

# 6:2 Fluorotelomer Sulfonate (6:2 FTS)

## TOXICOLOGY AT A GLANCE



6:2 FTS

- In 2012-2015, the U.S. metal plating industry transitioned from PFOS to short-chain fluorotelomers (e.g., 6:2) FTS in their chromium electroplating processes.
- The standard suite of tests conducted for regulatory approval of industry manufacture and use is available for 6:2 FTS.
- Based on currently available data, 6:2 FTS is less toxic and less persistent in the environment compared to PFOS and does not bioaccumulate.

### Mammalian Toxicology

- ✓ Several short duration studies show that 6:2 FTS can cause kidney and liver damage in rodent models.
- ✓ 6:2 FTS does not cause DNA damage.
- ✓ 6:2 FTS does not cause damage to the reproductive system or to the developing fetus in available rodent models.
- ✓ No chronic studies are currently available.
- ✓ No studies have been conducted to assess cancer, immune system toxicity, or endocrine disruption following 6:2 FTS exposure.

### Ecological Toxicology

- ✓ 6:2 FTS is less toxic than PFOS in studies with fish, algae, water fleas (*Daphnia*), and earthworms.
- ✓ 6:2 FTS does not bioaccumulate in fish.
- ✓ A peer-reviewed aquatic hazard assessment concluded that 6:2 FTS presents little risk to aquatic organisms.

### Human Exposure

- ✓ Human exposure is assessed by analyzing blood for the presence of 6:2 FTS; so far, only 4 studies have looked for 6:2 FTS in human blood.
- ✓ Available data indicate that the general population's exposure to 6:2 FTS is low and infrequent.
- ✓ 6:2 FTS has been detected at low levels in some consumer products, drinking water, air, and fish; human exposure may occur through any of these sources.

### Environmental Occurrence

- ✓ 6:2 FTS has been found in air, snow, soil, groundwater, and surface water.
- ✓ 6:2 FTS has been detected at sites associated with fluorochemical manufacture or use of certain fire-fighting foams.
- ✓ 6:2 FTS is less persistent than PFOS.
- ✓ 6:2 FTS can degrade to short-chain perfluorinated compounds, but does not degrade to PFOS.
- ✓ Perfluorohexanoic and perfluoropentanoic acids are the primary degradation products, however, not all degradation products have been identified or well-studied.

Historically, the metal plating industry has used, and continues to use, per- and polyfluoroalkyl substances (PFAS) in some metal plating applications. Most notably, beginning in the 1980s, perfluorooctanesulfonic acid (PFOS) was used as a mist suppressant in hard and decorative chromium plating, chromic acid anodizing, and chromium etch for plating on plastic processes. Due to concerns relating to toxicity and environmental persistence, the chrome plating industry transitioned from using PFOS to using a newer formulation, primarily using 6:2 fluorotelomer sulfonate (6:2 FTS), between 2012-2015. Compared to PFOS, 6:2 FTS has an improved toxicity profile in both rodent and ecological models, and is less persistent than PFOS in the environment and is not bioaccumulative. Further, available studies indicate that human exposure to 6:2 FTS is low and infrequent; comparatively, PFOS is detected in the blood of >99% of Americans. Collectively, available toxicology studies indicate that 6:2 FTS is a safer alternative to PFOS. However, significant data gaps do exist.

## 1. Mammalian Toxicology of 6:2 FTS

Hundreds of studies have been conducted on PFAS, such as PFOS, in laboratory animals including mice, rats, and primates. Furthermore, over 100 human epidemiology studies have been published on PFOS. Comparatively, the toxicology database for 6:2 FTS can be considered “limited”, however, standard testing for regulatory approval of industry manufacture and use have been completed. Toxicology studies that have been completed for 6:2 FTS include (1) six DNA damage studies; (2) three skin irritation and/or sensitization studies; (3) two acute toxicity studies (i.e., single exposure studies); (4) two systemic toxicity studies (i.e., studies investigating multi-organ toxicity following repeated exposure); (5) one liver toxicity study; and (6) one reproductive and developmental toxicity study. Toxicity data following chronic exposure is currently not available. No human epidemiology studies investigating the relationship between exposure to 6:2 FTS and associated health effects have been conducted. 6:2 FTS has not been assessed for its ability to cause cancer, immune system effects, or endocrine (i.e., hormone) disruption, which are all health effects that have been associated with exposure to some PFAS.

Collectively, results from toxicology studies indicate that 6:2 FTS does not (1) cause damage to DNA; (2) does not act as a skin sensitizer (i.e., cause allergic skin reactions); and (3) does not cause toxicity to reproductive organs or to the developing fetus. In contrast, several studies have shown that PFOS can cause developmental toxicity. Furthermore, several acute toxicity studies (i.e., single dose studies testing for lethality) have demonstrated that 6:2 FTS is less acutely toxic than PFOS in laboratory animals. 6:2 FTS has been shown to cause skin irritation; however, this effect is unlikely to be relevant for the general population as it requires dermal contact with high concentrations of 6:2 FTS that is likely to only occur in settings with concentrated and specific use. Finally, rodent studies have demonstrated that exposure to 6:2 FTS can cause kidney and liver toxicity; comparatively, PFOS is not typically associated with kidney toxicity, but has been shown to

### 6:2 FTS Toxicology Database

- DNA damage studies x 6
- Skin irritation/sensitization studies x 3
- Acute toxicity studies x 2
- Systemic toxicity studies x 2
- Liver toxicity study x 1
- Reproductive/developmental toxicity study x 1

### 6:2 FTS does not cause:

- Skin sensitization
- DNA damage
- Reproductive or developmental toxicity

### 6:2 FTS does cause:

- Skin irritation
- Kidney and liver toxicity

cause adverse liver effects in numerous studies. Although results from these studies indicate that 6:2 FTS can cause kidney and liver toxicity, these results occur at higher exposure levels than typically seen in environmental settings. Laboratory studies of longer duration, multiple exposure levels, and with additional endpoints are still needed.

## 2. Human Exposure to 6:2 FTS

Human exposure to 6:2 FTS (and other PFAS) can be assessed by collecting and analyzing human blood samples for the presence of 6:2 FTS. Exposure of the general U.S. population to PFAS, such as PFOS, has been closely tracked via several large-scale studies, including the Center for Disease Control's National Health and Nutrition Examination Survey (NHANES); however, 6:2 FTS has not been included in NHANES. Four studies have measured human exposure to 6:2 FTS in populations from Australia, China, Hong Kong, and the United States. All four studies consistently demonstrate that human exposure to 6:2 FTS is low and infrequent, and that the average human blood level of 6:2 FTS is approximately 1000 times lower than that of PFOS. However, results from these studies are nearly a decade old, and it is unknown if trends in human exposure to 6:2 FTS have changed over time. Furthermore, no exposure data is available for workers exposed in occupational settings. More human exposure studies are needed.

Many PFAS, including PFOS, have been measured in both maternal and umbilical cord blood, which indicates that PFAS can cross the placenta, resulting in exposure to the developing fetus.

One study has demonstrated that 6:2 FTS can also cross the placenta, although available toxicity data indicate that 6:2 FTS does not cause toxicity to the developing fetus in animal models.

Detection of 6:2 FTS in human blood demonstrates that human exposure occurs; however, the routes by which the general population may be exposed to 6:2 FTS are poorly understood. Exposure may occur through consumption of contaminated drinking water or food products, through inhalation of contaminated air, or through contact with certain consumer products. It is likely that human exposure to 6:2 FTS occurs through a combination of all of these routes, as 6:2 FTS has been detected in consumer products (i.e., polishes, carpets, circuit boards), drinking water, air, and in certain species of edible fish. Finally, there is evidence that certain PFAS used in food packaging products may breakdown to 6:2 FTS, and thus exposure to these "precursor" compounds may also indirectly contribute to human exposure.

### Human Exposure to 6:2 FTS

- Human exposure to 6:2 FTS appears to be low and infrequent
- Humans may be exposed to 6:2 FTS through contaminated air, water, food products, or consumer products

## 3. Ecological Toxicology of 6:2 FTS

Several laboratory studies have been conducted to investigate the toxicity of 6:2 FTS to aquatic organisms such as rainbow trout, *Daphnia magna* (aquatic invertebrates), and green algae following both short-term (i.e., acute) and long-term (i.e., chronic) exposure. For both acute and chronic studies, 6:2 FTS was less toxic than PFOS to aquatic organisms. Further, a peer-reviewed aquatic hazard assessment concluded that 6:2 FTS "presents little risk to aquatic organisms<sup>1</sup>."

<sup>1</sup> Hoke et al. 2015. Aquatic hazard, bioaccumulation and screening risk assessment for 6: 2 fluorotelomer sulfonate. *Chemosphere*, 128, pp.258-265.

The toxicity of 6:2 FTS to terrestrial organisms has been assessed in one species, the earthworm. In short-term acute studies, 6:2 FTS and PFOS caused toxicity at similar exposure levels. Alternatively, in long-term chronic studies, 6:2 FTS was less toxic than PFOS to earthworms. There is uncertainty surrounding the effects that 6:2 FTS may have on terrestrial organisms – more studies are needed.

Bioaccumulation is the accumulation of a chemical in an organism, and occurs when exposure exceeds the rate at which an organism can metabolize and/or excrete a chemical from the body. Bioaccumulation can be problematic, as it can result in the accumulation of a chemical in an organism to a level that may lead to adverse effect on organismal health. Both laboratory and field-based studies indicate that 6:2 FTS is unlikely to be bioaccumulative.

#### 6:2 FTS is not bioaccumulative

- Available laboratory and field-based studies indicate that 6:2 FTS is unlikely to be bioaccumulative.

## 4. Environmental Occurrence and Fate of 6:2 FTS

PFAS can enter the environment through a variety of routes, including through waste streams (i.e., landfill leachate, wastewater treatment plant effluent), through production and manufacturing processes, or through consumer use. Environmental monitoring studies have reported detection of 6:2 FTS in a variety of environmental media, including air, snow, rain, groundwater, surface water (i.e., rivers, lakes, estuaries, oceans), sediment, and in biota such as amphipods, birds, bird eggs, earthworms, and fish. Environmental monitoring studies indicate that 6:2 FTS occurs at low-levels in the environment at most sites; however, higher levels of 6:2 FTS have been detected in environmental media at sites associated with point-sources of contamination such as fluorochemical manufacturing facilities or fire fighter training sites where PFAS-containing aqueous film forming foam (AFFF) has been used. For example, the highest level of 6:2 FTS reported in surface water not associated with point-sources of contamination is 36 ng/L (parts per trillion, ppt), whereas detection levels of up to 28,700 ng/L (ppt) 6:2 FTS have been detected in surface water in close proximity to sites where AFFF has been used.

Once in the environment, some PFAS such as PFOS are highly persistent and do not degrade. Alternatively, studies have demonstrated that 6:2 FTS can be degraded by bacteria in the environment under certain conditions. Studies have consistently demonstrated that degradation of 6:2 FTS leads to the formation of the short-chain perfluorocarboxylic acids (PFCAs) perfluorohexanoic acid (PFHxA) and perfluoropentanoic acid (PFPeA); however, over a dozen additional intermediate PFAS may also be formed during the degradation process. Although PFHxA has been shown to pose minimal risk to human health<sup>2</sup>, very little information on the toxicity of the other PFAS formed during 6:2 FTS degradation is available, and the effects of these PFAS on ecological and human health need to be better understood.

### Additional Detailed Information on 6:2 FTS Toxicology – See Appendix 1

<sup>2</sup> Luz et al. 2019. Perfluorohexanoic acid toxicity, part I: Development of a chronic human health toxicity value for use in risk assessment. *Regulatory Toxicology and Pharmacology*, 103, pp.41-55.

<sup>2</sup> Anderson et al. 2019. Perfluorohexanoic acid toxicity, part II: Application of human health toxicity value for risk characterization. *Regulatory Toxicology and Pharmacology*, 103, pp.10-20.

# Appendix 1. Technical Support Document: 6:2 Fluorotelomer Sulfonate (6:2 FTS)



## 1. Overview of 6:2 FTS Toxicology

Compared to per- and polyfluoroalkyl substances (PFAS) such as perfluorooctanoic acid (PFOA) and perfluorooctanesulfonic acid (PFOS), the toxicology database for 6:2 fluorotelomer sulfonate (6:2 FTS) may be considered “limited” even though the standard testing for regulatory approval for industry manufacture and use have been done. These data are available on the European Union (EU)’s REACH dossier and consists of industry-conducted guideline studies that do not appear to have undergone independent expert peer-review (ECHA 2018).

Between the EU dossier and available peer-reviewed publications, the toxicology database for 6:2 FTS consists of:

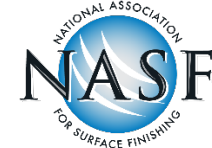
- (1) six genotoxicity studies;
- (2) three studies designed to test for skin sensitization and/or irritation;
- (3) two acute toxicity studies;
- (4) one reproductive/developmental toxicity study;
- (5) two sub-chronic systemic toxicity studies; and
- (6) one liver toxicity study.

Chronic (2-year) systemic toxicity or carcinogenicity studies, two-generational reproductive toxicity studies, or studies specifically designed to test for immunotoxicity, developmental neurotoxicity, or endocrine disruption have not yet been conducted for 6:2 FTS.

Additionally, several studies have been conducted to assess the ecological toxicity of 6:2 FTS, and include acute toxicity tests conducted with fish, invertebrates (*Daphnia magna*), algae, and earthworms; and chronic toxicity studies conducted with fish and earthworms.

A summary of toxicity studies and the main conclusions, as presented by the study authors, are provided in Table 1.

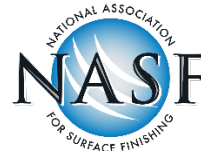
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**Table 1. Summary of 6:2 FTS Toxicology Studies.**

Study	Main conclusion	Reference
<b>Genotoxicity Studies</b>		
OECD 471 - Bacterial reverse mutation assay	• 6:2 FTS is not mutagenic	ECHA
OECD 473 - In vitro mammalian chromosome aberration test in CHO cells	• 6:2 FTS-related chromosomal aberrations were not observed	ECHA
OECD 474 - Mammalian erythrocyte micronucleus test	• 6:2 FTS did not induce micronucleus formation	ECHA
OECD 475 - Mammalian bone marrow chromosome aberration test	• 6:2 FTS did not induce chromosomal aberrations	ECHA
OECD 486 - Unscheduled DNA synthesis (UDS) test with mammalian liver cells in vivo	• 6:2 FTS did not induce unscheduled DNA synthesis	ECHA
OECD 489 - In vivo mammalian alkaline comet assay	• 6:2 FTS did not induce DNA damage in vivo	ECHA
<b>Mammalian Toxicology Studies<sup>1</sup></b>		
OECD 429 - Skin sensitization (local lymph node assay) - conducted with mice	• 6:2 FTS is not a dermal sensitizer	ECHA
OECD 435 - In vitro membrane barrier test method for skin corrosion	• 6:2 FTS is irritating to skin • 6:2 FTS is classified as skin corrosive Category 1A with the accompanying hazard statement (H314) "Causes severe skin burns and eye damage."	ECHA
In vivo (rabbit) skin irritation test	• 6:2 FTS is not irritating to the skin	Buck, 2015
OECD 402 - Acute (single dose) dermal toxicity - conducted with Sprague Dawley rats	• 6:2 FTS is not acutely toxic via the dermal exposure route	ECHA
OECD 420 - Acute (single dose) oral toxicity - fixed dose procedure - conducted with Wistar rats	• The oral LD50 is >300, but less than 2,000 mg/kg 6:2 FTS • 6:2 FTS is classified as GHS Category 4, with the hazard statement (H302) "Harmful if swallowed."	ECHA
14-Day oral dose range finding study with Wistar rats	• Kidney toxicity observed (i.e., increased kidney weight, altered creatinine and urea levels)	ECHA
OECD 422 - Combined repeated dose (90-day) toxicity study with the reproduction/developmental toxicity screening test - conducted with Wistar rats	• 6:2 FTS is not a reproductive or developmental toxicant • Kidney toxicity observed (i.e., elevated urea levels, increased incidence of multi-focal tubular dilation in male and female kidneys)	ECHA
28-Day subchronic study with CD1 mice (only 1 dose used; 5 mg/kg-day)	• Exposure to 6:2 FTS (ammonium salt) was associated with liver toxicity (i.e., increased liver weight, increased incidence of necrosis, hepatocellular hypertrophy)	Sheng et al. (2017)
<b>Aquatic Toxicology Studies</b>		
OECD 201 - Freshwater alga and cyanobacteria, growth inhibition test with green alga ( <i>P. subcapitata</i> )	• The 72-hour EC50 ranges from >96 mg/L (potassium salt of 6:2 FTS) to >125 mg/L (6:2 FTS)	ECHA; Hoke et al., 2015
OECD 202 - Daphnia sp. acute immobilization test	• The 48-hour EC50 ranges from >109 mg/L (potassium salt of 6:2 FTS) to >112 mg/L (6:2 FTS)	ECHA; Hoke et al., 2015
OECD 203 - Acute toxicity test - conducted with rainbow trout	• The 96-hour LC50 ranges from >107 mg/L (potassium salt of 6:2 FTS) to >108 mg/L (6:2 FTS)	ECHA; Hoke et al., 2015
OECD 210 - Fish early-life stage toxicity test (90-day) - conducted with rainbow trout	• The 90-day NOEC is 2.62 mg/L 6:2 FTS (potassium salt)	ECHA; Hoke et al., 2015
Conclusions by Hoke et al. (2015)	• 6:2 FTS is not expected to pose a risk to aquatic organisms	Hoke et al., 2015
<p><sup>1</sup> Results from several unpublished toxicology and bioaccumulation studies for 6:2 FTS were presented at the Society of Environmental Toxicology and Chemistry Meeting (SETAC; Buck, 2018). Unpublished toxicology studies included 28-day oral and 4-hour inhalation studies, both conducted with rats. Further, a bioaccumulation study was conducted in rats in which 6:2 FTS was not found to be bioaccumulative.</p> <p><b>Abbreviations:</b> EC50 = effective concentration that elicits 50% of the response; LC50 = lethal concentration that elicits 50% of the response; LD50 = lethal dose that elicits 50% of the response; NOEC = No observable effect concentration</p>		

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### 2. Mammalian Toxicology

**6:2 FTS is less acutely toxic than PFOS.** Results from two acute toxicity studies are listed in the REACH registration dossier for 6:2 FTS (ECHA, 2018), and include oral and dermal exposure studies. 6:2 FTS was not found to be acutely toxic via the dermal route of exposure at doses of up to 2000 mg/kg in an Organization for Economic Cooperation and Development (OECD) Guideline 402 study (OECD 2017; Acute Dermal Toxicity). Alternatively, 6:2 FTS was found to have moderate acute toxicity via the oral exposure route in an OECD Guideline 420 study (OECD, 2002; Acute Oral Toxicity), with an LD<sub>50</sub><sup>1</sup> value of between 300 to 2,000 mg/kg. Based on this result, 6:2 FTS was GHS (Globally Harmonized System) classified category 4 for acute oral toxicity, which has the accompanying hazard statement “H302: Harmful if swallowed.” Additionally, Field & Seow (2017) report the acute oral LD<sub>50</sub> for rats to be 1,871 mg/kg; however, the study authors did not provide a complete reference and this LD<sub>50</sub> could not be verified. Comparatively, the acute oral LD<sub>50</sub> value for PFOS has been reported to be 251 mg/kg in rats (Dean et al., 1978). These results demonstrate that 6:2 FTS is less acutely toxic than PFOS via the oral exposure route.

**6:2 FTS is not genotoxic.** No chronic toxicity studies investigating the carcinogenicity of 6:2 FTS have been conducted. However, a variety of *in vitro* and *in vivo* studies investigating the genotoxic and/or mutagenic potential of 6:2 FTS have been conducted and are reported in the REACH registration dossier for 6:2 FTS (ECHA, 2018). Results from these studies indicate that 6:2 FTS is:

- not mutagenic in the bacterial reverse mutation assay (Guideline 471; OECD, 1997a);
- does not cause DNA damage in an *in vivo* mammalian comet assay (Guideline 489; OECD, 2016a);
- does not induce micronuclei formation (indication of chromosomal damage) in a *in vivo* bone marrow assay (Guideline 474; OECD, 2016b);
- does not induce chromosomal aberrations *in vivo* (Guideline 475; OECD, 1997b) or *in vitro* (Guideline 473; OECD, 1997c) test systems;
- does not causes unscheduled DNA synthesis (Guideline 486; OECD, 1997d).

Collectively, these results indicate that 6:2 FTS is not genotoxic or mutagenic. Similarly, numerous studies have demonstrated that PFOS is not genotoxic [reviewed in USEPA, 2016].

**6:2 FTS can cause kidney and liver toxicity.** Three studies have been conducted that evaluate the toxicity of 6:2 FTS following repeat exposure. These studies include a 14-day dose-range finding study in rats (ECHA, 2018), a 28-day subchronic study in mice (Sheng et al., 2017), and a 90-day subchronic toxicity study in rats (ECHA, 2018). In the 14-day study, male and female

<sup>1</sup> The LD<sub>50</sub> is the lethal dose that causes 50% mortality.

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rats were orally exposed to 10, 50, or 100 mg/kg-day 6:2 FTS. No mortality or clinical signs of toxicity were reported in either sex at any dose. Signs of toxicity included reduced body weight gains and reduced food consumption in male (50 and 100 mg/kg-day treatment groups) and female (100 mg/kg-day group only) rats. Signs of kidney toxicity were observed, and included alterations in serum levels of creatinine and urea, and increased kidney weight in male (50 and 100 mg/kg-day treatment groups) and female (100 mg/kg-day group only) rats (ECHA, 2018).

In the 90-day OECD Guideline 422 study (OECD 1996; combined repeated dose toxicity study with the reproduction/developmental toxicity screening test) male and female rats were orally exposed to 5, 15, or 45 mg/kg-day 6:2 FTS. 6:2 FTS treatment had no effect on mortality, food consumption, or animal behavior, and no gross pathological or neoplastic histopathological findings were reported for either sex at any dose. Treatment-related reduced body weight gains were detected in both sexes in the highest treatment group (45 mg/kg-day). Several clinical signs of toxicity were observed, and included effects related to the skin (sparse hair, encrustations), eye (blepharospasm in one low-dose male rat), and respiratory system (sniffing respiration in two high-dose male rats); however, due to low-incidence and distribution, these effects were not considered treatment-related by the study authors. Hematological findings were reported, including reduced monocytes in male rats (5 mg/kg-day only); however, these effects were not considered treatment-related, as they did not occur in a dose-dependent manner. Mean total protein and albumin serum levels were slightly reduced in male rats (5 and 45 mg/kg-day, but not 15 mg/kg-day group); these effects did not occur in a dose-dependent manner and were not considered treatment-related. Alternatively, a dose-dependent increase in urea levels was reported for high-dose male rats, and was considered treatment related. Additional signs of kidney toxicity were also reported, and these effects were more pronounced in male rats. These effects included increased kidney weight in low- and high-dose male rats, and mild to moderate multifocal tubular dilation in the kidneys of high-dose male (5/12) and female (1/12) rats (ECHA, 2018).

In the 28-day study conducted by Sheng et al. (2017), male CD1 mice were orally exposed to 5.0 mg/kg-day 6:2 FTS, and liver toxicity was investigated. Exposure to 6:2 FTS resulted in increased liver weight, increased serum levels of aspartate transaminase and albumin, and signs of hepatocellular hypertrophy and necrosis. Collectively, these results indicate that 6:2 FTS is hepatotoxic. However, this study has limitations, including the small number of endpoints measured (kidney toxicity not investigated), and only a single exposure group was included in the study, which prevents any dose-response analysis.

Collectively, results from Sheng et al. (2017) and ECHA (2018) indicate that 6:2 FTS can cause kidney and liver toxicity in highly exposed rodent models. Comparatively, the majority of rodent toxicology studies conducted with PFOS do not report kidney toxicity [reviewed in USEPA, 2016], while subchronic and chronic toxicology studies have consistently demonstrated PFOS-induced liver toxicity [reviewed in USEPA, 2016].



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**6:2 FTS is not a reproductive or developmental toxicant.** One study investigating the reproductive and developmental effects of 6:2 FTS has been conducted (ECHA, 2018). The study adhered to OECD Guideline 422 (OECD, 1996; Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test) in which male and female rats were orally exposed to 6:2 FTS (5, 15, or 45 mg/kg-day) prior to mating, during mating, and throughout gestation and lactation for a total of approximately 90-days. For parental rats, no treatment-related changes were reported for any reproductive parameter, such as reproductive organ weight, estrous cyclicity, serum T4 hormone levels, or reproductive performance. Similarly, no clinical signs of toxicity, or treatment-related effects on survival, body weight, sexual maturation, organ weight, gross pathology or hormone levels were reported for pups. Collectively, these results indicate that 6:2 FTS is not a reproductive or developmental toxicant at doses of up to 45 mg/kg-day.

Alternatively, numerous studies have reported developmental effects associated with PFOS exposure in rats, mice, and rabbits [for a comprehensive review of PFOS-related developmental and reproductive effects see USEPA, 2016], and these effects have been reported as exposure levels as low as 1.6 – 10 mg/kg-day (Luebker et al., 2005a,b; Thibodeaux et al., 2003).

**6:2 FTS can cause skin irritation, but not sensitization.** One study has been conducted with mice to investigate the ability of 6:2 FTS to act as a skin sensitizer (i.e., cause allergic skin reactions). Results from the OECD Guideline 429 study (OECD 2010; Local Lymph Node Assay) indicate that 6:2 FTS is not a skin sensitizer (ECHA, 2018). Alternatively, 6:2 FTS is GHS classified category 1 for skin corrosivity, which has the following hazard statement “H314: Causes severe skin burns and eye damage.” The GHS classification is based on results from an *in vitro* OECD Guideline 435 study (OECD, 2006; In Vitro Membrane Barrier Test Method for Skin Corrosion) that indicated 6:2 FTS is corrosive to skin (ECHA, 2018). 6:2 FTS was reported to be not irritating to the skin of rabbits in a non-peer-reviewed book chapter (Buck, 2015); however, no additional study details were provided. The reason for the discrepancies are unclear, but may related to the chemical form of 6:2 FTS administered. 6:2 FTS acid, which was used in the *in vitro* study, is expected to be more irritating/corrosive than non-acidic 6:2 FTS salts, which may have been used in the *in vivo* rabbit study; however, the form of 6:2 FTS used was not reported in Buck (2015).

**6:2 FTS is classified as an eye irritant.** No formal studies have been conducted to test if 6:2 FTS is an eye irritant. However, based on Regulation No. 1272/2008 skin corrosive chemicals are to be classified as serious eye damage category 1, which has the accompanying hazard statement H318: Causes serious eye damage” (ECHA, 2018). Comparatively, *in vivo* studies have demonstrated that PFOS can also cause severe eye irritation (Riker Laboratories, Inc., 1981).

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## 3. Ecological Toxicology

The acute and chronic toxicity of 6:2 FTS has been investigated in several aquatic (fish, *Daphnia*, algae) and terrestrial (earthworms) species. In general, and as discussed in more detail below, 6:2 FTS is less toxic to aquatic and terrestrial organisms than PFOS (Table 2).

**Table 2. Comparison of 6:2 FTS and PFOS ecotoxicity.**

	6:2 FTS	PFOS
96-Hour Rainbow Trout LC <sub>50</sub> (mg/L)	>107 <sup>a</sup>	7.8 – 22 <sup>b</sup>
48-Hour <i>Daphnia magna</i> Immobilization EC <sub>50</sub> (mg/L)	>109 <sup>a</sup>	67.2 <sup>b</sup>
72-Hour <i>Pseudokirchneriella subcapitata</i> Growth Rate (ErC <sub>50</sub> ; mg/L)	>96 <sup>a</sup>	48.2 <sup>b</sup>
72-Hour <i>Pseudokirchneriella subcapitata</i> NOEC <sub>r</sub> (mg/L)	47.6 <sup>a</sup>	42 <sup>b</sup>
90-Day Rainbow Trout NOEC (mg/L)	2.62 <sup>a</sup>	0.29 <sup>b,c</sup>
14-Day Earthworm LC <sub>50</sub> (mg/kg)	373 <sup>d</sup>	365 <sup>e</sup>
56-Day Earthworm EC <sub>50</sub> (mg/kg) - # of cocoons	566 <sup>f</sup>	103 <sup>f</sup>
56-Day Earthworm EC <sub>50</sub> (mg/kg) - juvenile weight	253 <sup>f</sup>	29 <sup>f</sup>
<sup>a</sup> Hoke et al., 2015 <sup>b</sup> Beach et al., 2006 <sup>c</sup> NOEC is for a 47-d test with fathead minnows, not rainbow trout <sup>d</sup> 3M, 2003 <sup>e</sup> Juong et al. (2010) <sup>f</sup> Stubberud (2006)  <b>Acronyms:</b> EC <sub>50</sub> = effective concentration that gives half-maximal response; ErC <sub>50</sub> = EC <sub>50</sub> in terms of reduced growth rate; LC <sub>50</sub> = lethal concentration that causes 50% mortality; NOEC = no observable effect concentration; NOEC <sub>r</sub> = NOEC for growth rate		

### 3.1 Aquatic Toxicology

**6:2 FTS is less acutely toxic to aquatic organisms than PFOS.** The acute toxicity of 6:2 FTS has been investigated in several species, including *Oncorhynchus mykiss* (rainbow trout), *Daphnia magna* (aquatic invertebrate), and *Pseudokirchneriella subcapitata* (green algae). Compared to PFOS, 6:2 FTS is less acutely toxic to rainbow trout, with a 96-hour LC<sub>50</sub> value of >107 mg/L (Hoke et al., 2015), while the 96-hour LC<sub>50</sub> value for PFOS ranges from 7.8 to 22 mg/L (Beach et al., 2006). Similarly, *Daphnia* are less sensitive to 6:2 FTS than to PFOS, with EC<sub>50</sub> values of >109 mg/L 6:2 FTS (Hoke et al., 2015) and 67.2 mg/L PFOS (Beach et al., 2006). Alternatively, 6:2 FTS and PFOS inhibit green algae growth at similar concentrations, with no observable effect concentrations (NOECs) of 47.6 mg/L for 6:2 FTS (Hoke et al., 2015) and 42 mg/L for PFOS (Beach et al., 2006). However, the concentration at which 6:2 FTS inhibited green algae growth by 50% (EC<sub>50</sub>) is >96 mg/L (Hoke et al., 2015), while the EC<sub>50</sub> for PFOS is 48.2 mg/L (Beach et al., 2006). These results indicate that the slope of the PFOS dose-response curve is steeper than that of 6:2 FTS, which indicates that 6:2 FTS is less toxic to green algae than PFOS.

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**6:2 FTS is less chronically toxic to fish than PFOS.** One study investigating the chronic, 90-day, toxicity of 6:2 FTS in early-life stage rainbow trout has been conducted (Hoke et al., 2015). In this study, the most sensitive toxicological endpoint was embryo hatching, with a NOEC of 2.62 mg/L. No 90-day early-life stage studies with rainbow trout were identified for PFOS. However, results from a 47-day PFOS chronic toxicity study conducted with Fathead minnows is available (Beach et al., 2006). The lowest NOEC identified in this study was 0.29 mg/L. Although the studies were conducted in different species of fish, both were early-life stage chronic toxicity studies. Further, the PFOS NOEC is nearly 10-fold lower than the 6:2 FTS NOEC. This result indicates that fish are more sensitive to chronic PFOS exposure than to chronic 6:2 FTS exposure.

### 3.2 Terrestrial Toxicology

**6:2 FTS and PFOS display similar acute toxicity to earthworms.** One study investigating the acute toxicity of 6:2 FTS to terrestrial organisms has been conducted. In a study conducted by 3M (2003), the 14-day LC50 of 6:2 FTS for earthworms was determined to be 373 mg/kg soil (3M, 2003). Similarly, Juong et al. (2010) determined the 14-day LC50 value of PFOS to be 365 mg/kg soil. Both studies were conducted under similar experimental conditions. Thus, these results indicate 6:2 FTS and PFOS are similarly acutely toxic to earthworms.

**6:2 FTS is less chronically toxic than PFOS to earthworms.** A study by Stubberud (2006) reports results from an earthworm reproduction test in which the number of cocoons laid, hatching success, and juvenile worm weight was reported. The EC50 values for number of cocoons laid and juvenile weight were calculated to be 566 and 253 mg/kg soil, respectively, for 6:2 FTS. Alternatively, EC50 values for PFOS were 103 (cocoons laid) and 29 mg/kg soil (juvenile weight). These results indicate that 6:2 FTS is less chronically toxic to earthworms than PFOS.

More research on the potential terrestrial and mammalian toxicity of 6:2 FTS is needed.

## 4. Toxicokinetics and Bioaccumulation

**6:2 FTS is eliminated more rapidly than PFOS.** Toxicokinetics is the study of how the body handles a chemical, and includes analysis of a chemical's rate of adsorption, tissue distribution, metabolism, and excretion. Limited information is available on the toxicokinetics of 6:2 FTS. One *in vivo* toxicokinetics study and one *in vitro* metabolism study are reported in the REACH registration dossier for 6:2 FTS; however, minimal study details are provided (ECHA, 2018). For the toxicokinetic study, two single doses (dosing levels not provided) of 6:2 FTS were administered (species tested was not reported) and then fat, liver, plasma, and urine samples were collected to investigate the distribution and excretion of 6:2 FTS. Fat-to-plasma ratios could not be calculated for females, while ratios were <0.1 (low dose) to 0.1 (high dose) for

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males indicating 6:2 FTS does not accumulate in fat. Similarly, liver-to-plasma ratios could not be determined for females, while ratios were 3.0 (low dose) to 3.1 (high dose) for males, indicating partitioning of 6:2 FTS to the liver. 65-68% of the administered dose of 6:2 FTS was recovered in urine 96-hours after dosing, and elimination half-lives ranged from 20.9 to 23.8 hours. Comparatively, the elimination half-life of PFOS following oral administration has been reported to range from 30.5 to 42.8 days for mice and 39.8 to 66.7 days for rats (Chang et al. 2012). These results indicate that 6:2 FTS will be eliminated more rapidly than PFOS.

***In vitro studies indicate 6:2 FTS may not be readily metabolized.*** Two *in vitro* studies investigating the metabolism of 6:2 FTS have been conducted. In the first, 6:2 FTS was incubated with male rat liver S9 microsomes for 2-hours, which is a common *in vitro* method employed to estimate *in vivo* metabolism. No metabolism of 6:2 FTS was detected (ECHA, 2018). In a second study, 6:2 FTS was incubated with rainbow trout hepatocytes for 2-hours; no metabolism of 6:2 FTS was detected (Hoke et al., 2015). However, *in vitro* test systems do not completely replicate *in vivo* metabolism, thus, *in vivo* studies should be conducted to confirm *in vitro* results. Numerous studies have demonstrated that PFOS is recalcitrant to metabolism *in vitro* and *in vivo* [reviewed in USEPA, 2016].

***6:2 FTS is not bioaccumulative.*** Bioaccumulation is the accumulation of a chemical in an organism, and occurs when exposure and adsorption of a chemical occurs at a faster rate than metabolism and/or excretion. Bioaccumulation factors (BAFs) and bioconcentration factors (BCFs) are the ratio of a chemical in an organism to the concentration in the surrounding environment. According to the U.S. EPA, chemicals with BCFs >1000 are considered bioaccumulative, while other regulatory agencies in Canada, the European Union, and the United Nations consider chemicals with BAFs/BCFs of 2,000 to 5,000 to be bioaccumulative (Arnot and Gobas, 2006).

Laboratory- and field-based BCFs/BAFs for 6:2 FTS have been calculated for fish (rainbow trout, white sucker), earthworms, midge, and biofilm. As can be seen in Table 3, all estimated BCFs are below 1000 indicating that 6:2 FTS is not classifiable as bioaccumulative by the most conservative regulatory standard.

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**Table 3. Summary of 6:2 FTS BCFs and BAFs**

Species	Exposure Details	BCF/BAF	Reference
<i>Oncorhynchus mykiss</i> (rainbow trout)	Aqueous exposure to 6:2 FTS	3 - 36	Hoke et al., 2015
	Dietary exposure to 6:2 FTS. <sup>1</sup>	0.3	
<i>Oncorhynchus mykiss</i> (rainbow trout)	Aqueous exposure to 6:2 FTS containing AFFF	ND	Yeung & Mabury, 2013
<i>Chironomus riparius</i> (midge)	Exposure to 6:2 FTS contaminated environmental sediments.	0.018	Bertin et al., 2014
<i>Gammarus</i> spp. (Crustacea)	Exposure to 6:2 FTS contaminated environmental sediments.	0.88	Bertin et al., 2016
<i>Catostomus commersonii</i> (white sucker)	Field-based estimates	0.23 - 0.95	Munoz et al., 2017
Biofilm <sup>2</sup>	Field-based estimates	148	Munoz et al., 2018
<i>Eisenia fetida</i> (earthworms)	Exposure to 6:2 FTS contaminated soil from fire training facilities.	2.4	NPCA, 2008

<sup>1</sup> Dietary biomagnification factors are estimated for dietary exposures.  
<sup>2</sup> Log BCF values were estimated to be 1.4, 1.5, and 3.6 from three different locations for a mean value of 2.17, which is equivalent to a BCF of 148.  
 ND = Not determined; accumulation was not sufficient for BCFs to be estimated.

**Compared to PFOS, 6:2 FTS has reduced binding affinity to some proteins.** In contrast to most bioaccumulative chemicals, which are lipophilic and accumulate in fat, PFOS bioaccumulation is associated with binding to proteins such as serum albumin, fatty acid binding protein in the liver, and organic anion transporters in the kidney. One study investigating 6:2 FTS protein binding has been published (Sheng et al. 2018). In this study, a fluorescent displacement assay was used to investigate PFOS and 6:2 FTS binding to human liver FABP (hL-FABP). The concentrations required to cause a 50% fluorescent displacement (IC<sub>50</sub>) were 1.34 and 78.97 μM for PFOS and 6:2 FTS, respectively, indicating that 6:2 FTS has reduced binding affinity to hL-FABP. Furthermore, Sheng et al. (2018) used molecular docking software to investigate the molecular interactions of PFAS with the hL-FABP binding pocket. Using this approach, no binding of 6:2 FTS to the hL-FABP was observed, whereas PFOS binding could be modelled.

### 5. Human Exposure to 6:2 FTS

**Human exposure to 6:2 FTS appears to be low and infrequent.** 6:2 FTS has been detected in human serum, thus demonstrating that exposure to 6:2 FTS can occur (Table 4). However, compared to PFOS, 6:2 FTS human biomonitoring data is limited, and only four studies reporting human serum levels of 6:2 FTS are available. In contrast, 100s of studies investigating

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human exposure to PFOS have been conducted. Additionally, results from all 6:2 FTS biomonitoring studies are based on small sample sizes, and were conducted nearly a decade ago. Thus, it is unclear how human exposure to 6:2 FTS has changed over the past decade, or how occupational exposure levels compares to that of the general population. Additional research on the potential sources of 6:2 FTS and extent of human exposure are needed.

**Table 4. Summary of 6:2 FTS Biomonitoring Data**

Location	Sampling Year	Sample/ gender/ age	N	FOD	LOD (ng/L)	Min (ng/L)	Median (ng/L)	Arithmetic Mean (ng/L)	Max (ng/L)	Reference
U.S.	2009	Serum, M	20	42%	5	<LOD	--	5.91	18.39	Lee & Mabury (2011) <sup>1</sup>
		Serum, F	20	65%	5	<LOD	--	9.28	29.54	
China	2009	Maternal serum	50	64%	3	<LOD	11.55	13.39	48.24	Yang et al. (2016) <sup>2</sup>
		Cord serum	50	68%	3	<LOD	13.53	20.99	90.21	
Hong Kong	--	Blood, M + F	20	100%	--	0.34	1.17	2.19	7.89	Loi et al. (2013) <sup>4</sup>
Australia	2011	Serum, Age: 0-4	4	50%	--	<LOD	--	10	20	Eriksson et al. (2017) <sup>1,3</sup>
		Serum, Age: 5-15	4	0%	--	--	--	--	--	
		Serum, Age: 16-30	4	25%	--	<LOD	--	10	50	
		Serum, Age: 31-45	4	25%	--	<LOD	--	10	30	
		Serum, Age: 46-60	4	0%	--	--	--	--	--	
		Serum, Age: >60	4	0%	--	--	--	--	--	

<sup>1</sup> For purposes for calculating the mean, samples with 6:2 FTS levels below the LOD were substituted with a value of zero.  
<sup>2</sup> For purposes of calculating the mean, samples with 6:2 FTS levels below the LOD were substituted with a value of the LOD divided by the square root of two.  
<sup>3</sup> N = 4 pooled serum samples; each sample consisted of 100 individual pooled serum samples.  
<sup>4</sup> Serum data is reported in units of pg/g, which is equivalent to parts per trillion (ppt); ng/L is also equivalent to ppt  
"--" = Value not provided; "FOD" = frequency of detection; "LOD" = limit of detection

One biomonitoring study was conducted in the United States in 2009 (Lee & Mabury, 2011). In this study, 6:2 FTS was detected in the serum of 42% of male participants and 65% of female participants with arithmetic mean serum levels ranging from 5.9 ng/L (males) to 9.3 ng/L (females). These serum levels are significantly lower than the arithmetic mean serum levels of PFOS reported in the general U.S. population. During the 2009-2010 NHANES survey period, PFOS was detected in the serum of >99% of participants with median levels ranging from 7,800 ng/L (females) to 11,800 ng/L (males) (CDC, 2018). These findings indicate that human exposure to 6:2 FTS is lower than that of PFOS.

**6:2 FTS can cross the placenta resulting in fetal exposure.** One study has demonstrated that 6:2 FTS can cross the placental resulting in exposure to the developing fetus (Yang et al., 2016). In this study, 6:2 FTS was measured in paired maternal and cord serum from 50 Chinese mothers. The frequency of detection and mean serum levels of 6:2 FTS were similar for maternal and cord serum, and the median placental transfer ratio was 1.2:1 indicating that 6:2 FTS can freely cross the placenta. This finding is similar to PFOS, which has also been shown to cross the placenta.

### 6. Exposure Routes

Human exposure to 6:2 FTS may occur via a variety of routes, including consumption of contaminated drinking water or food products, through inhaling 6:2 FTS in the air, or through contact with consumer products that may contain 6:2 FTS. Field and Seow (2017) recently reviewed available monitoring data, and demonstrated that exposure to 6:2 FTS through these routes is possible, as 6:2 FTS has been detected in (1) consumer products including circuit boards, carpets, and polishes; (2) in drinking water in Spain, Germany, and France; (3) in air; and (4) in certain species of fish (see Field and Seow (2017) for a complete review).

Although, it is apparent that human exposure to 6:2 FTS occurs, it remains unknown whether humans are exposed directly to 6:2 FTS or to PFAS precursors that can degrade to 6:2 FTS. Lee & Mabury (2011) suggest that indirect exposure to 6:2 FTS may occur first through exposure to disubstituted thioether phosphates (S-diPAPS; also known as fluorotelomer mercaptoalkyl phosphate esters or FTMAPs), which are used in food packaging products (Trier et al., 2011), and can be metabolized to 6:2 FTS. A wide variety of additional 6:2 FTS precursors have been proposed based on chemical structures (See Table 12 of Field & Seow, 2017), many of which are constituents of firefighting foams (i.e., AFFF); however, little empirical data exists to directly link degradation of these compounds to 6:2 FTS. It is likely that direct exposure to 6:2 FTS and precursors both contribute to human exposure.

### 7. Environmental Occurrence & Persistence

#### 7.1 Environmental Occurrence

***6:2 FTS is detected at low levels and frequencies at sites associated with non-point-sources of contamination.*** Several studies have monitored the environmental occurrence of 6:2 FTS at both sites associated with non-point sources and with point sources (i.e., firefighting training facilities or fluoropolymer facilities) of contamination [reviewed in Field and Seow, 2017]. 6:2 FTS has been detected in (1) landfill leachate and sediment in Sweden, Norway, Germany, and the U.S.; (2) in wastewater treatment plant influent, effluent, and sludge; (3) in rain and snow; (4) in surface waters including rivers, lakes, estuaries, and oceans; and (5) in organisms including amphipods, birds, bird eggs, worms, and fish. In general, 6:2 FTS is detected at low levels and frequencies in environmental samples collected from sites with non-point sources of contamination, while higher detection frequencies and levels are often reported at sites with known point sources of contamination (Field and Seow, 2017). For example, the highest level of 6:2 FTS reported in surface waters not associated with point sources of contamination is 36 ng/L (Nguyen et al, 2011), while the highest level of 6:2 FTS reported in surface water with known point sources of contaminate (fire-fighting foam) is 28,700 ng/L (Boiteux et al., 2016).

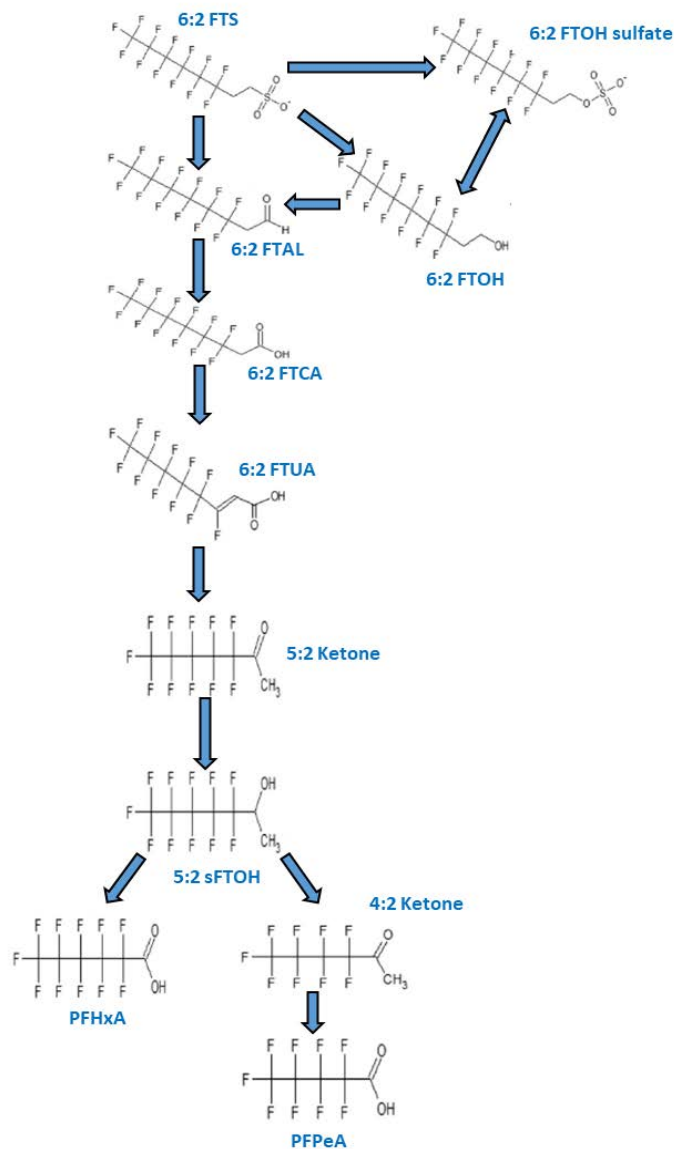
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## 7.2 Environmental Persistence

*Biodegradation of 6:2 FTS occurs under aerobic, sulfur-limiting, conditions.*

Several studies have been conducted to investigate biodegradation of 6:2 FTS under varying conditions. An OECD Guideline 301B (CO<sub>2</sub> Evolution Test; OECD 1992) study was conducted to test whether 6:2 FTS could be utilized as a carbon source by bacteria. Over 28-days a maximum loss of 42% was observed; based on test guidelines this result indicates that 6:2 FTS is not readily biodegradable (ECHA, 2018). Similarly, several studies have demonstrated that 6:2 FTS is not readily biodegradable under anaerobic conditions (Zhang et al. 2016), or in activated sludge from WWTPs under anaerobic or aerobic conditions (Ochoa-Herrera et al., 2016; Wang et al., 2011). Alternatively, several studies have demonstrated that 6:2 FTS can be utilized as a sulfur source by bacteria under aerobic, sulfur-limiting conditions (Key et al., 1998; Shaw et al., 2019; Van Hamme et al., 2013; Zhang et al., 2016). Zhang et al. (2016) report that 6:2 FTS undergoes rapid biodegradation in aerobic sediment, with a biodegradation half-life of less than five days. Biodegradation pathways of 6:2 FTS have also been proposed in several publications, and PFHxA (PFCA with 5 fluorinated carbons), PFPeA (PFCA with 4 fluorinated carbons) and the 5:3 fluorotelomer acid are consistently reported to be the primary terminal degradation products (Shaw et al., 2019; Van Hamme et al., 2013; Wang et al., 2011; Zhang et al., 2016). However, numerous intermediary PFAS are formed throughout the biodegradation process. Shaw et al. (2019) identified 16 intermediary metabolites, many of which are shown in the proposed major degradation pathway for 6:2 FTS (Figure 1). Major metabolites identified by Shaw et al. (2019) include: 6:2 fluorotelomer (6:2 FT) alcohol (6:2



**Figure 1. Proposed major degradation pathway for 6:2 FTS.** Adapted from Shaw et al. (2019).



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FTOH), 6:2 FT alcohol sulfate (6:2 FTOH sulfate), 6:2 FT aldehyde (6:2 FTAL), 6:2 FT acid (6:2 FTAC), 6:2 FT unsaturated acid (6:2 FTUA), 5:2 FT ketone, 5:2 FT secondary alcohol (5:2 sFTOH), 4:2 FT ketone, and the short-chain PFCAs PFHxA and PFPeA. Although, the terminal degradation product PFHxA has been shown to pose minimal risk to human health (Anderson et al., 2019), very little toxicological information is available for the other metabolites formed during 6:2 FTS biodegradation, or the proposed terminal degradation products formed through proposed minor degradation pathways, such as PFBA and 4:2 FTUA (Shaw et al., 2019).

Significant and important data gaps related to the environmental and *in vivo* degradation of 6:2 FTS remain.

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