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Report of the Persistent Organic Pollutants Review Committee on the work of its fourteenth meeting

Addendum

Risk profile on perfluorohexane sulfonic acid (PFHxS), its salts and PFHxS-related compounds

Note by the Secretariat

At its fourteenth meeting, by its decision POPRC-14/1, the Persistent Organic Pollutants Review Committee adopted a risk profile on perfluorohexane sulfonic acid (PFHxS), its salts and PFHxS-related compounds on the basis of the draft contained in the note by the Secretariat (UNEP/POPS/POPRC.14/2), as revised during the meeting. The text of the risk profile as adopted is set out in the annex to the present addendum. It has not been formally edited.

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Annex

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

RISK PROFILE

September 2018

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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, defined as any substances that contain the chemical moiety $C_6F_{13}SO_2$ 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, in many cases as a replacement for PFOS. In addition, PFHxS, its salts and related compounds have been used in certain per- and poly-fluoroalkyl substances (PFASs) based consumer products. PFHxS are and have been unintentionally produced during the electrochemical fluorination (ECF) processes of some 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 the parent compound perfluorohexane sulfonyl fluoride (PFHxSF) in the US in 1997. Current manufacturers of PFHxS, its salts and PFHxS related compounds include at least one producer in Italy and a few producers located in China. Information in the public domain on the current production and historic volumes of PFHxS, its salts and PFHxS-related compounds is very limited.

4. Limited research has been conducted on releases of PFHxS, its salts and PFHxS-related compounds to the environment. In general terms, releases to the environment occur from the production of the parent compound (i.e. PFHxSF) and its derivatives (i.e. PFHxS, its salts and PFHxS-related compounds), during processing, use and disposal, as well as from consumer products containing the derivatives. Release of PFHxS and perfluorohexane sulfonamides (FHxSA) from consumer products is documented by their detection in indoor dust and in wastewater, sludge and leachate from landfills and releases due to use of aqueous film-forming foams (AFFFs) containing PFHxS and PFHxS-related compounds such as FHxSA.

5. PFHxS is extremely 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 C_nF_{2n+1}- in general is very resistant to chemical, thermal and biological degradation due to its strong carbon-fluorine (C-F) bonds. Based on a read-across approach from the conclusions applied to the persistence of perfluorobutansulfonic acid (PFBS), PFOS and PFOA, it can be concluded that PFHxS is not degradable under natural conditions and is very persistent in water, soil and sediment. Due to the combined hydrophilic and hydrophobic properties as well as the high acid dissociation of PFHxS (pKa ≈ -5.8 to -3.3), it is very challenging to experimentally measure log K_{ow} of the undissociated acid. It should be noted that PFHxS is present in its anionic form under environmental conditions due to its low pKa. Furthermore, the PFHxS ion is relatively water-soluble and it binds to proteins in target organisms. In fish, the substance is not expected to be accumulated by the organism but excreted rather rapidly via the gills, resulting in bioaccumulation factors (BAFs)/bioconcentration factors (BCFs) under the Annex D criteria of 5000. Based on the identified protein-binding associated bioaccumulation, standard BCF/BAF in aquatic organisms are less meaningful descriptors for bioaccumulation for PFASs including PFHxS. However, biomagnification does occur, with biomagnification factors (BMFs) and trophic magnification factors (TMFs) >1 (BMF range 1.4–48 and TMF range 0.1–4.3) available for PFHxS, including from the organisms in the Arctic food chains. The estimated serum elimination half-life of PFHxS in humans is higher than other PFASs with an average of 8.5 (range 2.2-27 years).

6. PFHxS is distributed in the environment including in urban cities, rural areas and in regions that produce or use PFHxS or its precursors in the processing or manufacture of commercial products. It is also found in Arctic regions far away from any sources of release. Worldwide monitoring of water, air, sediment and biota (including humans) at remote locations have detected the presence of PFHxS. At Svalbard, Norway, an annual change has been observed in PFHxS levels in polar bears most likely due to transport through water and air to the Arctic. The highest levels of PFHxS measures in biota, are found in polar bears. Direct transport through ocean currents is likely the main mechanism of transport to remote regions, in addition to atmospheric transport of PFHxS and its precursors.

PFHxS has been detected in air, snow, meltwater, rainwater and lichen, indicating that atmospheric transport of precursors that may degrade to PFHxS locally, has occurred. Furthermore, PFHxS as well as FHxSA have 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, drinking water, by inhalation of indoor air and respiratory and oral uptake of dust containing PFHxS, its salts and PFHxS-related compounds. PFHxS has been detected in human blood and breast milk in many regions, and is together with perfluorooctane sulfonic acid (PFOS), perfluorooctanoic acid (PFOA) and perfluorononanoic acid (PFNA) one of the most frequently detected and predominant PFASs in human blood. The foetus is exposed to PFHxS via the umbilical cord blood, and breast milk may be an important source of exposure for the infant. In women post-menarche and males, PFHxS levels increase with age, and in general, the highest levels have been observed in men.

8. In regions where regulations and phase-outs have been implemented, human concentrations of PFOS, perfluorodecane sulfonic acid (PFDS), and PFOA are generally declining, while previously increasing concentrations of PFHxS have begun to level off. However, there are also observations of no decline or increasing levels of PFHxS in the same regions, most often connected to households receiving PFHxS contaminated drinking water, but in a few cases also in individuals that get their exposure from unknown sources. Limited data are available on levels and trends of PFHxS in humans in Asia where production continued after the 3M phase out.

9. PFHxS affects liver function, lipid and lipoprotein metabolism and activates the peroxisome proliferating receptor (PPAR)-alpha. In studies on rodents, increased liver weight as well as marked hepatocellular hypertrophy, steatosis and necrosis have been observed. Furthermore, alterations in serum cholesterol, lipoproteins, triglycerides, and alkaline phosphatase have been observed in rodents after PFHxS exposure. Effects on lipid metabolism and serum enzymes has been observed in human epidemiology studies. Effects on reproduction (decreased live litter size) have been observed in mice after PFHxS exposure. PFHxS binds to the thyroid transport protein, and has been associated with changes in serum thyroid hormones across species. Some evidence suggests that exposure to PFHxS may affect the developing brain and immune system. Effect on the antibody response to vaccination has been shown in epidemiology studies.

10. 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, the atmosphere, dust, as well as 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 PFHxS-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.

1. Introduction

11. 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.

12. PFHxS, its salts and PFHxS-related compounds belong to the per- and poly-fluoroalkyl substances (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 (see also 2.2.1 Persistence). Therefore, substances like PFHxS are not degradable in the environment. However, PFHxS-related compounds can degrade to PFHxS under environmental conditions and are therefore known as precursors. A number of PFHxS-related substances including some polymers, have been identified (See section 2.1.1 and 2.1.2; Norwegian Environment Agency, 2017a, M-792/2017; OECD 2018; http://www.oecd.org/chemicalsafety/portal-perfluorinated-chemicals/) and included in the proposal submitted by Norway (UNEP/POPS/POPRC.13/4).

13. The read-across approach has been applied mainly for the persistence criteria in this document. Guidance from the European Chemical Agency (ECHA, 2017c) and from the Organisation for Economic Co-operation and Development (OECD, 2014) has been used in terms of the definition of grouping of substances and use of the approach. In general, the read-across approach can be applied for substances of which physico-chemical and/or toxicological and/or ecotoxicological properties are likely to be similar or follow a regular pattern as a result of structural similarity. PFHxS belongs to a group of PFASs of which several similar substances already have been assessed with respect to their

POP- or persistent, bioaccumulation and toxicity properties. The substances in this group have a highly similar chemical structure with a perfluorinated carbon chain and a terminal acid group, sulfonic acid (PFSA) or carboxylic acid (PFCA), which justifies the use of read-across. It is clearly stated in the present document when the read-across approach has been applied.

1.1 Chemical Identity

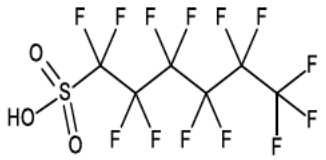
14. The proposed compounds included in the nomination of PFHxS, its salts and PFHxS-related compounds were defined in document UNEP/POPS/POPRC.13/4 and in decision POPRC-13/3 (UNEP/POPS/POPRC.13/7). In line with decision POPRC-13/3, the following apply:

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

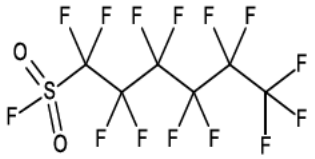
(b) Any substance that contains the chemical moiety $C_6F_{13}SO_2$- as one of its structural elements and that potentially degrades to PFHxS.

15. A number of chemicals are included in the group of PFHxS, its salts and PFHxS-related compounds including isomers. Some examples are given in Figure 1. The OECD has identified 72 PFHxS-related/precursor/polymer substances including PFHxS (CAS No: 355-46-4) (see Appendix 1 in UNEP/POPS/POPRC.14/INF/4) which all contain the fluorinated alkyl moiety $C_6F_{13}SO_2$ (OECD 2018; http://www.oecd.org/chemicalsafety/portal-perfluorinated-chemicals/). A study published by the Norwegian Environment Agency identified 79 commercially available compounds, including PFHxS and PFHxSF, based on a literature study and a theoretical assessment of abiotic degradation pathways leading to PFHxS (Norwegian Environment Agency, 2017a, M-792/2017; Appendix 2 in UNEP/POPS/POPRC.14/INF/4).

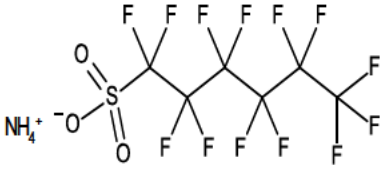
a) Perfluorohexanesulfonic acid (CAS No:



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



c) Perfluorohexanesulfonate ammonium salt (CAS No: 68259-08-5)



d) Potassium N-ethyl-N-[(tridecafluorohexyl)sulfonyl] glycinate (CAS No: 67584-53-6)

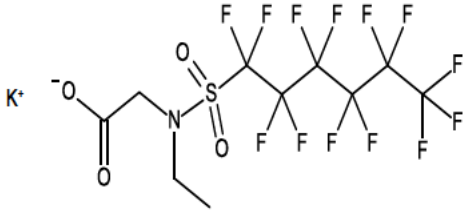


Figure 1. Structural formula for PFHxS (a), its raw material PFHxSF (b), and examples of its related compounds $PFHxSNH_4$ (c) and potassium N-ethyl-N-[(tridecafluorohexyl) sulfonyl] glycinate (d). Non-exhaustive lists of compounds are given in UNEP/POPS/POPRC.14/INF/4.

16. PFHxS is a strong acid with six fully fluorinated carbons, having both hydrophobic- and hydrophilic properties (Kissa, 2001). 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

17. Table 1 below lists the chemical identity of PFHxS, and Table 2 lists selected modelled and experimental physico-chemical 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-sulfonic acid
Molecular formula:	$C_6F_{13}SO_3H$
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 PFHxSK	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)
pK_a	-3.45 -3.3±0.5 -5.8±1.3	Wang et al., 2011 (COSMOtherm) ACD/Percepta 14.2.0 (Classic) ACD/Percepta 14.2.0 (GALAS)
Vapour pressure	58.9 Pa (0.0046 mmHg)	Wang et al., 2011(COSMOtherm)*
Water solubility	1.4 g/L (PFHxSK; 20–25°C) 2.3 g/L (non-dissociated)	Campbell et al., 2009 (measured) Wang et al., 2011 (COSMOtherm)*
Air/water partition coefficient, K_{aw} (log value)	-2.38	Wang et al., 2011 (COSMOtherm)*
n-Octanol/water partition coefficient, K_{ow} (log value)	5.17	Wang et al., 2011 (COSMOtherm)*
Octanol-air partition coefficient K_{oa} (log value)	7.55	Wang et al., 2011 (COSMOtherm)*
Organic carbon/water partition coefficient K_{oc} (log value) (mobility)	2.05 2.40 2.31 (range 1.8–2.76)	Guelfo and Higgins, 2013 (measured) D'Augostino & Mabury, 2017 (measured) Chen et al., 2018 field-based

* Estimates from Wang et al. (2011) refer to the neutral form of PFHxS only. It should be noted that PFHxS is present in its anionic form under environmental conditions due to its low pKa. Therefore, to describe partitioning of both the neutral and ionized species of PFHxS in the environment, estimated partition coefficients of the neutral form need to be converted to respective distribution ratios, as suggested in Schwarzenbach et al. (2002) and Wang et al. (2011).

18. 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, e.g. COSMOtherm that are used to calculate partition coefficients of neutral PFASs. 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 PFASs (Arp et al., 2006; Wang et al., 2011).

1.2 Conclusion of the POPs Review Committee regarding Annex D information

19. 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

20. The draft risk profile is based on the following data sources:

(a) The proposal to list perfluorohexane sulfonic acid (PFHxS), its salts and PFHxS-related compounds submitted by Norway (UNEP/POPS/POPRC.13/4);

(b) Information submitted by the following Parties and observers according to Annex E to the Convention: Australia, Canada, Denmark, Ecuador, Germany, Japan, Monaco, The Netherlands, Sweden, The United Kingdom, The 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;

(c) The supporting documents for the identification of PFHxS as a Substance of Very High Concern (SVHC) in the European Union prepared by Sweden, where PFHxS was recently identified as very persistent and very bioaccumulative (vPvB) (ECHA, 2017a, b);

(d) Peer-reviewed scientific journals, as well as information from reports and other grey literature;

(e) The Australian National Industrial Chemicals Notification and Assessment Scheme (NICNAS) various tier II assessments for perfluoroalkane sulfonates (C_5–C_7) (NICNAS, 2017a, b, c, d);

(f) 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 national regulations and international forums

21. 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). Toxicity and ecotoxicity have not been evaluated in the SVHC evaluation process. Inclusion on this list means that the substances can be subject to an authorization procedure under which the substances can only be 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 above a concentration of 0.1%.

22. In Norway, PFHxS, its salts and PFHxS-related compounds 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 by 2020. Some PFHxS-related substances 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. Any person who intends to import or manufacture a substance in Canada that is not listed on the DSL (such as PFHxS or PFHxSF) must submit a notification required under the New Substances Notification Regulations. These regulations ensure that new substances are not introduced into the Canadian marketplace before undergoing ecological and human health assessments. Management measures may be imposed under this process to mitigate any risks to the environment or human health. 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; 2007). The US EPA published an action plan on long-chain PFASs, including PFHxS, and their salts and precursors in 2009. All chemicals were identified as persistent, bioaccumulative and toxic (US EPA, 2009). In Australia NICNAS has developed an action plan for assessment and management of chemicals which may degrade to PFCAs, PFASs, and similar chemicals. The primary assumption outlined in this action plan is that chemicals with a perfluorinated chain terminated by a sulfonyl group will degrade to the perfluoroalkyl sulfonate (of the same chain length) (NICNAS 2017, a, b, c or d).

23. Perfluorinated chemicals were identified under the Strategic Approach to International Chemicals Management (SAICM) as an issue of concern. Efforts are focused on gathering and

exchanging information on perfluorinated chemicals and to support the transition to safer alternatives (http://www.saicm.org/tabid/5478/Default.aspx).

24. 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.

25. No harmonized classification or labelling is available for PFHxS in EU or globally. However, in Australia PFHxS-related compounds are included in the Inventory Multi-tiered Assessment and Prioritisation (IMAP) framework, which includes both human health and environmental assessments (NICNAS 2017c). Based on the NICNAS action plan to assess and manage chemicals which may degrade to perfluorinated carboxylic acids, perfluoroalkyl sulfonates and similar chemicals, where chemical specific data was not available, the perfluorooctane sulfonate (PFOS) hazard information was used to estimate the systemic health hazard of potassium PFHxS, ammonium PFHxS, diethanolammonium PFHxS and PFHxSF. In relation to human health risks, potassium PFHxS, ammonium PFHxS, diethanolammonium PFHxS and PFHxSF were identified as: toxic if swallowed - Cat. 3 (H301), causes serious eye irritation - Cat. 2A (H319), causes damage to organs through prolonged or repeated exposure if swallowed - Cat. 1 (H372), suspected of causing cancer - Cat. 2 (H351) using the Globally Harmonized System of Classification and Labelling of Chemicals (GHS). In EU, self-classifications have been submitted by industry with the notification to the C&L inventory under the EU legislation, for PFHxS and several PFHxS-related substances for acute Tox. 4 and Skin Corr. 1B, STOT SE 3 (inhalation, lung), Skin Irrit.2, Eye Irrit. 2 (https://www.echa.europa.eu/en/information-on-chemicals/cl-inventory-database).

2. Summary of the information relevant to the risk profile

2.1 Sources

2.1.1 Production, trade, stockpiles

26. 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 ECF of hexanesulfonyl chloride ($C_6H_{13}SO_2Cl$ + 14 HF → $C_6F_{13}SO_2F$ + HCl + byproducts) with a yield of about 36% (Gramstad and Haszeldine, 1957).

27. In addition, PFHxSF may be unintentionally produced as a byproduct from the ECF of octanesulfonyl fluoride or chloride, the process to produce perfluorooctane sulfonyl fluoride (POSF) (Gramstad and Haszeldine, 1957; Jiang et al., 2015). 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). Of the PFHxS impurities from the 3M ECF production process for PFOS also branched isomers of PFHxS were detected e.g. 18% branched from 4.7% PFHxS impurity in one lot (Benskin et al., 2010).

28. 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 sulfonamido 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 (3M, 1999).

29. 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. However, the substances are produced- and available on the world market and some of the substances (CAS Nos: 423-50-7; 355-46-4; 3871-99-6; 68259-08-5; 41997-13-1; 68259-15-4; 34455-03-3) are reported to the EU classification and labelling inventory notification system (C & L Inventory, https://echa.europa.eu/information-on-chemicals), which shows that substances are produced, used and/or imported to the European market. However, after the final deadline for registration of

substances exceeding a 1000 kg under REACH, no PFHxS related substances are registered (ECHA database) i.e. are not produced or used in the EU above 1 tonne. Furthermore, it is noted that PFHxS, its salts and many PFHxS-related compounds have been listed on multiple national chemical registration inventories (see UNEP/POPS/POPRC.14/INF/4, Table 2 and Annex 1), indicating historical production, importation and/or uses of products containing these substances, historically and/or ongoing. 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). Further historical and/or current manufacturers or suppliers 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.

30. In 2016 Fu et al. reported that the annual productions of PFOS and PFHxS at Hengxin Chemical Plant (Yingcheng, Hubei province, China) were approximately 60 and 0 tonnes in 2008, respectively. The production of PFOS was considerably reduced after PFOS was restricted in 2009 by the Stockholm Convention, and PFHxS then became a new product of the plant. The annual production volumes of PFOS from 2009 to 2011 were 30, 10, and 10 tonnes, respectively, whereas those of PFHxS were 10, 10 and 30 tonnes, respectively. Furthermore, it was reported that in 2012, the plant expanded the annual production of PFOS to 65 tonnes and ceased PFHxS production in light of changing market requirements. Simultaneously, the synthesis of PFHxS-based fabric finishing agent continued in 2012 using the PFHxS in stock (Fu et al., 2016).

31. 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, and stakeholder consultations, 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, such as possible manufacturers and producers of consumer products, 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. Historical production or import of PFHxS, its salts and PFHxS-related compounds in the United States is extracted from the US Toxic Substances Control Act (TSCA) Inventory Update 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 TSCA Inventory Update 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

32. 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).

2.1.2 Uses

33. Due to the thermal and chemical stability as well as the hydro- and oleophobicity of the perfluoroalkyl moiety (C_nF_{2n+1}-), PFHxS, its salts and PFHxS-related compounds can be used as effective surfactants and/or surface protectors. PFHxS is found in elevated amounts in the environment and is used as one replacement for PFOS (Swedish Chemicals Agency, KEMI 2015; Chen et al., 2018a). In the 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: (1) AFFFs for firefighting; (2) metal plating; (3) textiles, leather and upholstery; (4) polishing agents and cleaning/washing agents; (5) coatings, impregnation/proofing (for protection from damp, fungus, etc.); and (6) within the manufacturing of electronics and 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; Norwegian Environment Agency M-961/2018).

AFFFs for firefighting

34. Historically, 3M used PFHxS in the production of its AFFF formulations (Olsen et al., 2005). According to Olsen et al., 3M produced PFHxS (or PFHS) as a building block for compounds incorporated in firefighting foams and this information is in accordance with patents from 3M (3M, 1972, 1973, 1992) and from another potential historical producer (reviewed in Norwegian Environment Agency M-961/2018). 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 investigations of AFFF formulations, some of which were legacy formulations, where PFHxS-related compounds were identified (D’Agostino et al., 2014; Barzen-Hanson et al., 2017; Place and Field, 2012; Backe et al., 2013) and PFHxS was detected at 820 ± 140 mg/kg (Vecitis et al., 2010), 370 mg/L (Herzke et al., 2012), 500−1400 mg/L (Houtz et al., 2013), 20.0–1330 mg/L (Weiner et al., 2013), 760–1700 mg/L (Backe et al., 2013 and 0.2–1025.5 mg/kg (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 possible that such “PFOS-based AFFFs” containing PFHxS-related compounds have been discontinued after 3M ceased its global production in 2000–2002 (3M, 2000a), however, production by companies other than 3M cannot be excluded. Furthermore, 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-extinguishers (Vatten, 2018; Huang et al., 2015).

Metal plating

35. A number of patents (Dainippon, 1979, 1988; 3M, 1981; Hengxin, 2015) were identified for the use of PFHxS, its salts and various PFHxS-related compounds in metal plating as mist suppressants, suggesting that such use may have occurred. 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 (tridecafluorohexanesulfonic 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 EPA Significant New Use Rule on perfluoroalkyl sulfonates and long-chain perfluoroalkyl carboxylate chemical substances (US EPA, 2013).

Textiles, leather and upholstery

36. 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 possible that such aftermarket carpet and upholstery protector products produced by 3M have been discontinued after the company ceased its global production in 2000–2002 (3M, 2000a). However, it is reported that

water-proofing textile finishes based on PFHxS-related compounds have recently been developed by at least Hubei Hengxin Chemical Co., Ltd. (CAS No: 68259-15-4, (tridecafluoro-N-methylhexanesulfonamide); CAS No: 68555-75-9 (tridecafluoro-N-(2-hydroxyethyl)-N-methylhexanesulfonamide); and CAS No: 67584-57-0, (2-[methyl[(tridecafluorohexyl) sulfonyl]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).

Polishing agents and cleaning/washing agents

37. 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).

Coating and impregnation/proofing

38. One PFHxS-related compound (CAS No: 67584-61-6, 2-[Methyl[(Tridecafluorohexyl) Sulfonyl]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).

Manufacturing of semiconductors

39. 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 province of China (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 at this site.

Other potential uses

40. Hubei Hengxin has marketed the potassium salt of PFHxS and PFHxS-related compounds (CAS No: 68259-15-4, tridecafluoro-N-methylhexanesulfonamide) for potential uses as a flame retardant and in pesticides, respectively (Hengxin, 2018). PFHxS has been detected in food packaging materials (Schaider et al., 2017). Information regarding use of PFHxS in a company that develops, manufactures, and distributes analogue and digital imaging products has been reported (The Netherlands submission to PFOA intersessional work, 2018).

2.1.3. Releases to the environment

41. 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). This is in line with recent studies on source identification for PFHxS in groundwater samples (n=102) from non-industrial areas in China and drinking water in the U.S. (n=36977), showing that PFHxS clustered/occurred together with PFOS. Thus, for these sites, PFHxS may have originated from similar sources as PFOS such as AFFFs, pesticide applications, landfill leachates and WWTP effluents (Wei et al., 2018; Guelfo and Adamson et al., 2018). However, this was not the case in a study by Ma et al., (2018) where levels of PFHxS exceeded PFOS levels in Taihu Lake
(Ma et al., 2018). This increase of PFHxS was linked to production and use of PFHxS as an alternative due to recent regulation of PFOS (and PFOA and related compounds) (Ma et al., 2018). A recent paper reports concentrations in rivers in China. The estimated load of PFHxS to these rivers were 21.6 tonnes in 2016, up from 0.09 tonnes in 2013 (Pan et al., 2018).

42. 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 remains 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).

43. 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 process 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 was found at low levels.

44. 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 United States (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; Ahrens et al., 2015; 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 releases to indoor environments such as from dust (Norwegian Environment Agency, Report M-806/2017c). 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

45. There are some characteristics which are valid for the whole group of PFASs, and therefore also for PFHxS; high electronegativity, low polarizability, and high bond energies make highly fluorinated alkanes extremely stable organic compounds. Based on the persistency of all other PFASs it can be assumed that PFHxS is persistent as well, and this was concluded in the EU when PFHxS was identified as very persistent and very bioaccumulative substance. This conclusion was made based on the knowledge of the stability of the C-F bonds and the read-across approach (ECHA, 2017c) with PFOS and PFOA (ECHA, 2017a, b).

46. PFASs are very resistant to chemical, thermal and biological degradation due to their strong C-F bonds (Kissa, 2001) and resistance to degradation makes them persistent in the environment. The stability of PFASs 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 low 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).

47. Experimental data on the persistence of PFHxS are very sparse. However, in a field study on photolysis of PFHxS in water 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).

48. PFHxS is found in soil, water and a variety of biota (see UNEP/POPS/POPRC.14/INF/4, Tables 1.1–1.5) 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.

49. There are no available experimental biodegradation data in water or soil for PFHxS. 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) classification (vP; persistence criteria under REACH (https://echa.europa.eu/documents/10162/13632/information_requirements_r11_en.pdf) are similar to the criteria for persistence in Annex D under the Stockholm Convention) of PFOA in water, sediment and soil has also been confirmed (ECHA, 2013). Furthermore, Quinete et al. (2010) demonstrated that PFBS is not biodegradable and expected to be a highly stable transformation product which several precursors ultimately degrade into (Quinete et al., 2010; D'Agostino and Mabury, 2017; Wang et al., 2013). In addition, the results of a ready biodegradability test of perfluorobutane sulfonate in compliance with Good Laboratory Practice provided in a conference room paper from Japan showed that PFBS is not readily biodegradable. Measurements of BOD and chemical analysis of the parent substance indicated zero biodegradation occurred in the study. 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 (ECHA, 2017a).

50. In Australian assessments, multiple studies conducted on a range of PFASs, including the C_4 and C_8 homologues of PFHxS, have found no evidence of potential for biodegradation, hydrolysis or aqueous photolysis under environmental conditions (NICNAS, 2017a; 2017b; 2017c).

51. PFHxS is not expected to undergo hydrolysis or photolysis, and biodegradation and, like other PFASs, is found to be poorly removed in waste water treatment plants (Danish Ministry of Environment, 2015). Based on a read-across approach from the conclusions applied to the persistence of PFBS, PFOS and PFOA, it can be concluded that PFHxS is not degradable under natural conditions and is very persistent in water, soil and sediment.

2.2.2 Occurrence of PFHxS related compounds and degradation

52. 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 $C_6F_{13}SO_2$ may undergo abiotic degradation resulting in the release of PFHxS and C_6 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) (Norwegian Environment Agency, 2017a, M-792/2017 and references within), whereas major products from biotic degradation would be almost solely PFHxS (Wang et al., 2014).

53. Analytical methods for identifying and quantifying PFHxS-related compounds (e.g. perfluorohexane sulfonamides (FHxSA)) are at present very limited. Two studies using non-target analysis detected FHxSA in AFFF-impacted groundwater, 3M historical AFFF, and consumer products as well as in drinking water (Barzen-Hanson et al., 2017; Kabore et al., 2018). Although the data are not quantitative, they do show that PFHxS precursors have been used and that they are present in the environment and that human exposure can occur via drinking water. 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).

54. 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 (Codling et al., 2014). 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).

55. 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-life. In a recent review, it was reported that PFASs are routinely detected in landfill leachate with PFASs (C_4–C_7) 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 (C_4–C_7) 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 PFASs (Guelfo & Higgins, 2013). Following disposal, PFASs are released from the waste through both biological and abiotic leaching either from precursor degradation (biological or abiotic) or from direct use of PFASs such as PFHxS or PFOS (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 and/or their parent compounds 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. The 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). 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).

56. Applying the read-across approach (see Section 1) and results from studies on other PFASs, indicates that PFHxS-related compounds may have the potential to degrade to PFHxS in the environment. Biodegradation data available for the C_8N-ethylperfluorooctanesulfonamidoethyl alcohol (CAS No: 1691-99-2) demonstrate conversion with the ultimate biodegradation product being PFOS (Hekster, et al., 2002; Martin, et al., 2010). Other chemicals containing the perfluorooctyl sulfonate group are expected to be susceptible to a similar biotransformation process (Martin, et al., 2010). Further, data available for the C_4N-methylperfluorobutanesulfonamidoethyl alcohol (CAS No: 34454-97-2) indicate potential for atmospheric degradation to PFBS through oxidation by hydroxyl radicals (D'eon, et al., 2006; Martin, et al., 2010). Moreover, PFBS is expected to be a highly stable transformation product in which several precursors ultimately degrade into (Quinete et al., 2010; D'Agostino and Mabury, 2017; Wang et al., 2013; Norwegian Environment Agency, 2017a, M-792/2017).

2.2.3 Bioaccumulation and toxicokinetics

57. 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 compounds. Even if the reported BCF and BAF for PFHxS are below the numerical criteria of 5000 (Martin et al., 2003; Yeung and Mabury, 2013; Kwadijk et al., 2010; Casal et al., 2017; Ng and Hungerbuhler, 2014; Naile et al., 2013), the numerical criterion for BCF or BAF are not appropriate for PFHxS since PFHxS does not follow the behaviour of traditional hydrophobic compounds by partitioning into fatty tissues (UNEP/POPS/POPRC.3/INF/8). 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).

58. Studies on uptake of PFHxS from soil to earthworms have also been performed. In these studies, low bioaccumulation in earthworms were reported by biota-to-soil accumulation factors (BSAF) (Zhao et al., 2013; 2014). Furthermore, PFSAs have also been reported to be taken up by plant roots from spiked soil in the order PFOS>PFHxS>PFBS (Felizeter et al., 2012).

59. 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. BMFs and 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 have 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 22 (Haukås et al., 2007; Routti et al., 2016; Tartu et al., 2017). 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. Monitoring data also reveal that polar bears contain the highest levels of PFHxS of any investigated animal (see Table 1.3 UNEP/POPS/POPRC.14/INF/4).

60. A study on pigs fed a diet contaminated with known concentrations of PFHxS, calculated dietary BMFs for whole pig, meat and liver for PFHxS were 20.1, 13.1 and 48, respectively (Numata et al., 2014).

61. An overview of the BMFs from the above-mentioned studies are shown in Table 4. Limitation of these BMF/TMF studies was discussed in the nomination dossier (UNEP/POPS/POPRC.13/4) and the SVHC dossier also reviews some of the bioaccumulation studies listed in Table 4 in detail (ECHA, 2017a).

Table 4. 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)	Plasma	22		As calculated from Routti et al., 2016 and Tartu et al., 2017
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 (Sole/flat fish/crab/clams and polychaetes)	Whole		4.3	Munoz et al., 2017
Bentho-pelagic (demersal; top predators seabass and meagre)	Whole		1.5	Munoz et al., 2017

62. 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, age and tissue versus whole body calculations may affect the calculation of TMF (Borgå et al., 2012; Franklin, 2016). 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 4 above).

63. The use of the elimination half-life is a useful addition to the use of BMF and TMF as an indicator of bioaccumulation potential that should be considered in a weight-of-evidence bioaccumulation assessment (Franklin, 2016). Average half-lives for PFHxS, PFOS and PFOA in humans 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). The reported half-life of PFHxS in men is on average 8.5 years (range 2.2–27 years) (Olsen et al., 2007) but estimates up to 35 years have been made (see Table 3 in UNEP/POPS/POPRC.14/INF.4), which is the longest of all PFASs for which data are available. The half-life of PFHxS is 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 (22 males and 2 females) has been reported (Olsen et al., 2007). 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. Furthermore, serum elimination times in humans are affected by female menstruation as well as child-birth (Gomis et al., 2017).

64. 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).

See Table 3 UNEP/POPS/POPRC.14/INF/4) for comparison of half-lives. 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).

65. 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 PFASs.

66. In a Spanish human 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. 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

67. The potential for long-range transport of PFHxS was reviewed in the nomination dossier (UNEP/POPS/POPRC.13/4). In support of the long-range transport, data show that PFHxS is found in various environmental compartments in the remote regions of the Arctic including in air, snow, soil, sediment as well as in biota (including humans). In the Antarctica PFHxS was found in biota and snow, strengthening the evidence that PFHxS can be transported over long distances far from the primary source. For monitoring data from both the Arctic and Antarctica see UNEP/POPS/POPRC.14/INF/4, Tables 1.1, 1.2 and 1.3 for biota and Table 1.4 for abiota.

68. 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 and on geographical locations (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 and semivolatile 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; Rauert et al., 2018a,b). 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). A recent study measured PFASs (including PFHxS) in a number of matrixes, at local and remote locations at Svalbard in the Norwegian Arctic and found that the amount of PFHxS detected was dependent on whether the sampling site was close to local sources such as firefighting training sites. Levels at background sites were found to be low and seawater along harbours was also low in contamination (<0.005 ng/L PFHxS), hence the authors concluded that potential local PFAS sources do not yet contribute significantly to the local marine and terrestrial pollution (Skaar et al., 2018).

69. Recent data from Svalbard indicate that levels of PFASs detected in polar bears are most likely not due to local sources, but is rather a result of global emissions. 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 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 have a large proportion of terrestrial food in their diet (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 PFAS concentrations and home range longitude position in polar bears accords with a study that showed that PFAS 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).

70. 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).

71. 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 one of the major transportation pathways 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 (Hansen et al., 2015; 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.

72. Due to detection of PFHxS in Arctic air and snow, long-range transport of PFHxS and/or PFHxS-related compounds through the atmosphere occurs (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). A recent study reporting a significant increase in concentrations of PFHxS ($p<0.006$) during the period 2009–2015 in Arctic air both in Canada and Norway indicating that an increase in long-range transport has occurred (Rauert et al., 2018a). PFHxS was also recently detected in air at remote locations in the Latin American and Caribbean region (Rauert et al., 2018b). 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 PFSA 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. 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). This argument is strengthened by the detection of increasing amounts 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.

73. Recent studies of polar bears from Norwegian Arctic showed that plasma levels of PFSA (Σ_2PFSA; PFHxS and PFOS) were found in the highest concentration compared to other already regulated POPs. Total concentration (ng/g ww) of Σ_2PFSA were 264.35±12.45 (PFHxS 30 ng/g ww; PFOS 233 ng/g ww), ΣPCB were 39.98±3.84 ng/g ww while ΣPBDE were 0.18±0.01 ng/g ww (Bourgeon et al., 2017). Hence in these studies the concentration of PFHxS is similar to the total PCB concentrations. In general, it is between 2–18 times more PFOS than PFHxS detected in animals from the Norwegian Arctic, and 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).

74. 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
PFHxS-precursors.

2.3 Exposure

2.3.1 Environmental levels and trends

75. 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, as well as biota, and humans globally (ECHA 2017a, annex II, Table 13; Tables 1.1–1.12 in UNEP/POPS/POPRC.14/INF/4). Degradation of PFHxS-related substances may add to the total exposure. There are likely to be many precursors, many of which are unknown. Quantification of these substances is challenging as commercial analytical standards are seldom available.

76. The highest environmental levels of PFHxS measured are found in urban and/or industrial areas both in terms of biotic- and abiotic matrices (Gewurst et al., 2013; 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 Taihu 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 compounds (Ma et al., 2018).

77. 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) derivatives (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 (0.3–25 pg/L) has been detected in infiltrated rainwater likely originating from atmospheric transport of precursors (Eschauzier et al., 2010).

78. For a number of studies, exposure in limited areas (such as snowpack, melt water) 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.

79. Furthermore, recent studies report that PFHxS is found at the highest concentration among species- and is the third most abundant PFAS in polar bears (Tartu et al., 2017a; Routti et al., 2017; Norwegian Environment Agency 2017d, M-817/2017; Table 1.3 in UNEP/POPS/POPRC.14/INF/4). Similarly, for polar bears from Hudson Bay, Canada, PFHxS was second only to PFOS in concentration in the liver (Letcher et al., 2018). In plasma from polar bears at Svalbard (Norway), PFHxS levels were in the range 4.9–70 ng/g wet weight (ww) for the time period 2000-2014 (Routti et al., 2017). The concentrations in polar bears from Svalbard are similar to those reported for humans living at the proximity of a fluorochemical manufacturing plant in China (which in turn are an order of magnitude higher than in general populations in China) (Fu et al., 2015). Concentration of PFHxS in polar significantly decreased during the period 2003–2009 (-8.8%, range from 12.5% to -4.8% within 95% confidence interval), whereas the annual change during the period 2009-2014 was +5%, although not significant within 95% of the confidence interval. The annual change varied between -1% per year to +11% per year within 95% confidence interval (Routti et al., 2017). Furthermore, the authors propose that the fast drop in PFAS concentration following the phase out of C_{6-8} perfluoroalkyl sulfonates 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 PFASs (Routti et al., 2017). However, a study of PFHxS levels in Norwegian Arctic air recently revealed that significant increasing amounts (<0.007–2.2 pg/m^3; $p<0.006$) has been detected during the period 2009–2015 (Rauert et al., 2018a) and these results correspond with the observed increase in polar bears levels described in Routti et al. (2017) above. In the Routti study, levels of PFHxS in liver from Arctic foxes collected during 1997–2014 were in the range <0.05–139 ng/g ww. PFHxS

concentrations in Arctic foxes decreased 11% per year from 2002 to 2014, and the annual change with 95% probability was between -17% to -5%. PFHxS trends for both polar bears and Arctic foxes were similar prior and after they were corrected to the climate-related variation in feeding habits and food availability, the first reflecting the actual trends in the animals and the latter one reflecting the trends in their food web.

80. 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 but consistently 2 orders of magnitude lower than PFOS. 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 of 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 which the authors indicate may be due to uneven sex distribution (14 male and 6 females) and the limited number of females' studies (Greaves et al., 2012). 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 1.1–1.4 in UNEP/POPS/POPRC.14/INF/4 for additional data on exposure levels in remote- and other regions.

81. A number of studies have reported time-trends for PFHxS in various species and matrixes. However, there are some discrepancies in these data and trends are increasing (Rauert et al., 2018a; Holmstrom et al., 2010), decreasing (Lam et al., 2016; Huber et al., 2012), and without any significant trend (Routti et al., 2017; Ullah et al., 2014; Roos et al., 2013). In a systematic review of trend studies most data on PFHxS showed no significant change, while an increasing or decreasing trends were observed in a few matrices and regions (Land et al., 2018). However, as mentioned above, the trend of PFHxS in polar bears in the European Arctic (Svalbard, Norway) has an annual change of 5% (although not significant within 95% of the confidence interval) in the time-period 2010–2014, while the trend in the Arctic fox from the same area is decreasing (Routti et al., 2017). The observed trend in polar bears (Routti et al., 2017) corresponds with a recent study reporting increasing trends in Arctic air during the same time-period (Rauert et al., 2018a). Hence, the 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

82. Exposure pathways for PFASs, 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/4). PFHxS, along with PFOS and PFOA, is the most frequently detected PFAS in blood-based samples from the general population world wide (ECHA 2017a, annex II, Table 14; Table 1.10 in UNEP/POPS/POPRC.14/INF/4) and present in the umbilical cord blood and breast milk (Kärrman et al., 2007; Gützkow et al., 2012). PFHxS is transferred to the foetus through the placenta in humans and is excreted via lactation. 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), as well as frequent use of stovetop PTFE cookware and preheated packaged foods, and increased use of carpet for floor covering (Hu et al., 2018) and use of stain repellents (Kingsley et al., 2018).

83. A number of studies have reported presence of PFHxS in food items (EFSA 2012; Gebbink et al., 2015a; Noorlander et al., 2011¸ Food Standards Australia New Zealand, 2016; Table 1.7 in UNEP/POPS/POPRC.14/INF/4). 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., 2015a). 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). Levels of PFHxS in 2948 human food samples on the European marked quantified PFHxS in samples from vegetables (2%), fruits (21%), meat (1%), fish and other seafood (2%) and drinking water (12%) (EFSA, 2012). The PERFOOD Project developed robust and reliable analytical tools including reference materials for the determination of PFAS including PFHxS in food items and calculated upper bound dietary intake for different European countries that range from 35 to 105 pg/kg

bw per day for adults and 69 to 329 pg/kg bw per day (mean estimates) for children (https://ibed.fnwi.uva nl/perfood/). 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 found that higher levels of PFHxS in serum were associated with consumption of fruits and juices (Jain 2018). There is data indicating that food packaging materials constitute a source of human PFHxS exposure (Hu et al., 2018) as well as canned food (Averina et al., 2018).

84. A study from Australia of PFHxS in food and water environmental samples mainly from contaminated sites, found highest mean upper bound 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 (Food Standards Australia New Zealand, 2016).

85. It is estimated that drinking water consumption from sources near or in contaminated areas is one of the most important exposure pathways of PFASs for humans. Human biomonitoring studies concluded that exposure to PFHxS (and other PFASs) 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 PFASs 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). PFHxS was detected in more than 200 samples from >5000 public watersystems screened for PFASs in the USA (Guelfo and Adamson, 2018). Contamination of tapwater with PFHxS at low levels has been observed world 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/4 for details).

86. Exposure may also occur via indoor air, mainly through particulate matter. In a Canadian household with carpets treated with Scotchgard^{TM} 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 the highest levels (Beesoon et al., 2012). Hu et al., also reported that PFHxS in a study from the USA that fully or partially carpet covered floors were associated with 37.2% increase in serum PFHxS concentrations in children (Hu et al., 2018). Furthermore, serum PFHxS concentrations in children enrolled in the Health Outcomes and Measures of the Environment (HOME) Study at the 8-year visit were 33% higher among those who reported having ever used stain repellents compared with those who reported never using stain repellents (Kingsley et al., 2018). A Canadian study (Kubwabo et al., 2005) shows a median of 23.1 ng/g in dust from 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). See also Table 1.9 in UNEP/POPS/POPRC.14/INF/4 for details on PFHxS detection in products.

87. PFHxS has been detected in humans globally with high levels (1790 µg/L in blood serum) detected in people consuming PFHxS contaminated drinking water (Li et al., 2018). Levels in serum range from <1–1790 µg/L, (ECHA 2017a, annex II, Table 14; Table 1.10 in UNEP/POPS/POPRC.14/INF/4). The PFHxS detection rate was above 98% in pregnant women in birth cohorts from Shanghai, Northern Norway, Greenland and two from Denmark (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). 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).

88. Furthermore, PFHxS was detected in umbilical cord blood (ECHA 2017a, annex II, Table 14; Table 1.11 in UNEP/POPS/POPRC.14/INF/4) 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).

89. Infants 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). After the first six months infants' serum concentrations increased 4- to 3.5-fold for PFOS and PFHxS, respectively, in relation to cord blood (Fromme et al., 2010, Winkens et al., 2017). PFHxS was detected in more than 70% of breast milk 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/4). 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). Commonly a reduction of 3% in the mother's serum for PFOS and PFOA and 1% for PFHxS per month of breastfeeding has been observed (Kim et al., 2011). In a Swedish monitoring study, PFHxS was analysed in breast milk samples from Stockholm and Gothenburg. In Stockholm, the concentrations of PFHxS, (low pg/mL range), have increased over the whole time-period (1972–2015), although if only considering the last 10 years 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 children age 3–11 from NHANES 2013–2014, at concentrations similar to those of NHANES 2013–2014 adolescents and adults. This suggest prevalent exposure to PFHxS or its precursors among U.S. population and 3-11 years old children, most of whom were born after the phase out of PFOS in the United States in 2002 (Ye et al., 2018).

90. 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), with the concentrations in 2010 being approximately 6.5 ng/mL, reaching the same level as PFOS (Glynn et al., 2012 and supporting info). A doubling time of 11.7 years was found for the same sample group with samples from 1997-2012 for PFHxS (Gebbink et al., 2015b). A significant reducing trend for linear vs linear + branched PFOS was observed for the time period, but only a non-significant reduction was observed for PFHxS (Gebbink et al., 2015b). 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.

91. In the area of Arnsberg, Germany, there was a large environmental contamination incident of PFASs in 2006. Wilhelm and co-workers, 2009, evaluated the levels of some PFASs, 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).

92. In a recent human biomonitoring study in the city of Ronneby in Sweden people have been exposed to high levels of PFASs 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) (Li et al., 2018).

93. 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). A decline of 61% was seen for PFHxS age- and sex-adjusted geometric mean concentrations from 2000–2001 to 2015 in American Red Cross adult blood donors (Olsen et al., 2017). 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 PFASs 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). In a study of blood spots from newborn in New York, USA from 1997 to 2007, PFHxS levels (and PFOS and PFOSA) increased and peaked around year 2000 and then declined. Levels of PFOS and PFOSA declined well below 1997 levels, but PFHxS levels were only slightly lower than 1997 levels (Spliethoff et al., 2008). In pooled human sera from the Australian population, PFHxS levels ranged from 1.2 to 5.7 ng/mL (08/09) and from 1.4 to 5.4 ng/mL (10/11) but overall the median levels of PFHxS have not

significantly changed from 2002 (Toms et al., 2014). In a systematic review excluding data from occupational exposure and or populations exposed to point sources such as contaminated drinking water, the concentrations of PFOS, PFDS, and PFOA in humans are generally declining, and increasing concentrations of PFHxS have started to level off in recent years (Land et al., 2018). However, in a study reconstructing past human exposure by using serum biomonitoring data from USA and Australia using a population based pharmacokinetic model, significant declines were observed for PFOS and PFOA but no trend was observed for PFHxS (Gomis et al., 2017). Furthermore, the concentrations of PFHxS in serum followed a different age pattern than PFOS indicating that global exposure to PFHxS is still ongoing and has not significantly declined since the early 2000s.

94. 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). 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 average concentration was 0.80 ng/L in that study. Serum concentrations of PFHxS were in the range 12.8–10546 ng/mL, and indoor dust levels rang from nd-257201 ng/g (mean = 15726) (Gao et al., 2015). In another study from a fluorochemical manufacturing plant in the same district, serum concentrations of PFHxS in family members of occupational workers were in the range 4.33-3164 ng/mL, dust in residences connected to the plant had PFHxS in the range 0.44 to 708 ng/g, both significantly higher than in ordinary residents in the plant area, 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 in occupational workers 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).

2.4 Hazard assessment for endpoints of concern

2.4.1 Toxicity to aquatic organisms and birds

95. Ecotoxicity data for PFHxS are limited, and fish toxicity studies are lacking for PFHxS. The findings available for other perfluorinated acids indicate that toxicity increases with increasing carbon length, and sulfonates are more potent than carboxylates (Giesy et al., 2010, Hagenaars, et al., 2011; Ulhaq, et al., 2013). The findings available for perfluorinated acids other than PFHxS indicate that the primary toxicity concern for these substances is chronic, intergenerational toxicity. Read-across from the C_4 and C_8-homologes (PFBS and PFOS) could indicate potential effects from exposure to PFHxS. Fish toxicity data available for the C_8 homologue, PFOS, indicate potential for increased mortality in offspring when the parent generation is exposed to concentrations as low as 0.01 mg/L (Ji et al., 2008). Although PFBS has been shown to cause low acute toxicity to fish (reviewed in Giesy et al., 2010), PFBS was recently shown to induce multi-generational disturbance of the thyroid system in marine medaka in a life-cycle exposure at environmentally relevant levels (Chen et al., 2018c). Exposure to PFBS (0, 1.0, 2.9 and 9.5 μg/L) was from F0 egg until sexual maturity, while F1 and F2 was not exposed. Bodyweight was significantly reduced for both female and male F0 fish exposed to 2.9 μg/L and 9.5 μg/L for 6 months, and in female F0 plasma T3 level was significantly reduced (41%) in the 9.5 μg/L group. In the F1 larvae a significant increase in T3 was observed in 1 μg/L group. Delayed hatching was coupled to elevated T3 levels in F1 larvae. Also, the F2 larvae TH disruption was exhibited with increased T4 levels (significantly increased in the 9.5 μg/L group) observation was strengthened by alteration in gene expression of TH-related genes (deiodinase 1 and thyroid binding globulin) was increased (Chen et al., 2018c).

96. In a chronic life-cycle test using a nominal concentration of PFOS in the range of 1 to 100 μg/L, the chironomid *Chironomus tentans* EC 50 values were ~95 μg/L for the endpoints survival, growth and emergence, 2-3 orders of magnitude lower than those reported for other aquatic organisms (MacDonald et al., 2004). This might reflect effects on haemoglobin as the larvae gradually became pale losing the colour associated with haemoglobin. Microorganisms and algae in an aquatic ecosystem could be affected by membrane effect from PFASs in their environment. Fitzgerald et al (2018) observed increased membrane permeability and quorum sensing response (which is important for initiating bacterial responses such as biofilm, toxin or antibiotic production) in a model bacterium exposed to PFBS, PFHxS or PFOS. A pattern for increasing potency with increasing chain length was observed, significant changes were observed at 50 mg/L for PFHxS but PFOS showed significant effects at 0.3 mg/L.

97. Sub lethal effects of PFHxS on amphibian at current environmental levels have been observed in one study (Hoover et al., 2017). Northern leopard frog (Rana pipiens) tadpoles (n=36 x 2 replicates) were exposed to 0, 10, 100 or 1000 µg/L PFHxS, PFOS, PFOA or 6:2 fluorotelomer sulfonate (6:2 FTS) for 40 days. Survival for all treatments was above 90%. Although PFOS showed a higher BCF (2 orders of magnitude higher) than other test compounds in this study, PFHxS was more potent for the endpoints (gosner stage (development) and snout-vent length) at day 40. Statistical significance was observed for all doses of PFHxS tested and the two highest doses of PFOS. However, all tested PFASs showed the same tendency in delaying frog development.

98. A study on the African clawed frog (*Xenopus laevis*) tadpoles, indicates possible endocrine-disrupting potential when testing PFBS and PFOS at 0, 0.1, 1, 100 and 1000 µg/L from stage 46/47 to 2 months post metamorphosis. The PFOS used in this study was 98% pure, and detectable levels of PFHxS in the range of 3.4–4.8 and 18.1–42.6 µg/L were observed in the water with PFOS 100 and 1000 µg/L, respectively. However, it should be anticipated that effects observed are caused by the PFOS. Survival exceeded 85% for all treatments and no reduction in body weight was observed after 4 months of exposure. 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 impairments (hepatocyte degeneration, hepatocyte hypertrophy and increase in blood sinusoids) were observed at high concentrations (100–1000 µg/L) for both PFOS and PFBS, however, no change in hepatosomatic index was observed. 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). Read-across from the C_4 and C_8-homologes (PFBS and PFOS) could indicate potential effects from exposure to PFHxS.

99. 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). Based on egg injection, the lowest observed effect concentration (LOEC) was 890 ng PFHxS/g ww for developing leghorn chicken embryos (plasma free T4) (Cassone et al., 2012b). Plasma free 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). Effect on gene expression was observed in avian primary neuronal culture in the concentration range 0.1-10 µM (Vongphachan et al., 2011). Furthermore, negative correlations between plasma PFHxS and ratio total T3/ free T3 thyroid hormones have been observed in Arctic seabird (Rissa tridactyla) (Nøst et al., 2012).

2.4.2 Toxicity in rodents relevant for humans

100. Experimental studies in rodents exposed to PFHxS consistently show adverse effects to the liver (Butenhoff et al., 2009; Bijland et al., 2011; Chang et al., 2018; 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 include a dose-dependent increase in hepatocellular hypertrophy associated with a significant enlargement of the liver (56% increase in absolute liver weight) in male rats following 42 days of exposure at 10 mg/kg bw/d, and significant increase in relative liver weight at doses of 3 and 10 mg/kg/d (Butenhoff et al., 2009). In another study, 110% increase in absolute liver weight was observed following 28 days of PFHxS exposure at 6 mg/kg/d in genetically modified male mice (APO3*-Leiden.CETP (E3L.CETP), which has an increased clearance of apoB-containing lipoproteins (Bijland et al., 2011). The exposure caused hepatomegaly with steatosis as well as reduced serum total cholesterol and triglycerides. 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). In a reproductive/developmental toxicity study in mice, significantly increased liver weights were observed in F0 males and females from 1 mg/kg bw/day dosed for 42 days (Chang et al., 2018). At the highest dose, 3 mg/kg bw/day, the 70% increased liver weight was associated with moderate to marked hepatocellular hypertrophy, steatosis, single-cell necrosis and increased alkaline phosphatase (ALP) as well as significantly reduced serum cholesterol. 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. Significantly increased absolute and relative liver weight in male rats and hepatocellular hypertrophy in this study was seen from 3 mg/kg bw/d.

101. 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 20 and 10 µM) in transiently transfected

African green monkey kidney cells (COS-1 cells). 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 occur also 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 a pre-adipocyte culture PFHxS was more potent than PFOS in inducing triglyceride accumulation, and both PFSAs produced strong changes in gene expression with similarities to those observed with PPAR-gamma agonist (Watkins et al., 2015). 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).

102. 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 were significantly reduced at 3 mg/kg bw/d, haemoglobin concentration significantly reduced from the 1 mg/kg/d group and prothrombin time was altered at all doses tested except for 1 mg/kg bw/d. However, no alteration of haematology parameters was observed in male mice exposed to PFHxS for 3 mg/kg bw for 42 days (Chang et al., 2018).

103. Thyroid organ toxicity has been observed following exposure to PFHxS. In F0 male rats exposed to PFHxS at 0, 0.1, 1.0, 3.0 or 10 mg/kg for 42 days, a dose-dependent increase in thyroid hypertrophy/hyperplasia of the follicular epithelium was observed, no effect was observed in F0 females, however, serum concentrations in female rats were approximately 8 times lower than in males (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 LOAEL of 3 mg/kg bw/d could be determined for hyperplasia of thyroid follicular epithelial cells (not reported in the paper). 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 at low concentrations (10^{-8} to 10^{-5} Molar (M)) but increased cell proliferation at higher concentrations (10^{-4} M) (Long et al., 2013).

104. In a reproductive/developmental toxicity screening study in CD-1 mice exposed to PFHxS at 0, 0.3, 1.0 or 3.0 mg/kg bw/day, significantly decreased mean live litter size were observed from 1.0 mg/kg bw/day and reduced fertility index was observed at 3.0 mg/kg bw/day, although not significantly different from control (Chang et al., 2018). However, a clear dose-response relationship was lacking for these responses and the highest dose is considered low. For comparison, PFOS has been shown to reduce litter size by perinatal mortality at 2 mg/kg for rats and 10 mg/kg for mice (Lau et al., 2003). Adverse effect on reproductive or developmental parameters in dams or offspring in rats was not shown (Butenhoff et al., 2009, Ramhøj et al., 2018). However, a marked reduction in T4 was observed both in dams and offspring, with a significant reduction from 5 mg/kg/day, when dams were orally exposed from gestation day 7 (Ramhøj et al., 2018).

105. Adult dose-dependent behaviour and cognitive disturbance was observed in mice after a single neonatal dose of PFHxS in the vulnerable brain developmental period (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 behaviour 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 indicative of normal brain development and cognitive function were affected 24 h after exposure, and taurine levels in the cerebral cortex 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) or mice dosed from 0-3 mg/kg bw/d (Chang et al., 2018). 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.

106. 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 potency 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).

107. Endocrine modalities have been investigated 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 (Kjeldsen and Bonefeld-Jørgensen 2013). PFHxS antagonize androgen induced androgen receptor (AR) transactivation in vitro (IC_{50}=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) IC_{50}=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).

108. The immunotoxic effect of PFHxS has not been investigated in vitro or in vivo 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.

2.4.3 Human epidemiology

109. Most epidemiology studies investigating the association between PFHxS levels and health effects are cross-sectional (measuring effect and exposure at the same time) with the limitations typical for those studies. Although the long half-life of PFHxS (8.5 years, with a range from 2.2 to 27 years) increases the likelihood that current serum measurements represent past exposure that would be biologically relevant for the observed effect, there is likely to be some exposure misclassification. Prospective studies that evaluate effects in children relative to early childhood exposures could increase confidence in this body of evidence. The study design and covariates do also differ between the studies, and in some studies levels of PFHxS are highly correlated with other serum PFASs and thus weakening the results observed for PFHxS. An overview of outcome and study design from identified studies on serum lipids and thyroid effects are shown in Tables 4.1 and 4.2, respectively, in UNEP/POPS/POPRC.14/INF/4. Please also notice the difference in elimination time between species and gender summarized in Table 3, UNEP/POPS/POPRC.14/INF/4.

110. 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 an evaluation of the epidemiological studies on PFASs, increases in serum enzymes and increases in serum bilirubin were observed in the studies of PFOA PFOS and PFHxS, suggestive of liver damage (ATSDR 2018). In a cross-sectional analysis of adults in Canada a significant association between PFHxS and cholesterol outcomes (total cholesterol (TC), low density lipoprotein cholesterol (LDL), TC/high density lipoprotein (HDL) ratio and non-HDL cholesterol) were observed after weighting for sampling strategy (Fisher et al., 2013). No evidence to support the association between PFOA and PFOS with the cholesterol outcomes was observed. A positive monotonic increase in cholesterol with increasing decile of PFHxS, as well as for PFOA and PFOS, were observed in a study from the C_8 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 (NHANES 2002-3), while positive associations were observed for PFOA, PFOS and PFNA. In pregnant women in Norway a positive association with HDL-cholesterol was observed for 5 PFASs including PFHxS (Starling et al., 2014). A study of pregnant women from the Spain found that PFOS and PFHxS were positively associated with impaired glucose tolerance and gestational diabetes mellitus (Matilla-Santander et al., 2017).

111. Effects on the thyroid hormone pathway have been shown for PFHxS in epidemiological studies. Levels of total T4 levels were found to increase with increasing PFHxS levels in the general U.S population, positive but non-significant associations were also seen with total T4, PFOS and PFOA (Jain, 2013). In another study of the same population higher serum levels of PFHxS were associated with increase in total T3 and total T4 in women (Wen et al., 2013). In men, a negative

association was observed for serum PFHxS and free T4 of the U.S. general population (Wen et al., 2013). The authors also found that the risk of subclinical hyperthyroidism among women increased with increased serum PFHxS (Wen et al., 2013). No causal link between serum PFHxS, PFOA or PFOS levels and the risk of hypothyroxinemia was observed in pregnant women in a case control study from Canada (Chan et al., 2011). In a retrospective birth cohort study in the Republic of Korea the association of certain PFASs and thyroid hormones in cord blood was explored. Gender-specific analysis showed that prenatal PFHxS exposure was positively associated with T3 in girls and PFOS was not associated with any thyroid-related parameter (Shah-Kulkarni et al., 2016). T4 level in male neonates were negatively correlated with increasing prenatal exposure to PFHxS in a birth cohort study from USA (Preston et al., 2018). Webster (et al., 2016) used data from the general U.S population and found that two indicator stressors, thyroid-peroxidase antibody (TPOAb) and iodine status, did not modify the association between certain PFASs and TH alone. However, PFHxS and PFOS were negatively associated with free T4. In the small 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, but no significant association with T3 and T4 (Ballesteros et al., 2017).

112. Human epidemiological studies have looked at the correlation between serum PFASs including PFHxS and neurotoxic or neuro developmental effects in children. From the C_8-health project Stein and Stavitz (2011) examined the cross-sectional association in children (age 5–18 years; n=10,456) between serum PFOS, PFOA PFNA and PFHxS 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 odds ratio (OR)s 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). No strong association with ADHD was observed with PFOS, PFOA and PFNA (Stein and Stavitz 2011). Significant increased odds for ADHD was also found in another study from U.S. using data from NHANES 1999–2000 and 2003–2004, with 1 ug/mL increase in PFHxS serum level, n=571 (Hoffman et al., 2010). However, in this study both PFOA, PFOS and PFNA were also positively associated with parental reported ADHD. In a study, investigating blood levels of various perfluoro- compounds in children and associations with behavioural inhibition, the results showed that blood levels of PFHxS were significantly associated with behavioural inhibition deficits in children (n=83) (Gump et al., 2011). High compared to low prenatal exposure to PFHxS was also associated with problematic behaviour assessed using the Strength and Difficulties Questionnaire in a prospective study of children age 5–9 years from both Greenland and Ukraine (n=1023) (Høyer et al., 2018). In Voung et al (2016) increased tendency but no significant association was observed between prenatal PFHxS levels (as well as PFOS) and behavioural regulation in children at 5 and 8 years in a cohort from the USA (n=256).

113. Epidemiological studies indicate immunotoxic or modulative effects caused by certain PFASs 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 in Japan. Prenatal exposure to PFOS and PFHxS were found to be associated with occurrence of infectious diseases (such as ottis media, pneumonia, RS virus and varicella) in early life. For PFHxS the association was observed only among girls (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 (also observed for PFOA, PFOS and PFNA) (n=50). A positive association was observed between serum levels of PFHxS and number of episodes of gastroenteritis at age 3 (also observed for PFOA) (n=66) (Granum et al., 2013). Grandjean et al., 2012, observed odds ratios in a well conducted cohort study of 1.78 (95% CI: 1.08; 2.93) for inadequate antibody concentrations at age 7 for tetanus vaccine with doubling of the PFHxS serum concentration at age 5. 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. A similar reduction was seen for PFOA (Grandjean et al., 2017a). Structural equation models showed that a doubling in PFAS exposure at 7 y was associated with losses in diphtheria antibody concentrations at 13 y of 10–30% for the five PFASs. The present study extends the previous findings of deficient antibody responses in this cohort at younger ages and therefore adds support to the notion that substantially strengthened prevention of PFAS exposure is indicated (Grandjean et al., 2017b). 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 (n=132), a significant association between increasing PFHxS serum level and decreases in pulmonary function was observed (Qin et al., 2017). PFAS (PFHxS, PFOS and PFCA C_{8-10}) exposure at age 5 was associated with increased risk of

asthma among a small subgroup of measles, mumps and rubella (MMR)-unvaccinated children. The association was reversed in the MMR vaccinated group, but a doubling of serum PFHxS at age 5 was associated with elevated odds of non-atopic asthma and atopic eczema at age 13, but this could be chance findings (Timmermann et al., 2017). However, no associations were observed between serum PFHxS and asthma or wheezing in a cross-sectional study of children age 12-19 in the United States (n=1877) (Humblet et al., 2014). A Canadian study (n=1242) 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., 2018b).

114. Some studies indicate that PFHxS and certain PFASs 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 PFAS levels (PFDA and PFNA) and miscarriage and an almost significant association with PFHxS was observed with adjusted odds ratio 1.53 (95% CI:0.99, 2.38) while no association was observed for PFOA and PFOS (n=56 cases (miscarriage) and 336 controls (birth)) (Jensen et al., 2016). In a birth 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).

115. In the U.S. population in NHANES 2009–2010 (n=1566) prevalence of osteoporosis was significantly higher in the high versus lowest quartiles of serum PFHxS with OR 13.2 (95% CI: 2.72–64.15), significant ORs were also observed for PFOA and PFNA (Khalil et al., 2016). In a case-control study (n=77 cases and 81 controls) 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

116. The following section summarizes a number of published studies, both experimental laboratory- and field studies, where combined effects of chemicals (including PFHxS) has been revealed. The compounds have been studied in combination and the effect observed can not necessarily be attributed to a specific substance rather to the mixtures of substances tested. As shown throughout many of the references cited in this Risk Profile, PFHxS is almost always detected together with a range of other PFAS (e.g. PFOS and PFOA) in the blood samples from children and others. Therefore, the multiple pathways of exposure as well as the multiple pathways of adverse effects must be taken into account, especially for developing children (Winkens et al., 2017). 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, and PFDA, when tested for anti-androgen activity in vitro at concentration corresponding to 1 μM of each single component in the mixture (Kjeldsen and Bonefeld-Jørgensen, 2013). 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 PFASs (PFHxS included) at equimolar doses (final concentrations of each PFAS: 1.56–50 μM) acted in an additive manner when tested for transactivation of PPAR-alpha from baikal seal (Ishibashi et al., 2011). Viability studies of individual and mixtures of PFASs (C_4–C_{11}) 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/PFHxS, showed that synergistic effects occurred under effective concentrations of IC_0, IC_{10}, and IC_{50} in mixtures while under IC_{-20} the synergistic effect only occurred under a higher proportion of PFSA (Hu et al., 2014).

117. In a recent developmental toxicity study in rats, a more marked effect on serum T4 levels, antiandrogenic endpoints and liver weight were observed in the group co-exposed to PFHxS and an endocrine disruption mix (EDmix) than observed for PFHxS or EDmix alone indicating that PFHxS and the EDmix potentiate the effect of each other on various endpoints, despite their different modes of action (Ramhøj et al., 2018).

118. 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 PFSAs (C_4-C_{10}) was 28.8 ng/g ww, where PFOS accounted for 91% (PFHxS average 1.1 ng/g ww ~3.81%). 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 both sum PFCAs and sum PFSAs 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 bioaccumulative 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).

119. A recent study on polar bear from Svalbard found a negative relationship between Σ_8PFASs (including PFHxS) plasma levels and some thyroid hormones, and indicate that PFASs contribute to possible alteration of the thyroid hormone homeostasis in polar bears by altering the levels of free T3 (Bourgeon et al., 2017). For all studied substances (PCB, chlorinated pesticides and ΣPFAS), T3 levels were negatively related to the pollutants indicating that T3 could be more sensitive than other THs. In a study of polar bear mothers and cubs from Svalbard, there was no significant change in PFHxS levels 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).

120. There is evidence from experimental studies 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 were the main factors determining the amount of PFASs in female polar bears from Svalbard and that factors such as fasting affect the levels of PFHxS accumulated by female 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 (Σ_6PFCA with carbon chain 8 to 13 and Σ_2PFSA with 6 and 8 carbons) contribute to the multiple-stressor effects observed in polar bears from Svalbard. A recent study by Tartu et al., 2017b, showed that PFAS exposure was related to biomarkers of energy metabolism (lipid-related genes, and plasma cholesterol, HDL and triglycerides). The relationship between PFASs and cholesterol as well as HDL was more pronounced when combined with reduced sea ice extent and thickness suggesting that climate driven sea ice decline and PFASs (and other organohalogenated compounds) have a synergistic negative effect on polar bears (Tartu et al., 2017b).

121. 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 including PFHxS 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 PFASs and a possible alteration of the toxic potential. Cocktail effects due to increased concentration of traditional POPs in fat storage as well as climate changes will also affect these periods. PFHxS has high affinity to proteins and are not subject to biotransformation (Jones et al., 2003). In Arctic fox, adipose tissue was the only tissue affected by body condition, with lean foxes having three times (95% CI: 1.1, 12) higher concentrations of PFHxS than fat foxes (Aas et al., 2014). The large seasonal variability in fat content in Arctic mammals may thus affect tissue concentrations of certain PFASs including PFHxS 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).

122. Cumulative limits for PFASs in drinking water and ground water have been set in Sweden and Denmark, when PFASs are believed to act together in a mixture. In Sweden, a concentration limit of 90 ng/L is set for $PFAS_{11}$ (PFBS, PFHxS, PFOS, 6:2 FTS, PFBA, PFPeA, PFHxA, PFHpA, PFOA, PFNA, PFDA) 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 similar approach is enforced in Denmark (http://mst.dk/media/91517/pfas-administrative-graensevaerdier-27-april-2015-final.pdf). The United States (https://www.epa.gov/sites/production/files/2016-06/documents/drinkingwaterhealthadvisories_pfoa_pfos_updated_5.31.16.pdf) and Germany (https://www.umweltbundesamt.de/sites/default/files/medien/pdfs/pft-in-drinking-water.pdf) have made recommendations for content of PFOS and PFOA in drinking water. 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. Values of 0.1 µg/L for each 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

123. PFHxS, its salts and PFHxS-related compounds belong to the PFAS group and have been used as surfactants, water- and stain protective coatings for carpets, paper, leather and textiles and in fire-fighting foams among other applications, often as a replacement for PFOS. It is also known that PFHxS has been unintentionally produced during the electrochemical fluorination processes used in production of other PFASs 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.

124. Information about current global manufacture of PFHxS, its salts and PFHxS-related compounds are limited. Historical production was mainly carried out by 3M. One European manufacturer with production of less than 1 tonne per year and a few producers located in China have been identified in respect of on-going production, however, quantitative production data are not publically available. PFHxS, its salts and many PFHxS-related compounds have been listed on national chemical inventories (US, Canada, Japan, Australia, EU, 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 through air, dust, water, waste, wastewater and sludge.

125. 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 received waste from a number of sources. FHxSAs has also been detected in historical AFFF manufactured by 3M.

126. PFHxS has been detected in numerous environmental matrixes worldwide including in the Arctic and Antarctica. Due to historical use of AFFF containing PFHxS and PFHxS-related compounds, 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 PFASs in general, the known extreme stability of the C-F bond and the monitoring data showing the ubiquitous presence of PFHxS in the environment, it is concluded that PFHxS is persistent to abiotic and biotic degradation. Based on physical properties, PFHxS is known to undergo protein-binding associated bioaccumulation rather than lipid partitioning, which makes standard BCF/BAF analysis less meaningful. Thus, as with PFOA and PFOS, the use of log Kow and BCF have been demonstrated to be inappropriate measures of bioaccumulation. Several studies have reported bioaccumulation and biomagnification of PFHxS with field based 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 reported half-lives of PFHxS in human serum, which is in general known to be a good indicator of bioaccumulation, is very high 8.5 (range 2.2-27 years).

127. PFHxS is found ubiquitously spread throughout the environment and in biota globally. A number of studies have reported exposure in remote areas that can be attributed to long-range environmental transport. PFHxS is detected in water, snow, air and biota (including humans) at remote locations. Increasing trends, most likely due to increased emissions, have recently been detected in polar bears at Svalbard (Norway) and in air in the Canadian- and Norwegian Arctics. In polar bears, PFHxS was the third most abundant PFAS measured in the plasma of these animals. The main mechanism of transport to remote regions like the Arctic is presently most likely through ocean currents, supported by detection in a number of studies of PFHxS in waters worldwide. However, transport of PFHxS and PFHxS-related compound 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 both PFHxS and PFHxS-related compounds are transported through air to remote regions and that PFHxS-related compounds degraded to PFHxS locally.

128. Environmental trend data of PFHxS levels are not conclusive, in most regions and matrices no obvious trend has been observed, while a few matrices show a declining or increasing trend. Limited data are available on levels of PFHxS in humans in Asia where production continued after the 3M phase out.

129. 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. Exposure to PFHxS through dust from carpeting is a prominent source of exposure to toddlers. Following PFOS and PFOA, PFHxS is the most frequently detected PFAS in blood-based samples from the general population worldwide. 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.

130. In rodents, liver effects such as increased liver weight, marked hepatocellular hypertrophy, steatosis, necrosis, increased serum alkaline phosphatase have been observed from PFHxS exposure. Effect on liver lipid and lipoprotein metabolism and altered serum cholesterol, triglycerides and lipoproteins has been observed in both rodents and humans. PFHxS activates peroxisome proliferating receptor (PPAR)-alpha, however, effects on liver are also observed in mice without PPAR-alpha, showing mechanisms of action independent of PPAR-alpha. In addition, effect on reproduction (significantly decreased live litter size) has been observed in mice following PFHxS exposure.

131. 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 PFASs (and PFHxS) exposure prenatally and in childhood. Effects on the thyroid hormone system have been reported cross-species (bird, rat, polar bear and human). Furthermore, several epidemiology studies indicate that the naïve and developing immunesystem might be vulnerable to certain PFASs and PFHxS exposure, observed associations between serum PFHxS levels and reduced effect of vaccines and higher incidences of infections and asthma in children.

132. Certain PFASs, including PFHxS, contribute to the multiple-stressor effects observed in Arctic animals. Studies indicate that the level of certain PFASs 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 levels increased in fat tissue. Combined exposure of PFASs with other POPs have unknown consequences and may cause increased toxicity for heavily stressed species.

Table 5. POP characteristics of PFHxS

Criterion	Meets the criterion (Yes/No)	Remarks
Persistence	Yes	• No 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 is 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 PFBS, PFOS and PFOA demonstrate that these substances are very persistent (Quinete et al., 2010, ECHA 2017a; ECHA 2013), and based on the stability of PFASs 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). • 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). • Highest levels of PFHxS in biota are detected in polar bears (Smithwick et al., 2005 a, b; Routti et al., 2017) • Half-life of PFHxS in humans are the highest reported for any PFAS. An average of 8.5 years (range 2.2-27 years) have been reported (Olsen et al., 2007)

Criterion	Meets the criterion (Yes/No)	Remarks
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, Rauert et al., 2018a) • 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). • Transport pathways are most likely both through water and air (reviewed in Butt et al., 2010; Rauert et al., 2018 a,b). • Transport of 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 far away from local sources (Routti et al., 2017; Tartu et al., 2017b; 2018).
Adverse effects	Yes	PFHxS exerts effects on liver, serum lipids and cholesterol, and affects serum thyroid hormones and may impair neuro development. Key data include: • Effects on liver; increased liver weight, marked hepatocellular hypertrophy, steatosis, necrosis and altered serum cholesterol, triglycerides, lipoproteins and alkaline phosphatase in rodents (Butenhoff et al., 2009; Bijland et al., 2011; Das et al., 2017, Chang et al., 2018). 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). Significantly increased absolute and relative liver weight in male rats and hepatocellular hypertrophy in this study was seen from 3 mg/kg bw/d. • Effects on reproduction (decreased live litter size) was observed in mice from 1.0 mg/kg bw/day (Chang et al., 2018). • 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). Some epidemiology studies show association between PFHxS serum levels and thyroid hormones (Jain 2013; Wen et al., 2013; Webster et al., 2016). • 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., 2018). • Effect on the immune system has been shown in epidemiology studies, both reduced effects to vaccination (Granum et al., 2013; Grandjean et al., 2012; 2017a,b), increased incidence of asthma (Dong et al., 2013; Zhu et al., 2016; Qin et al., 2017; Timmermann 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).

4. Concluding statement

133. PFHxS is released into the environment, including from degradation of PFHxS related substances, and 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.

134. 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 of 8.5 years (range 2.2-27 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.

135. 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.

136. The concern for adverse effects relates to observed effects on the liver, thyroid hormone system, reproduction, and immune modulating effects, as well as indications of neurotoxic and neurodevelopmental effects have been shown. Furthermore, effects on lipid and lipoprotein metabolism add to the concern both for humans and Arctic animals.

137. Recent data from polar bear studies at Svalbard (Norway) revealed increasing levels of PFHxS in plasma. PFASs, including PFHxS, contribute to the multiple-stressor effects observed in polar bears from Svalbard indicating a risk for adverse effects in wildlife.

138. 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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