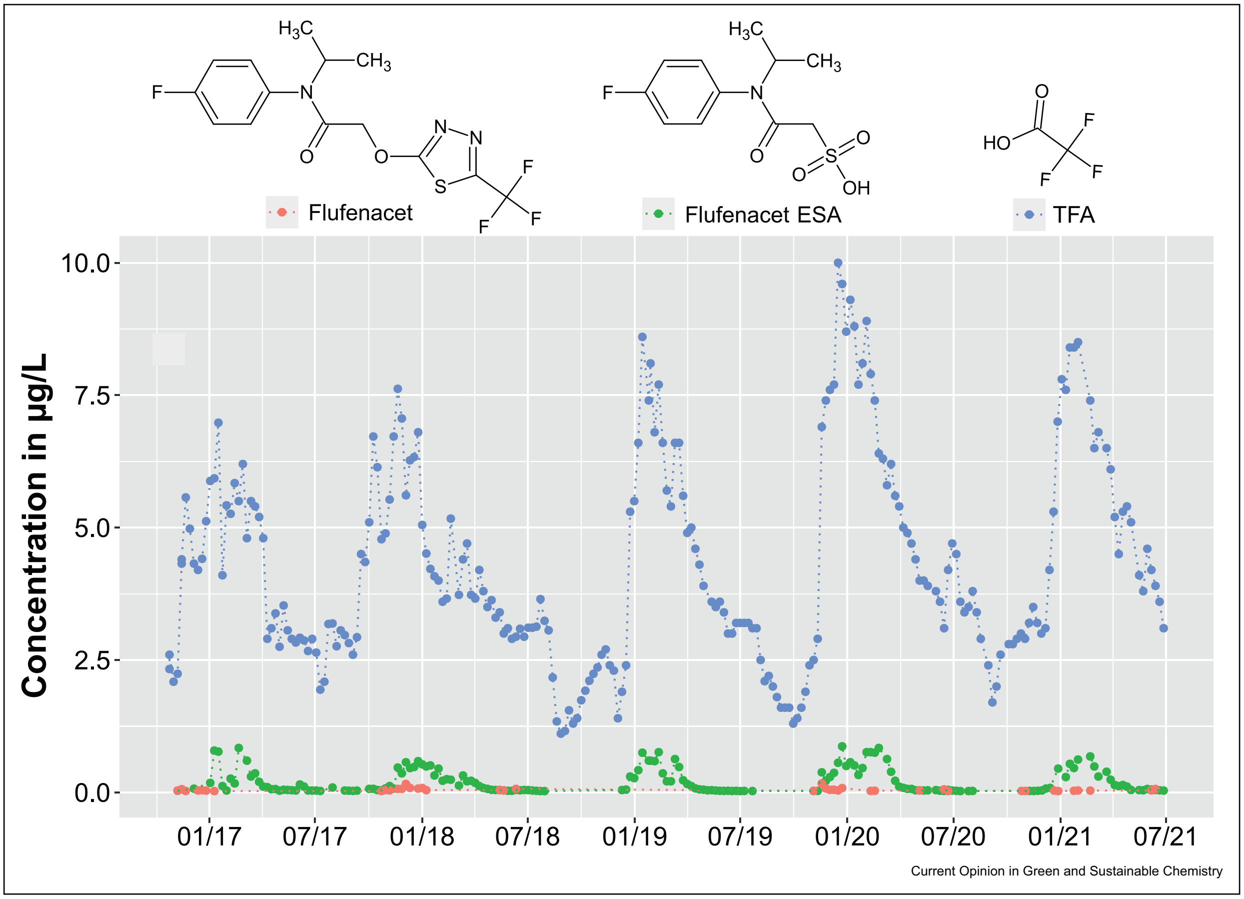
Agriculture

Nödler et al. studied the occurrence of various vPvM substances, including TFA, in surface waters in the state of Lower Saxony, Germany. The highest TFA concentration (3 μg/L) of samples collected in May 2018 ($n = 51$) was detected in a sample that also had the second highest sum concentration of 70 pesticides, among them representatives with C-CF_3-substructure such as flufenacet and diflufenican [42]. Moreover, the sample showed a high formation potential of TFA (concentration increase of 41%) when treated with an ozone concentration of 0.5 mg/L per mg of dissolved organic carbon, indicating the existence of TFA precursors (e.g. pesticides and their transformation products) in the sample [43]. A monitoring study conducted over multiple years in the catchment of the river Stever ($A = 590\ km^2$; area covered by arable land: 72%) in Germany revealed pronounced seasonal changes in the TFA concentration. Minimum concentrations (between 1 and 2 μg/L) were always observed in late summer. Subsequently, concentrations showed a stark increase, reaching maximum values between 7 and 10 μg/L in the winter months. TFA levels then gradually decreased again until late summer (Figure 3). The observed seasonality of TFA in the Stever is most likely due to the degradation of C-CF_3-containing pesticides after their application and the subsequent export of the formed TFA by the surface water system [44]. This hypothesis is supported by the high synchrony of the time series of TFA and flufenacet sulfonic acid (flufenacet ESA), another mobile and stable metabolite of flufenacet. The decrease in TFA and flufenacet ESA concentrations during the winter months could be explained by the leaching of TFA from soils in consequence of the ongoing precipitation in the winter months. These results indicate that the application of C-CF_3-bearing pesticides can, at least in Germany, induce TFA concentrations in surface waters significantly greater than the annual precipitation-weighted TFA concentration in precipitation, which currently is around 0.3–0.4 μg/L [12].

(Eco)toxicological relevance

The microalgae *Raphidocelis subcapitata* showed to be the most sensitive freshwater species toward TFA in studies compiled in the ECHA registration dossier [45]. In the dossier, a freshwater predicted no-effect concentration (PNEC) of 560 μg/L was derived for the species on the basis of a 10% effect concentration (EC_{10}; growth

Figure 3



Concentrations (in µg/L) of flufenacet and its metabolites flufenacet ESA and TFA in the river Stever upstream of the Hullern reservoir in Germany between October 2016 and July 2021. Graph was based on [44] and modified accordingly.

inhibition) of 5.6 mg/L. This indicates that the aquatic toxicity of TFA is relatively low. For terrestrial plants, the ECHA registration dossier lists a no-observed-effect concentration (NOEC) of 830 µg/kg (dry weight of soil), which was based on growth tests conducted with three types of crop [45]. It has to be noted that TFA can be efficiently taken up and accumulated by vascular plants due to its hydrophilic nature and small molecular size [46,47]. TFA concentrations >1 mg/kg dry weight have already been detected in the leaves of deciduous and coniferous tree species [13,48]. However, no ecotoxicological effect data currently exists to adequately assess the risk of such high TFA concentrations to these species.

The reported toxicity of TFA in animals is rather low [49]. For example, Ulhaq et al. derived an EC_{50} and NOEC for Zebra fish embryos of 700 mg/L and 300 mg/L, respectively [50]. In a one-year feeding study on rats conducted in 2019, a no-observed-effect level (NOEL) of 1.8 mg TFA per kg body weight and day was determined. This was used by the German Environmental Agency to derive a drinking water guidance value for TFA of 60 µg/L [51]. The guidance value is the concentration of a substance in drinking water that is tolerable for lifelong consumption. Because of its very hydrophilic nature, TFA is not expected to accumulate over time in animals and humans. Nevertheless, human biomonitoring indicates widespread exposure to TFA. As such, TFA was found in 97% of serum samples from 252 Chinese adults in 2017 (detection limit: 0.12 µg/L), at a median concentration of 8.5 µg/L [52]. Despite using a relatively insensitive analytical method with a detection limit of 20 µg/L, TFA was still detected in urine in 30% of 83 Flemish adolescents in 2016/17 [53]. The presence of high concentrations of TFA in human samples is not unanticipated, considering the widespread occurrence of TFA in drinking water resources [3,18,20,41,54] and food [55,56]. This could indicate that the dietary uptake of TFA is currently underestimated.

Conclusion

Although the currently known toxicity of TFA is rather low, the ubiquitous presence of TFA in environmental samples highlights the need to better study potential human and environmental toxicity at a chronic low dose exposure. TFA will remain in the environment once released due to its exceptionally high persistence. With ongoing and increasing emissions of TFA from multiple anthropogenic sources, in combination with its high mobility in water and soil, high potential for long-range transport, as well as the absence of economically feasible remediation techniques, concentrations of TFA in various environmental compartments will increase. Therefore, in addition to continued monitoring of TFA in the environment, TFA and its precursors should be considered for regulation to minimize the risk of potentially irrevocable harm in the future.

Author contributions

All authors contributed equally to the conceptualization, writing, and editing of the paper.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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12. ** Freeling F, Behringer D, Heydel F, Scheurer M, Ternes TA, Nödler K: **Trifluoroacetate in precipitation: deriving a benchmark data set**. *Environ Sci Technol* 2020, **54**:11210–11219. https://doi.org/10.1021/acs.est.0c02910.

In this study a systematic and nation-wide field monitoring campaign was conducted to assess the occurrence of TFA in precipitation in Germany. The study revealed a pronounced seasonality of the TFA concentration and wet deposition flux of collected samples with maximum values in the summer.

13. ** Freeling F, Scheurer M, Koschorreck J, Hoffmann G, Ternes TA, Nödler K: **Levels and temporal trends of trifluoroacetate (TFA) in archived plants: evidence for increasing emissions of gaseous TFA precursors over the last decades**. *Environ Sci Technol Lett* 2022, **9**:400–405. https://doi.org/10.1021/acs.estlett.2c00164.

First study describing the concentrations and temporal trends of TFA in biota by analyzing archived leaf samples (observation period: 1989–2020). Study showed increasing trends in the TFA concentration, which is likely the result of both bioaccumulation as well as increasing emissions of gaseous TFA precursors over the last three decades.

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Sci Eur 2020, **32**:6856. https://doi.org/10.1186/s12302-020-00440-4.

The authors of this study emphasize that persistent, mobile and toxic (PMT) and very persistent and very mobile (vPvM) substances exhibit comparable (eco-)toxicological effects to persistent, bioaccumulative and toxic (PBT) and very persistent and very bioaccumulative (vPvB) subtances.

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