

SOURCES, FATES, TOXICITY, AND RISKS OF TRIFLUOROACETIC ACID AND ITS SALTS: RELEVANCE TO SUBSTANCES REGULATED UNDER THE MONTREAL AND KYOTO PROTOCOLS

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Abstract

This assessment report provides background information on trifluoroacetic acid (TFA) together with its potential relevance as a risk factor to the environment and human health. In addition, the report draws attention to some of the current concerns of substances controlled by and relevant to the Montreal Protocol. Based on current projections of uses, the amount of TFA formed from hydrochlorofluorocarbons (HCFCs), hydrofluorocarbons (HFCs), and hydrofluoroolefines (HFOs) in the troposphere is too small to be a risk to the health of humans and the environment. However, the formation of TFA from the degradation of HCFCs, HFCs, and HFOs warrants continued attention, in part because of its very long environmental lifetime. TFA is produced naturally and synthetically and is widely used in the chemical industry, and is a potential environmental breakdown product of a large number (>one million) of chemicals. These chemicals include pharmaceuticals, pesticides, and polymers. The contribution of these chemicals to global amounts of TFA is very uncertain, in contrast to that from HCFCs, HFCs, and HFOs. TFA-salts are stable in the environment and accumulate in terminal sinks such as playas, salt-lakes, and oceans where the only process for loss of water is evaporation. Total contribution to existing amounts of TFA in the oceans as a result of the continued use of HCFCs, HFCs, and HFOs up to 2050 is estimated to be a small fraction (<7.5%) of the $\approx 0.2 \mu\text{g/L}$ acid equivalents/L estimated to be present at the start of the millennium. TFA, as an acid or as a salt is low to moderately toxic to a range of organisms. Based on worst-case exposure scenarios for salts of TFA, risks to mammals, to plants growing in soil and to aquatic organisms is currently considered *de minimis*. Risks are potentially greater for plants exposed directly to TFA-acid but the short times of exposure in most natural terrestrial environments likely mitigate any adverse effects.

1 Introduction

A critical evaluation is given of the recent literature on the potential effects of trifluoroacetic acid TFA in the environment and future scenarios of production and exposure to TFA. These are assessed in the context of potential risks to humans and the environment.

Fluorinated organic chemicals are widely used in industry, medicine, agriculture and household products. A search of the Sci-Finder® database (CAS 2015) reveals that more than a million man-made substances contain a trifluoromethyl group ($-\text{CF}_3$) as part of their structure. As was pointed out in the 1990s, many of these chemicals are released directly into the environment as part of their use or are lost through fugitive emissions from industry or equipment (Key et al. 1997). Because of the strength of the carbon-fluorine bond, the $-\text{CF}_3$ group is resistant to degradation in the environment. This results in the release of TFA as a terminal residue after environmental degradation of the parent materials.

Many of the substitutes for the ozone-depleting substances (ODSs) contain fluorine. However, only those that contain the CF_3 group (see below) degrade in the atmosphere to produce TFA as a final breakdown product. The degradation of refrigerants that produce TFA has raised environmental concerns (UNEP EEAP 1998, et seq). However, there are benefits from the use of these compounds as they have a short lifetime in the atmosphere, which prevents them reaching the stratosphere in large

enough amounts to significantly deplete the ozone and minimizes their global warming potential.

Concerns over TFA have sometimes been erroneously linked to longer-chain perfluorinated compounds (PFCAs) and perfluorinated sulfonates (PFSAs), which have been subjected to recent bans and withdrawals at the global and regional level (USEPA 2009). All fluorinated compounds with every C-H bond replaced with a C-F are called perfluorinated chemicals, but it is only those with a chain length of more than six carbons that are of toxicological concern (USEPA 2009). It is important to distinguish between the long-chain and short-chain perfluorinated compounds. The short-chain (≤ 6 carbons) compounds have different physical properties, which mitigate risks to the environment and human health.

TFA has the shortest chain of all PFCAs, with just two carbons (see Figure 1). The long-chain PFCs comprise two major sub-categories: perfluoroalkyl sulfonates (PFAS) and long-chain perfluoroalkyl carboxylates (PFACs). The PFAS sub-category includes perfluorooctane sulfonic acid (PFOS) and all have eight or more carbons in the chain. Long-chain PFCs are found world-wide in the environment, wildlife, and in humans (Giesy and Kurunthachalam 2001). They are bioaccumulative in the food chains of air-breathing vertebrates (Houde et al. 2006) and are toxic to mammals in laboratory tests (USEPA 2009). It is very important to recognize that the short-chain fluorinated compounds, such as TFA, do not bioaccumulate in food chains. These compounds are not included in the bans discussed above. This report therefore deals only with TFA.

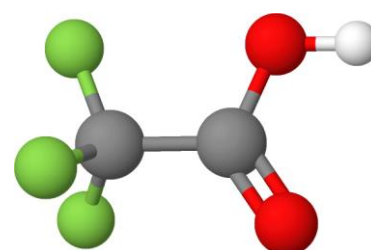


Figure 1. Structure of TFA. Green = fluorine, grey = carbon, red = oxygen, white = hydrogen.

The problem of TFA has been addressed in several assessments by the UNEP Panels that advise the Parties (countries) to the Montreal Protocol. The Scientific Assessment Panel (Cox et al. 1994, Prinn et al. 1998, Montzka et al. 2006, Montzka et al. 2010, Daniel et al. 2010, Carpenter et al. 2014, Harris et al. 2014), the Environmental Effects Assessment Panel (UNEP EEAP 1998, 2006, 2009, 2010, 2011, 2014) and the Technical Effects Assessment Panel (UNEP 2011) have included sections on TFA in their reports since 1998. This current evaluation is an extension of what has been reported in those assessments from the main starting point of the review conducted by the UNEP EEAP (1998) and the papers by Key et al. (1997) and Boutonnet et al. (1999). These papers thoroughly summarize earlier work and we now focus on more recent information.

2 Problem formulation

2.1 Chemical and physical properties of TFA

Trifluoroacetic acid (Figure 1; perfluoroacetic acid, CAS #76-05-1; MW = 114.02 g/mol) is a strong acid with a dissociation constant, pKa, of 0.23. It is the terminal residue formed from the degradation of a large number of chemicals used commercially. These include refrigerants used as replacements for the ODSs. TFA is a liquid with a boiling point of 74°C and is miscible with water. The vapor pressure of TFA

is relatively large (11 kilo Pascals, (kPa), at 20°C). Its partition coefficient (Log P_{OW}) with octanol is -0.2 (PubChem 2015) and the air:water partition coefficient, K_{aw} , is 4.75×10^{-6} (Ellis et al. 2001b). In many ways it is chemically similar to nitric or hydrochloric acid. Because of its small pKa, it rapidly forms salts when released to the terrestrial environment and surface waters. The salts have different properties from the acid. For example, the sodium salt (CAS# 2923-18-4; MW = 136.01) is highly soluble in water (625 g/L) but is neutral, not corrosive, and has negligible volatility. It is this salt form of TFA that is relevant to exposures in the environment and the abbreviation “TFA-salt” will be used from this point on. Where concentrations of salts were measured as TFA-acid, the abbreviation a.e. (acid equivalents) is used.

2.2 Sources in the environment

There are a number of sources of TFA and TFA-salts in the environment. Some of these are natural and others are anthropogenic. These are discussed in the sections below.

2.2.1 Natural sources of TFA

Concentrations of TFA-salts in the ocean have been measured and are in the range of 200 ng a.e./L. Even in remote locations, such as the Southern Oceans, the concentration of TFA does not vary with depth (Frank et al. 2002). Sampling in various parts of the Arctic, Atlantic, and Pacific Oceans for TFA-salts revealed that concentrations in deep (>1,000 m) waters of the Atlantic were close to 160 ng/L (Scott et al. 2005a). Based on radiocarbon dating (ageing) with ^{14}C , the water at this depth was older than 1,000 years, suggesting significant natural sources of TFA-salts in the oceans. Samples in the region of undersea hydrothermal vents revealed greater concentrations than surrounding water, suggesting that hydrothermal vents are one of these natural sources of TFA-salts. Annual inputs of 6,000 kg a.e. of TFA were estimated from a hydrothermal vent (Scott et al. 2005a).

The concentrations of TFA-salts reported from contemporary samples of surface freshwaters, fog, and rain range from 20 ng a.e./L to hundreds of ng/L (see below). This is much greater than the concentration of TFA-salts in pre-industrial (>2,000 year-old) freshwater from Greenland and Denmark, which were below the level of detection (2 ng a.e./L) (Nielsen et al. 2001). What is clear from these data is that a large amount of TFA-salts in the ocean are from natural rather than human-made sources. However, salts of TFA in surface freshwaters are more likely of anthropogenic origins.

2.2.2 Anthropogenic chemicals

TFA is manufactured as an industrial chemical (PubChem 2015). In addition, a vast array of chemicals could possibly yield TFA and/or its salts as a final (terminal) degradation product. The following sections summarize possible sources, including those from the substitutes for the ODSs.

2.2.2.1 TFA as a reagent and intermediate in chemistry

TFA is widely used in industry and production in the USA and, in 2002, was estimated at between 450 and 4,500 tonnes (t) a.e. (PubChem 2015). More recent data on its manufacture in the USA or globally and its use were not available. Whether and in what quantities TFA and its salts are released into the environment from its indus-

trial uses is highly uncertain. The use of this chemical does not appear to be reportable in any jurisdiction.

2.2.2.2 HCFCs, HFCs, and other related chemicals.

Several of the HCFCs and HFCs can break down into TFA (Figure 2). These include halothane, isoflurane, HCFC 123, HCFC-124, HFC-134a, HFC-143a, HFO-1234yf, and HFO-1234ze. The degradation of many of these compounds in the atmosphere and the pathways of formation of TFA have been thoroughly examined in a recent review (Burkholder et al. 2015). The yield of TFA from each precursor molecule depends on the specific molecule because of competition between several degradation pathways, of which, only some lead to TFA. The relative importance of the different pathways can depend on environmental conditions such as low/high NO_x regime, and the availability of photolytic UV radiation, as discussed in detail by Burkholder (2015). Because of this dependence on atmospheric conditions, detailed chemistry-transport modeling is required to estimate temporal and spatial average yields, but such studies have been few, e.g. by Leuken et al. (2010) to estimate a molar yield of TFA of 21% on average from HFC134a for conditions typical of the USA.

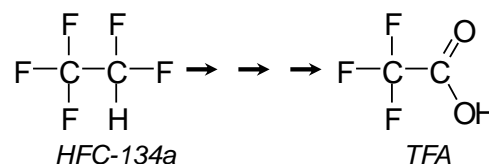


Figure 2. Formation of trifluoroacetic acid (TFA) from an example HFC

Once formed in the atmosphere, TFA partitions almost entirely into fog and cloud water (Bowden et al. 1996) and is carried to the surface in precipitation. There are many other fluorinated refrigerants, solvents, and agents for blowing plastic foams that do not contain a -CF₃ group and thus cannot be degraded to TFA. These and several compounds that do degrade to TFA but are not produced in large quantities are not included in this report. In the UNEP Review (1998), releases to the atmosphere were estimated to be 2,500 t for HCFC-123 and 2,300 t for HCFC-124 with a flux of 760 and 320 t TFA/year in 1998. These historical contributions of TFA are much smaller than those estimated from other HFCs (Table 1) and are not included in the total production of TFA in this report. Two medical anaesthetics, halothane and isofurane, that degrade or are metabolized to produce TFA were included in the UNEP Review (1998) and were estimated to produce about 800 t of TFA/year. However, these two compounds are no longer in use and total historical volumes of production are not known.

Sources of TFA from substitutes for the ozone-depleting substances of current interest are listed in Table 1. Data on production of these sources were used rather than emissions, in order to present a worst case scenario in which all HFCs and HFOs could be released to the atmosphere. Data for the production of HFC-134a, HFC-143a, and HFC-227ea were from upper range estimates from data in Velders et al. (2015). Data on global production of HFO-1234yf for 2015 were not available but projected production for North America is estimated to be from 50,000 to 100,000 t/y in the next 50-100 years (Tang et al. 2011). HFO-1234yf is a replacement for HFC-134a, global production of which (without a ban) is projected to be 600,000 t/year in 2050 (Velders et al. 2015). Thus, global production of HFO-1234yf might be expected to be of similar magnitude by 2050 if replacement is complete. For the purposes of this report, it is assumed that production of HFO-1234yf would begin in 2016 and increase to 100,000 t/year by 2050 for a total of about 3,255,000 t. This is

probably an under-estimate as HFO-1234yf is currently being introduced as a propellant for aerosol products (Reisch 2015).

The atmospheric lifetime of HFO-1234yf is estimated at about 6 days (Luecken et al. 2010) and the conversion to TFA is 1:1 on a molar and w/w basis (Tang et al. 2011). Two modeling studies (Henne et al. 2012, Russell et al. 2012) on potential releases of TFA from HFO-1234yf in the EU and the USA have predicted increased deposition of TFA in precipitation over Europe and N. America. After complete conversion of the European “vehicle fleet” to HFO-1234yf, maximum concentrations in rainwater as large as 2,500 ng/L were predicted over the Mediterranean and Northern Africa (Henne et al. 2012).

The isomer of the refrigerant HFO-1234yf is HFO-1234ze. Little information on the production and use of HFO-1234ze was available but it has been considered for use as a blowing agent for plastic foams (UNDP 2010). In this use, it will be a substitute for HFC-134a. From studies in smog-chambers, it was predicted that degradation of HFO-1234ze will result in the formation of TFA degradation of HFO-1234ze will result in the formation of TFA in yields of <10% (Javadi et al. 2008). Depending on future use, this product might contribute to the formation of TFA in the atmosphere.

The yield of TFA from HFC-134a is only 21% (Luecken et al. 2010), whereas that from the other HFCs and HFO-1234yf is 100%. Thus, substitution of HFC-134a by other products on a molecule-for-molecule basis might result in an increase in the overall production of TFA (Luecken et al. 2010).

Table 1. Historical (from 1990) and projected upper range of production of relevant HFCs and HCFCs in tonnes.

Compound ¹	HFC-134a	HFC-143a	HFC-227ea	HFO-1234yf	HFO-1234ze
Molecular weight	102.03	84.04	170.03	114.02	114.02
Molar yield	0.21	1	1	1	NA
Yield of TFA a.e. w/w	0.23	1.36	0.67	1.00	
Total production from 1990 to 2015	3,869,000	537,000	57,000	0	0
Lifetime, year ²	14	51	36	<0.1	<0.1
2011 concentration, ppt ³	63	12	0.6	NA	NA
2011 TFA production flux, tonnes per year	18,000	3,600	510		
Estimated total production by 2050	22,047,000	8,725,000	533,000	3,255,000	NA
Total cumulative contribution to TFA a.e. in the global environment	5,174,000	11,838,000	358,000	3,256,000	
Total yield of TFA a.e. from HFC and HFOs up to 2050	20,625,000				

¹a.e. = acid equivalents

²Lifetimes from Burkholder et al. (2015).

³Concentrations (ppt = parts per trillion, 10⁻¹²) from (Vollmer et al. 2011b) for HFC-134a and HFC-143a, and from Vollmer et al. (2011a) for HFC-227ea.

For comparison, Table 1 also shows the annual TFA production rate for 2011 from three major precursors, computed as $[x] (M)(m_{\text{TFA}}/m_{\text{air}}) y/T$, where $[x]$ is the precursor mole fraction, T is its lifetime, y is the molar yield of TFA, M is the mass of the atmosphere, and m_{TFA} and m_{air} are the molar masses of TFA and air, respectively.

The oceans contain 1.357 billion km^3 of water. Assuming that the above total yield of TFA formed in the atmosphere from 1990 to 2050 is transported to oceans as a terminal sink and then uniformly mixed, the added concentration in the ocean would be 15.3 ng a.e./L.

2.2.2.3 Perfluorinated chemicals

Although some long-chain perfluorinated chemicals are not easily degraded, they do decompose at high temperatures to produce TFA and other compounds (Ellis et al. 2001b). TFA was identified as a product of thermal decomposition (360-382°C) of several fluoropolymers (Ellis et al. 2001b). Based on models, Ellis et al. (2001a) suggested contributions of ~21 ng/L from these sources to rainfall in the air-shed of a large metropolitan area. The global input of TFA to the environment from these sources is uncertain.

2.2.2.4 Pharmaceuticals, pesticides, and reagents

A number of pesticides and pharmaceuticals contain the trifluoromethyl group (CF_3) and could degrade in the environment to produce TFA. Approximately 80 pesticides, e.g., trifluralin, lufenuron, thiazopyr, prosulfuron, tefluthrin, fipronyl, haloxyfop, fluazifop-butyl, fluvalinate, picoxystrobin, and the lampricide, 3-trifluoromethyl-4-nitrophenol (TFM), to mention but a few, contain the CF_3 group (BCPC 2003). Although aggregate data on global use of pesticides are available (FAOSTAT 2016), data for individual pesticides are not publically available. There are some data, for example, between 1992 and 2012, it is estimated that 119,500 tonnes of trifluralin were used in the USA (NAWQA 2015); however, between its initial registration in 1967 and 1992, amounts used were not reported. While pesticides could degrade to produce TFA as a terminal residue, there are few published studies that have followed the pathway of degradation beyond the initial degradation products. TFM has been reported to be photolytically degraded (365 nm) to TFA with a yield of about 17% (Ellis and Mabury 2000). Trifluralin and other $-\text{CF}_3$ -substituted phenols produce TFA (Ellis and Mabury 2000). It has been estimated that pesticides containing the $-\text{CF}_3$ group contribute small amounts (<1 ng/L) to TFA in rainfall (Russell et al. 2012). However, most pesticides that contain the $-\text{CF}_3$ group are not highly volatile and would degrade in the terrestrial environment rather than in the atmosphere, possibly with the contribution of greater amounts of TFA to the environment via runoff- or ground-water.

Not all compounds containing the $-\text{CF}_3$ group degrade to TFA as a terminal residue, for example, trifluoromethyl catechol (not a pesticide) undergoes successive removal of fluorine in bacterial culture without forming TFA (Kiel and Engesser 2015). However, because of stability conferred by its ionic nature, similar degradative reactions of TFA and its salts are unlikely to occur in the environment. Photocatalytic defluorination of TFA has been reported in water in the presence of tungstic heteropolyacid photocatalyst $\text{H}_3\text{PW}_{12}\text{O}_{40}\cdot 6\text{H}_2\text{O}$ (Hori et al. 2003), but whether this defluorination occurs in nature or has practical application for removal of TFA from water is uncertain.

Several pharmaceuticals, including rilizone, celocoxib, fluoxetine (Prozac), efavirenz, and bicalutamide, also contain the $-CF_3$ group (Quirnbach and Steiner 2009). While unlikely to be metabolized to large amounts of TFA in humans or animals, further degradation of the parent molecule and its metabolites in the environment might lead to the formation of TFA. It would seem that no studies have followed pharmaceuticals to TFA as a terminal degradation product, as has been the case for many pesticides. Although certain pharmaceuticals, such as fluoxetine, are widely prescribed, global use is not reported and the total amount used or released to the environment is uncertain. The contribution of pharmaceuticals to the global pool of TFA is thus unknown.

In summary, in addition to some of the HCFCs and HFCs, there are a large number of potential anthropogenic and natural sources of TFA in the environment. Under the auspices of the Montreal Protocol, production, use and emissions of HCFCs are relatively well understood and quantified. Emissions of HFCs are reported to the United Nations Framework Convention on Climate Change and its Kyoto Protocol, but only by developed countries. There are larger uncertainties in the emissions for the much larger number of other potential sources. This introduces large uncertainty into the estimated contribution to the global pool of TFA.

2.3 Conceptual model of routes of exposure

Because of the complexity of the ecosystem, ecological risk assessment makes use of conceptual models to refine and better understand exposure pathways and identify compartments and organisms at greatest risk. This simplifies the risk assessment and serves to focus on organisms at greatest risk. Because exposure is an integral component of risk, conceptual models of exposure are normally used in the initial stages of risk assessments to identify relevant, complete exposure pathways for relevant assessment endpoints.

2.3.1 Environmental fates of TFA

Whatever the source of TFA in the atmosphere or other compartments in the environment, the ultimate sink is in surface waters. TFA is soluble in water and dissolves or partitions into water (droplets in the atmosphere in the case of the atmospheric degradation of HFCs and HFOs). Upon contact with soil or surface waters, TFA forms salts with ions such as sodium, potassium, magnesium, and calcium, which are present in soils and most surface waters. TFA-salts released from other sources, such as industrial wastes and sewage treatment, also remain in the aqueous phase and eventually move to terminal sinks in the ocean, salt, or playas (endorheic lakes) from which there is no outflow and the only loss of water is via evaporation (see Table 2 and Figure 3). TFA-salts are extremely stable in the environment (Ellis et al. 2001a, Scott et al. 2005a) and are likely to have half-lives of centuries.

It is very important to recognize that, in the environment, salts of TFA behave in exactly the same way as salts of other minerals. Where mineral-salts have accumulated in salt lakes, playas, and oceans, TFA-salts from natural and anthropogenic sources also accumulate.

Table 2. Environmental compartments where TFA is found.

Environmental compartment	Inflow and outflow	Comments
Air	Formed in the air but rapidly partitioned to water droplets.	No accumulation in the atmosphere.
Clouds, rain, fog	Partitioning from air into water droplets.	No accumulation because of rapid deposition and recycling of water in the atmosphere.
Soil	Inflow from dry or wet precipitation. Outflow via runoff, soil- and ground-water.	No accumulation except in proximity to salt lakes and playas.
Oceans, salt lakes and playas	Inflow only, loss of water by evaporation only.	In addition to TFA-salts, these environmental compartments contain large concentrations of mineral salts leached from soils and/or groundwater. Salt lakes and playas usually have concentrations of salt greater than oceans. Non-volatile salts, including those of TFA have and continue to accumulate over time.
Vernal pools	Small pools formed in shallow depressions from snow-melt and/or spring rains. Outflow to groundwater and/or loss by evaporation.	Contain TFA- and mineral-salts but these do not accumulate because of outflow to ground- and soil-water. If there is no outflow, these pools are playas or brine pools and not vernal pools.
Streams and rivers	Inflow from snowmelt, glaciers, rain, runoff from land, groundwater (springs), and water-treatment facilities. Outflow to oceans, salt-lakes, or playas.	Contain TFA- and mineral-salts in lesser concentration than oceans, salt-lakes, and playas. Non-volatile salts do not accumulate over time. Concentrations vary over time and location, depending on inputs of water and salts.
Wetlands	Inflow from snowmelt, glaciers, rain, runoff from land, groundwater (springs), and water-treatment facilities water. Outflow to streams and rivers.	

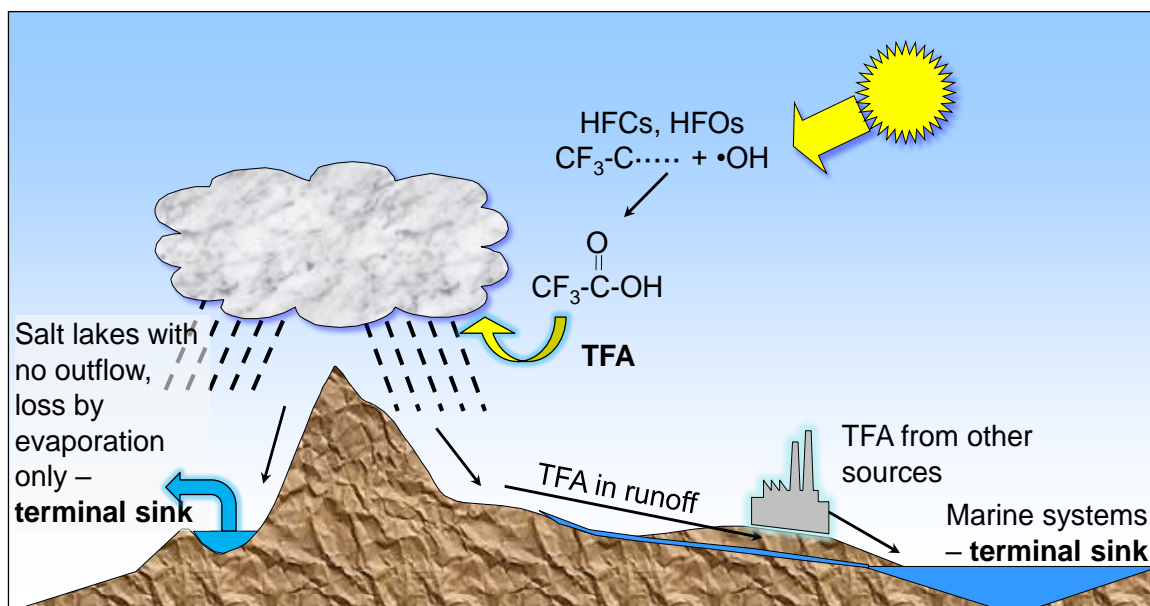


Figure 3. Diagrammatic representation of the fates of TFA and its salts in the environment.

Playas and salt lakes are terminal sinks for salts, including TFA. These water-bodies contain more than the 3.5 g/L of salt found in the oceans. For example, the Great Salt Lake in Utah has concentrations of salts that vary from 50 to 270 g/L. Expressed in the same units as used for the measured environmental concentrations of TFA (ng salt/L), this is 270,000,000,000 ng salts/L (Utah Geological Survey 1996). These salt lakes are inhabited by relatively few organisms, all of which are highly tolerant of salts (halophiles). For example, the Great Salt Lake has a very simple food web (Bozniak 2008). At the base of the food chain are bacteria and algae. These are fed upon by brine shrimp (*Artemia franciscana*) and larvae of brine flies (*Ephydra cinerea* and *E. hians*). These organisms are a food source for water-boatmen (*Tricorixia verticalis*), migratory shore-birds, and other insectivores from the terrestrial environment. No aquatic vertebrates are found in the Great Salt Lake.

2.3.2 Food chain and biomagnification

The fate of TFA has been studied in animals (Boutonnet et al. 1999) and, as would be expected from its water solubility, it is rapidly eliminated via the kidneys into the urine. The half-life in plasma of humans is 25-32 h and similar values have been reported for other mammals (see review by Boutonnet et al. 1999). No reports of the fate of TFA-salts in fish were found but the salts of TFA would not be expected to accumulate in aquatic organisms. The physical and chemical properties of TFA-salts are different from the hydrophobic persistent organic pollutants (POPs) such as the insecticide DDT and polychlorinated biphenyls (PCBs).

There is some evidence of incorporation of TFA into biomolecules. Radiolabeled TFA has been shown to be incorporated into biomolecules in plants and aquatic animals (Standley and Bott 1998) and to bind covalently to proteins in the blood of mammals (Boutonnet et al. 1999). It has been suggested that TFA-salts are incorporated into proteins and to a lesser extent into lipids via the same biochemical pathway as acetate (Standley and Bott 1998); however, this observation has not been

repeated and the amounts are small (<10 mg/kg lipid). Even if TFA were incorporated into biomolecules, it would not biomagnify in food chains in the same way as the POPs, because TFA that is covalently bound to macromolecules would be released during the digestion and catabolism of these molecules. While some TFA may be reincorporated into new macromolecules, it is likely that the balance will be excreted. Thus, concentrations would not be expected to increase in the food chain and trophic magnification would not occur. POPs do not covalently bind to macromolecules; they partition into lipids and move in food chains with lipids. No measurements of the concentrations of TFA in crops for human consumption have been reported; however, it is taken up in plants via the roots in laboratory studies (Smit et al. 2009) and in rooted plants in endorheic pools in California (Cahill et al. 2001). Uptake by plants clearly is possible but concentrations in raw and processed foods are unknown.

2.4 Risk hypotheses

The risk hypothesis (as a null) tested in this assessment is: *The total concentration of TFA from all sources in various environmental compartments is not greater than the no-observed-effect-concentration for the most sensitive representative species.* The data used to test this hypothesis are provided in the following sections.

3 Concentrations of TFA measured in the environment

3.1 Rainfall and snow

The presence of TFA in rain is well-known but the concentrations are highly variable from one location to another (see review by Boutonnet et al. 1999). Studies in California showed concentrations in fog and rain ranging over 31–3,779 ng a.e./L but were generally smaller in more remote areas (Wujcik et al. 1998). Further observations have confirmed this trend; measurements in rain and snow in Switzerland revealed concentrations from less than the level of detection (3 ng a.e./L in this study) to 1,550 ng/L (Berg et al. 2000). Concentrations of TFA in rain were large at the beginning of a rainfall event, with the greatest concentrations in the first mm of rain (Berg et al. 2000). This is consistent with the high solubility of TFA in water and rapid partitioning from air to water. In a study in Chile, Malawi, and Canada, concentrations of TFA in rainwater ranged from 6–87, 4–15 and <0.5–350 ng a.e./L, respectively (Scott et al. 2005b). Concentrations of TFA in rainwater collected in two cities in Japan ranged over 29–76 ng a.e./L (Taniyasu et al. 2008). Similarly in Guangzhou, located in the Pearl River Delta in China, concentrations of TFA in rainwater measured from Apr 2007–Mar 2008 ranged from 46–974 ng a.e./L (Wang et al. 2014a). Clearly rainfall, fog, and snow are the major routes of input of TFA into the surface environment. Several mechanisms exist, including evaporative concentration, vapor-liquid phase partitioning, lowered washout volumes of atmospheric deposition water, and dry deposition, which may lead to elevated concentrations of TFA in atmospheric and surface waters above levels expected from usual rainfall washout (Wujcik et al. 1999).

3.2 Soils

Rain, fog, and snow scavenge TFA from the atmosphere. In terrestrial systems, the first point of contact of precipitation (and therefore TFA) is vegetation, soil, and surface water. Once in contact with soil or surface water, TFA reacts with minerals to

form salts. In their review, Boutonnet et al. (1999) noted that TFA was poorly retained in soils in general but that retention in soils with more organic matter was greater. The binding constant for TFA and organic carbon in soils (K_{OC}) is small (PubChem 2015) and, as a salt, the anion form of the molecule binds even less to soil and is highly mobile. In experimental forest ecosystems, effects on mineral balance of addition of TFA-sodium salt at a high rate (three applications of 810,000,000 ng/m²) were investigated (Berger and Likens 1999). These treatments, spaced 34 and 35 days apart, decreased the acid-neutralizing capacity of the soil but recovery was observed 21 days after the last treatment. Measured concentrations of TFA in soils are relatively small (Scott et al. 2005b). In Canada, values ranged from <0.0–1,400 ng a.e./kg dry weight (d.w.) of soil; in Malawi, <100–7,500 ng a.e./kg d.w.; in the UK 850–5,000 ng a.e./kg d.w.; and 100–9,400 ng a.e./kg d.w. in Chile. These small concentrations suggest that soils are not a repository or terminal sink of TFA-salts in the environment. This is consistent with the known chemical properties of these salts. TFA was infrequently detected in groundwater and then only at small concentrations (≥ 23 ng/L Nielsen et al. 2001). Given its large mobility in soil, this is unexpected but may be due to slow percolation into the groundwaters tested to date.

3.3 Surface waters

Concentrations of TFA measured in surface waters vary widely with location, season, and type of water body (see review by Boutonnet et al. 1999). This is still the case; recent studies are listed in Table 3 as most relevant to current conditions. Data from playas and salt lakes are not included in the Table but environmental measurements in many diverse locations show existing concentrations of 100 to 300 ng a.e./L in water (Cahill et al. 2001) with one site (Dead Sea) having a concentration of 6,400 ng a.e./L (Boutonnet et al. 1999). This large concentration was attributed to collection of the TFA-salt over thousands of years.

Table 3. Concentrations of TFA in surface fresh waters

Location and type of water body	Range of concentrations in ng a.e./L ¹	Reference
N. California, surface water	5–300	(Cahill and Seiber 2000, Cahill et al. 2001)
Yukon and Alaska, surface waters	8–27	(Cahill and Seiber 2000)
British Columbia, surface waters.	21–63	(Cahill and Seiber 2000)
Switzerland, rivers	12–328	(Berg et al. 2000)
Midland lakes	37–204	
Mountain lakes	46–360	
Moor water	59–175	
Drinking water	16–123	
Beijing, surface waters	380–820	(Zhai et al. 2015). Samples taken in 2012; values had increased by 17-fold since 2002 by Zeng et al. (2004).
Drinking water	155	

¹ a.e. = acid equivalents

In a modelling study on the projected use of HFO-1234yf in the USA, Russell et al. (2012) predicted increases in concentrations of TFA-salts in terminal water bodies in North America of 1000–15,000 ng a.e./L after 50 years of use. In some locations, such as playas in the Sonoran Desert, increased concentrations of 40,000 to 200,000 ng a.e./L were predicted after the same period of time. The reason for this is likely the closeness of the Sonoran Desert to major sources of TFA, such as California.

3.4 Oceans

Concentrations of TFA have been measured in the oceans (Frank et al. 1996, Frank et al. 2002, Scott et al. 2005a). Concentrations in the mid-Atlantic and the Southern Ocean off Elephant Island were all close to 200 ng a.e./L at depths ranging from the surface to 4,150 m (Frank et al. 2002). Concentrations measured at various depths in the Western and Eastern Arctic, the North Atlantic, and the North and South Pacific were all ≤ 200 ng a.e./L and some were as small as 1 ng a.e./L (Scott et al. 2005a). The reason for the much smaller values in the Pacific as compared to the Atlantic is unclear. Overall, we consider a general value of 200 ng a.e./L for the concentration of TFA in the oceans to be representative. The estimated contribution from the use of HFC and HFO refrigerants and blowing agents (see Table 1) up to 2050 is 15.3 ng a.e./L, adding about 7.5% to amounts currently (year 2000) measured in the oceans. The total concentration of TFA expressed as the sodium salt is 256 ng/L.

4 Toxicity of TFA

Like other strong acids, such as sulfuric, nitric, or hydrochloric acid, high concentrations of TFA can cause damage to organisms by virtue of its acidity. This mode of toxicity is only relevant to organisms exposed to TFA in precipitation or via dry deposition (if any) from the atmosphere. However, the amounts of sulfuric and nitric acids in acid-rain are much greater than TFA and are well-known to cause increased acidity of surface waters. No reports were found that attributed a substantial lowering of pH to the presence of TFA. Based on the very large estimated concentration of 200,000 ng/L of TFA in playas in the Sonoran Desert (Russell et al. 2012), we calculate that, in the absence of any buffering from alkaline salts in the water, the pH in a playa would be lowered by a small amount of about 0.4 pH units. TFA-salts are neutral, chemically unreactive, and there is no known specific receptor to which TFA-salts will bind to initiate a biological response. However, effects have been reported at large exposures. These are discussed in the following sections.

4.1 Mammals

Mammals are insensitive to TFA and its salts. The acute oral no-observed-effect-concentration (NOEC) for TFA in rats is 250 mg a.e./kg body weight (b.w.) (Boutonnet et al. 1999). The threshold concentration for respiratory irritation after a one-minute exposure in humans is 0.25 mg a.e./L of air. In mice, TFA had similar toxicity to hydrochloric acid. The acute NOEC for the sodium salt of TFA in rats is $\geq 5,000$ mg/kg b.w. The 8-day chronic oral no-observed-effect-level (NOEL) for the sodium salt of TFA in rats is 114 mg/kg b.w./day. In a series of bacterial assays for mutagenicity, TFA-salt was found to be inactive. No carcinogenicity or reproductive toxicity tests on TFA or its salts have been published. Toxicity tests in other terrestrial vertebrates, such as birds, have not been published; however, TFA would not be expected to be significantly more toxic to other vertebrates than to mammals.

4.2 Environmental

Because of its ubiquitous presence in the environment and its solubility in water, exposures are most likely to be in terrestrial or aquatic organisms. These data are summarized below.

4.2.1 Terrestrial organisms (plants)

In 2-year-old pine (*Pinus ponderosa*) seedlings treated in fog chambers with TFA at concentrations of 150 and 10,000 ng a.e./L, no adverse physiological, morphological, or photosynthetic responses were observed (Benesch and Gustin 2002). Unfortunately, greater concentrations were not tested and the NOEC was not identified. The pine needles accumulated TFA in the high-concentration treatment up to 320 ng a.e./g d.w. after a four-month exposure but without apparent effects. In a water-culture system, bean (*Phaseolus vulgaris*) and maize (*Zea mays*) showed NOECs for growth (shoot- and root-mass) of 2,500,000 ng TFA salt/L (Smit et al. 2009). Physiological responses related to changes in photosynthesis were observed in maize at a concentration of 650,000 ng TFA-salt/L but did not affect growth. The lack of soil in the growth medium in these tests is a worst-case exposure as there is no reduction in exposure of the plant by binding of TFA to soil particles or organic matter, as would occur in the field.

4.2.2 Aquatic organisms

There are several reports on the toxicity of TFA to aquatic organisms. These data are summarized in Table 4 and were produced in well-conducted laboratory studies, many of which followed guidelines for toxicity testing from the Organization for Economic Cooperation and Development (OECD). Only studies for which no-observed-effect-concentrations (NOEC) values were calculated have been included. Where multiple studies were conducted with the same organism, the most sensitive toxicity value (lowest concentration) was used. Where multiple endpoints were measured in a study, the most sensitive endpoint for effects of TFA was selected. The data thus present a worst-case scenario of high sensitivity.

Table 4. No-observed-effect-concentrations (NOECs) of TFA-salts measured in laboratory studies with aquatic organisms.

Species	Taxon and media ¹	NOEC ng TFA-salt/L	Reference
<i>Raphidocelis (Pseudo-kirchneriella) subcapitata</i>	Alga fw	120,000	(Berends et al. 1999)
<i>Myriophyllum spicatum</i>	Plant fw	30,000,000	(Hanson and Solomon 2004)
<i>Brachionus calyciflorus</i>	Rotifer sw	70,000,000	(Wang et al. 2014b)
<i>Myriophyllum sibiricum</i>	Plant fw	100,000,000	(Hanson and Solomon 2004)
<i>Lemna gibba</i>	Plant fw	100,000,000	(Hanson and Solomon 2004)
<i>Euglena gracilis</i>	Alga fw	112,000,000	(Berends et al. 1999)
<i>Microcystis aeruginosa</i>	Alga fw	117,000,000	(Berends et al. 1999)
<i>Phaeodactylum tricornutum</i>	Alga sw	117,000,000	(Berends et al. 1999)
<i>Chlamydomonas reinhardtii</i>	Alga fw	120,000,000	(Berends et al. 1999)
<i>Navicula pelliculosa</i>	Alga fw	600,000,000	(Berends et al. 1999)
<i>Aphanizomenon flos-aquae</i>	Alga fw	600,000,000	(Berends et al. 1999)

Species	Taxon and media ¹	NOEC ng TFA-salt/L	Reference
<i>Chlorella vulgaris</i>	Alga fw	1,200,000,000	(Berends et al. 1999)
<i>Daphnia magna</i>	Crust fw	1,200,000,000	(Berends et al. 1999)
<i>Danio rerio</i>	Fish fw	1,200,000,000	(Berends et al. 1999)
<i>Skeletonema costatum</i>	Alga sw	2,400,000,000	(Berends et al. 1999)

¹fw = freshwater species, sw = saltwater species

In addition to the above data from laboratory studies, the effects of TFA-salt on aquatic plants were investigated in outdoor aquatic microcosms (Hanson et al. 2002). In a 35-day study with a mixture of TFA-salt and trichloroacetic acid salt, no effects were observed in the aquatic plants, *Myriophyllum spicatum* and *Myriophyllum sibiricum* (Hanson et al. 2002). The measured concentration of TFA-salt in the mixture was 11,800,000 ng salt/L. This suggests that, under more realistic conditions in the field, plants are less sensitive than in the laboratory. No degradation of TFA was observed in this field study.

To characterize the range of toxicity values, the data in Table 4 were ranked from small to large and the toxicity values plotted as a species-sensitivity distribution (SSD, Solomon and Takacs 2002). These values are shown in Figure 4 and are discussed in relation to measured and estimated concentrations in aquatic systems in the following sections.

The toxicity value for *Raphidocelis* (formerly *Pseudokirchneriella*) *subcapitata* (red data point in Figure 4) is an outlier and was excluded from the regression of toxicity data, but this organism is used in the risk assessment detailed below. The 5th centile concentration of the SSD, commonly used to characterize risks and water-quality criteria in the environment (CCME 2007), is almost exactly the same value as the NOEC for TFA from the microcosm study; 11,800,000 ng salt/L (Hanson et al. 2002).

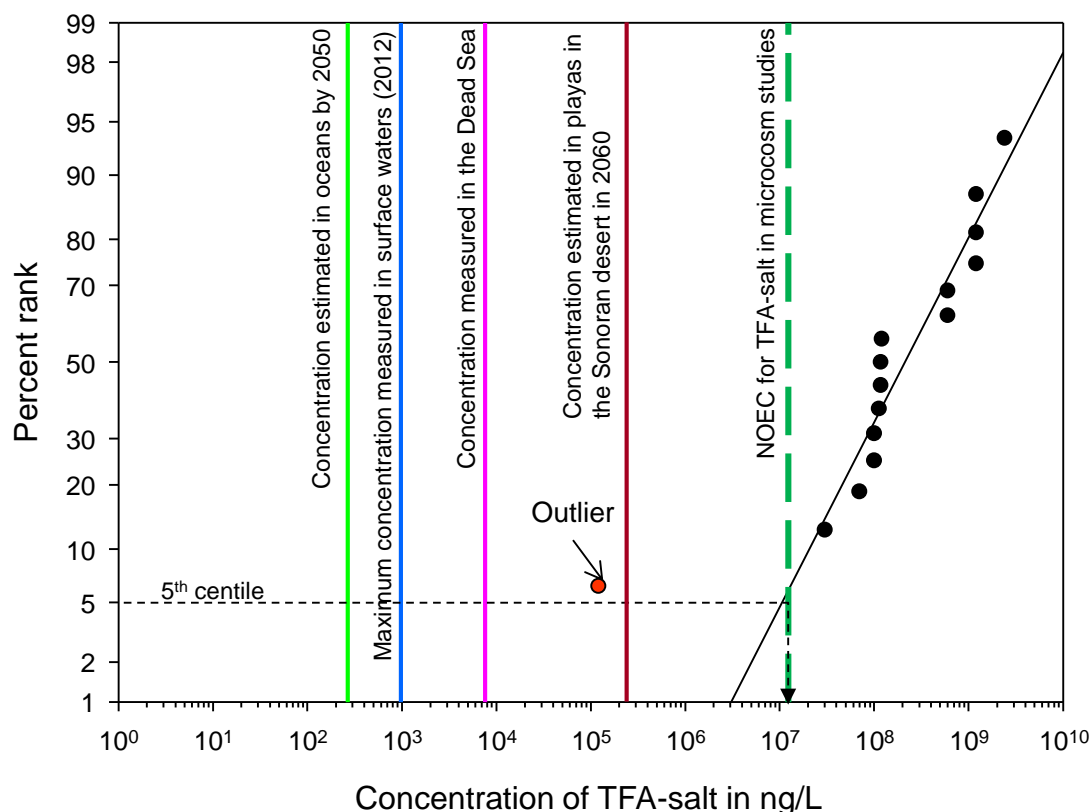


Figure 4. Species-sensitivity distribution of no-observed-effect-concentrations (NOECs) for TFA-salt in aquatic organisms (from data in Table 4). Solid vertical lines are environmental concentrations expressed as TFA-sodium salt and the dashed line is the No-observed-effect-concentration (NOEC) for aquatic plants in field microcosms. The red data point is an outlier (*Raphidocelis subcapitata*) that was excluded from the regression for calculation of the 5th centile.

5 Assessments of risks of TFA

The risks of TFA in various environments were estimated by comparing exposure values with toxicity values. The toxicity values were the most sensitive NOEC as described above. Exposure values were those from measured concentrations in surface waters as discussed in the above sections. The largest measured concentration was used in the estimation of the risk. These comparisons provide a worst-case scenario and were calculated by estimating a margin of exposure (MoE), which is the ratio of the exposure concentration to the toxicity value. This is a widely used measure of the risk of chemical toxicity. For non-carcinogenic compounds in humans, a MoE of 100 between the dose and the NOEC is considered acceptable (Health Canada 2008). For other organisms in the environment, MoEs between 1 and 100 are considered acceptable, depending on the response observed in the organism, their function in the ecosystem, and how rapidly they can recover from any adverse effects (USEPA 2004).

Exposure of humans to TFA (salts) via drinking water was based on the WHO default for consumption of 2 L of water per day in a 60 kg human (World Health Organization 2008). The maximum concentration measured in drinking water and surface water (Table 3) was used as the exposure concentration and the NOEC from

the rat (Boutonnet et al. 1999) was used as the toxicity value. The MoE was normalized to the daily dose in a 60 kg person. This value is judged to be sufficiently conservative to be protective for other vertebrates in the environment.

For terrestrial plants directly exposed to TFA via fog or rain, the maximum concentration of TFA acid reported in fog (Wujcik et al. 1998) was used as an exposure value. The toxicity value was from exposures of pine trees to TFA acid in fog chambers (Benesch and Gustin 2002). For plants exposed via soil, the maximum measured concentration of TFA-salt in soil (Scott et al. 2005b) was used as an exposure value and this was compared to a toxicity value for plants exposed via the roots from an aqueous solution (Smit et al. 2009). In this comparison, it was assumed that the density of soil is 1.5 kg/L and the toxicity value was normalized accordingly.

For aquatic organisms, maximum measured concentrations in surface waters (Table 3) and estimated concentration in 2050 of TFA-salt in the oceans resulting from the use of fluorinated refrigerants (Table 1 and Section 3.4) were used. Toxicity values were the NOEC for *R. subcapitata* from Table 4 and the 5th centile of the toxicity distribution in Figure 4, which is 11,800,000 ng TFA salt/L.

Risks for organisms inhabiting salt lakes and playas were not assessed as there were no reports on toxicity of TFA in these halophytic organisms. However; it should be noted that, in comparison to other natural mineral-salts, TFA-salts currently (and in the foreseeable future) are present in small concentrations in these playas and lakes. Any effects that TFA might have are probably mitigated by the same mechanisms that allow these organisms to survive in such highly saline environments. Nevertheless, this is a potential uncertainty

The MoEs for the above exposure-scenarios are shown in Table 5. Clearly, there are *de minimis* risks from TFA for humans and terrestrial vertebrates. MoEs are extremely large and, even if exposures increase in the near future, these risks would likely still be *de minimis*.

Risks for plants exposed via soil are *de minimis*; The MoE was >100. For plants exposed to TFA via fog or precipitation, the calculated MoE is small (3). However, this is based on an NOEC of 10,000 ng/L which is simply the highest concentration used in the one study (Benesch and Gustin 2002) to have tested the responses of plants to wet deposition of TFA. It may well be that had greater concentrations of TFA been used, then a larger NOEC would have been determined. Even using 10,000 ng/L as the NOEC, such a large concentration is likely to occur only at the beginning of a precipitation event (Berg et al. 2000). Continuing precipitation will contain lesser concentrations of TFA and will wash the initial deposit off the plant. This would reduce exposures of terrestrial plants to TFA-acid.

For aquatic plants and animals, risks also are *de minimis*. MoEs were all >100, even for the sensitive alga, *R. subcapitata*. It is noteworthy that the two aquatic animals for which toxicity data were available (*Daphnia magna* and *Danio rerio*) are relatively insensitive to TFA-salts as are several species of algae other than *R. subcapitata* (Table 4).

Table 5. Margins of exposure (MoE) for TFA-acid and TFA-salts for various species and various exposure scenarios.

Exposure scenario	Value	Units	Organism	Toxicity value	Units	MoE
Humans and terrestrial vertebrates						
Max measured conc. in drinking water	183	ng salt/L	Rat NOEC ¹	114,000,000	ng salt/kg/day	18,698,000
Max measured conc. in surface freshwater	968	ng salt/L				3,535,000
Terrestrial plants						
Max measured conc. in soil	11,092	ng salt/kg	Plant NOEC	3,750,000	ng salt/kg	338
Max measured conc. in fog and rain	3,779	ng acid/L	Plant NOEC	10,000	ng acid/L	3
Aquatic organisms						
Estimated conc. in the oceans in 2050	256	ng salt/L	NOEC for <i>R. subcapitata</i>	120,000	ng salt/L	469
			5 th centile of the SSD ²	11,800,000	ng salt/L	46,094
Max measured conc. in surface freshwater	968	ng salt/L	NOEC for <i>R. subcapitata</i>	120,000	ng salt/L	124
			5 th centile of the SSD	11,800,000	ng salt/L	12,195

¹ NOEC = no-observed-effect-concentration

² SSD = species-sensitivity distribution

6 Strengths and uncertainties

This assessment report has shown that there is a good understanding of the formation of TFA from HCFCs, HFCs and HFOs, and because of the Montreal Protocol, there are valid estimates of the use and potential release of HCFCs, HFCs and HFOs. There was satisfactory information on the toxicity of TFA and salts to mammals and aquatic organisms, the latter being most important as they inhabit the final sink of TFA. However, the alga, *R. subcapitata*, was unusually sensitive and should be re-tested.

A number of uncertainties are also identified in this assessment. There is less than satisfactory information on the toxicity of TFA and salts to terrestrial plants, and none on organisms found in salt lakes and playas. This latter uncertainty is particularly important because salt lakes are the most likely site for accumulation of TFAs in the natural environment due to the lack of flushing of these systems. They are by nature endorheic, with no outflow.

With respect to sources of TFA from compounds not regulated or monitored under the Montreal Protocol, there is almost no information on the amounts of TFA used globally on other potential sources of TFA in the environment and how much these contribute to the total global load. Very few of the more than one million molecules that contain the –CF₃ group have clearly defined degradation pathways. In addition, there is no global inventory of the use of the –CF₃ group in the synthesis of new chemicals or to what extent these could contribute to the global input. There is very little temporal and spatial sampling or measurements of TFA in the oceans and flowing waters and it is not yet possible to discern trends in concentrations of TFA in

these environments. Temporal monitoring of TFA in surface waters, including highly vulnerable settings (e.g. endorheic basins) should be undertaken to provide early assessments of potential accumulation trends. Although risks to humans and the environment from the current (and near future) amounts of TFA in the environment are judged to be *de minimis*, TFA is very persistent and concentrations will continue to increase in the terminal sinks.

7 Conclusions

This assessment tested the hypothesis that the concentrations of TFA in the environment are not greater than the no-observed-effect-concentration for a range of species. Using data from worst-case measured concentrations as well as those based on extrapolations to 2050 of inputs from sources of TFA regulated and monitored under the Montreal Protocol, it was found that TFA is not expected to exceed these toxicity values. The conclusion is that the current and estimated concentrations of TFA and its salts in the environment that result from the degradation of HCFCs, HFCs and HFOs in the atmosphere do not present a risk to humans and the environment. However, the formation of TFA from the degradation of HCFCs and HFCs warrants continued attention, in part because of its very long environmental lifetime.

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