Regulatory Toxicology and Pharmacology 103 (2019) 10–20

Contents lists available at ScienceDirect

Regulatory Toxicology and Pharmacology

journal homepage: www.elsevier.com/locate/yrtph

Perfluorohexanoic acid toxicity, part II: Application of human health toxicity value for risk characterization

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ARTICLE INFO

Keywords:
PFHxA
Perfluorohexanoic acid
Fluorotelomers
Human health
Risk characterization

ABSTRACT

Perfluorohexanoic acid (PFHxA) is a short-chain, six-carbon PFAA and is a primary impurity, degradant, and metabolite associated with the short-chain fluorotelomer-based chemistry used in the United States, Europe and Japan today. With the shift towards short-chain PFAA chemistry, uncertainties remain regarding human health risks associated with current exposure levels. Here, we present a critical review and assessment of data relevant to human health risk assessment to today's short-chain PFAA chemistry. Human biomonitoring surveys indicate that PFHxA is infrequently detected in the environment as well as in human serum and urine; however, human health concerns may persist in locations where PFHxA is detected. In a companion paper (Luz et al., 2019) we comprehensively evaluate the available toxicity data for PFHxA, and derive a chronic human health-based reference dose (RfD) for PFHxA of 0.25 mg/kg-day based on benchmark dose modeling of renal papillary necrosis in chronically exposed female rats. In this paper, we apply this RfD in human health-based screening levels calculations, and derive a drinking water lifetime health advisory of 1400 µg/L and a residential groundwater screening level for children of 4000 µg/L. Compared to environmental concentration data, even sites with more elevated concentrations of PFHxA in the environment are at least an order of magnitude lower than these screening levels. Available PFHxA human serum and urine biomonitoring data, used as a biomarker for general population exposure, demonstrates that the general human population exposures to PFHxA are low. Previous estimates of daily intake rates for infants exposed to PFHxA through breast milk, formula, and baby foods (Lorenzo et al., 2016) combined with the most conservative PFHxA peer-reviewed toxicity value (Luz et al., 2019) demonstrate that the margin of safety for PFHxA is high. Therefore, PFHxA and related fluorotelomer precursors currently appear to present negligible human health risk to the general population and are not likely to drive or substantially contribute to risk at sites contaminated with PFAS mixtures. PFHxA may also represent a suitable marker for the safety of fluorotelomer replacement chemistry used today.

1. Introduction

Short-chain perfluorocarboxylic acids (PFCAs) and precursor short-chain fluorotelomer-based products that degrade into short-chain PFCAs, such as 6:2 fluorotelomer alcohol, have been used within the fluorotechnology market since the 1970s. Short-chain PFCAs are not bioaccumulative and have a lower toxicity profile compared to long-chain PFCAs (Conder et al., 2008). Some short-chain PFCAs have demonstrated relatively high mobility, solubility, enhanced groundwater transport, and longer aerial transportation (Zhou et al., 2013). Therefore, concerns remain about the continued use of industrial and commercial fluorochemistry products (Scheringer et al., 2014; Wang et al., 2015; Ritscher et al., 2018).

The six-carbon (C6) PFCA, perfluorohexanoic acid (PFHxA), is an impurity of, and a metabolite and degradation product of, the short-chain fluorotelomer-based products including side-chain fluorinated polymers and fluorosurfactants on the market today (Buck, 2015). As a result of the use of short-chain C6 products since the 1970s, it is likely that PFHxA was historically present in fluorinated polymer production, aqueous firefighting foams, water/grease repellents, and other commercial products (Prevedouros et al., 2006). Within the United States, there are no PFHxA federal toxicity values, cleanup standards, or screening values to help guide risk management decisions. Through the European Chemicals Agency (ECHA), Germany recently proposed to list PFHxA as a “substance of very high concern” (SVHC), according to Article 57 of the EU REACH Regulation (Regulation [EC] No. 1907/

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https://doi.org/10.1016/j.yrtph.2019.01.020
Received 9 November 2018; Received in revised form 4 January 2019; Accepted 7 January 2019
Available online 08 January 2019
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2006) (ECHA, 2018). The proposal suggests that PFHxA should be an SVHC because it is "extremely persistent, mobile in the aquatic environment, can be distributed easily within and between environmental compartments by aqueous media, has a long-range transport potential and the potential to enrich in plants." Underlying this initiative is a belief that PFHxA is very difficult to remove from the environment and that chronic exposure may cause adverse effects (Annex XV Report, 2018). The objectives of this paper are to critically evaluate the available science on PFHxA, including environmental occurrence and human biomonitoring studies, and to compare exposure levels to plausible chronic human health toxicity values. A companion paper, Luz et al. (2019), provides the first comprehensive evaluation of PFHxA toxicology information and derives a Tier three[1] chronic human health based toxicity value using accepted state-of-the-art chemical risk assessment methodologies. In terms of relative potency, PFHxA is approximately four orders of magnitude less toxic than perfluorooctanoic acid (PFOA).[2] The chronic toxicity value from Luz et al. (2019) was converted to a human-health based drinking water screening level that can be used to assess risk associated with contaminated drinking water systems, and a default residential groundwater screening level that can be used at contaminated groundwater sites. Using this groundwater screening level, we compare published groundwater concentration levels from contaminated sites and show that the maximum reported PFHxA concentrations are 33–1000 times lower than the most conservative screening level for a standard residential child receptor scenario. Finally, we evaluate PFHxA human serum and urine biomonitoring data as a marker of general population exposure, and compare estimated daily exposures to human health-based threshold levels. This analysis demonstrates that for the general human population, exposures are significantly lower than threshold levels and the margin of safety is high. For example, the estimated daily intake of PFHxA for infants through breastmilk, cereals, and formula is 200,000 to 320,000 times lower than the chronic human toxicity values, demonstrating a large margin of safety even for the most sensitive subpopulations.

2. Methods

Scientific literature on PFHxA environmental occurrence and biomonitoring studies was identified via online searches of Google Scholar as well as from references cited by regulatory agency technical reports on PFAAs. Key words used in the literature search included PFHxA and associated chemical species that may be included in chemical analysis.

Then, a screening level for residential drinking water exposure was calculated using the PFHxA chronic toxicity value (Luz et al., 2019) and standard U.S. Environmental Protection Agency (EPA) Office of Water methods and default exposure assumptions for a lifetime (chronic exposure) health advisory (USEPA, 2018a). A modifying factor called a Relative Source Contribution (RSC) was included, per EPA methodology (USEPA, 2014; USEPA, 2018b). The RSC is the amount of total exposure (from all sources combined) that is assumed to be attributable to drinking water ingestion, and the usual constraint in the absence of site-specific information is an RSC of 20 percent (meaning that 80 percent of an absorbed dose is attributable to other non-water sources such as diet, soil, and indoor dust). For non-polymeric perfluoroalkyl and polyfluoroalkyl substances, particularly in areas where contaminated drinking water is a primary source of exposure, some regulatory agencies have logically increased the RSC to at least 50 percent (NJDEP, 2015; MDH, 2017, 2018). The following equation for a drinking water screening level was used, and is the same equation used by EPA to derive a lifetime health advisory for PFOA and perfluorooctane sulfonic acid (PFOS) (USEPA, 2016a, 2016b):

$$C = \frac{BW \times RSC \times CF}{IR \times \left(\frac{1}{RfD}\right)}$$

where:

C = chemical concentration in drinking water (μg/L)
BW = body weight, adult = 70 kg
IR = water ingestion rate, adult = 2 L/day
RSC = relative source contribution = 20%
RfD = reference dose (mg/kg-day)
CF = conversion factor (1000 μg/mg)

In addition, a residential groundwater screening level (residential groundwater used as tap water) was derived, protective of residential child or adult receptors, by using (a) the standard equation for residential water exposure to a noncarcinogen (USEPA, 1991); and (b) exposure factors for estimating reasonable maximum exposure (RME) recommended by USEPA (2014). A term for the RSC was not included in the back-calculation of a concentration in water, consistent with the approach used in human health risk assessments conducted under the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA, 40 CFR 300.5).

The following default equation for residential exposure to noncarcinogens in groundwater was used:

$$C = \frac{THI \times BW \times 365 \times CF}{EF \times IR \times \left(\frac{1}{RfD}\right)}$$

where:

C = chemical concentration in drinking water (μg/L)
THI = target hazard index (1)
BW = body weight: child = 15 kg; adult = 80 kg
EF = exposure frequency (350 days/year)
IR = water ingestion rate: child = 0.78 L/day; adult = 2.5 L/day
RfD = reference dose (mg/kg-day)
CF = conversion factor (1000 μg/mg)

3. Results

3.1. Overview of PFHxA environmental fate and transport properties

PFHxA has a fully fluorinated carbon tail and a carboxylic functional moiety head, $C_5F_{11}COOH$. The stability of the fluorine-carbon bond has been well described to be due to the electronegative shield provided by the fluorine ions around the carbon tail and the high bond energies between the two ions (Siegemund et al., 2000; Ahrens, 2011). PFHxA is a stable chemical, does not undergo biodegradation, and is environmentally persistent. PFCAs, in general, are not biodegradable under either aerobic or anaerobic environmental conditions (Lassen et al., 2013). The reported water solubility for PFHxA is approximately 29 mg/L (ENVIRON, 2014). Estimated pK_a values are reported to be < 1 and the anion is highly water soluble and nonvolatile (Vierke et al., 2014; ENVIRON, 2014). Studies with a variety of environmental matrices have demonstrated that sorption and retardation generally increases with increasing PFCA tail length (Higgins and Luthy, 2006; Guelfo and Higgins, 2013; Sepulvado et al., 2013). There are indications that PFHxA may be capable of long-range marine transport, as the

[1] According to USEPA policy and guidance (USEPA, 1989, 1993, 2003, 2013), tier three toxicity values are recent, derived with transparent methodology and standard risk assessment methods, have been peer-reviewed, and are publicly available. Alternatively, tier one and two toxicity values are derived via USEPA IRIS (Integrated Risk Information System) and PPRTV (Provisional Peer-Reviewed Toxicity Values) assessments, respectively.

[2] The RfD for PFHxA is 0.25 mg/kg-day (Luz et al., 2019) and is 4 orders of magnitude larger than the USEPA RfD (0.00002 mg/kg-day) for PFOA (USEPA, 2016a). Similarly, comparing the human equivalent dose points of departure for PFOA (0.0053 mg/kg-day) and PFHxA (24.8 mg/kg-day) also shows an approximately 4 orders of magnitude difference.

compound has been detected at low concentrations in snow, sediment, biota, and seawater in remote locations; however, it is still not well understood if these detections were a result of direct emission or degradation of PFHxA precursors or both (reviewed in ENVIRON, 2014; Rankin et al., 2016; AMAP, 2018). Several studies have demonstrated that some PFAAs can accumulate in plants (Felizeter et al., 2012; Krippner et al., 2014). Further, plant uptake and distribution appear to be dependent on chain length, with longer-chain (≥8-carbon) PFCAs tending to be retained in roots, while shorter chain PFAAs such as PFHxA undergo a wider distribution and have been detected in edible plant foliage (Felizeter et al., 2012). However, PFHxA does not appear to be bioaccumulative or to biomagnify in higher trophic levels of the food chain. Bioconcentration factors and bioaccumulation factors for PFHxA are consistently less than 500 L/kg (Conder et al., 2008; Zhou et al., 2013, reviewed in Ding and Peijnenburg, 2013).

3.2. Environmental occurrence, concentrations, and human exposure

In 2006, the major fluorochemical manufacturers voluntarily initiated a global stewardship program to eliminate long-chain PFCAs and potential precursors from emissions and products by year-end 2015. For fluorotelomer-based products, this meant shifting to products that contained a six-carbon perfluoroalkyl moiety (Buck et al., 2011). As such, this brought focus to a primary potential impurity, degradant and metabolite from short-chain fluorotelomer-based products, the short-chain PFCA, PFHxA. Given the environmental persistence of PFHxA and potential environmental and biological occurrence due to the degradation of short-chain fluorotelomer-based products, a review of available PFHxA environmental concentration and human exposure data was conducted.

3.2.1. Environmental occurrence and concentration

3.2.1.1. PFHxA detection in water is generally low and infrequent. In general, PFHxA has a low frequency of detection (FOD) and is detected at low levels in the majority of studies that have investigated its occurrence in groundwater, surface water, and drinking water at sites not associated with identified point-source contamination (Table 1). Gellrich et al. (2013) investigated the occurrence of various PFCAs, including PFHxA, in tap water, untreated water, bottled water, and spring water across Germany. PFHxA was generally not detected, with the exception of low concentrations (median: 2.0 ng/L; maximum: 6.4 ng/L) in 23% of samples of tap water. In another study, Skutlarek et al. (2006) measured the occurrence of various PFCAs in drinking water within and outside of the Ruhr area of Germany, a site of point-source contamination. Outside of the Ruhr area, PFHxA occurred at a very low frequency (6.3%) and concentration (≤9 ng/L) in drinking water, while PFHxA occurred at a higher frequency (75%) and level (≤56 ng/L) in drinking water within the Ruhr area of Germany.

In contrast to these studies of ambient levels, PFHxA has been detected at higher concentrations in surface water in areas with known point sources of PFCA contamination. For example, concentrations of up to 3800 ng/L PFHxA have been detected in the Metedeconk River in New Jersey, USA, which is suspected of being contaminated with PFAAs emanating from a nearby industrial park (Karl et al., 2016). However, even at this contaminated site, the FOD of PFHxA was low (32%). PFOA was detected in nearly every sample (95.8%) and at order-of-magnitude higher concentrations. Collectively, these findings indicate that drinking water is not expected to be an exposure route of concern for PFHxA for the general population.

3.2.1.2. House dust. PFOA has been frequently detected in house dust samples globally. Due to increased hand-to-mouth activity, and their close proximity to the floor, ingestion of house dust represents a potentially more important exposure pathway for young children than for adults. This is reflected by studies that have estimated daily intake (EDIs) via dust ingestion (Jogsten et al., 2012; Tian et al., 2016). Although only a handful of studies have attempted to measure PFHxA levels in house dust, PFHxA has been detected in every study conducted for which it was included as an analyte (Table 2). Most recently, Winkens et al. (2018) measured dust collected from 65 children's bedrooms in Finland. Of the PFCAs measured, PFOA, PFDA, PFDoDA, and PFNA were detected at a higher frequency than PFHxA (detected in ≥52%, but < 75% of samples). Further, PFOA (5.3 ng/g) was detected in house dust at a higher mean concentration than PFHxA (2.3 ng/g). PFHxA dust EDIs were calculated by Winkens et al. (2018) for 10.5-year-old children for low, medium, and high exposure scenarios and estimated to range from ~0.0025 to 0.010 ng/kg body weight per day, which were only slightly lower than the estimated PFOA dust EDIs (~0.0060–~0.014 ng/kg-day). Winkens et al. (2018) did not characterize the risk associated with PFHxA dust EDIs. However, other exposure assessments have characterized the risk associated with exposure to PFOA via dust ingestion and found that this

Table 1
Occurrence of PFHxA in Different Water Sources (concentration units are ng/L).

Sample Type	Location	Year	N	FOD	Min	Median	Mean	Max	Reference
SW, GW	NJ, USA	2011–15	96	32%	< LOD	9.4	190	3800	Karl et al. (2016) [a]
SW Rhine River and tributaries	Germany	2006	38	32%	< LOD	–	17.1	77	Skutlarek et al. (2006) [b]
SW Ruhr	Germany	2006	22	68%	< LOD	–	122.2	1248	Skutlarek et al. (2006) [b]
SW Moehne River and tributaries	Germany	2006	12	67%	< LOD	–	957.1	3040	Skutlarek et al. (2006) [b]
DW Ruhr	Germany	2006	21	67%	< LOD	–	19.2	56	Skutlarek et al. (2006) [b]
DW outside of Ruhr	Germany	2006	16	6.3%	< LOD	–	–	9	Skutlarek et al. (2006) [b]
TW	Germany	–	26	23%	< LOD	2.0	–	6.4	Gellrich et al. (2013) [b]
Untreated water	Germany	–	14	0%	< LOD	< LOD	< LOD	< LOD	Gellrich et al. (2013)
BW	Germany	–	119	0%	< LOD	< LOD	< LOD	< LOD	Gellrich et al. (2013)
Spring water	Germany	–	18	0%	< LOD	< LOD	< LOD	< LOD	Gellrich et al. (2013)
GW	USA	2014	149	94%	< LOD	820	–	120,000	Anderson et al., (2016), 2019 [c]
Source water	USA	–	25	96%	< LOD	2.0	–	55.1	Boone et al. (2019)
Treated DW	USA	–	25	100%	0.088	1.4	6.2	60.8	Boone et al. (2019)

BW = bottled water; DW = drinking water; FOD = frequency of detection; GW = groundwater; LOD = limit of detection; mean = arithmetic mean; N = sample size; NJ = New Jersey; SW = surface water; TW = tap water; "-" = not reported.

[a] Information on how non-detects were handled when calculating summary statistics were not provided.

[b] Summary statistics were calculated only from samples with PFHxA levels above the LOD.

[c] Non-detects were substituted with one-half the LOD for purposes of calculating summary statistics.

Table 2
Occurrence of PFHxA in Dust (concentration units are ng/g).

Type	Location	Year	N	FOD	LOD	Min	Median	Mean	Max	Reference
House	Canada	2007–08	18	–	–	–	35	–	–	Beesoon et al. (2011) [a]
House	Norway	2007–08	7	86	2.2	< LOD	10.1	–	27.5	Huber et al. (2011) [a]
House	Belgium	2008	45	> 47%	0.1	–	0.3	–	–	D'Hollander et al. (2010) [b]
Office	Belgium	2008	10	> 47%	0.1	–	1.3	–	–	D'Hollander et al. (2010) [b]
House	Norway	2008	41	73%	2.1	4.3	28	33	96	Haug et al. (2011) [c]
House	WI, USA	2008	39	20%	1.0	< LOD	–	–	180	Knobeloch et al. (2012) [d]
House	Spain	2009	10	100%	0.02	0.4	1.0	1.4	2.9	Jogsten et al. (2012)
House	Spain	2009	10	> 50%	–	< 3.2	3.4	3.2	5.5	Eriksson and Karrman (2015) [e,f]
House	USA	2009	30	57%	5	< LOD	–	8.7[g]	1380	Fraser et al. (2013) [c]
Office	USA	2009	31	68%	5	< LOD	–	10.8[g]	102	Fraser et al. (2013) [c]
Vehicle	USA	2009	13	54%	5	< LOD	–	5.9[g]	18	Fraser et al. (2013) [c]
House	CA, USA	2010–11	39	33%	5	< LOD	< LOD	9.5	100	Bradman et al. (2012) [c]
House	Czech Rep.	2013	18	< 20%	1	< LOD	–	–	9.7	Lankova et al. (2015)
House	Czech Rep.	2013	16	100%	–	1.4	3.8	12.8	69.1	Karaskova et al. (2016)
House	USA	2013	20	100%	–	2.5	6.5	20.9	190	Karaskova et al. (2016)
House	Canada	2013	20	100%	–	1.7	5.6	14.5	146	Karaskova et al. (2016)
House	Canada	2013–14	10	> 50%	–	2.7	7.4	17.7	97.1	Eriksson and Karrman (2015) [e,f]
House	Greece	2013–14	7	> 50%	–	< 3.2	3.9	6.2	26.2	Eriksson and Karrman (2015) [e,f]
House	Sweden	2013–14	10	> 50%	–	< 3.2	7.1	9.7	39.6	Eriksson and Karrman (2015) [e,f]
House	Australia	2013–14	10	> 50%	–	< 3.2	4.8	17.5	84.1	Eriksson and Karrman (2015) [e,f]
House	Faroe Islands	2013–14	10	> 50%	–	2.6	8.0	14.7	72.8	Eriksson and Karrman (2015) [e,f]
House	Japan	2013–14	5	> 50%	–	< 3.2	12.0	31.8	119	Eriksson and Karrman (2015) [e,f]
House	Nepal	2013–14	10	< 50%	–	< 3.2	–	–	< 3.2	Eriksson and Karrman (2015) [e,f]
House	NC, USA	2015	35	100%	0.02	1.2	–	7.2[g]	73.9	Siebanaler and Cameron (2016)
House	Finland	2014–15	65	52–75%	–	< LOD	2.3	–	–	Winkens et al. (2018) [c]

"-" = not reported; CA = California; FOD = frequency of detection; LOD = limit of detection; Mean = arithmetic mean, unless otherwise noted; N = sample size; NC = North Carolina; WI = Wisconsin.

[a] Information on how non-detects were handled when calculating summary statistics were not provided.

[b] Samples < LOD were substituted with the FOD*LOD.

[c] Samples < LOD were treated as LOD/square root of 2 for summary statistic calculations.

[d] Concentrations of PFHxA in samples < LOD were assumed to be zero.

[e] Samples < LOD were substituted with ½ LOD.

[f] FOD was not reported, however, median values were only reported if FOD was > 50%.

[g] Geometric mean.

exposure route is associated with minimal risk, even for the most sensitive populations, such as infants and children (Washburn et al., 2005). Given that PFHxA levels in house dust are generally lower than PFOA levels, and that PFHxA has more rapid elimination kinetics than PFOA (32 days vs. ~3.5 years) and is less toxic than PFOA (Luz et al., 2019), exposure to PFHxA via dust ingestion is not expected to pose a risk to human health.

3.2.1.3. PFHxA is detected at low concentration levels and frequency in food products. Due to their favorable repellency and grease-resistant properties, some long-chain (e.g., eight carbon) perfluoroalkyl products were previously used in food packaging applications such as grease- and waterproof-paper that come into direct contact with food products (Kissa, 2001). These substances may leach out of the packaging and into food, thus representing a potential dietary route of human exposure. However, long-chain substances have been phased out of use and have been replaced with short-chain fluorotelomer-based polymers, for which PFHxA may be an impurity. The occurrence of PFHxA in food products has been reviewed (Rice, 2015), and in general, most studies have reported low levels and low FODs of PFHxA in food products. Although outdated, a critical review conducted by Picó et al. (2011) concluded that PFHxA was not found at detectable levels in any type of food product tested. In agreement, the European Food Safety Authority (EFSA, 2011) tested 4881 food products between 2000 and 2009, and detected PFHxA in 0.9% of samples. A study conducted in France detected PFHxA at low levels (< 1 ng/g) in some food products, with the highest detection levels occurring in various dessert and pastry products (0.58–0.92 ng/g; Rivière et al., 2014). Jogsten et al. (2009) detected PFHxA in hotdogs and fried chicken nuggets in Catalonia, Spain; however, detection levels were low (~0.1 ng/g). Collectively, these results indicate that the occurrence and levels of PFHxA in food products is likely low and that consumption of food that has come into contact with paper treated with short-chain fluorotelomer-based polymeric products is not expected to be a major route of exposure to PFHxA.

3.2.2. Human biomonitoring data show human exposure is low and infrequent

PFHxA has generally been excluded from environmental monitoring surveys and blood serum analyses due to the continual low FOD and low levels of detection compared to the associated method detection limit. This is the stated reason why PFHxA was not included in EPA's Unregulated Contaminant Monitoring Rule evaluation or the Centers for Disease Control and Prevention's (CDC's) National Health and Nutrition Examination Survey (Cheremisinoff, 2016).

Human biomonitoring data on PFHxA are presented in chronological order in Tables 3 and 4. Biomonitoring surveys consistently demonstrate that PFHxA is infrequently detected in human serum, and when detected, PFHxA levels tend to be very low, often at or below the limit of quantification (LOQ) or the limit of detection (LOD; typically ranges between 0.03 and 0.1 ng/mL), particularly compared with most other PFAAs (Table 3). Furthermore, recent analysis conducted by the CDC to develop standard methods for detecting short-chain PFAAs in urine reveal that PFHxA is also not detected in preliminary evaluations of the general U.S. adult population (Table 4). Although preliminary, the lack of PFHxA detections in urine is striking, given that urine has reliably served as an important medium for detecting other non-biologically persistent pollutants, such as phthalates. The results are consistent with a urinary biomonitoring study in South Korea in which the FOD for PFHxA ranged from 5% to 11% in child and adult urine samples (Kim et al., 2014). Collectively, the available biomonitoring data provide another line of evidence that PFHxA exposure to the general

Table 3
Occurrence of PFHxA in Human Serum, Plasma, and Whole Blood (units are ng/mL).

Location	Year	Sample	N	FOD	LOD	Min	Median	Mean	Max	Reference
Sweden	1997–00	Blood	66	8%	0.1	< LOD	–	–	1.6	Kärrman et al. (2006) [a]
USA	2000–01	Serum	645	3%	–	< LOD	–	–	6.0	Olsen et al. (2012) [a]
USA	2001	Plasma	4	100%	–	0.088	–	0.27	0.60	Miyake et al. (2007)
Sri Lanka	2003	Serum	30	–	–	< LOD	0.047	0.30	–	Guruge et al. (2005) [b]
Poland	2003	Blood	60	–	–	< 0.002	–	0.03	0.24	Falandysz et al. (2006) [b]
Japan	2003	Blood	3	33%	–	< 0.020	–	< 0.020	0.027	Miyake et al. (2007)
Europe	2003	Blood	47	26%	–	0.1	0.11	–	0.24	WWF (2004) [c]
Japan	2003–09	Plasma	2062	47%	0.1	< LOD	< 0.1	< 0.1[d]	0.69	Okada et al. (2014) [e]
China	2004	Blood	30	57%	–	< LOD	–	–	0.18	Yeung et al. (2008) [a]
Ohio, USA	2005–06	Serum	66,899	53%	0.5	< LOD	0.5	0.9	–	Frisbee et al. (2009) [e]
USA	2006	Plasma	600	3%	–	< LOD	–	–	1.5	Olsen et al. (2012) [a]
Sweden[f]	2008–11	Blood	11	100%	–	0.65	–	–	15.0	Russell et al. (2013)
China	2009	Serum	227	27.9%	–	< LOD	0.02	0.0[d]	2.36	Li et al. (2011) [e]
Taiwan	2009–10	Serum	456	97–99%	0.05	< LOD	–	–	3.9	Dong et al. (2013) [g]
Canada	2009–11	Plasma	1524	2%	0.1	< LOD	–	–	–	Health Canada (2013) [a]
USA	2010	Plasma	600	18%	–	< LOD	–	–	0.4	Olsen et al. (2012) [a]
S. Korea	2009–10	Serum	1874	0%	0.11	< LOD	–	–	–	Lee et al. (2017) [a]
New Zealand	2011–13	Serum	747	0%	0.5	< LOD	–	–	–	New Zealand Ministry of Health (2013) [a]
S. Korea	2012	Serum	120	8%	–	< LOD	–	0.35	0.58	Kim et al. (2014) [e]
China	2012–14	Serum	202	53%	–	< LOD	0.01	0.07	1.1	Li et al. (2017) [g]
Norway	2013–14	Blood	58	100%	0.09	0.14	0.62	0.68	1.65	Poothong et al. (2017)
Norway	2013–14	Plasma	59	0%	0.045	< LOD	–	–	–	Poothong et al. (2017)
Norway	2013–14	Serum	61	0%	0.045	< LOD	–	–	–	Poothong et al. (2017)
USA	2015	Serum	616	3%	–	< LOD	–	–	0.27	Olsen et al. (2017) [a]
NC, USA	2015	Serum	37	84%	0.03	< LOD	–	0.14[d]	1.0	Siebenaler and Cameron (2016) [e]

Given the low frequency of detection for PFHxA in serum, summary statistics can be very sensitive to the method used to represent the PFHxA "nondetect level" (ND). ND concentrations may range from zero to the analytical detection limit, and a common approach is to substitute one-half the detection limit when calculating summary statistics, rather than use zero. Thus, analytical quality control measures should be reviewed prior to making comparisons in PFHxA detection levels across studies (see footnotes below).

"-" = not reported; FOD = frequency of detection; LOD = limit of detection; Mean = arithmetic mean, unless otherwise noted; N = sample size; NC = North Carolina.

[a] Summary statistics were not calculated as the FOD was < 50%.
[b] Information on how non-detects were handled when calculating summary statistics were not provided.
[c] Only samples > LOD were included in summary statistic calculations.
[d] Geometric mean.
[e] Samples < LOD were substituted with ½ LOD.
[f] Reported values are for occupationally exposed professional ski wax technicians.
[g] Samples < LOD were substituted with LOD/√2.

human population is low and that PFHxA does not bioaccumulate over time.

3.2.2.1. PFHxA is infrequently detected in human breast milk. Breastfeeding is considered an important pathway of exposure for infants for many contaminants. PFOA has been reported to be frequently detected in breast milk; however, fewer studies have investigated the presence of short-chain PFCAs in breast milk. Studies of populations in France and Spain have demonstrated that PFHxA is detected in 10% or less of the breast milk samples, at concentrations less than 100 ng/mL (Table 5). In two studies conducted in Korea, the FOD ranged from 40% to 71% and the maximum PFHxA concentration was 250 ng/mL (Table 5). The low FOD and levels detected are consistent with the biomonitoring results for human serum and urine discussed previously.

The samples collected from a population in Spain (Lorenzo et al., 2016) were part of a broader investigation of potential sources of PFCA exposure for infants. PFCAs, including PFHxA, were measured in samples obtained from baby food containers, dry cereals, infant formula, and breast milk. PFHxA was not detected in the majority of samples. Reported FODs were 0% for baby food jars, 23% for dry cereals, 25% for infant formula, and 10% for breast milk (i.e., PFHxA was detected in breast milk samples from 1 of 10 women at a concentration of 60 ng/mL). Using the levels of PFHxA detected in each medium and standard estimated daily consumption rates and body weights, the authors then calculated the EDI for infants up to 2 years of age. They found that potential exposure to infants up to 12 months of age from PFHxA in infant formula resulted in the highest EDI of 1 ng/kg-day. As discussed

Table 4
Occurrence of PFHxA in Human Urine (concentration units are ng/mL).

Location	Year	Gender[a]	N	FOD	LOD	Min	Mean	Max	Reference
USA	2001	M F	198	0%	0.1	< 0.1	< 0.1	< 0.1	Calafat (2018)
USA	2009	M F	127	0%	0.1	< 0.1	< 0.1	< 0.1	Calafat (2018)
USA	2012	M F	83	0%	0.1	< 0.1	< 0.1	< 0.1	Calafat (2018)
S. Korea	2012	M F	120	11%	–	< LOD	0.73	2.34	Kim et al. (2014) [a]
S. Korea	2012	M F	–	5%	–	< LOD	1.38	5.63	Kim et al. (2014) [a]
USA	2015	M F	70	3%	0.1	< 0.1	–	–	Calafat (2018)
GA, USA	2016	M F	50	0%	0.1	< LOD	< LOD	< LOD	Kato et al. (2018)

F = female; FOD = frequency of detection; GA = Georgia; M = male; N = sample size; LOD = limit of detection; "-" = not reported.

[a] One-half of the LOD value was used for calculating summary statistics when PFHxA was below LOD.

Table 5
Occurrence of PFHxA in Human Breast Milk (concentration units are ng/L, parts per trillion, ppt).

Location	N	FOD	Min	Median	Mean	Max	Reference
France	30	0%	< LOD	< LOD	< LOD	< LOD	Kadar et al. (2011)
France	48	2%	< LOD	–	–	53	Antignac et al. (2013)
France	61	0%	< LOD	< LOD	< LOD	< LOD	Cariou et al. (2015)
Korea	264	71%	< LOD	45	47[a]	250	Kang et al. (2016)
Korea	128	40%	< LOD	–	12.8	129	Lee et al. (2018)
Spain	10	10%	< LOD	60	6	60	Lorenzo et al. (2016)

FOD = frequency of detection; N = sample size; LOD = limit of detection; "-" = not reported.
[a] Geometric mean.

below, the estimated exposure levels for infants are several orders of magnitude lower than calculated screening levels expressed as average daily dose.

Collectively, low detection levels and rates of PFHxA in human serum, urine, and breast milk indicate that human exposure to PFHxA may be of negligible concern. The low FOD of PFHxA in serum and breast milk is likely due to the rapid serum elimination kinetics of PFHxA. However, the fact that PFHxA is thus far rarely detected in urine (a biomarker of exposure) further suggests that human exposure to PFHxA, when it occurs, is not of sufficient magnitude, frequency, and/or duration to be retained in serum or to accumulate in tissues.

3.3. Conclusion on potential human exposure

As the transition to short-chain chemistry proceeds, it will be important to monitor potential human exposure to PFHxA and other potential degradants and impurities. The data reviewed herein can serve as a baseline for future environmental sampling, exposure assessment, and tracking over time. The data available to date clearly demonstrate that there continues to be a low detection frequency and magnitude of PFHxA throughout the general global population (i.e., absent site-specific environmental contamination). Furthermore, human biomonitoring studies continue to report infrequent detections and extremely low levels of PFHxA in human biological fluids for the general population. Given that PFHxA is an impurity, primary degradant, and metabolite of short-chain fluorotelomer-based products used today, these data also suggest that human exposure to short-chain fluorotelomer-based products is likely low.

4. PFHxA human health-based screening levels and margin of safety

Numerous adverse effects have been suggested for long-chain PFAAs in humans and reported in various laboratory models. There is growing concern that short-chain PFAAs such as PFHxA may cause similar effects.

As demonstrated in the companion manuscript (Luz et al., 2019), compared to PFOA, PFHxA has a low level of acute and chronic toxicity, and is rapidly eliminated with a short biological half-life. A full suite of standard toxicity studies, including acute, subchronic (28- and 90-day), and chronic (2-year), have been conducted for PFHxA. All of the observed effects related to PFHxA were mild and/or reversible and noted at levels significantly higher than PFOA. A chronic PFHxA human health toxicity value of 0.25 mg/kg-day was derived from benchmark dose modeling of the kidney histopathology observed in female rats exposed orally to PFHxA in a 2-year chronic bioassay (Klaunig et al., 2015). Allometric adjustment based on body weight per EPA guidance (USEPA, 2011) was conducted as studies have shown PFHxA elimination kinetics scale to body weight (Russell et al., 2013). A total uncertainty factor of 100 (based on human variability [10], uncertainty in toxicodynamic differences between rodents and humans [3], and database uncertainties [3]) was applied (Luz et al., 2019). Human health-based toxicity values have also been derived for PFHxA by the French Agency for Food Safety, Environment and Labor (ANSES) (ANSES, 2017), and Germany (von der Trenck et al., 2018), and several other international bodies have reviewed and evaluated the human health risks associated with short-chain PFAAs, including PFHxA (NICNAS, 2018, Danish Environmental Protection Agency, 2015).

Table 6 shows the three available PFHxA chronic human health toxicity values and relevant derivation information for comparison. An oral toxicity value is a numerical value established to evaluate potential noncarcinogenic health effects for humans. These PFHxA toxicity values represent average daily exposure levels at which no adverse effects are expected during chronic or subchronic exposures (USEPA, 2002).

ANSES conducted an expert and peer-reviewed evaluation on the chronic risks associated with PFHxA exposure for the French General Directorate of Health. ANSES derived a chronic toxicity value for PFHxA based on the female kidney effects from the chronic rodent study (Klaunig et al., 2015), which was deemed protective of all other potential health endpoints of concern. A no-observed-adverse-effect-level (NOAEL) for PFHxA of 30 mg/kg-day was selected as the point of departure (POD); it is unclear if dose-response modeling was considered. The agency applied the standard allometric body weight scaling (USEPA, 2011) to convert the rodent administered dose to the human equivalent dose. The agency also applied uncertainty factors to account for variability in humans (10) and toxicodynamic variability and uncertainty between rodents and humans (2.5) for a total uncertainty factor adjustment of 25. ANSES determined that the database was sufficient to assess the toxicity of PFHxA, and no further adjustment for possible uncertainties within the database was applied. The final PFHxA chronic toxicity value derived by ANSES was 0.32 mg/kg-day (ANSES, 2017).

As reported by von der Trenck et al. (2018), the German States' Water Consortium (LAWA) will be issuing a final publication with groundwater threshold standards for seven PFAAs, including PFHxA, which have been accepted by the German Drinking Water Commission and by the German States' Soil Consortium. The PFHxA chronic human health toxicity value of 0.00184 mg/kg-day was derived by this group based on their interpretation of the Klaunig et al. (2015) study. They selected a POD of 15 mg/kg-day as a NOAEL for male rats based on changes in urine pH (Klaunig et al., 2015). The NOAEL was converted to a human equivalent dose by modifying the POD by a factor of 327 based on the ratio of the elimination half-life for humans compared to rats (further details were not provided). This adjustment factor used for PFHxA was larger than the half-life based adjustment factors for long-chain PFAAs; for example a factor of 50 was used for PFNA, and 90 for PFHxS. Both of these long-chain PFAAs have been shown to bioaccumulate and have species-specific toxicokinetics. No justification was provided by von der Trenck et al. (2018) for these adjustments; however, this does not appear to be consistent with available data on the species-specific elimination rates of PFAAs. The agency also applied uncertainty factors to account for variability in humans (10) and toxicodynamic variability and uncertainty between rodents and humans (2.5) for a total uncertainty factor adjustment of 25. A database uncertainty factor was not applied. An English-translated version of the German States' Water Consortium does not appear to be available at

Table 6
Summary of PFHxA Chronic Toxicity Values (all based on Klaunig et al., 2015, chronic 104-week study with rats).

Country, Agency	Study Details		Kinetics		Uncertainty Factors					Chronic Toxicity Value (mg/kg-day)
	Critical Effect	POD (mg/kg-day)	Internal Dose Conversion	HED Method	POD_{HED}	UF_H	UF_A	UF_S	UF_L	UF_D	UF Total	
France, ANSES	Kidney histology, ♀	30 (NOAEL)	NA; used administered dose	Standard allometric BW scaling	8	10	2.5	1	1	1	25	0.32
Germany, LAWA	↓Urine pH, ♂	15 (NOAEL)	NA; used administered dose	POD divided by 327	0.046	10	2.5	1	1	1	25	0.0018
Luz et al. (2019)	Kidney histology, ♀	90.4 ($BMDL_{10}$)	NA; used administered dose	BW scaling to the ¾ power	24.8	10	3	1	1	3	100	0.25

$BMDL_{10}$ = benchmark dose lower bound at a 10% response level; BW = body weight; HED = human equivalent dose; NA = not applicable; NOAEL = no observed adverse effect level; POD = point of departure; UF = uncertainty factor; UF_H = UF for human interindividual variability; UF_A = UF for animal to human species extrapolation; UF_S = UF for study duration (subchronic to chronic); UF_L = UF for LOAEL to NOAEL; UF_D = UF for database uncertainty. Note: 1 mg/kg-day is equivalent to 1×10^3 µg/kg-day and 1×10^6 ng/kg-day.

this time. Given the limited information available on the derivation of the Germany PFHxA toxicity value, including uncertainty in the selection of the critical effect (reduced urine pH in male mice) and inconsistent and seemingly erroneous toxicokinetic extrapolation methods for PFHxA, this value is considered highly uncertain and will not be utilized further for the analyses herein.

The National Industrial Chemicals Notification and Assessment Scheme (NICNAS) established by the Australian Industrial Chemical (Notification and Assessment) Act issued a human health assessment for short-chain PFAAs (NICNAS, 2018). Consistent with the human-health based toxicity values derived for PHFxA discussed above, NICNAS concluded that short-chain PFAAs, including PFHxA, demonstrate a lower toxicity profile than PFOA. NICNAS did not develop a chronic toxicity value for PFHxA.

The number of U.S state and federal entities that have derived chronic human health toxicity values for PFAAs continues to grow. As of July 2018, the U.S. Interstate Technology Regulatory Council lists approximately 20 unique drinking water and/or groundwater screening levels for PFOA, and chronic human health toxicity values for PFOA range from 2×10^{-6} mg/kg-day to 7.7×10^{-5} (ITRC, 2018). The daily human health-based exposure limits protective of a lifetime of exposure to PFOA (i.e. chronic toxicity values) are 4–6 orders of magnitude lower (i.e., more stringent) than those derived for PFHxA, as described above.

4.1. Calculations of screening levels

Human health-based screening levels are conservative estimates of the concentration of a chemical in an environmental exposure medium (e.g., drinking water) that reflect a level of chemical exposure associated with high confidence of negligible risk. The conservative assumptions in the underlying processes for chemical risk assessment, including the methods used, default assumptions employed, and parameters included, all combine to result in a human health screening levels that are "more likely to overstate than understate" risk (USEPA, 2005, p. 1–7). If a screening level is exceeded, this information is useful for risk managers and public health officials for identifying chemicals and sites and/or exposure pathways that may need further investigation and action. Screening levels are developed, based on several standard methodologies that combine toxicity information (i.e., toxicity values such as an RfD) with exposure assumptions. The available PFHxA chronic human health RfD (Luz et al., 2019) is combined with the default exposure parameters for screening public water supply systems and for screening contaminated groundwater that may be used for residential consumption.

4.1.1. Derivation of a PFHxA drinking water screening level (e.g., health advisory)

To date, no PFAA is regulated under the U.S. Safe Drinking Water Act (SDWA), the federal law that protects public drinking water supplies throughout the nation (USEPA, 1974). Under the SDWA, EPA has authority to set enforceable maximum contaminant levels (MCLs) for specific chemicals and require testing of public water supplies. EPA has not proposed or promulgated MCLs for any PFAAs; however, in 2016, EPA established a lifetime health advisory for PFOA and PFOS in drinking water of 70 ng/L, individually, or in combination (USEPA, 2016a, 2016b). The health advisory for PFOA and PFOS is advisory in nature; it is not a legally enforceable federal standard and is intended for use only as a screen tool to inform risk management decisions. EPA states that the health advisories "provide Americans, including the most sensitive populations, with a margin of protection from a life-time of exposure to PFOA and PFOS from drinking water" (USEPA, 2016c).

Using EPA's default lifetime health advisory equation and chronic toxicity values discussed above (Luz et al., 2019; ANSES, 2017), a similar drinking water screening level can be derived for PFHxA. As shown in Table 7, the result is a drinking water health advisory that ranges from 1.4 to 2.2 mg/L (parts per million, ppm). Compared to the

Table 7
Chronic toxicity values and corresponding drinking water screening levels (health advisories) for PFHxA and PFOA expressed in a range of units.

PFAA	Source	Chronic Toxicity Value (mg/kg-day)	Lifetime Health Advisory		
			mg/L, or ppm	μg/L, or ppb	ng/L, or ppt
PFHxA	Luz et al. (2019)	0.25	1.4	1400	1,400,000
PFHxA	ANSES (2017)	0.32	2.2	2200	2,200,000
PFOA	USEPA (2016a)	0.00002	0.00007	0.070	70

ppm = parts per million; ppb = parts per billion; ppt = parts per trillion.

EPA lifetime health advisory, which is based on parameters for a lactating woman to be protective of fetuses, infants, and all adults, the PFHxA drinking water screening level is between 20,000 and 31,000 times higher than the EPA health advisory for PFOA of 0.00007 ppm (70 ppt[3]; note: 70 ppt is for PFOS and PFOA either individually or combined) (Table 7). This finding underscores that PFHxA is significantly less toxic than PFOA.

As discussed above, PFHxA is not commonly included as a target analyte in drinking water studies. When it is included, PFHxA is infrequency detected and measured concentrations are extremely low for non-impacted drinking water systems. The EPA Unregulated Contaminant Monitoring Rule sampling of six PFAS in select U.S. public drinking water systems did not include PFHxA. One study, Gellrich et al. (2013), surveyed tap water across Germany and found a maximum concentration of PFHxA of 6.4 ng/L; Skutlarek et al. (2006) reported a maximum PFHxA concentration of 56 ng/mL in drinking water in Germany; and Boone et al. (2019) reported a maximum PFHxA concentration of 60.8 ng/mL in treated drinking water in the U.S. Compared to the drinking water screening levels derived above, these concentrations are at least 23,000 to 200,000-fold lower than threshold levels protective of human health.

4.1.2. Derivation of PFHxA residential groundwater screening level

In the U.S., PFAAs, including PFOA and PFOS, are not listed as CERCLA hazardous substances but may be addressed as CERCLA pollutants or contaminants (40 CFR 300.5). EPA recently announced in its four-step action plan for PFAAs that the agency will develop groundwater cleanup recommendations for at least some PFAAs. According to EPA, as of May 2018, there were active PFAAs cleanup investigations occurring at 49 National Priority List sites, and these numbers were expected to continue to increase as PFAAs are included in more remediation programs. Under CERCLA, PFAAs risk-based cleanup goals may be calculated when chemical-specific regulations and requirements are not available (USEPA, 1997). EPA's Regional Screening Level (RSL) table currently provides screening levels only for PFBS and its potassium salt (USEPA, 2018a); however, the online RSL calculator supports calculations for PFOA and PFOS in tap water and soil, and this same general equation can be used in combination with toxicity values that meet EPA's policy requirements (USEPA, 2003). The available PFHxA toxicity values (Luz et al., 2019; ANSES, 2017) qualify as "tier three" toxicity values for use by site managers because they are recent, derived with transparent methodology and standard risk assessment methods, have been peer-reviewed, and are publicly available (USEPA, 1989, 1993, 2003, 2013).

As described in the "Methods" section, the default equation for residential child and adult exposure to noncarcinogens in groundwater was used. As shown in Table 8, using the standard child (age 0–6 years) exposure parameters and available PFHxA chronic toxicity values, the child-specific screening value for drinking water exposure to PFHxA ranges between 4.0 and 6.4 mg/L (rounded to two significant figures). Using standard adult exposure parameters and available chronic toxicity values, the resulting chronic drinking water screening level for PFHxA ranges between 6.7 and 10.7 mg/L (rounded to two significant figures).

Table 8
Residential child and adult groundwater screening levels for PFHxA.

Toxicity Value Source	Chronic Toxicity Value (mg/kg-day)	Groundwater Screening Level (μg/L) at Hazard Index = 1	
		Residential Child	Residential Adult
Luz et al. (2019)	0.25	4000	6700
ANSES (2017)	0.32	6400	10,700

As presented above, PFHxA is infrequently sampled for and infrequently detected in environmental media. In a known impacted region of the Metedeconk River in New Jersey, USA, PFHxA was detected in 32% of groundwater and surface water samples, at a maximum concentration of 3.8 μg/L.

Anderson et al. (2016, 2019) analyzed data collected from known U.S. Air Force locations impacted with aqueous film-forming foam (AFFF) and reported a maximum PFHxA concentration in groundwater of 120 μg/L. As the number of impacted environmental site investigations continues to grow, additional data will become available to assess the relative FOD and impact of PFHxA specifically compared to a more complete set of PFAAs and other fluorinated substances that may be present in mixtures found at impacted sites. However, using the residential child screening level and a target hazard index of 1 as the most conservative screening level, areas of known PFAA contamination report a maximum PFHxA concentration in groundwater that is 33–1000 times lower than the most conservative screening level.

4.2. PFHxA margin of safety calculation for estimated daily intake rates

A chemical's margin of safety is often defined as the ratio between either the POD from toxicology studies (also often called the margin of exposure), or the final chronic toxicity value, to the estimated or measured human exposure level and is often used to assess the safety of chemicals used in personal care products and food, for example. Although there is not an agreed upon margin of safety threshold that clearly indicates concern or no concern, the European Food Safety Authority and the World Health Organization agree that, in general, a margin of safety based of an animal study POD of 10,000 or higher would be of low concern to public health (EFSA, 2012).

The potential for PFHxA-mediated noncancer health effects was evaluated by comparing estimated daily doses with the available chronic toxicity values (ANSES, 2017; Luz et al., 2019). As described above, Lorenzo et al. (2016) recently calculated the estimated daily intake for infants exposed to PFHxA from consumption of breast milk, formula, dry cereal, or baby foods. The highest estimated daily intake of 1 ng/kg-day for infants can be compared with the chronic toxicity value to evaluate the potential for PFHxA-mediated noncancer health effects to occur in infants in the general population. The estimated daily intake for infants from Lorenzo et al. (2016) is 320,000 times lower than the

[3] USEPA (2016a) used the standard drinking water equation when deriving the health advisory for PFOA, but applied exposure factors (e.g., drinking water intake rate) characteristic of lactating women. This approach was used because EPA determined the critical effect for PFOA was a developmental endpoint.

Table 9
Margin of Safety Values for PFHxA, based on Lorenzo et al. (2016) Estimated Daily Intake Rate for Infants.

	Chronic Toxicity Value (mg/kg-day)	Margin of Safety
Luz et al. (2019)	0.25	200,000
ANSES (2017)	0.32	320,000

chronic daily human reference value derived by ANSES (2017) and 200,000 times lower than the chronic reference dose derived by Luz et al. (2019) (Table 9). Given that both chronic toxicity values already include uncertainty factors to ensure protection for human variability and other uncertainties within the derivation, these ranges demonstrate large margins of safety for even the most sensitive human subpopulations.

5. Conclusions

PFHxA and its potential precursor short-chain fluorotelomer-based products, such as perfluorohexyl iodide and 6:2 fluorotelomer alcohol, have been present in the market since the 1970s. Following the phase-out of long-chain fluorotelomer-based chemistries in 2006, the fluorochemistry industry shifted to short-chain fluorotelomer-based chemistries, which has brought focus to PFHxA, a primary potential impurity, degradant and metabolite from short-chain fluorotelomer-based products. In addition, according to the FluoroCouncil, present-day manufacturing practices for short-chain fluorotelomer-based products and more efficient customer usage have reduced environmental releases and thereby potential future contamination levels.

Using standard U.S. methodologies and default exposure assumptions, a PFHxA drinking water supply screening level (1400 μg/L) and a child residential groundwater screening level (4000 μg/L) was derived. Based on available data, PFHxA is not widely detected, nor present at high concentrations, in groundwater, surface water, or drinking water. This is despite historical use and releases, continued potential releases as the degradation product of fluorotelomers, and potential degradation or impurity in fluorosurfactants and fluorinated side-chain polymers used in today's PFAA industry. At locations with known potential point sources of PFHxA (AFFF products, fluorosurfactants, relevant precursors), levels detected in groundwater and drinking water have been significantly lower than the health-based thresholds dervied herein. The calculated drinking water screening levels and residential groundwater screening levels provided in this paper are intended to provide regulatory and public health agencies with tools to continue to monitor and assess potential health risk related to PFHxA and precursor short-chain fluorotelomer-based products. The data presented here demonstrate that PFHxA levels currently present in the environment are well below levels that may present a concern for human health. The focus on PFHxA, and the findings of continued low levels of exposure and low human health risks, are important because PFHxA is a marker for impurities and environmental and biological exposure to short-chain fluorotelomer-based products in use today. Future research needs to include further study of PFHxA exposures to children and continued environmental monitoring to confirm that levels do not rise over time.

Acknowledgment

This work was funded by the FluoroCouncil. The authors thank members of the FluoroCouncil Panel for their helpful comments on this paper. The funders were given the opportunity to review the draft paper to ensure accuracy and clarity of the science presented but not on interpretation of the research findings. The researchers' scientific conclusions and professional judgments were not subject to the funders' control; the contents of this paper reflect solely the view of the authors.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.yrtph.2019.01.020.

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