

Trifluoroacetic acid: a pressing need for human biomonitoring, chronic toxicity assessment, and epidemiological research

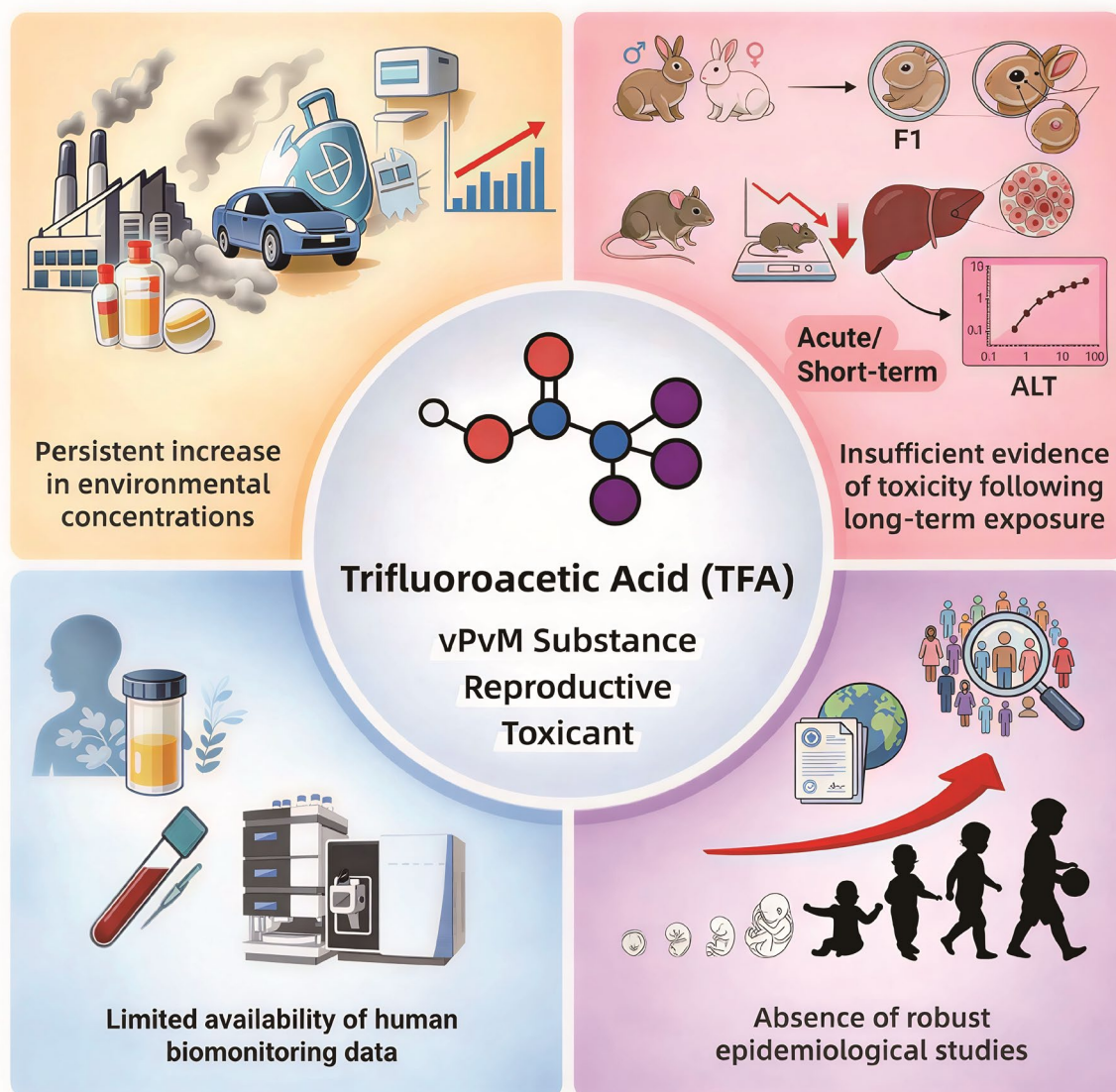
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Graphical Abstract



Highlights:

- TFA is classified as reproductive toxicant and vPvM substance.
- Human exposure to TFA is widespread, but its long-term health risks are unclear.
- Urgent research is needed on TFA biomonitoring, chronic toxicity, and epidemiology.

Trifluoroacetic acid: a pressing need for human biomonitoring, chronic toxicity assessment, and epidemiological research

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Abstract: On May 26, 2025, the German Federal Office for Chemicals (BfC) officially classified trifluoroacetic acid (TFA) as a substance with reproductive toxicity and very persistent and very mobile (vPvM) properties, and submitted the corresponding classification proposal to the European Chemicals Agency (ECHA). Drawing on current evidence, this commentary examines the primary anthropogenic sources of TFA, synthesizes toxicological findings from mammalian studies, and reports the current state of human exposure. Currently, driven by continuous emissions from various anthropogenic sources, environmental concentrations of TFA have been steadily increasing. This widespread environmental exposure has directly led to the prevalent detection of TFA in human. Although the acute toxicity of TFA is relatively low, its ability to accumulate in human body fluids and its potential to bind to proteins collectively constitute long-term health risks that cannot be overlooked. However, data on the toxicological mechanisms of long-term TFA exposure, and epidemiological evidence remain very limited. In this context, we call for stricter regulation of such highly persistent substances while prioritizing research on human biomonitoring, chronic toxicity assessment, and epidemiological research of TFA and other short-chain PFAS, thereby providing scientific support for developing effective environmental control strategies.

Keywords: trifluoroacetic acid; anthropogenic sources; mammalian toxicity; human exposure; health risks

1. Introduction

Trifluoroacetic acid (TFA, CF_3COOH) is the shortest-chain perfluoroalkyl carboxylic acids (PFCAs). Due to its extremely low pKa and high water solubility (Figure 1), TFA exists almost entirely in anionic form (CF_3COO^-) under environmental pH conditions. This property facilitates it easy to penetrate soil and sediment and undergo long-range transport in aquatic systems. At the same time, the extremely strong C–F bonds confer high resistance to chemical, photochemical, and biological degradation, resulting in extreme environmental persistence. Although TFA has long been considered to be relatively low acute toxicity^[1,2], its extreme persistence and high mobility in the environment enable it widely distributed in rainwater, groundwater, surface water and even drinking water, forming a continuous and widespread human exposure pathway^[3,4]. This long-term exposure risk, which is difficult to get eliminated, has prompted regulatory agencies including Germany to reassess its potential health effects.

On May 26, 2025, Environmental Action Germany (DUH) announced that the Federal Office for Chemicals (BfC), in

cooperation with the German Federal Environment Agency (UBA) and the German Federal Institute for Risk Assessment (BfR), has formally proposed to classify TFA as toxic to reproduction as well as a very persistent and very mobile (vPvM) substance^[5]. The corresponding classification dossier has been submitted to the European Chemicals Agency (ECHA). The BfR has assessed TFA as reprotoxic, proposing an official hazard classification of “Toxic to reproduction, category 1B” with the hazard statements H360Df: “May damage the unborn child. Suspected of impairing fertility”. Meanwhile, the UBA classified TFA as vPvM. Substances with these properties are resistant to degradation in environmental systems and hardly bind to sediments or activated carbon filters.

We believe that the proposal by BfC fills a regulatory gap for PFAS with high persistence and high mobility, such as TFA, and prompts the scientific community and regulatory agencies to re-examine the potential toxicity of ultrashort- and short-chain PFAS. This commentary systematically analyzes the primary anthropogenic sources of TFA in the environment and highlights that its environmental concentrations are projected to continue rising in the future, a trend that further

increase the exposure risks of TFA to humans. Although current evidence from human and animal studies on the toxicity of TFA remains limited, the reality of long-term global human exposure to TFA can no longer be overlooked. Therefore, we emphasize the urgent need to human biomonitoring,

chronic toxicity assessment, and epidemiological research on TFA and other ultrashort-/short-chain PFAS, in order to scientifically support their risk assessment and the development of control strategies.

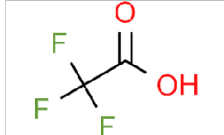
 $\text{C}_2\text{HF}_3\text{O}_2$ MW:114.02 g/mol	property	value
	boiling point	72-74 °C
	vapor pressure	11-13 kPa
	pKa	0.23
	solubility	miscible
	log K_{ow}	-2.1

Figure 1. Physicochemical properties of TFA.

2. Trifluoroacetic acid: the ubiquitous and rising environmental contaminant

Compare to other short-chain homologues such as perfluorobutanoic acid (PFBA) and perfluorobutanesulfonic acid (PFBS), the extremely high water solubility and very low octanol/water partition coefficient (log K_{ow}) endow TFA with greater mobility in the atmosphere water cycle, leading to its enhanced transfer and persistent presence in aquatic systems, particularly in the oceans. This characteristic also explains why TFA has been widely detected in a variety of environmental media (e.g., rainwater, soil), food chains (e.g., plants, drinking water), and ultimately in human serum.

There are two main anthropogenic sources of TFA in the environment: one is derived from direct industrial production and emission of synthetic TFA, its salts or derivatives, which are widely used in organic synthesis, biochemistry, pharmaceutical research, and analytical chemistry [6]. As a result, TFA has become the most widespread and predominant PFAS in the environment. For example, it constitutes over 90% of the total mass of PFASs (based on the analysis of 46 PFAS) in various drinking water sources [7]. Recent monitoring data reveal significant and widespread levels of TFA in both precipitation and drinking water. In precipitation, median concentrations have been measured at 0.01–1.8 µg/L across twenty-eight Chinese cities [8], with reported values of 0.29 µg/L in the USA [9], 0.21 µg/L in Germany [10], and 0.30 to 0.96 µg/L in Switzerland [11]. Similarly, drinking water concentrations vary considerably by region, ranging from 0.08 µg/L in USA [2], and 0.23 µg/L across 19 non-German countries, to as high as 1.5 µg/L in Germany [7]. A comparison of pre- and post-2010 data reveals an increase of over an order of magnitude in both the maximum and mean TFA concentrations across multiple compartments, from precipitation and various water bodies to drinking water, soil, and plants [12].

The indirect formation of TFA from the atmospheric degradation of certain refrigerants and other fluorinated precursors represents another major environmental source [13,14]. As alternatives to chlorofluorocarbons (CFCs), hydrofluorocarbons (HFCs) and hydrofluoroolefins (HFOs) are widely used in the fields of refrigerants and foaming

agents [15]. After use or emission, HFO-1234yf can completely degrade into TFA within approximately two weeks, absorbed by rainwater, and widely dispersed in the environment including surface water, groundwater, soil, dust, and air [16]. In the EU, the use of HFO-1234yf resulted in TFA emissions of 6,900 t/year in 2020, with projections indicating an increase to 47,650 t/year by 2050 [14]. In addition, most compounds containing a C–CF₃ group, such as fluorinated pesticides [17], pharmaceuticals [18] and fluoropolymers [19], can also degrade into TFA in the environment. In the future, the continuous release of these compounds may lead to an increase in TFA emissions by several orders of magnitude in the short term.

3. Toxicity profile of TFA: documented effects and data gaps

Different from other short-chain PFAS that act mainly as weak agonists of nuclear receptors (e.g., peroxisome proliferator activated receptor), TFA exerts its toxicity through direct interference with mitochondrial function [20] and basic energy metabolism. TFA has been detected in humans, however, its toxicity remains controversial. For instance, although TFA is a strong acid with corrosive properties, a single oral dose as high as 2000 mg/kg (with an LD50 of 500 mg/kg body weight) did not cause mortality in rats, indicating relatively low acute toxicity [21]. Current mammalian toxicity data on TFA remain limited, primarily derived from studies conducted in accordance with the OECD and UBA guidelines. Most of these studies are based on rat models and have preliminarily established no-observed-adverse-effect levels (NOAELs) under different exposure conditions, providing a basis for risk assessment.

In a 28-day dietary exposure experiment, at exposure doses of 5400 ppm and 16,000 ppm, rats exhibited increased liver weight and hepatomegaly, but no histopathological damage was observed. Even at the highest dose, TFA did not cause mortality, weight loss, or abnormal feeding behavior in rats, and only led to a slight increase in alanine aminotransferase (ALT) activity [22]. When the exposure period was extended to 90 days, doses above 160 ppm caused changes in hematological parameters and increased liver weight in female mice, accompanied by hepatocellular

hypertrophy. At an exposure concentration of 16,000 ppm, male rats showed weight loss and an increased incidence of hepatocellular necrosis foci [23]. In a one-year drinking water exposure study conducted by UBA, even at a relatively low dose (120 ppm), a slight increase in ALT was observed [24]. This may suggest that chronic toxicity of TFA needs to be paid the attention.

A dietary exposure study in rats (0, 120, 600, 3000 ppm) to simulate continuous TFA exposure in parental and offspring generations across different life stages, systematically evaluating the potential effects of TFA on parental reproductive function and offspring growth/development. The results showed that TFA did not significantly affect the estrous cyclicity, thyroid hormones, or sperm parameters in the parental animals. Although changes in liver weight and decreased thyroid hormone T4 levels were observed in the offspring, other thyroid-related indicators (T3, TSH), body weight, histopathology, and reproductive parameters were not affected. Consequently, these changes were not deemed adverse effects [25]. Additionally, a prenatal developmental toxicity study assessed the embryotoxic potential of TFA and found that TFA did not exhibit embryo-fetal toxicity at doses as high as 150 mg/kg/day. Only slight increases (< 10%) in liver and kidney weights were observed, but no reproductive damage such as spontaneous abortions, pre- and post-implantation loss, or early or late resorptions. No signs of developmental toxicity such as abnormal fetal weight, visceral malformations, or skeletal abnormalities were found in any dose group [26].

However, in an embryo-fetal developmental toxicity study using New Zealand White rabbits, four groups totaling 30 pregnant females were orally administered sodium trifluoroacetate (at doses of 30, 60, 250, or 750 mg/kg/day) from gestation day 6 to 28. An equal number of animals served as the control group. On day 29 post mating, the animals were sacrificed for reproductive evaluation and fetal examination. The results indicated that in the high dose group (750 mg/kg/day), the incidence of fetal ocular malformations increased significantly, primarily manifested as multiple retinal folds, absence of aqueous/vitreous humor, hemorrhage in the aqueous/vitreous humor, and lens deformities [27]. Based on this finding, BfR recommended classifying TFA as a reproductive toxicant.

In real-world environments, organisms may be subject to lifelong exposure to relatively high concentrations of TFA, compared with other chemical pollutants. It is noteworthy that toxicity data on long-term, environmentally relevant dose exposure to TFA remains highly limited, which poses a significant challenge to a comprehensive assessment of its health risks.

4. The ubiquitous body burden of TFA and its uncertain health risks

TFA exhibits a low octanol/water partition coefficient ($\log K_{ow} = -2.1$), indicating a lack of bioaccumulation potential [28]. Human toxicokinetic studies reveal that TFA is rapidly absorbed after oral administration, enters the enterohepatic circulation, and distributes in body via

blood, including translocation across the placental barrier. The primary routes of excretion are urinary and biliary [21]. However, the persistent accumulation of TFA in various exposure media, such as indoor dust, drinking water, edible plants, grains, wine, fruit juices, and vegetable juices, suggests that humans may be at risk of long-term continuous exposure [2,7,29].

Indeed, TFA has been detected in human blood and urine (Table 1). In China, a study in Tianjin reported a median TFA concentration of 8.46 ng/mL in human blood, with detection levels comparable to several long-chain perfluoroalkyl acids (PFAAs) [30]. Meanwhile, a cohort study in Shijiazhuang reported a blood TFA concentration of 0.23 ng/mL and a detection rate of 55% [31]. In the United States, analysis of 324 resident samples from Indiana found that TFA was the predominant perfluorinated compound in serum, with a detection frequency of 74% and a median concentration of 6.0 ng/mL. In urine samples, TFA was detected less frequently (31%), but the maximum concentration reached 290 ng/mL [2]. Another study analyzing serum samples from residents in Wilmington, North Carolina, between 2010 and 2016 showed a notably high median TFA concentration of 17 ng/mL, with a detection frequency of 77% [32]. In Europe, a cohort study in Norway reported a serum TFA concentration of 6.75 ng/mL with a detection rate of 100% [33]. Additionally, TFA concentrations in human urine samples from Belgium [34] and Australia exceeded 20 ng/mL, with a detection rate of 100% observed in the Australian population [35]. These findings further confirm the widespread presence and accumulation trend of TFA in human bodily fluids. Moreover, TFA can be transferred across the placenta to the fetus [31,36], as evidence by its detection in neonatal cord blood samples [31]. Therefore, future research should quantitatively analyze paired maternal and cord blood TFA concentrations in more representative pregnant cohorts, calculate the placental transfer rate, and explore its potential exposure risks.

At current environmental concentrations, TFA demonstrates relatively low toxicity to humans [37]. Recently, Sodani *et al.* employed advanced *in vitro* testing technologies, ToxProfiler and ReproTracker, to explore the potential toxicological mechanisms of TFA and other ultrashort-chain PFAS [38]. ToxProfiler is a set of human *in vitro* experiments containing seven fluorescence reporting systems, which can visualize and quantitatively evaluate the activation of major cellular stress pathways [39]. ReproTracker is a testing platform based on human induced pluripotent stem cells (hiPSCs), which is used to identify developmental toxicity risks of new drugs and chemical substances by differentiating them into cardiomyocytes, hepatocytes, and neural rosettes [40]. The results showed that even at the highest tested concentration (10 mM), TFA did not activate any ToxProfiler stress response reporters and caused no significant effects on the morphology or functionality of the three differentiated cells [38]. In a separate study, Đurđević Delmaš *et al.* explored the binding properties of TFA and other perfluoroalkyl acids to human fibrinogen (a key blood protein). The study found that TFA exhibits moderate binding affinity to fibrinogen, with a dissociation constant ranging between 10^{-4} and 10^{-5} M.

Although this binding did not significantly interfere with the coagulation function of fibrinogen, the study identified multiple binding sites of TFA on the protein [41]. This finding challenges the conventional view that short-chain PFAS

have low bioaccumulation potential and underscores the necessity for further investigation into their long-term health effects.

Table 1 Concentration of TFA in human serum and urine.

Sample Type	N	DF (%)	Median (ng/mL)	Location	Reference
Serum	66	55	0.23	China	[31]
	252	62	8.46	China	[30]
	81	74	6.0	USA	[2]
	119	77	17	USA	[32]
	144	100	6.75	Norway	[33]
Urine	83	30	> 20	Belgium	[34]
	81	31	< 3.5	USA	[2]
	58	100	23.5	Australia	[35]

5. Epidemiological evidence for Health effects of short-chain PFAS

To date, no epidemiological studies have investigated the association between TFA exposure and long-term health outcomes in humans. Most research has focused on a few of long-chain PFAS, leaving a substantial gap in the detection coverage of (ultra-)short-chain compounds. In fact, exposure to (ultra-)short-chain PFAS is already widespread among general populations, and a growing number of epidemiological evidence is revealing their potential adverse effects on the liver, nervous system, and reproductive system.

The liver is a primary target organ for PFAS toxicity. In adults, higher serum concentrations of short-chain PFAS mixtures have been significantly associated with elevated ALT levels, indicating increased risk of liver injury [42]. Furthermore, Schlezinger *et al.* reported positive associations between PFBA and perfluorohexanoic acid (PFHxA) and serum gamma-glutamyl transferase concentrations [43]. These findings collectively suggest that short-chain PFAS may exert adverse effects on hepatic function. Recent evidence has implicated perfluoroheptanoic acid (PFHpA) in the pathogenesis of metabolic dysfunction-associated steatotic liver disease among adolescents, highlighting the critical role of protein dysregulation in disease development [44]. Additionally, short-chain PFAS may contribute to childhood obesity, as evidenced by a study reporting positive associations between prenatal PFBS exposure and obesity in five-year-old girls [45], suggesting a potential role of short-chain PFAS in pediatric metabolic health.

The neurodevelopmental effects of short-chain PFAS are equally concerning. Zhou *et al.* demonstrated that perfluorohexane sulfonate (PFHxS) exposure may impair neurodevelopment in children by altering neonatal gut microbiome diversity and metabolic pathways, ultimately contributing to increased behavioral problems [46]. Moreover, prenatal exposure to specific short-chain PFAS has been linked to cognitive development in a sex-specific manner: higher maternal PFBA concentrations were significantly

associated with lower verbal comprehension index scores in boys, while elevated maternal PFHxS levels associated with reduced working memory index scores [47]. These findings suggest that prenatal exposure to short-chain PFAS may impair early cognitive development through sex-specific and potentially non-linear patterns.

The reproductive toxicity of short-chain PFAS is also being progressively elucidated. Regarding male reproductive health, combined maternal exposure to multiple PFAS has been associated with reduced sperm concentration, decreased total sperm count, and increased proportions of non-progressive and immotile sperm in young adult males, with PFHpA identified as a primary contributor [48]. A cross-sectional study further confirmed that exposure to PFBS and PFHxS is associated with diminished semen concentration, total sperm count, and sperm motility [49]. At the fetal developmental level, a prospective cohort study revealed that prenatal exposure to short-chain PFAS, particularly PFBS and PFHpA, is associated with decreased levels of follicle-stimulating hormone and luteinizing hormone and reduced free androgen index, further emphasizing that the reproductive toxicity of short-chain PFAS warrants serious attention [50].

Although the long-term health effects of TFA remain to be characterized, accumulating epidemiological evidence indicates that various short-chain PFAS pose potential health risks encompassing hepatic function, neurodevelopment, reproductive health, and metabolic regulation. These findings underscore the necessity for future investigations to expand the scope of PFAS biomonitoring, incorporate (ultra-) short-chain compounds into routine surveillance programs, and further elucidate their underlying biological mechanisms and long-term health implications.

6. Conclusion remarks

The proposal by BfC to classify TFA as a very persistent and very mobile substance with reproductive toxicity marks a significant paradigm shift in PFAS regulation. Our systematic analysis demonstrates that environmental concentrations of TFA continue to rise due to its ongoing release from industrial sources such as refrigerants. This widespread

environmental exposure has directly led to its prevalent detection in human blood across different regions. Although TFA exhibits low acute toxicity, its documented accumulation in humans, potential for binding to human proteins, and possible reproductive toxicity collectively constitute long-term health concerns that cannot be ignored. Furthermore, the detection of TFA in maternal and cord blood not only confirms its ability to cross the placental barrier but also directly indicates a risk of intrauterine exposure. Future research should focus on the long-term effects of early-life exposure on offspring health, particularly its potential hazards to developmental and metabolic functions.

Data availability statement

No supplementary or additional data were generated in this study.

Declaration of generative AI and AI-assisted technologies

During the preparation of this manuscript, the authors used generative AI tools only to improve language and readability. The authors take full responsibility for the content of the manuscript.

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Authors' contribution

Yanmei Wu: writing—original draft, writing—review and editing and investigation; Kangao Sun: writing—original draft and investigation; Jingchuan Xue: writing—review and editing, supervision and funding acquisition. All authors have read and agreed to the published version of the manuscript.

Conflicts of interest

Jingchuan Xue holds the position of Editorial Board Member for *International Journal of Environmental Epidemiology* and has not peer reviewed or made any editorial decisions for this paper.

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