Solvent Suitability for HFPO-DA ("GenX" Parent Acid) in Toxicological Studies

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Abstract

Per- and polyfluorinated alkyl substances (PFAS) are of significant interest because of their prevalence and environmental persistence. Further, for many PFAS, including fluorinated ethers, such as hexafluoropropylene oxide dimer acid (HFPO-DA, or the parent acid of "GenX"), toxicological data are sparse. In general, *in vitro* testing frequently uses dimethyl sulfoxide (DMSO) as a carrier solvent due to its low toxicity, solubility across vast chemical space, and permeation across biological barriers. For PFAS, laboratory practice has assumed that the materials are stable across a wide range of solvents, pHs, and temperatures. In this study, HFPO-DA stability was evaluated with DMSO and other commonly used solvents to determine each solvent's suitability for use in toxicity assays. The formation of HFPO-DA's degradation product, heptafluoropropyl 1,2,2,2-tetrafluoroethyl ether (Fluoroether E-1), was monitored by headspace gas chromatography-mass spectrometry (GC-MS) over time. These experiments revealed degradation of HFPO-DA to Fluoroether E-1 in DMSO and other aprotic, polar solvents, with half-lives on the order of hours (1 h, 1.25 h, and 5.2 h for DMSO, acetone, and acetonitrile, respectively). This rapid degradation suggests the need for caution when performing or using data from toxicity assessments on HFPO-DA and closely related PFAS compounds.
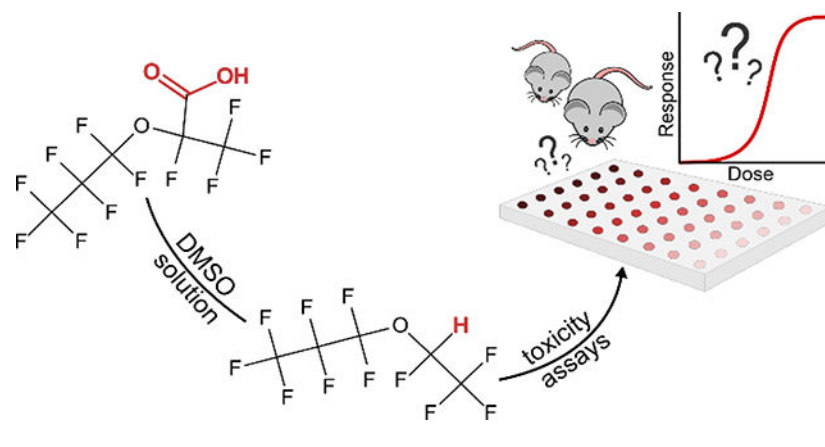
Graphical Abstract

INTRODUCTION

Per- and polyfluorinated alkyl substances (PFAS) are a diverse chemical class containing aliphatic chains of fluorine-bonded carbons[1] and have long been a focus of significant public and ecological health interest due to their environmental persistence.[2] This class of compounds is broadly used in commercial products, including applications in flame-retardants/fire-suppressants, water-resistant coatings, and as surfactant additives.[3, 4] Concerns over the health impacts of the legacy PFAS, perfluorooctanoic acid (PFOA) and perfluorooctanesulfonic acid (PFOS)[5], led to their voluntary phase-out in the U.S. in the early 2000s.[6, 7] Despite the phase-out of these specific chemicals, the number of extant PFAS species is believed to be in the thousands[1] with a more limited number, on the order of hundreds, in active commercial usage.[8]

To specifically address concerns related to PFOS/PFOA toxicity, replacement chemistries have been developed with shorter fluoroalkyl chains, such as perfluorobutanesulfonic acid (PFBS), and/or the inclusion of fluoroether moieties, such as perfluoro-2-propoxypropanoic acid, also referred to as hexafluoropropylene oxide dimer acid (HFPO-DA) or its trade name "GenX". PFAS with these newer chemistries have been increasingly detected in drinking water and soil, including many chemicals which are not explicitly in commercial usage.[9–13] The continued discovery of new PFAS with limited health effects information has, unsurprisingly, led to a heightened demand for toxicity data.[14–16] The prospect of generating mammalian toxicity data for all emerging PFAS species is daunting, and has resulted in substantial investment in new approach methodologies, including alternate model organisms and *in vitro* toxicity assays,[8, 10, 11, 17–19] which can yield high-throughput data at a rate consistent with the breadth of chemical substances being identified.

The chemical, HFPO-DA ("GenX" parent acid), has offered an exemplary scenario demonstrating the need for rapid integration of environmental monitoring information with relevant toxicity testing. HFPO-DA contamination was first reported in the Cape Fear River of North Carolina in 2015, downstream of a chemical manufacturing plant in Fayetteville, NC.[10, 11, 18] Intense scrutiny of the compound ensued due to its relatively high abundance in drinking water and the scarcity of information regarding long-term exposure effects in

biological organisms. Focus on the compound in NC also triggered interest in its prevalence in areas near other fluorochemical facilities in the U.S.[20, 21] and worldwide.[22–24]

As toxicologists have begun to assess HFPO-DA, we have had reason to doubt the stability of HFPO-DA in dosing solutions relative to the long lifetimes of legacy PFAS species. A study by Sheng et al. noted the apparent loss of HFPO-DA in the solvents they used for testing purposes,[25] hypothesizing "high volatility" of the compound, and we had previously noted loss of HFPO-DA in DMSO in some of our own studies.[19, 26, 27] Based on our observations of solvent-specific stability issues with HFPO-DA, we hypothesize that degradation is occuring to produce the H-substituted ether derivative, Fluoroether E-1 (heptafluoropropyl 1,2,2,2-tetrafluoroethyl ether [Figure 1]), mediated by reaction with solvent. If not assessed and accounted for, degradation in stock and dosing solutions is likely to result in underestimation of HFPO-DA's toxicological effects *in vitro* and *in vivo*, perhaps instead quantifying the combined effects of parent and product compound or the product compound alone. We therefore set out to assess the stability of HFPO-DA in a variety of toxicologically relevant solvents by monitoring the formation of its degradation product, Fluoroether E-1, by headspace gas chromatography-mass spectrometry (GC-MS) analysis.

MATERIALS AND METHODS

Standards and Solvents

HFPO-DA (EPA DSSTox[28] substance identifier [DTXSID] 70880215) and Fluoroether E-1 (DTXSID8052017) standards were purchased from SynQuest Laboratories, Inc. (Alachua, FL) at the highest purity available (97%). All solvents evaluated for HFPO-DA degradation were HPLC-grade or of equivalent purity (99.5%). Methanol (MeOH), dimethyl sulfoxide (DMSO), acetone (ACE), dichloromethane (DCM) and acetonitrile (ACN) were Burdick & Jackson (Muskegon, MI) brand solvents; methyl *tert*-butyl ether (MTBE) and ethanol (EtOH) were obtained from Sigma-Aldrich (St. Louis, MO). Laboratory-grade refined sesame seed oil was obtained from Jedwards International, Inc. (Quincy, MA) and deionized water was obtained from a laboratory deionized water system (EASYPure II, Thermo Scientific) and measured resistivity 18MΩ-cm.

Headspace GC-MS Method for Fluoroether E-1

A headspace gas chromatography-mass spectrometry (GC-MS) method was developed for the quantification of Fluoroether E-1 using a Thermo Scientific (Waltham, MA) Trace 1310 gas chromatograph coupled to a Q Exactive GC Orbitrap mass spectrometer. All samples and standards were prepared in 20-mL headspace vials containing 10 mL solvent and analyzed according to the instrument method outlined in Table S1. Samples were maintained at room temperature (~22 °C) between injections, with a 2-min incubation/agitation period at 30 °C before 0.5 mL was drawn from the headspace and injected onto the GC. It should be noted that a short incubation period above ambient temperature was required as fluctuations in laboratory air temperature would cause variation in the measurements. The incubation temperature of 30 °C was chosen so there would be consistency between measurements, but the results for rate of formation of E-1 would not be markedly different than what would be observed at typical room temperatures.

The GC inlet was maintained at 200 °C with a split flow of 22.5 mL/min and helium carrier gas maintained at a constant flow rate of 1.5 mL/min (split ratio 15:1). GC separations were conducted using a Thermo TraceGOLD TG-5SilMS capillary column (30 m × 0.25 mm × 0.25 μm, 5% diphenyl/95% dimethyl polysiloxane). The 17-min GC oven program began at an initial temperature of 35 °C, which was held for 2 min, then ramped at 15 °C/min to 150 °C and held for 0.25 min. An electron ionization (EI) MS source was used, with an electron energy of 70 eV and 50 μA emission current. The ion source and MS transfer line were both maintained at 280 °C. MS data were acquired for m/z range 40–600 with a resolving power of 60,000 (at m/z 200). Area counts obtained from extracted ion chromatograms (XICs) of two characteristic ions, m/z 168.9882 and 68.9946 (within 5 ppm mass accuracy), were used for calibration and concentration determination of E-1 (Figure S1).

Calibrations of Fluoroether E-1

A high-concentration (~10 parts-per-thousand [ppth; mg/mL]) standard of E-1 was prepared in ACN and utilized as the stock solution for all calibration standards prepared in this study. This stock solution was used within 20 days of preparation and stored at −20 °C between uses. Calibration standards of E-1 were prepared in each test solvent at 0.05, 0.1, 0.5, 1, 5, 10, 15, and 20 parts-per-million (ppm; mg/L; μg/mL) Because analyte volatilization and method sensitivity are solvent-dependent (Figure S2), care was taken to maintain consistent solvent composition across all calibration samples. A neat ACN-calibration set was first prepared at 100-fold higher concentrations (5 to 2,000 ppm), and 100 μL of each was diluted in 9.9 mL solvent, with each resulting headspace-analysis standard consisting of 1% ACN. Linear regressions (R^2 0.99) were used for E-1 quantification in each solvent, and calibrations were run within three days prior to each respective degradation study performed. Immediately before each timed experiment, a randomly chosen calibration standard was re-analyzed as a check standard to verify calculated concentration from constructed calibration curves were accurate within 15% error.

Degradation Studies of HFPO-DA

A high-concentration (~10 ppth) stock solution of HFPO-DA was prepared in MeOH and used within ten days for all degradation experiments. Degradation experiments were performed with 20 ppm HFPO-DA in a series of solvent vehicles (DMSO, ACE, ACN, MeOH, EtOH, water, DCM, MTBE, and sesame oil). Each solvent's respective calibration curve was used to calculate E-1 concentration over time in solvent spiked with HFPO-DA. Percent conversion of HFPO-DA to E-1 was calculated based on the initial spike of 20 ppm HFPO-DA (equivalent to 60.6 μM, 17.3 ppm as E-1).

The degradation of HFPO-DA to Fluoroether E-1 was monitored over 25-h periods in all solvents included in this study, with time point intervals as often as every 17 min (minimum allowable due to GC run time of 17 min). For toxicologically relevant solvents (DMSO, EtOH, water, and sesame oil), degradation experiments were performed in triplicate. Half-lives of HFPO-DA in different solvent conditions were estimated using a single-first order decomposition equation implemented in R package, *mkin (v. 0.9.49.8)*.[29]

RESULTS AND DISCUSSION

Stability/Degradation of HFPO-DA in Solvent

Degradation experiments (25-h) of HFPO-DA were performed for all solvents in this study, with E-1 headspace measurements taken in 96-min intervals for each. Conversion of HFPO-DA to E-1 in DMSO And ACE was rapid enough to reach 100% by the third time point; additional experimental replicates were conducted for DMSO and ACE with shorter, 17-min sampling intervals to more accurately model the degradation (Figure 2).

As shown in Figure 2, degradation of HFPO-DA was observed in DMSO and ACE with estimated half-lives of 59 min (0.98 h) and 75 min (1.25 h), respectively. In ACN, degradation was slower, reaching 100% conversion to E-1 in 15 h (half-life of 312 min [5.2 h]). In water, MeOH, EtOH, MTBE, DCM, and sesame oil, no significant formation of E-1 was observed. Replicates for the degradation in toxicologically relevant solvents are shown in Figures S3 and S4.

Solvent-mediated degradation was observed in three of the nine solvents tested (DMSO, ACE, ACN) to produce the hypothesized Fluoroether E-1 product. No additional volatile products of degradation were observed in any of the tested solvents based on the GC-high-resolution-MS scans. The degradation pathway for this particular molecule is believed to be mediated by the solvent parameters, with degradation occurring only in polar, aprotic solvents with H-bond accepting character.[30] Computational modeling of similar decarboxylation of a perchlorinated species found the process was likewise solvent dependent, being most favored in polar, aprotic solvents like DMSO.[31]

The carboxylic acid moiety of HFPO-DA has been noted to be highly thermally labile,[11] and we conclude that observed formation of Fluoroether E-1 was not due to thermal degradation of HFPO-DA in the hot GC inlet, as: (1) sample incubation at 30 °C would not volatilize a significant portion of HFPO-DA (boiling point ~190 °C), and (2) even if HFPO-DA was present in the headspace and injected, E-1 would have been detected in every HFPO-DA standard analyzed, and formation over time would not have been observed under these conditions. We hypothesize aprotic solvents facilitate decarboxylation and protonation of the stabilized carbanion intermediate via solvent-mediated proton transfer (Figure S5), even at room temperature, whereas protic solvents stabilize the carboxylic acid via hydrogen bonding. Stability of the intermediate carbanion would be crucial to this pathway, which likely explains why we have only observed this effect in branched fluoroether PFAS and not in linear, legacy compounds such as PFOA. Efforts to fully understand the mechanism and effects of various solvent compositions and additives on the stability of different emerging PFAS is a vital focus for future work.

Implications for Toxicological Assessment of HFPO-DA

Traditional handling of PFAS has assumed that they are stable across a wide range of solvents and conditions.[2] DMSO is one of the most commonly used solvents in toxicological assays, especially *in vitro*, due to its low acute toxicity, wide-ranging compound solubilization capability, and high degree of permeation through biological membranes.[32, 33] However, results of this study indicate that it is unsuitable for use as the carrier solvent in

toxicity testing of HFPO-DA. It is probable that other compounds with a similar branched perfluorinated carboxylic acid (e.g., perfluoro-2-methoxypropanoic acid [PMPA], perfluoro-2-ethoxypropanoic acid [PEPA], other HFPO-polymer acids) could undergo degradation by a similar mechanism. For example, HFPO-trimer acid (HFPO-TA; DTXSID00892442) and tetramer acid (HFPO-TeA; DTXSID40892441) likely degrade to Fluoroethers E-2 (DTXSID50880192) and E-3 (DTXSID10880193), respectively.

There is an ongoing large-scale effort at the U.S. Environmental Protection Agency to test PFAS materials and ensure the presence of testing materials, as well as determine solvent stability and appropriateness for assay usage. These efforts have also noted loss of HFPO-DA, -TA, and -TeA from DMSO stocks of these compounds.[17] As toxicological efforts on PFAS expand, consideration of sample stability in any solvent should be carefully assessed. For example, while methanol provides stability for HFPO-DA, it is known that perfluorinated carboxylic acids, such as PFOA, can react in methanol to form fluorinated fatty acid methyl esters (FAMEs), and the reaction rates can be modified by pH.[34]

Our results indicate that toxicological assessment must take care in the preparation of both stock solutions and dosing solutions involving HFPO-DA. Stock solutions of HFPO-DA should not be prepared in DMSO, ACE, or ACN, given these solvents facilitated degradation of the analyte within hours at room temperature; alternatives such as MeOH should be used preferably, while still monitoring for stability. For assay dosing, we suggest that procedural adjustments are made to utilize either EtOH or water, including all appropriate negative and positive controls. In general, these results indicate the importance of monitoring effective concentrations of chemicals (i.e., in-serum, in-well, etc.) in addition to nominal dose concentrations. Failure to verify the nominal dose could result in toxicity results that underestimate the effect of PFAS due to loss of parent, or combined effects of parent and product compound.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGEMENTS

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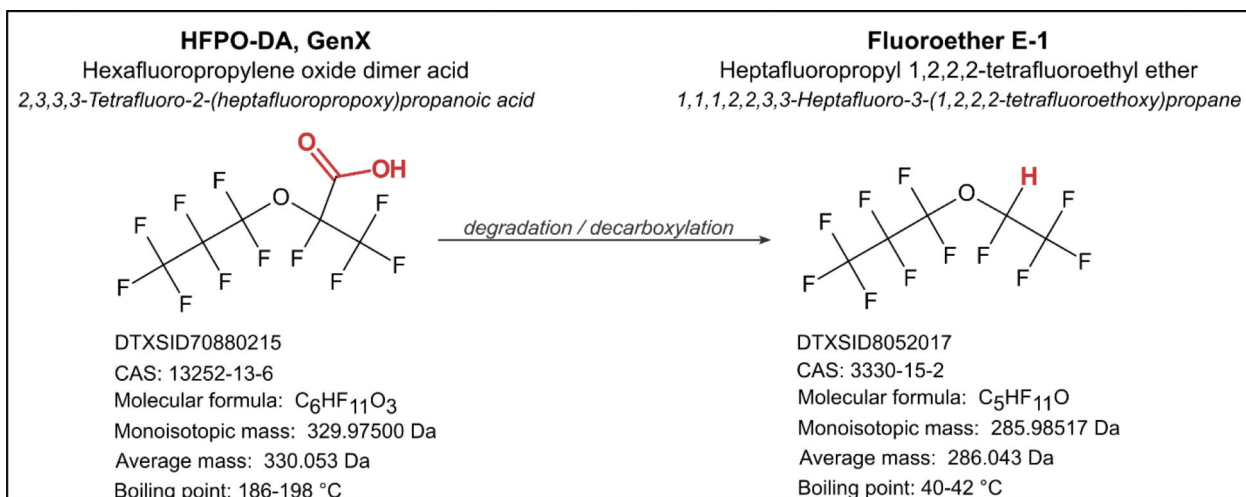
Figure 1.
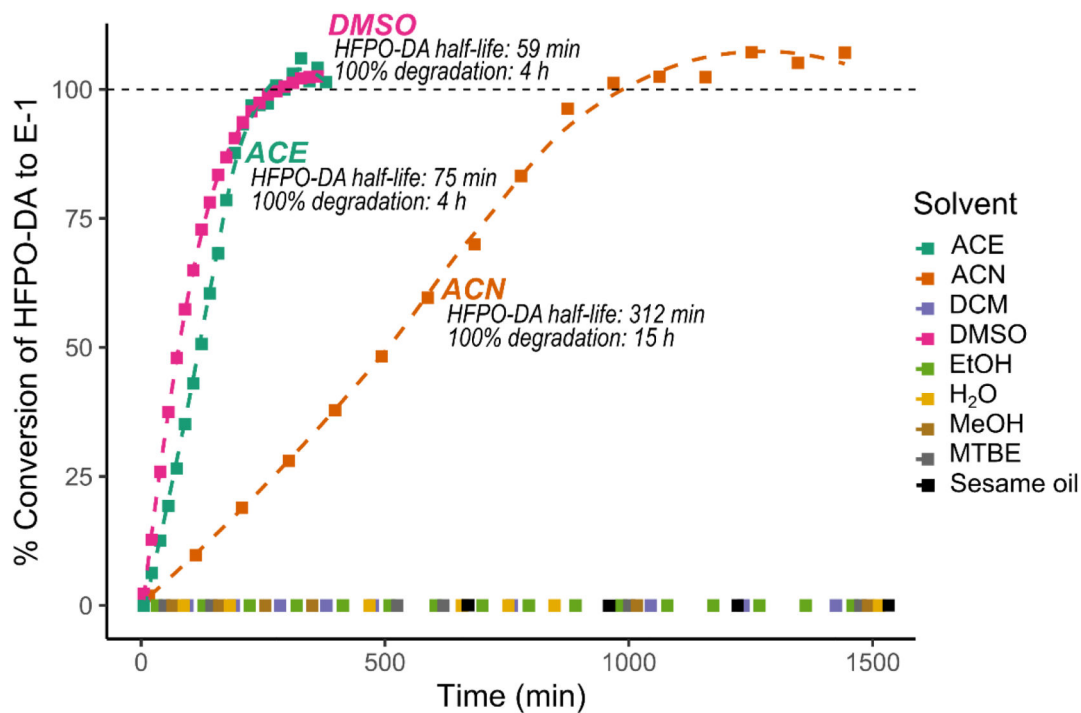HFPO-DA degradation via decarboxylation to Fluoroether E-1.

Figure 2.
Formation of E-1 from HFPO-DA spiked into each solvent monitored over time; HFPO-DA half-life calculated using fit of single first-order kinetics using R package *mkin*; 100% degradation time based on observed degradation curve.