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Persistent Organic Pollutants Review Committee
Thirteenth meeting
Rome, 17–20 October 2017
Item 5 (b) of the provisional agenda**

Technical work: consideration of a proposal for the inclusion of perfluorhexane sulfonic acid (CAS No: 355-46-4, PFHxS), its salts and PFHxS-related compounds in Annexes A, B and/or C to the Convention

Proposal to list perfluorohexane sulfonic acid (CAS No: 355-46-4, PFHxS), its salts and PFHxS-related compounds in Annexes A, B and/or C to the Stockholm Convention on Persistent Organic Pollutants

Note by the Secretariat

I. Introduction

1. Norway has submitted a proposal to list perfluorohexane sulfonic acid (CAS No: 355-46-4, PFHxS), its salts and PFHxS-related compounds in Annexes A, B and/or C to the Convention pursuant to paragraph 1 of Article 8 of the Convention (see annex). The proposal is being circulated as submitted and has not been formally edited. The Secretariat's verification of whether the proposal contains the information specified in Annex D is set out in document UNEP/POPS/POPRC.13/INF/8.

II. Possible action by the Committee

2. The Committee may wish:

(a) To consider the information provided in the present note;

(b) To decide whether it is satisfied that the proposal fulfils the requirements of Article 8 of and Annex D to the Convention;

(c) To develop and agree on, if it decides that the proposal fulfils the requirements referred to in subparagraph 2 (b) above, a workplan for preparing a draft risk profile pursuant to paragraph 6 of Article 8.

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** UNEP/POPS/POPRC.13/1.

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Annex

Proposal to list perfluorohexane sulfonic acid (CAS No: 355-46-4, PFHxS), its salts and PFHxS-related compounds in Annexes A, B and/or C to the Stockholm Convention on Persistent Organic Pollutants

1. Introduction

1. Perfluorohexane sulfonic acid (PFHxS, PFHS), its salts and related substances is a member of the perfluoroalkyl substance (PFAS) group and has been widely used as surfactants, to make fluoropolymers and as water- and stain protective coatings for carpets, paper and textiles. High levels are found in the environment and exposure occurs through several routes, including drinking water supplied from groundwater. PFHxS is present in some fire-fighting foams, paper, water proofing agents and textiles treatments and other products (Hertzke et al., 2012). PFHxS and its salts and precursors have also been used as raw materials to produce PFAS based products such as surfactant and surface protection products but are also unintentionally produced during industry processes. PFHxS is a member of the same chemical category as perfluorooctane sulfonic acid (PFOS) a PFAS that is already listed in the Stockholm Convention.

2. This nomination report specifically addresses the information requirements and screening criteria of Annex D in the Stockholm Convention on Persistent Organic Pollutants and summarizes relevant evidence relating to the screening criteria for persistence, bioaccumulation, adverse effects and long-range transport. The proposal is based on a risk management option assessment for PFHxS prepared by Sweden (ECHA, 2017), reports and other grey literature as well as information from peer-reviewed scientific journals.

2. Chemical identity

3. A number of chemicals are included in the group of PFHxS, its salts and related substances and some examples are given in Figure 1. Organisation for Economic Co-operation and Development (OECD) has identified 48 PFHxS-related/precursor/polymer substances which all contain the fluorinated alkyl moiety [C6F13SO2] (OECD, 2007, Annex 2). Perfluorohexane sulfonic acid (PFHxS) is a strong acid with a fully fluorinated six carbons long chain, making it both oil- and water repellent (Kissa, 2001). Data on the experimental physicochemical properties of PFHxS are scarce (Kim et al., 2015), however, some studies (Wang et al., 2011; Ding and Peijnenburg, 2013; Kim et al., 2015; Sepulvado et al., 2011) have reported both calculated and estimated physicochemical properties of PFHxS and its related compounds although there are discrepancies in the data. Selected physicochemical properties are shown in Table 2.

4. The raw material for production of PFHxS, its salts and related substances is perfluorohexane sulfonyl fluoride (PFHxSF, PFHSF) which also can be found as an impurity of PFAS-based formulations (Li et al. 2008). 3M produced PFHxSF as a building block compound incorporated in fire-fighting foam and specific post-market carpet treatment application. PFHxS is the sulfonate form of PFHxSF, and also a residual by-product of perfluorooctanesulfonyl fluoride (PFOSF)-related production (i.e. production of PFOS) (3M, 2002).

5. Table 1 lists the chemical identity of PFHxS and Table 2 lists the modelled and experimental physicochemical properties for PFHxS. As seen in Table 2 there are discrepancy in the physicochemical properties of PFHxS that might be due to the properties of this substance which makes it difficult to experimentally study its chemistry.

Table 1

The chemical identity of PFHxS

CAS number:	*355-46-4*
IUPAC name:	1,1,2,2,3,3,4,4,5,5,6,6,6-Tridecafluorohexane-1-sulfonic acid
EC number:	206-587-1
EC name:	Perfluorohexane-1-sulphonic acid
Molecular formula:	$C_6F_{13}SO_3H$
Molecular weight:	400.11
Synonyms:	PFHxS PFHS Tridecafluorohexane-1-sulfonic acid, Octafluoropentanosulfonylfluoride,Tridecafluorohexane-1-sulfonic acid, 1,1,2,2,3,3,4,4,5,5,6,6,6-Tridecafluorohexane-1-sulfonic acid, 1,1,2,2,3,3,4,4,5,5,6,6,6-Tridecafluoro-1-hexanesulfonic 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)

Table 2

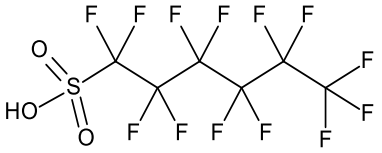
Overview of selected physicochemical properties

Property	*Value*	*Reference*
Physical state at 20°C and 101.3 kPa	Solid white powder	ECHA, 2017
Melting/freezing point	272-274 °C	ECHA, 2017
Vapour pressure	58.9 Pa	Wang et al., 2011 (calculated)
Water solubility	2.3 g/L (20-25° C)	Wang et al., 2011 (estimated)
n-Octanol/water partition coefficient, K_{ow} (log value)	5.17	Wang et al., 2011 (estimated)
Octanol-air partition coefficient K_{oa} (log value)	7.55	Wang et al., 2011 (estimated)
Organic carbon/water partition coefficient K_{oc} (log value)	1.78	Wang et al., 2011 (estimated)

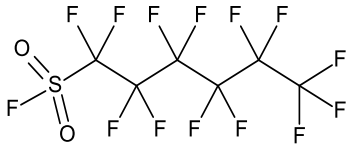
Figure 1

Examples of chemical structures of PFHxS, its salts and related substances

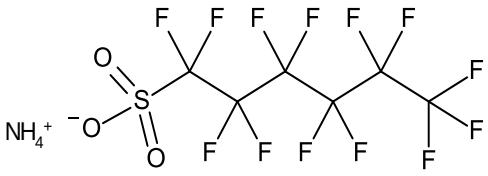
Perfluorohexane sulfonic acid (CAS No. 355-46-4)



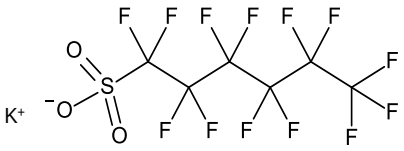
Perfluorohexane sulfonyl fluoride (CAS No. 423-50-7)
Precursor/start material



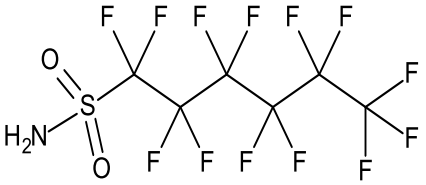
Perfluorohexanesulfonate ammonium salt
(CAS No. 68259-08-5)



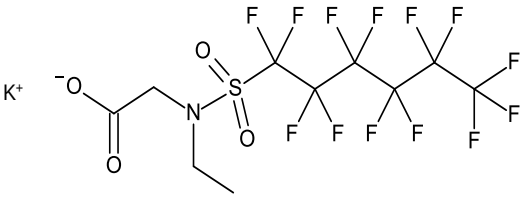
Perfluorohexanesulfonate potassium
(CAS No. 3871-99-6)



Perfluorohexane sulfonamide (CAS No. 41997-13-1)



Potassium N-ethyl-N-
[(tridecafluorohexyl)sulfonyl]-



3. Global consumption and use of PFHxS, its salts and related substances

6. Traditionally, perfluoroalkane sulfonates and sulfonic acids are used as surfactants while perfluoroalkane- sulfonyl fluorides and sulfonamides are major raw materials for surfactant and surface protection products (reviewed in Buck et al., 2011). Therefore, these substances are used in a wide variety of applications and consumer products (Hertzke et al., 2012). Historically, 3M produced PFHxS as a building block for compounds incorporated in fire-fighting foams and specific postmarked carpet treatment applications (Olsen et al., 2005). A present Chinese advertisement on a web page of a producer selling the raw material, PFHxSF, used for manufacture of PFHxS, its salts and related compounds states the following: "PFHxSF is one of the most essential raw materials for preparing fluorine containing surfactants. The fluorine containing surfactant can be widely used in textile, leather, papermaking, pesticide, electroplating, oilfield, fire control, photosensitive material, synthetic material and other fields" (http://worldyachem.en.made-in-china.com/product/OvqmATeKnbkR/China-Perfluorohexane-Sulphonyl-Fluoride-CAS-No-423-50-7.html).

7. PFHxS, its salts and related substances have unique properties such as high friction resistance, dielectrical properties, resistance to heat and chemical agents, low surface energy, and are used as water-, grease-, oil- and soil repellent. Salts of PFHxS have been reported to have been used as components of etchants for electroplating, in antireflective coatings for photolithography, in photoresists, in carpet, paper and textiles treatments, in fire-fighting foams (Beesoon et al., 2012; Liu and Chang, 2014; Hertzke et al., 2012; OECD, 2011; Olsen et al., 2005; UNEP, 2016) in surfactants, and production of fluoropolymers. In a formulation of ScotchGard™ Carpet Protector, produced by 3M (US), but discontinued in 1999, PFHxS was a major constituent that was intentionally added to an after-market carpet protector (Beesoon et al., 2010). However, subsequent to the cessation in production by the major manufacturer, the diethanolammonium salt of PFHxS was reported to be used as a component of etchants for electroplating (US SNUR exemption), carpets, leather and apparel, textiles and upholstery (UNEP, 2016). Limited data are available to evaluate the degree to which the remaining salts in this group are used for the above listed purposes. However, it is noted that the use of three potassium salts in this group was reported in 2012 in Denmark (SPIN data base/Nordic Council

of Ministers, 2015) and that PFHxS and some of the related substances are pre-registered under REACH (ECHA web site) indicating continuous use of these substances. Nonetheless, many PFASs are entering the global market through imported articles, and for those there are virtually no controls. Some PFAS-manufacturers in China and Italy have initiated the production of perfluorohexane sulfonyl fluoride (PFHxSF) and its derivatives as replacements of PFOSF-based chemicals (e.g., in textile finishing agents) (Swedish environment agency, KEMI, 2015b). According to Wang et al. (2013), it is estimated that in the next five to 10 years production of surface treatment products containing PFHxSF- or perfluorobutane sulfonyl fluoride (PFBSF)-derivatives will reach more than 1000 tonnes annually. In a survey of PFASs in consumer products, Herzke et al. (2012) found PFHxS in 12 of 29 analysed consumer products and in one (one old aqueous film forming foam (AFFF) formulation) out of 5 fire-fighting foam products. It was also found in printing inks, sealants for use in bathrooms, electronic toy bought in Sweden and in none-stick ware (Swerea/IVF, 2009). Furthermore, a recent Swedish survey reported that PFHxS was detected in four of the fire-fighting foam analysed (Swedish environment agency, KEMI, 2015a).

4. National and international administrative actions on PFHxS

8. Harmonized classification is missing for PFHxS. The substances are still produced- and available on the world market and some of the substances are reported to the EU classification and labelling inventory (C & L Inventory) registration system, which shows that substances are produced in- or imported to the European market at a tonnage of the substances that are 1 metric ton (100,000 kg) or more. Furthermore, a risk management option analysis (RMAO) was recently developed by the Swedish Chemical Agency (KEMI) for the EU that concluded that PFHxS, its salts and related substances are persistent, bioaccumulative and toxic (PBT) substances (ECHA, 2017). In addition, a number of PFHxS, its salts and related substances are found in the SPIN database which is a register of the use of chemicals in products in the Nordic countries (http://195.215.202.233/DotNetNuke/Home/tabid/58/Default.aspx). The database is based on data from the Product Registries of Norway, Sweden, Denmark and Finland and indicates that products contain PFHxS, its salts or related substances are found on the market in these countries. In Norway, PFHxS has recently been added to the national list of priority substances (Prioritetslista) with a national goal to phase out the use within 2020.

9. Some of the substances belonging to the PFHxS group of chemicals are listed on the Canadian Domestic Substances List (DSL) (Environment Canada, 2013a), an inventory of substances manufactured in, imported into or used in Canada on a commercial scale. The DSL categorizes substances according to whether they are persistent and/or bioaccumulative and/or toxic.

10. In the United States, major fluoropolymer and telomer manufacturers (Arkema, Asahi, BASF Corporation (successor to Ciba), Clariant, Daikin, 3M/Dyneon, DuPont (now Dow Chemical), and Solvay Solexis) are committed to phase out long-chain polyfluorinated substances such as PFHxS in their operations by the end of 2015 in the context of the U.S. Environment Protection Agency (US EPA) Stewardship Programme (US EPA, 2006). However, according to an amendment of significant new use rule (SNUR) under the Toxic Substance Control Act (TSCA, US EPA, 2007) the use of PFHxS-related substances in certain applications are exempted from the rule indicating that some use is still ongoing (US EPA, 2007). In Australia in 2008, a factsheet published by National Industrial Chemicals Notification and Assessment Scheme (NICNAS, Department of Health, Australian Government) recommended that PFOS-based and related PFAS-based chemicals should be restricted to essential uses only, and that importers ensure that alternative chemicals are less toxic and not persistent in the environment (NICNAS, 2013). Furthermore, an environment assessment of precursors (direct- and indirect) of PFHxS concluded that the identified precursors had the potential to give rise to adverse outcomes for the environment (NICNAS, 2016).

5. Information on PFHxS and how it fulfils the Annex D screening criteria

5.1. Persistence

11. PFASs are generally recognized as persistent (Reviewed in ECHA, 2017). Their chemical structure consists of a hydrophobic alkyl chain and a hydrophilic functional group and their high stability comes from the strong carbon-fluorine chemical bond, making some of them ubiquitous in the environment, wildlife and human blood (Giesy and Kannan, 2001; Reviewed by Xu et al., 2013). Fate data on PFHxS are very sparse. Based on a read-across approach, conclusions applied to the fate of other PFASs such as PFOS can be anticipated to be valid for PFHxS as well. Thus, PFHxS is not expected to undergo hydrolysis or photolysis, and biodegradation and, like other PFASs, found to be poorly removed in waste water treatment plants (Danish Ministry of Environment, 2015). PFHxS does not undergo photolysis as confirmed by Taniyasu and co-workers (2013) who performed a field study on photolysis of several PFASs, including PFHxS, at high altitude in Mt. Mauna and Mt. Tateyama.

No significant photolysis was observed for PFHxS in this study following respectively 106 and 20.5 days exposure to intensive solar radiation. This indicates that PFHxS does not degrade via photolysis. To our knowledge there are no other degradation studies available on PFHxS. However, PFOS, a substance structurally very similar to PFHxS and already listed in the Stockholm Convention (reviewed in UNEP, 2006), is considered extremely persistent and does not hydrolyse, photolyse or biodegrade in any environmental condition tested (OECD, 2002).

12. There are some characteristics which are valid for the whole group of PFASs, and therefore also PFHxS. PFASs are very resistant to chemical, thermal and biological degradation due to their strong carbon-fluorine bonds (Kissa, 2001) and resistance to degradation that makes many of them persistent in the environment. In the environment and biota, perfluorinated sulfonates are generally found in their non-volatile acid forms (Houde et al., 2006).

Conclusion on persistence according to the criteria in Annex D

13. Based on known persistence of perfluorinated alkyl substances and the close structural similarity with the very persistent PFOS, it is concluded that PFHxS, its salts and related substances meet the Annex D criteria for persistency.

5.2. Bioaccumulation

14. Experimental log K_{ow} values are not reported for PFHxS. PFASs have combined properties of oleophobicity, hydrophobicity and hydrophilicity over portions of the particular molecule and are expected to form multiple layers in an octanol-water mixture, which make it experimentally difficult to measure the log Kow (OECD, 2002 and 2006; Conder et al., 2008). In addition, it has been shown that PFHxS preferentially binds to proteins in liver and blood (Ahrens et al., 2009; Martin et al., 2003; Goeritz et al., 2013) and therefore the log Kow as descriptor for the bioaccumulation potential is not appropriate for PFHxS and related substances. This was also seen for the PFOS-group of substances assessed and listed in the Stockholm Convention (UNEP, 2006; Kitano, 2007).

15. The reported bioconcentration factors (BCF) and bioaccumulation factors (BAF) for PFHxS are below the numerical criteria of 5000, indicating a low bioaccumulation potential in aquatic organisms. BCF for rainbow trout exposed to AFFF containing PFHxS were reported to be 133 (Yeung and Mabury, 2013) while the BCF for PFHxS in a similar study ranged from 9.6 (whole body) to 100 (liver) (Martin et al., 2003). However, the numerical criterion for BCF or BAF, which are based on considerations of lipid-partitioning substances, are not appropriate for PFHxS as it does not follow the behaviour of traditional hydrophobic compounds with partitioning into fatty tissues. Instead, it behaves similarly to what previously have been observed for PFOS and other perfluorinated compounds which preferentially binds to proteins in blood and liver (Martin et al., 2003; Ahrens et al., 2009; Goeritz et al., 2013). Furthermore, due to its water solubility PFHxS is expected to quickly be excreted through gill permeation in fish (Martin et al., 2003; Goeritz et al., 2013).

16. Biomagnification factors (BMFs) and trophic magnification factors (TMFs) explicitly account for biomagnification resulting from trophic transfer where the chemical concentration in one organism exceeds that of the organism at a lower level of the food chain (reviewed by Counder et al., 2012). Investigation of biomagnification in selected species from the Barents Sea food web was performed by Haukås et al. (2007). Trophic level-corrected BMFs reported for black guillemot/polar cod, glaucous gull/polar cod and glaucous gull/black guillemot were 6.0, 7.2 and 8.5, respectively. In a study published by Butt et al. (2008), BMFs ranging between 163 and 373 were reported for the polar bear/ringed seal predator-prey relationship at several locations in the Canadian Arctic. BMFs were calculated using liver concentrations in both species, but since PFASs have been shown to accumulate preferentially in protein rich tissues, accumulation may have been overestimated compared to whole-body calculated BMFs. Data on biomagnification in several predator/prey relationships are available. Houde et al. (2006) investigated the accumulation of PFHxS in the Bottlenose dolphins/pray food web at two different locations in the United States. BMFs ranged from 3.3 to 14 at the two Charleston locations (industrialized). At the Sarasota Bay location (residential), two individual dolphin/prey relationships and two fish/zooplankton relationships were studied and the BMF ranged from 1.8 to 10. In the above mentioned studies TMFs using both plasma-based and whole-body-based calculations were performed in the marine food web. Neither showed trophic magnification with TMFs ranging from 0.2 ± 0.9 to 0.1 ± 0.4 (Houde et al., 2006). However, there is large variation in the TMFs, reflected in standard errors being larger than their corresponding TMFs. Furthermore, the samples were collected over a period of several years (2002 to 2004) and it has been reported that a number of factors such as temperature, time of sampling, reproduction status, migration and age can affect the calculation of TMF (Borgå et al., 2012). Studies investigating trophic magnification of PFHxS in food webs are limited; hence no conclusion can be made from TMFs of PFHxS. However, predator-prey

studies clearly indicate bioaccumulation in several animals and a number of BMF > 1 has been reported.

17. Studies on pigs fed a diet contaminated with known concentrations PFASs including PFHxS has been reported (Numata et al., 2014). Results showed that blood plasma was the largest reservoir of unexcreted PFHxS followed by muscle. Among the PFASs detected (perfluorohexanoic acid (PFHxA), perfluoroheptanoic acid (PFHpA), perfluorooctanoic acid (PFOA), perfluorobutane sulfonic acid (PFBS), perfluoroheptane sulfonic acid (PFHpS) and PFOS), PFHxS had the lowest percentage of excretion during the 21-day experiment period, indication that PFHxS accumulate in the pig tissues. Furthermore, the ability to strongly bind to blood proteins and the low clearance/slow excretion have been proposed as the best predictor for bioaccumulation potential and long half-life of a chemical (Tonnelier et al., 2012). In the Numata et al. (2014) study, the elimination half-life for PFHxS in plasma was 713 days and the calculated BMFs for whole pig, meat and liver for PFHxS were 20.1, 13.1 and 48, respectively. For comparison, half-lives for PFOS and PFOA in these pigs were 634 and 236 days, respectively (Numata et al., 2014).

18. PFHxS is frequently detected in human samples globally (Christensen et al., 2016; Fromme et al., 2017; Gibson et al., 2016; Jin et al., 2016). A Swedish study showed increasing levels of PFHxS in the blood of pregnant women in the period 1996-2010 (Glynn et al., 2012). Furthermore, PFHxS was detected in umbilical cord blood and transmitted to the embryo in a larger extent compared to what has been reported for PFOS (Gützkow et al., 2012). PFHxS was also detected in breast milk in several studies (Posner et al., 2013). The elimination half-life of PFHxS, PFOS and PFOA in serum of 26 retired fluorochemical production workers has been reported (Olsen et al., 2007). Half-lives for PFHxS, PFOS and PFOA were 8.5, 5.4, and 3.8 years, respectively. Hence, the half-life of PFHxS is approximately 1.5 times longer than for PFOS. Pharmacokinetic studies in non-humans have demonstrated that serum elimination half-lives of PFHxS can vary considerably between species (Hundley et al., 2006; Sundstrom et al., 2012) 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. PFHxS in addition to PFOS and PFOA is among the perfluorinated compounds detected most frequently in the blood of humans, and the concentration of PFOS is generally higher compared to PFHxS and PFOA (Posner et al., 2013).

19. In addition to the above mentioned accumulation and magnification studies, PFHxS have been found in air, soil, sewage sludge and in many species, including in polar cod, glaucous gull, ringed seals and polar bears in the Arctic (Posner et al., 2013; Haukås et al., 2007). In a field study of polar bears from five locations in the North American Arctic and two locations in the European Arctic, PFHxS was detected at all locations (Smithwick et al., 2005b). 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. For comparison, the detected amount of PFOS in the same samples was an average of 1290 ng/g (wt); hence approximately 2.5 times lower than the PFHxS concentration. In an additional study by Smithwick et al. (2005a), the mean concentration of PFHxS in polar bear liver at Eastern Greenland were 140 ng/g wt, while the amount of PFOS detected was more than 15 times higher. The differences between PFHxS and PFOS concentrations observed at these locations may be attributed to the differences in the long-range transportation pathways and the global source for these substances (Smithwick et al., 2005b).

Conclusion on bioaccumulation according to the criteria in Annex D

20. PFHxS biomagnifies in the food chain in the Arctic with BMF > 1. Furthermore, monitoring data show concentrations of PFHxS in biota and this is a clear indication that the substance is taken up by the organism. Humans accumulate PFHxS and its elimination is very slow with a half-life of approximately 8 years. Based on reported BMF, the very high half-life in humans and the high levels detected in Arctic polar bears, PFHxS fulfils the Annex D screening criterion.

5.3. Potential for long-range environmental transport

21. The source of PFASs to Arctic and Antarctic environments is complex and has been the subject of considerable scientific interest. While two major potential transport mechanisms have been postulated, the relative contribution of each pathway remains unresolved. One pathway involves the transport of volatile precursors via the atmosphere, degradation by atmospheric oxidation to PFAS and subsequent wet and dry deposition. The second pathway involves the transport of directly emitted PFAS via oceanic currents to the marine environment. Furthermore, local inputs from anthropogenic activities may be another source to PFAS in Arctic regions (reviewed in Butt et al., 2010).

22. PFHxS is globally distributed and has been detected in the Arctic and Antarctic areas (e.g. Butt et al., 2010; NCP 2013; Alava et al., 2015; Llorca et al., 2012; Rankin et al., 2016). Detection of PFHxS in the Arctic include different environmental matrices such as air (Stock et al., 2007; Genualdi et al., 2010), snow (Theobald et al., 2007 as cited in Butt et al., 2010), seawater (e.g. Caliebe et al., 2005 as cited in González-Gaya et al., 2014; Theobald et al., 2007 as cited in Butt et al., 2010; Rosenberg et al., 2008; Busch et al., 2010; Cai et al., 2012; Benskin et al., 2012; Zhao et al., 2012), freshwater lakes and sediment (Stock et al., 2007) and various biota ranging from fish and seabirds, to marine and terrestrial mammals (e.g. Butt et al., 2010; NCP, 2013; Reiner et al., 2011; Riget et al., 2013; Carlsson et al., 2014; Lescord et al., 2014; Braune et al., 2014; Aas et al., 2014; Routti et al., 2016). PFHxS has also been detected in fur seal liver (Schiavone et al., 2009), lichen (Alava et al., 2015) and penguin faeces (Alava et al., 2015; Llorca et al., 2012), but not in soil (Rankin et al., 2016; Llorca et al.,2012), seawater (Ahrens et al., 2010; Bengtson Nash et al., 2010; Wei et al., 2007), algae, penguin tissue, fur seal muscle, blood plasma of adult lactating Weddell seals, penguin eggs, seabird or penguin feathers in the Antarctic (Schiavone et al., 2009; Llorca et al., 2012; Alava et al., 2015; Routti et al., 2015).

23. PFAS, like PFHxS, are emitted into the environment from human activities e.g. from manufacturing processes, product use and disposal and management of waste (Paul et al., 2009). Emissions come from point- (e.g. manufacturing, wastewater treatment plants, landfills, contaminated ground) and non-point sources (e.g. street surface runoff, dry and/or wet atmospheric deposition) (Ahrens et al., 2011). While there is scientific consensus that PFASs are subject to long-range environmental transport, the dominant transport pathway governing the long-range environmental transport of individual PFASs have not been conclusively characterized to date (Butt et al., 2010; Ahrens et al., 2011; Rankin et al., 2016). Processes that transport PFASs to the Arctic include direct transport of parent compounds in air or water and/or indirect transport by transport of neutral volatile precursor compounds that can undergo transformation/subsequent degradation by atmospheric oxidation or biological degradation (Butt et al., 2010; Ahrens et al., 2011; Alava et al., 2015, Wang et al., 2015).

24. According to Butt et al. (2010), snow samples can act as a surrogate for atmospheric deposition. The detection of PFHxS in Arctic air and snow may thus suggest that PFHxS, similar to other PFASs, can undergo atmospheric long-range transport and deposit in the Arctic environment (Theobald et al., 2007 as cited in Butt et al., 2010; Stock et al., 2007; Genualdi et al., 2010; Butt et al., 2010). The potential for PFHxS to undergo long-range environmental transport via air is further supported by the detection of PFHxS at concentrations ranging from 0.19 to 1.16 ng/g ww in lichen from the Antarctic Peninsula (Alava et al., 2015). Lichens accumulate pollutants from air and are used as bioindicators for air pollution (Augusto et al. 2013). Atmospheric transport of PFHxS to remote regions via air is, however, not well documented and there is limited knowledge about the identity of any PFHxS precursors, their half-lives in air and their presence in the Arctic/Antarctic air. An atmospheric source could involve neutral precursors akin to those implicated in the production of perfluorinated carboxylic acids (PFCAs) and PFOS (Martin et al., 2006; D'Eon et al., 2006). The PFHxS detected in environmental samples in remote regions may thus result from either atmospheric oxidation and/or 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). Atmospheric measurements confirm that volatile precursors to perfluorosulfonic acids reach Arctic latitudes where they degrade. For example, in a study from Cornwallis Island in Nunavut in the Canadian Arctic, Stock et al. (2007) reported the detection of perfluorosulfonamide and sulfonamide ethanol precursors at mean concentrations in air ranging from 11 to 29 pg/m^3 (particulate + gas phase). Degradation products were also observed and was said to confirm that degradation of PFAS and PFCA precursors is occurring in the Arctic atmosphere (Stock et al., 2007). Furthermore, in a more recent study, the C_4 PFAS precursor, methylperfluorobutane sulfonamidoethanol (MeFBSE), and its degradation product, methylperfluorobutane sulfonamide (MeFBSA), was detected at 2.9 and 3.8 pg/m^3 in air sampled in coastal areas of the Western Antarctic Peninsula (Del Vento et al., 2012). Similarly, Dreyer et al. (2009) detected MeFBSE and MeFBSA in "background" air in the Southern Ocean, although at approximately 10-fold lower levels than those reported by Del Vento et al. (2012). Furthermore, Wei et al. (2007) reported the detection of perfluorobutane sulfonic acid (PFBS), a possible degradation product of MeFBSE and MeFBSA in seawater near Antarctica. Overall, these findings suggests that volatile PFASs are transported to the both the Arctic and the Antarctic where they may degrade to perfluorosulfonic acids such as PFHxS and PFBS and deposit in the environment.

25. Recent findings could however suggest that direct transport via ocean water, not direct or indirect transport via air or ocean spray is the most prominent route for long-range environmental transport of PFHxS (MacInnis et al., 2017; Kwok et al., 2013). Furthermore, according to reported usage, the synthetic precursor to PFHxS, perfluorohexane sulfonyl fluoride (PFHxSF), has never been

used for the production of commercial volatile perfluoroalkane sulfonamido substances compounds (MacInnis et al., 2017 and references therein).

26. Similar to other perfluorosulfonic acids, PFHxS is water soluble (Wang et al., 2011), and is transported in water (dissolved) to remote areas where it is detected in open-ocean and costal water (Caliebe et al., 2005 as cited in González-Gaya et al., 2014; Theobald et al., 2007 as cited in Butt et al., 2010; Rosenberg et al., 2008; Busch et al., 2010; Cai et al., 2012; Benskin et al., 2012; Zhao et al., 2012; Ahrens et al., 2010; Wei et al., 2007). Ocean water is assumed to be an important sink and a long-term reservoir of PFASs in the environment (e.g. Yamashita et al., 2008; Prevedouros et al., 2006; Ahrens et al., 2011; Gonzales-Gaya et al., 2012). The Globo-POP model developed by Lohmann et al., 2007, predicts that PFHxS, like most other PFASs, is a "swimmer" i.e. a chemical that based on its log K_{aw} and log K_{ow}, is anticipated to undergo long-range environmental transport in water (Llorca et al., 2012). The global occurrence of PFHxS and other PFASs in open-ocean water was first described by Yamashita et al. (2005). Other studies have since confirmed PFHxS as a contaminant of the Pacific and Atlantic Ocean, and has also documented its presence in the Arctic, Indian Oceans and the Mediterranean Sea (Caliebe et al., 2005 as cited in González-Gaya et al., 2014; Busch et al., 2010; Benskin et al., 2012; González-Gaya et al., 2014; Brumovský et al., 2016).

27. Detections in Arctic seawater include measurements from the open Arctic Ocean, the Beaufort Sea, the Chukchi Sea, Bering Strait, the Bering Sea, the Canadian Arctic Archipelago, the North West and Western Pacific Ocean in the Arctic, the Labrador Sea, Davis Strait, North Baffin Bay, the Greenland Sea and the Norwegian Sea (Caliebe et al., 2005 as cited in 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; see overview in Benskin et al., 2012, Supporting Information, Gonzalez-Gaya et al., 2012, Supporting Information). PFHxS levels range from n.d. to 45 pg/L (Caliebe et al., 2005 as cited in González-Gaya et al., 2014; Yamashita et al., 2005; Benskin et al., 2012; Zhao et al., 2012). Overall, similar to what has been proposed for other PFASs, and as indicated also above, the available data are consistent with global ocean circulation as one mechanism for long-range environmental transport of PFHxS. In a study from 2010, Busch et al. identified oceanic and atmospheric transportation, as well as ice-melt/precipitation from the Greenlandic mainland as possible sources to PFHxS and other PFASs detected in the Arctic Ocean. Surface water samples were collected from the East Greenland Arctic Ocean from 67.5 to 80.4°N in this study. Along the transect PFHxS was found at a mean concentration of 5.2±9 pg/L (range n.d. to 14.5 pg/L). Higher PFHxS levels were detected in coastal water 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). In contrast, it has been suggested that oceanic long-range transport of PFHxS and other PFASs to the Antarctic is more limited, at least at present.

28. As explained by Bengtson Nash et al. (2010), the Southern Ocean that surrounds the Antarctica is supplied by water from the deep layers of the Atlantic, Indian and Pacific oceans. These deep-sea layers have been isolated from contact with the atmosphere for hundreds of years and are assumed to be essentially PFAS-free (Ahrens et al., 2010; Bengtson Nash et al., 2010). Another net effect of the Antarctic circumpolar current that drives the circulation in the Arctic Ocean is that surface waters carrying PFASs are transported away from Antarctica. In other words, the hydrodynamics in the Southern Ocean is at present believed to isolate Antarctica from water bodies carrying PFAS and may partially explain why detection levels and frequencies for PFASs are lower in this region than in the Arctic (Bengtson Nash et al., 2010; Yamashita et al., 2008). Distance to important source regions, limited chemical manufacture of PFASs on the southern hemisphere and low effectiveness of delivery to the Antarctic via the atmospheric route and low yield of ionic PFASs produced via oxidation are indicated as other possible explanations (Bengtson Nash et al., 2010; Alava et al., 2015). Furthermore, trans-Atlantic Ocean currents and related dilution effects are suggested to explain why a decreasing PFAS concentration gradient was observed in sea water on a cruise from Northern Europe to the South Atlantic Ocean (52°N-69°S) (Ahrens et al., 2010). A permeation of PFAS into the Antarctic system, via hydrospheric transport, is however predicted to occur within the next few decades.

Conclusion on long-range transport according to the criteria in Annex D

29. PFHxS is detected in remote regions, including in the Arctic and Antarctic where it is found in the environment and in biota. Available research is consistent with results for other PFASs and supports that PFHxS undergoes long-range environmental transport to these remote regions via the hydrosphere (oceanic transport), and possibly via air in the form of volatile precursors that degrade to PFHxS locally.

5.4. Adverse effects

30. Mammalian studies indicate toxicity to the liver and show effects on nuclear receptors that regulate metabolism, as well as effects that could reflect interference with metabolic homeostasis including effects on levels of cholesterol, lipoproteins, triglycerides and free fatty acids in humans and rodents. There are also other indications that PFHxS could act as an endocrine disruptor by acting as an anti-androgen/weak estrogen and by affecting the thyroid hormone axis. Furthermore, neurotoxic and neurodevelopmental effects of PFHxS has been observed in controlled experiments. In addition, an effect on the activity of enzymes involved in corticosteroid hormone metabolism and inhibition of intracellular communication has been observed in vitro. Read-across from other PFASs suggests that immunotoxic effects may also be anticipated. While the main bulk of data on adverse effects come from mammalian studies more specifically in vitro and in vivo studies and human epidemiological data, there is also some evidence for similar and potential adverse effects also from ecotoxicity studies.

31. Ecotoxicity data for PFHxS are limited, but available studies comparing toxic effects of PFBS and PFOS in aquatic organisms indicate that toxicity increase with increasing carbon length, and suggest a likelihood for adverse effects also in non-mammalian species (Giesy et al., 2010). For example, in African clawed frog (Xenopus laevis), both PFOS and PFBS promoted expression of estrogen and androgen receptors in the brain at environmental relevant concentrations (from 0.1 µg/L), and caused adverse effects on hepato-histology and sexual development at high concentrations (100-1000 µg/L) (Lou et al., 2013). From other laboratory studies, PFOS is known to be moderate acute and slightly chronic toxic to aquatic organisms and the few PFBS studies available indicate lower toxicity of PFBS (Ding and Peijnenburg, 2013; Giesy et al., 2010).

32. In birds, PFHxS has been shown to influence thyroid hormone pathways and genes related to neuronal development. Based on egg injection, the lowest observed effect concentration (LOEC) were 890 ng PFHxS/g ww for developing leghorn chicken embryos. Pipping success was reduced to 63%, and decreased tarsus length and embryo mass was observed for the highest dose (38,000 ng/g egg), and plasma thyroxine (T4) hormone was dose dependently reduced. Gene expression in liver and cerebral cortex of thyroid and neurodevelopment related genes were also affected (Cassone et al., 2012a, b). The effect on gene expression was also observed in avian primary neuronal culture in concentration rang 0.1-10 µM (Vongphachan et al. 2011). The lowest observed adverse effect level (LOAEL) 890 ng/g for developing leghorn chicken embryos is 18 times greater than the highest reported mean concentration in avian wild life (50 ng/g ww liver, range <3.2–120.7) of grey herons (Meyer et al., 2009). Furthermore, a negative correlation has been observed between serum PFHxS levels and the ratio of total and free triiodothyronine (T3) in fulmar and kittiwake chicks sampled in Kongsfjorden Svalbard, (median sum PFAS =79.9 and 12.1 ng/g ww, respectively) (Nøst et al., 2012).

33. In polar bears from East Greenland both brain-specific accumulation of PFASs and the correlation with neurochemical markers and steroid hormones has been investigated (Eggers Pedersen et al. 2015; 2016). Average brain sum PFAS was 25 ng/g ww, where PFOS accounted for 91% (PFHxS average 1.09 ng/g ww), and sum PFCA was 88 ng/g ww where perfluoroundecanoic acid (PFUnDA), perfluorododecanoic acid (PFDoDA) and perfluorotridecanoic acid (PFTrDA) accounted for 88%. The highest concentrations of PFASs were measured in brain stem, cerebellum and hippocampus. Significant correlations between PFCAs and PFAS and neuro transmitter enzyme activity and neuro transmitter receptor density were observed. This indicate that PFAS concentration in polar bears from East Greenland have exceeded the threshold limit for neurochemical alterations (Eggers Pedersen et al., 2015). 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 PFAS and 17alpha- hydroxypregnenolone (OH-PRE) and several steroids were significantly correlated with sum PFCAs. The results indicate that an increase in PFASs concentration concur with an increase in brain steroid hormones (Eggers Pedersen et al., 2016).

34. Repeated toxicity data for PFHxS are available and indicate toxicity to the liver and thyroid in male rats. Administered potassium PFHxS (K+PFHxS) at 0, 0.3, 1, 3 or 10 mg/kg bw per day to Sprague Dawley rats by oral gavage, during cohabitation, gestation and lactation through to study day 42 (males) or postnatal day (PND) 21 (females) gave effects in parental males. Observed effects included reduced serum cholesterol (all doses), decreased prothrombin time (0.3, 3 and 10 mg/kg bw per day), increased liver-to-body- and liver-to-brain weight ratio, centrilobular hypertrophy, hyperplasia of thyroid follicular cells, decreased haematocrit (3 and 10 mg/kg bw per day), decreased triglycerides and increased albumin, urea nitrogen, alkaline phosphatase, Ca2+ and albumin/globulin ratio (10 mg/kg bw per day). There were no treatment related changes in dams or offspring and changes in haematological parameters gave a LOAEL of 0.3 mg/kg bw per day (Butenhoff et al., 2009).

35. Several studies have explored the mechanistic effects of PFHxS on liver function, effects on peroxisome proliferator-activated receptor (PPAR) activation, plasma lipoprotein levels and cholesterol. In a study by Wolf et al. (2008), PFHxS was found to activate both mouse and human PPARα-receptor *in vitro* with LOEC at 8.76 and 4.38 ppm, respectively, (equals to µg/mL, or 10 and 5 µM). 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). PFHxS inhibits 11-beta-dehydrogenase isozyme 2 (11β-HSD2) involved in corticosteroid hormone metabolism in human and rat kidney microsomes. The half-maximal inhibitory concentrations (IC50s) of human and rat 11β-HSD2 activities were 18.97 and 62.87 µM PFHxS, respectively (Zhao et al., 2011).

36. The effects of PFHxS on liver function may be partly independent of PPAR-α as many of the observed responses were also observed in PPAR-α null mice (Das et al., 2016). Liver steatosis occurred in both wildtype and PPAR-α null mice after 7 days oral exposure to 10 mg/kg/d PFHxS, as well as the APOE*3-Leiden.human Cholesteryl Ester Transfer Protein (E3L.CETP) mice exposed daily to 6 mg/kg bw for 4-6 weeks (Brijland et al., 2011). Furthermore, several genes related to cholesterol and lipoprotein metabolism were affected in both wild type and null mice (Das et al., 2016) as well as the mice model APOE*3-Leiden.E3L.CETP (Brijland et al., 2011). Reduced levels of triglycerides, cholesterol, non-high density lipoprotein cholesterol (non-HDL-C) and high density lipoprotein cholesterol (HDL-C) in blood plasma were observed. In addition, reduced levels of the plasma lipoprotein components, as well as free fatty acid and glycerol were observed, whereas the enzyme lipase activity and the clearance of the triglyceride triolein increased (Bijland et al., 2011).

37. The immunotoxic effect of PFHxS has not been investigated in controlled experiments, however, PFBS, PFOS, perfluorooctane sulfonamide (PFOSA), PFOA, perfluorodecanoic acid (PFDA) and 8:2 fluorotelomer alcohol (FTOH) were included in the *in vitro* study by Corsini et al. (2012), and one can assume PFHxS would give an immunosuppressive effect in between those observed for PFBS and PFOS. All PFASs tested suppressed lipopolysaccharide (LPS)-induced tumour necrosis factor (TNF)-alpha production in both human peripheral primary leucocytes and in a promyelocytic cell line (THP-1), PFBS and PFOS at 0.1 µg/mL. Phytohemagglutinin (PHA)-stimulated secretion of interleukin (IL)-6 and interferon (INF)-gamma were suppressed by PFOS, and IL-10 was affected by both PFOS and PFBS (10 µg/mL). All PFASs decreased LPS-induced nuclear factor-kappaB activation, and PFBS and PFDA prevented LPS induced 1-kappaB degradation (Corsini et al., 2012).

38. Neurotoxic and neurodevelopmental effects of PFHxS have been observed in controlled experiments. Adult dose-dependent behavior and cognitive disturbance was observed in mice after a single neonatal dose of PFHxS in the vulnerable brain developmental period (6.1 and 9.2 mg/ kg bw, oral single dose PND 10) (Viberg et al., 2013). PFHxS affected the cholinergic system, manifested as altered nicotine-induced behavior in adult animals, which is in agreement with previous findings for PFOA and PFOS (Viberg et al., 2013). Levels of several proteins important in the brain growth spurt were affected 24 h after exposure, and taurine levels were different from control at 4 months in males (Lee and Viberg, 2013). In another study on developmental effects in rats, no effect on motoric activity was observed for rats exposed *in utero* and through lactation to 0.3-10 mg/kg/d (Butenhoff et al., 2009). However, female rats are more efficient in excretion than male rats or mice of both gender, with estimated half-lives of 2 days compared to 30 days for male rats or mice (Sundstrøm et al., 2012). This extreme gender difference seems to be specific to rats (Kim et al., 2016; Sundstrøm et al., 2012), and may contribute to the diverging neurodevelopment effects observed between rats and mice.

39. Neurotoxic effects of PFHxS have been further explored *in vitro*. Long-term potentiation (LTP) as a physiological basis of learning and memory has been employed as the primary cellular and molecular model to evaluate synaptic plasticity. PFHxS (100 µM) has been shown to decrease the LTP in hippocampus CA1 region in adult rats with comparative potential as PFOS (Zhang et al., 2016). 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 induced apoptosis in vitro in the dopaminergic neuronal cell line (PC12) and glutamatergic primary cells (cerebellar granule cells). Doses tested corresponded to 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).

40. Some mechanistic studies have explored the effect of PFHxS on thyroid hormone pathway. PFHxS competed with thyroxine (T4) for binding to the human thyroid hormone transport protein transthyretin (TTR), which is a highly conserved plasma protein and the main T4 carrier in cerebrospinal fluid, and expressed at high levels during prenatal and early postnatal life (Larsen and Delallo, 1989). PFHxS IC50= 717 nM (~286 ng/mL) and binding affinity were ~12.5 times lower than

the natural ligand T4, (Weiss et al. 2009). PFHxS did also dose-dependently inhibit triiodothyronine (T3)-dependent cell growth in vitro from 10^{-8} Molar (Long et al., 2013).

41. PFHxS was shown to have anti-androgenic activity and weak estrogenic effect *in vitro*. 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) (Kieldsen and Bonefeld-Jørgensen 2013). PFHxS had weak inhibitory effect on aromatase activity (CYP19) IC50= 298 µM (human placental carcinoma cells JEG-3) (Gorrochategui et al., 2014).

42. In contrast to the rodent studies, both positive and negative association between PFHxS serum levels and serum cholesterol and lipoproteins have been observed in human adults. In a Canadian study a significant association between PFHxS and total cholesterol (TC, i.e. sum of free cholesterol and cholesterol bound to low-density lipoprotein (LDL) and high-density lipoprotein (HDL)), LDL-cholesterol, TC/HDL ratio TC/HDL and non-HDL cholesterol as well as an elevated odds of high cholesterol were observed (Fisher et al., 2013). There was a significant increasing trend for TC, LDL and non-HDL as well as increased odds of higher cholesterol per log increase in PFHxS both in unweighted and weighted analysis. The geometric mean of PFHxS (2.18 µg/L) were slightly higher than in a study performed on data from The National Health and Nutrition Examination Survey (NHANES), a program of studies designed to assess the health and nutritional status of adults and children in the United States (Nelson et al., 2010) and the PFOS and PFOA levels were slightly lower. A positive monotone increase in cholesterol with increasing decile of PFHxS was also observed in a study from the C8 Health project of a population living near a chemical plant (Steenland et al., 2009). However, Nelson et al. (2010) found a negative association with PFHxS and TC, non-HDL and LDL in the general US population. In the Norwegian Mother and Child Cohort Study in 2003–2004 plasma concentrations of 7 PFAS were positively associated with HDL cholesterol, and specifically PFOS but not PFHxS was positively associated with TC in this sample of pregnant Norwegian women (Starling et al., 2014). The median concentrations of PFOS and PFHxS were 13 ng/mL and 0.6 ng/mL, respectively.

43. Human studies indicate that prenatal exposure to PFAS leads to suppressed immune responses in early childhood. Pre-natal exposure to PFOA, perfluorononanoic acid (PFNA), PFHxS, PFOS were determined in maternal blood from 99 participants included in a sub-cohort (BraMat) of the Norwegian MoBa-cohort. Results showed an inverse association between the level of anti-rubella antibodies in the children's serum at age 3 years and the concentrations of the four PFAS. Furthermore, there was a positive association between the maternal concentrations of PFOA and PFHxS and the number of episodes of gastroenteritis (Grannum et al., 2013). Grandjean et al. (2012) examined antibody response to vaccinations in 587 children, reporting strong negative association with antibody concentrations to diphtheria and tetanus. A 2-fold increase in PFHxS concentrations at age 5 years was associated with odds ratio of 1.48 (95% confidence interval = 0.96-2.28) for falling below a clinically protective level of 0.1 IU/mL for diphtheria antibodies at age 7 years. For tetanus the odds ratio was 1.78 (95% confidence interval = 1.08-2.93). In two studies from Taiwan, province of China, serum levels of PFHxS were reported to be significantly higher in children with asthma compared to children without asthma (Dong et al., 2013; Zhu et al., 2016).

44. Several studies have compared serum levels of PFAS including PFHxS with thyroid hormone and related effects in humans. Data (n= 1540) from NHANES (2007–2008) were used to evaluate the effect of PFOS, PFOA, PFNA, PFDA, PFHxS, and 2-(N-methyl-perfluorooctane sulfonamide) acetic acid on six thyroid function variables. Levels of T3 were found to increase with the levels of PFOA and total T4 levels were found to increase with increasing PFHxS levels (Jain et al. 2013). In another study of NHANES data including cohort 2007-2010 (n=1181), higher serum levels of PFOA and PFHxS were associated with altered total T3, total T4 and free T4 in the U.S. general population (Wen et al., 2013). A higher risk of subclinical hyperthyroidism with increased serum PFHxS was indicated for women (Wen et al., 2013). Chan et al. (2011) reported that the risk of hypothyroxinemia (96 cases; 175 controls) was slightly increased with PFHxS exposure (geometric mean: cases = 2.86 nmol/L; controls = 2.59 nmol/L) (adverse odds ratio = 1.12, 95 % confidence interval = 0.89-1.41) in pregnant mothers. When regression analyses were performed, controlling for exposure to PFOA and PFOS, PFHxS exposure remained associated with an elevated adverse odds ratio (1.27, 95 % confidence interval = 0.93-1.72) risk of maternal hypothyroxinemia. In a retrospective birth cohort study (2006-2010) in the Republic of Korea the association of PFAS and thyroid hormones in cord blood was explored using a generalized linear model (n=301). Cord blood perfluoro n-pentanoic acid (PFPeA) was positively associated with cord blood T4 level. Gender-specific analysis showed that prenatal PFPeA and PFHxS exposure significantly increased T4 and T3, respectively, while PFNA

decreased thyroid-stimulating hormone (TSH) concentration in newborn girls (Cordblood geometric mean PFHxS = 0.34 ± 1.81 ng/mL) (Shah-Kulkarni et al., 2016).

45. A few human epidemiological studies have looked at the correlation between serum PFHxS and neurotoxic or neuro developmental effects. Hoffman and co-workers (2010) evaluated the association between exposure to PFAS and attention deficit hyperactivity disorder (ADHD) among children 12-15 years of age (n=571) in the US using data from the NHANES 1999-2000 and 2003-2004. The study showed a significant increased odds of ADHD with higher serum PFHxS levels (odds ratio=1.06, 95% confidence interval= 1.02-1.11). Stein and Stavitz (2011) examined the cross-sectional association in children (5-18 years of age; n=10456) between serum PFAS concentrations and parent or self-report of doctor-diagnosed ADHD with and without current ADHD medication in the US. The prevalence of ADHD plus medication increased with increasing concentrations of PFHxS, with an adjusted odds ratio of 1.59 (95% confidence interval = 1.21-2.08).

46. Little is known about the mixture toxicity of PFAS at environmental relevant conditions, but some studies have investigated the mixture effects of the most commonly detected PFASs in human serum. More than additive effect was observed for a mixture of PFHxS, PFOS, PFOA, PFNA, PFDA when tested for anti-androgen activity *in vitro* (Kieldsen and Bonefeld-Jørgensen, 2013). In a follow up study, using the PFCA mixture extracted from serum of pregnant women in gestation week 11-13, the concentration of all the PFASs in the serum were positively correlated to the ER-transactivities (Bjerregaard-Olesen et al., 2015). Mixtures of PFOA and either PFNA, PFHxA, PFOS or PFHxS tested for activation of PPAR-α *in vitro* indicate both response addition and concentration addition at low concentration (1-32 µM) when tested in binary combinations (Wolf et al. 2014). In the human placental choriocarcinoma cell line JEG-3, a mixture of PFASs (PFBA, PFHxA, PFOA, PFNA, PFDoDA, PFBS, PFHxS and PFOS, each 0.6 µM), led to a relative increase up to 3.4-fold of several lipid classes, which indicate an interference of PFAS with membrane lipids (Gorrochategui et al., 2014).

47. PFHxS is efficiently transferred to the foetus via *in utero* and lactation exposure in rats (Butenhoff et al., 2009), while PFHxS is efficiently taken up by oral exposure and primarily excreted by urine in rodents and monkey (Sundstrøm et al., 2012). The long half-lives in humans (and male rats) may be caused by enterohepatic circulation (Zhao et al., 2015 and 2017). In a recent study of Chinese workers, the estimated median half-life for PFHxS was 14.5 years in males and 7.6 years in females. The half-lives in females were also shorter with regard to PFOA and PFOS, and thus the sex difference seen in animals is observed in humans. The difference was explained by a lower female reabsorption in the kidneys and a comparable excretion with menstruation blood (Fu et al., 2016). Occupational exposure in a PFOS plant in China results in serum levels of PFHxS in the range of 12.8-10546 ng/mL and geometric mean serum levels of 863 ng/mL. The branched isomers of PFOS, PFOA and PFHxS showed a faster renal clearance than the linear (Gao et al., 2015).

48. PFHxS is together with PFOS and PFOA, the most frequently detected PFAS in blood-based samples in the general population (Calafat et al., 2007; Olsen et al., 2008). PFHxS has been detected in human umbilical blood, serum and breast milk (Kärrman et al., 2007; Sundstrøm et al., 2011, Gutzkow et al., 2012). Concentrations in human breast milk ranges from 0.04 to 0.1 ng/mL (So et al., 2006; Kärrman et al., 2010). Serum levels of PFHxS in children has been reported to be greater than in adults (Calafat et al., 2007; Toms et al., 2009), serum levels reported are 1.2-77 ng/mL (Kärrman et al., 2007; Stubleski et al., 2016; Eriksson et al., 2017).

Conclusion on adverse effects according to the criteria in Annex D

49. Long-chained PFASs, including PFHxS are persistent and have long half-lives in organisms. Available experimental and epidemiological evidence indicate that PFHxS, its salts and PFHxS-related substances can cause adverse effects to human health and wildlife. Effects on the nervous system and brain development, effects on the endocrine system, including in particular the thyroid hormone system and metabolism have been reported. Globally, PFHxS is one of the most frequently detected PFAS in humans together with PFOS and PFOA. The very long elimination time of PFHxS in humans combined with its distribution to ground and drinking water, where also other PFAS such as PFOS are detected, are alarming. Together this give reasons for concern in particularly for foetuses, infants and young children as well as for adults and suggest a risk for mixture toxicity with other PFASs.

6. Statement of the reasons for concern and need for global action

50. Based on the existing data, PFHxS, its salts and PFHxS-related substances can be considered to meet the screening criteria in Annex D for persistence, bioaccumulation, long-range transport and adverse effects under the Stockholm Convention.

51. Due to its many applications and ongoing use, PFHxS is emitted into the environment from human activities e.g. from manufacturing processes, product use and disposal and management of waste. PFHxS, its salts and related substances are highly persistent, bioaccumulating and toxic, and have the potential to undergo long-range environmental transport, making emissions of these substances a transboundary pollution problem also in remote areas. Globally, the occurrence and distribution of PFHxS is shown for humans, a range of wildlife species other organisms and the environment. Detections include measurements in the Arctic and Antarctic. In humans, PFHxS is one of the most frequently detected PFAS in blood-based samples in the general population. This is of concern given that PFHxS has a very long half-life in humans (approximately 8 years) and that it has been detected in human umbilical blood, serum and breast milk. Furthermore, high concentrations of PFHxS have been detected in soil, ground and drinking water near airports or fire-fighting training sites.

52. Available scientific literature suggest that there is a risk for adverse effects on the general population, in particular for children and population groups that are exposed to elevated levels of PFHxS and other PFASs through drinking water. The concern for adverse effects relates to observed effects on endpoints involved in metabolism/metabolic homeostasis, the thyroid hormone system, as well as neurotoxic and neurodevelopmental effects. Although limited in number the available ecotoxicity studies combined with read-across from other PFASs provide highlights that similar effects may occur also in other organisms and that there is a potential for adverse effects also in wildlife.

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