Archives of Toxicology
https://doi.org/10.1007/s00204-023-03454-y

MOLECULAR TOXICOLOGY

Mammalian toxicity of trifluoroacetate and assessment of human health risks due to environmental exposures

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Received: 18 December 2022 / Accepted: 2 February 2023

Abstract

While trifluoroacetic acid has limited technical uses, the highly water-soluble trifluoroacetate (TFA) is reported to be present in water bodies at low concentrations. Most of the TFA in the environment is discussed to arise from natural processes, but also with the contribution from decomposition of environmental chemicals. The presence of TFA may result in human exposures. For hazard and risk assessment, the mammalian toxicity of TFA and human exposures are reviewed to assess the margin of exposures (MoE). The potential of TFA to induce acute toxicity is very low and oral repeated dose studies in rats have identified the liver as the target organ with mild liver hypertrophy as the lead effect. Biomarker analyses indicate that TFA is a weak peroxisome proliferator in rats. TFA administered to rats did not induce adverse effects in an extended one-generation study and in a developmental toxicity study or induce genotoxic responses. Based on recent levels of TFA in water and diet, MoEs for human exposures to TFA are well above 100 and do not indicate health risks.

Keywords Trifluoroacetate · Trifluoracetic acid · Margin of exposure · Human safety · Environmental exposures

Introduction

Trifluoroacetic acid is a strong organic acid (pK_a of app. 0.43) with high volatility and limited industrial uses as a solvent and as an intermediate in the synthesis of agrochemicals and pharmaceuticals (Solomon et al. 2016). It is miscible with water and its low octanol/water partition coefficient (log Pow = − 2.1) indicates no potential to bioaccumulate (Boutonnet et al. 1999). At the pH levels of environmental media (pH ranges from app. 4.0–8.5), trifluoroacetic acid is present as salt, often as sodium trifluoroacetate (TFA). TFA has been detected as a ubiquitous and highly mobile contaminant present in low concentrations in ocean and rainwater at most sampling sites including remote areas and deep ocean waters (Cahill 2022; Frank et al. 2002; Scheurer et al. 2017).

A variety of sources may contribute to TFA in the environment. While a natural formation of TFA along other fluorinated chemicals by volcanic activity and deep ocean vents is discussed as a major source of trifluoroacetate in the environment, TFA is also formed from fluorinated refrigerants, pharmaceuticals, and pesticides. TFA is a degradation product formed by the reaction of some fluorinated hydrocarbons used as refrigerants (e.g., 1,1,1,2-tetrafluoroethane, HFC-134a, and 2,3,3,3-tetrafluoropropane, HFO-1234yf) with atmospheric hydroxyl radicals (Ball and Wellington 1993; David et al. 2021). Release of such refrigerants followed by their atmospheric degradation will result in a wide distribution of formed TFA that will be cleared from the atmosphere by precipitation (Solomon et al. 2016). However, mass balance considerations do not suggest that degradation of fluorinated refrigerants constitutes a major contributing factor to the TFA background (David et al. 2021; Solomon et al. 2016). In addition, trifluoroacetate is a urinary metabolite of inhalation anesthetics such as halothane (2-bromo-2-chloro-1,1,1-trifluoroethane), desflurane (2-(difluoromethoxy)-1,1,1,2-tetrafluoroethane), and isoflurane ((*RS*)-difluormethoxy-1-chlor-2,2,2-trifluorethane) and a number of marketed pharmaceuticals may also be degraded/metabolized to release TFA (Inoue et al. 2020). Excretion of TFA by patients undergoing anesthesia with these compounds will also contribute to the presence of TFA in surface waters. Moreover, TFA is formed as a plant metabolite and/or degradation product of a number of

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Published online: 17 February 2023

herbicides such as flufenacet (*N*-(4-fluorphenyl)-*N*-isopropyl-2-(5-trifluormethyl-(1,3,4)-thiadiazol-2-yloxy)acetamid) or saflufenacil (2-chloro-4-fluoro-5-[3-methyl-2,6-dioxo-4-(trifluoromethyl)-3,6-dihydropyrimidin-1(2H)-yl]-*N*-[methyl(propan-2-yl)sulfamoyl]benzamide). Application of such products contributes to TFA residues in crops besides uptake of TFA from soil (EFSA 2014; Johnson et al. 2020).

This review summarizes the available mammalian toxicity data on trifluoroacetate and integrates this information with potential human exposures to trifluoroacetate based on the measured concentrations of TFA in water and food using the margin of exposure methodology.

Mammalian toxicity of TFA

Local effects

Irritation and corrosivity Undiluted trifluoroacetic acid is highly corrosive on contact with skin, and inhalation of pure trifluoroacetic acid irritates the upper airways. As undiluted trifluoroacetic acid is only handled in industrial applications and laboratories with adequate safety measures, the toxicity information has little relevance to humans exposed from the environment, since these exposures are to diluted TFA or its salts (ECHA 2022).

A single exposure inhalation toxicity study in rats ($n = 5$) is also available for undiluted trifluoroacetic acid with nose-only exposures for 4 hours at three concentrations (0; 30 or 300 mg/m^3). The intention of the study was to characterize the irritant potential of the free trifluoroacetic acid on the respiratory tract and covered analysis of respiratory tract histopathology. Assessment of an LC_{50} was not intended. A very slight focal degeneration of the respiratory epithelium was observed at the high exposure concentration of 300 mg/m^3. The effect was considered to be due to the irritant properties of undiluted trifluoroacetic acid and was reversible within the 2-week observation period. Based on these, a no-observed adverse-effect concentration (NOAEC) of 300 mg/m^3 was established (ECHA 2022).

Effects of repeated inhalation of trifluoroacetic acid in rats are described in a cursory form in the ECHA registration dossier for trifluoroacetic acid (ECHA 2022). Apparently, animals were exposed to a mixture of vapors and aerosols (no information on compositions) for 4 h/day and 6 days/week for a period of 4 (guinea pigs) or 5 (rats) months, but detailed information on the study design and effect incidences are not available. According to the summary, inhalation of trifluoroacetic acid caused severe irritation of the respiratory pathway and the eyes in both rats and guinea pigs. "Dystrophy" of liver and kidneys and a loss of body weight gain are also described. The validity of the study and the relevance of the results cannot be assessed due to the very limited information available, but effects on the respiratory tract are expected due to the corrosive properties of trifluoroacetic acid and in line with the observations of the single exposure inhalation study. The study was used in the ECHA registration dossier to establish a "derived no-effect level" (DNEL) for inhalation of trifluoroacetic acid of 3.37 ppm for acute exposures and as basis for extrapolation to a long-term DNEL of 0.56 ppm by dividing by a "worst-case" extrapolation factor (ECHA 2022).

Skin sensitization: Skin sensitization may be considered as a potential hazard of TFA, since elicitation thresholds in sensitized individuals may be sufficiently low to induce effects. Apparently, due to the strong skin corrosive properties of trifluoroacetic acid, the potential of the acid to induce sensitization has not been assessed. However, read-across to TFA is possible from data on skin sensitization obtained with trifluoroacetic acid ethyl ester in the local lymph node assay (LLNA) following OECD test guideline (TG) 429. Trifluoroacetic acid ethyl ester is more reactive as compared to trifluoroacetate, as the ester has some reactivity with nucleophilic sites in proteins that trifluoroacetate does not have. Formation of protein adducts is the molecular initiating events in the adverse outcome pathway for skin sensitization. Trifluoroacetic acid ethyl ester is rapidly hydrolyzed to give TFA. Application of trifluoroacetic acid ethyl ester in acetone/olive oil (4.1, v:v) at six concentrations ranging from 0 to 100% to the dorsum of both ears of mice did not induce skin irritation, lymph node proliferative responses, clinical signs, or mortality. Therefore, TFA is not a skin sensitizer (ECHA 2022).

Systemic toxicity

Effects after single dose administration According to ECHA, despite the high corrosivity, the oral LD_{50} of free trifluoroacetic acid is above 500 mg/kg body weight (bw). Potential effects of TFA were assessed after a single oral dose level of 2000 mg/kg bw in rats, with absence of mortality showing that the acute toxicity of TFA is very low (ECHA 2022).

Effects after repeated administration The availability of a number of oral repeated dose toxicity studies on TFA with different durations permit a well-informed evaluation of the oral toxicity of TFA as the most relevant human exposure pathway from environmental sources (ECHA 2022; EFSA 2014).

To characterize the repeated dose oral toxicity of TFA, results of a 28-day and a 90-day dietary toxicity studies and a 1-year drinking water toxicity study are available. In addition, a 2-week oral study with TFA focused on the mode of action for liver effects seen in these studies. In the 28-day oral study performed according to OECD-TG407, TFA was administered with diet (concentrations of 0, 600,

1800, 5400, and 16,000 ppm) to male and female Wistar rats ($n = 5$/dose group) resulting in average intakes of 0, 50, 149, 436, and 1315 mg/kg bw/day in males and 0, 52, 157, 457, and 1344 mg/kg bw/day in females. Administration of TFA did not result in mortality, effects on body weight, or food consumption. The clinical chemistry evaluation indicated a small increase in the activity of alanine aminotransferase (ALT) at the highest dose levels in both males and females and small effects on serum cholesterol and glucose levels. The minor changes in ALT were accompanied by dose-dependent increases in absolute and relative liver weight and liver to body/brain weight ratios at TFA concentrations > 600 ppm and liver enlargement at 5400 and 16,000 pm. However, liver enlargement was not accompanied by histopathological changes in the liver. Effects of TFA on other parameters relative to controls were not noted and the study states that the highest dose administered is considered as NOAEL (Bayer 2014).

In the 90-day oral study in Wistar rats performed along OECD-TG408, sodium TFA was administered to male and female rats ($n = 10$/group) at 0, 160, 1600, and 16,000 ppm in diet. Received doses were approximately 0, 9.9, 98, and 1043 mg TFA/kg body weight/day in males and 0, 12.2, 123, and 1216 mg TFA/kg body weight/day in females. A reduced body weight gain was seen in males at the highest dose level and treatment-related changes in hematology parameters occurred in females at dose levels of > 160 ppm. A number of treatment-related effects on clinical chemistry (bilirubin, glucose, "liver enzymes") and urine composition (higher ketone bodies) were observed at dietary concentrations > 160 ppm. Both mean absolute and relative liver weights were also increased at feed concentrations > 160 ppm and were accompanied by minimal to moderate diffuse centrilobular hepatocellular hypertrophy and an increased incidence of hepatocellular necrotic foci in males at 16,000 ppm. Based on these observations, a dietary concentration of 160 ppm of TFA (10 mg/kg bw/day in males and 12 mg/kg bw/day in females (sodium TFA) resp. 8.4 and 10.1 mg/kg bw for TFA) was considered as NOAEL (Bayer 2014). The ECHA registration dossier used the NOAEL from this study to establish a DNEL of 0.042 mg/kg bw/day applying an extrapolation factor of 200 (ECHA 2022).

Results of a 1-year drinking water study with TFA are summarized in the justification document of the German Environment Agency (Umweltbundesamt, UBA) for a drinking water limit for TFA (UBA 2020). According to the information presented by UBA, TFA was administered with drinking water for 1 year to rats at concentrations of 0, 30, 120, and 600 ppm. Apparently, the conducting laboratory concluded that the highest TFA concentration of 600 ppm included in the study design (received dose of 37.8 mg/kg body weight) represented a NOAEC/NOAEL in male animals. However, UBA considered small changes in ALT that were observed in the study at 120 and 600 ppm as relevant points of departure. In the context of changes in liver enzymes and some TFA-related histopathology in liver effects seen in other oral studies at much higher concentrations of TFA, a highly conservative NOEL of 30 ppm (1.8 mg/kg bw/day) was established to derive a safe level for TFA in drinking water.

To assess possible modes of action to explain the changes in "liver enzyme" and the mild liver hypertrophy seen after repeated administration of TFA, a repeated dose oral study integrated a number of additional end points indicative of mode of action for liver changes. Male and female ($n = 5$/group) were given diets with sodium TFA at concentrations of 0, 600, 1200, and 2400 ppm (received doses were 0, 43, 85, and 170 mg/kg bw/day in males and 0, 45, 91, and 190 mg/kg bw/day in females) for 14 days. Clofibric acid at 5000 ppm (received dose of 291 mg/kg bw/day in males and 359 mg/kg bw/day in females) was used as a positive control to assess the activity of TFA as peroxisome proliferator. Animals were killed after 14 days and cytochrome P450 (P450) enzyme content and activity of specific P450 enzymes were determined in the liver in addition to cell cycle and biomarkers of peroxisome proliferation (palmitoyl-CoA oxidation). In this study, TFA did not affect body weight gain, food consumption, hematology, and clinical chemistry, but resulted in increased liver weights and hepatocellular hypertrophy. Increased palmitoyl-CoA oxidation was also observed at the two top dose levels in males and with the positive control in both males and females. Based on these observations, TFA has to be considered a weak peroxisome proliferator (Bayer 2014).

In summary, the liver can be considered as the target organ after repeated oral administration of TFA. However, the effects of TFA on liver are generally mild as judged by the small changes in "liver enzymes" and the minimal to slight liver hypertrophy seen even at daily doses > 1000 mg/kg bw in the 90-day oral study. Effects of TFA on the liver seem to be mediated by peroxisome proliferation, which is a mode of action not considered relevant to humans (see discussion below).

Reproductive and developmental toxicity

Fertility Aspects of fertility and developmental toxicity of TFA were assessed in a recently conducted extended one-generation reproductive toxicity study in rats (EOGRTS) following OECD-TG443. Sodium TFA was administered with diet to Wistar rats. In the F0 generation, male and female rats (25 males and females/dose group) were fed diets containing 0, 120, 600, or 3000 ppm TFA for 10 weeks during premating, gestation, and lactation. Received doses were 0 and app. 10, 50, and 250 mg/kg bw/day. To compensate for the higher food intake during lactation, dietary concentrations

of TFA were reduced to 60, 300, and 1500 ppm in females during lactation. The two cohorts of F1 animals (20 males and females/group in each cohort) were not exposed to TFA during lactation, and received TFA-containing diets (60, 300, and 1500 ppm) from postnatal day (PND) 21 to PND 35 and of 10, 600, and 3000 ppm from PND 35 to killing. As requested in the guidance, the study also covered estrous cyclicity, thyroid hormones, and sperm parameters (ECHA 2022).

Treatment-related adverse effects on the many parameters to be monitored in the OECD-TG443 study design were not observed in the parental animals. Offspring (F1) showed treatment-related changes including changes in relative liver weights, some clinical chemistry parameters, and reductions in serum T4 to values below the concurrent controls in F0 animals (3000 ppm in males and 1500/3000 ppm in females), and in F1 animals (at 1500 ppm in males and females at day 22 and 600 and 3000 ppm at termination in males). However, no other thyroid parameters (T3, TSH, weight, histopathology) or reproductive parameters were affected and these changes thus are not considered as adverse. The applicant therefore concluded that the top dose level in the study (3000/1500 ppm) with intakes between 242 and 265 mg of the sodium salt of TFA/kg bw/day can be considered as NOAEL for reproductive performance, offspring development, and general toxicity.

Developmental toxicity The potential of TFA to induce embryo–fetal toxicity was assessed in a prenatal developmental toxicity study (following OECD-TG414) summarized in the ECHA registration dossier (ECHA 2022). TFA was administered to groups of pregnant female rats ($n = 22$/group) from gestational day (GD) 6–19. TFA doses were at 0, 37.5, 75, and 150 mg/kg bw/day by gavage administration in water. Fetuses were collected by cesarean section on GD 20. The only effect of TFA administration in maternal animals was a small increase in liver and kidney weights. TFA did not increase the number of spontaneous abortions, pre- and post-implantation loss, or early or late resorptions. Fetal effects of TFA administration (body weight, sex ratio, litter size and weight, and incidences of both skeletal and visceral malformations) were also not observed. Due to absence of maternal and embryo–fetal effects, the applicant derived the highest dose administered as NOAEL (150 mg/kg bw/day) and considered the small increases in maternal liver and kidney weight as not adverse (< 10% change).

Genotoxicity

The genotoxicity of TFA has been investigated in the recommended panel of in vitro test systems in bacteria and mammalian cell with consistently negative results permitting the conclusion that TFA does not have a genotoxic potential (ECHA 2022; EFSA 2014).

Mutagenicity in bacteria Sodium TFA was assessed for potential mutagenic activity using the bacterial reverse mutation assay (following OECD-TG414) in five histidine-requiring strains of *Salmonella typhimurium* (TA1535, TA1537, TA102, TA100 and TA98) in the absence and in the presence of metabolic activation by rat liver subcellular fractions (S_9). TFA did not induce toxicity to the bacteria and thus could be applied up to the limit concentrations specified in TG 471 (5 mg/plate). An increase in revertant colonies was only observed with TFA at one concentration (0.625 mg/plate) in one experiment and only in strain TA98. Due to the absence of dose–response for this single positive response, this was correctly considered a chance finding. The study included positive controls (as specified in OECD-TG471) that gave the expected responses and confirm that the test results are valid. Therefore, TFA is not considered as mutagenic in the bacterial reverse mutation test (ECHA 2022).

In vitro mammalian cell gene mutations The potential of TFA to induce gene mutations in mammalian cells was assessed in mouse lymphoma L5178Y cells using the thymidine kinase locus (following OECD-TG476). Sodium TFA was applied in seven graded concentrations from 0 to 1.36 mg/mL (highest concentration represents 10 mM TFA) in the absence and presence of a bioactivation system (S_9) in two experiments (the 1st experiment included a 3 h treatment with S_9, and the 2nd experiment included both a 24 h treatment without S_9 and a 3 h treatment in the presence of S_9). Appropriate positive controls were included and performed as expected. Besides one small, but statistically significant increase in mutant frequencies at an intermediate concentration in the presence of S_9 in the first experiment, no statistically significant increases in mutant frequency were observed. The single increase did not indicate a dose–response and was small in magnitude and thus not considered biologically relevant. Therefore, TFA is not mutagenic in the mammalian cells (ECHA 2022).

In vitro mammalian chromosome aberrations The potential of TFA to induce chromosome aberration was assessed in cultured human primary lymphocytes (following OECD-TG473). Cells were exposed both in the presence and absence of S_9 to four concentrations of sodium TFA (0, 0.34, 0.68, 1.34 mg/mL) for 3 h and sampled at 20 h after the beginning of treatment in the presence of S_9. In a second experiment, cells were exposed for 20 h (0, 0.085, 0.17, 0.34, 1.36 mg/mL) in the absence of S_9 or 3 h in the presence of S_9 (0, 0.34, 0.68, 1.34 mg/mL). Positive controls as requested in TG 473 were included and positive control-induced responses were consistent with historic controls. In

the TFA-exposed cultures, only one increase in the percentage of cells with structural chromosomal aberrations was observed at the highest concentration of TFA applied. Since the percentage of cells with aberrations at this concentration (10 mM) remained in the range of historical controls and a high degree of mitotic inhibition was seen at this response level, it was judged as not representing a positive response. In all other samples, the incidence of chromosome aberrations were not above background in the absence and presence of S_9. In conclusion, TFA is not considered to be clastogenic (ECHA 2022).

The absence of a mutagenic or clastogenic response for TFA is reasonable, since interaction with macromolecules requires the presence of certain structural prerequisites (electrophilicity or bioactivation to an electrophilic metabolite or a radical ability to intercalate). Such prerequisites are not present with TFA, as the stable and highly water-soluble molecule is not electrophilic, not subjected to biotransformation, and does not carry the planar structure required for intercalation. Thus, absence of a response in the three-well validated in vitro test systems supports the conclusion that TFA is not genotoxic and consistent with predictions based on the structure and principles of biotransformation.

Toxicokinetics

While the justification of German UBA for the derived drinking water limit for TFA mentions the availability of a toxicokinetic study with TFA conducted in combination with the 1-year exposure study, neither design nor results of this study are described. In the assessment of an acceptable daily intake for TFA, EFSA mentions an elimination half-life for TFA of 34.4 h, apparently for elimination from blood after intravenous application of TFA to rabbits (EFSA 2014). However, more detailed information on kinetics of uptake after oral administration, time course of resulting blood levels of TFA, and kinetics of elimination is not available. Information on the kinetics of elimination of TFA from rodents and humans can be derived from studies that assessed the urinary elimination. Once formed from the precursors as stable metabolite, oxidative biotransformation of TFA is not expected due to the high water solubility and stability. In addition, urine is the only expected pathway of elimination of TFA due to the high water solubility and low molecular weight. Kinetics of excretion of TFA formed as a metabolite of halothane in humans indicate a urinary elimination half-life of 42 h in humans (Wark et al. 1990). A comparatively slow elimination of TFA was also observed in human subjects after desflurane anesthesia, but the available information does not permit conclusions on a urinary half-life (Sutton et al. 1991). In rats, the kinetics of urinary elimination of TFA were assessed after exposure to 2,2-dichloro-1,1,1-trifluoroethane. TFA was eliminated with an apparent half-life in the range of 36 h (Urban and Dekant 1994) and urinary elimination of TFA was also observed after inhalation exposure of rats to 1,1,1,3,3-pentafluoropropane (HFC-245fa) with a similar elimination half-life (Bayer et al. 2002).

The comparatively slow elimination of the highly polar and ionized TFA is probably due to enterohepatic circulation of TFA, likely of TFA-glucuronide, as biliary elimination of TFA has been observed after halothane exposure (Wark et al. 1991) and biliary cannulation resulted in significant decrease of elimination half-life of TFA from blood in rabbits (EFSA 2014).

Human exposures of the general population to TFA

Sources of TFA release into the environment are diverse. While some of the TFA present in the environment can be attributed to anthropogenic sources, TFA may also occur naturally. For instance, most of TFA in sea water (average oceanic concentration ranging from 10 to 200 ng/L) is proposed to originate from geological sources (Frank et al. 2002; Scott et al. 2005). This assumption is based on the comparatively large quantity of TFA present in the oceans (approximately 268 million tons in total) that cannot solely be attributed to anthropogenic sources. Furthermore, TFA in seawater collected from different depths (10–4000 m below sea level) and analyzed by ^{14}C radiocarbon dating has been formed more than 1000 years ago (Frank et al. 2002; Scott et al. 2005) indicating natural sources for TFA. However, the natural occurrence of TFA in the ocean is controversial (Joudan et al. 2021).

Nevertheless, the presence of TFA in rainwater, fog, snow, surface waters (e.g., lakes, rivers, leachates) and soil may be attributed to anthropogenic sources. While TFA is intentionally produced as a reagent for industrial processes at estimated annual production volumes between 450 and 4500 tons (Solomon et al. 2016), about 2000 chemicals are known that degrade to TFA in the environment (UBA 2021a,b). These include refrigerants, aerosols, and blowing agents such as hydrofluorocarbons (HFCs), hydrochlorofluorocarbons, (HCFCs) and hydrofluoroolefins (HFOs), but also perfluorinated chemicals (attributable for around 21 ng TFA/L precipitation in metropolitan areas (Ellis et al. 2001). In addition, approximately 80 pesticides (e.g., trifluralin, thiazopyr, fluvalinate and lampricide) and halogenated compounds used in pharmaceutical and medicinal applications (inhalation anesthetics, e.g., halothane, desflurane, and isoflurane) degraded to TFA (Solomon et al. 2016). Among the currently used halogenated carbons, HFC-134a, HFO-143a, and HFO-1234yf present sources of environmental TFA as their degradation gives high yields of TFA. Contribution of

halogenated carbons to TFA is reviewed in detail (Behringer et al. 2021; Solomon et al. 2016). Precipitation of TFA by rain, fog, or snow to the surface leads to the pollution of surface waters (rivers, lakes, groundwater) and soil. As drinking and tap water is in parts obtained from surface waters, contamination of drinkable water with TFA is reported in literature (see Table 1).

Furthermore, plants can take up TFA into leaves and crops, leading to exposure of humans by intake with diet. TFA was detected in corn (maize kernels: 14.2–105 µg/kg), beer (< 0.1–51 µg/L) and tea (0.39–13 µg/L) (Lan et al. 2020; Scheurer and Nodler 2021).

Human risk characterization

Regarding hazard characterization for repeated exposure from environmental sources, most relevant end points for effects in mammals are covered by appropriate toxicity studies with TFA (ECHA 2022; EFSA 2014). The NOAEL of 10 mg/kg bw/day obtained from the oral 90-day study is considered as the most appropriate point of departure (POD) for human risk characterization and was used by EFSA to derive a human acceptable intake of 0.05 mg TFA/kg bw/day, applying an assessment factor of 200 due to absence of a long-term study (EFSA 2014). While the German UBA used a NOAEL of 1.8 mg TFA/kg bw/day from a 1-year drinking water study with TFA to derive a drinking water guide value of 60 µg/L (UBA 2021a), the interpretation of the data was based on a change in the activity of one "liver enzyme" (ALT) as POD and liver hypertrophy seen in other studies

Table 1 Presence of trifluoroacetate (TFA) in water of different origins

Source	Location	Sampling period	Concentration of TFA [ng/L]	References
Rainwater/snow				
Germany	Karlsruhe	2017	< 50–2400 (min.–max. values)	(Behringer et al. 2021)
	Berlin	2018	370–1556 (min.–max. values)	(Dorgerloh et al. 2019)
	Different sampling sites	2018–2020	28–4780 (min.–max. values)	(Behringer et al. 2021)
China	Western Mainland	2016	8.8–1800 (min.–max. values)	(Wang et al. 2019)
Tab water				
USA	Nevada/California	1995–1996	41–150 (min.–max. values)	(Zehavi and Seiber 1996)
China	Beijing	2012	155 (mean)	(Zhai et al. 2015)
	Jinan	2016	384 (mean)	(Xie et al. 2020)
Germany	Different sampling sites	2016	310 (median)	(Scheurer et al. 2017)
Surface water				
Germany	River water (Karlsruhe, Basel)	2017	350–510 (min.–max. values)	(Behringer et al. 2021)
USA	Lake water (Nevada/California)	1994	140–40,900 (min.–max. values)	(Zehavi and Seiber 1996)
	Lake water (California/Alaska)	2021	102–714 (mean values)	(Cahill 2022)
China	Urban landscape waters	2012	345–828 (min.–max. values)	(Zhai et al. 2015)
	River water (Jinan)	2016	500–1100 (min.–max. values)	(Xie et al. 2020)
Spring water				
Germany	Several springs in Germany	1995–1996	< 10–320 (min.–max. values)	(Frank et al. 1996; Jordan and Frank 1999)
China	Jinan	2016	1800 (mean)	(Xie et al. 2020)
Leachates and effluents from waste disposal sites				
China	Tianjin	2016	2000–59,000 (median: 17,000)	(Wang et al. 2020)
Soil				
Germany	Various sampling sites	2017/2019	< 200–2400 (min.–max. values)	(Behringer et al. 2021; Sacher et al. 2019)
China	Jinan	2016	60–2080 (min.–max. values)	(Xie et al. 2020)
Beverages				
Beer	104 samples, 23 countries	n.s.	< 100–51,000 (min.–max. values)	(Scheurer and Nodler 2021)
Tea	19 samples, origin n.s.	n.s.	390–13,000 (min.–max. values)	(Scheurer and Nodler 2021)

n.s. not specified, *min.–max.* minimal–maximal

Table 2 Margin of exposure assessment for human exposures to trifluoroacetate (TFA) from environmental sources based on a NOAEL of 10 mg TFA/kg bw/day from a 90-day oral study in rats

Source of human exposure	Dose received (water consumption of 2 L/day, body weight of 60 kg)	Margin of exposure to NOAEL of 10 mg/kg bw/day in rats
Drinking water, based on the highest concentration (4.8 µg TFA/L) detected in environmental water samples taken from 2014 to 2022	0.16 µg/kg bw/day	62,500
Drinking water, based on the highest concentration (0.63 µg TFA/L) used by EFSA	0.021 µg/kg bw/day	476,190
Diet, based on the assessment of dietary exposure to TFA by EFSA in 2014	2.5 µg/kg bw/day	4000

with TFA at higher doses. However, adverse effects are to be used a PODs and a change in a single "liver enzyme" without accompanying histologic changes or changes in liver weight is not considered as adverse (Hall et al. 2012). The highly conservative approach applied by UBA is more based on philosophical considerations regarding the presence of contaminants in drinking water in Germany (Dieter et al. 1997).

Results of the 90-day study are thus considered as a more appropriate POD (ECHA 2022; EFSA 2014) despite the limited data that indicate that liver hypertrophy induced by TFA is mediated by an interaction of TFA with the peroxisome proliferated-activated receptor α, a mode of action that is not relevant to humans (Felter et al. 2018), as human liver, in contrast to rodents, does not respond to the proliferative effects of peroxisome proliferator-activated receptor α-agonists.

Both the extended one-generation reproductive and developmental toxicity study and the developmental toxicity studies with TFA did not show treatment-related effects and thus provided higher NOAELs. While serum T4 was reduced in the EORGTS, a change in T4 without effects on other thyroid hormones (T3, TSH) levels, thyroid weight, or histopathology is unlikely treatment related (Colnot and Dekant 2017). Moreover, the NOEL (25 mg/kg bw/day) from the EOGRTS is higher as compared to the NOAEL of 10 mg/kg bw/day from the 90-day study. Therefore, the NOAEL of 10 mg/kg bw/day is appropriated for risk characterization by assessing margin of exposure (Table 2).

For exposure assessment, the MoE assessment in Table 2 uses the highest surface water concentrations measured over the last 8 years and compares the obtained MoE to the one based on EFSA assessment for water exposures to TFA in 2014. The value for dietary exposure is based on EFSA exposure assessment for TFA with diet that incorporated TFA released from plant protection products, the only dietary exposure assessment available.

As shown in Table 2, the MoEs regarding potential exposures of the general population to TFA from drinking water are very large and orders of magnitude above the required MoE > 100 even when using the highest measured concentrations of TFA in surface water as a surrogate for drinking water levels. The lower MoE for dietary exposures remains sufficient, but indicates that dietary intake of TFA, mainly from plant protection products containing the trifluoroalkyl moiety, is a larger contributor to overall TFA intake as compared to drinking water (EFSA 2014). However, the EFSA assessment also applied highly conservative exposure estimates and MoEs based on more representative data will also be higher. In summary, the approach using MoE does not indicate human health risks due to the presence of TFA in the environment and conforms previous assessments (EFSA 2014; Solomon et al. 2016).

Acknowledgements Preparation of this review was supported by Honeywell. The support was provided to Prof. Dr. Wolfgang Dekant, a retired Professor of Toxicology at the Department of Pharmacology and Toxicology of the University of Würzburg.

Author contributions Conceptualization, WD; writing—original draft preparation, RD, WD; writing—review and editing: RD, WD; All authors have read and agreed to the published version of the manuscript.

Data availability The datasets analysed during the current study are available in the cited references/web sites.

Declarations

Conflict of interest The authors certify that their freedom to design, conduct, interpret, and publish research was not compromised by the sponsor. The authors declare no conflicts of interest.

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