**Perfluorohexane sulfonic acid (PFHxS), its salts and PFHxS-related compounds**

**DRAFT RISK PROFILE**

**NL NFP Comments 20180406**

The Netherlands appreciates the work done by the drafters of the Risk Profile for PFHxS. The Netherlandswishes to contribute to the further development of this Profile by providing some comments below.

Together with PFOS and PFOA, PFHxS is one of the PFCs most appearing in environmental or human monitoring data. The available data suggest that marketed volumes of PFHxS are or have been up to a factor of 10 lower than those of PFOS and PFOA (see for instance Sundström et al 2011). Literature also indicates that on a lot of places concentrations of PFOS and PFOA are decreasing, whereas PFHxS is levelling off. Land et al 2018 - Temporal trends of perfluoroalkyl acids in humans and in the environment: “In regions where regulations and phase-outs have been implemented, human concentrations of PFOS, PFDS, and PFOA are generally decli­ning, while previously increasing concentrations of PFHxS have begun to level off.” This trend could be better reflected in the risk profile.

The PFHxS risk profile summarizes in paragraph 2 the knowledge of the use of PFHxS with the following sentence: "2. PFHxS, its salts and PFHxS related compounds are or have been widely used in fire-fighting foams, as surfactants, in metal plating as well as in cleaning, waxing, polish and other surface treatment products, and/or water- and stain-protective coatings for carpets, paper, leather and textiles." In the Norwegian Environment Agency Report M-961/2018, cited in paragraph 28 of the risk profile, the conclusion on page 18 states: "Across all sources, it was found that there is in general a lack of information on the quantitative production levels and regarding descriptions of product specific uses of PFHxS and related substances in the public domain." This is quite a different conclusion than the message provided in paragraph 2 of the risk profile. The Netherlands would like to know whether there is a clear picture of the applications of PFHxS and the amounts used and if these data are available, can they be provided in the risk profile? If not, we would recommend to take the conclusion in the report of the Norwegian Environment Agency as a proper one to communicate in the summary of the risk profile and to convey that message as well in the remaining part of the profile, e.g. in paragraph 32.

Following above, the dossier contains a limited information on the amounts PFHxS produced and the applications in which it is used. Data provided (paras 3, 13, 27, 29, 35, 40 and 29) do not enable to come to a comprehensive picture, but suggest amounts of a few tonnes up to 1000 tonnes/year (China). The European annex XV dossier and the RMOA on PFHxS indicate: ‘At present there is no available data on the production and use of PFHxS globally or in the EU.’

The dossier would substantially be improved if the authors indicate the range of production based on the data provided and the uncertainty in these amounts. The fact that production within the European Union still takes place (Italy is mentioned in para 29), but that until now PFHxS is not registered under REACH is a fact worth mentioning, taking into account that registration by the Italian producer is still possible until June 1, 2018. If not, the production in Italy is below 1 tonne per year or might even have ceased. Insight would also be improved if the amounts are provided in the broader picture of PFC production in use, e.g. by comparison with PFOS and PFOA. The time trend described in Norwegian Environmental Agency (2018) coincides with the trend described in Land et al 2018 and the time trend in human milk in Sundström et al 2011.

Do the authors have any idea on the amounts of PFHxS intentionally produced and applied and the amount being present in mixtures of other PFCs? Furthermore the dossier could be improved by providing information about the concentrations of PFHxS for a number of uses.

The Netherlands supports meeting the bioaccumulation criterion. In our view the use of BMF and TMF data from literature is not the best way to support that criterion and can be handled in a more critical way. In quite a number of references liver concentrations are devided by whole body concentrations with relatively high values as a result. For a discussion on the topic we refer to the article of Franklin (2016), IAEM 12(1): 6-20. Half-life seems to be a better proof of bioaccumulation potential as indicated in Franklin (2016).

Persistent Organic Pollutants Review Committee

**February 2018**

**Table of contents**

[Executive summary 3](#_Toc506994602)

[1. Introduction 5](#_Toc506994603)

[1.1 Chemical Identity 5](#_Toc506994604)

[1.2 Conclusion of the POPs Review Committee regarding Annex D information 7](#_Toc506994605)

[1.3 Data sources 7](#_Toc506994606)

[1.4 Status of the chemical under international conventions and forums 8](#_Toc506994607)

[2. Summary of the information relevant to the risks profile 8](#_Toc506994608)

[2.1 Sources 8](#_Toc506994609)

[2.1.1 Production, trade, stockpiles 8](#_Toc506994610)

[2.1.2 Uses 11](#_Toc506994611)

[2.1.3. Releases to the environment 12](#_Toc506994612)

[2.2. Environmental fate 13](#_Toc506994613)

[2.2.1 Persistence 13](#_Toc506994614)

[2.2.2 PFHxS precursors and degradation 13](#_Toc506994615)

[2.2.3 Bioaccumulation and toxicokinetics 14](#_Toc506994616)

[2.2.4 Potential for long-range transport 16](#_Toc506994617)

[2.3 Exposure 17](#_Toc506994618)

[2.3.1 Environmental levels and trends 17](#_Toc506994619)

[2.3.2 Human exposure 18](#_Toc506994620)

[2.4 Hazard assessment for endpoint of concern 20](#_Toc506994621)

[2.4.1 Toxicity to aquatic organisms 20](#_Toc506994622)

[2.4.2 Toxicity in terrestrial mammals 21](#_Toc506994623)

[2.4.3 Human toxicity 23](#_Toc506994624)

[2.4.4 Mixture toxicity and combined effects of multiple stressors 24](#_Toc506994625)

[4. Concluding statement 27](#_Toc506994626)

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## Executive summary

1. The POPs Review Committee at its thirteenth meeting concluded that perfluorohexane sulfonic acid (PFHxS) fulfilled the screening criteria in Annex D and decided that issues related to the inclusion of PFHxS salts and PFHxS-related compounds that potentially degrade to PFHxS should be dealt with in developing the draft risk profile (decision POPRC-13/3). The substances covered in this risk profile include PFHxS (CAS No: 355-46-4), its salts and PFHxS-related compounds, which are any substances that contain the chemical moiety C6F13SO2 as one of their structural elements and that potentially degrade to PFHxS.
2. PFHxS, its salts and PFHxS related compounds are or have been widely used in fire-fighting foams, as surfactants, in metal plating as well as in cleaning, waxing, polish and other surface treatment products, and/or water- and stain-protective coatings for carpets, paper, leather and textiles. PFHxS is widely distributed in the environment including urban cities, rural areas and in regions with industrial activities as well as in the Arctic regions that are far away from any sources of release. In addition, PFHxS, its salts and related compounds have also been used as raw materials to produce per- and poly-fluoroalkyl substances (PFASs) based consumer products, and may also be, and have been, unintentionally produced during the electrochemical fluorination processes of other PFASs.
3. Historically, 3M was most likely the main manufacturer of PFHxS, its salts and PFHxS-related compounds with an annual production of about 227 tonnes of PFHxSF in the US in 1997. Current manufacturers of PFHxS, its salts and PFHxS related compounds include at least one producer in Italy and most likely a number of producers in China, but information in the public domain on current production volumes is limited.
4. Limited research has been conducted to specifically study the releases of PFHxS, its salts and PFHxS-related compounds in the environment. In general terms, releases to the environment occur from the production of the raw material (i.e. PFHxSF) and related compounds (i.e. PFHxS, its salts and PFHxS-related compounds), during the processing, use and disposal of these chemicals, and from consumer products containing the substances. Release of PFHxS and perfluorohexane sulfonamide (FHxSA) from consumer products has been revealed in the form of detection of the substances in dust and in wastewater, sludge and leachate from landfills. Furthermore, releases due to use of aqueous film-forming foams (AFFFs) containing PFHxS and PFHxS-related compounds such as FHxSA has been thoroughly documented publicly.
5. PFHxS is persistent in the environment. Numerous studies have reported elevated levels of PFHxS in soil, water and a variety of biota. Contamination with PFHxS is especially apparent in the vicinity of fire-fighting training areas as a result of the historical (and ongoing) use of PFHxS-containing foams. The perfluoroalkyl moiety CnF2n+1- in general is very resistant to chemical, thermal and biological degradation due to its strong carbon-fluorine bonds which makes many PFASs, particularly perfluoroalkyl acids such as perfluoroalkyl sulfonic acids, very persistent in the environment. Due to the combined hydrophilic and hydrophobic properties as well as the acid dissociation of PFHxS, it is very challenging to experimentally measure logKow. Furthermore, PFHxS is relatively water-soluble, it binds to proteins, and in fish the substance is expected to be excreted rather rapidly via the gills, resulting in that reported BAFs/BCFs are under the criteria of 5000. However, BMFs and TMFs >1 (BMF range 1.4–373 and TMF range 0.1–4.3) are available for PFHxS, including from the Arctic food chains.
6. Worldwide monitoring of water, air, sediment and biota at remote locations have detected the presence of PFHxS. At Svalbard, Norway, an annual increase has been observed in PFHxS levels in polar bear, which is most likely a result of elevated emissions due to increased volume of water transported to the Arctic. Direct transport through ocean currents is likely the main mechanism of transport to remote regions, in addition to air transport of PFHxS and its volatile precursors. PFHxS has been detected in snow, meltwater, rainwater and lichen, indicating that air transport of volatile precursors that may degrade to PFHxS locally, has occurred. Furthermore, PFHxS as well as FHxSA has been detected in leachates from landfills receiving waste from many sources, indicating possible uses of PFHxS precursors in consumer products.
7. Exposure of the general population takes place by consumption of food, including breast milk and drinking water, by inhalation of indoor air and uptake of dust from consumer products containing PFHxS, its salts and related compounds. PFHxS has been detected in human blood and breast milk from various countries worldwide, and is together with perfluorooctane sulfonic acid (PFOS), pentadecafluorooctanoic acid (PFOA) and perfluorononanoic acid (PFNA) one of the most frequently detected and predominant PFASs in human blood. The estimated serum elimination half-life of PFHxS in humans is higher than other PFASs and varies from 5.3 to 14.7 years. In women post-menarche and males, PFHxS levels increase with age, and in general, the highest levels have been observed in men.
8. PFHxS affects liver function, lipid protein metabolism and activate peroxisome proliferating receptor (PPAR)-alpha. Alterations in serum cholesterol, lipoproteins and triglycerides have been observed both in rodents and humans after PFHxS exposure. PFHxS binds to the thyroid transport protein, and affects serum thyroid hormones across species causing effects on the thyroid. Furthermore, some evidence suggests that exposure to PFHxS might affect the developing brain and immune system.
9. PFHxS is ubiquitous in environmental compartments such as surface water, deep-sea water, drinking water, waste-water treatment plants and leachates from landfills, sediment, groundwater, soil, atmosphere, dust, biota (including wildlife), and humans globally. PFHxS is persistent, bioaccumulative, toxic to animals including humans and transported to locations far from its production and use. Therefore, it is concluded that PFHxS, its salts and related compounds are likely, as a result of their long-range environmental transport, to lead to adverse human health and/or environmental effects such that global action is warranted.

# **Introduction**

1. In May 2017, Norway submitted a proposal to list perfluorohexane sulfonic acid (PFHxS), its salts and related compounds in Annexes A, B and/or C to the Convention. The proposal (UNEP/POPS/POPRC.13/4) was submitted in accordance with Article 8 of the Convention, and reviewed by the POPs Review Committee (POPRC) at its thirteenth meeting in October 2017.
2. PFHxS, its salts and PFHxS-related compounds belong to the per- and poly-fluoroalkyl substance (PFAS) group. PFASs consist of carbon chains of different chain length, where the hydrogen atoms are completely (perfluorinated) or partly (polyfluorinated) substituted by fluorine atoms (Buck et al., 2011). The very stable bond between carbon and fluorine is only breakable with high energy input. Therefore, substances like PFHxS are not degradable in the environment. However, PFHxS salts and other PFHxS related compounds (See UNEP/POPS/POPRC.14/INF/[…]) can degrade to PFHxS under environmental conditions and are therefore known as precursors.
3. PFHxS, its salt and PFHxS-related compounds have been widely used as surfactants, and to make fluoropolymers and for water- and stain-protective coatings for carpets, paper, leather and textiles (Herzke et al., 2012). Some producers in China and Italy have initiated the production of perfluorohexane sulfonyl fluoride (PHxSF)-based derivatives as alternatives in surface treatment products (Wang et al., 2013) and in certain contaminated areas high levels are found in the environment (Ma et al., 2018; Lin et al., 2009). Exposure occurs through several routes, including house dust and drinking water supplied from groundwater and surface water. PFHxS is present in some fire-fighting foams, paper, water-proofing agents and textile treatments and other products (UNEP/POPS/POPRC.13/4). PFHxS, its salts and precursors have also been used as raw materials to produce PFAS based consumer products and is also unintentionally produced during electrochemical fluorination processes in the production of other perfluoroalkanesulfonic acids (PFSAs) (such as e.g. PFOS).
4. Historically, 3M produced PFHxS as a building block for compounds incorporated in fire-fighting foams and specific postmarked carpet treatment applications (Olsen et al., 2005). According to Huang et al., 2010 as referenced in Wang et al., 2013, it is estimated that in the next 5 to 10 years production of surface treatment products containing PFHxSF- or perfluorobutansulfonyl fluoride (PFBSF)-derivatives will reach more than 1000 tonnes annually in China.

## 1.1 Chemical Identity

1. The proposed compounds included in the nomination of PFHxS, its salts and PFHxS-related compounds were defined in document UNEP/POPS/POPRC.13/4 and in decision POPRC-13/3 (UNEP/POPS/POPRC.13/7). A non-exhaustive list of substances including CAS numbers are contained in the information document (UNEP/POPS/POPRC.14/INF/[…]). In line with decision POPRC-13/3, the following apply:
2. Perfluorohexane sulfonic acid (CAS No: 355-46-4, PFHxS);
3. Any substance that contains the chemical moiety C6F13SO2 as one of its structural elements and that potentially degrades to PFHxS.
4. A number of chemicals are included in the group of PFHxS, its salts and PFHxS-related compounds and some examples are given in Figure 1. The Organisation for Economic Co-operation and Development (OECD) has identified [number to be inserted] PFHxS-related/precursor/polymer substances which all contain the fluorinated alkyl moiety C6F13SO2 (OECD, […]) and a study published by the Norwegian Environment Agency identified 79 commercially available compounds including PFHxS and PFHxSF (Norwegian Environment Agency, 2017a, M-792/2017).

a) Perfluorohexane sulfonic acid (CAS No: 355-46-4)



c) Perfluorohexanesulfonate ammonium salt

(CAS No: 68259-08-5)



d) Perfluorohexanesulfonate potassium salt

(CAS No: 3871-99-6)

b) Perfluorohexanesulfonyl fluoride (CAS No: 423-50-7)

Precursor/start material

**Figure 1.** Structural formula for PFHxS (a), its raw material PFHxSF (b), and its related compounds FHxSNH4 (c) and PFHxSK (d)

1. PFHxS is a strong acid with six fully fluorinated carbons, having both hydrophobic- and hydrophilic properties making it oil- and water-repellent ([Kissa, 2001](#_ENREF_63)). Experimental data on the physicochemical properties of PFHxS are limited (Kim et al., 2015), however, some studies (Wang et al., 2011; Ding and Peijnenburg, 2013; Kim et al., 2015) have reported some empirical and estimated physicochemical properties of PFHxS and its related compounds. Table 1 lists the chemical identity of PFHxS, and Table 2 lists selected modelled and experimental physicochemical properties for PFHxS.

**Table 1.** Chemical identity of PFHxS

|  |  |
| --- | --- |
| CAS number: | 355-46-4 |
| IUPAC name: | 1,1,2,2,3,3,4,4,5,5,6,6,6-tridecafluorohexane-1-sulfonic acid |
| EC number: | 206-587-1 |
| EC name: | Perfluorohexane-1-sulphonic acid |
| Molecular formula: | C6F13SO3H |
| Molecular weight: | 400.11 |
| Synonyms: | PFHxS  PFHS  Perfluorohexanesulfonic acid;  1,1,2,2,3,3,4,4,5,5,6,6,6-Tridecafluorohexane-1-sulfonic acid;  Tridecafluorohexane-1-sulfonic acid;  1-Hexanesulfonic acid, 1,1,2,2,3,3,4,4,5,5,6,6,6-tridecafluoro-;  1,1,2,2,3,3,4,4,5,5,6,6,6-Tridecafluoro-1-hexanesulfonic acid;  Tridecafluorohexanesulfonic acid |
| Trade names | RM70 (CAS No: 423-50-7), RM75 (3871-99-6), and RM570 (CAS No: 41997-13-1) (PFHxS-related substances produced by Miteni SpA, Italy).  FC-95 Fluorad brand fluorochemical surfactant (CAS No: 3871-99-6). Contains PFHxS-K produced by 3M. |

**Table 2.** Overview of selected physicochemical properties for PFHxS

|  |  |  |
| --- | --- | --- |
| **Property** | **Value** | **Reference** |
| Physical state at 20°C and 101.3 kPa | Solid white powder for PFHxS-K | As referenced in ECHA, 2017a (Company provided) |
| Melting point | 320 K (41°C) | Kim et al., 2015 |
| Boiling point | 238–239°C | Kosswig, 2000 (measured) |
| pKA | -3.45  -3.3±0.5  -5.8±1.3 | Wang et al., 2011 (COSMOterm)  ACD/Percepta 14.2.0 (Classic)  ACD/Percepta 14.2.0 (GALAS) |
| Vapour pressure | 58.9 Pa (0.0046 mmHg) | Wang et al., 2011(COSMOterm ) |
| Water solubility for PFHxS-K | 1.4 g/L (20–25°C) | Campbell et al., 2009 (measured) |
| Air/water partition coefficient, Kaw (log value)\* | -2.38 | Wang et al., 2011 (COSMOterm) |
| n-Octanol/water partition coefficient, Kow (log value) | 5.17 | Wang et al., 2011 (COSMOterm ) |
| Octanol-air partition coefficient Koa (log value) | 7.55 | Wang et al., 2011 (COSMOterm ) |
| Organic carbon/water partition coefficient Koc (log value)  (mobility) | 2.05  2.40 | Guelfo and Higgins, 2013 (measured)  D'Augostino & Mabury, 2017 (measured) |

\* The estimate refers to the neutral form, i.e. does not consider the fact that PFHxS is present in its anionic form under environmental conditions.

1. As discussed in ECHA 2017a, the experimental determination of partition coefficients is difficult because of the surface-active properties of the ionic PFSAs. The presence of ionic PFSAs depends on the dissociation of PFSAs in aqueous media. There are models available, i.e. COSMOtherm calculating partitioning coefficients of neutral PFAS. COSMOtherm is a quantum chemistry-based method that requires no specific calibration and is the method used in Wang et al., 2011. Therefore, COSMOtherm is expected to be able to estimate properties for PFSAs and PFCAs. Studies have shown that properties estimated with COSMOtherm showed good agreement with the experimental data for a number of PFAS (Arp et al., 2006; Wang et al., 2011).

## 1.2 Conclusion of the POPs Review Committee regarding Annex D information

1. The POPs Review Committee evaluated the proposal by Norway to list PFHxS, its salts and PFHxS-related compounds under the Convention as well as additional scientific information provided by members and observers at its thirteenth meeting. The committee concluded that PFHxS met the screening criteria specified in Annex D (decision POPRC-13/3). It was decided to review the proposal further and to prepare a draft risk profile in accordance with Annex E to the Convention and that issues related to the inclusion of PFHxS salts and PFHxS-related compounds that potentially degrade to PFHxS should be dealt with in developing the draft risk profile.

## 1.3 Data sources

1. The draft risk profile is based on the following data sources:
2. The proposal to list perfluorohexane sulfonic acid (PFHxS), its salts and PFHxS-related compounds submitted by Norway (UNEP/POPS/POPRC.13/4);
3. Information submitted by the following Parties and observers according to Annex E to the Convention: Canada, China, Denmark, Ecuador, Germany, Japan, Monaco, Netherlands, Sweden, United Kingdom, United States, Alaska Community Action on Toxics and International POPs Elimination Network (ACAT/IPEN), Council of Chemists of the Province of Treviso, FluoroCouncil, Basel and Stockholm Conventions Regional Centre in China;
4. The supporting documents for the identification of PFHxS as a Substance of Very High Concern (SVHC) prepared by Sweden, where PFHxS was recently identified as very persistent and very bioaccumulative (vPvB) in the European Union (ECHA, 2017a, b);
5. Reports and other grey literature as well as information from peer-reviewed scientific journals;
6. The Australian National Industrial Chemicals Notification and Assessment Scheme (NICNAS) various tier II assessment for perfluoroalkane sulfonates (C5–C7) (NICNAS, 2017a, b, c, d);
7. AMAP, 2017. AMAP Assessment 2016: Chemicals of Emerging Arctic Concern. Arctic Monitoring and Assessment Programme (AMAP), Oslo, Norway. xvi+353pp.

## 1.4 Status of the chemical under international conventions and forums

1. In 2017, PFHxS and its salts were identified as Substances of Very High Concern (SVHC) and added to the REACH Candidate List due to their persistent and bioaccumulative properties (ECHA, 2017a). Inclusion on this list means the substances can be subject to further review and only used for specific authorized purposes under strictly controlled conditions. Moreover, upon request industry is obliged to inform consumers on the occurrence of the listed substances in consumer articles.
2. In Norway, PFHxS was recently added to the national list of priority substances (Prioritetslista http://www.miljostatus.no/prioritetslisten) with a national goal to phase out the use within 2020. Some of the substances belonging to the PFHxS substance group (not PFHxSF) are listed on the Canadian Domestic Substances List (DSL) (Environment Canada, 2013), an inventory of substances manufactured in, imported into or used in Canada on a commercial scale. The DSL categorizes substances according to whether they are persistent and/or bioaccumulative and/or toxic. In the United States new uses of the chemicals in this group are prohibited without prior approval from the United States Environmental Protection Agency (US EPA) ([United States Government, 2002](https://www.nicnas.gov.au/chemical-information/imap-assessments/imap-assessments/tier-ii-environment-assessments/direct-precursors-to-perfluoroheptanesulfonate-pfhps,-perfluorohexanesulfonate-pfhxs-and-perfluoropentanesulfonate-pfpes#_ENREF_55); [2007](https://www.nicnas.gov.au/chemical-information/imap-assessments/imap-assessments/tier-ii-environment-assessments/direct-precursors-to-perfluoroheptanesulfonate-pfhps,-perfluorohexanesulfonate-pfhxs-and-perfluoropentanesulfonate-pfpes#_ENREF_56)). The US EPA published an action plan on long-chain PFAS, including PFHxS, and their salts and precursors in 2009. All chemicals were identified as persistent, bioaccumulative and toxic ([US EPA, 2009](https://www.nicnas.gov.au/chemical-information/imap-assessments/imap-assessments/tier-ii-environment-assessments/direct-precursors-to-perfluoroheptanesulfonate-pfhps,-perfluorohexanesulfonate-pfhxs-and-perfluoropentanesulfonate-pfpes#_ENREF_57)).
3. OECD provided a recent overview on risk reduction approaches for PFASs across countries (OECD, 2015). Responses from participating countries indicated that risk reduction approaches for PFASs are mainly covered under existing national and/or regional regulatory frameworks and cover principally long chain PFASs and their precursors and salts. The type of risk reduction approaches implemented across countries varies, but there is often a combination of voluntary and regulatory approaches that are used.
4. No harmonized classification or labelling is available for PFHxS in EU or globally.

# **2. Summary of the information relevant to the risks profile**

## 2.1 Sources

### 2.1.1 Production, trade, stockpiles

1. As with PFOS, its salts and PFOS-related compounds, PFHxS, its salts and PFHxS-related compounds have been produced from a common parent compound, perfluorohexane sulfonyl fluoride (PFHxSF). PFHxSF may be intentionally produced from the electrochemical fluorination of hexanesulfonyl chloride (C6H13SO2Cl + 14 HF 🡪 C6F13SO2F + HCl + byproducts) with a yield of about 36% (Gramstad and Haszeldine, 1957).
2. In addition, PFHxSF may be unintentionally produced as a byproduct from the electrochemical fluorination of octanesulfonyl fluoride or chloride, the process to produce perfluorooctane sulfonyl fluoride (POSF) (Gramstad and Haszeldine, 1957). Unless manufacturers remove PFHxSF from POSF, it would stay in POSF and also react with reactants to form PFHxS, its salts and/or PFHxS-related compounds as byproducts in PFOS and its related compounds, as shown in, e.g., 3M, 2015; Herzke et al., 2012; Huang et al., 2015. It is likely that the ratios of PHxSF yields to POSF yields in the production of POSF are between 4% (Gramstad and Haszeldine, 1957) and 14.2% (reported by a Chinese manufacturer; Ren, 2016). This is supported by measured ratios of PFHxS to PFOS in commercial PFOS product, namely 3.5%–9.8% in 3M’s FC-95 (3M, 2015) and 11.2%–14.2% in three products from China (Jiang et al., 2015).
3. PFHxS and its salts may be produced after the hydrolysis of PFHxSF (Gramstad and Haszeldine, 1957). As with POSF (3M, 1999), PFHxSF may be further reacted with methyl- or ethylamine to form N-methyl or N-ethyl perfluorohexane sulfonamide (N-MeFHxSA or N-EtFHxSA), which may subsequently react with ethylene carbonate to yield N-methyl or N-ethyl perfluorhexane sulfonamide ethanols (N-MeFHxSE or N-EtFHxSE). N-MeFHxSA, N-EtFHxSA, N-MeFHxSE and N-EtFHxSE may be used as the building blocks of PFHxS-related compounds.
4. The information on the production of PFHxS, its salts and PFHxS-related compounds is scarce in the public domain and mostly qualitative rather than quantitative. Historically, 3M was likely the biggest global manufacturer of PFHxS, its salts and PFHxS-related compounds, with an annual production of about 227 tonnes of PFHxSF in the US in 1997 (3M, 2000a); in 2000–2002, 3M ceased its production of PFHxS, its salts and PFHxS-related compounds (3M, 2000a). In addition, there may have been some (historical) production by Dainippon Ink and Chemicals in Japan (Dainippon, 1979, 1983a,b, 1985, 1986, 1988; Dainippon and Kawamura, 1981, 1983a,b,c). Further historical and/or current manufacturers of PFHxS, its salts and PFHxS-related compounds include at least Miteni from Italy (Miteni, 2018) as well as Hubei Hengxin (Hengxin, 2018), Wuhan Defu (Defu, 2018), Wuhan Yangtze River (Yangtze River, 2018), Wuhan Fengfan (Huang et al., 2015), Shanghai Vatten (Vatten, 2018; Huang et al., 2015) and Time Chemical (Time, 2018) from China.
5. Using market research reports for PFHxS (CAS No: 355-46-4) and PFHxSF (CAS No: 423-50-7), review of peer-reviewed literature and other information sources in the public domain seach, and stakeholder consulations the Norwegian Environment Agency (Report M-961/2018) performed a project to shed light on the sources to PFHxS in the environment. Information on the global production and use of PFHxS, its salts and related compounds and content in consumer products were collected. Across all evaluated sources of information as well as from consultation of stakeholders, it was found that there is a lack of publicly available information on the quantitative production levels and descriptions of product-specific uses of PFHxS and PFHxS-related compounds. There was also a lack of willingness from stakeholders to release such information. In addition, the quality of the market research reports is questionable and did not cover the global producers since only two producers in China were reflected in the reports.
6. Historical production or import of PFHxS, its salts and PFHxS-related compounds in the US is extracted from the United States Environmental Protection Agency (US EPA) Inventory Updating Reporting Database and summarized in Table 3 below. In addition, an OECD survey in 2004 reported that <4000 kg of PFHxSF, <1500 kg of PFHxS, and <600 kg of FHxSA were produced in 2003 in Italy (OECD, 2005). Similarly, the subsequent two OECD surveys reported the production of some PFHxS, its salts and PFHxS-related compounds, but with no information on their respective production volumes and locations (OECD, 2006, 2010).

**Table 3.** Overview of PFHxS salts and PFHxS-related compounds manufactured or imported in the US (source: US EPA Inventory Updating Reporting).

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **CAS number** | **Chemical** | **Reporting years (in tonnes)** | | | | |
| **1986** | **1990** | **1994** | **1998** | **2002** |
| 423-50-7 | PFHxSF | 4.5–226 | 4.5–226 | No Reports | 4.5–226 | No Reports |
| 3871-99-6 | PFHxSK | No Reports | 4.5–226 | No Reports | No Reports | No Reports |
| 34455-03-3 | EtFHxSE | 4.5–226 | 4.5–226 | 4.5–226 | 4.5–226 | No Reports |
| 50598-28-2 | FHxSA-derivative | No Reports | 4.5–226 | 4.5–226 | 4.5–226 | 10 – 500 |
| 68555-75-9 | MeFHxSE | 4.5–226 | 4.5–226 | 4.5–226 | 4.5–226 | No Reports |
| 67584-57-0 | MeFHxSE-acrylate | 4.5–226 | 4.5–226 | 4.5–226 | 4.5–226 | No Reports |
| 38850-58-7 | FHxSA-derivative | 4.5–226 | > 226–450 | 4.5–226 | No Reports | No Reports |
| 73772-32-4 | FHxSA-derivative | No Reports | No Reports | No Reports | 4.5–226 | No Reports |
| 68815-72-5 | PFHxS-ester | 4.5–226 | 4.5–226 | 4.5–226 | 4.5–226 | No Reports |

1. Furthermore, it is noted that PFHxS, its salts and many PFHxS-related compounds have been listed on multiple national chemical registration inventories (see Table 4), indicating historical production, importation and/or uses of products containing these substances, historically and/or ongoing.
2. Despite being manufactured in a limited number of countries, PFHxS, its salts and PFHxS-related compounds have been distributed globally through the trade of products containing these substances, particularly some old generations of aqueous film-forming foams (AFFFs) that are previously known as “PFOS-based AFFFs” (for more details on such products, see the next section).

**Table 4**. Overview of PFHxS, its salts and PFHxS-related compounds identified in various national chemical inventories, including the Australian Inventory of Chemical Substances (AICS), the Canadian Domestic Substance List (DSL) (Environment Canada, 2013), the Inventory of Existing Chemical Substances in China (IECSC), the Japanese Existing and New Chemical Substances Inventory (ENCS), the Substances in Preparations in Nordic Countries (Nordic SPIN), and the United States Toxic Substances Control Act Inventory (US TSCA).

| **CAS number** | **Chemical** | **AICS** | **Canada**  **DSL** | **China**  **IECSC** | **Japan**  **ENCS** | **Nordic**  **SPIN** | **US**  **TSCA\*** |
| --- | --- | --- | --- | --- | --- | --- | --- |
| 423-50-7 | PFHxSF | yes |  | yes |  |  | yes; S |
| 355-46-4 | PFHxS |  |  |  |  |  | yes; S |
| 3871-99-6 | PFHxS, K | yes | yes | yes | yes | yes | yes; S |
| 55120-77-9 | PFHxS, Li |  |  | yes | yes |  | yes; P,S |
| 68259-08-5 | PFHxS, NH4+ | yes | yes | yes |  |  | yes; S |
| 70225-16-0 | PFHxS, NH(CH2CH­2OH)2 | yes | yes | yes |  | yes | yes; S |
| 68259-15-4 | MeFHxSA |  | yes | yes |  |  | yes; S |
| 68555-75-9 | MeFHxSE | yes | yes | yes |  | yes | yes; S |
| 34455-03-3 | EtFHxSE | yes | yes | yes |  | yes | yes; S |
| 50598-28-2 | FHxSA-derivative |  |  | yes |  |  | yes; S |
| 68957-61-9 | FHxSA-derivative | yes | yes |  |  |  | yes; S |
| 68957-32-4 | EtFHxSE-derivative |  |  |  |  |  | yes; S |
| 67584-53-6 | EtFHxSE-derivative | yes | yes | yes | yes | yes | yes; S |
| 68555-70-4 | EtFHxSE-derivative |  |  |  |  |  | yes; S |
| 68298-09-9 | FHxSA-derivative |  |  |  |  |  | yes; S |
| 68957-58-4 | FHxSA-derivative | yes | yes | yes | yes | yes | yes; S |
| 52166-82-2 | FHxSA-derivative | yes | yes | yes | yes | yes | yes; S |
| 66008-72-8 | MeFHxSA-derivative |  | yes |  |  |  | yes; S |
| 68227-98-5 | MeFHxSE-acrylate |  |  |  |  |  | yes; S |
| 67584-57-0 | MeFHxSE-acrylate |  |  | yes |  | yes | yes; S |
| 67584-61-6 | MeFHxSE-acrylate |  |  | yes |  | yes | yes; S |
| 38850-52-1 | FHxSE-derivative |  |  |  |  |  | yes; S |
| 1893-52-3 | EtFHxSE-acrylate | yes |  | yes |  |  | yes; S |
| 38850-60-1 | FHxSA-derivative |  |  |  |  |  | yes; S |
| 80621-17-6 | FHxSA-derivative |  |  | yes | yes |  |  |
| 67906-70-1 | EtFHxSE-acrylate |  |  | yes |  |  | yes; S |
| 38850-58-7 | FHxSA-derivative | yes | yes | yes |  | yes | yes; S |
| 73772-32-4 | FHxSE-derivative | yes |  | yes |  |  | yes; S |
| 81190-38-7 | FHxSE-derivative | yes |  | yes |  |  | yes; S |
| 67939-92-8 | EtFHxSE-derivative |  |  |  |  |  | yes; S |
| 68815-72-5 | PFHxS-ester | yes | yes | yes |  | yes | yes; S |
| 68555-90-8 | MeFHxSE-acrylate polymer mixtures | yes | yes | yes |  |  | yes; S |
| 56372-23-7 | EtFHxSE-driv. polyethoxylates | yes | yes | yes |  | yes | yes; S |
| 30295-56-8 | FHxSA-derivative |  |  | yes |  |  |  |
| 70776-36-2 | MeFHxSE-acrylate polymer mixtures | yes | yes | yes |  |  | yes; S |
| 68877-32-7 | EtFHxSE-acrylate polymer mixtures |  | yes |  |  |  | yes; S |
| 68586-14-1 | MeFHxSE-acrylate polymer mixtures | yes | yes | yes |  |  | yes; S |
| 68555-92-0 | MeFHxSE-acrylate polymer mixtures | yes | yes | yes |  |  | yes; S |
| 68555-91-9 | EtFHxSE-acrylate polymer mixtures | yes | yes | yes |  |  | yes; S |

\* S=substances listed under the Significant New Use Rule; P=chemicals with a commenced pre-manufacture notice (P).

### 2.1.2 Uses

1. Due to the thermal and chemical stability as well as the hydro- and oleophobicity of the perfluoroalkyl moiety (CnF2n+1-), PFHxS, its salts and PFHxS-related compounds can be used as effective surfactants and/or surface protectors. PFHxS, its salts and PFHxS-related compounds have been intentionally used at least in the following applications: (1) AFFFs for firefighting; (2) metal plating; (3) textiles, leather and upholstery; (4) polishing agents and cleaning/washing agents; (5) impregnation/proofing (for protection from damp, fungus, etc.); and (6) within the manufacturing of semiconductors. In addition, other potential use may include pesticides and flame retardants. Details on these identified uses and potential uses are elaborated below. Furthermore, it should be noted that information on the volumes and uses of many PFHxS, its salts and PFHxS-related compounds has been reported to the competent authorities in Denmark, Sweden and Norway, but most of such information has been claimed as confidential business information (SPIN, 2018). In light of information identified recently by the Norwegian Environment Agency (M-961/2018) and in other public sources, PFHxS, its salts and PFHxS-related compounds have been intentionally used at least in the following applications textile, electronics and semiconductors, coatings, packaging, industrial fluids, agrichemicals, surfactants and foams, in intermediate feedstocks as well as other unspecified uses.

**AFFFs for firefighting**

1. Historically, 3M used PFHxS in the production of its AFFF formulations (Olsen et al., 2005). This is in accordance with patents from 3M (3M, 1972, 1973, 1992) and from another potential historical producer (Dainippon and Kamura, 1983c; Dainippon, 1983b, 1985, 1986). In particular, 3M (1992) indicates that PFHxS-related compounds and PFOS were likely used in the same AFFF formulations, i.e. previously known as “PFOS-based AFFFs” (e.g. FC-600). This is in good agreement with measurements of legacy AFFF formulations (Vecitis et al., 2010; Herzke et al., 2012; Place et al., 2012; Houtz et al., 2013; Weiner et al., 2013; D’Agostino et al., 2014; Barzen-Hanson et al., 2017; Favreau et al., 2017). It is also well supported by measurements of environmental media at AFFF-impact sites (Backe et al., 2013; Houtz et al., 2013; Baduel et al., 2017; Barzen-Hanson et al., 2017; Bräunig et al., 2017; Lanza et al., 2017) and by measurements of firefighters’ serum levels (Jin et al., 2011; Rotander et al., 2015), where similar or higher levels of PFHxS than that of PFOS were detected, and in some cases, elevated levels of PFHxS-related compounds were identified. It is likely that such PFHxS-related compounds containing “PFOS-based AFFFs” have been discontinued after 3M ceased its global production in 2000–2002 (3M, 2000a). However, there may still be substantial stockpiles of such legacy AFFF formulations around the world (UN Environment, 2011; Zushi et al., 2017). Furthermore, Shanghai Vatten has recently developed and commercialized at least one new PFHxS-related amphoteric surfactant for foam fire-extinguisher (Vatten, 2018; Huang et al., 2015).

**Metal plating**

1. A number of patents (Dainippon, 1979, 1988; 3M, 1981; Hengxin, 2015) were identified, suggesting PFHxS, its salts and various PFHxS-related compounds may have been used in metal plating as mist suppressants. It is likely that at least Hubei Hengxin from China has marketed the potassium salt of PFHxS for metal plating (Hengxin, 2018). Furthermore, it should be noted that the manufacturing (including importing) or processing of one salt of PFHxS (tridecafluorohexanesulphonic acid, compound with 2,2'-iminodiethanol (1:1); CAS No: 70225-16-0) for use as a component of an etchant, including a surfactant or fume suppressant, used in the plating process to produce electronic devices shall not be considered a significant new use subject to reporting under the US Environmental Protection Agency Significant New Use Rule on perfluroalkyl sulfonates and long-chain perfluoroalkyl carboxylate chemical substances (US EPA, 2013).

**Textiles, leather and upholstery**

1. Historically, 3M used PFHxS-related compounds in some of its aftermarket (post-production) carpet protection products (Olsen et al., 2005), e.g., those carpet and upholstery protector containing FC-228 (ITEM, 2004). This is in accordance with the measured higher serum PFHxS concentrations (range 27.5–423 ng/mL) than that of PFOS (15.2–108 ng/mL), as well as highly elevated levels of PFHxS in household dust and carpets of a Canadian family, whose household carpets were treated 8 times with Scotchgard formulations over 15 years (Beesoon et al., 2012). It is likely such aftermarket carpet and upholstery protector productshave been discontinued after 3M ceased its global production in 2000–2002 (3M, 2000a). However, it is reported that water-proofing textile finishes based on PFHxS-based compounds have recently been developed by at least Hubei Hengxin Chemical Co., Ltd. (CAS No: 68259-15-4, (tridecafluoro-N-methylhexanesulphonamide); CAS No: 68555-75-9 (tridecafluoro-N-(2-hydroxyethyl)-N-methylhexanesulphonamide); and CAS No: 67584-57-0, (2-[methyl[(tridecafluorohexyl)sulphonyl]amino]ethyl acrylate)) and Wuhan Fengfan Surface Engineering Co., Ltd. from China (Huang et al., 2015; Hengxin, 2018), as alternatives to PFOS-based compounds (Huang et al., 2015). The industrial activities with C-6 waterproofing agent for textiles in the Taihu Lake region in China might be a potential source of PFHxS where recent production and use of PFHxS as an alternative to PFOS and PFOA has been reported (Ma et al., 2017). In 2010, it was estimated that the production of surface treatment products containing PFHxS- or perfluorobutane sulfonic acid (PFBS)-related compounds in China would reach 1000 tonnes per year in the next 5–10 years (Huang et al., 2010); no recent update of this estimate is currently available.

**Polishing agents and cleaning/washing agents**

1. One PFHxS-related compound (CAS No: 67584-53-6, [N-Ethyl-N-(tridecafluorohexyl) sulfonyl]glycine, potassium salt) was reportedly used in polishing agents and cleaning/washing agents at least between 2000 and 2015 in Denmark, Norway and Sweden with the use volumes claimed as confidential business information (SPIN, 2018). For example, the FCP102 Floor Sealer and FCP300 Duro Gloss Floor Sealer & Finish from Fritztile contain this compound (Fritztile, 2018a,b).

**Impregnation/proofing**

1. One PFHxS-related compound (CAS No: 67584-61-6, 2-[Methyl[(Tridecafluorohexyl) Sulphonyl]Amino]Ethyl Methacrylate) was reportedly used in impregnation/proofing for protection from damp, fungus, etc. at least in four products between 2003 and 2009 in Denmark (SPIN, 2018).

**Within the manufacturing of semiconductors**

During the POPRC-13 meeting in 2017, an industry representative noted that PFHxS, its salts and PFHxS-related compounds are currently being used as replacements to PFOS, PFOA and their related compounds in the semiconductor industry. This information is further strengthened by published information that indicates that PFHxS is used in the semiconductor industry in Taiwan (Lin et al., 2010). PFHxS (133–330 ng/L), together with PFOS (128–670 ng/L), was one of the primary contaminants at a semiconductor fabrication plant waste water effluent site. Both PFSAs are present in the effluent in similar amounts showing that PFHxS is a primary substance in this process and are not unintentionally present.

**Other potential uses**

1. Hubei Hengxin has marketed the potassium salt of PFHxS and PFHxS-related compounds (CAS No: 68259-15-4, tridecafluoro-N-methylhexanesulphonamide) for potential uses as a flame retardant and in pesticides, respectively (Hengxin, 2018).

### 2.1.3. Releases to the environment

1. To date, limited research has been conducted to specifically study the releases of PFHxS, its salts and PFHxS-related compounds in the environment, resulting in a lack of quantitative information on releases, although various studies have detected the ubiquitous presence of PFHxS in the environment (for details, see section Environmental levels and trends below). The occurrence of PFHxS and its related compounds in the environment is a result of anthropogenic production, use and disposal, since they are not naturally occurring substances. Unintentionally produced PFHxS, its salts and PFHxS-related compounds that are byproducts contained in PFOS, its salts and PFOS-related compounds are likely to have the same release pathways as the respective PFOS, its salts and PFOS-related compounds, which have been described in detail previously (3M, 2000b; UN Environment, 2006). In addition, as with PFOA, PFOS and their related compounds (3M, 2000b; UN Environment, 2006, 2016), intentionally produced PFHxS and its related compounds may be released during their whole life cycle: they can be released at their production, at their assembly into a commercial product, during the distribution and industrial or consumer use, as well as from waste treatment facilities such as landfills and wastewater treatment plants (Shafique et al., 2017), including from land treatment using contaminated sludge from wastewater treatment plants. Studies indicate that PFHxS remain relatively unchanged throughout the successive treatment steps (Kunacheva et al., 2011, Thompson et al., 2011).Furthermore, PFHxS-related compounds may be transformed to PFHxS in the environment and biota (for details, see section on PFHxS precursors and degradation below).
2. Investigations revealed that PFHxS was the main PFAS constituent in the final waste effluent from a semiconductor fabrication plant and that the amount of waste effluent was estimated to be >5000 tonnes/day. The corresponding mass of PFHxS generated each day from the manufacturing prosess was estimated to be >0.67 kg (Lin et al., 2009). In the same study, raw waste effluent from an electronic/optoelectronic fabrication plant was analysed for content of PFASs. However, in this effluent the main constituent was PFOA, and PFHxS as found at low levels.
3. The contributions of individual stages to overall releases throughout the life cycle, and receiving environmental media, may vary across compounds and applications. In general, manufacturing processes constitute a major source of PFHxS, its salts and PFHxS-related compounds to the local environment, e.g., in elevated levels of PFHxS in water and the population close to a production plant in Minnesota, the US (Oliaei et al., 2012). In addition, some uses of PFHxS, its salts and PFHxS-related compounds may result in direct environmental releases. For example, the use of relevant AFFFs in fire-fighting training and real incidences, as well as accidental releases, contribute a substantial amount of PFHxS, its salts and PFHxS-related compounds in the environment (e.g., Backe et al., 2013; Houtz et al., 2013; Baduel et al., 2017; Barzen-Hanson et al., 2017; Bräunig et al., 2017; Lanza et al., 2017). In contrast, some other uses of PFHxS, its salts and PFHxS-related compounds may lead to first releases to indoor environment. One example is releases of PFHxS, its salts and PFHxS-related compounds from treated carpets to household dusts (Beesoon et al., 2012).

## 2.2. Environmental fate

### 2.2.1 Persistence

1. There are some characteristics which are valid for the whole group of PFASs, and therefore also for PFHxS. PFASs are very resistant to chemical, thermal and biological degradation due to their strong carbon-fluorine bonds ([Kissa, 2001](#_ENREF_63)) and resistance to degradation makes them persistent in the environment. The stability of organic fluorine compounds has been described in detail (Siegemund et al., 2000 as referenced in ECHA, 2017a). When all valences of a carbon chain are saturated by fluorine, the carbon skeleton is twisted out of its plane in the form of a helix and this structure shields it from chemical attack. Several other properties of the carbon fluorine bond contribute to the fact that highly fluorinated alkanes are the most stable organic compounds. These include polarizability and high bond energies, which increase with increasing substitution by fluorine. The influence of fluorine is greatest in highly fluorinated and perfluorinated compounds (Siegemund et al., 2000 as referenced in ECHA, 2017a).
2. Experimental data on the persistence of PFHxS are very sparse. However, in a field study on photolysis of PFHxS in water was conducted at high altitude in Mt. Mauna and Mt. Tateyama, no photolysis was observed for PFHxS following, respectively, 106 and 20.5 days of exposure (Taniyasu et al., 2013; Wang et al., 2015a).
3. PFHxS is found in soil, water and a variety of biota (see UNEP/POPS/POPRC.14/INF/[…]) in the vicinity of fire-fighting training areas following historical (and ongoing) use of PFHxS-containing foams (Braunig et al., 2017; Filipovic et al., 2015). Although no degradation studies were performed, results show that PFHxS is persistent and does not undergo significant abiotic or biotic degradation under normal environmental conditions after use of AFFF.
4. There are no available experimental biodegradation data in water or soil for PFHxS. However, results for PFOS and PFOA used in a read-across approach indicate that PFHxS is not readily biodegradable. Biodegradation of the structural analogue PFOS has been evaluated in a number of tests in several studies. Aerobic biodegradation has been tested in activated sewage sludge, sediment cultures and soil cultures (ECHA, 2017a). Anaerobic biodegradation has been tested in sewage sludge. PFOS did not in any of these tests show any sign of biodegradation (UNEP/POPS/POPRC.2/17/Add.5). The very Persistence (vP) of PFOA in water, sediment and soil has also been confirmed (ECHA, 2013). Since the stability of PFSAs is in general based on the stability of the fluorinated carbon chain, it can also be concluded for PFHxS that no biodegradation can be expected in water, soil or sediment. Thus, it can be assumed that PFHxS is not biodegradable and is very persistent in water soil and sediment (ECHA, 2017a).
5. Furthermore, based on a read-across approach, conclusions applied to the persistence of other PFASs such as PFOS and perfluorobutane sulfonic acid (PFBS) can be anticipated to be valid for PFHxS as well. Thus, PFHxS is not expected to undergo hydrolysis or photolysis, and biodegradation and, like other PFASs, found to be poorly removed in waste water treatment plants (Danish Ministry of Environment, 2015). To our knowledge, there are no other degradation studies available on PFHxS.

### 2.2.2 PFHxS precursors and degradation

Due to the lack of experimental data, a theoretical assessment of abiotic degradation pathways to PFHxS has been performed (Norwegian Environment Agency, 2017a, M-792/2017). Based on available data on the degradation of PFBS- and PFOS-precursors, PFHxS precursors are anticipated to degrade to PFHxS in the environment. Results from this study indicated that substances containing the moiety C6F13SO2 may undergo abiotic degradation resulting in the release of PFHxS and C6 perfluoralkyl carboxylic acids (PFCA). However, comparing with PFOS degradation studies, one may expect that major products from abiotic degradation would rather be PFCA (PFHxA) than PFHxS (10:1), whereas major products from biotic degradation would be almost solely PFHxS (Wang et al., 2014¸ Norwegian Environment Agency, 2017a, M-792/2017).

1. Analytical methods for identifying and quantifying PFHxS-related compounds (e.g. perfluorohexane sulfonamides (FHxSA)) are at present very limited. One study using non-target analysis detected FHxSA in AFFF-impacted groundwater, 3M historical AFFF, and consumer products (Barzen-Hanson et al., 2017). Although the data is not quantitative, they do show that PFHxS precursors have been used and that they are present in the environment. A recent study by D'Agostino and Mabury, 2017, reported that precursors of PFHxS are broadly present in urban- and AFFF-impacted Canadian surface waters. FHxSA was detected in surface water from sites with AFFF-impact and from sites without known FHxSA sources (D'Agostino and Mabury, 2017). FHxSA was found ubiquitously in all urban waters but at significantly lower levels than in AFFF-impacted waters. The study does not reveal whether the detected FHxSA was a result of direct use of FHxSA or indirect unintentional use due to contamination, but the authors conclude that these precursors are present in Canadian urban- and AFFF-impacted surface water and that they so far have been rarely considered (D'Agostino and Mabury, 2017). However, FHxSA has previously been detected in AFFF as well as AFFF-impacted water, soil, and aquifer solids (Houtz et al., 2013; McGuire et al., 2014) and in tapwater from Canada, EU, Ivory Coast and China (Kabore et al., 2018).
2. A study from the north of Sweden showed that the concentration of PFHxS increased over a time-period of 1–14 days in a snowpack during seasonal melt. Furthermore, the PFHxS detected at different depths of the snowpack showed the highest concentration in the deepest layer (Codling et al., 2014). The reason for this increase during melting is unknown but one possible explanation is that PFHxS precursors transported through air precipitate locally and photodegrade to PFHxS during snowmelt. Meyer et al., 2011, also observed this phenomenon of enrichment in the melting snowpack of an urban watershed in Toronto, Canada. The fate of PFHxS and/or its precursors during snowpack ageing and the release during periods of melt could therefore influence their loading to both surface and ground waters. Furthermore, in a Dutch study, PFHxS was detected in infiltrated rainwater and the authors suggested that the presence of PFHxS could be due to degradation of precursors in the atmosphere (Eschauzier et al., 2010).
3. A variety of consumer products (e.g., textiles, paper, and carpets) and packaging containing PFASs and PFAS precursors are sent to municipal landfills at the end of their use life time. In a recent review it was reported that PFASs are routinely detected in landfill leachate with PFASs (C4–C7) being most abundant, possibly an indication of their greater mobility, and reflecting the shift toward usage of shorter-chain substances (Hamid et al., 2018). Furthermore, PFAS (C4–C7) substances are more easily released and prone to leach from landfills due to their higher water solubility and lower log Koc relative to longer-chain PFAS (Guelfo & Higgins, 2013). Following disposal, PFASs are released from the waste through biological and abiotic leaching (Allred et al., 2015). In a study by Allred et al., 2014, several PFHxS precursors (FHxSAA, MeFHxSAA, EtFHxSAA) were detected in leachates from landfills indicating that these PFHxS precursors may be used in a variety of applications since the landfills had received residential and commercial waste, construction and demolition waste, biosolids from waste water treatment plants as well as non-hazardous industrial waste. A study of influent and effluent sewage water and sludge from waste water treatment plants found a net mass increase in PFHxS content between influent and effluent at 3 different waste water treatment plants in Sweden suggesting that degradation of precursor compounds during waste water treatment can be contributing to PFHxS contamination in the environment (Eriksson et al., 2017). Detection of PFHxS precursors is in line with what has been detected for precursors of PFBS and PFOS in other matrixes (see section 2.2.4; Stock et al., 2007; Del Vento et al., 2012; Dreyer et al., 2009).

### 2.2.3 Bioaccumulation and toxicokinetics

1. Due to the surface-active properties of PFHxS it is not possible to experimentally measure log Kow since the substance is expected to form multiple layers in an octanol-water mixture (OECD, 2002; 2006; Conder et al., 2008). In addition, PFHxS is relatively water soluble and has been shown to preferentially bind to proteins in liver and blood (Jones et al., 2003; Ahrens et al., 2009; Martin et al., 2003; Goeritz et al., 2013) and therefore the log Kow as descriptor for the bioaccumulation potential is not appropriate for PFHxS and related substances. Furthermore, the reported BCF and BAF for PFHxS are below the numerical criteria of 5000, indicating a low bioaccumulation potential in aquatic organisms (Martin et al., 2003; Yeung and Mabury, 2013; Kwadijk et al., 2010; Casal et al., 2017; Ng and Hungerbuhler, 2014). The numerical criterion for BCF or BAF, which are based on considerations of lipid-partitioning substances, are not appropriate for PFHxS since PFHxS does not follow the behaviour of traditional hydrophobic compounds by partitioning into fatty tissues. As mentioned above, PFHxS preferentially binds to proteins in the organism and due to its water solubility is expected to quickly be excreted through gill permeation in gill-breathing organisms such as fish (Martin et al., 2003; Goeritz et al., 2013).
2. However, other factors such as high bioaccumulation in other species and monitoring data indicating a bioaccumulation potential of the chemical is sufficient to justify consideration of PFHxS within the Stockholm Convention. Biomagnification factors (BMFs) and trophic magnification factors (TMFs) explicitly account for biomagnification resulting from trophic transfer where the chemical concentration in one organism exceeds that of the organism at a lower level of the food chain (reviewed by Conder et al., 2012). As reviewed in the nomination dossier (UNEP/POPS/POPRC.13/4) a number of studies has reported BMFs over 1. Investigation of biomagnification in selected species from different Arctic regions, including the European- and Canadian Arctic, showed BMFs in the range 6.9 to 373 (Haukås et al., 2007; Butt et al., 2008). Furthermore, Houde et al., 2006, investigated the accumulation of PFHxS in the Bottlenose dolphins prey food web at two different locations in the United States and BMFs ranged from 1.8 to 14. In addition, in the SVHC dossier (ECHA, 2017a) authors have calculated from Riget et al., 2013, the BMFs for polar bear/ringed seal food chain to 16.7
3. A study on pigs fed a diet contaminated with known concentrations of PFHxS, calculated BMFs for whole pig, meat and liver for PFHxS were 20.1, 13.1 and 48, respectively (Numata et al., 2014).
4. An overview of the BMFs from the above-mentioned studies are shown in Table 5. Limitation of these BMF/TMF studies was discussed in the nomination dossier (UNEP/POPS/POPRC.13/4) and the SVHC dossier also review some of the bioaccumulation studies listed in Table 5 in detail (ECHA, 2017a).

**Table 5.** Available BMFs and TMFs from different food chains and diet studies.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Specie/Food web** | **Tissue** | **BMF** | **TMF** | **Reference** |
| Bird/Fish (Arctic) | Liver | 6.0–8.5 |  | Haukås et al., 2007 |
| Polar bear/Ringed seal (Arctic) | Liver | 163–373 |  | Butt et al., 2008 |
| Dolphin/Fish | Plasma/whole | 1.8–14 | Dolphin 0.2 ± 0.9 (plasma)  Dolphin 0.1 ± 0.4 (whole) | Houde et al., 2006 |
| Fish/Zoo plankton | Whole | 9.1–10 |  | Houde et al., 2006 |
| Polar bear/Ringed seal (Arctic) | Liver | 16.7 |  | Riget et al., 2013  (as reported in ECHA 2017a) |
| Fish/Chironomids (Lake fly) | Fillet/whole | 1.43–4.70 |  | Babut et al., 2017 |
| Pig diet study | Whole/meat/liver | 13.1–48 |  | Numata et al., 2014 |
| Benthic | Whole |  | 4.3 | Munoz et al., 2017 |
| Bentho-pelagic (demersal) | Whole |  | 1.5 | Munoz et al., 2017 |

1. Studies investigating trophic magnification of PFHxS in food webs are limited. TMFs were estimated, using both plasma-based and whole-body-estimate based calculations, in a marine food web (Houde et al., 2006). The reported TMFs ranged from 0.2 ± 0.9 to 0.1 ± 0.4. However, there are large variations in the TMFs, reflected in standard errors being larger than their corresponding TMFs. A number of factors such as temperature, time of sampling, reproduction status, migration and age may affect the calculation of TMF (Borgå et al., 2012). In a recent study, two estuary intertwined sub-food web were investigated. TMFs for PFHxS were reported to be 4.3 for the benthic food web and 1.5 for the bentho-pelagic food web (Munoz et al., 2017; see Table 5 above).
2. The reported half-life of PFHxS in humans varies between 5.3 and 14.7 years (Olsen et al., 2008; Fu et al., 2016; Li et al., 2018; Section 2.3.2), which is the longest of all perfluoroalkyl and polyfluoroalkyl substances (PFAS) for which data are available. It is also comparable to the longest human elimination half-lives recorded for known PBT/vPvB- and POP-substances such as some PCBs (ECHA, 2017a). The elimination half-life of PFHxS, PFOS and PFOA in serum of 26 retired fluorochemical production workers has been reported (Olsen et al., 2007). Half-lives for PFHxS, PFOS and PFOA were 8.5, 5.4, and 3.8 years, respectively. Hence, the half-life of PFHxS is approximately 1.5 times longer than for PFOS. Elimination half-life in other species has also been reported (Sundstrom et al., 2012). However, pharmacokinetic studies in non-humans have demonstrated that serum elimination half-lives of PFHxS can vary considerably between species (Sundstrom et al., 2012; Numata et al., 2014) and, in some cases, between genders within species (Hundley et al., 2006; Sundstrom et al., 2012), but are generally much shorter than the reported human serum elimination half-lives. The species-specific and sex-specific elimination of PFHxS is highly expressed in the study by Sundstrom et al., 2012. Male and female rats were investigated in terms of serum elimination and results showed that females much more efficiently eliminated PFHxS than male rats. Furthermore, rats and mice appeared to be more effective at eliminating PFHxS than monkeys (Sundstrom et al., 2012). PFHxS is highly bound to plasma proteins (Kim et al., 2017; Jones et al., 2003) and pharmacokinetic studies have revealed that certain PFASs interact with proteins (e.g. albumin, liver fatty acid binding proteins, organic anion transporters) and that their clearance is species-, gender- and chain length-dependent (Andersen et al., 2008; Ng & Hungerbuhler, 2014).
3. The ability to strongly bind to blood proteins and the low clearance and slow excretion in the urine were recently proposed as the best predictors for a chemical’s bioaccumulation potential and long half-life (Tonnelier et al., 2012). In a study of pigs fed a diet contaminated with PFASs, PFHxS was found to have the slowest urinary excretion as well as the highest serum half-life among the investigated PFASs (Numata et al., 2014). In addition, blood plasma contained the largest amount of unexcreted PFHxS. Interestingly, studies on cows revealed a different pattern of PFHxS with regard to partitioning to blood, liver and edible tissues (Kowalczyk et al., 2013). In dairy cows, muscle tissue contained the highest concentration of PFHxS indicating a lower tendency for PFHxS to accumulate in plasma than was seen for pigs (Numata et al., 2014). Furthermore, in the dairy cow study, PFHxS was detected in urine as well as milk during the experimental period showing a higher rate of elimination in cows than in pigs. These studies indicate that both elimination and tissue distribution is species-specific for PFHxS and other PFAS. It was later discussed whether ruminants such as cows have the possibility to biodegrade PFHxS and other PFAS by ruminal microoganisms in the rumen, but this study was inconclusive (Kowalczyk et al., 2015).
4. The tissue distribution of PFHxS in humans is similar to what is observed in other mammals (e.g. Numata et al., 2014; Perez et al., 2013; Kowalczyk et al., 2013). In a Spanish autopsy study PFHxS was found in all studied human (general public) organs/tissues: liver, kidneys, bone, brain and lungs, with highest levels observed in lungs and kidney, and was most frequently detected in lungs (43%) (Perez et al., 2013). The highest concentrations of PFHxS are found in blood, liver, kidney and lung. Urine is the primary route of excretion. Humans have a very slow elimination compared with other species, with an elimination half-life of 7 years or above. The human elimination half-life of PFHxS is the longest of all PFASs and PFCAs for which there are available data, and comparable to the longest human elimination half-lives recorded for known PBT/vPvB and POP-substances such as PCBs. PFHxS has been shown to be transferred to the foetus through the placenta in humans and excreted via lactation. Transfer to breast milk appears to be a significant route of elimination during breastfeeding. Time trend studies indicate that the human bioaccumulation potential of PFHxS may be larger than that of PFOS (ECHA, 2017a).

### 2.2.4 Potential for long-range transport

1. The potential for long-range transport of PFHxS was reviewed in the nomination dossier (UNEP/POPS/POPRC.13/4). PFHxS is found in various environmental compartments in the remote regions of the Arctic and Antarctic including in air, sediment, snow, ice, soil, sediment and biota strengthening the evidence that PFHxS can be transported over long distances far from the primary source (see UNEP/POPS/POPRC.14/INF/[…], Tables 1.1, 1.2 and 1.3 for biota and Table 1.4 for abiota).
2. While there is scientific consensus that PFASs are subject to long-range environmental transport, the pathway governing the long-range environmental transport of individual PFASs are dependent on the substance’s physiochemical properties (Butt et al., 2010; Ahrens et al., 2011; Rankin et al., 2016). Processes that transport PFHxS, its salts and PFHxS-related compounds to the Arctic include direct transport of compounds in air or water and/or indirect transport of neutral volatile precursor compounds that can undergo degradation by atmospheric oxidation or by biological degradation (Butt et al., 2010; Ahrens et al., 2011; Alava et al., 2015, Wang et al., 2015). The PFHxS detected in environmental samples in remote regions may thus partially result from biological or abiotic degradation of such precursors prior to or after deposition (D’Eon et al., 2006; Xu et al., 2004; Tomy et al., 2004). Furthermore, local inputs from anthropogenic activities may be another source to PFHxS in the Arctic regions (reviewed in Butt et al., 2010).
3. Recent data from Svalbard indicate that levels of PFAS detected in polar bears are most likely not due to local sources. PFAS concentrations in polar bears were higher (30–35%) in animals that have a wider home range (offshore bears) than animals that live in coastal areas close to the populated area of Svalbard (Tartu et al., 2018). Furthermore, using isotope analysis it was shown that polar bears with a wider home range eat more marine food than animals living close to the coast that feed more terrestrially (Tartu et al., 2017b; 2018). In areas with more sea ice, such as those used by offshore bears, environmental PFAS levels were likely higher than in areas with less sea ice such as the coast of Svalbard. The positive relationship between PFHxS concentrations and home range longitude position in polar bears accords with a study that showed that PFHxS concentrations in ivory gull eggs from more eastern colonies at Franz Josef Land were slightly higher than concentrations in eggs from Svalbard (Miljeteig et al., 2009). It has also been reported that PFSA emissions from China have increased since 2003 (Wang et al., 2017).
4. PFHxS is water soluble and transported through water to remote areas. Yamashita et al., 2005, first described global occurrence of PFHxS and other PFASs in open ocean water. Since then, a number of studies have reported frequent detection of PFHxS in open ocean and coastal water world-wide (reviewed in Butt et al., 2010; González-Gaya et al., 2014; Rosenberg et al., 2008; Busch et al., 2010; Benskin et al., 2012; Zhao et al., 2012; Ahrens et al., 2010; Wei et al., 2007; Brumovský et al., 2016). A number of studies reported the detection of PFHxS in Arctic seawater (Caliebe et al., 2005 as cited González-Gaya et al., 2014; Rosenberg et al., 2008; Busch et al., 2010; Cai et al., 2012; Benskin et al., 2012; Zhao et al., 2012; Yeung et al., 2017). In contrast, it has been suggested that oceanic long-range transport of PFHxS and other PFASs to the Antarctic has been more limited. Ocean currents and related dilution effects cause a decreasing concentration gradient from Northern Europe to the South Atlantic Ocean (Ahrens et al., 2010) explaining the lower concentrations detected in the Southern Ocean. Long distance from important source regions in the northern hemisphere, limited chemical manufacture of PFASs in the southern hemisphere, low effectiveness of delivery to the Antarctic via the atmospheric route and low yield of ionic PFASs produced from atmospheric oxidation are indicated as other possible explanations (Bengtsson Nash et al., 2010; Alava et al., 2015).
5. The higher frequency and levels of PFHxS detected in ocean waters compared to what has been detected in air, as well as its relatively high water solubility, gives an indication that the major transportation pathway for PFHxS to remote regions is through water currents (discussed in UNEP/POPS/POPRC.13/4). The ocean acts as a long-term reservoir of PFASs. Hence the input of PFHxS to the Arctic will likely continue over the long-term, particularly as the volume of Atlantic water masses transported northwards has increased during the last two decades (Routti et al., 2017; UNEP/POPS/POPRC.13/4). In addition, Llorca et al., 2012, predicted that PFHxS, like most other perfluoroalkyl acids, is a “swimmer”, i.e., a chemical that is anticipated to undergo long-range environmental transport in water, by using the modelling result from Lohmann et al., 2007.
6. Due to detection of PFHxS in Arctic air and snow, long-range transport of PFHxS and/or PFHxS related compounds through the atmosphere cannot be excluded (Theobald et al., 2007 as cited in Butt et al., 2010; Stock et al., 2007; Genualdi et al., 2010; Butt et al., 2010; Wong et al., 2018; Norwegian Environment Agency M-757, 2017b). Furthermore, higher PFHxS levels were detected in coastal water of Greenland compared to seawater, a finding that was attributed to precipitation in the form of rain, snow and/or ice melting at the Greenlandic mainland (Busch et al., 2010). An atmospheric source could involve neutral PFHxS related compounds as with those reported for PFBS and PFOS (Martin et al., 2006; D'Eon et al., 2006). A number of studies show evidence that PFAS precursors are transported through air and degrade to e.g. PFBS, PFOS (Stock et al., 2007; Dreyer et al., 2009; Del Vento et al., 2012) and most likely also PFHxS. This argument is strengthened by the detection of increasing amount of PFHxS during snow melt (Codling et al., 2014; Meyer et al., 2011) and detection of PFHxS in rain water (Eschauzier et al 2010). See section 2.2.2 for further details. The potential for PFHxS to undergo long-range environmental transport via air is further supported by the detection of PFHxS in lichen from the Antarctic Peninsula. Lichen accumulates pollutants from air and is used as bioindicators for air pollution (Augusto et al., 2013). PFHxS has also been detected in the feathers of an accipiter bird in rural areas of Tibet (Li et al., 2017).
7. Recent studies of polar bears from Norwegian Arctic showed that levels of PFSA (ΣPFSA2; PFHxS and PFOS) where found in the highest concentration compared to other already regulated POPs. Total concentration (ng/g ww) of ΣPFSA2 were 264.35±12.45 (PFHxS 28 ng/g ww; PFOS 237 ng/g ww), ΣPCB were 39.98±3.84 while ΣPBDE were 0.18±0.01 (Bourgeon et al., 2017; Routt et al., 2017). Hence in these studies the concentation of PFHxS is similar to the total PCB concentations. In general, it is between 2–18 times more PFOS that PFHxS detected in animals from the Norwegian Arctic, on the other hand the amount of PFHxS is 2 – 7 times higher compared to PFOA (Miljeteig et al., 2009; Bytningsvik et al., 2012; Aas et al., 2014; Routti et al., 2017).
8. In summary, there is strong evidence that PFHxS is transported to remote regions through water and ocean currents and there is indication of long-range transport also through atmospheric transport of PFHxS and volatile precursors.

## 2.3 Exposure

### 2.3.1 Environmental levels and trends

1. Environmental monitoring shows that PFHxS is ubiquitous in the environment. Numerous studies have reported detection of PFHxS in compartments such as surface water, deep-sea water, drinking water, wastewater treatment plant effluent, sediment, groundwater, soil, atmosphere, dust, biota, and humans globally (ECHA 2017a, annex II, Table 13; Tables 1.1–1.12 in UNEP/POPS/POPRC.14/INF/[…]).
2. The highest environmental levels of PFHxS measured are found in urban and/or industrial areas both in terms of biotic- and abiotic measures (Gewurst et al., 2016; Ma et al., 2018). In China, PFHxS (ranging between 45.9–351 ng/L) was found to be the predominant PFAS in the water of a lake and its in-flow rivers (Ma et al., 2018). The rivers were considered the main input of PFHxS to the lake since some of the rivers mainly collect discharge water from bigger cities with local PFAS-related plants. The level of PFHxS in the lake has increased in the period 2009–2014 while levels of PFOA and PFOS have remained more or less the same, which may be an indication of increased direct use of PFHxS and/or PFHxS related substances (Ma et al., 2018).
3. Numerous studies have reported environmental contamination due to use of AFFF based on fluorosurfactants (reviewed in Dauchy et al., 2017). PFHxS and/or PFHxS related compounds may be found in these foams either as an unintentional contamination due to the use of PFOS or as an intentionally added ingredient most likely in the form of perfluorohexane sulfonamide (FHxSA) (Barzen-Hanson et al., 2017; D'Agostino & Mabury, 2017). In Canada, PFHxS has been found in variety of matrixes including urban and rural surface water, air, Arctic ocean water and sediment (low frequency) at sites impacted- and not impacted by contamination from AFFF (D' Agostino and Mabury 2017; Lescord et al., 2015; Wong et al., 2018; Genualdi et al., 2010; Gewurtz et al., 2013). PFHxS has been detected in ground- and surface waters close to airports and metal plating facilities, in surface water in the vicinity of waste water treatment plant, and in sludge and effluent/influent water from waste management facilities in Sweden (Ericson Jogsten and Yeung, 2017; Eriksson et al., 2017; Norwegian Environment Agency M-806, 2017c; Swedish EPA, 2016; Hu et al., 2016). In the Netherlands PFHxS has been detected in infiltrated rainwater likely originating from atmospheric transport of precursors (Eschauzier et al., 2010).
4. For a number of studies, exposure in local areas can be attributed to long-range environmental transport (Zhao et al., 2012; Routti et al., 2017; Codling et al., 2014; Kwok et al., 2013; Yeung et al., 2017; Li et al., 2017). For example, PFHxS has been detected in snowpack in a remote area of northern Sweden (Codling et al., 2014), in surface- snow and water at Svalbard, Norway (Kwok et al., 2013) and in marine Arctic and Antarctic surface waters (Zhao et al., 2012). In a study by Yeung et al., 2017, PFHxS was detected in Arctic snow/meltpond water as well as in ocean water. Furthermore, recent studies report that PFHxS is the third most abundant PFAS in polar bears at Svalbard (Tartu et al., 2017a; Routti et al., 2017; Norwegian Environment Agency 2017d, M-817/2017). Similarly, for polar bears from Hudson Bay, Canada, PFHxS was second only to PFOS in concentration in the liver (Letcher et al., 2018). In serum from polar bears at Svalbard (Norway), PFHxS levels were in the range 4.9–70 ng/g wet weight (ww), furthermore results show that after the concentration of PFHxS levelled off during the period 2003–2009, the levels are now increasing with an annual increase of PFHxS in polar bears between 4.9% adjusted for feeding habits and food availability, and non-adjusted 5.1% (Routti et al., 2017). According to the author (personal communication) PFHxS has an average increasing non-significant trend of 5% per year during the period 2009-2014 with 95% confidence intervals of – 1.1% and 11.2%. Furthermore, the authors propose that the fast drop in PFAS concentration following the phase out of certain PFAS was due to decreased air transport of volatile precursors, while the recent increase in PFHxS levels is most likely due to the much slower oceanic transport of PFAS (Routti et al., 2017). In the same study, levels of PFHxS in Arctic fox were in the range <0.05–139 ng/g ww but with no trend. Climate-related changes in feeding habits and food availability moderately affected PFAS trends.
5. The results indicate that PFAS concentrations in polar bears and arctic foxes are mainly affected by emissions. In a previous study, polar bears from five locations in the North American Arctic and two locations in the European Arctic as well as Greenland were studied and PFHxS was detected in polar bears at all locations (Smithwick et al., 2005a,b). At the Svalbard location in the European Arctic, a mean concentration of 2940 ng/g (range 2260–4430 ng/g wt) was detected in polar bear liver, which to our knowledge is the highest concentration of PFHxS reported in polar bears. In polar bears from East Greenland and in samples collected in 2006, a tissue distribution study showed that levels of PFHxS were highest in the liver followed by blood > brain ≈ muscle ≈ adipose (Greaves et al., 2012), but consistently 2 orders of magnitude lower than PFOS. In a complementary study in various brain regions of the same polar bears, PFHxS concentrations were consistently the same throughout the brain (Greaves et al., 2013). Other studies have also detected PFHxS in marine mammals (Fair et al., 2012). See Table […] in UNEP/POPS/POPRC.14/INF/[…] for additional data on exposure levels in remote regions.
6. A number of studies have reported time-trends for the levels of PFHxS in various species and matrixes. However, there are some discrepancies in these data and trends are both increasing (Routti et al., 2017; Holmstrom et al., 2010), decreasing (Lam et al., 2016; Huber et al., 2012), and without any significant trend (Ullah et al., 2014; Roos et al., 2013). As mentioned above the trend of PFHxS in polar bears in the European Arctic (Svalbard, Norway) is increasing (although non-significant within 95% of the confidence interval) while there was no trend in the Arctic fox (Routti et al., 2017, and personal communication with the author). Hence, temporal trend in each case is most likely dependent of emission sources, food choices (terrestrial, marine) and location (urban versus rural) among other factors.

### 2.3.2 Human exposure

1. PFHxS, along with PFOS and PFOA, is the most frequently detected PFAS in blood-based samples from the general population (Calafat et al., 2007; ECHA 2017a, annex II, Table 14; Table 1.10 in UNEP/POPS/POPRC.14/INF/[…]) and present in the umbilical cord blood and breast milk (Kärrman et al., 2007; Gützkow et al., 2012). Exposure pathways for PFAS, including PFHxS, include indoor dust, diet, drinking water and indoor/outdoor air (ECHA 2017a; Table 1.4 and 1.6 to 1.8 in UNEP/POPS/POPRC.14/INF/[…]). PFHxS is transferred to the foetus through the placenta in humans and is excreted via lactation, and breast milk may therefore be an important source of exposure to breast-fed infants. Lifestyle factors contribute to the exposure; microwavable food intake and low frequency of indoor dust removal by vacuuming are connected to higher serum levels of PFHxS and other PFASs (Siebenaler et al., 2017).
2. A number of studies have reported presence of PFHxS in food items (Gebbink et al., 2015; Noorlander et al., 2011¸ Food Standards Australia New Zealand, 2016; Table 1.7 in UNEP/POPS/POPRC.14/INF/[…]). In a Swedish study, decreasing human dietary exposure in the period 1999–2010 from food stuff was observed (from 55 to 20 pg/kg bw/day), with egg and fish contributing most to human dietary exposure of PFHxS (Gebbink et al., 2015). In a Dutch study, crustaceans, lean fish, flour and butter (44, 23, 18 and 16 pg/g dw, respectively) had highest levels of PFHxS, low levels (<10 pg/g dw) were also found in fatty fish, industrial oil, bakery products and chicken (Noorlander et al., 2011). A study from Northern-Norway Mother-Child Contaminant Cohort Study (2007–2009) determined that high consumers of game had elevated levels of PFHxS, with “a 20% difference between the highest and lowest intake group” (Berg et al., 2014). A study using data from the US National Health and Nutrition Examination Survey (NHANES) 2013–2014 for children aged 3–11 years-old (n=639) found that higher levels of PFHxS in serum were associated with consumption of fruits and juices (Jain 2018).
3. A study from Australia and New Zealand of PFHxS in food and water samples from contaminated sites, found highest PFHxS amounts in cattle meat (13.31 μg/kg), rabbit meat (4.94 μg/kg) and eggs (4.27 μg/kg). Other foods with high concentrations were crustaceans, fish liver and sheep meat and occasionally in some vegetables (e.g. spices, berries) (Food Standards Australia New Zealand, 2016).
4. It is estimated that drinking water consumption from sources near or in contaminated areas is one of the most important exposure pathways of PFAS for humans. Human biomonitoring studies concluded that exposure to PFHxS (and other PFAS) via drinking water can lead to much higher blood serum levels compared to unexposed groups, as observed in USA, Germany, Sweden and Italy (Hu et al., 2016; Wilhelm et al., 2009; Li et al., 2018; Annex E submission by Council of Chemists of the Province of Treviso, Italy). In Sweden exposure to PFHxS via drinking water lead to 180-times higher blood serum level compared to reference group (Li et al., 2018). Starting February 2014, the Swedish National Food Agency (NFA) conducted a survey of the drinking water in Sweden. The results indicate that just over one-third, or 3.6 million of the Swedish population, gets their drinking water from a water source that is affected by PFAS including PFHxS (Banzhaf et al., 2017). In 2010– 2015, PFHxS was detected in drinking water in 23 US States among 134 water utilities serving 5.5 million people (EWG's Tap Water Database). Contamination of tapwater with PFHxS at low levels has been observed word wide (Mak et al 2009; Kabore et al., 2018; Zafeiraki et al., 2015; Boiteux et al., 2012; Ericson et al., 2009, see Table 1.6 in UNEP/POPS/POPRC.14/INF/[…] for details).
5. Exposure may also occur via indoor air, mainly through dust. In a Canadian family treating carpets with ScotchgardTM regularly for the last 20 years, the carpet in the family room contained ~3000 ng/g PFHxS and blood levels in the family varied from 27.3–423 ng/mL, with the youngest child having highest levels (Beesoon et al., 2012). PFHxS has been recorded in Norwegian homes and an office (Huber et al., 2011). Seven of eight analysed dust samples contained PFHxS at a median value of 1.4 ng/g, whereas the dust of the indoor environment in a Norwegian office contained approx. 30 ng/g. Dust from Belgian homes and offices were studied in D’Hollander et al., 2010, and reported median values of 0.1 and 0.2 ng/g respectively. A Canadian study (Kubwabo et al., 2005) shows a median of 23.1 ng/g in the indoor environment while 45.5 ng/g was detected in US homes and day care centres (Strynar and Lindstrom 2008). Recently, PFHxS levels in dust from a furniture centre and a hotel in Norway ranged from 1600 to 2300 ng/g. PFHxS was the predominant PFAS in the sample together with 6:2 diPAP, which was found at equally high levels in the range 330–3300 ng/g (Norwegian Environment Agency, Report M-806/2017c).
6. PFHxS has been detected in humans globally with the highest levels (1790 μg/L in blood serum) detected in people consuming PFHxS contaminated drinking water (Li et al., 2018). Levels in plasma range from <0.05–80 μg/L, in serum from <1–1790 μg/L, (ECHA 2017a, annex II, Table 14; Table 1.10 in UNEP/POPS/POPRC.14/INF/[…]). PFHxS has been found in human populations in a number of birth cohorts, where PFHxS was detected at >98% in all five cohorts, and concentrations were highest in Danish women followed by Greenlandic women (Bjerregaard-Olesen et al., 2017). PFHxS was detected in every sample of maternal and umbilical cord whole blood and plasma in a study of women and their newborn children (n=7) from Arctic Russia (Hanssen et al., 2013). Concentrations of PFHxS in maternal blood were negatively correlated with parity and maternal age (Fisher et al., 2016). Increasing levels of PFHxS have also been associated with infertility (Velez et al., 2015) and completion of menopause (Taylor et al., 2014). A marked gender difference for elimination has been observed, with women aged between 15 and 50 years being more efficient than men in excreting PFHxS, with half-lives of 4.7 and 7.4 years, respectively (Li et al., 2018).
7. Furthermore, PFHxS was detected in umbilical cord blood (ECHA 2017a, annex II, Table 14; Table 1.11 in UNEP/POPS/POPRC.14/INF/[…]) and seems to be transmitted to the embryo to a larger extent than what was reported for PFOS (Kim et al., 2011; Gützkow et al., 2012; Pan et al., 2017). Cord serum albumin was a positive factor for higher transfer efficiency, while maternal plasma albumin was a negative factor (Pan et al., 2017).
8. Children are also exposed to PFHxS through breast milk, however, PFHxS seems to be less efficiently transferred from mothers’ blood to breast milk compared to PFOS (Kim et al., 2011; Mogensen et al., 2015). PFHxS was detected in more than 70% of samples analysed from Japan, Malaysia, Philippines, and Vietnam at mean concentrations ranging from 6.45 (Malaysia) to 15.8 (Philippines) pg/mL (Tao et al., 2008). Other studies report levels ranging from <0.005 to 0.3 ug/L (ECHA 2017a, annex II, Table 14; Table 1.12 in UNEP/POPS/POPRC.14/INF/[…]). Breastfeeding can be an efficient route of PFHxS elimination from the maternal blood. Comparisons of serum concentrations of women who did or did not breastfeed their infants showed that breastfeeding significantly decreases maternal serum concentrations of PFHxS, PFOS, and PFOA (Bjermo et al., 2013; Brandtsæter et al., 2013; Papadopoulou et al., 2015). In a Swedish monitoring study, PFHxS was analysed in breast milk samples from Stockholm and Gothenburg. The concentrations of PFHxS, (low pg/mL range), have increased over the whole time-period (1972–2015) in Stockholm, though if only considering the last 10th year there seemed to be a decrease during the last 10 years both in Stockholm and Gothenburg (Nyberg et al., 2017). PFHxS were detected in all 639 children age 3–11 from NHANES 2013–2014, a nationally representative subsample of the U.S population. This suggest prevalent exposure to PFHxS or its precursors among U.S. 3–11years old children, most of whom were born after the phase out of PFOS in the United States in 2002 (Ye et al., 2018).
9. In a temporal trend study of different PFASs in serum of primiparous women in Uppsala, Sweden, there was a significant increase in PFHxS serum levels between 1996 and 2010 (8.3%/year) and with the concentrations in 2010 being approximately 6.5 ng/mL, reaching same level as PFOS (Glynn et al., 2012 and supporting info). It was later discovered to be due to drinking water contamination coming from historical use of AFFF at a closed military airport (Gyllenhammar et al., 2015). The levels of PFHxS in ground/drinking water varied from 16 ng/L (upstream of the airport) to 690 ng/L (downstream of the airport). The concentration in the communal water well was 83 ng/L.
10. In the area of Arnberg, Germany, there was a large environmental contamination incident of PFAS in 2006. Wilhelm and co-workers, 2009, evaluated the levels of some PFAS, including PFHxS, in human blood sampled before the contamination (during the period 1977–2004), and the PFHxS plasma levels had increased steadily (p<0.001) from 1977 to 2004. This was in contrast to PFOS and PFOA which remained fairly stable with a small increase during the first 10–15 years followed by a decrease from about 1990–1995. The total median concentration of PFHxS for the entire time period was 1.7 μg/L (range 0.5–4.6 μg/L, LOD=0.1 μg/L).
11. Increasing trend of PFHxS was also observed in archived serum samples from Norway (Haug et al., 2009); Serum levels in men (age 40–50 years) for PFHxS increased from 1976 to the early 1990s where the levels stabilised until 2006. The concentrations for PFHxS ranged from a minimum of 0.1 μg/L in 1977 to a maximum of 3.4 μg/L (2000) and the concentration was 1.4 μg/L in 2006. No temporal patterns were observed for PFHxS in archived serum samples from two German cities from 1980–2010 (Yeung et al., 2013), which is similar to observation from American Red Cross adult blood 2000–2010 (Olsen et al., 2012). No decline in PFHxS serum levels were observed in Californian women age 50–80 years in the period 2011 to 2015 in contrast to other PFAS which significantly declined (Hurley et al., 2018), this was also evident after removing participants with known drinking water exposure. In a longitudinal study of men conducted in Northern Norway, concentrations of PFOS and PFOA were highest during 1994–2001 and 2001, respectively, whereas PFHxS levels increased to 2001, however did not decrease between 2001 and 2007 (Nøst et al., 2014).
12. Occupational exposure can lead to high serum levels of PFHxS. In firefighters’ serum levels of PFOS and PFHxS were in the range of 92–343 and 49–326 ng/mL, respectively (whereas the control group had 1–40 and 0.2–22 ng/mL of PFOS and PFHxS, respectively) (Rotander et al., 2015). PFNS, CL-PFOS, ketone-PFOS, ether-PFHxS and Cl-PFHxS were significantly more frequent in firefighters. At a Chinese fluorochemical manufacturing plant for PFOS-related compounds, indoor dust (67.3%) and diet (31.6%) was found to be the largest sources to human PFHxS exposure (Gao et al., 2015). The drinking water PFHxS concentration was 0.78 ng/L in that study. In another study from a fluorochemical manufacturing plant in the same district, serum concentrations of PFHxS were in the range 12.8–10546 ng/mL, dust in residences connected to the plant had PFHxS in the range 0.44 to 708 ng/g, (while dust in the plant had PFHxS in the range 1481–257201 ng/g), diet PFHxS was in the range 0.067–0.448 ng/g ww and drinking water PFHxS from n.d to 3.2 ng/L (Fu et al., 2015). In the Fu et al., 2016, study serum concentrations of PFHxS were in the ranges of <LOD to 19,837 ng/mL (median=764 ng/mL). The serum levels of PFHxS in the exposed workers showed an obviously increasing trend with length of service. Concentrations in urine ranged from <LOD–77.1 ng/mL (median=1.7 ng/mL).
13. The half-life of PFHxS was determined in a recent human biomonitoring study in the city of Ronneby in Sweden where people have been exposed to high levels of PFAS via drinking water, including PFHxS (1700 ng/L in 2013) from a nearby military airport. The levels of PFHxS were the highest ever reported in Sweden, (277 ng/mL, range 12–1660) and the mean half-life was estimated to 5.3 years, shorter than previously reported, however, there were large inter-individual differences and differences between males and females ranging from approximately 2 to >10 years (Li et al., 2018). See also section 2.2.3 of this document for further information on half-lives.

## 2.4 Hazard assessment for endpoint of concern

### 2.4.1 Toxicity to aquatic organisms

1. Ecotoxicity data for PFHxS are limited, but available studies comparing toxic effects of PFBS and PFOS in aquatic organisms indicate that toxicity increases with increasing carbon length, and suggest a likelihood for adverse effects also in non-mammalian species (Giesy et al., 2010). One recent study observed delayed development in northern leopard frog (*Rana pipiens*) tadpoles exposed to 10 g/L PFHxS for 40 days. Although PFOS showed a higher BCF than PFHxS in this study, PFHxS was more potent for the endpoints (goosner stage (development) and snout-vent length) at day 40. This is the first study to show sublethal effects of PFHxS on amphibians at current environmental levels (Hoover et al., 2017). Another study on the African clawed frog (*Xenopus laevis*) tadpoles, indicates possible endocrine-disrupting potential of perfluoroalkyl sulfonic acids (PFSA). Both PFOS and PFBS promoted expression of estrogen and androgen receptors in the brain, and estrogen receptor in the liver, from exposure levels of 0.1 µg/L for 2 months. Hepato-histology changes (hepatocyte degeration and hepatocyte hypertrophy) was observed at high concentrations (100–1000 µg/L). PFOS at concentration at 1, 100 and 1000 µg/L induced degenerative spermatogonia while no such effect was observed for PFBS (Lou et al., 2013). (The PFOS used in this study was 98% pure, and detectable levels of PFHxS in range of 3.4–4.8 and 18.1–42.6 µg/L was observed in the water with PFOS 100 and 1000 µg/L, respectively).
2. From other laboratory studies, PFOS is known to be moderately acute and slightly chronicly toxic to aquatic organisms and the few PFBS studies available indicate lower toxicity of PFBS (Ding and Peijnenburg, 2013; Giesy et al., 2010). However, PFOS is much more toxic to chironomids which live in sediment environments with low oxygen and where effects on haemoglobin are more relevant. Thus MacDonald et al., 2004, have concluded that PFOS toxicity thresholds for the chironomid *Chironomus tentans* are 2–3 orders of magnitude lower than those reported for other aquatic organisms. PFOS is also known to cause intergenerational toxicity to fish (Ji et al., 2008). No result for such studies are available for PFHxS but similar toxicity is quite possible.

### 2.4.2 Toxicity in terrestrial mammals

1. Experimental studies in rodents exposed to PFHxS constistently show adverse effects to the liver (Butenhoff et al., 2009; Bijland et al., 2011; Das et al., 2016), and associated metabolic effects, such as effects on serum levels of cholesterol, lipoproteins, triglycerides and free fatty acids (Butenhoff et al., 2009; Das et al., 2016; Bijland et al., 2011). Effects on the liver included a dose-dependent increase in hepatocellular hypertrophy associated with a significant enlargement of the liver (56% increase in male rats following 42 days of exposure at 10 mg/kg bw/d (Butenhoff et al., 2009). In another study, 110% increase in liver weight was observed following 28 days of PFHxS exposure at 6 mg/kg/d in male mice. The exposure caused hepatomegaly with steatosis as well as reduced serum total cholesterol and triglycerides (Bijland et al., 2011). The authors hypothesis that the PFHxS-impaired lipoprotein secretion from the liver is the underlying mechanism, leading to accumulation of lipoproteins and triglycerides in the liver, causing hepatomegaly and steatosis and reduced serum lipoproteins and triglycerides (Bijland et al., 2011). A LOAEL of 0.3 mg/kg bw/day based on reductions of total serum cholesterol at all doses was derived from the Butenhoff et al., 2009, as well as NOAELs of 0.3 mg/kg bw/d for effects on increased liver weight and hepatocellular hypertrophy.
2. The effect of PFHxS on the liver is believed to be, at least partly, mediated via activation of nuclear receptors. Several studies have explored the mechanistic effects of PFHxS on liver function, gene expression and peroxisome proliferator-activated receptor (PPAR)-alpha activation. In a study by Wolf et al., 2008, PFHxS was found to activate both mouse and human PPAR-alpha-receptor *in vitro* with LOECs of 8.76 and 4.38 µg/mL, respectively, (equals 10 and 5 µM). PFHxS also activated PPAR-alpha receptors from Baikal seals in a transactivation assay in a dose dependent manner (Ishibashi et al., 2011). In a study on wild type and PPAR-alpha null mice exposed orally to 10 mg/kg/d PFHxS for 7 days, liver effects (significant increase in liver weight, steatosis) was observed in both strains, whereas exposure to the PPAR-alpha agonist WY-14643 did not induce this effect in the PPAR-alpha null mice, indicating that the effects on the liver by PFHxS is partly independent of PPAR-alpha (Das et al., 2017; Rosen et al., 2017). Gene expression profile also indicate that certain PFASs have the potential to activate constitutive activated receptor (CAR) and PPAR-gamma (Rosen et al., 2017). PFHxS also affected hepatic expression of genes involved in lipid and cholesterol metabolism in mice (Bijland et al., 2011; Das et al., 2017; Rosen et al., 2017). In another study, PFHxS was found to rapidly inhibit gap junctional intercellular communication (GJIC) in a dose-dependent and reversible manner (Hu et al., 2002).
3. Exposure to PFHxS has also been shown to alter haematological parameters in male rats exposed for 42 days (Butenhoff et al., 2009). Hematocrit and red blood cell counts was significantly reduced from 3 mg/kg bw/d, haemoglobin concentration significantly reduced from the 1 mg/kg/d group and prothrombin time was altered in all doses tested. Changes in haematological parameters gave a LOAEL of 0.3 mg/kg bw per day (Butenhoff et al., 2009).
4. Thyroid organ toxicity has been observed following exposure to PFHxS. In a study on male rats exposed to PFHxS at 10 mg/kg for 42 days a dose-dependent increase in thyroid hypertrophy/hyperplasia was observed (Butenhoff et al., 2009). The underlying mechanism for the thyroid effects were believed to be due to increased plasma turnover of thyroxine (T4) resulting in a stimulation in thyroid stimulating hormone (TSH) and a compensatory hypertrophy/hyperplasia. A NOAEL of 0.3 mg/kg bw/d was shown for hyperplasia of thyroid follicular cells. Some mechanistic studies have explored the effect of PFHxS on the thyroid hormone pathway. PFHxS competed with thyroxine (T4) for binding to the human thyroid hormone transport protein transthyretin (TTR) (Weiss et al., 2009; Ren et al., 2016), which is the main T4 carrier in cerebrospinal fluid, and expressed at high levels during prenatal and early postnatal life (Larsen and Delallo, 1989). PFHxS did also dose-dependently inhibit triiodothyronine (T3)-dependent cell growth in vitro from 10-8 Molar (Long et al., 2013).
5. Studies in birds have shown that PFHxS affects thyroid hormone pathways and genes related to neuronal development at 8.9 to 38,000 ng/g (Cassone et al., 2012 a,b; Vongphachan et al., 2011). Based on egg injection, the lowest observed effect concentration (LOEC) was 890 ng PFHxS/g ww for developing leghorn chicken embryos (Cassone et al., 2012b). Plasma T4 levels were reduced in a dose-dependent manner in embryos exposed to PFHxS from 8.9 ng/g, with statistically significant changes occurring at 890 ng/g (Cassone et al., 2012b). Furthermore, negative correlations between serum PFHxS and thyroid hormones T3 has been observed in Arctic birds (Nøst et al., 2014).
6. Adult dose-dependent behavior and cognitive disturbance was observed in mice after a single neonatal dose of PFHxS in the vulnerable brain developmental period (6.1 and 9.2 mg/kg bw, oral single dose at postnatal day 10) (Viberg et al., 2013). PFHxS affected the cholinergic system, manifested as altered nicotine-induced behavior in adult animals, which is in agreement with previous findings for PFOA and PFOS (Viberg et al., 2013). Levels of several proteins important in the brain growth spurt were affected 24 h after exposure, and taurine levels were different from control at 4 months in males (Lee and Viberg, 2013). In another study on developmental effects in rats, no effect on motoric activity was observed for rats exposed in utero and through lactation to 0.3–10 mg/kg/d (Butenhoff et al., 2009). However, the difference in elimination time between female rats and mice (2 vs 30 days) may contribute to the diverging results on neurodevelopment effects observed between rats and mice.
7. Neurotoxic effects of PFHxS have been further explored, and PFHxS was found to reduce neuronal activity involved in learning and memory. PFHxS (100 µM) decreased the long-term potentiation in hippocampus CA1 region in adult rats with comparable potential as PFOS (Zhang et al., 2016). Furthermore, increased frequencies of spontaneous miniature postsynaptic currents as well as increased voltage dependent calcium influx were observed after exposure of hippocampal primary neuronal cultures to 100 µM PFHxS (Liao et al., 2009). PFHxS was also shown to induce apoptosis in vitro in the dopaminergic neuronal cell line (PC12) and glutamatergic primary cells (cerebellar granule cells). Doses tested corresponded to the Butenhoff et al., 2009, in vivo study (0.3–10 mg/kg/d which gave serum concentrations of 111–505 µM) (Lee et al., 2014a, 2014b and 2016).
8. Endocrine disrupting activity has been observed for PFHxS in vitro. PFHxS inhibits 11-beta-dehydrogenase isozyme 2 (11b-HSD2) involved in corticosteroid hormone metabolism in human and rat kidney microsomes. The half-maximal inhibitory concentrations (IC50s) of human and rat 11b-HSD2 activities were 18.97 and 62.87 µM PFHxS, respectively (Zhao et al., 2011). PFHxS was shown to have anti-androgenic activity and weak estrogenic effect in vitro. PFHxS antagonize androgen induced androgen receptor (AR) transactivation in vitro (IC50=30 µM), and induced estrogen receptor (ER) transactivation between 10-5 and 10-4 M (20% of E2 activation). However, in co-exposure with E2 (25 pM), PFHxS further enhanced E2-induced ER response up to 187% (~similar enhancement was observed with PFOA and PFOS) (Kjeldsen and Bonefeld-Jørgensen 2013). PFHxS had weak inhibitory effect on aromatase activity (CYP19) IC50=298 µM (human placental carcinoma cells JEG-3) (Gorrochategui et al., 2014), and displace corticosterone hormone from serum binding proteins isolated from chicks and bald eagle (Jones et al., 2003).
9. The immunotoxic effect of PFHxS has not been investigated in controlled experiments. However, in an in vitro study, a range of related PFASs (PFBS, PFOS, perfluorooctane sulfonamide (PFOSA), PFOA, perfluorodecanoic acid (PFDA) and 8:2 fluorotelomer alcohol (8:2 FTOH)) showed immunosuppressive potential (Corsini et al., 2012), suggesting this might occur for PFHxS through the same mechanisms as observed for PFBS and PFOS.
10. Polar bear studies from Greenland investigated the tissue distribution of PFAS; overall, PFSAs and PFCAs concentrations were highest in liver followed by blood > brain > muscle ≈ adipose. For PFHxS, concentrations were by far the highest in liver (30.9 ± 2.1 ng/g) and blood (18.0 ± 1.1 ng/g), and concentrations in brain, muscle and adipose tissues were on similar levels (1.37 ± 0.10; 1.87 ± 0.1; 1.55 ± 0.20 ng/g respectively. In the liver, PFHxS was found to be significantly higher in females (Greaves et al., 2012). The highest concentrations of PFHxS have been detected (>500 µg/kg) in polar bear liver (ECHA, 2017a Further studies from East Greenlandic polar bears (n=10) found significant correlations between PFCAs and PFSAs and neuro transmitter enzyme activity and neuro transmitter receptor density (Pedersen et al., 2015). Average brain sum PFAS was 28.8 ng/g ww, where PFOS accounted for 91% (PFHxS average 1.1 ng/g ww, PFBS and PFDS average were 0.55 nd 0.66 ng/gww, respectively). Both PFCAs and PFSAs showed negative association with density of muscarine acetylcholinesterase receptor. The cholinergic-system was also affected in the mice study of Viberg et al., 2013. Furthermore, the concentrations of eleven steroid hormones were determined in eight brain regions, and levels could not be explained by concentrations in serum. Correlative analysis showed positive association between sum PFASs and 17-alpha- hydroxypregnenolone (OH-PRE) and several steroids were significantly correlated with the sum of PFCAs. The results indicate that an increase in the concentration of certain PFASs concurs with an increase in brain steroid hormones (Pedersen et al., 2016). These studies indicate that the concentration of certain PFASs in polar bears from East Greenland have exceeded the threshold limit for neuro-chemical and hormonal alterations (Pedersen et al., 2015; 2016). A recent study on polar bear from Svalbard found a negative relationship between certain PFAS (including PFHxS) serum levels and some thyroid hormones, and indicate that PFAS contribute to possible alteration of the thyroid hormone homeostasis in polar bears (Bourgeon et al., 2017). In a study of polar bear mothers and cubs from Svalbard, PFHxS levels did not decline between 1998 and 2008, with levels exceeding those associated with health effects in humans, including neurobehavioral effects and alterations in serum cholesterol (Bytingsvik et al., 2012).

### 2.4.3 Human toxicity

1. Epidemiological studies have shown the association between serum levels of PFASs and PFHxS and serum levels of cholesterol, lipoproteins, triglycerides and free fatty acids (Fisher et al., 2013; Steenland et al., 2009; Starling et al., 2014). In a cross-sectional analysis of adults from cycle 1 (2007–2009) of the Canadian Health Measures Survey (CHMS), a significant association between PFHxS and total cholesterol (TC, i.e. sum of free cholesterol and cholesterol bound to low-density lipoprotein (LDL) and high-density lipoprotein (HDL)), LDL-cholesterol, non-HDL cholesterol and TC/HDL ratio as well as elevated odds of high cholesterol were observed (Fisher et al., 2013). There was a significant increasing trend for TC, LDL and non-HDL as well as increased odds of higher cholesterol per log increase in PFHxS both in unweighted and weighted analysis. The geometric mean of PFHxS (2.18 µg/L) were slightly higher than in a study performed on data from The National Health and Nutrition Examination Survey (NHANES), a program of studies designed to assess the health and nutritional status of adults and children in the United States (Nelson et al., 2010) and the PFOS and PFOA levels were slightly lower. A positive monotone increase in cholesterol with increasing decile of PFHxS was also observed in a study from the C8 Health project of a population living near a chemical plant (Steenland et al., 2009). However, Nelson et al., 2010 found a negative association with PFHxS and TC, non-HDL and LDL in the general US population. In the Norwegian Mother and Child Cohort Study in 2003–2004 plasma concentrations of 7 PFAS were positively associated with HDL cholesterol, and specifically PFOS but not PFHxS was positively associated with TC in this sample of pregnant Norwegian women (Starling et al., 2014). The median concentrations of PFOS and PFHxS were 13 ng/mL and 0.6 ng/mL, respectively. A study of 1240 pregnant women from the Spanish Environment and Childhood Project found that PFOS and PFHxS were positively associated with impaired glucose tolerance and gestational diabetes mellitus (Matilla-Santander et al., 2017).
2. Endocrine-disrupting effects on the thyroid hormone pathway have been shown for PFHxS in epidemiological studies. Data (n=1540) from National Health and Nutrition Examination Survey NHANES (2007–2008) were used to evaluate the effect of PFOS, PFOA, PFNA, PFDA, PFHxS, and 2-(N-methyl-perfluorooctane sulfonamide) acetic acid on six thyroid function variables. Levels of T3 were found to increase with the levels of PFOA and total T4 levels were found to increase with increasing PFHxS levels (Jain, 2013). In another study of NHANES data including cohort 2007–2010 (n=1181), higher serum levels of PFOA and PFHxS were associated with altered total T3, total T4 and free T4 in the U.S. general population (Wen et al., 2013). A higher risk of subclinical hyperthyroidism with increased serum PFHxS was indicated for women (Wen et al., 2013). Chan et al., 2011, reported that the risk of hypothyroxinemia (96 cases; 175 controls) was slightly increased with PFHxS exposure (geometric mean: cases=2.86 nmol/L; controls=2.59 nmol/L) (adverse odds ratio=1.12, 95% confidence interval=0.89–1.41) in pregnant mothers. When regression analyses were performed, controlling for exposure to PFOA and PFOS, PFHxS exposure remained associated with an elevated adverse odds ratio (1.27, 95% confidence interval=0.93–1.72) risk of maternal hypothyroxinemia. In a retrospective birth cohort study (2006–2010) in the Republic of Korea the association of certain PFAS and thyroid hormones in cord blood was explored using a generalized linear model (n=301). Cord blood perfluoro *n-*pentanoic acid (PFPeA) was positively associated with cord blood T4 level. Gender-specific analysis showed that prenatal PFPeA and PFHxS exposure significantly increased T4 and T3, respectively, while PFNA decreased thyroid-stimulating hormone (TSH) concentration in newborn girls (Cordblood geometric mean PFHxS=0.34±1.81 ng/mL) (Shah-Kulkarni et al., 2016). Webster et al., 2016, used data from the NHANES 2007–2008, (n=1525 adults) and investigated the relationship between PFAS and serum thyroid hormones. Data indicate that two indicator stressors, thyroid-peroxidase antibody (TPOAb) and iodine status, did not modify the association between certain PFAS and TH alone. However, PFHxS and PFOS were negatively associated with free T4. In the group with joint exposure to high TPOAb and low iodine, PFHxS, PFOA, PFOS and PFNA were positively associated with free T3, free T3/freeT4, TSH and TT3 (Webster et al., 2016). A systematic review of certain PFASs effects in pregnant women and children found some evidence of positive association of PFHxS and PFOS exposure and TSH levels in maternal blood (Ballesteros et al., 2017).

Human epidemiological studies have looked at the correlation between serum PFAS including, PFHxS and neurotoxic or neuro developmental effects. From the C8-health project Stein and Stavitz (2011) examined the cross-sectional association in children (5–18 years of age; n=10,456) between serum certain PFAS concentrations and parent or self-report of doctor-diagnosed ADHD with and without current ADHD medication. Although this population had highest exposure for PFOA, the strongest association between exposure and outcome was observed for PFHxS, with elevated ORs for quartiles 2–4 compared with the lowest quartile, ranging from 1.44 to 1.59 (PFHxS levels ranged from 0.25–276.4 ng/mL). Significant increased odds for ADHD was also found in another study from U.S. using data from the National Health and Nutrition Examination Survey (NHANES) 1999–2000 and 2003–2004, with 1 ug/mL increase in PFHxS serum level, n=571 (Hoffman et al., 2010). In a study, investigating blood levels of various perfluoro- compounds in children and associations with behavioral inhibition, the results showed that blood levels of PFHxS were significantly associated with behavioral inhibition deficits in children (Gump et al., 2011). High compared to low prenatal exposure to PFHxS was also associated with problematic behaviour in children age 5–9 years from both Greenland and Ukraine (n=1023) (Høyer et al., 2017).

1. Epidemiological studies indicate immunotoxic or modulative effects caused by certain PFAS and PFHxS exposure prenatal and in childhood. The relationship between prenatal exposure to certain PFASs and prevalence of infectious diseases up to 4 years of life were investigated in 1558 mother-child pairs, enrolled in the Hokkaido Study on Environment and Children’s Health. Prenatal exposure to PFOS and PFHxS were found to be associated with infectious diseases occurrence in early life. PFHxS was associated with a higher risk of total infectious diseases only among girls (Q4 vs. Q1 OR: 1.55, 95% CI: 0.976, 2.45; p for trend=0.045) (Goudarzi et al., 2017). An inverse association was observed between maternal PFHxS serum levels and the level of anti-rubella antibodies and number of episodes of gastroenteritis at age 3 (Granum et al., 2013). Grandjean et al., 2012, observed odds ratios of 1.78 (1.08; 2.93) (95% CIs) for inadequate antibody concentrations at age 7 for tetanus vaccine with doubling of the PFHxS serum concentration. In a follow-up study combining two birth cohorts from Faroe Island, 1997–2000 and 2007–2009, a significant reduction of pre-boost serum antibodies to tetanus vaccine at age 5 years was associated with doubling of serum concentrations at birth for PFHxS (Grandjean et al., 2017). Furthermore, increased incidence of asthma has been indicated in children exposed to PFHxS (Dong et al., 2013; Zhu et al., 2016; Qin et al., 2017). In asthmatic children a significant association between increasing PFHxS serum level and decreases in pulmonary function was observed (Qin et al., 2017). In contrast, a Canadian study of prenatal exposure to PFHxS and cord blood immune markers (IgE, IL-33, TSLP) reported no significant associations (Ashley-Martin et al., 2015). A prospective birth cohort study of 1056 woman found that prenatal exposure to PFOA, PFDA, PFDOA and PFHxS significantly increased the risk of childhood atopic dermatitis in female children during the first 24 months of life (Chen et al., 2018).
2. Some studies indicate that PFHxS and certain PFAS might impact reproduction in humans. Both epidemiological and in vitro studies suggest that perfluoroalkyl acids might influence ovarian cell signalling and measures of overall reproductive health. In a recent study, blood and follicular fluid was collected from 36 subjects undergoing in vitro fertilization in the United States. Results showed that baseline follicle count was inversely related to plasma PFHxS concentrations, flagging this particular PFAS as a potential compound of interest in the context of ovarian pathology (McCoy et al., 2017). In a case control study from Denmark a strong significant association between serum certain PFAS levels (PFDA and PFNA) and miscarriage and an almost significant association with PFHxS was observed with adjusted odds ratio (OR) 1.53 and (95% CI) (0.99–2.38) (Jensen et al., 2016). In a cohort study from Canada between 2008–2011, n=1625, increased concentrations of PFOA and PFHxS in the female plasma were associated with decreased fecundability as measured by a longer time-to-pregnancy and increased odds of infertility, while no significant association was observed for PFOS (Velez et al., 2015).
3. In the U.S. population in NHANES 2009–2010 prevalence of osteoporosis was significantly higher in the high versus lowest quartiles of PFHxS with OR 13.2 (95% CI: 2.72–64.15) (Khalil et al., 2016). In a case-control study of the relationship between serum levels of certain POPs and risk for breast cancer in Greenlandic Inuit women, Wielsøe et al. found a significant positive association between breast cancer risk and PFHxS (Wielsøe et al., 2017).

### 2.4.4 Mixture toxicity and combined effects of multiple stressors

1. Little is known about the mixture toxicity of PFASs at environmental relevant conditions, but some studies have investigated the mixture effects of the most commonly detected PFASs in human serum. More than additive effect was observed for a mixture of PFHxS, PFOS, PFOA, PFNA, PFDA when tested for anti-androgen activity in vitro at concentration corresponding to 1 M of each single component in the mixture (Kjeldsen and Bonefeld-Jørgensen, 2013). In a follow up study, using the PFCA mixture extracted from serum of pregnant women in gestation week 11–13, the concentration of the combined mixture of extractable PFASs from the serum were positively correlated to the ER-transactivities (Bjerregaard-Olesen et al., 2015). Binary combinations of PFOA + either PFNA, PFHxA, PFOS or PFHxS tested for activation of PPAR-alpha in vitro produced concentration-response curves that were closely aligned with predicted curves for both response addition and concentration addition at low concentration (1–32 µM) (Wolf et al., 2014). A mixture of 10 PFAS (PFHxS included) at equimolar doses (final concentrations of each PFAS: 1.56–50 M) acted in an additive manner when tested for transactivation of PPAR-alpha from baikal seal (Ishibashi et al., 2011). In the human placental choriocarcinoma cell line JEG-3, a mixture of PFASs (PFBA, PFHxA, PFOA, PFNA, PFDoDA, PFBS, PFHxS and PFOS, each 0.6 µM), led to a relative increase up to 3.4-fold of several lipid classes, which indicate an interference of these PFASs with membrane lipids (Gorrochategui et al., 2014).
2. Viability studies of individual and mixtures of PFASs (C4–C11) had an obvious non-monotonic concentration-response relationship on human liver cells. Results of the three binary mixtures of PFASs, one with the combination PFHxA/S, showed that synergistic effects occurred under effective concentrations of IC0, IC10, and IC50 in mixtures while under IC-20 the synergistic effect only occurred under a higher proportion of PFSA (Hu et al., 2014).
3. There is evidence from experimental and indications from human epidemiology studies that PFHxS can affect lipid metabolism (see section 2.4.2 and 2.4.3). Tartu et al., 2017a, reported that diet and metabolic state was the main factors determining the amount of PFAS in female bears from Svalbard and that factors such as fasting, habitat and breeding status affect the levels of PFAS accumulated (including PFHxS) by the polar bears (Tartu et al., 2017a). In this study, levels of PFHxS were significantly negative related to urea: creatine ratios indicating a fasting state. Certain PFASs contribute to the multiple-stressor effects observed in polar bears from Svalbard. A recent study by Tartu et al., 2017b, showed that PFAS affect biomarkers of energy metabolism (lipid-related genes, fatty acid synthesis and elongation in adipose tissue, and serum cholesterol, HDL and triglycerides). These effects were more pronounced when combined with reduced sea ice extent and thickness suggesting that climate driven sea ice decline and PFAS (and other organohalogenated compounds) have a synergistic negative effect on polar bears (Tartu et al., 2017b).
4. Arctic top predators such as polar bears are among the most polluted species in the world (Letcher et al., 2010) and undergo seasonal energy-demanding periods due to variation in temperature, food availability, reproduction and hibernation. As described in section 2.2.3, it is well known that certain PFASs will bioaccumulate in protein rich compartments (kidney, liver and blood etc) but it is not clear how body condition (such as starvation) affect tissue concentration and distribution of these PFASs and a possible alteration of the toxic potential. Cocktail effect due to increased concentration of traditional POPs in fat storage as well as climate changes will also affect these periodes. PFHxS has high affinity to proteins and are not subject to biotransformation (Jones et al., 2003). In Arctic fox, PFHxS was detected at higher concentrations of lean foxes in all tissue measured (liver, blood, adipose tissue, muscle, kidney) compared to in fat foxes (Aas et al., 2014). For PFHxS, adipose tissue was the only tissue affected by body condition with lean foxes having three times (95% CI: 1.1, 12] higher concentration of PFHxS, than fat foxes. The large seasonal variability in fat content in arctic mammals may thus affect tissue concentrations of certain PFASs and increase their potential effects during seasonal emaciation. The effects are not only related to the increased concentration of PFASs, but also to increased concentration of other POPs in target organs during decreased body condition which may further increase toxicity (discussed in Aas et al., 2014).
5. Finally, countries such as Sweden and Denmark have set cumulative limits for PFAS in drinking water and ground water, when PFAS is believed to act together in a mixture. In Sweden, a concentration limit of 90 ng/L is set for PFAS11 (PFBS, PFHxS, PFOS, 6:2 FTS, PFBa, PFPeA, PFHxA, PFHpA, PFOA, PFNA, PFDA9) and above this concentration risk reducing action is to be taken (https://www.livsmedelsverket.se/en/food-and-content/oonskade-amnen/miljogifter/pfas-in-drinking-water-fish-risk-management#Action levels). A simmilar approach is enforced in Denmark (<http://mst.dk/media/91517/pfas-administrative-graensevaerdier-27-april-2015-final.pdf>). Furthermore, in the proposal for a new European Drinking Water Directive, which is under discussion, a limit value is proposed for the group of PFASs, as defined by the OECD. Values of 0.1 μg/l for individual PFAS and 0.5 μg/l for PFASs in total in as been suggested (http://ec.europa.eu/environment/water/water-drink/pdf/revised\_drinking\_water\_directive\_annex.pdf).

**3. Synthesis of information**

1. PFHxS belongs to the perfluoroalkyl substance (PFAS) group and has been used as surfactants, water- and stain protective coatings for carpets, paper, leather and textiles and in fire-fighting foams among other applications. It is also known that PFHxS can be unintentionally produced during the electrochemical fluorination processes used in production of other PFAS e.g. PFOS. These compounds have provided surfactant, water- and stain protective functions in various products due to their thermal stabilities and hydrophobic and lipophobic nature.
2. Information about current global manufacture of PFHxS, its salts and PFHxS-related compounds are limited. Historical production was mainly carried out by 3M and possibly also by some producers in Japan. One European manufacturer and a number of producers located in China have been identified, however, quantitative production data are not publically available. PFHxS, its salts and many PFHxS-related compounds have been listed on many national chemical inventories (USA, Canada, Japan, Australia, Nordic countries and China) indicating historical/present production, importation and/or uses of products containing these substances. Possible direct and indirect sources of PFHxS to environmental releases are many and emissions may take place at least through air, dust, water, wastewater and sludge.
3. While analytical methods for detection of PFHxS are well established, it is presently a challenge to qualify and analytically quantify PFHxS precursors due to the lack of established methods. However, precursors such as perfluorohexane sulfonamides were detected/identified in leachates from landfills indicating that these PFHxS precursors may be used in a variety of applications since the landfills had received waste from a number of sources. FHxSAs has also been detected in historical AFFF manufactured by 3M.
4. PFHxS has been detected in numerous matrixes worldwide including in the Arctic. Due to historical use of AFFF containing PFHxS, high levels of PFHxS has been detected in the vicinity of fire-fighting training fields, both at commercial airports and at military facilities. Based on the persistence of PFAS in general, the known extreme stability of the C-F bonding and the monitoring data showing the ubiquitous presence of PFHxS in the environment, it is concluded that PFHxS is persistent to environmental- and biological degradation. Bioaccumulation for PFHxS is complicated due to its physiochemical properties (combined hydrophilic/hydrophobic characteristics) making it difficult to experimentally measure its log Kow. However, several studies have reported bioaccumulation of PFHxS with BMFs and TMFs > 1 for different food chains, including from the Arctic. PFHxS binds strongly to proteins and this phenomenon is observed across species. The half-life of PFHxS in human serum is high (approx. 8.5 years), which is known to be a good indicator of bioaccumulation.
5. PFHxS is found ubiquitously spread throughout the environment and in biota globally.A number of studies have reported exposure in local areas that can be attributed to long-range environmental transport. PFHxS is detected in water, snow, air and biota at remote locations. Increasing trends, most likely due to increased emissions, have recently been detected in polar bears at Svalbard (Norway). In this study, PFHxS was the third most abundant PFAS measured in the serum of these animals. The main mechanism of transport to remote regions like the Arctic is most likely through water. A number of studies have reported detection of PFHxS in waters worldwide. However, transport via the atmosphere cannot be excluded since PFHxS has been measured in snow, rainwater and air as well as in lichen. It is likely that volatile PFHxS-related substances are transported through air and degraded to PFHxS locally.
6. Humans are exposed to PFHxS mainly through intake of food and drinking water but also through the indoor environment via exposure to dust or consumer products containing PFHxS or its precursors. Following PFOS and PFOA, PFHxS is the most frequently detected PFAS in blood-based samples from the general population. PFHxS is present in the umbilical cord blood and breast milk. Breast milk may be an important source of exposure to breast-fed infants since it is documented that PFHxS is excreted via lactation. Contamination of drinking water can result in highly increased PFHxS serum levels due to the long elimination-time in humans.
7. PFHxS affects liver function and lipoprotein metabolism and alters serum cholesterol, triglycerides and lipoproteins in both rodents and humans. PFHxS activates peroxisome proliferating receptor (PPAR)-alpha, however, effects on liver are also observed in mice without PPAR-alpha. Neurotoxic and neurodevelopmental effects have been observed in controlled laboratory experiments in mice and rats, and some studies indicate association between behavioural inhibition in children and certain PFAS (and PFHxS) exposure prenatal and in childhood. Effects on the endocrine system, including in particular the thyroid hormone system have been reported cross-species (frog, bird, rat, polar bear and human). Furthermore, several epidemiology studies indicate that the naïve and developing immunesystem might be vulnerable to certain PFAS and PFHxS exposure, observed as associations between serum PFHxS levels and reduced effect of vaccines and higher incidences of infections and asthma in children.
8. Certain PFASs, including PFHxS, contribute to the multiple-stressor effects observed in Arctic animals. Studies indicate that the level of certain PFAS in polar bear brain exceeded the threshold limit for neurochemical and hormonal alterations, and can affect the thyroid homeostasis. PFHxS bioaccumulate in protein-rich tissue, but during seasonal emaciation PFHxS also reach high levels in fat tissue. Combined exposure of PFASs with other POPs have unknown consequences and may case increased toxicity for heavily stressed species.

**Table 6. POP characteristics of PFHxS**

| **Criterion** | **Meets the criterion**  **(Yes/No)** | **Remarks** |
| --- | --- | --- |
| Persistence | Yes | * No significant photolysis in water was observed for PFHxS following, respectively, 106 and 20.5 days of exposure in a field study of PFHxS conducted at high altitude in (Taniyasu et al., 2013). * PFHxS are found in soil, water and a variety of biota in the vicinity of  fire-fighting training areas following the historical use of PFHxS-containing foams, showing that it is persistent and does not undergo any abiotic or biotic degradation under normal environmental conditions (Bräunig et al., 2017; Filipovic et al., 2015). * Read across from experimental degradation data for PFOS and PFOA demonstrate that these substances are very persistent (ECHA 2017a; ECHA 2013), and based on the stability of organic fluorine compounds in general (Siegemund et al., 2000) one can expect that PFHxS have the same persistent characteristics. |
| Bio-accumulation | Yes | * Found in elevated concentrations in top predators in the Arctic (Routti et al., 2017; Tartu et al., 2017b; Smithwick et al., 2005b). * Log Kow is estimated to 5.17 and this is in line with estimated log Kow for PFOS (Wang et al., 2011) * BMFs>1 in aquatic organisms (Haukås et al., 2007; Houde et al., 2006; Babut et al., 2017) * BMFs >1 in terrestrial organisms (Riget et al., 2013 as reported in ECHA 2017a). * TMFs> 1 in aquatic organisms (Munoz et al., 2017). * Half-life of PFHxS in humans are the highest reported for any PFAS and varies between 5.3 and 14.7 years (Olsen et al., 2008; Fu et al., 2016; Li et al., 2018) |
| Potential for Long-Range Environmental Transport | Yes | * PFHxS is found in air and snow in the Arctic (Theobald et al., 2007 as cited in Butt et al., 2010; Stock et al., 2007; Genualdi et al., 2010; Butt et al., 2010; Wong et al., 2018; Norwegian Environment Agency M-757, 2017b) * Detection of PFHxS in Arctic seawater (Caliebe et al., 2005 as cited González-Gaya et al., 2014; Rosenberg et al., 2008; Busch et al., 2010; Cai et al., 2012; Benskin et al., 2012; Zhao et al., 2012¸ Yeung et al., 2017). * Main transport pathway is through water due to higher frequency of PFHxS in ocean water than in air. * Transport of volatile PFHxS-related compounds through air indicated by detection of increasing amounts of PFHxS in snowmelt (Codling et al., 2014; Meyer et al., 2011) and in rain water (Eschauzier et al., 2010). * Detection in top predators in Arctic with increasing levels further away from local sources (Routti et al., 2017; Tartu et al., 2017b; 2018). |
| Adverse effects | Yes | PFHxS exerts effect on liver, serum lipids and cholesterol, and affect serum thyroid hormones and neuro development. Key data include:   * Effect on liver function and serum cholesterol, triglycerides and lipoproteins in rodents (Butenhoff et al., 2009; Bijland et al., 2011; Das et al., 2016). A LOAEL of 0.3 mg/kg bw/day based on reductions of total serum cholesterol at all doses was derived from the Butenhoff et al. (2009) as well as NOAELs of 0.3 mg/kg bw/d for effects on increased liver weight and hepatocellular hypertrophy. * Epidemiology studies show association between PFHxS exposure level and serum concentration of cholesterol, lipoproteins (Fisher et al., 2013: Steenland et al., 2009). * Thyroid organ effects were observed in male rats exposed to PFHxS at 10 mg/kg for 42 days, a dose-dependent increase in thyroid hypertrophy/hyperplasia was observed (Butenhoff et al., 2009). Epidemiology studies show association between PFHxS serum levels and thyroid hormones (Jain 2013; Wen et al., 2013; Chan et al., 2011, Webster et al., 2016). * Correlation between serumlevels of PFHxS and thyroid hormones has also been observed in field studies in Arctic birds (Nøst et al., 2013) and polar bears (Bourgeon et al., 2017). * Developmental neurotoxicity observed in mice (Viberg et al., 2013; Lee and Viberg, 2013). Epidemiological indications for cognitive developmental effects in humans (Stein and Stavitz 2011; Høyer et al., 2017). * Effect on the immunesystem has been shown in epidemiology studies, both reduced effects to vaccination (Granum et al., 2013; Grandjean et al., 2012; 2017), increased incidence of asthma (Dong et al., 2013; Zhu et al., 2016; Qin et al., 2017) and higher risk of infection in children has been observed in correlation with PFHxS serum levels (Goudarzi et al., 2017; Grannum et al., 2013). * Delayed development in northern leopard frog (Rana pipiens) tadpoles exposed to 10 g/L PFHxS for 40 days (Hoover et al., 2017). |

# **4. Concluding statement**

1. PFHxS is emitted into the environment from human activities e.g. from manufacturing processes, product use and disposal and management of waste. PFHxS is persistent, bioaccumulative and has the potential to undergo long-range environmental transport, making emissions of this substance a transboundary pollution problem including in remote areas. Globally, the occurrence and distribution of PFHxS is shown for humans, wildlife and the environment. Detections include measurements in the Arctic and Antarctic.
2. PFHxS is one of the most frequently detected PFAS in human blood in the general population and has a very long half-life in humans (range 5.3–14.7 years). Furthermore, PFHxS has been detected in human umbilical blood, serum and breast milk. High concentrations of PFHxS have been detected in soil, ground and drinking water near airports or fire-fighting training sites, sludge and wastewater from waste water treatment plants, as well as in the vicinity of PFAS/PFHxS production/usage plants and in leachate from landfills.
3. Available scientific literature suggests that there is a risk for adverse effects on the general population, in particular for children and population groups that are exposed to elevated levels of PFHxS and other PFASs through drinking water. The concern for adverse effects relates to observed effects on endpoints involved in metabolism/metabolic homeostasis. Effects on the liver, thyroid hormone system, as well as neurotoxic and neurodevelopmental effects has been shown. Recent data from polar bear studies at Svalbard (Norway) revealed increasing levels of PFHxS in polar bear serum. Furthermore, studies of polar bears from Svalbard have shown possible alteration in thyroid hormones due to some PFASs (including PFHxS) exposure. Factors such as fasting, habitat and breeding status affect the levels of some PFASs, including PFHxS, in polar bears at Svalbard. Delayed development in frog tadpoles exposed to PFHxS has also been observed. Altogether, these studies indicate that there is a risk for adverse effects in wildlife.
4. Based on the persistence, bioaccumulation, toxicity in mammals including humans and the widespread occurrence in environmental compartments including at remote regions, it is concluded that PFHxS, its salts and PFHxS related compounds are likely, as a result of their long-range environmental transport, to lead to significant adverse human health and environmental effects such that global action is warranted.

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