

Assessment of POP Criteria for Specific Short-Chain Perfluorinated Alkyl Substances

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Date:
January 2014

Project Number:
0134304A

ENVIRON

Contents

List of Tables

List of Appendices

Acronyms and Abbreviations

Acronym	Definition
°C	Degrees Celsius
6:2 FTAC	6:2 Fluorotelomer acrylate
6:2 FTMAC	6:2 Fluorotelomer methacrylate
6:2 FTOH	6:2 Fluorotelomer alcohol
AFFF	Aqueous Film-Forming Foam
amu	Atomic Mass Units
B	Bioaccumulative
BAF	Bioaccumulation Factor
BCF	Bioconcentration Factor
BMF	Biomagnification Factor
BSAF	The Biota-Sediment (or Biota-Soil) Accumulation Factor
CAS	Chemical Abstracts Service
cm	centimeter
cm^3	Cubic centimeters
d	Day
dm^3	Cubic decimeters
dw	Dry weight
EC50	Effective Median Concentration
g	Gram
IUPAC	International Union of Pure and Applied Chemistry
K_{AW}	Air-water Partition Coefficient
kg	Kilogram
K_{OA}	Octanol-air Partition Coefficient
K_{OW}	Octanol-water Partition Coefficient
L	Liter
LC50	Median Lethal Concentration
LC-MS/MS	Liquid Chromatography-Mass Spectrometry/ Mass Spectrometry
LD50	Mean Lethal Dose
LOAEL	Lowest Observed Adverse Effect Level
LOEC	Lowest Observed Effect Concentration
LOEL	Lowest Observed Effect Level
log	Logarithmic
m^3	Cubic meters
mg	Milligram
mM	Millimoles per Liter
mol	Mole
n	Number of Samples
ND	Non-detect
ng	Nanogram
NOAEL	No Observed Adverse Effect Level
NOEC	No Observed Effect Concentration

Acronym	Definition
NOEL	No Observed Effect Level
P	Persistent
Pa	Pascals
PBT	Persistent, Bioaccumulative, and Toxic
PFASs	Perfluoroalkyl and Polyfluoroalkyl Substances
PFCA	Perfluorocarboxylic Acid
PFHx	Perfluorohexanoate
PFHxA	Perfluorohexanoic Acid
PFO	Perfluorooctanoate
PFOA	Perfluooctanoic Acid
PFOS	Perfluorooctane Sulfonic Acid
pg	Picogram
pKa	Acid Dissociation Constant
POP	Persistent Organic Pollutant
REACH	Registration, Evaluation, Authorization, and Restriction of Chemicals
TMF	Trophic Magnification Factor
ww	Wet Weight
wt. %	Weight Percent
µL	Microliter
µM	Micromoles

1 Executive Summary

ENVIRON International Corporation (ENVIRON) was asked by the FluoroCouncil to review available data and prepare a whitepaper evaluating the persistent organic pollutant (POP) characteristics of several short-chain fluorinated chemicals:

- Commercial Product:
    - Short-chain polyfluoroalkyl acrylic polymer based on 6:2 fluorotelomer chemistry (Methacrylate Polymer; No CAS #)
- Manufacturing Intermediates:
    - 6:2 fluorotelomer alcohol (6:2 FTOH; CAS # 647-42-7)
    - 6:2 fluorotelomer acrylate (6:2 FTAC; CAS # 17527-29-6)
    - 6:2 fluorotelomer methacrylate (6:2 FTMAC; CAS # 2144-53-8)
- Degradation Product:
    - Perfluorohexanoic acid (PFHxA; CAS # 307-24-4) and its anion perfluorohexanoate (PFHx)

This document describes the available data for these chemicals that address their environmental fate, persistence, bioaccumulation, and toxicological properties. In compiling these data, we followed the template used for the fact sheets on chemical alternatives to endosulfan produced by the Stockholm Convention Persistent Organic Pollutants Review Committee (UNEP 2009; UNEP 2012), but this document broadens the scope to include the assessment of raw materials and a degradation product.

In evaluating these substances, we followed the criteria laid out in Annex D of the Stockholm Convention Persistent Organic Pollutants, supplemented by draft guidance from the European Chemicals Agency (ECHA 2012) on PBT assessment.

The Stockholm Convention Annex D identifies four criteria that must all be met for a chemical to be identified as a POP (UNEP 2009):

> ***"(b) Persistence:***
>
> *(i) Evidence that the half-life of the chemical in water is greater than two months, or that its half-life in soil is greater than six months, or that its half-life in sediment is greater than six months; or*
>
> *(ii) Evidence that the chemical is otherwise sufficiently persistent to justify its consideration within the scope of this Convention;*

(c) Bioaccumulation:

(i) Evidence that the bio-concentration factor or bioaccumulation factor in aquatic species for the chemical is greater than 5,000 or, in the absence of such data, that the log K_{OW} is greater than 5;

(ii) Evidence that a chemical presents other reasons for concern, such as high bioaccumulation in other species, high toxicity or ecotoxicity;

or

(iii) Monitoring data in biota indicating that the bioaccumulation potential of the chemical is sufficient to justify its consideration within the scope of this Convention;

(d) Potential for long-range environmental transport:

(i) Measured levels of the chemical in locations distant from the sources of its release that are of potential concern;

(ii) Monitoring data showing that long-range environmental transport of the chemical, with the potential for transfer to a receiving environment, may have occurred via air, water or migratory species; or

(iii) Environmental fate properties and/or model results that demonstrate that the chemical has a potential for long-range environmental transport through air, water or migratory species, with the potential for transfer to a receiving environment in locations distant from the sources of its release. For a chemical that migrates significantly through the air, its half-life in air should be greater than two days;

and

(e) Adverse effects:

(i) Evidence of adverse effects to human health or to the environment that justifies consideration of the chemical within the scope of this Convention; or

(ii) Toxicity or ecotoxicity data that indicate the potential for damage to human health or to the environment."

Because Annex D of the Stockholm Convention (UNEP 2009) does not provide numerical criteria for the "Adverse effects" criterion, other criteria laid out in Annex XIII of the REACH regulations, and guidance issued by the European Chemicals Agency (ECHA 2012) on identifying persistent, bioaccumulative, and toxic (PBT) substances were also considered.

The data relied on for this assessment come from literature searches conducted by FluoroCouncil scientists of the published, peer-reviewed scientific literature and unpublished

studies performed by FluoroCouncil members.[1] Although a complete quantitative Data Quality Review was not conducted, publicly available studies were selected in a tiered review process based on whether the study included the chemicals of interest and whether the study was relevant to assessing POP characteristics. Selected studies were of high scientific quality and many were compliant with Good Laboratory Practice (GLP) procedures and submitted to relevant regulators.

The following sections present the database that was collected on each of the substances of interest that is relevant to their evaluation in Annex D. For each one, a brief summary table is followed by more detailed descriptions of the available data. This is supplemented by additional information in the appendices.

Conclusions

Based on the data reviewed for each substance (i.e., the raw materials, the commercial product, and the potential degradation products), none of the substances meet all of the criteria required to be classified as a POP and none of the substances meet more than one criterion. A summary of the evaluation against each of the Annex D criteria is provided in Table 1.1. In the case of the Methacrylate Polymer, although there was very little pertinent data, because polymer molecules in general are too large to cross biological membranes, they are of low toxicity, and would, therefore, not be expected to trigger the toxicity criterion for identification of a POP. More data were available for the fluorotelomer raw materials (i.e., 6:2 FTOH, 6:2 FTAC, and 6:2 FTMAC) and their degradation product, PFHxA. While PFHxA may persist in the environment, PFHxA, 6:2 FTOH, 6:2 FTAC, and 6:2 FTMAC are rapidly metabolized and eliminated from mammalian systems. None of these materials appear to bioaccumulate or biomagnify based on laboratory data and available field monitoring data, and none show severe toxicity of the types that would warrant designation as POPs. Lastly, although 6:2 FTOH may be subject to long-range atmospheric transport, 6:2 FTAC and 6:2 FTMAC are not likely to be transported long distances in the environment. Additional data are necessary to determine if PFHxA meets the Annex D 1 (d) (ii) persistence criteria based on concentrations of “potential concern” in remote environments.

References

European Chemicals Agency (ECHA). 2012. *Guidance on information requirements and chemical safety assessment: Part C: PBT and vPvB Assessment*.

United Nations Environment Programme (UNEP). 2009. *Stockholm convention on persistent organic pollutants (POP) as amended in 2009*.

United Nations Environment Programme (UNEP). 2012. *Stockholm Convention on Persistent Organic Pollutants: Fact sheets on chemical alternatives to endosulfan*. UNEP/POPS/POPRC.8/INF/29.

[1] Copies of company specific data reports quoted in this study are available upon request, subject to limitations due to business confidentiality. Please contact Jessica_steinhilber@fluorocouncil.com.

Table 1.1 Summary of POP criteria for specific short-chain perfluoroalkyl substances

Fluorochemical	Environmental Source	Stockholm Convention POP Criteria					Conclusion
		Persistence	Bioaccumulation	Long-range Environmental Transport	Toxicity		
					Ecotoxicity	Toxicity to Humans	
Methacrylate Polymer	Commercial product	Meets criteria	Does not meet criteria	Does not meet criteria	Does not meet criteria	Does not meet criteria	Does not meet POP criteria (meets 1 of 4)
6:2 FTOH	Manufacturing intermediate	Parent does not meet criteria *	Does not meet criteria	Meets criteria based on atmospheric transport**	Does not meet criteria	Does not meet criteria	Does not meet POP criteria (meets 1 of 4)
6:2 FTAC	Manufacturing intermediate	Parent unlikely to meet criteria *	Does not meet criteria	Unlikely to meet criteria	Does not meet criteria	Does not meet criteria	Does not meet POP criteria (meets 0 of 4)
6:2 FTMAC	Manufacturing intermediate	Parent unlikely to meet criteria *	Does not meet criteria	Does not meet criteria	Does not meet criteria	Does not meet criteria	Does not meet POP criteria (meets 0 of 4)
PFHxA / PFHx	Degradation product	Meets criteria	Does not meet criteria	Indeterminate**	Does not meet criteria	Does not meet criteria	Does not meet POP criteria (meets 1 of 4)

* Parent chemical forms PFHxA as a terminal degradation product

**Additional information is necessary to determine if concentrations in remote environments are of “potential concern” according to Annex D 1 (d) (i).

2 Commercial Product: Methacrylate Polymer

Summary of the Assessment of POP Characteristics of Methacrylate Polymer – comparison with the criteria of Annex D and other hazard indicators	
Persistence	**Fulfills Annex D 1 (b) criteria for persistence** • Methacrylate Polymers consist of hydrocarbon backbones with perfluoroalkyl side chains. These polymers are expected to be stable (i.e., half-lives >>10-100 years) under normal environmental conditions (Russell 2008; Washington 2009).
Bioaccumulation	**Does not fulfill the bioaccumulation criteria according to Annex D 1 (c) (i)** • No studies were available that evaluated the bioaccumulation potential of Methacrylate Polymer. However, polymers larger than 1,000 amu are typically too large to cross biological membranes and do not bioaccumulate (US EPA 2010). • Therefore, Methacrylate Polymer is not expected to bioaccumulate to any significant degree.
Long-Range Environmental Transport (LRET)	**Does not fulfill Annex D 1 (d) criteria for LRET** • Due to their high molecular weight, low solubility, and negligible vapor pressure, Methacrylate Polymers are not anticipated to be transported long distances in the environment.
Aquatic Toxicity	**Does not fulfill the REACH criterion for aquatic toxicity (NOEC < 0.01 mg/L)** • No studies were available that evaluated the aquatic toxicity of Methacrylate Polymer. Polymer molecules are typically too large to cross biological barriers and thus have low toxicity; however, surfactant polymers may exhibit some aquatic toxicity.
Toxicity to Human Health	**Does not fulfill the REACH criterion for toxicity to human health** • No studies were available that evaluated the toxicity of Methacrylate Polymer. However, polymer molecules are typically too large to cross biological barriers, thus having low toxicity.

2.1 Identity and Physical and Chemical Properties

The Methacrylate Polymer belongs to a class of fluorochemicals, known as fluorinated polymers. These polymers have been manufactured since the 1970s using fluorotelomer monomers (e.g., FTOHs, FTACs) as raw materials and manufacturing intermediates (Prevedouros et al. 2006).

Table 2.1: Chemical Identity of the Methacrylate Polymer

IUPAC Name	Common Name	Abbreviation	CAS Number	Molecular Weight (amu)	Chemical Structure
Various	Methacrylate Polymer	NA	NA	>10,000 (avg. of 40,000)[1] (Russell et al. 2008)	Nonfluorinated polymer backbone with fluorinated side chains ending in $-C_nF_{2n+1}$ Backbone-$C(CH_3)$-C(O)O-X-C_nF_{2n+1} where X is either $-CH_2CH_2N(R')SO_2-$ with R'= $-C_nH_{2n+1}$ (n=0,1,2,4) or $-CH_2CH_2-$

[1] Molecular weight range for an acrylate polymer manufactured from 8:2 and larger FTOHs (99% by weight). Polymers manufactured from smaller monomers are expected to have slightly lower molecular weights.

Although data on the physical and chemical properties of the Methacrylate Polymer are limited, fluorinated polymers are known to have high molecular weights (>10,000 amu) and are both water insoluble and hydrophobic (Honda et al. 2005 as cited in Russell et al. 2008). Additionally, polymers with molecular weights greater than 1,000 amu typically have extremely low vapor pressures (e.g., $<1.3 \times 10^{-5}$ Pa) and low Henry's Law constants ($<10^{-8}$ atm-m^3/mol) (US EPA 2010).

Table 2.2: Physical and Chemical Properties of the Methacrylate Polymer

No specific Physical or Chemical properties are available.

2.2 Environmental Fate

a) Abiotic degradation

No data available in the studies reviewed.

b) Hydrolysis

No data available in the studies reviewed.

c) Phototransformation/photolysis

No data available in the studies reviewed.

d) Biodegradation

Polymers with molecular weights greater than 1,000 amu typically do not biodegrade under normal environmental conditions (Kawai 1995 as cited in Russell et al. 2008; US EPA 2010). Russell et al. (2008) studied the biodegradation of a fluoroacrylate polymer in four aerobic soils over a two-year test period. The test polymer was synthesized from a FTOH mixture composed of 1 wt. % 6:2 FTOH, 55 wt. % 8:2 FTOH, 29 wt. % 10:2 FTOH, 10 wt. % 12:2 FTOH, and 5 wt. % 14:2 FTOH and larger. Although the polymer was found to be relatively resistant to biodegradation, several terminal degradation products were measured over the course of the study, including PFO. Based on the PFO formation rate, Russell et al. (2008) calculated a biodegradation half-life of 1,200-1,700 years for the fluoroacrylate polymer in aerobic soils.

Similarly, Washington et al. (2009) measured the degradation rate of an acrylate linked fluorotelomer polymer in soil microorganisms during a 546 day test period. The researchers calculated a degradation half-life of 870-1,400 years based on the formation rate of PFOA, PFHxA, and other degradation products. Lastly, Koch et al. (2007) measured the aerobic biodegradation rate of an 8:2 fluorotelomer-based acrylate polymer in soil. The results of this study were similar to those described above. The acrylate polymer was found to be recalcitrant to biodegradation with a degradation half-life of approximately 6,350 years (Koch et al. 2007). These studies suggest that Methacrylate Polymers are resistant to biodegradation under normal environmental conditions and will likely meet the persistence criteria according to Annex D 1 (b).

e) Potential for long-range environmental transport

Due to their high molecular weight and low volatility, polymers are not expected to travel long distances in the environment.

f) Bioaccumulation

Empirical Bioaccumulation Evidence from Aquatic Species/Log K_{OW}

No studies were available that evaluated the bioaccumulation potential of Methacrylate Polymer. However, polymer molecules are typically too large to cross biological membranes and do not bioaccumulate. For example, molecules with molecular weights of more than 700 g/mol to 1,000 g/mol cannot be absorbed through respiratory membranes of aquatic organism and are less likely to bioaccumulate (European Commission 2003; Boethling and Nabholz 1997). Although variable, depending on polymer length, the molecular weight of the 6:2 Methacrylate Polymer is approximately 40,000 amu. This indicates that this Methacrylate Polymer is very unlikely to be bioaccumulative.

Empirical Bioaccumulation Evidence from Other Species/High Ecotoxicity Concerns

No studies were available that evaluated bioaccumulation of Methacrylate Polymers in other species. As discussed below, the toxicity of Methacrylate Polymer is expected to be low due to the large size of polymers and their inability to cross biological membranes and result in toxicity.

Wildlife Monitoring Data

No monitoring data was available that indicated the presence of Methacrylate Polymers in wild biota.

2.3 Human Health Hazard Assessment

No relevant data are available. However, typically polymers are too large to cross biological membranes and are therefore low in toxicity.

2.4 Environmental Hazard Assessment

a) Aquatic compartment (including sediment)

No studies were found that evaluated the toxicity of Methacrylate Polymer. However, typically nonionic polymers have low solubility and are too large to cross biological membranes and are therefore low in toxicity. However, polymers with monomers that are blocked for use as a surfactant or dispersant, may exhibit some aquatic toxicity (Boethling and Nabholz 1997).

b) Terrestrial compartment

No studies were found to evaluate the toxicity of Methacrylate Polymer to terrestrial organisms.

2.5 References

Boethling RS and Nabholz JV. 1997. Environmental Assessment of Polymers under the U.S. Toxic Substances Control Act. In: *Ecological Assessment of Polymers Strategies for Product Stewardship and Regulatory Programs,* eds Hamilton JD and Sutcliffe R, 187-234. Van Nostrand Reinhld.

European Commission. 2003. Technical Guidance Document on Risk Assessment: Part II. *European Chemicals Bureau*

Prevedouros K, Cousins IT, Buck RC, and Korzeniowski SH. 2006. Sources, fate and transport of perfluorocarboxylates. *Environ Sci Technol* 40:32-44.

Russell MH, Berti WR, Szostek B, and Buck RC. 2008. Investigation of the biodegradation potential of a fluoroacrylate polymer product in aerobic soils. *Environ Sci Technol* 42:800-807.

U.S. Environmental Protection Agency (US EPA). 2010. *Interpretive Assistance Document for Assessment of Polymers: Sustainable Futures Summary Assessment*.

Washington JW, Ellington J, Jenkins TM, Evans JJ, Yoo H, and Hafner SC. 2009. Degradability of an acrylate-linked, fluorotelomer polymer in soil. *Environ Sci Technol* 43:6617-6623.

3 Manufacturing Intermediate: 6:2 Fluorotelomer Alcohol, 6:2 FTOH

Summary of the Assessment of POP Characteristics of 6:2 FTOH – comparison with the criteria of Annex D and other hazard indicators	
Persistence	**Parent compound does not fulfill the persistence criteria according to Annex D 1 (b)** • Numerous studies have measured 6:2 FTOH degradation rates in soil and sediment. • No data are available for 6:2 FTOH degradation in water. • Available data suggest that 6:2 FTOH quickly degrades to shorter-chain perfluorinated carboxylates and polyfluoroalkyl compounds in soil and sediment with a half-life of less than two days. Therefore, 6:2 FTOH does not meet the persistence criteria outlined in Annex D (b) (i). • 6:2 FTOH degrades to the persistent degradation product PFHxA in low yields.
Bioaccumulation	**Does not fulfill the bioaccumulation criteria according to Annex D 1 (c) (i)** • 6:2 FTOH is rapidly eliminated in aquatic and mammalian systems. • BCF values from 8.4 L/kg to 48 L/kg in fish (carp) are well below the Annex D criteria of >5,000 L/kg. • Data from terrestrial plants indicate that 6:2 FTOH does not bioaccumulate. • Therefore, 6:2 FTOH is not expected to bioaccumulate to any significant degree.

Long-range Environmental Transport (LRET)	**Fulfills the LRET criteria according to Annex D 1 (d)** • 6:2 FTOH meets the Annex D 1 (d) (iii) criteria for long-range transport based on an atmospheric half-life greater than two days. Piekarz et al. (2007) calculated a 50-day half-life for 6:2 FTOH, which is generally consistent with previous estimates of FTOH half-lives of greater than 10-20 days (Ellis et al. 2003; Martin et al. 2006 as cited in Dreyer and Ebinghaus 2009). • Additionally, measurements of 6:2 FTOH in the air in remote environments (ND-165 pg/m^3) indicate that this compound may be transported long distances in the atmosphere.
Aquatic Toxicity	**Does not fulfill the REACH criterion for aquatic toxicity (NOEC < 0.01 mg/L)** • 6:2 FTOH is expected to have low toxicity to aquatic organisms. • Effect concentrations were all greater than the < 0.01 mg/L REACH criteria for aquatic toxicity (Table 3.3), indicating a lack of significant toxicity.
Toxicity to Human Health	**No evidence of significant toxicity at exposure levels likely to be encountered by humans** • Acute oral LD50 in rats: 1,750 mg/kg; acute dermal LD50 >5,000 mg/kg. • Mild, reversible eye irritation seen in rabbits. • Negative for skin sensitization. • Effects in liver, blood, and clinical chemistry endpoints seen in subchronic oral studies in rats at doses of 25 mg/kg/day or more. • Reduced pup weights and delayed development seen in rats, but only at maternally toxic dose levels. • No evidence of mutagenicity in bacterial and mammalian cell studies. Genotoxicity tests were largely negative, with an increase in structural chromosome aberrations observed in one of four tests, but only in the presence of S9 activation.

3.1 Identity and Physical and Chemical Properties

FTOHs are primarily manufactured for use as raw materials in fluorotelomer production. As such, these chemicals may be released into the environment during the production and use of fluorotelomer-based products. FTOHs degrade to PFCAs in the environment, although conversion rates have been shown to be relatively low.

Table 3.1: Chemical Identity of 6:2 FTOH

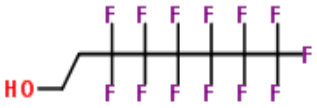
IUPAC Name	Common Name	Abbreviation	CAS Number	Molecular Weight (amu)	Chemical Structure
3,3,4,4,5,5,6,6,7,7,8,8,8-Tridecafluoro-1-octanol	6:2 Fluorotelomer alcohol	6:2 FTOH	647-42-7	364.1	

Table 3.2: Physical and Chemical Properties of 6:2 FTOH

Property	Value	Reference and Remarks
Vapor Pressure	18-44 Pa @ 25°C	Extrapolated from experimental data; Krusic et al. 2005
Water solubility	18.8 mg/L @ 22.5°C	Experimentally determined; Liu and Lee 2007
Partition coefficient n-octanol/water ($logK_{OW}$)	4.54 - 4.70	Experimentally determined; Carmosini and Lee 2008, Arp et al. as cited in Rayne and Forest 2009
Partition coefficient air/water ($logK_{AW}$)	-0.55 @25°C	Experimentally determined; Goss et al. 2006 as cited in Ding and Peijnenburg 2013
Partition coefficient octanol/air ($logK_{OA}$)	4.79 @ 25°C	Experimentally determined; Thuens et al. 2008 as cited in Ding and Peijnenburg 2013

3.2 Environmental Fate

a) Abiotic degradation

No data available in the studies reviewed.

b) Hydrolysis

No data available in the studies reviewed.

c) Phototransformation/photolysis

Although data on the photolysis of 6:2 FTOH are limited, the atmospheric fate of FTOHs as a chemical class is well documented. FTOHs are unlikely to undergo direct photolysis in the environment, because alcohols do not absorb light within the actinic spectrum of the lower atmosphere (Waterland et al. 2005 as cited in Young and Mabury 2010). FTOHs are, however, oxidized by photochemically-derived hydroxyl radicals in the atmosphere to form fluorotelomer aldehydes (FTALs). FTALs are known precursors to PFCAs (Young and Mabury 2010). After considering other atmospheric removal mechanisms, such as wet and dry deposition, Young and Mabury (2010) concluded that FTOHs are predominantly removed from the atmosphere through oxidation by hydroxyl radicals. As these studies are not specific to 6:2 FTOH, this information is considered suggestive. Piekarz et al. (2007) did, however, calculate a 50 day half-life for 6:2 FTOH. This is generally consistent with previous estimates of FTOH half-lives of greater than 10-20 days (Ellis et al. 2003; Martin et al. 2006 as cited in Dreyer and Ebinghaus 2009).

d) Biodegradation

Numerous studies have investigated the biodegradation of 6:2 FTOH in soil and sediment. No data are available for 6:2 FTOH biodegradation in water. Studies suggest that 6:2 FTOH has an initial transformation half-life of less than two days in both soil and sediment. Products of 6:2 FTOH biodegradation in soil and sediment include 5:2 secondary FTOH, 5:3 FTCA, PFPeA, and PFHxA, with measured PFHxA yields of 4.5-8% in soil and 8.4% in sediment (Butt et al. 2013). These metabolites, including PFHxA, were not shown to completely degrade in the environment with a half-life less than the six month criterion provided in Annex D 1 (b) (i). It is also notable that Liu et al. (2010a) observed several differences in the biodegradation of 6:2 FTOH and the more commonly measured 8:2 FTOH in aerobic soil. PFOA is the major metabolite of 8:2 FTOH degradation (40% in Sassafras soil treatment), whereas the analogous compound, PFHxA, is formed in much smaller yields (8%) during 6:2 FTOH degradation. In contrast, the major metabolite of 6:2 FTOH degradation in aerobic soil is PFPeA (30%) (Liu et al. 2010a).

Table 3.3: Measures of Biodegradation of 6:2 FTOH

Degradation 50% Method	Days	Reference and Remarks
DT50 mixed bacteria culture (closed bottle)	1.3	Liu et al. 2010a
DT50 aerobic soil (closed bottle)	1.6	
DT50 aerobic soil (continuous head space air flow)	1.3	Liu et al. 2010b
DT50 aerobic sediment microcosms (closed bottle)	1.8	Zhao et al. 2013a
DT50 aerobic, activated sludge (closed system)	0.9	He et al. 2013 (paper not in English; data extracted from English abstract)
DT50 aerobic, activated sludge (diluted)	< 3	Half-life estimated based on >97 mol % conversion in 3 days; Zhao et. al 2013b
DT50 anaerobic, digester sludge under methanogenic conditions	30	Zhang et al. 2013

e) Potential for long-range environmental transport

Several researchers have measured 6:2 FTOH in remote environments, including the Arctic. These measurements have primarily focused on 6:2 FTOH in ambient air (Table 3.4), although Xie et al. (2013) measured 6:2 FTOH in the North Sea at concentrations ranging from 0.3-3.6 pg/L. While measurements of 6:2 FTOH in remote environments are suggestive of long-range environmental transport, local and/or regional emissions sources are still a possibility in some remote areas.[2]

Table 3.4: Identification of 6:2 FTOH in Remote Environments

Location	Date	Concentration (pg/m^3)	Phase	Reference
Okinawa, Japan	March-May 2004	<0.4-5.0	Gas	Piekarz et al. 2007
Mount Bachelor, Oregon	April-July 2004	<0.4-4.0, <0.4-2.1	Gas, Particle	
Canadian High Arctic	July, August 2004	ND-20	Gas + Particle	Stock et al. 2007 as cited in Young and Mabury 2010
North Atlantic/ Canadian Arctic	July 2005	<1.1-5.98, <0.001	Gas, Particle	Shoeib et al. 2006 as cited in Young and Mabury 2010
North Sea	October 2005	157	Gas + Particle	Jahnke et al. 2007 as cited in Young and Mabury 2010
Atlantic Ocean (46 N/6 W - 45 N/4 W)	October 2005	11	Gas + Particle	
Atlantic Ocean	October 2005	9.4	Gas +	

[2] Although a thorough review of 6:2 FTOH emissions in the Arctic and other remote environments was not conducted, four million people live above the Arctic Circle. This area also has a large number of air strips and airports. Further, many remote areas are home to industrial mining operations and oil production activities as well as military bases, which conduct firefighting activities and may have historically used aqueous fire-fighting foams containing perfluorinated compounds (Collins 1998).

Location	Date	Concentration (pg/m^3)	Phase	Reference
(40 N/10 W - 18 N/20 W)			Particle	
Atlantic Ocean (30 N/16 W 18 N/20 W)	October 2005	14	Gas + Particle	
Atlantic Ocean (18 N/20 W - 6 N/16 W)	October, November 2005	20	Gas + Particle	
Atlantic Ocean (6 N/16 W - 4 S/8 W)	November 2005	ND	Gas + Particle	
Atlantic Ocean (8 S/5 W – 17 S/2 E)	November 2005	ND	Gas + Particle	
Atlantic Ocean (17 S/2 E – 26 S/9 E)	November 2005	ND	Gas + Particle	
Mount Bachelor Oregon	April, May 2006	<0.4-16, <0.4-1.2	Gas, Particle	Piekarz et al. 2007
North Atlantic	April, May 2007	1.7-165	Gas	Dreyer et al. 2009 as cited in Young and Mabury 2010
Atlantic, Southern Oceans and Baltic Sea	April 2007 – May 2009	0.1	Particle	
Labrador Sea in the Canadian Arctic	Summer 2007	<1.1–6.7, <0.6	Gas, Particle	Ahrens et al. 2011
Hudson Bay in the Canadian Arctic	Summer 2007	<1.1-29, <0.6	Gas, Particle	
Elbe River Germany	October, November 2007	5.0	Gas	Dreyer and Ebinghaus 2009
German Bight	October, November 2007	8.6	Gas	
German Bight	October, November 2007	5.8	Gas	
North Sea	October, November 2007	5.7	Gas	
German Bight	October, November 2007	3.3	Gas	
German Bight	October, November 2007	15	Gas	
South Atlantic	October, November 2007	1.1-40	Gas	Dreyer et al. 2009 as cited in Young and Mabury 2010
South Atlantic	January 2008	ND-34	Gas	
Beaufort Sea in the Canadian Arctic	Spring and Summer 2008	<1.1-26, <0.6	Gas, Particle	Ahrens et al. 2011
Baltic Sea	June, July 2008	1.6-102	Gas	Dreyer et al. 2009 as cited in Young and Mabury 2010
North Atlantic	August 2008	12-26	Gas	
South Atlantic	October-December 2008	ND-3.1	Gas	
Southern Ocean	December 2008-May 2009	ND-0.9	Gas	
North Sea	May 2009	4.0-12	Gas	Xie et al. 2013
Western Antarctic Peninsula	February 2009	0.4-1.9	Gas	Del Vento et al. 2012
Cruise track from Japan to Artic Seas	June-September 2010	0.8-1.2, 0-0.2	Gas, Particle	Cai et al. 2012

Additionally, 6:2 FTOH has a sufficiently large atmospheric half-life to be transported long distances in the atmosphere. Piekarz et al. (2007) calculated a 50 day half-life for 6:2 FTOH, which is generally consistent with previous estimates of FTOH half-lives of greater than 10-20 days (Ellis et al. 2003; Martin et al. 2006 as cited in Dreyer and Ebinghaus 2009). As such, 6:2 FTOH meets the Annex D criteria for long-range transport based on remote monitoring data and an atmospheric half-life longer than two days.

f) Bioaccumulation

Empirical Bioaccumulation Evidence from Aquatic Species/Log K_{OW}

Two studies (Asahi-43771 and Daikin-44807 as cited in 6:2 FTOH REACH Dossier 2014) measured the bioconcentration factor (BCF) for 6:2 FTOH in carp (*Cyprinus carpio).* Both studies used a 28-day, flow-through exposure of carp to nominal concentrations of 1 μg/L and 10 μg/L 6:2 FTOH. BCFs in the Asahi study were less than 36 L/kg for the 1 μg/L and 46 L/kg in the 10 μg/L exposure groups. BCFs from the Daikin study ranged from 8.4 L/kg to 58 L/kg in the 1 μg/L exposure group, and from 24 L/kg to 99 L/kg in the 10 μg/L group. These BCF values are well below the Annex D criteria of >5,000 L/kg and indicate that 6:2 FTOH does not bioaccumulate.

The log K_{ow} for 6:2 FTOH has been reported to be 4.54-4.70, which is below the Annex D Bioaccumulation criteria (log K_{ow} > 5), indicating that 6:2 FTOH is not expected to have significant bioaccumulation potential. Log K_{OW} values do not generally apply for screening bioaccumulation potential of perfluorinated substances, because K_{ow} values cannot be accurately measured for perfluorinated and polyfluorinated substances. The surface active nature of surfactants prevent empirical determination of a K_{ow}, thus only modeled values for K_{ow} are available and these are not reliable enough to determine bioaccumulation potential. Therefore, it is not appropriate to determine bioaccumulation potential from a K_{ow} for perfluorinated substances (Conder et al. 2008). However, as K_{ow} values are an explicit metric used in Annex D to evaluate bioaccumulation potential of compounds, they are discussed in this document.

Empirical Bioaccumulation Evidence from Other Species/High Ecotoxicity Concerns

Yoo et al. (2011) measured levels of PFCAs and FTOHs in plants and soil taken from fields amended with biosolids near Decatur, AL. 6:2 FTOH was found at trace levels in soils (approximately 1 to 4 ng/g, dw, when detected; Yoo et al. 2010). 6:2 FTOH was also detected in plants grown in these soils at concentrations ranging from 0.07 to 0.26 ng/g, ww. Although exact soil-plant pairings were unclear, the narrow range of concentrations suggests that the Biota-Sediment/Biota-Soil Accumulation Factor (BSAF) value for 6:2 FTOH is likely to approximate 0.1 kg soil/kg plant, ww. Based on this BSAF value, 6:2 FTOH is not likely to bioaccumulate in plant species.

6:2 FTOH does not exhibit high ecotoxicity that would supersede the evidence that 6:2 FTOH is not likely to exhibit bioaccumulation potential according to Annex D.

Wildlife Monitoring Data

No studies were found in the literature to indicate the presence of 6:2 FTOH in biota.

3.3 Human Health Hazard Assessment

In general, the toxicity of 6:2 FTOH is low based on the evidence below. The low toxicity of 6:2 FTOH may, in part, be due to its rapid elimination in mammalian blood. Subchronic inhalation studies in rats suggest a rapid bioelimination of 6:2 FTOH from plasma following single and/or repeated exposures (DuPont-18063-1388; DuPont-18063-781 SU1). Plasma concentrations of 6:2 FTOH declined to below the limit of quantification 6 hours after exposure. Predominant metabolites measured in plasma were the intermediates: 6:2 FTCA and 6:2 FTUCA and the terminal metabolites: 5:3 polyfluorinated carboxylic acid and the perfluorinated carboxylic acids (PFBA, PFHxA, and PFHpA). At high exposures, the 5:3 acids was the most prominent, while PFCAs and 6:2 FTCA were barely detectable.

a) Acute and subchronic toxicity

Clinical signs of toxicity were observed in rats following oral exposure to 6:2 FTOH at doses ranging from 175 to 5,000 mg/kg. Toxic effects included wet fur, diarrhea, ear twitch, hair loss, stained fur/skin, lethargy, leaning, slow breathing, high or prostrate posture, ataxia, hyperreactivity, vocalization, and/or moribundity. Body weight loss of approximately 3% by day 7 was observed following a dose of 1,750 mg/kg. No other body weight loses were observed after dosing. The outcome resulting from the lowest exposure in this study was wet fur following a dose of 175 mg/kg. The LD50 for 6:2 FTOH was 1,750 mg/kg (DuPont-23572). An LD50 of >2000 mg/kg in rats was noted in one other study (Asahi-408/329 as cited in 6:2 FTOH REACH Dossier 2014).

The median LC50 in rats following a four-hour inhalation exposure fell between 5.2 and 9.9 mg/L. Ocular or nasal discharges were observed in most male and some female rats at concentrations as low as 0.65 mg/L (DuPont-18063-721).

Two cases of mortality were observed in rats following dermal exposure to 5,000 mg/kg of body weight when applied to the skin. It was noted that the skin absorption LD50 of 6:2 FTOH was greater than 5,000 mg/kg when applied to the skin of male and female rats for 24 hours. No other clinical signs of systemic toxicity or irritation were observed (DuPont-23377). No clinical signs of toxicity were observed following a single dermal application of 0.5 mL 6:2 FTOH (99.7%) to the shaved skin of a New Zealand White rabbit (DuPont-23364).

Ocular toxicity was not observed in rabbits following administration of 0.1 mL of 6:2 FTOH (99.7%) other than irritation that reversed within 48 hours following exposure (DuPont-23558).

Though subchronic inhalation studies of rats indicate no clinical signs of toxicity, there were some effects observed that were considered non-adverse or non-test “substance-related” by the study authors following exposures ranging from 96 to 100 ppm 6:2 FTOH. These effects

include some changes in organ weight and microscopic findings present in teeth (DuPont-18063-781; DuPont-18063-782 RV1). Two subchronic oral studies of rats identified a NOAEL of 5 mg/kg/day in females based on changes observed in the hematology and clinical chemistry parameters, increases in organ weights, and varied histopathological effects in the liver at a dose of 25 mg/kg/day (DuPont-23864 RV1; Daikin-B11-0839 as cited in 6:2 FTOH REACH Dossier 2014). A third subchronic oral study in rats identified a NOAEL of 25 mg/kg/day in males and females based on effects on body weight and body weight gain observed at a dosage level of 75 mg/kg/day. Excess mortality and systemic toxicity was also observed at the highest dose of 225 mg/kg/day (Asahi-WIL-534001 as cited in 6:2 FTOH REACH Dossier 2014).

Clinical signs of toxicity were observed in two chronic oral reproductive (one-generation) and developmental studies of rats at doses as low as 125 mg/kg/day, with no effects observed at 25 mg/kg/day (DuPont-23865; DuPont-25283).

b) Mutagenicity and carcinogenicity

Nine studies have investigated the potential mutagenicity or genotoxicity of 6:2 FTOH. 6:2 FTOH was not found to be mutagenic in the Bacterial Reverse Mutation Test or the Mouse Lymphoma Mutagenesis Assay in four studies (DuPont-22935; DuPont-25477; Asahi-408/330 as cited in 6:2 FTOH REACH Dossier 2014; Daikin-KDI-3688 as cited in 6:2 FTOH REACH Dossier 2014). A definite judgment could not be made by the authors of a fifth study concerning potential mutagenicity of 6:2 FTOH on mouse lymphoma cells due to results that were not “forceful” or reproducible (Asahi-V6203/14 as cited in 6:2 FTOH REACH Dossier 2014).

In two studies of genotoxicity, 6:2 FTOH was not found to induce an increase in structural or numerical chromosome aberrations in the *in vitro* mammalian chromosome aberration test in human peripheral blood lymphocytes (DuPont-25912) or in Chinese hamster ovaries (Asahi-V6202/18 as cited in 6:2 FTOH REACH Dossier 2014). The authors of one other genotoxicity study also found that 6:2 FTOH did not cause an increase in numerical aberrations in hamster lung fibroblasts; however, an increase in structural aberrations was found in the presence of liver homogenate fraction (S9), but was not found in its absence (Daikin-KD6-1192 as cited in 6:2 FTOH REACH Dossier 2014). In one *in vivo* genotoxicity study, 6:2 FTOH did not induce unscheduled DNA synthesis in rat liver hepatocytes (Asahi-V6657/02 as cited in 6:2 FTOH REACH Dossier 2014).

No studies on carcinogenicity were identified.

c) Reproductive and Developmental toxicity

The results of two reproductive studies of rats orally exposed to 6:2 FTOH indicate maternal and developmental toxicity at 125 mg/kg/day and 250 mg/kg/day. Outcomes involved reductions in pup body weight, a reduction in food consumption, developmental effects of the skull, rib and pelvic bones, and increases in pup mortality (DuPont-23865; DuPont-25283). No evidence of maternal or developmental toxicity in rats was observed at 25 mg/kg/day. The results of a third reproductive study of rats orally exposed to 6:2 FTOH indicate a NOAEL of 75 mg/kg/day based on a high incidence of pup mortality observed at 225 mg/kg/day. Increased pup mortality may be explained by increased maternal mortality and systemic toxicity observed at the highest dose. No parental reproductive effects were observed at the highest dose level (225 mg/kg/day) (Asahi-WIL-534001 as cited in 6:2 FTOH REACH Dossier 2014).

d) *Neurotoxicity*

Two studies present evidence of neurotoxicity in rats following both oral and inhalation exposure to 6:2 FTOH. Following acute oral exposure to 1,750 mg/kg, rats exhibited ataxia, a potential sign of neurotoxicity. Ataxia was not observed in rats following acute exposure at doses of 550 mg/kg (DuPont-23572). In the other study, male rats exposed to 100 ppm of 6:2 FTOH had decreased motor activity that appeared to be secondary to other systemic effects of the test substance based on the absence of other neurobehavioral changes in males or females exposed to 100 ppm 6:2 FTOH. Under the conditions of the study, the NOAEL for neurobehavioral effects was 10 ppm for males and 100 ppm for females based on decreased motor activity in 100 ppm males (DuPont-18063-782 RV1).

e) Immunotoxicity

No studies on immunotoxic effects were found (DuPont-23864 RV 1).

f) Acceptable exposure levels

A subchronic NOAEL of 5 mg/kg/day was observed in female rats. This NOAEL is based on changes observed in the hematology and clinical chemistry parameters, increases in organ weights, and varied histopathological effects in the liver at a dose of 25 mg/kg/day (DuPont-23864 RV1). No adverse effects have been reported at lower doses in other studies.

3.4 Environmental Hazard Assessment

a) Aquatic compartment (including sediment)

Annex D of the Stockholm Convention does not have a specific screening criteria or approach for interpreting aquatic toxicity information. However, REACH Annex XIII Toxicity criterion indicates toxicity for substances exhibiting a chronic NOEC less than 0.01 mg/L (ECHA 2012). This value is the chronic toxicity NOEC endpoint value applied to the classification of rapidly degradable substances and results in a CLP/GHS classification of Chronic Category 1 for hazards to the aquatic environment (the most conservative hazard

classification possible for the aquatic environment). All available effect concentrations for 6:2 FTOH (Table 3.5) are greater than the REACH Annex XIII Toxicity criteria of a chronic NOEC < 0.01 mg/L (ECHA 2012), indicating 6:2 FTOH would not be considered toxic under REACH PBT criteria. A chronic study on *Daphnia magna* (DuPont 18063-254) determined a chronic NOEC for effects on reproduction at 2.16 mg/L, a value 200 times greater than the < 0.01 mg/L REACH Annex XIII criteria. The same study determined the LC50 for *Daphnia magna* to be 3.87 mg/L. The most sensitive NOEC observed (NOEC = 0.623 mg/L; DuPont-23291), from a chronic study on algal (*Pseudokirchneriella subcapitata*) growth inhibition (measured as biomass), was over 60 times greater than the < 0.01 mg/L criteria. Other 72-hour studies on chronic toxicity to green algae determined NOECs based on growth rate to range from 1.3 to 3.8 mg/L (Asahi-1742/023 and Daikin-94232 as cited in 6:2 FTOH REACH Dossier 2014). All studies indicate a lack of toxicity under REACH Annex XIII PBT criteria. A prolonged-acute study on Carp (Asahi-42771 as cited in 6:2 FTOH REACH Dossier 2014), which evaluated mortality and behavioral endpoints during a 28-day bioconcentration test exposure, determined a NOEC of greater than 9.11 mg/L, nearly 1,000 times the 0.01 mg/L criteria.

A number of acute studies on the toxicity of 6:2 FTOH were also evaluated. Acute studies on *Daphnia magna* (DuPont-23290; Asahi-1742/022 and Daikin-94233 as cited in 6:2 FTOH REACH Dossier 2014) determined a range of EC50 values for immobility from 7.84 to 8.3 mg/L. Additional acute studies on fathead minnow (DuPont-23284), rainbow trout (Asahi-1742/021 as cited in 6:2 FTOH REACH Dossier 2014) and medaka (Daikin -94234 as cited in 6:2 FTOH REACH Dossier 2014) determined a range of LC50 values from 4.48 mg/L to 9.0 mg/L. Results from acute studies indicate 6:2 FTOH would be classified as Category 2 for Acute Toxicity under REACH CLP Criteria (ECHA 2011).

b) Terrestrial compartment

No studies were found to evaluate the toxicity of 6:2 FTOH to terrestrial organisms.

Table 3.5: Ecotoxicity Data for 6:2 FTOH

Species Name	Common Name	Effects Endpoint	Test Conditions	Duration	Acute or Chronic	Exposure Basis	NOEC	LOEC	EC50/ LC50	Units	Reference
Pimephales promelas	Fathead Minnow	Lethality	Static-renewal	96-hour	Acute	Measured			4.84	mg/L	DuPont-23289
Cyprinus carpio	Carp	Lethality	Flow-through	28-days	Prolonged Acute	Measured	> 9.11				6:2 FTOH REACH Dossier 2014
Oncorhynchus mykiss	Rainbow trout	Lethality	Static-renewal	96-hour	Acute	Nominal			9.0	mg/L	6:2 FTOH REACH Dossier 2014
Oryzias latipes	Medaka (Ricefish)	Lethality	Static-renewal	96-hour	Acute	Nominal			5.78	mg/L	6:2 FTOH REACH Dossier 2014
Daphnia magna	Water flea	Reproduction, growth, immobility	Static-renewal	21-days	Chronic	Measured	2.16	4.46		mg/L	DuPont-18063-254
Daphnia magna	Water flea	Survival	Static-renewal	21-days	Chronic	Measured			3.87	mg/L	DuPont-18063-254
Daphnia magna	Water flea	Immobility	Unaerated, static	48-hour	Acute	Measured			7.84	mg/L	DuPont-23290
Daphnia magna	Water flea	Immobility	Unaerated, static	48-hour	Acute	Nominal			8.3	mg/L	6:2 FTOH REACH Dossier 2014
Daphnia magna	Water flea	Immobility	Unaerated, static	48-hour	Acute	Measured			8.2	mg/L	6:2 FTOH REACH Dossier 2014
Pseudokirchneriella subcapitata	Green algae	Growth Inhibition	Static	72-hour	Acute/ Chronic	Measured	0.623	2.22	4.52	mg/L	DuPont-23291

Species Name	Common Name	Effects Endpoint	Test Conditions	Duration	Acute or Chronic	Exposure Basis	NOEC	LOEC	EC50/ LC50	Units	Reference
Pseudokirchneriella subcapitata	Green algae	Growth Inhibition	Static	72-hour	Acute/ Chronic	Measured	1.47		> 5.19	mg/L	6:2 FTOH REACH Dossier 2014
Scenedesmus subspicatus	Green algae	Growth Inhibition	Static	72-hour	Acute/ Chronic	Measured	1.3		3.8	mg/L	6:2 FTOH REACH Dossier 2014

3.5 References

6:2 FTOH REACH Dossier 2014. International Uniform Chemical Information Database: 647-42-7 3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctan-1-ol.

Ahrens L. 2011. Polyfluoroalkyl compounds in the aquatic environment: a review of their occurrence and fate. *J Environ Monit* 13:20-31.

Cai M, Xie Z, Moller A, Yin Z, Huang P, Cai M, Yang H, Sturm R, He J, and Ebinghaus R. 2012. Polyfluorinated compounds in the atmosphere along a cruise pathway from the Japan Sea to the Arctic Ocean. *Chemosphere* 87:989-997.

Carmosini N and Lee LS. 2008. Partitioning of fluorotelomer alcohols to octanol and different sources of dissolved organic carbon. *Environ Sci Technol* 42:6559-6565.

Collins JM. 1998. Military Geography for Professional and the Public. National Defense University Press, Washington, DC.

Conder JM, Hoke RA, de WW, Russell MH, and Buck RC. 2008. Are PFCAs bioaccumulative? A critical review and comparison with regulatory criteria and persistent lipophilic compounds. *Environ Sci Technol* 42:995-1003.

Del Vento S, Halsall C, Gioia R, Jones K, and Dachs J. 2012. Volatile per– and polyfluoroalkyl compounds in the remote atmosphere of the western Antarctic Peninsula: an indirect source of perfluoroalkyl acids to Antarctic waters? *Atmospheric Pollution Research* 3:450-455.

Ding G and Peijnenburg WJGM. 2013. Physicochemical Properties and Aquatic Toxicity of Poly- and Perfluorinated Compounds. *Critical Reviews in Environmental Science and Technology* 43:598-678.

Dreyer A and Ebinghaus R. 2009. Polyfluorinated compounds in ambient air from ship- and land-based measurements in northern Germany. *Atmospheric Environment* 43:1527-1535.

DuPont. 2007. *H-28078: Static-Renewal, Acute, 96-Hour Toxicity Test with Fathead Minnow, Pimephales promelas*. Report Number 23289.

DuPont. 2007. *H-28078: Static, Acute, 48-Hour Toxicity Test with Daphnia magna*. Report Number 23290.

DuPont. 2007. *Acute oral toxicity study in rats - Up-and-Down procedure*. Report Number 23572.

DuPont. 2007. *Acute dermal irritation study in rabbits*. Report Number 23364.

DuPont. 2007. *Acute eye irritation study in rabbits*. Report Number 23558.

DuPont. 2007. *Bacterial Reverse Mutation Test*. Report Number 22935.

DuPont. 2007. *Acute dermal toxicity study in rats*. Report Number 23377.

DuPont. 2008. *In Vitro Mammalian Cell Gene Mutation Test (L5178Y/TK+/- Mouse Lymphoma Assay)*. Report Number 25477.

DuPont. 2008. *H-28078: Static, 72-Hour Growth Inhibition Toxicity Test with the Green Alga, Pseudokirchneriella subcapitata*. Report Number 23291.

DuPont. 2008. *Developmental toxicity study in rats*. Report Number 25283.

DuPont. 2008. *Oral gavage one-generation reproduction study of H:28078 in rats*. Report Number 23865.

DuPont. 2008. *In Vitro Mammalian Chromosome Aberration Test in Human Peripheral Blood Lymphocytes*. Report Number 25912.

DuPont. 2009. *Inhalation median lethal concentration (LC50) study in rats*. Report Number 18063-721.

DuPont. 2010. *Five-day inhalation toxicity study in rats*. Report Number 18063-781.

DuPont. 2011. *Four-week inhalation toxicity study in rats*. Report Number 18063-782 RV1.

DuPont. 2012. *A one-day, nose-only, inhalation toxicokinetic study in the rat*. Report Number 18063-1388.

DuPont. 2012. *Five-day inhalation toxicity study in rats*. Report Number 18063-781 SU1.

DuPont. 2012. *Oral gavage repeated dose 90-day toxicity study of H:28078 in rats*. Report Number 23864 RV1.

DuPont. 2012. *A one-day, nose-only, inhalation toxicokinetic study in the rat*. Report Number 18063-1388.

DuPont. 2012. *Five-day inhalation toxicity study in rats*. Report Number 18063-781 SU1.

DuPont. 2013. *21-Day Chronic, Static-Renewal, Zero Headspace Toxicity Test with the Cladoceran, Daphnia magna*. Report Number 18063-254.

Ellis DA, Martin JW, Mabury SA, Hurley MD, Andersen MP, and Wallington TJ. 2003. Atmospheric lifetime of fluorotelomer alcohols. *Environ Sci Technol* 37:3816-3820.

European Chemicals Agency (ECHA). 2011. Guidance on the Application of the CLP Criteria. ECHA-11-G-06-EN.

European Chemicals Agency (ECHA). 2012. *Guidance on information requirements and chemical safety assessment: Chapter R.11: PBT Assessment*.

He N, Zhou M, and Sun H. 2013. Biodegradation of 6-2 fluorotelomer alcohol in activated sludge. *Acta Scientiae Circumstantiae* 33:383-388.

Krusic PJ, Marchione AA, Davidson F, Kaiser MA, Kao CP, Richardson RE, Botelho M, Waterland RL, and Buck RC. 2005. Vapor pressure and intramolecular hydrogen bonding in fluorotelomer alcohols. *J Phys Chem A* 109:6232-6241.

Liu J and Lee LS. 2007. Effect of fluorotelomer alcohol chain length on aqueous solubility and sorption by soils. *Environ Sci Technol* 41:5357-5362.

Liu J, Wang N, Szostek B, Buck RC, Panciroli PK, Folsom PW, Sulecki LM, and Bellin CA. 2010a. 6-2 Fluorotelomer alcohol aerobic biodegradation in soil and mixed bacterial culture. *Chemosphere* 78:437-444.

Liu J, Wang N, Buck RC, Wolstenholme BW, Folsom PW, Sulecki LM, and Bellin CA. 2010b. Aerobic biodegradation of [14C] 6:2 fluorotelomer alcohol in a flow-through soil incubation system. *Chemosphere* 80:716-723.

Piekarz AM, Primbs T, Field JA, Barofsky DF, and Simonich S. 2007. Semivolatile fluorinated organic compounds in Asian and western U.S. air masses. *Environ Sci Technol* 41:8248-8255.

Prevedouros K, Cousins IT, Buck RC, and Korzeniowski SH. 2006. Sources, fate and transport of perfluorocarboxylates. *Environ Sci Technol* 40:32-44.

Rayne S and Forest K. 2009. Perfluoroalkyl sulfonic and carboxylic acids: a critical review of physicochemical properties, levels and patterns in waters and wastewaters, and treatment methods. *J Environ Sci Health A Tox Hazard Subst Environ Eng* 44:1145-1199.

Xie Z, Zhao Z, Moller A, Wolschke H, Ahrens L, Sturm R, and Ebinghaus R. 2013. Neutral poly- and perfluoroalkyl substances in air and seawater of the North Sea. *Environ Sci Pollut Res Int* 20:7988-8000.

Young CJ and Mabury SA. 2010. Atmospheric perfluorinated acid precursors: chemistry, occurrence, and impacts. *Rev Environ Contam Toxicol* 208:1-109.

Yoo H, Washington JW, Ellington JJ, Jenkins TM, and Neill MP. 2010. Concentrations, distribution, and persistence of fluorotelomer alcohols in sludge-applied soils near Decatur, Alabama, USA. *Environ Sci Technol* 44:8397-8402.

Yoo H, Washington JW, Jenkins TM, and Ellington JJ. 2011. Quantitative determination of perfluorochemicals and fluorotelomer alcohols in plants from biosolid-amended fields using LC/MS/MS and GC/MS. *Environ Sci Technol* 45:7985-7990.

Zhao L, Folsom PW, Wolstenholme BW, Sun H, Wang N, and Buck RC. 2013a. 6:2 fluorotelomer alcohol biotransformation in an aerobic river sediment system. *Chemosphere* 90:203-209.

Zhao L, McCausland PK, Folsom PW, Wolstenholme BW, Sun H, Wang N, and Buck RC. 2013b. 6:2 Fluorotelomer alcohol aerobic biotransformation in activated sludge from two domestic wastewater treatment plants. *Chemosphere* 92:464-470.

4 Manufacturing Intermediate: 6:2 Fluorotelomer Acrylate, 6:2 FTAC

Summary of the Assessment of POP Characteristics of 6:2 FTAC – comparison with the criteria of Annex D and other hazard indicators	
Persistence	**Parent compound unlikely to be persistent according to Annex D 1 (b)** • No half-life data are available for 6:2 FTAC degradation in soil, sediment, or water. • Experimental data suggest that 6:2 FTMAC will undergo hydrolysis with a half-life less than the Annex D criterion of two months in water (DuPont-17784-1644). Based on the structural similarities between 6:2 FTAC and 6:2 FTMAC, 6:2 FTAC is unlikely to be persistent in water. • One study measured 6:2 FTAC biodegradation in a solution with activated sludge microorganisms. This study suggests that 6:2 FTAC may partially degrade to 6:2 FTOH (Daikin-14738). 6:2 FTOH has been shown to degrade to PFHxA in small yields with an initial transformation half-life of less than two days (Liu et al. 2010a; Liu et al. 2010b; Zhao et al. 2013). • Therefore, 6:2 FTAC likely biodegrades, but may result in low yields of persistent degradation products.
Bioaccumulation	**Does not fulfill the bioaccumulation criteria according to Annex D 1 (c) (i)** • No studies were found to evaluate the bioaccumulation of 6:2 FTAC. However, evidence suggests that PFCAs with less than 7 carbons do not bioaccumulate. • Therefore, 6:2 FTAC is not expected to bioaccumulate to any significant degree.

Summary of the Assessment of POP Characteristics of 6:2 FTAC – comparison with the criteria of Annex D and other hazard indicators	
Long-range Environmental Transport (LRET)	**Unlikely to fulfill the LRET criteria of Annex D 1 (d)** • Young and Mabury (2010) calculated a degradation half-life of one day for FTACs in the atmosphere. This suggests that 6:2 FTAC does not meet the Annex D 1 (d) (iii) criteria for long-range transport, based on an atmospheric half-life less than two days. • Although data are extremely limited, low concentrations of 6:2 FTAC have occasionally been detected in air (ND-8.9 pg/m^3) and seawater (ND-7.8 pg/L) in remote locations. Additional data are necessary to determine if 6:2 FTAC concentrations in these locations are of "potential concern" according to Annex D 1 (d) (i).
Aquatic Toxicity	**Does not fulfill the REACH criterion for aquatic toxicity (NOEC < 0.01 mg/L)** • 6:2 FTAC is not significant toxicity to aquatic organisms based on the lack of effects seen in acute toxicity tests at concentrations of 6:2 FTAC near its solubility limit in water. All reported NOECs were greater than the REACH Annex XIII toxicity criteria of < 0.01 mg/L.
Toxicity to Human Health	**No evidence of significant toxicity at exposure levels likely to be encountered by humans** • Oral LD50 in rats was 2,000 to 5,000 mg/kg; not a skin irritant or skin sensitizer; minimal, reversible eye irritant. • Subchronic toxicity effects (increased kidney weight) at ≥25 mg/kg/day. • No genotoxic effects in bacteria or mammalian cells.

4.1 Identity and Physical and Chemical Properties

FTACs are the fundamental building blocks used to synthesize fluorotelomer polymers. As such, these chemicals may be released into the environment during the production and use of fluorotelomer-based products. There is some evidence to suggest that FTACs degrade to PFCAs and may be a minor source of PFCAs in the environment (Prevedouros et al. 2006).

Table 4.1: Chemical Identity of 6:2 FTAC

IUPAC Name	Common Name	Abbreviation	CAS Number	Molecular Weight (amu)	Chemical Structure
3,3,4,4,5,5,6,6,7,7,8,8,8-Tridecafluorooctyl acrylate	6:2 Fluorotelomer acrylate	6:2 FTAC	17527-29-6	418.15	

Table 4.2: Physical and Chemical Properties of 6:2 FTAC

Property	Value	Reference and Remarks
Vapor pressure	44.3 Pa @ 25°C	Modeled[1]; Xie et al. 2013 and ChemSpider.com (retrieved December 17, 2013)
Water solubility	0.378 mg/L	Experimentally determined for 6:2 FTMAC; DuPont-17784-1644; Calculated values from property estimation software for 6:2 FTAC are extremely variable and are unlikely to be accurate.
Partition coefficient n-octanol/water ($logK_{OW}$)	5.2 @ 23°C	Experimentally determined for 6:2 FTMAC; DuPont-17784-1644; ChemSpider.com predicts 6.96 @ 25°C using EPI Suite (retrieved December 17, 2013)
Partition coefficient air/water ($logK_{AW}$)	1.3 @ ~25°C	Calculated based on a solubility of 0.378 mg/L and a vapor pressure of 44 Pa
Partition coefficient octanol/air ($logK_{OA}$)	4.5 (±11%) @ 25°C	Interpolated from experimental data; Dreyer et al. 2009
[1] Modeled using property estimation software. These software packages are not known to accurately predict the physical and chemical properties of perfluorinated substances.		

4.2 Environmental Fate

a) Abiotic degradation

No data available in the studies reviewed.

b) Hydrolysis

A 2010 DuPont study indiates that 6:2 FTMAC undergoes hydrolysis with a half-life of 15.7 days (±31%) at a pH of 7 and 20° C (DuPont-17784-1644). Based on the structural similarities between 6:2 FTMAC and 6:2 FTAC, 6:2 FTAC is also likely to undergo hydrolysis.

c) Phototransformation/photolysis

Butt et al. (2009) determined that FTACs react with photochemical-derived hydroxyl radicals in the atmosphere and measured the rate constant for the atmospheric oxidation of 4:2 FTAC (Butt et al. 2009 as cited in Young and Mabury 2010). Since FTAC reactivity has been shown to be independent of perfluorinated chain length, Young and Mabury (2010) used this rate constant to calculate an atmospheric half-life of one day for FTACs. Experimental data suggest that the atmospheric oxidation of FTACs forms fluorotelomer aldehyde, which then reacts to form PFCAs in small yields (Young and Mabury 2010). Although FTACs may also react with ozone, this reaction is not expected to significantly impact the atmospheric lifetime of FTACs (Young and Mabury 2010).

d) Biodegradation

No data are available for the biodegradation of 6:2 FTAC in soil, sediment, or water. However, Daikin studied 6:2 FTAC degradation in a solution with activated sludge microorganisms (Daikin-14738). In this study, approximately 18% of the test substance degraded to acrylic acid, 6:2 FTCA (3%), and 6:2 FTOH (12%) after 28 days (Daikin-14738). These transformation rates may be used to estimate a degradation half-life of approximately 98 days for 6:2 FTAC by activated sludge microorganisms. Although PFHxA was not measured in the Daikin study, 6:2 FTOH has been shown to biodegrade to PFHxA in small yields in soil and sediment (Liu et al. 2010a; Liu et al. 2010b; Zhao et al. 2013). This suggests that 6:2 FTAC biodegrades, although 6:2 FTAC biodegradation may result in low yields of persistent degradation products.

e) Potential for long-range environmental transport

Although the atmospheric half-life of 6:2 FTAC has not been directly measured, Young and Mabury (2010) calculated a degradation half-life of one day for all FTAC homologues in the atmosphere. This calculation was based on the oxidation rate of 4:2 FTAC by hydroxyl radicals (Butt et al. 2009 as cited in Young and Mabury 2010) and is expected to apply to all FTAC homologues, since reaction kinetics have been shown to be independent of perfluorinated chain length (Young and Mabury 2010). Young and Mabury's calculations

suggest that 6:2 FTAC does not have a long enough atmospheric half-life to be subject to long-range transport.

6:2 FTAC has occasionally been detected at low concentrations in remote environments, although measurement data are extremely limited. A handful of researchers have measured 6:2 FTAC in air (Table 3.3), while Xie et al. 2013 measured 6:2 FTAC in sea water collected from the North Sea during the summer of 2009 at concentrations ranging from <1.0-7.8 pg/L.

Although remote monitoring data could be suggestive of long-range transport, measured concentrations were either low or below detection limits. Further, many remote locations could still be impacted by local or regional emission sources, [3] and a thorough review of 6:2 FTAC emission sources has not been conducted. As such, additional data would be necessary to determine if the 6:2 FTAC levels measured in remote environments are of "potential concern" according to Annex D 1 (d) (i).

Table 4.3: Identification of 6:2 FTAC in Remote Environments

Location	Date	Concentration (pg/m^3)	Phase	Reference
Mount Bachelor Oregon	April, May 2006	<0.7-5.9 <0.7-4.3	Gas, Particle	Piekarz et al. 2007
Atlantic, Southern Oceans and Baltic Sea	April 2007 – May 2009	0.0	Particle	Dreyer et al. 2009 as cited in Young and Mabury 2010
Elbe River Germany	October, November 2007	ND, ND	Gas, Particle	Dreyer and Ebinghaus 2009
German Bight	October, November 2007	5.7, ND	Gas, Particle	
German Bight	October, November 2007	ND	Gas	
North Sea	October, November 2007	ND, ND	Gas, Particle	
German Bight	October, November 2007	ND	Particle	
German Bight	October, November 2007	ND, ND	Gas, Particle	
South Atlantic	October, November 2007	ND-16	Gas	Dreyer et al. 2009 as cited in Young and Mabury 2010
South Atlantic	January 2008	ND-5.5	Gas	
Baltic Sea	June, July 2008	ND-7.3	Gas	
North Atlantic	August 2008	ND-8.9	Gas	
South Atlantic	October-December 2008	ND	Gas	
Southern Ocean	December 2008-May 2009	ND-0.9	Gas	
North Sea	May 2009	<0.9-1.2	Gas	Xie et al. 2013

[3] For example, four million people live above the Arctic Circle and this area has a large number of air strips and airports. There are also industrial mining operations and oil production activities in this area as well as military bases, which conduct firefighting activities and may use (or have historically used) aqueous fire-fighting foams containing perfluorinated compounds (Collins 1998).

Location	Date	Concentration (pg/m^3)	Phase	Reference
Western Antarctic Peninsula	February 2009	0.37-1.75	Gas	Del Vento et al. 2012
Cruise track from Japan to Artic Seas	June-September 2010	0.1-0.2, ND-0.1	Gas, Particle	Cai et al. 2012

f) Bioaccumulation

Empirical Bioaccumulation Evidence from Aquatic Species/Log K_{OW}

No studies were found that explicitly measured the bioaccumulation potential of 6:2 FTAC. The log K_{ow} is predicted to be 5.2, which is slightly above the Annex D bioaccumulation criterion (log K_{ow} > 5). However, it is not appropriate to determine bioaccumulation based solely on a K_{ow} for perfluorinated chemicals, as discussed above for 6:2 FTOH and by Conder et al. (2008). Additionally, Conder et al. (2008) concluded that PFCAs with less than 7 carbons do not bioaccumulate. This indicates that 6:2 FTAC is not likely to bioaccumulate.

Empirical Bioaccumulation Evidence from Other Species/High Ecotoxicity Concerns

No studies were found that measured the bioaccumulation potential of 6:2 FTAC in terrestrial organisms. As noted below, 6:2 FTAC does not exhibit high ecotoxicity that would cause additional concern for the bioaccumulation assessment.

Wildlife Monitoring Data

No monitoring data was available that indicated the presence of 6:2 FTAC in wild biota.

4.3 Human Health Hazard Assessment

a) Acute and subchronic toxicity

Studies in experimental animals provide information on the acute toxicity of 6:2 FTAC. Acute toxicity has been evaluated via the oral, dermal, and ocular route in rat, mouse, and rabbit studies (unpublished studies). Clinical signs of toxicity were evaluated via functional and morphological changes such as mortality, changes in body weight, liver and kidney effect, signs of gross toxicity and behavioral changes. Oral LD50s observed in females rats were as low as 2,000 mg/kg bw and high as 5,000 mg/kg bw (Daikin-1458/0061 and DuPont-18776-834).

In rats exposed via the oral (gavage) route for 28 days, treatment-related incisor effects, liver effects (such as periportal hypertrophy), renal effects (e.g. dilation of the tubules and ballooning of the epithelium), and changes in organ weight were observed (Daikin- B11-0836). In this study, the NOAEL was 5 mg/kg/day based on increased relative kidney weight in males given 25 mg/kg bw/day or more. No mortality was observed at doses up 125 mg/kg/day (highest dose administered).

In dermally-exposed rodents, 6:2 FTAC produced “very slight erythema” which was reversible after exposures ceased (Daikin-1458/0062 and DuPont-18776-1008). 6:2 FTAC was considered to be a non-skin sensitizer and non-irritant (Daikin-1458/0064).

Ocular toxicity was evaluated in two rabbit studies via one time exposure to 6:2 FTAC (Daikin-1458/0063 and DuPont-18776-602). In both studies, no effects on the cornea and iris were observed; however, one study reported minimal eye irritation on the conjunctiva; but effects were reversible during the observation period.

b) Mutagenicity and carcinogenicity

Assays employed to evaluate mutagenicity and genotoxicity of 6:2 FTAC were conducted in mice *in vivo* (Daikin 7958-102) and *in vitro* using bacterial cell lines and cultured Chinese hamster cells (Daikin-1165/200; Daikin K01-3687; Daikin K06-1189). These studies reported that 6:2 FTAC produced negative results in the test systems analyzed, thereby suggesting no evidence of mutagenicity or genotoxicity.

No studies on carcinogenicity were identified.

c) Reproductive toxicity

No studies on reproductive toxicity were identified.

d) Neurotoxicity

Hypoactivity was seen following acute oral exposure at 400 mg/kg bw (maximum tolerated dose) in mice, but this likely represents a nonspecific response to the near-lethal dose (some deaths were seen at 500 mg/kg in a range-finding study) rather than a specific neurotoxic effect (Daikin-7958-102).

e) Immunotoxicity

No studies on immunotoxicity were identified.

f) Acceptable exposure levels

The most sensitive species in subchronic toxicity test were rats, with a NOAEL of 5 mg/kg/day in females based on increased relative kidney weight in males given 25 mg/kg bw/day or more (Daikin-B11-0836).

4.4 Environmental Hazard Assessment

a) Aquatic compartment (including sediment)

All effect concentrations for 6:2 FTAC were greater than the REACH Annex XIII Toxicity criteria of a chronic NOEC < 0.01 mg/L (ECHA 2012), indicating 6:2 FTAC would not be considered toxic under REACH PBT criteria The only chronic toxicity study was 72-hour growth inhibition for green algae with a NOEC based on growth rate greater than 0.0215

mg/L. This limit test was performed around the solubility of the substance in the test medium, and therefore the highest possible test concentration.

A number of acute toxicity studies were available for 6:2 FTAC (Table 4.4), which show that 6:2 FTAC has low toxicity to aquatic organisms. Acute EC50s for *Daphnia magna* and LC50s medaka (Japanese rice fish) were greater than the < 0.01 mg/L REACH Criteria, indicating a lack of significant toxicity. In each of these studies, no effects were seen at the maximum test concentration; therefore, the true (bounded) LC50/EC50 is higher than the reported value (but cannot be determined precisely). For all studies, the maximum tested concentrations (from 0.022 mg/L to 0.306 mg/L) were near the limits of solubility of 6:2 FTAC in water at the test temperature. As the acute studies at or near the solubility of the substance in water resulted in unbounded EC50/LC50 values, these values would be inappropriate to use for classifying 6:2 FTAC for CLP Acute Toxicity Categories, and the chemical would not be classified as very toxic (acutely) to aquatic life (i.e., Category 1 designation for EC50 or LC50 values < 1 mg/L) (ECHA, 2011). 6:2 FTAC does not appear to be toxic to aquatic organisms at concentrations near its solubility in water based on the reviewed studies.

b) Terrestrial Compartment

No studies were found to evaluate the toxicity to terrestrial species.

Table 4.4: Ecotoxicity Data for 6:2 FTAC

Species Name	Common Name	Effects Endpoint	Test Conditions	Duration	Acute or Chronic	Exposure Basis	NOEC	EC50/ LC50	Units	Ref.
Daphnia magna	Water flea	Immobility	Semi-static	48-hour	Acute	Measured		> 0.141	mg/L	Daikin-94224
Oryzias latipes	Japanese rice fish	Lethality	Semi-static	96-hour	Acute	Measured		> 0.306	mg/L	Daikin-94225
Pseudokirchneriella subcapitata	Green algae	Growth Inhibition	Static	72-hour	Chronic	Measured	> 0.022		mg/L	Daikin-94223
Pseudokirchneriella subcapitata	Green algae	Growth Inhibition	Static	72-hour	Acute	Measured		> 0.022	mg/L	Daikin-94223

4.5 References

Butt CM, Berger U, Bossi R, and Tomy GT. 2010. Levels and trends of poly- and perfluorinated compounds in the arctic environment. *Sci Total Environ* 408:2936-2965.

Cai M, Xie Z, Moller A, Yin Z, Huang P, Cai M, Yang H, Sturm R, He J, and Ebinghaus R. 2012. Polyfluorinated compounds in the atmosphere along a cruise pathway from the Japan Sea to the Arctic Ocean. *Chemosphere* 87:989-997.

Collins JM. 1998. Military Geography for Professional and the Public. National Defense University Press, Washington, DC.

Daikin Industries. 2007. *Chromosomal aberration test of 13F-SFA using cultured mammalian cells*. Report Number K06-1189.

Daikin Industries. 2007. *Mutagenicity test of 13F-SFA using microorganisms*. Report Number K01-3687.

Daikin Industries. 2007. *Acute dermal irritation in the rabbit*. Report Number 1458/0062.

Daikin Industries. 2007. *Twenty-eight day repeated-dose oral toxicity study of 13F-SFA in rats*. Report Number B11-0836.

Daikin Industries. 2007. *Local lymph node assay in the mouse*. Report Number 1458/0064.

Daikin Industries. 2007. *Acute eye irritation in the rabbit*. Report Number 1458/0063.

Daikin Industries. 2007. *A 48-hour immobilization study of 13F-SFA with Daphnia magna*. Report Number 94224.

Daikin Industries. 2007. *A 96-hour acute toxicity study with 13F-SFA with Medaka*. Report Number 94225.

Daikin Industries. 2007. *Algae growth inhibition study of 13F-SFA with Pseudokirchneriella subcapitata*. Report Number 94223.

Daikin Industries. 2007. *Biodegradation study of 13F-SFA by microorganisms*. Report Number 14738.

Daikin Industries. 2008. *Gene mutation assay in Chinese hamster V79 cells in vitro (V79/HPRT) with C6SFA monomer*. Report Number 1165/200.

Daikin Industries. 2008. *In vivo mouse bone marrow micronucleus assay*. Report Number 7958-102.

Del Vento S, Halsall C, Gioia R, Jones K, and Dachs J. 2012. Volatile per– and polyfluoroalkyl compounds in the remote atmosphere of the western Antarctic Peninsula: an indirect source of perfluoroalkyl acids to Antarctic waters? *Atmospheric Pollution Research* 3:450-455.

Dreyer A, Langer V, and Ebinghaus R. 2009. Determination of Octanol-Air Partition Coefficients (KOA) of Fluorotelomer" Acrylates, Perfluoroalkyl Sulfonamids, and Perfluoroalkylsulfonamido Ethanols. *J Chem Eng Data* 54:3022-3025.

Dreyer A and Ebinghaus R. 2009. Polyfluorinated compounds in ambient air from ship- and land-based measurements in northern Germany. *Atmospheric Environment* 43:1527-1535.

DuPont. 2010. *Physical and Chemical Characteristics of 62-FMA: State of the Substance. Boiling Point, Water Solubility, Partition Coefficient n-Octanol/Water, Flash Point and Hydrolysis as a Function of pH*. Report Number 17784-1644.

DuPont. 2010. *Primary eye irritation in rabbits*. Report Number 18776-602.

DuPont. 2010. *Primary skin irritation in rabbits*. Report Number 18776-1008.

European Chemicals Agency (ECHA). 2011. Guidance on the Application of the CLP Criteria. ECHA-11-G-06-EN.

European Chemicals Agency (ECHA). 2012. *Guidance on information requirements and chemical safety assessment: Chapter R.11: PBT Assessment*.

Liu J, Wang N, Szostek B, Buck RC, Panciroli PK, Folsom PW, Sulecki LM, and Bellin CA. 2010a. 6-2 Fluorotelomer alcohol aerobic biodegradation in soil and mixed bacterial culture. *Chemosphere* 78:437-444.

Liu J, Wang N, Buck RC, Wolstenholme BW, Folsom PW, Sulecki LM, and Bellin CA. 2010b. Aerobic biodegradation of [14C] 6:2 fluorotelomer alcohol in a flow-through soil incubation system. *Chemosphere* 80:716-723.

Piekarz AM, Primbs T, Field JA, Barofsky DF, and Simonich S. 2007. Semivolatile fluorinated organic compounds in Asian and western U.S. air masses. *Environ Sci Technol* 41:8248-8255.

Royal Society of Chemistry. 2014. ChemSpider. http://www.chemspider.com/.

Xie Z, Zhao Z, Moller A, Wolschke H, Ahrens L, Sturm R, and Ebinghaus R. 2013. Neutral poly- and perfluoroalkyl substances in air and seawater of the North Sea. *Environ Sci Pollut Res Int* 20:7988-8000.

Young CJ and Mabury SA. 2010. Atmospheric perfluorinated acid precursors: chemistry, occurrence, and impacts. *Rev Environ Contam Toxicol* 208:1-109.

Zhao L, Folsom PW, Wolstenholme BW, Sun H, Wang N, and Buck RC. 2013. 6:2 fluorotelomer alcohol biotransformation in an aerobic river sediment system. *Chemosphere* 90:203-209.

5 Manufacturing Intermediate: 6:2 Fluorotelomer Methacrylate, 6:2 FTMAC

Summary of the Assessment of POP Characteristics of 6:2 FTMAC – comparison with the criteria of Annex D and other hazard indicators	
Persistence	**Parent compound unlikely to meet persistence criteria according to Annex D 1 (b)** • Experimental data indicate that 6:2 FTMAC will undergo hydrolysis with a half-life less than the Annex D criterion of two months in water (DuPont-17784-1644). This suggests that 6:2 FTMAC is not persistent in water. • Data on the degradation half-life of 6:2 FTMAC in soil and sediment are not available. Studies of structurally similar compounds suggest that 6:2 FTMAC degrades to 6:2 FTOH through cleavage of the ester linkage (Wang et al. 2011, Lee and Maybury 2010, and Dasu et al. 2012 as cited in 6:2 FTMAC REACH Dossier 2014). 6:2 FTOH has been shown to degrade to PFHxA in small yields with an initial transformation half-life of less than two days (Liu et al. 2010a; Liu et al. 2010b; Zhao et al. 2013). This suggests that 6:2 FTMAC is biodegradable, but may result in low yields of persistent degradation products.
Bioaccumulation	**Does not fulfill the bioaccumulation criteria according to Annex D 1 (c) (i)** • No studies were found that measured the bioaccumulation of 6:2 FTMAC. However, significant metabolism was observed in rainbow trout hepatocytes cells, with low bioaccumulation potential as indicated by a predicted BCF of 268 L/kg. This BCF is well below the Annex D criteria of >5,000 L/kg. • Therefore, 6:2 FTMAC is not expected to bioaccumulate to any significant degree.

Summary of the Assessment of POP Characteristics of 6:2 FTMAC – comparison with the criteria of Annex D and other hazard indicators	
Long-range Environmental Transport (LRET)	**Does not meet Annex D 1 (d) criteria for long-range atmospheric transport** • Although the atmospheric half-life of 6:2 FTMAC has not been directly measured, laboratory studies indicate that methacrylates are more susceptible to atmospheric oxidation than acrylates (Blanco et al. 2009). This suggests that the atmospheric half-life of 6:2 FTMAC is less than two day criterion provided in Annex D 1 (d). • No monitoring data are available that indicate the presence of 6:2 FTMAC in the environment.
Aquatic Toxicity	**Does not fulfill the REACH criterion for aquatic toxicity (NOEC < 0.01 mg/L)** • 6:2 FTMAC is not significant toxicity to aquatic organisms, as all chronic NOECs reviewed were greater than the REACH Annex XIII criteria of < 0.01 mg/L or were greater than the highest concentration tested. • None of the acute toxicity tests reviewed showed any effects at the highest concentrations tested.
Toxicity to Human Health	**No evidence of significant toxicity at exposure levels likely to be encountered by humans** • Oral LD50 in rats and mice: 2,000 and 5,000 mg/kg; dermal LD50 in rats >5,000 mg/kg; not a significant skin irritant or sensitizer; minimal reversible eye irritation. • Subchronic exposure produced mild effects at ≥ 25 mg/kg/day. • No data on reproductive toxicity, neurotoxicity, or immunotoxicity. • Weight of evidence shows a lack of genotoxicity.

5.1 Identity and Physical and Chemical Properties

FTMACs are used in the production of fluorotelomer polymers and may be released into the environment during the production and use of fluorotelomer-based products (Prevedouros et al. 2006).

Table 5.1: Chemical Identity of 6:2 FTMAC

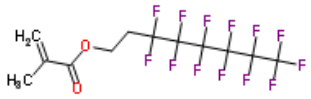
IUPAC Name	Common Name	Abbreviation	CAS Number	Molecular Weight (amu)	Chemical Structure
3,3,4,4,5,5,6,6,7,7,8,8,8-Tridecafluorooctyl methacrylate	6:2 Fluorotelomer methacrylate	6:2 FTMAC	2144-53-8	432.18	

Table 5.2: Physical and Chemical Properties of 6:2 FTMAC

Property	Value	Reference and Remarks
Vapor pressure	8.6 Pa @ 25°C	Experimentally determined; Asahi-497972 as cited in 6:2 FTMAC REACH Dossier 2014
Water solubility	0.378 mg/L @ 25°C	Experimentally determined; DuPont-17784-1644
Partition coefficient n-octanol/water ($logK_{OW}$)	5.2 @ 23°C	Experimentally determined; DuPont-17784-1644
Partition coefficient air/water ($logK_{AW}$)	0.8 @ ~25°C	Calculated from vapor pressure and solubility
Partition coefficient octanol/air ($logK_{OA}$)	4.98 @ 25°C	Modeled[1]; ChemSpider.com (retrieved December 17, 2013); Similar to ~4-5 calculated as $logK_{OW}$ - $logK_{AW}$
[1] Modeled using property estimation software. These software packages are not known to accurately predict the physical and chemical properties of perfluorinated substances.		

5.2 Environmental Fate

a) Abiotic degradation

No data available in the studies reviewed.

b) Hydrolysis

A 2010 DuPont study suggests that 6:2 FTMAC is likely to undergo hydrolysis with a half-life of 15.7 days (±31%) at a pH of 7 and 20° C (DuPont-17784-1644). This suggests that the half-life of 6:2 FTMAC in water is less than the Annex D 1 (b) criterion of two months.

c) Phototransformation/photolysis

FTMACs are unlikely to undergo direct photolysis in the environment, since esters do not absorb light within the actinic spectrum of the lower atmosphere (Blanco et al. 2009). These compounds may, however, be oxidized by photochemically-derived hydroxyl radicals in the atmosphere. Further, laboratory studies suggest that methacrylate monomers are more susceptible to atmospheric oxidation than the corresponding acrylate monomers (Blanco et al. 2009). This suggests that 6:2 FTMAC would have an atmospheric half-life of less than one day, based on the half-life of 6:2 FTAC.

d) Biodegradation

No data are available on the degradation half-life of 6:2 FTMAC in soil, sediment, or water. Studies have measured 6:2 FTMAC degradation in solution with activated sludge microorganisms. These studies indicate that 6:2 FTMAC is not readily degradable, but is inherently biodegradable, with up to 78.1% of a 30 mg/L solution degrading over a 28 day test period (DuPont-17784-1723 as cited in 6:2 FTMAC REACH Dossier 2014). Additionally, 6:2 FTMAC is structurally similar to 6:2 fluorotelomer sulfonate, 6:2 monosubstituted polyfluoroalkyl phosphate, and 8:2 fluorotelomer stearate. These substances have been shown to degrade to 6:2 FTOH through cleavage of the ester linkage (Wang et al. 2011, Lee and Maybury 2010, and Dasu et al. 2012 as cited in 6:2 FTMAC REACH Dossier 2014). Further, 6:2 FTOH has been shown to biodegrade to PFHxA in small yields in both soil and sediment with an initial transformation half-life of less than two days (Liu et al. 2010a; Liu et al. 2010b; Zhao et al. 2013). These data suggest that 6:2 FTMAC also biodegrades.

e) Potential for long-range environmental transport

6:2 FTMAC is likely to have an atmospheric half-life of less than one day (Blanco et al. 2009; Young and Mabury 2010). This suggests that 6:2 FTMAC would not be transported long distances in the atmosphere. No monitoring data are available that indicate the presence of 6:2 FTMAC in the environment.

f) Bioaccumulation

Empirical Bioaccumulation Evidence from Aquatic Species/Log K_{OW}

No studies were found that explicitly measured the bioaccumulation potential of 6:2 FTMAC. However, a study of metabolism of 6:2 FTMAC using trout hepatocyte cells indicated that it is readily metabolized to 6:2 FTOH. Using the model in Han et al. (2007) hepatocyte clearance was used to calculate a BCF for rainbow trout of 268 L/kg. This BCF value is well below the Annex D criteria of >5,000 L/kg.

The log K_{ow} is 5.2, which is slightly above the Annex D Bioaccumulation criteria (log K_{ow} > 5). However, it is not appropriate to determine bioaccumulation based solely on a K_{ow} for perfluorinated chemicals, as discussed above for 6:2 FTOH and by Conder et al. (2008).

Additionally, Conder et al. (2008) concluded that PFCAs with less than 7 carbons do not bioaccumulate. This indicates that 6:2 FTMAC is unlikely to bioaccumulate.

Empirical Bioaccumulation Evidence from Other Species/High Ecotoxicity Concerns

No studies were found in the literature to evaluate the bioaccumulation of 6:2 FTMAC to other species. As discussed below, 6:2 FTMAC does not have high ecotoxicity to be of concern in the bioaccumulation assessment.

Wildlife Monitoring Data

No monitoring data available indicating presence of 6:2 FTMAC in wild biota.

5.3 Human Health Hazard Assessment

The metabolism of 6:2 FTMAC was evaluated *in vitro* in mammalian hepatocytes and *in vivo* in rats (DuPont-17784-1388 and DuPont-17784-1599 as cited in 6:2 FTMAC REACH Dossier 2014). *In vivo*, blood, fat, and liver samples from dosed rats were analyzed for 6:2 FTMAC to provide an estimate of the tissue-plasma ratio. 6:2 FTMAC was detected in very small amounts in plasma (< 40.0 ng/mL at the 1-, 2- and 4-hour post-dosing time points), liver (< 20.0 ng/mL at the 6-, 12-, and 24-hour post-dosing time points), and fat (<20.0 to 99.9 ng/g at the 6-, 12-, 24-, 48-, 72-, and 96-hour post-dosing time points) (DuPont-17784-1388 as cited in 6:2 FTMAC REACH Dossier 2014). The very small amounts of 6:2 FTMAC detected precluded determination of plasma clearance or tissue/plasma ratios.

In vitro, 6:2 FTMAC was rapidly metabolized in live rat and mouse hepatocytes compared to heat inactivated controls (DuPont-17784-1599 as cited in 6:2 FTMAC REACH Dossier 2014). The major metabolite was 6:2 uFTOH-glutathione; additional metabolites were 6:2 GTOH-Gluc, 6:2 diOH-diGluc, 6:2 FTOH, 6:2 FTMAC-GS (male hepatocytes only), 6:2 FTOH-Sulf (female hepatocytes only), and 6:2 UAL-GS (isomer II DNPH derivative) (female hepatocytes only). In rat hepatocytes, the half-life was reported as <3 minutes, as an actual rate was not attainable due to the fact that there was <5% of the parent compound remaining 5 minutes after incubation and no parent compound remaining after 15 minutes of incubation. Significant metabolism was also observed in male mouse hepatocytes, but half-life and clearance rates could not be calculated due to the shape of the data curve. The steep portion of the curve between 0 and 3 minutes indicated rapid metabolism.

a) Acute and subchronic toxicity

Studies in experimental animals provide information on the acute toxicity of 6:2 FTMAC. Acute toxicity has been evaluated via the oral, dermal, ocular, and inhalation route in rodents. Clinical signs of toxicity were evaluated via functional and morphological changes such as mortality, changes in body weight, liver and kidney effects, signs of gross toxicity, and behavioral changes. Oral LD50 observed were >2000 mg/kg bw in female rats and >5000 mg/kg bw in female mice (Daikin-1458/0065; DuPont-17784-835; DuPont-25862; Asahi-174/006 as cited in 6:2 FTMAC REACH Dossier 2014).

In rats exposed to 6:2 FTMAC orally for 14 days, a NOAEL of 1,000 mg/kg/day was observed based on the lack of adverse effects on in-life, clinical and anatomic pathology parameters (DuPont-7784-1583). In one mouse study, a NOEL of 350 mg/kg bw/day was observed based on no signs of clinical toxicity (DuPont-17784-553/572).

In rats exposed via the oral (gavage) route for 28 days, treatment-related incisor effects, and changes in organ weight were observed (Daikin-B11-0837). The NOAEL was 5 mg/kg/day based on decreased iron pigment of the ameloblasts at maturation stage in the incisors in both sexes, increased relative kidney weight in males and increased absolute and relative liver weights in females of the 25 mg/kg bw dosing group.

In dermal-exposed rodents, 6:2 FTMAC produced “very slight erythema” which was reversible after exposure stopped, and incidence and severity decreased with time (Daikin-1458/0066; DuPont-25860; Asahi-497973 as cited in 6:2 FTMAC REACH Dossier 2014). In mouse local lymph node assays, 6:2 FTMAC was considered to be a non-sensitizer (Daikin-1458/0068; DuPont-17784-1234; Asahi-497975 as cited in 6:2 FTMAC REACH Dossier 2014). Lastly, a dermal LD50 greater than 5000 mg/kg was observed in male and female rats (DuPont-17784-673).

Ocular toxicity was evaluated in three rabbit studies via one time exposure to 6:2 FTMAC (Daikin- 1458/0067; DuPont-25861; Asahi-497974 as cited in 6:2 FTMAC REACH Dossier 2014). In all studies, no effects on the cornea and iris were reported. Minimal eye irritation on the conjunctiva was observed; however, this effect was reversible. The overall incidence and severity of irritation decreased with time.

b) Mutagenicity and carcinogenicity

Assays employed to evaluate mutagenicity and genotoxicity of 6:2 FTMAC were conducted *in vitro* using bacterial and mammalian cell lines and *in vivo* (mice). Of the nine studies reviewed, only one was positive. 6:2 FTMAC induced structural aberrations in the *in vitro* mammalian chromosome aberration test in human peripheral blood lymphocytes under non-activated test conditions. Numerical aberrations were not observed in either activated or non-activated test conditions (DuPont-25846). In the remaining studies, no evidence of mutagenicity, genotoxicity, or clastogenicity was reported in 8 of the 9 studies (Daikin-USA-R-06397; Daikin-K06-1190; DuPont-17784-553/572; DuPont-25478 RV1; DuPont-25845; Asahi studies: V6205/11, V6202/13, and V6203/13 as cited in 6:2 FTMAC REACH Dossier 2014).

No studies on carcinogenicity were identified.

c) Reproductive toxicity

No studies on reproductive toxicity were identified.

d) Neurotoxicity

No studies on neurotoxicity were identified.

e) Immunotoxicity

No studies on immunotoxicity were identified.

f) Acceptable exposure levels

In acute studies, the NOEL observed in rats was 1,000 mg/kg/day based on the lack of adverse effects on in-life, clinical, and anatomic pathology parameters and in mice, the NOEL was 350 mg/kg bw/day based on no signs of clinical toxicity (DuPont-17784-1583, DuPont-17784-553/572).

In an oral subchronic toxicity study in rats, the NOAEL was 5 mg/kg/day based on decreased iron pigment of the ameloblasts at maturation stage in the incisors in both sexes, increased relative kidney weight in males, and increased absolute and relative liver weights in females of the 25 mg/kg bw dosing group (LOAEL) (Daikin-B11-0837).

5.4 Environmental Hazard Assessment

a) Aquatic compartment (including sediment)

All effect concentrations for 6:2 FTMAC are greater than the REACH Toxicity criteria of a chronic NOEC < 0.01 mg/L (ECHA 2012), or were the greater than the maximum concentration tested, indicating 6:2 FTMAC would not be considered toxic under REACH PBT criteria. Most chronic studies found for 6:2 FTMAC were tests on green algae for effects on growth (based on growth rate and cell count), and resulted in NOECs ranging from greater than 0.0078 mg/L (Asahi-1742/017 as cited in 6:2 FTMAC REACH Dossier 2014) to greater than 24.6 mg/L (DuPont-17784-315).

A number of acute studies were found which presented unbounded EC50 or LC50 values (Table 5.3). 96-hour LC50s in four fish species (rainbow trout, fathead minnow, rare gudgeon, and medaka) were all greater than the < 0.01 mg/L criteria, indicating a lack of toxicity (DuPont-17784-295; DuPont-17784-316; Daikin-94228; Asahi-1742/015 as cited in 6:2 FTMAC REACH Dossier 2014). Three studies on the effects of 6:2 FTMAC on *Daphnia magna* resulted in EC50s greater than 0.017 mg/L (DuPont-17784-296; Daikin-94227; Asahi-1742/016 as cited in 6:2 FTMAC REACH Dossier 2014) and one chronic (96-hour) NOEC of greater than 0.017 mg/L. One of these studies (DuPont-17784-296) only reported the nominal concentration; the actual concentration of 6:2 FTMAC in the test solution is unknown. In all tests, no effects were observed at the highest test concentrations; therefore the true (bounded) NOEC or L(E)C50 value is unknown. Differences in effect concentrations reported for the same species result from the different ranges of test concentrations, rather than a difference in effect levels. The results of the acute studies were unbounded EC50/LC50 values determined from the highest test concentrations used in the studies (ranging from > 0.0078 to > 29.3 mg/L). In all experiments conducted with exposure concentrations higher than the Category 1 threshold of 1 mg/L, toxicity was not observed. Therefore, the chemical would not be classified as very toxic (acutely) to aquatic life. The lack of adverse effects seen in any of the reported acute toxicity studies (many of which were tested at the solubility of 6:2 FTMAC in water) as well as the rapid conversion to

6:2 FTOH (6:2 FTMAC REACH Dossier 2014), indicate that 6:2 FTMAC does not pose a risk to aquatic organisms.

b) Terrestrial compartment

One study on the toxicity of 6:2 FTMAC in terrestrial species was found in the literature (Table 5.3). A 14-day chronic NOEC was reported for earthworms at greater than 1000 mg/kg dry weight of soil (DuPont-17784-1501). No effects were seen at the highest test concentration in soil; however, only the nominal concentration was reported. Therefore, the measured concentration in soil is unknown. There are no available NOEC thresholds for toxicity to terrestrial organisms listed in Annex D or REACH guidance.

Table 5.3: Ecotoxicity Data for 6:2 FTMAC

Species Name	Common Name	Effects Endpoint	Test Conditions	Duration	Acute or Chronic	Exposure Basis	NOEC	EC50/ LC50	Units	Reference
Oncorhynchus mykiss	Rainbow trout	Lethality	Static-renewal	96-hour	Acute	Measured		> 0.077	mg/L	6:2 FTMAC REACH Dossier 2014
Pimephales promelas	Fathead Minnow	Lethality	Static-renewal	96-hour	Acute	Measured		> 14.5	mg/L	DuPont-17784-295
Gobiocypris rarus	Rare Gudgeon	Lethality	Static-renewal	96-hour	Acute	Measured		> 29.3	mg/L	DuPont-17784-316
Oryzias latipes	Japanese rice fish	Lethality	Static-renewal	96-hour	Acute	Measured		> 0.133	mg/L	Daikin-94228
Daphnia magna	Water flea	Immobility	Unaerated, static	48-hour	Acute	Nominal		> 120	mg/L	DuPont-17784-296
Daphnia magna	Water flea	Immobility	Static-renewal	48-hour	Acute	Measured		> 0.038	mg/L	Daikin-94227
Daphnia magna	Water flea	Immobility	Static-renewal	48-hour	Acute	Measured		> 0.017	mg/L	6:2 FTMAC REACH Dossier 2014
Daphnia magna	Water flea	Immobility	Static-renewal	96-hour	Chronic	Measured	> 0.017		mg/L	6:2 FTMAC REACH Dossier 2014
Pseudokirchneriella subcapitata	Green algae	Growth Inhibition	Static	72-hour	Acute/ Chronic	Measured	> 24.6	> 24.6	mg/L	DuPont-17784-315

Species Name	Common Name	Effects Endpoint	Test Conditions	Duration	Acute or Chronic	Exposure Basis	NOEC	EC50/ LC50	Units	Reference
Pseudokirchneriella subcapitata	Green algae	Growth Inhibition	Static	72-hour	Acute/ Chronic	Measured	> 0.013	> 0.013	mg/L	Daikin-94226
Pseudokirchneriella subcapitata	Green algae	Growth Inhibition	Static	72-hour	Acute/ Chronic	Measured	> 0.0078	> 0.0078	mg/L	6:2 FTMAC REACH Dossier 2014
Eisenia fetida	Earthworm	Lethality, Growth	Soil exposure	14-days	Chronic	Nominal	> 1000		mg/kg dw	DuPont-17784-1501

5.5 References

6:2 FTMAC REACH Dossier. 2014. International Uniform Chemical Information Database (IUCLID): 2144-53-8 3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl methacrylate.

Blanco MB, Bejan I, Barnes I, Wiesen P, Teruel MA. 2009. OH-Initiated Degradation of Unsaturated Esters in the Atmosphere: Kinetics in the Temperature Range of 287-313 K. *J. Phys. Chem. A* 113:5958-5965.

Conder JM, Hoke RA, de WW, Russell MH, and Buck RC. 2008. Are PFCAs bioaccumulative? A critical review and comparison with regulatory criteria and persistent lipophilic compounds. *Environ Sci Technol* 42:995-1003.

Daikin Industries. 2006. *Mutagenicity test of C6 Methylacrylate (M-1620) using microorganisms*. Report Number USA-R-06397.

Daikin Industries. 2007. *Local lymph node assay in the mouse*. Report Number 1458/0068.

Daikin Industries. 2007. *A 48-hour immobilization study of 13F-SFMA with Daphnia magna*. Report Number 94227.

Daikin Industries. 2007. *A 96-hour acute toxicity study with 13F-SFMA with Medaka*. Report Number 94228.

Daikin Industries. 2007. *Twenty-eight day repeated-dose oral toxicity of 13F-SFMA in rats*. Report Number B11-0837.

Daikin Industries. 2007. *Algae growth inhibition study of 13F-SFMA with Pseudokirchneriella subcapitata*. Report Number 94226.

Daikin Industries. 2007. *Chromosomal aberration test of 13F-SFMA using cultured mammalian cells*. Report Number K06-1190.

Daikin Industries. 2007. *Acute eye irritation in the rabbit*. Report Number 1458/0067.

Daikin Industries. 2007. *Acute oral toxicity in the rat - fixed dose method*. Report Number 1458/0065.

Daikin Industries. 2007. *Acute dermal irritation in the rabbit*. Report Number 1458/0066.

Daikin Industries. 2007. *Biodegradation study of 13F-SFA by microorganisms*. Report Number 14738.

DuPont. 2008. *Acute oral toxicity - Up-And-Down procedure in rats*. Report Number 25862

DuPont. 2008. *Primary skin irritation in rabbits*. Report Number 25860.

DuPont. 2008. *Primary eye irritation in rabbits*. Report Number 25861.

DuPont. 2008. *In Vitro Mammalian Chromosome Aberration Test in Human Peripheral Blood Lymphocytes*. Report Number 25846.

DuPont. 2008. *Bacterial Reverse Mutation Test*. Report Number 25845.

DuPont. 2008. *H-28574: Static, Acute, 48-Hour Toxicity Screening Test with Daphnia magna*. Report Number 17784-296.

DuPont. 2008. *In Vitro Mammalian Cell Gene Mutation Test (L5178Y/TK+/- Mouse Lymphoma Assay)*. Report Number 25478 RV1.

DuPont. 2009. *In Vivo micronucleus and chromosome aberration assay in mouse bone marrow cells*. Report Number 17784-553/572.

DuPont. 2009. *Acute oral toxicity in mice - Up-And-Down procedure*. Report Number 17784-835.

DuPont. 2009. *Dermal toxicity study in rats*. Report Number 17784-673.

DuPont. 2009. *Local Lymph Node Assay (LLNA) in mice*. Report Number 17784-1234.

DuPont. 2009. *62-FMA: static-renewal, acute toxicity to rare gudgeon (Gobiocypris rarus)*. Report Number 17784-316.

DuPont. 2009. *Two-week repeated-dose oral toxicity study by gavage in rats*. Report Number 17784-1583.

DuPont. 2009. *H-28574: Static, 72-Hour Growth Inhibition Toxicity Screening Test to the Green Algae, Pseudokirchneriella subcapitata*. Report Number 17784-315.

DuPont. 2009. *H-28574: Static-Renewal, Acute, 96-Hour Toxicity Screening Test with Pimephales promelas*. Report Number 17784-295.

DuPont. 2010. *6-2 FMA: Acute toxicity to the earthworm eisenia fetida in artificial soil with 5% peat*. Report Number 17784-1501.

DuPont. 2010. *Physical and Chemical Characteristics of 62-FMA: State of the Substance. Boiling Point, Water Solubility, Partition Coefficient n-Octanol/Water, Flash Point and Hydrolysis as a Function of pH*. Report Number 17784-1644.

European Chemicals Agency (ECHA). 2012. *Guidance on information requirements and chemical safety assessment: Chapter R.11: PBT Assessment*.

Han X, Nabb DL, Mingoia RT, and Yang CH. 2007. Determination of xenobiotic intrinsic clearance in freshly isolated hepatocytes from rainbow trout (Oncorhynchus mykiss) and rat and its application in bioaccumulation assessment. *Environ Sci Technol* 41:3269-3276.

Liu J, Wang N, Szostek B, Buck RC, Panciroli PK, Folsom PW, Sulecki LM, and Bellin CA. 2010a. 6-2 Fluorotelomer alcohol aerobic biodegradation in soil and mixed bacterial culture. *Chemosphere* 78:437-444.

Liu J, Wang N, Buck RC, Wolstenholme BW, Folsom PW, Sulecki LM, and Bellin CA. 2010b. Aerobic biodegradation of [14C] 6:2 fluorotelomer alcohol in a flow-through soil incubation system. *Chemosphere* 80:716-723.

Royal Society of Chemistry. 2014. ChemSpider. http://www.chemspider.com/.

Young CJ and Mabury SA. 2010. Atmospheric perfluorinated acid precursors: chemistry, occurrence, and impacts. *Rev Environ Contam Toxicol* 208:1-109.

Zhao L, Folsom PW, Wolstenholme BW, Sun H, Wang N, and Buck RC. 2013. 6:2 fluorotelomer alcohol biotransformation in an aerobic river sediment system. *Chemosphere* 90:203-209.

6 Degradation Product: Perfluorohexanoic Acid, PFHxA, and Perfluorohexanoate, PFHx

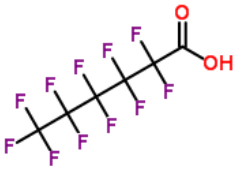
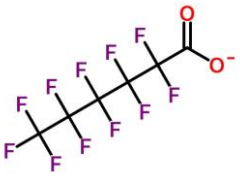
Summary of the Assessment of POP Characteristics of PFHxA and PFHx – comparison with the criteria of Annex D and other hazard indicators	
Persistence	**Meets the persistence criteria according to Annex D 1 (b)** • Data on the degradation half-life of PFHxA in soil, sediment, and water are not available. However, based on a read-across from degradation studies of PFOA, PFHxA is likely to be environmentally persistent. • PFHxA may meet the Annex D persistence criteria according to 1 (b) (ii).
Bioaccumulation	**Does not fulfill the bioaccumulation criteria according to Annex D 1 (c) (i)** • BCF (0.07 L/kg to <9 L/kg) and BAF (0.02 L/kg to <520 L/kg) values are well below the Annex D criteria of BCF >5,000 L/kg. • PFHxA is rarely detected in biota, and the limited number of studies of multiple wild organisms from the same food web indicates that PFHxA does not biomagnify. • Therefore, PFHxA is not expected to bioaccumulate to any significant degree.
Long-range Environmental Transport (LRET)	**Potential for long-range environmental transport is indeterminate** • Low concentrations of PFHxA have been detected in snow, sediment, and seawater in remote locations since the mid-1980s (e.g., ND-1,850 pg/L in seawater). Studies suggest that PFCA levels in the environment are primarily related to direct emissions (e.g., historical use of aqueous firefighting foams), rather than the degradation of PFHxA-precursors (Yarwood et al. 2007; Prevedouros et al. 2006). Additional data are necessary to determine if PFHxA concentrations in remote environments are of "potential concern" and meet the LRET criteria according to Annex D 1 (d) (i). • PFHxA is a strong acid that dissociates at environmentally relevant pHs. The anion, PFHx, is non-volatile, but highly soluble in water. Therefore, PFHxA and PFHx are unlikely to be transported long distances in the atmosphere.

Summary of the Assessment of POP Characteristics of PFHxA and PFHx – comparison with the criteria of Annex D and other hazard indicators	
	• Although PFHxA is unlikely to be transported long distances in the atmosphere, volatile PFHxA-precursors, such as 6:2 FTOH, may be subject to long-range atmospheric transport. However, PFHxA yields from 6:2 FTOH degradation have been shown to be relatively low.
Ecotoxicity	**Does not fulfill the REACH criterion for aquatic toxicity (NOEC < 0.01 mg/L)** • PFHxA is not significant toxicity to aquatic organisms, as no toxicity was reported in studies in fish, and EC50/LC50 levels in algae, diatoms and marine bacteria were 1,000 mg/L or more.
Toxicity to Human Health	**No evidence of significant toxicity at exposure levels likely to be encountered by humans** • Rat oral LD50 between 1,750 and 5,000 mg/kg. • Some toxic effects in liver at ≥100 mg/kg/day in subchronic studies. • No evidence of genotoxicity in bacteria or mammalian cells. • No evidence of reproductive or developmental toxicity in rodent studies, except reduced fetal weight, but only at maternally toxic dose levels (500 mg/kg/day). • No effects on neurobehavioral parameters during functional observational studies or motor activity assessments following 90 days or 2 years of daily oral dosing. • No evidence of carcinogenicity in 2-year bioassay in rats.

6.1 Identity and Physical and Chemical Properties

PFHxA is not currently manufactured or used in fluorinated polymer production. Instead, this compound is considered to be a potential degradation product of the 6:2 fluorotelomer compounds used to manufacture fluorinated polymers and other fluorotelomer-based products. However, PFCAs, including small amounts of PFHxA, were historically used in fluorinated polymer production, aqueous firefighting foams, water/grease repellents, and other commercial products. As such, PFCAs were released directly into the environment during the historical manufacture and use of PFCA-containing products (Prevedouros et al. 2006).

Table 6.1: Chemical Identity of PFHxA and PFHx

IUPAC Name	Common Name	Abbreviation	CAS Number	Molecular Weight (amu)	Chemical Structure
2,2,3,3,4,4,5,5,6,6,6-Undecafluorohexanoic acid	Perfluorohexanoic acid	PFHxA	307-24-4	314.05	
2,2,3,3,4,4,5,5,6,6,6-Undecafluoro-hexanoate	Perfluorohexanoate	PFHx	N/A	313.05	

PFHxA is a strong acid (pK_A <1) that dissociates at environmentally relevant pHs. The anion, PFHx, is highly water soluble and relatively non-volatile. The physical and chemical properties of PFHxA and PFHx are very different, as demonstrated in Tables 6.2 and 6.3.

Table 6.2: Physical and Chemical Properties of PFHxA

Property	Value	Reference and Remarks
Vapor pressure	114-121 Pa @ 25°C	Modeled[1]; Bhhatarai and Gramatica 2010 and Arp et al. 2006 as cited in Ding and Peijnenburg 2013
pKa	0.840 @ 25°C	Experimentally determined; Moroi et al. 2001 as cited in Ding and Peijnenburg 2013
Water solubility	<<29 mg/L	Solubility of protonated acid would be much lower than that of the anion
Partition coefficient n-octanol/water ($logK_{OW}$)	3.12-3.26	Modeled[1]; Arp et al. 2006 as cited in Armitage et al. 2009
Partition coefficient air/water ($logK_{AW}$)	~2.2	Calculated using a vapor pressure of 115 Pa and a solubility of 100 ppb (i.e., <<29 mg/L)
Partition coefficient octanol/air ($logK_{OA}$)	~1	Calculated from $logK_{OW}$ and $logK_{AW}$ ($logK_{OA} = logK_{OW} - logK_{AW}$)
[1] Modeled using property estimation software. These software packages are not known to accurately predict the physical and chemical properties of perfluorinated substances.		

Table 6.3: Physical and Chemical Properties of PFHx

Property	Value	Reference and Remarks
Vapor pressure	~0 Pa	Anions are essentially non-volatile
pKa	0.840 @ 25°C	Experimentally determined; Moroi et al. 2001 as cited in Ding and Peijnenburg 2013
Water solubility	29.5 mg/L @ 25°C	Modeled[1]; Bhhatarai and Gramatica 2010 as cited in Ding and Peijnenburg 2013
Partition coefficient n-octanol/water ($logK_D$) [2]	0.70 @ 22°C	Experimentally determined; Jing et al. 2006 as cited in Ding and Peijnenburg 2013
Partition coefficient air/water ($logK_{AW}$)	Very small (e.g., <-5)	$logK_{AW}$ will be very small because the vapor pressure is essentially 0
Partition coefficient octanol/air ($logK_{OA}$)	Very large (e.g., >5)	$logK_{OA}$ will be very large. For example, Rayne and Forest 2009 and Arp et al. 2006 modeled values between (5.24-7.08)
[1] Modeled using property estimation software. These software packages are not known to accurately predict the physical and chemical properties of perfluorinated substances. [2] $LogK_D$ is the analog to $LogK_{OW}$ for dissociating molecules.		

6.2 Environmental Fate

Although information on the environmental degradation of PFHxA is limited, the more extensively studied eight-carbon PFCA, PFOA, is stable under normal environmental conditions (Liou et al. 2010; Post et al. 2012). This suggests that PFHxA and PFHx are not likely to degrade under normal environmental conditions.

a) Abiotic degradation

No data available in the studies reviewed.

b) Hydrolysis

No data available in the studies reviewed.

c) Phototransformation/photolysis

Limited experimental data suggest that PFCAs may react with photochemically-generated hydroxyl radicals in the atmosphere. Taniyasu et al. (2013a) conducted a field study on the photolysis of perfluoroalkyl substances at Mt. Mauna Kea, Hawaii (4200 m). PFHxA concentrations decreased by 0.8% after 106 days of solar irradiation. This suggests that the atmospheric oxidation of PFHxA occurs extremely slowly and is not expected to impact the half-life of PFHxA in the atmosphere.

d) Biodegradation

Although, the biodegradation of PFHxA has not been directly studied, PFHxA is a metabolite of 6:2 FTOH degradation (Butt et al. 2014). Studies of 6:2 FTOH degradation in soil and sediment do not indicate that PFHxA completely mineralizes with a half-life less than the six month criterion listed in Annex D 1 (b) (i).

e) Potential for long-range environmental transport

Researchers have detected PFHxA in urban and remote environments. In general, PFHxA measurements in remote environments, such as the Arctic, have focused on snow, sediment, and seawater. Snow cores collected by Wang et al. (2013) suggest that PFHxA was deposited on the Tibetan Plateau as early as 1985-1986. PFHxA concentrations in snow in this region increased from 22 pg/L in the mid-1980s to 100 pg/L in 1999 (Wang et al. 2013). More recently, Theobald et al. measured PFHxA at relatively low concentrations (10–34.8 pg/L) in surface snow in Greenland (Theobald et al. 2007 as cited in Butt et al. 2010).

Kallenborn et al. measured PFHxA in Faroe Island sediment at 0.35 ng/g wet weight, but did not detect PFHxA in marine sediment from Gufunes Bay, Iceland (Kallenborn et al. 2004 as cited in Butt et al. 2010). Lastly, in addition to the measurements in Table 6.4, Rosenberg et al. also detected PFHxA in seawater collected from the Arctic and Subarctic in the Canadian archipelago (Rosenberg et al. 2008 as cited in Butt et al. 2010).

Table 6.4: Identification of PFHxA in Remote Environments

Location	Year	Conc. (pg/L)	Reference
Iceland and Faroe Islands	Not listed	630-1850	Kallenborn et al. 2004 as cited in Butt et al. 2010
Greenland Sea	2004	10.2-37.6	Theobald et al. 2007 as cited in Butt et al. 2010
North Atlantic Ocean	2007	<5.7-127	Ahrens et al. 2009
Middle Atlantic Ocean	2007	<5.7	
Southern Atlantic Ocean	2007	<5.7	
Greenland Sea	2009-2010	<5.9-38	Zhao et al. 2012
Northern Atlantic Ocean	2009-2010	<5.7-88	
Middle Atlantic Ocean	2009-2010	<5.7-38	
Southern Atlantic Ocean	2009-2010	<5.7-26	
Eastern Greenland Arctic Ocean	2009	ND-22.0	Busch et al. 2010

While the remote monitoring data is suggestive of long-range transport, most researchers do not believe that PFHxA is transported long distances in the atmosphere. Instead, two alternative theories have been proposed to account for PFCA measurements in remote environments. The first is the indirect transport of volatile PFCA-precursors (e.g., FTOHs) in the atmosphere. These precursors eventually oxidize to PFCA and are deposited in remote environments, such as the Arctic. The second is the direct transport of PFCAs in seawater due to ocean currents. There is evidence to support both theories and PFCAs likely migrate by a combination of transport mechanisms. Lastly, there is the possibility that local or regional emission sources contribute to PFHxA concentrations in remote environments, although the impact such sources has not been thoroughly investigated.[4]

Several studies support the hypothesis that PFHxA may be transported through volatile precursors, such 6:2 FTOH. First, 6:2 FTOH has a sufficient atmospheric lifetime to undergo long-range transport. Piekarz et al. (2007) calculated an atmospheric half-life of 50 days for 6:2 FTOH, which is longer than the two-day criterion listed in Annex D 1 (d) (iii). Additionally, 6:2 FTOH has been detected in Arctic air and FTOHs have been shown to degrade to PFCAs (Young and Mabury 2010). Finally, PFCAs, including PFHxA, have been detected in precipitation and surface snow in remote environments (e.g., Taniyasu et al. 2013b; Wang et al. 2013).

[4] Although a thorough review of PFHxA emissions in the Arctic and other remote environments was not conducted, four million people live above the Arctic Circle. This area also has a large number of air strips and airports. Further, many remote areas are home to industrial mining operations, oil production activities, and military bases, which conduct firefighting activities and may have historically used aqueous fire-fighting foams containing perfluorinated compounds (Collins 1998).

Evidence to support the direct transport of PFHxA by ocean currents consists of modeling studies and measurements of PFHxA in seawater. Although modeling studies have focused on PFOA fluxes to the Arctic, these studies suggest that ocean transport may deliver PFCAs more efficiently to Arctic surface waters than atmospheric transport. The reasons for this are twofold. First, historic emissions of PFCA-precursors are much lower than direct PFCA emissions. Secondly, FTOHs have a relatively low conversion rate to PFCAs in the atmosphere (Yarwood et al. 2007; Armitage et al. 2006 and Wallingford et al. 2006 as cited in Butt et al. 2010).

Although not generally considered a major transport pathway, some researchers have suggested that PFCAs could be directly transported in the atmosphere since these substances were recently detected in the vapor phase in outdoor air samples (CEMN 2008 and Prevedouros et al. 2006 as cited in ATSDR 2009). Additionally, ASTDR estimates that PFCAs have an atmospheric half-life on the order of 10 days, due to wet and dry deposition (ATSDR 2009). These findings are not specific to PFHxA and are accordingly considered suggestive.

f) Bioaccumulation

Empirical Bioaccumulation Evidence from Aquatic Species/Log K_{OW}

Several controlled laboratory and field bioaccumulation experiments with aquatic species indicate that PFHxA is not a bioaccumulative substance. BCF and BAF values are all significantly below the Annex D Bioaccumulation Criteria of > 5000 L/kg (Table 6.5), indicating a lack of bioaccumulation potential. All studies reported undetectable concentrations in organism tissues. BCF and BAF values were estimated by dividing method detection limits in tissue by the exposure concentration in the water to which organisms were exposed, or via models that rely on non-detect data in tissue. Thus, the values shown in Table 6.5 represent maximum values and indicate all available BCF and BAF values for PFHxA are less than 500 L/kg, which is at least 10 times less than the Annex D Bioaccumulation Criterion of BCF or BAF values > 5000 L/kg.

An additional study on the uptake of PFHxA by marine ogliochetes in sediment also determined a BSAF of 2.2 to 3.5 g, dw/g, ww, indicating some uptake of PFHxA into sediment dwelling invertebrates (Lasier et al. 2011). However PFHxA does not accumulate in predators of invertebrates as indicated by Martin et al. (2003b). There are currently no regulatory screening criteria for bioaccumulation based on BSAFs in sediment, however typically BSAFs > 1 are associated with a potential for bioaccumulation.

The Log K_{OW} for PFHxA is well below the Annex D Bioaccumulation Criteria of 5, indicating an absence of bioaccumulation potential; however, K_{OW} values are not an appropriate measure of bioaccumulation potential for surfactants as discussed above for 6:2 FTOH and by Conder et al. (2008).

Empirical Bioaccumulation Evidence from Other Species/High Ecotoxicity Concerns

Controlled laboratory bioaccumulation experiments with terrestrial worms indicate that BSAF values for PFHxA are greater than 1 g, dw/g, ww (Table 6.5). Although there are no formal criteria for interpreting BSAF values, BSAF values greater than one indicate that PFHxA may accumulate from soil or sediment to invertebrates.

BSAFs for a number of terrestrial plants were available in the literature, ranging from 0.3 to 7.7 g, dw/g, ww for plants (Table 6.5).

Although the above data suggest some minor potential for bioaccumulation from soil, this bioaccumulation potential is insignificant to higher trophic level predators of worms and plants because PFHxA is not bioaccumulated from the diet, as indicated in a study with fish (Martin et al. 2003b).

As discussed below, PFHxA does not exhibit high ecotoxicity that would supersede the evidence that PFHxA does not exhibit bioaccumulation potential according to Annex D.

Wildlife Monitoring Data

Two studies reporting monitoring data from multiple trophic levels of the same food web indicate a lack of bioaccumulation potential for PFHxA:

- Falandysz et al. (2007) evaluated PFCAs in multiple species in Poland. While PFHxA was detected at low levels in beaver (liver sample, 0.08 ng/g ww) and cod (0.17 pg/mL whole blood), it was not detected in predators of cod (velvet scoter, eider duck, long-tailed duck, red-throated diver, and razorbill were all < 0.05 ng/g ww). The lower concentrations in predators indicate that PFHxA did not biomagnify, indicating a lack of bioaccumulation potential for PFHxA.

- Llorca et al. (2012) evaluated PFCAs in biota in the Antarctic and Tierra del Fuego. Due to sampling restrictions, multiple species of the same food chain were only collected from Tierra del Fuego. The highest concentrations of PFHxA in biota were observed in lower trophic levels such as algae (4 to 200 ng/g) and fish (207 to 232 ng/g liver) collected in Tierra del Fuego. While algae are not a common diet item of the fish sampled in this study (rainbow trout), similar concentrations of PFHxA in the lower and upper trophic levels of Tierra del Fuego indicate a lack of bioaccumulation. Concentrations in penguins in Antarctica were not detectable (< 2.28 ng/g), although the concentration of PFHxA in their dung ranged from 20 to 237 ng/g. Assuming that concentrations of PFHxA in dung are at least partly reflective of concentrations in the diet item originally consumed, a biomagnification factor is likely much less than 0.1 kg diet/kg penguin tissue. This indicates a lack of bioaccumulation potential for PFHxA.

A small number of additional studies have detected PFHxA in biota from various locations around the world, including the Antarctic and Arctic (Falandysz et al. 2006, 2007; Llorca et al. 2012; Keller et al. 2005; Wang et al. 2008; D'Hollander et al 2010). Detection of PFHxA in wildlife in remote locations may indicate evidence of long-range transport; however, the

detection of chemicals in wildlife does not necessarily imply high bioaccumulation potential for a chemical (Conder et al. 2008). Bioaccumulation potential in chemical registration and classification programs is evaluated on the basis of metrics calculated from chemical concentrations in multiple environmental compartments, such as an organism and its food, its water, or the food web to which it belongs (Gobas et al. 2009; Conder et al. 2012). Detection of a chemical in an organism may be simply a reflection of extremely sensitive analytical chemistry techniques, not evidence of significant bioaccumulation potential.

Table 6.5: Bioaccumulation Metrics for PFHxA/PFHx *

Species	Common Name	BCF	BAF	BSAF	Units	Basis	Reference
Oncorhynchus mykiss	Rainbow trout		0.02		L/kg	Regression model	Martin et al. 2003b
Oncorhynchus mykiss	Rainbow trout	0.07			L/kg	Regression model	Martin et al. 2003a
Oncorhynchus mykiss	Rainbow trout	< 1			L/kg	Modelled	Rayne et al. 2009
Oncorhynchus mykiss	Rainbow trout	< 9			L/kg	Lab	Yeung & Mabury 2013
Mugil cephalus	Sea mullet		< 270		L/kg	Field	Thompson et al. 2011
Saccostrea commercialis	Oyster		< 520		L/kg	Field	Thompson et al. 2011
Lumbriculus variegatus	Freshwater worm			2.5 - 3.3	g, dw/g, ww	Lab	Lasier et al. 2011
Eisenia fetida	Earthworm			0.5 – 1.6	g, dw/g, ww	Lab	Zhao et al. 2014
Eisenia fetida	Earthworm			0.87 ± 0.08	g, dw/g, ww	Lab	Zhao et al. 2013
Triticum aestivum	Wheat			5.7 – 7.7	g, dw/g, ww	Lab	Zhao et al. 2014
Lactuca sativa	Lettuce			1.17 ± 0.21	g, dw/g, ww	Lab	Blaine et al. 2013
Lactuca sativa	Lettuce			0.99 ± 0.14	g, dw/g, ww	Lab	Blaine et al. 2013
Lycopersicon lycopersicum	Tomato			0.29 ± 0.09	g, dw/g, ww	Lab	Blaine et al. 2013
Lycopersicon lycopersicum	Tomato			0.68 ± 0.08	g, dw/g, ww	Field	Blaine et al. 2013
Lolium arundinaceum	Tall fescue grass			0.34	g, dw/g, ww	Field	Yoo et al. 2011

*Under most environmental and biological pH levels, PFHx is likely to be the predominant form of PFHxA.

6.3 Human Health Hazard Assessment

In general, the toxicity of PFHxA is low based on the evidence below. This may in part be due to its rapid elimination in mammalian blood. In a study of PFHx absorption, distribution, metabolism, and excretion in mice and rats, Gannon and colleagues (2011) noted that essentially 100% of the dose was eliminated in urine within 24 hours, and that the route and extent of elimination was unchanged after 14 days of daily dosing. PFHx was also not quantifiable in all tissues except skin at time points ranging from 0.5 to 24 hours following dosing. The authors noted that though PFHx is present in the environment at levels similar to PFOA and PFOS, human blood monitoring data indicates much lower (often undetectable) amounts of PFHx. The authors concluded that this finding strongly suggests that humans rapidly eliminate PFHx similarly to rats and mice (Gannon et al. 2011).

Russell and colleagues (2013) analyzed biomonitoring data in a cohort of professional ski wax technicians to estimate the apparent half-life of PFHxA in humans. Comparisons were also made with the kinetic studies of PFHx elimination from mice, rats, and monkeys. The apparent elimination half-life of PFHx in highly exposed humans ranged between 13 and 49 days with a geometric mean of 32 days. The authors noted that the half-lives of PFHx in mice, rats, monkeys, and humans were proportional to body weight with no differences observed between genders, indicating similar volumes of distribution and similar elimination mechanisms among mammalian species. The authors concluded that PFHx is rapidly eliminated compared to long-chain perfluoroalkyl acid homologs and that the results in this study suggest that results obtained from animal models are suitable for the establishment of PFHx benchmark dose and reference dose hazard endpoints used in human risk assessments (Russell et al. 2013). By contrast, the human elimination half-life of perfluorooctanoate has been estimated as 3.5 to 4.4 years (Olsen et al. 2007; Butenhoff et al. 2004), indicating a relatively low potential for accumulation of PFHx in the body.

a) Acute and repeat-dose toxicity

Toxic effects following acute doses have not been reported in studies of monkeys, rats, or mice with dose levels at or below 100 mg/kg (Chengelis et al. 2009a; Gannon et al. 2011; Loveless et al. 2009). All rats dosed with 175 or 550 mg/kg survived, whereas one of four rats dosed with 1,750 mg/kg died on the day of dosing, and all three rats dosed with 5,000 mg/kg died on the day of dosing (Loveless et al. 2009). Clinical signs of systemic toxicity were observed in most rats receiving doses from 175 to 5,000 mg/kg of the sodium salt of PFHxA (NaPFHx); however, no specific NOAEL or LOAEL is provided for systemic toxicity following the acute dosing (Loveless et al. 2009).

Toxic effects following subchronic dosing in rats and mice from 14-90 days have been reported in two of four studies. Among the two studies with no reported adverse effects in rats or mice, doses were as high as 100 mg/kg/day (Chengelis et al. 2009a; Gannon et al. 2011). Though no clinical signs of toxicity or mortality were observed in the other two studies at dose levels up to 500 mg/kg/day, doses as low as 10 mg/kg/day resulted in lower body weight gains in male rats (Chengelis et al. 2009b). Reversible clinical pathology changes, including liver histopathology and weight changes, were observed at doses of at least 100 mg/kg/day (Chengelis et al. 2009b; Loveless et al. 2009). NOAELs of 50

mg/kg/day and 200 mg/kg/day were noted for male and female rats, respectively, based on liver weight increases and hepatocellular hypertrophy (Chengelis et al. 2009b).

A 24-month chronic toxicity study was carried out on rats that received oral doses of 2.5, 15, and 100 mg/kg/day for males and 5, 30, and 200 mg/kg/day for females. There were no PFHxA-related effects on body weight, food consumption, functional observational battery, hematology, serum chemistry, or hormone parameters. However, the authors identified NOAELs of 15 mg/kg/day for males and 30 mg/kg/day for females based on non-neoplastic systemic toxicity observed in the highest dose groups of males and females. These effects involved histological changes in the kidneys of the 200 mg/kg/day female group and lower urine pH values in the 100 mg/kg/day male group (Asahi and Daikin-WIL-534009).

b) Mutagenicity and carcinogenicity

Two studies have investigated the potential mutagenicity of PFHxA. PFHxA did not generate reactive oxygen species or cause DNA damage in human HepG2 cells (Eriksen et al. 2010), and was found not to be genotoxic based on negative results from both the bacterial reverse mutation assay and the *in vitro* chromosomal aberration assay (Loveless et al. 2009).

The potential carcinogenicity of PFHxA was also investigated in the 24-month chronic toxicity study of rats discussed previously. Overall, about 300 rats receiving treatment with PFHxA were assigned to the 2-year carcinogenicity phase of the study, in addition to a control group of about 50 rats receiving a vehicle control of deionized water. There was no evidence that PFHxA induced tumorigenesis in the 24-month oral gavage study in male or female rats at doses of 2.5, 15, and 100 mg/kg/day for males and 5, 30, and 200 mg/kg/day for females; thus, NOAELs for neoplasia of 100 mg/kg/day for males and 200 mg/kg/day for females, the highest dosages examined, were identified (Asahi and Daikin-WIL-534009).

c) *Reproductive and Developmental Toxicity*

Loveless and colleagues (2009) observed decreases in maternal and fetal rat weights following 500 mg/kg/day, but no effects on other developmental indices such as fetal, visceral, or skeletal variations were observed at any dose. Reproductive effects were limited to decreases in maternal body weight gains and F1 pup weights at 500 mg/kg/day. No mortality or effects were observed at any dose on any reproductive indices including mating, fertility, gestation length, number of implantation sites, estrous cyclicity, sperm parameters, litter size, sex ratio, and pup clinical observations. A maternal and developmental NOAEL for developmental toxicity of 100 mg/kg/day was identified. For the reproductive portion of the 90-day subchronic study, the P1 adult rat NOAEL was 20 mg/kg/day, based on reduced body weight parameters, whereas the NOAEL for reproductive toxicity was 100 mg/kg/day, based on reduced F1 pup weights.

d) *Neurotoxicity*

The authors of three studies have reported no neurotoxic effects in rats following oral dosing of PFHxA as high as 500 mg/kg. Loveless and colleagues (2009) noted that clinical signs of

systemic toxicity were observed in most rats exposed to acute doses of PFHxA ranging from 175 to 5,000 mg/kg, which included potential signs of neurotoxicity including abnormal gait and ataxia. However, no specific NOAEL or LOAEL is provided for symptoms of systemic toxicity following the acute dosing. The authors further noted that no effects on any neurobehavioral endpoints were observed in the subchronic study involving doses up to 500 mg/kg/day for 90 days. Chengelis et al. (2009b) also reported that no changes in autonomic and central nervous system function or somatomotor activity and behavior patterns were observed following oral doses of 10, 50, or 200 mg/kg/day for 90 days in rats. The authors (Daikin-WIL-534009) noted that no PFHxA-related effects on motor-activity assessments were observed in rats chronically exposed to up to 200 mg/kg/day for 24 months.

e) *Immunotoxicity*

No indications of immune system-related effects (e.g., spleen, thymus, lymph node weights/histopathology) were observed following 90 days or 2 years of daily oral dosing (Chengelis et al. 2009b; Asahi and Daikin-WIL-534009).

f) Acceptable exposure levels

In a health risk assessment of 17 perfluoroalkylated and polyfluoroalkylated substances, Borg et al. (2013) identified various substances, including PFHxA, in serum in the general population and among occupationally exposed individuals in Sweden (<0.22 ng/ml and 24 ng/ml, respectively). They also identified hepatotoxicity NOAELs (external dose: 20 mg/kg bw/day; internal dose: 6.2 µg/ml serum) and reproductive NOAELs (external dose: 100 mg/kg bw/day; internal dose: 11.9 µg/ml serum) based on animal studies. Borg et al. (2013) concluded that there was no safety concern for PFHxA based on these NOAELs and observed exposure levels in the general or occupationally exposed population.

6.4 Environmental Hazard Assessment

a) Aquatic compartment (including sediment)

PFHxA has low toxicity to aquatic species, based on laboratory toxicity data (Table 6.6). A 28-day, chronic study of effects on early life stages of rainbow trout indicated a chronic NOEC greater than 10.1 mg/L – the highest tested concentration in the study (Daikin-2901/001). The chronic NOEC for rainbow trout is at least approximately 100 times higher than the REACH Toxicity criterion, therefore PFHxA would not be considered toxic under REACH PBT criteria. Another prolonged acute study by Martin et al. (2003a) determined a NOEC during a bioaccumulation test where rainbow trout were exposed to low concentrations of PFCAs. No effects to growth rates were observed at the test concentration for PFHxA (0.0017 mg/L). The test concentration is reported as the NOEC in Table 6.6; however the true (bounded) NOEC is greater than the reported NOEC by an unknown amount. Liu et al. (2008) observed a lower NOEC (>628 mg/L) for the algae *Scenedesmus obliquus,* based on growth rate; however, this was the highest concentration tested and so the true (bounded) NOEC is unknown.

Additional acute studies focusing on effects to algae by Latała et al. (2009) result in acute, EC50 values ranging from 999 to 4,032 mg/L for growth inhibition based on biomass. Additionally, Mulkeiwicz et al. (2007) observed an EC50 for inhibition of bioluminescence of marine algae of 1,339 mg/L. These tests were all acute studies using nominal, rather than measured concentrations of PFHxA, therefore are less reliable for use in the toxicity assessment than the Daikin-2901/001 and Martin et al. (2003a) studies. The results of the acute studies reviewed indicate PFHxA would be regarded as “practically non-toxic” (EC50/LC50 > 100 mg/L) (ECHA 2011).

b) Terrestrial compartment

Zhao et al. (2014) performed bioaccumulation studies on PFCAs for earthworm and wheat, while monitoring changes to weight of earthworms and biomass of wheat between treatment and control groups. At their highest test concentration, no significant differences were seen between control and treatment groups and all sample organisms appeared in good health. A NOEC was determined to be greater than 1 mg/kg, dw (the highest test concentration used), indicating low toxicity to terrestrial plants and invertebrates.

Table 6.6: Ecotoxicity Data for PFHxA/PFHx

Species Name	Common Name	Effects Endpoint	Test Conditions	Duration	Acute or Chronic	Exposure Basis	NOEC	EC50/ LC50	Units	Reference
Oncorhynchus mykiss	Rainbow trout	Growth	Flow through	12-days	Prolonged acute	Measured	≥ 0.0017		mg/L	Martin et al. 2003a
Oncorhynchus mykiss	Rainbow trout	Hatching success of eggs	Flow through	56-day	Chronic	Measured	≥ 10.1		mg/L	Daikin-2901/001
Oncorhynchus mykiss	Rainbow trout	28-day post-hatch survival, length and weight of hatchlings	Flow through	56-day	Chronic	Measured	≥ 10.1		mg/L	Daikin-2901/001
Chlorella vulgaris	Green algae	Growth Inhibition	Static	72-hour	Acute	Nominal		4,032	mg/L	Latała et al. 2009
Geitlerinema amphibium	Blue-green algae	Growth Inhibition	Static	72-hour	Acute	Nominal		998.7	mg/L	Latała et al. 2009
Scenedesmus obliquus	Green algae	Growth Inhibition	Static	72-hour	Chronic	Nominal	≥ 628		mg/L	Liu et al. 2008
Scenedesmus subspicatus	Green algae	Growth Inhibition	Static	72-hour	Chronic	Nominal	50	86	mg/L	AsahiGlass Co. 1742-020
Skeletonema marinoi	Diatom	Growth Inhibition	Static	72-hour	Acute	Nominal		1,482	mg/L	Latała et al. 2009
Vibrio fischeri	Marine bacteria	Bioluminescence Inhibition	Static	30-min	Acute	Nominal		1,339	mg/L	Mulkeiwicz et al. 2007
Eisenia fetida	Earthworm	Weight	Static	30-days	Chronic	Nominal	> 1		mg/kg, dw	Zhao et al. 2014
Triticum aestivum	Wheat	Biomass	Static	30-days	Chronic	Nominal	> 1		mg/kg, dw	Zhao et al. 2014

*Under most environmental and biological pH levels, PFHx is likely to be the predominant form of PFHxA.

6.5 References

Asahi and Daikin Industries. 2010. *A 24-month oral (gavage) combined chronic toxicity/carcinogenicity study of perfluorohexanoic acid (PFHxA) in Rats*. Report Number WIL-534009.

Agency for Toxic Substances and Disease Registry (ATSDR). 2009. *Toxicological Profile for Perfluoroalkyls*. Atlanta, Georgia.

Armitage JM, MacLeod M, and Cousins IT. 2009. Comparative assessment of the global fate and transport pathways of long-chain perfluorocarboxylic acids (PFCAs) and perfluorocarboxylates (PFCs) emitted from direct sources. *Environ Sci Technol* 43:5830-5836.

Asahi. 2004. *PFHA: algal Inhibition Test*. Report Number 1742/020.

Blaine AC, Rich CD, Hundal LS, Lau C, Mills MA, Harris KM, and Higgins CP. 2013. Uptake of Perfluoroalkyl Acids into Edible Crops via Land Applied Biosolids: Field and Greenhouse Studies. *Environ Sci Technol* 47:14062-14069.

Borg D, Lund BO, Lindquist NG, and Hakansson H. 2013. Cumulative health risk assessment of 17 perfluoroalkylated and polyfluoroalkylated substances (PFASs) in the Swedish population. *Environ Int* 59:112-123.

Busch J, Ahrens L, Xie Z, Sturm R, and Ebinghaus R. 2010. Polyfluoroalkyl compounds in the East Greenland Arctic Ocean. *J Environ Monit* 12:1242-1246.

Butenhoff JL, Gaylor DW, Moore JA, Olsen GW, Rodricks J, Mandel JH, Zobel LR. 2004. Characterization of risk for general population exposure to perfluorooctanoate. *Regul Toxicol Pharmacol.* 39(3):363-80.

Butt CM, Berger U, Bossi R, and Tomy GT. 2010. Levels and trends of poly- and perfluorinated compounds in the arctic environment. *Sci Total Environ* 408:2936-2965.

Butt CM, Muir DC, and Mabury SA. 2014. Biotransformation pathways of fluorotelomer-based polyfluoroalkyl substances: A review. *Environ Toxicol Chem* 33:243-267.

Chengelis CP, Kirkpatrick JB, Myers NR, Shinohara M, Stetson PL, and Sved DW. 2009a. Comparison of the toxicokinetic behavior of perfluorohexanoic acid (PFHxA) and nonafluorobutane-1-sulfonic acid (PFBS) in cynomolgus monkeys and rats. *Reprod Toxicol* 27:400-406.

Chengelis CP, Kirkpatrick JB, Radovsky A, and Shinohara M. 2009b. A 90-day repeated dose oral (gavage) toxicity study of perfluorohexanoic acid (PFHxA) in rats (with functional observational battery and motor activity determinations). *Reprod Toxicol* 27:342-351.

Collins JM. 1998. Military Geography for Professional and the Public. National Defense University Press, Washington, DC.

Conder JM, Hoke RA, de WW, Russell MH, and Buck RC. 2008. Are PFCAs bioaccumulative? A critical review and comparison with regulatory criteria and persistent lipophilic compounds. *Environ Sci Technol* 42:995-1003.

Conder JM, Gobas FA, Borga K, Muir DC, and Powell DE. 2012. Use of trophic magnification factors and related measures to characterize bioaccumulation potential of chemicals. *Integr Environ Assess Manag* 8:85-97.

D'Hollander W, de VP, De CW, and Bervoets L. 2010. Perfluorinated substances in human food and other sources of human exposure. *Rev Environ Contam Toxicol* 208:179-215.

Daikin Industries. 2008. *PFH Ammonium Salt: Fish, Early Life Stage Toxicity Test to Oncorhynchus mykiss (Rainbow Trout)*. Report Number 2901/001.

Ding G and Peijnenburg WJGM. 2013. Physicochemical Properties and Aquatic Toxicity of Poly- and Perfluorinated Compounds. *Critical Reviews in Environmental Science and Technology* 43:598-678.

European Chemicals Agency (ECHA). 2011. Guidance on the Application of the CLP Criteria. ECHA-11-G-06-EN.

European Chemicals Agency (ECHA). 2012. *Guidance on information requirements and chemical safety assessment: Chapter R.11: PBT Assessment*.

Eriksen KT, Raaschou-Nielsen O, Sorensen M, Roursgaard M, Loft S, and Moller P. 2010. Genotoxic potential of the perfluorinated chemicals PFOA, PFOS, PFBS, PFNA and PFHxA in human HepG2 cells. *Mutat Res* 700:39-43.

Falandysz J, Taniyasu S, Yamashita N, Jecek L, Rostkowski P, Gulkowska A, Mostrag A, Walczykiewicz B, Zegarowski L, Falandysz J, and Zalewski K. 2006. [Perfluorinated chemicals in the environment, food and human body]. *Rocz Panstw Zakl Hig* 57:113-124.

Falandysz J, Taniyasu S, Yamashita N, Rostkowski P, Zalewski K, and Kannan K. 2007. Perfluorinated compounds in some terrestrial and aquatic wildlife species from Poland. *J Environ Sci Health A Tox Hazard Subst Environ Eng* 42:715-719.

Gannon SA, Johnson T, Nabb DL, Serex TL, Buck RC, and Loveless SE. 2011. Absorption, distribution, metabolism, and excretion of [1-(1)(4)C]-perfluorohexanoate ([(1)(4)C]-PFHx) in rats and mice. *Toxicology* 283:55-62.

Gobas FA, de WW, Burkhard LP, Verbruggen E, and Plotzke K. 2009. Revisiting bioaccumulation criteria for POPs and PBT assessments. *Integr Environ Assess Manag* 5:624-637.

Keller JM, Kannan K, Taniyasu S, Yamashita N, Day RD, Arendt MD, Segars AL, and Kucklick JR. 2005. Perfluorinated compounds in the plasma of loggerhead and Kemp's ridley sea turtles from the southeastern coast of the United States. *Environ Sci Technol* 39:9101-9108.

Lasier PJ, Washington JW, Hassan SM, and Jenkins TM. 2011. Perfluorinated chemicals in surface waters and sediments from northwest Georgia, USA, and their bioaccumulation in Lumbriculus variegatus. *Environ Toxicol Chem* 30:2194-2201.

Latala A, Nedzi M, and Stepnowski P. 2009. Acute toxicity assessment of perfluorinated carboxylic acids towards the Baltic microalgae. *Environ Toxicol Pharmacol* 28:167-171.

Liu W, Chen S, Quan X, and Jin YH. 2008. Toxic effect of serial perfluorosulfonic and perfluorocarboxylic acids on the membrane system of a freshwater alga measured by flow cytometry. *Environ Toxicol Chem* 27:1597-1604.

Llorca M, Farre M, Tavano MS, Alonso B, Koremblit G, and Barcelo D. 2012. Fate of a broad spectrum of perfluorinated compounds in soils and biota from Tierra del Fuego and Antarctica. *Environ Pollut* 163:158-166.

Loveless SE, Slezak B, Serex T, Lewis J, Mukerji P, O'Connor JC, Donner EM, Frame SR, Korzeniowski SH, and Buck RC. 2009. Toxicological evaluation of sodium perfluorohexanoate. *Toxicology* 264:32-44.

Martin JW, Mabury SA, Solomon KR, and Muir DC. 2003a. Dietary accumulation of perfluorinated acids in juvenile rainbow trout (Oncorhynchus mykiss). *Environ Toxicol Chem* 22:189-195.

Martin JW, Mabury SA, Solomon KR, and Muir DC. 2003b. Bioconcentration and tissue distribution of perfluorinated acids in rainbow trout (Oncorhynchus mykiss). *Environ Toxicol Chem* 22:196-204.

Mulkiewicz E, Jastorff B, Skladanowski AC, Kleszczynski K, and Stepnowski P. 2007. Evaluation of the acute toxicity of perfluorinated carboxylic acids using eukaryotic cell lines, bacteria and enzymatic assays. *Environ Toxicol Pharmacol* 23:279-285.

Olsen GW, Burris JM, Ehresman DJ, Froehlich JW, Seacat AM, Butenhoff JL, Zobel LR. 2007. Half-life of serum elimination of perfluorooctanesulfonate, perfluorohexanesulfonate, and perfluorooctanoate in retired fluorochemical production workers. *Environ Health Perspect*. 115(9):1298-305.

Piekarz AM, Primbs T, Field JA, Barofsky DF, and Simonich S. 2007. Semivolatile fluorinated organic compounds in Asian and western U.S. air masses. *Environ Sci Technol* 41:8248-8255.

Post GB, Cohn PD, Cooper KR. 2012. Perfluorooctanoic acid (PFOA), an emerging drinking water contaminant: A critical review of recent literature. *Environmental Research* 116: 93-117.

Prevedouros K, Cousins IT, Buck RC, and Korzeniowski SH. 2006. Sources, fate and transport of perfluorocarboxylates. *Environ Sci Technol* 40:32-44.

Rayne S, Forest K, and Friesen KJ. 2009. Estimated bioconcentration factors (BCFs) for the C(4) through C(8) perfluorinated alkylsulfonic acid (PFSA) and alkylcarboxylic acid (PFCA) congeners. *J Environ Sci Health A Tox Hazard Subst Environ Eng* 44:598-604.

Rayne S and Forest K. 2009. Perfluoroalkyl sulfonic and carboxylic acids: a critical review of physicochemical properties, levels and patterns in waters and wastewaters, and treatment methods. *J Environ Sci Health A Tox Hazard Subst Environ Eng* 44:1145-1199.

Russell MH, Nilsson H, and Buck RC. 2013. Elimination kinetics of perfluorohexanoic acid in humans and comparison with mouse, rat and monkey. *Chemosphere* 93:2419-2425.

Taniyasu S, Yamashita N, Yamazaki E, Petrick G, and Kannan K. 2013a. The environmental photolysis of perfluorooctanesulfonate, perfluorooctanoate, and related fluorochemicals. *Chemosphere* 90:1686-1692.

Taniyasu S, Yamashita N, Moon HB, Kwok KY, Lam PK, Horii Y, Petrick G, and Kannan K. 2013b. Does wet precipitation represent local and regional atmospheric transportation by perfluorinated alkyl substances? *Environ Int* 55:25-32.

Thompson J, Roach A, Eaglesham G, Bartkow ME, Edge K, and Mueller JF. 2011. Perfluorinated alkyl acids in water, sediment and wildlife from Sydney Harbour and surroundings. *Mar Pollut Bull* 62:2869-2875.

Wang Y, Yeung LW, Taniyasu S, Yamashita N, Lam JC, and Lam PK. 2008. Perfluorooctane sulfonate and other fluorochemicals in waterbird eggs from south China. *Environ Sci Technol* 42:8146-8151.

Wang J, Zhang Y, Zhang F, Yeung LW, Taniyasu S, Yamazaki E, Wang R, Lam PK, Yamashita N, and Dai J. 2013. Age- and gender-related accumulation of perfluoroalkyl substances in captive Chinese alligators (Alligator sinensis). *Environ Pollut* 179:61-67.

Yarwood G, Kemball-Cook S, Keinath M, Waterland RL, Korzeniowski SH, Buck RC, Russell MH, and Washburn ST. 2007. High-resolution atmospheric modeling of fluorotelomer alcohols and perfluorocarboxylic acids in the North American troposphere. *Environ Sci Technol* 41:5756-5762.

Yeung LW and Mabury SA. 2013. Bioconcentration of aqueous film-forming foam (AFFF) in juvenile rainbow trout (Oncorhyncus mykiss). *Environ Sci Technol* 47:12505-12513.

Yoo H, Washington JW, Jenkins TM, and Ellington JJ. 2011. Quantitative determination of perfluorochemicals and fluorotelomer alcohols in plants from biosolid-amended fields using LC/MS/MS and GC/MS. *Environ Sci Technol* 45:7985-7990.

Young CJ and Mabury SA. 2010. Atmospheric perfluorinated acid precursors: chemistry, occurrence, and impacts. *Rev Environ Contam Toxicol* 208:1-109.

Zhao S, Fang S, Zhu L, Liu L, Liu Z, and Zhang Y. 2014. Mutual impacts of wheat (Triticum aestivum L.) and earthworms (Eisenia fetida) on the bioavailability of perfluoroalkyl substances (PFASs) in soil. *Environ Pollut* 184:495-501.

Zhao Z, Xie Z, Moller A, Sturm R, Tang J, Zhang G, and Ebinghaus R. 2012. Distribution and long-range transport of polyfluoroalkyl substances in the Arctic, Atlantic Ocean and Antarctic coast. *Environ Pollut* 170:71-77.

Appendix A

Persistence and Long-range Transport Studies

Appendix B

Toxicity and Health Effects Studies

Appendix C

Bioaccumulation and Ecotoxicity Studies

Appendix D

List of References Reviewed