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**Stockholm Convention  
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**Persistent Organic Pollutants Review Committee**

**Fourteenth meeting**

Rome, 17–21 September 2018

Item 4 (a) of the provisional agenda\*

**Technical work: consideration of a draft risk profile on  
perfluorohexane sulfonic acid (CAS No: 355-46-4,  
PFHxS), its salts and PFHxS-related compounds**

**Comments and responses relating to the draft risk profile on  
perfluorohexane sulfonic acid (CAS No: 355-46-4, PFHxS), its  
salts and PFHxS-related compounds**

**Note by the Secretariat**

As referred to in the note by the Secretariat on a draft risk profile on perfluorohexane sulfonic acid (CAS No: 355-46-4, PFHxS), its salts and PFHxS-related compounds (UNEP/POPS/POPRC.14/2), the annex to the present note sets out a compilation of comments and responses relating to the draft risk profile. The present note, including its annex, has not been formally edited.

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\* UNEP/POPS/POPRC.14/1.

## Annex

## Comments and responses relating to the draft risk profile on perfluorohexane sulfonic acid (CAS No: 355-46-4, PFHxS), its salts and PFHxS-related compounds

Minor grammatical or spelling changes have been made without acknowledgment. Only substantial comments are listed. Text in red denotes suggested insertions.

Source of Comment	Para	Comments on the third draft of the risk profile on PFHxS, its salts and PFHxS-related compounds	Response
Canada	13	Improvement to the document has been made in regard to articulating a framework as to when and how read across information is used for instance in section 2.2.1 in relation to the persistence. However, this is not evident for Section 2.2.2 Occurrence of PFHxS precursors and degradation and Section 2.4.1. Toxicity to aquatic organisms and birds.	Usage of read-across has been stated in section 2.2.1. Text has been added to Section 2.2.2 (see below) However, for section 2.4.1 it will not be correct to mention read-across as no predictions based on dose-responses from PFOS and PFBS were made/ used.
Canada	22	Any person who intends to import or manufacture a substance in Canada that is not listed to 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.	Text has been added.
Canada	47	"Taniyasu et al., 2013"; Suggest that, since we are doing a read-across approach, it should also be noted that some photodegradation did occur for PFOA, PFOS, 2 long-chain PFCAs (PFNA (C9) and PFDA (C10)), and one long-chain PFSA (PFDS, C10).	Some text added.
Canada	Sec. 2.2.2	Suggest to explicitly indicate that a read-across approach has been used for this section.	Text has been added.
Canada	Table 4	BMF/TMF data is also available from: Haukas M, Berger U, Hop H, Gulliksen B, Gabrielsen GW. 2007, Bioaccumulation of per- and polyfluorinated alkyl substances (PFAS) in selected species from the Barents Sea food web. Environmental Pollution 148: 360-371. Kannan K, Tai L, Sinclair E, Pastva SD, Jude DJ, Giesy JP. 2005. Perfluorinated compounds in aquatic organisms at various trophic levels in Great Lakes food chain. Arch Environ Contam Toxicol 48: 559-566. Naile JE, Khim JS, Hong S, Park J, Kwon B-O, Ryu JS, Hwang JH, Jones PD, Giesy JP. 2013. Distributions and concentration characteristics of perfluorinated compounds in environmental samples collected from the west coast of Korea. Chemosphere 90: 387-394. BSAFs in earthworms: Zhao S, Zhu L, Liu L, Liu Z, Zhang Y. 2013. Bioaccumulation of perfluorocarboxylates (PFCAs) and perfluoroalkane sulfonates (PFASs) by earthworms ( <i>Eisenia fetida</i> ) in soil. Environmental Pollution 179: 45-52. Zhao S, Fang S, Zhu L, Liu L, Liu Z, Zhang Y. 2014. Mutual impacts of wheat ( <i>Triticum aestiva</i> L.) and earthworms ( <i>Eisenia fetida</i> ) on the bioavailability of perfluoroalkyl substances (PFASs) in soil. Environmental Pollution 184: 495-501	Haukas et al 2007 is already reflected in the text (as Haukås). Kannan et al 2005 do not report any BMF for PFHxS (PFHS) only for PFOS. A reference to Naile et al 2013 has been added in para 57. Zhao et al 2013; 2014 and Felizeter et al 2012 have been referenced in para 57.

Source of Comment	Para	Comments on the third draft of the risk profile on PFHxS, its salts and PFHxS-related compounds	Response
		<p>Bioaccumulation uptake in plants:</p> <p>Felizeter S, McLachlan MS, de Voogt P. 2012. Uptake of perfluorinated alkyl acids by hydroponically grown lettuce (<i>Lactuca sativa</i>). <i>Environ Sci Technol</i> 46: 11735-11743</p> <p>Felizeter S, McLachlan MS, de Voogt P. 2014. Root uptake and translocation of perfluorinated alkyl acids by three hydroponically grown crops. <i>J Agric Food Chem</i> 62:3334-3342.</p>	
Canada	62	<p>Suggest mentioning that these half-lives are derived from men as it is known that half-lives of PFOS and PFOA in women are shorter because menstruation is an additional elimination pathway for women.</p> <p>Reference:</p> <p>Gomis et al., (2017) Historical human exposure to perfluoroalkyl acids in the United States and Australia reconstructed from biomonitoring data using population-based pharmacokinetic modelling. <i>Environ. International</i>, 108, 92-102.  <a href="https://doi.org/10.1016/j.envint.2017.08.002">https://doi.org/10.1016/j.envint.2017.08.002</a></p>	Text has been added.
Canada	Chap. 2.4	<p>Suggest to explicitly indicate the interpretation of endocrine disruption effects and how it supports hazard profile.</p> <p>For instance, there are references to effects associated with thyroid hormone and hormone receptor modulations. However, it is not clear if the interpretation is evidence of adverse effects or supporting information on toxicity.</p> <p>In the absence of an interpretation of these facts, it may still be useful to retain the data in the report but with a statement indicating the difficulties in interpreting these data. Doing so acknowledges that these types of “nontraditional” endpoints may be useful but present challenges in their interpretation.</p>	<p>No, we have not done any calculations and estimates based on dose response curves for PFOS and PFBS to predict PFHxS expected response so it would not be right to mention read across here.</p> <p>No statement was made for endocrine effects since it is believed that the audience are familiar with the different vulnerability in different life stages of an organism’s life and the importance of right hormones balance in developmental-windows.</p>
Canada	Chap. 2.4.1.	Suggest to explicitly indicate that a read-across approach has been used for this section.	<p>No, we have not done any calculations and estimates based on dose response curves for PFOS and PFBS to predict PFHxS expected responses so it would not be right to mention read across here.</p> <p>A general read-across has been made, as we are largely relying on data for PFOS and PFBS. However, this should be clear enough from the text itself with the latest editions.</p>
Canada	Chap. 2.4.4	<p>Suggest to explicitly indicate that results from mixture toxicity and combined effects of multiple stressors cannot be attributed to PFHxS alone.</p> <p>For example, in paragraph 105, testing was conducted where test system was dosed with a mixture heavily weighted to PFOS compared to PFHxS (91% vs 3.8%). It is not obvious in this case that the results can be attributed to PFHxS.</p> <p>There is an expectation that the total PFAS and PFCAs concentrations in biota remain higher than PFHxS, making read across challenging in attributing adverse effects solely to PFHxS.</p> <p>It is suggested that a statement be provided indicating the weight that should be attributed to such evidence.</p>	<p>Text has been amended.</p> <p>In this chapter controlled lab studies of mixtures (which include PFHxS in the mixture) are presented as well as environmental studies which correlate levels of PFHxS and other PFAS with observed effects. Many PFAS accumulating in biota has similar mode of action but different potency.</p> <p>There is not necessary to mention read-across in this section.</p>

Source of Comment	Para	Comments on the third draft of the risk profile on PFHxS, its salts and PFHxS-related compounds	Response
Japan	12	Further amendment is required using technical terms: PFHxS salts dissociate to give PFHxS anions and its cations in solution and other PFHxS-related compounds can degrade to PFHxS under environmental conditions and are therefore known as precursors.	Text has been amended.
Japan	52	We should discuss the criteria of degradation rate. Although we can anticipate that some PFHxS-precursors might degrade to some extent by Read-Across method, precursors with the half-life of e.g. hundreds of years should be excluded.	We do not exclude precursors that take a long time to degrade. If a precursor has the potential to degrade to PFHxS, no matter the time the degradation takes, it is included as a PFHxS-related compound. Theoretically, precursors with very long half-lives would be relevant in their own right or in a cumulative toxicity assessment on PFHxS toxicity/exposure
Japan	70	Further explanation is necessary. It is still doubtful whether detected PFHxS during snow melt and in rain water is derived from the precursors.	No changes made to the text. The statement in para 70 is made to support the possible long-range transport of PFHxS-precursors. Please make available literature that show indications/evidence that PFHxS-precursors are not subject to long-range transport and not degraded during snow melt and in rain.
Japan	Table 5	Before concluding that PFHxS-related compounds meet the criterion, Table of POP characteristics of PFHxS-related compounds would be also required.	The table only covers POP criteria of PFHxS (see also response below).
Japan	134	Before concluding that PFHxS-related compounds meet the criterion, Table of POP characteristics of PFHxS-related compounds would be also required.	PFHxS-related compounds are included in the statement because they can degrade to PFHxS which fulfils the criteria of the convention. The same wording was used when concluding on the draft risk profile for PFOA, its salts and PFOA-related compounds.
United Kingdom of Great Britain and Northern Ireland (UK)	General	<p>In many instances, more description needs to be provided for the different studies to understand their validity, endpoints and significance.</p> <p>We previously made the comment that <i>the quality, reliability and relevance of the various cited studies is unclear</i> [...]. The RCOM stated <i>All data included in the risk profile are peer-reviewed data</i>. For us it is insufficient to effectively assume data are valid simply because they have been published in the peer-reviewed literature. Given the UN Globally Harmonised System for classification, and the OECD Cooperative Chemicals Assessment Programme (whose outputs are published by the UN) both require data to be critically reviewed for validity (for example <a href="http://www.oecd.org/chemicalsafety/risk-assessment/49191960.pdf">http://www.oecd.org/chemicalsafety/risk-assessment/49191960.pdf</a>), we see no reason to use a different approach for the UN POPs programme. We also note that the heavily cited ECHA SVHC dossier (ECHA, 2017a) provided validity assessments of the studies used in that report.</p> <p>Therefore, please ensure that all data in the Risk Profile is critically reviewed by the dossier submitter, with a validity rating assigned to each study. In previous comments we suggested validity being assessed using Klimisch scores, or potentially CRED (<a href="https://setac.onlinelibrary.wiley.com/doi/full/10.1002/etc.3259">https://setac.onlinelibrary.wiley.com/doi/full/10.1002/etc.3259</a>).</p>	<p>First of all, the risk profile under Annex E of the SC is not a full risk assessment. The document is a risk evaluation that has a page limit of 20 pages and in this regard, it is not possible to provide a very detailed description of the studies referenced/used in the risk profile. However, all studies are from published peer reviewed papers or from reports provided in English. The evaluation of risk under the SC convention is very different from the SVHC/restriction process under REACH hence the level of detail and the approach is also very different from the REACH processes. Furthermore, we do not have a requirement to follow OECD guidelines or to use any score system to rate the peer reviewed studies used in the risk evaluations performed under the Stockholm Convention. The total amount of available data are evaluated using a "weight of evidence approach".</p>
UK	29	Based on paragraph 26, can you provide an estimate of the likely unintentional production of PFHxS compounds resulting from PFOS manufacture?	No not more accurate than the reported % that are already given in para 26.

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UK	29	Following the REACH registration deadline of 31 <sup>st</sup> May 2018, we recommend the dossier submitter checks for PFHxS registrations (as EU supply >1 t/y should then be clear) and include these data in the Risk Profile.	Comment noted.
UK	34	" <i>substantial stockpiles of legacy products</i> "; How likely is it that "substantial stockpiles of legacy products" will remain some 16-18 years since manufacture?	It is highly likely that there are "substantial stockpiles" present world wide. This could be both due to AFFF made using PFHxS and PFHxS-related substances in the fire-fighting foam intentionally and due to the use of PFOS AFFF which can have PFHxS as an unintentional content. The use of PFOS in AFFF is exempted under the Stockholm convention and some countries have it registered for this use. Furthermore, the shelf life of AFFF is 20 – 25 years, hence the concentrate can be available for a long time.
UK	58	Please provide more information on the cited BMF studies. In particular a number rely on extrapolation (for example liver to whole body). Please ensure the uncertainties are recognised in the description in the Risk Profile (which are discussed in ECHA, 2017a).	Paragraph 60 in the RP states "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)." The bioaccumulation criteria are evaluated using "weight of evidence" please see Annex E requirement in the convention for further details.
UK	61	"Houde et al 2006"; The TMFs in this study were considered to be invalid (Klimisch 3) in ECHA 2017a, which states <i>It is not, due to the limited reliability on the available data, possible to make a conclusion on bioaccumulation potential TMFs for PFHxS</i> . Please ensure the Risk Profile is consistent with that assessment.	See answer to comment above.
UK	61	"Munoz et al 2017"; If this paper indicates that trophic magnification occurs, these are important data. Therefore, please provide a full description of the study and an assessment of its validity.	See answer to question above and answer to the general comment at the top of the table.
UK	67	With respect to local sources, it would be helpful to discuss any contribution from visiting cruise ships as well as local sewage discharges in this section.	We are aware that there could be a contribution of many chemicals from cruise ships. However, we are not aware of any studies discussing contribution of PFHxS, its salt and PFHxS-related compounds in this regard. Some text regarding local sources has been added in 2.2.4 (para 68).
UK	73	" <i>Ubiquitous</i> "; Some summary of actual monitoring would be helpful here.	A number of exposure levels and monitoring data are listed in the tables in the Supplementary document.
UK	77	" <i>the levels increased towards the end of the time series (2014) with an average annual increase of 5%. However, the increase was not significant and with 95% probability the annual change varies between -1% per year to +11% per year</i> " Please delete this text. If the increase was not significant, these data should not be reported in the risk profile.	No changes made. The information is of value even though the increases are not significant within 95 % of the confidence interval. The text has been quality assured by the author to avoid any misunderstanding/wrong interpretation of the data.

Source of Comment	Para	Comments on the third draft of the risk profile on PFHxS, its salts and PFHxS-related compounds	Response
UK	93	To improve readability, we suggest splitting this paragraph so that there is a more general discussion of hypothesised effects in one paragraph, and a second paragraph discussing the specific data available for fish. It would also help to provide short discussion comparing the results of studies reported in NICNAS, 2015c (on PFOS) and the results of Chen et al, 2018c to show where there is a common effect – i.e. where interpolation of effects of PFHxS can reasonably be expected.	Done.
UK	93	<i>suggest a likelihood for adverse effects also in non-mammalian species (Giesy et al., 2010, Hagenaaers, et al., 2011; Ulhaq, et al., 2013)</i> Please specify which non-mammalian species are being referred to as the three references (based on their titles) all refer to Zebrafish studies. If there are no other species, please provide reasoning to explain why there is a likelihood for adverse effects in non-mammalian species. Please also indicate which substances or chain lengths were tested in these studies. Based on this information please then indicate whether there are consistent data for both PFBS and PFOS – i.e. whether interpolation of effects of PFHxS can reasonably be expected or not.	Giesy et al 2010 is a review article covering available aquatic toxicity studies for PFOS and PFBS (both acute and chronic for both freshwater and marine microorganisms, invertebrates, amphibian and fish). This section has been considerably reconstructed.
UK	93	NICNAS, 2015c Please provide details of the studies cited in the NICNAS report	This reference was deleted due to the difficulties to find the studies included in their assessment.
UK	93	Chen et al 2018c Please provide more description of this study, including the following: <ul style="list-style-type: none"> <li>• End points assessed</li> <li>• Concentrations run</li> <li>• Number of organisms</li> <li>• Exposure conditions</li> <li>• Details of chemical analysis</li> <li>• Statistical significance of effects observed</li> <li>• Any similarities to internationally recognized test guidelines, for example OECD 240.</li> </ul>	Due to the format of a traditional SC risk profile which has more in common with a review article than a full risk assessment (which often has several hundred pages) it is impossible to include all details for each study discussed. Concentrations used are already included "(0, 1.0, 2.9 and 9.5 µg/L)".
UK	93	Comment to Chen et al., 2018c Please only report statistically significant effects. Effects which are not statistically significant are not relevant for the risk profile.	Comment noted.
UK	93	Chen et al 2018c Please add text to indicate whether increased F1 mortality was observed in the PFBS study (i.e. as per the PFOS study described in the same paragraph). This is important to understand whether there is a consistency in effect to allow interpolation of effects for PFHxS.	Exposure doses in this study were determined in a preliminary experiment, where the hatching, mortality and malformation of medaka larvae were not changed significantly at 15 days post fertilization. This study was thus not conducted to look for mortality but subtler endocrine related effects that could have an impact in the environment.
UK	93	Chen et al 2018c Please consider whether other effects (i.e. not endocrine related) might have led to delayed hatching.	No other effects were considered for the delayed hatching in this paper.
UK	93	<i>Chen et al 2018c) but in the F1 larvae a significant increase in T3 was observed in 1 µg/L group</i> Please state whether any effect was observed at 2.9 or 9.5 µg/L? If not, please include a comment about how robust the observations at 1 µg/L are.	Full description of this study will not be included in the PFHxS risk profile. However, many endocrine responses are non-linear, and the response in the 1 µg/L group are supported by mRNA studies of relevant genes and the 1 µg/L

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			group had a different response than the two higher groups. A sentence of the dose response relationship has been added.
UK	93	<i>(Chen et al 2018c) Also, the F2 larvae TH disruption was exhibited with increased T4 levels.</i> Please indicate which treatment concentration(s) this was observed for.	Added.
UK	94	For clarity, please split this paragraph so that Hoover et al (2017) is described in one paragraph, and Lou et al (2013) is described in a second paragraph.	Done.
UK	94	Hoover et al 2017. This amphibian study is the only cited study exposing aquatic organisms to PFHxS, and there needs to be substantially more description of the test. As an absolute minimum, this should include the following: <ul style="list-style-type: none"> <li>• End points assessed</li> <li>• Concentrations run</li> <li>• Number of organisms</li> <li>• Exposure conditions</li> <li>• Details of chemical analysis</li> <li>• The level of delayed development</li> <li>• Statistical significance of effects observed</li> <li>• Any similarities to internationally recognized test guidelines, for example OECD 231 or 241.</li> </ul> Did this study include thyroid histology? Following the description of the test, please then provide a critical review of the study assessing its validity the weight that can be placed on the effects seen in the study. (also bearing in mind our next comment)	Some more details of the study have been included. However, due to the format of a risk profile all details cannot be provided. This study did not include histology. A critical review of each study included in the risk profile cannot be provided. However, this is a peer reviewed study.
UK	94	<i>One recent study observed delayed development in northern leopard frog (Rana pipiens) tadpoles exposed to 10 µg/L PFHxS</i> [Hoover et al 2017] We have only been able to obtain an abstract of this study. However, it suggests that concentrations of 10, 100, and 1000 µg/L were run in the test? If this is the case, were effects observed at the higher concentrations? How do the effects compare to those seen for other PFAS in the study?	Details were included.
UK	94	Lou et al (2013) Please provide the purity of the PFBS used in the study	No changes made to the text, but purity of PFBS was >98% in this study. No PFOS or PFHxS was detected in the PFBS water.
UK	94	Lou et al (2013) Please provide more description of this study. Please also provide more discussion of whether the effects observed indicate liver toxicity.	Liver toxicity was not discussed in depth in this study, and just brief description without numeric values was provided together with representative hepatohistology pictures from the different doses of PFOS and PFBS. Text has been amended to include some more details.
UK	94	<i>Lou et al (2013). Hepato-histology changes (hepatocyte degeneration and hepatocyte hypertrophy) was observed at high concentrations (100–1000 µg/L)</i> Please indicate which chemical(s) these effects occurred for.	Text has been amended.

Source of Comment	Para	Comments on the third draft of the risk profile on PFHxS, its salts and PFHxS-related compounds	Response
UK	95	<i>PFOS is much more toxic to chironomids which live in sediment environments with low oxygen and where effects on haemoglobin are more relevant.</i> Please indicate whether greater toxicity is observed to Chironomids for other chemicals under these conditions.	Comment noted but no changes made to the text as this was not discussed, the low oxygen is related to the environment the organism lives in.
UK	95	<i>Thus MacDonald et al., 2004, have concluded that PFOS toxicity thresholds for the chironomid Chironomus tentans are 2–3 orders of magnitude lower than those reported for other aquatic organisms</i> Please quantify the level of toxicity exhibited in <i>Chironomus</i> by PFOS. Please indicate whether any data exist for lower homologues, and provide a comparison as appropriate.	Text has been amended.
UK	95	<i>PFOS is also known to cause intergenerational toxicity to fish (Ji et al., 2008). No result for such studies are available for PFHxS but similar toxicity is quite possible.</i> These sentences should be moved to paragraph 93 as it discusses fish toxicity. Please also re-word as follows: <i>No result for such studies are available for PFHxS.</i> The risk profile should avoid speculation unless there is supporting evidence. In paragraph 93 you indicate that toxicity increases with chain length. Therefore, unless comparative effects have been observed in PFBS, it is not known whether similar or less effect will be seen with PFHxS. There is also a possibility that different trends are seen (i.e. PFHxS could be more toxic).	These paragraphs have been considerably restructured and rewritten.
UK	96	<i>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</i> Please be clear what specific effect is observed – changes in hormone or gene level, etc. This is particularly important for the effects at low concentrations. Given the LOEC in the next sentence is 890 ng/g w/w, what does the effect at 8.9 ng/g w/w represent?	Please see our nomination UNEP/POPS/POPRC.13.4 for more details. <a href="http://chm.pops.int/TheConvention/POPsReviewCommittee/Meetings/POPRC13/Overview/tabid/5965/Default.aspx">http://chm.pops.int/TheConvention/POPsReviewCommittee/Meetings/POPRC13/Overview/tabid/5965/Default.aspx</a>
UK	96	<i>Based on egg injection, the lowest observed effect concentration (LOEC) was 890 ng PFHxS/g ww for developing leghorn chicken embryos (Cassone et al., 2012b)</i> Please specify what endpoint the LOEC is for. Please provide more information on the study, for example: <ul style="list-style-type: none"> <li>• End points assessed</li> <li>• Concentrations run</li> <li>• Number of organisms</li> <li>• Exposure conditions</li> <li>• Details of chemical analysis</li> <li>• Statistical significance of effects observed</li> <li>• Any similarities to internationally recognised test guidelines</li> </ul>	Please see our nomination UNEP/POPS/POPRC.13.4 for more details or the original articles. Birds seems to be less sensitive than other species for the endpoints investigated, so no more details were added due to comments from other. LOEC was for plasma free T4 level, text was amended.
UK	96	<i>Cassone et al., 2012 a</i> Please provide a description of this study.	Please see our nomination UNEP/POPS/POPRC/13/4 for more details. <a href="http://chm.pops.int/TheConvention/POPsReviewCommittee/Meetings/POPRC13/Overview/tabid/5965/Default.aspx">http://chm.pops.int/TheConvention/POPsReviewCommittee/Meetings/POPRC13/Overview/tabid/5965/Default.aspx</a>
UK	96	<i>Vongphachan et al., 2011</i> Please provide a description of this study.	See above. Some information was added.

Source of Comment	Para	Comments on the third draft of the risk profile on PFHxS, its salts and PFHxS-related compounds	Response
UK	96	Please include a discussion for whether consistent effects are seen in the three studies ( <i>Cassone et al., 2012 a, Cassone et al., 2012 b, and Vongphachan et al., 2011</i> ).	Consistent effects were observed in these studies as they all are related to thyroid effects in common, and brain development.
UK	115	We suggest this paragraph is moved to section 2.3.1 as it discussed exposure to environmental organisms rather than under the mixture toxicity section.	The first part of the para was moved; however, the rest belongs in the mixture toxicity section.
UK	115	Please consider either splitting the paragraph, or restructuring it, so that the same effects are discussed together. At present neurotoxic effects, thyroid effects, etc., are mixed together, which makes the results difficult to follow.	Paragraph has been split to show thyroid effects separate.
UK	115	" <i>In the liver, PFHxS was found to be significantly higher in females (Greaves et al., 2012)</i> "; Please add text about whether the authors suggested any explanation for this observation.	Text added.
UK	115	" <i>Average brain sum PFAS was 28.8 ng/g ww, where PFOS accounted for 91% (PFHxS average 1.1 ng/g ww)</i> "; Please re-word this sentence as we find it confusing. Was the average concentration of the sum of PFAS 28.8 ng/g? Also, please use a consistent comparative unit – what percentage did PFHxS account for?	Text has been amended.
UK	115	" <i>Average brain sum PFAS was 28.8 ng/g ww, where PFOS accounted for 91% (PFHxS average 1.1 ng/g ww)</i> "; Is this a measurement made by Pedersen et al, 2015? If so please state this and indicate what correlation was seen for PFHxS	For the PFASs correlations were made between the sum PFASs and neurotransmitter enzymes or receptors, and in some cases PFOS alone. No change has been made to the text.
UK	115	" <i>...and indicate that PFAS contribute to possible alteration of the thyroid hormone homeostasis in polar bears (Bourgeon et al., 2017)</i> "; Please include an explanation of why possible alteration was concluded? Was there a reason that a more definitive conclusion could not be reached?	Text has been added.
UK	115	" <i>The results indicate that an increase in the concentration of certain PFASs concurs with an increase in brain steroid hormones (Pedersen et al., 2016).</i> "; Please specify which PFAS. Does this include PFHxS? Also, please then add a comment about interpolation (or not) to PFHxS if relevant	Some changes were made to the paragraph to clarify but it is related to the total load of bioaccumulative PFAS SUM PFASs (C4-C10, where PFOS account for 91%) and sum PFCAs (C6-C15, where PFUnDA and PFTrDA account for 22.4 and 38%, respectively of sum PFCAs)
UK	115	" <i>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).</i> "; Please specify which PFAS. Does this include PFHxS? Also, please then add a comment about interpolation (or not) to PFHxS if relevant	See above.
UK	115	" <i>PFHxS levels did not decline between 1998 and 2008...</i> (Bytingsvik et al., 2012)."; If they did not decline, please indicate what trend was observed	There is no trend. Measurements were done in 1998 and 2008 and the concentration has not changed during these 10 years.
UK	116	" <i>Certain PFASs contribute to the multiple-stressor effects observed in polar bears from Svalbard.</i> "; Please specify which PFAS. Also, please then add a comment about interpolation (or not) to PFHxS	Text has been added. Data is reported as sum of PFASs.
UK	116	"Tartu et al 2017"; Please be clear whether the effects observed are directly linked to PFHxS, to PFAS or to all organohalogenated compounds.	The effects are observed for a sum of all pollutant at "high" and "low" concentrations.

Source of Comment	Para	Comments on the third draft of the risk profile on PFHxS, its salts and PFHxS-related compounds	Response
UK	117	Please consider revising this paragraph as there is little mention of what adverse effects can be clearly related to PFHxS, or the significance.	Comment noted. No changes were made to the paragraph. PFHxS are detected in these animals and together with the other PFASs. In the body, it binds to proteins in the blood that also serves as transport and "buffer capacity" of the body to tolerate fat accumulating pollutants that will be released during starvation. It is highly plausible that the total mixture (including PFHxS) lead to adverse effects that add to the mixture toxicity effect.
UK	118	Please indicate whether the USA, German and European drinking water standards have been proposed based on a belief that PFAS act together as a mixture.	No, it is not based on calculation of additive effects of PFAS. It is based on available peer-reviewed studies most often on the effects of PFOA and PFOS since these substances are the most investigated PFAS. It is furthermore known that many PFASs are present at the same time and also very often reported as ΣPFAS.
UK	123	Please discuss the influence of any local source in this paragraph.	Although local sources are present at Svalbard these are at known locations, and measurements for long-range transport are taken at other locations to avoid the local sources. The polar bears in particular hunt at remote places.
UK	127	" <i>Effects on the endocrine system, including in particular the thyroid hormone system have been reported cross-species (frog, bird, rat, polar bear and human).</i> "; Paragraph 94 does not describe endocrine effects on frogs as a result of PFHxS exposure, therefore frogs should not be included here.	Frog has been removed, although it might be anticipated that the effects observed in Lou et al., 2013 for both PFOS and PFBS might be expected to occur for PFHxS also.
UK	127	" <i>Effects on the endocrine system, including in particular the thyroid hormone system have been reported cross-species (frog, bird, rat, polar bear and human).</i> "; Please differentiate between species where an adverse apical effect occurs compared to perturbation of hormones.	There are not enough studies to conclude in which species an adverse apical effect occurs compared to perturbation of hormones. However, effects are seen a cross-species indicating concern considering the persistent and bio accumulative behavior of this substance.
UK	Table 5	" <i>Delayed development in northern leopard frog (Rana pipiens) tadpoles exposed to 10 µg/L PFHxS for 40 days (Hoover et al., 2017).</i> "; Please update this remark following our comments this study (paragraph 94).	No changes made.
UK	132	" <i>The concern for adverse effects relates to observed effects on the liver, thyroid hormone system, reproduction, as well as neurotoxic and neurodevelopmental effects has been shown</i> "; Please modify this sentence to note which animals the effects have been observed in.	No changes made to the text, this is related to the table above.
UK	132	" <i>Furthermore, effects on lipid and lipoprotein metabolism add to the concern both for humans and Arctic animals</i> "; Is there evidence that <i>effects on lipid and lipoprotein metabolism</i> occur in Arctic animal due to PFHxS?	Tartu et al., 2017b, showed that PFAS exposure was related to biomarkers of energy metabolism (lipid-related genes, fatty acid synthesis and elongation in adipose tissue, and serum cholesterol, HDL and triglycerides). Although PFOS levels in polar bear are higher than PFHxS levels, both PFOS and PFHxS have shown this type of effects in controlled rodent experiments so it is highly likely that PFHxS contributes to the effects observed.

Source of Comment	Para	Comments on the third draft of the risk profile on PFHxS, its salts and PFHxS-related compounds	Response
UK	133	" Furthermore, studies of polar bears have shown possible alteration in thyroid hormones due to exposure of some PFASs (including PFHxS)."; Please delete this sentence as this does not demonstrate a risk of adverse effects.	This is related to the study of Bourgeon et al., (2017). Due to the climate and tough conditions for these animals and the importance of thyroid hormones to orchestrate metabolic responses in an organism, alterations may add a burden to the organism in vulnerable stages.
UK	133	" Delayed development in frog tadpoles exposed to PFHxS has also been observed."; Please update this text following our comments this study (paragraph 94).	Sentence removed.
UK	Over-all	Re-iterating our comment in a previous commenting round, while we agree that PFHxS is highly persistent and has bioaccumulative properties of concern, we would like to see a more transparent description of the adverse effects and comparison with exposure levels before we would agree that there is a significant risk to wildlife.	An exercise comparing exposure levels and adverse effects is not mandatory in the risk profile under the SC convention. Furthermore, Article 1 of the Convention states "Mindful of the precautionary approach as set forth in Principle 15 of the Rio Declaration on Environment and Development, the objective of this Convention is to protect human health and the environment from persistent organic pollutants". There are limited data on ecotoxicity for PFHxS, however, toxicity data from rodents indicate that PFHxS has mode of actions relevant across species. In the Convention Text Article 8 para graph 7 a) state that: "Lack of full scientific certainty shall not prevent the proposal from proceeding."
International POPs Elimination Network/ Alaska Community Action on Toxics (IPEN/ACAT)	33	Add text: "Studies of PFAS in food packaging materials as well as sources of dietary exposure has detected PFHxS in non-stick surfaces of paper materials and in tinned food stuffs that might indicate intentional use".	Reference added in para 40.
IPEN /ACAT	34	" It is likely that such PFHxS-related compounds containing "PFOS-based AFFFs" have been discontinued after 3M ceased its global production in 2000–2002 (3M, 2000a)". This statement should be verified using independent sources or removed, noting that very little information has been supplied by relevant industries that may still produce these.	Text has been edited.
IPEN /ACAT	36	" It is likely that such aftermarket carpet and upholstery protector products PFHxS-related compounds containing "PFOS-based AFFFs" have been discontinued after 3M ceased its global production in 2000–2002 (3M, 2000a)". This statement should be verified using independent sources or removed, noting that very little information has been supplied by relevant industries that may still produce these.	Text has been edited.
IPEN /ACAT	35	Suggested text: "PFHxS has also been detected in carpeting in several other studies. In a study in the Faroe Island, fully or partially carpet covered floors were associated with 37.2% increase in serum PFHxS concentrations in children. "	Text added.
IPEN /ACAT	40	Suggested text: "PFHxS has been detected in various food packaging materials or traced to food packaging through dietary studies such as canned food, fast food packaging and paper food packaging."	Reference added.

Source of Comment	Para	Comments on the third draft of the risk profile on PFHxS, its salts and PFHxS-related compounds	Response
IPEN /ACAT	80	Please add: " Also, 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 repellants. (Kingsley et al., 2018) <a href="https://www.sciencedirect.com/science/article/pii/S0013935118302354">https://www.sciencedirect.com/science/article/pii/S0013935118302354</a>	Text added in another para (new 85).
IPEN /ACAT	81	Please add: "There is evidence that food packaging materials constitute a source of human PFHxS exposure."	Text inserted.
IPEN /ACAT	87	The exposure of toddlers and infants to PFHxS through various routes is especially concerning given that they are especially vulnerable to the harmful effects of PFAS exposure. It also underscores the importance of assessing the combined PFAS exposure (see further below on this issue). <a href="https://pubs.acs.org/doi/abs/10.1021/acs.est.7b06044">https://pubs.acs.org/doi/abs/10.1021/acs.est.7b06044</a>	Text not added, since the reference does not give any further understanding of PFHxS exposure to children that is not yet reflected in the text
IPEN /ACAT	113	Please insert: "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." <i>While a general consideration, this is an important point to make. Ref already in list: K. Winkens et al. / Emerging Contaminants 3 (2017) 55e68</i>	Text inserted.
IPEN /ACAT	125	Exposure to PFHxS through dust from carpeting is a prominent source of exposure to toddlers.	Text added.
Inuit Circumpolar Council (ICC)	6	Worldwide monitoring of water, air, sediment and biota (including humans) at remote locations	Text added.
ICC	30	« Stakeholder » is very unclear term here. Is industry meant?	Text added.
ICC	Chap. 2.1.3	You may want to consider this paper (just came out): Skaar et al. 2018 Elucidation of contamination sources for poly- and perfluoroalkyl substances (PFASs) on Svalbard (Norwegian Arctic). Environmental Science and Pollution Research. <a href="https://doi.org/10.1007/s11356-018-2162-4">https://doi.org/10.1007/s11356-018-2162-4</a>	Text added to section 2.2.4 and reference added.
ICC	62	As stated elsewhere, half- lives have been found to be different based on gender. Therefore, suggest mentioning that these half-lives are derived from men. Good paper about trends and human exposure and elimination of PFHxS: Gomis et al., (2017) Historical human exposure to perfluoroalkyl acids in the United States and Australia reconstructed from biomonitoring data using population-based pharmacokinetic modelling. Environ. International, 108, 92-102. <a href="https://doi.org/10.1016/j.envint.2017.08.002">https://doi.org/10.1016/j.envint.2017.08.002</a>	Text has been added.
ICC	64	" The tissue distribution of PFHxS in humans is similar to what is observed in other mammals"; Can you specify which ones since it seems to be very different for mammals generally as you point out above.	Text has been added.
ICC	65	Probably should also reference the additional information table here. It is listed one sentence later but	Text has been edited.

Source of Comment	Para	Comments on the third draft of the risk profile on PFHxS, its salts and PFHxS-related compounds	Response
		it is not quite clear that this also includes Arctic data, which also includes humans living in the Arctic.	
ICC	80	Insert: "...", increased use of stovetop Teflon cookware and preheated packaged foods" Hu et al. 2018. Can profiles of poly- and Perfluoroalkyl substances (PFASs) in human serum provide information on major exposure sources? Environmental Health. 17:11 DOI 10.1186/s12940-018-0355-4	Text has been amended.
ICC	81	Insert: " which is agreement with findings of a study of dietary PFC exposure from traditional foods of Inuit in Nunavut, Canada (Ostertag et al 2009) Ostertag et al 2009. Estimated dietary exposure to fluorinated compounds from traditional foods among Inuit in Nunavut, Canada. Chemosphere Volume 75, Issue 9, May 2009, Pages 1165-1172, <a href="https://doi.org/10.1016/j.chemosphere.2009.02.053">https://doi.org/10.1016/j.chemosphere.2009.02.053</a>	This study did not include PFHxS so text was not amended.
ICC	88	Include reference from Gebbink et al. 2015 on PFHxS in Swedish serum from 1997-2012. Temporal changes (1997-2012) of perfluoroalkyl acids and selected precursors (including isomers) in Swedish human serum. Environ Pollut, 199, 166-173. <a href="http://dx.doi.org/10.1016/j.envpol.2015.01.024">http://dx.doi.org/10.1016/j.envpol.2015.01.024</a>	Study was included.
ICC	110	Should also include Grandjean et al 2017. Serum Vaccine Antibody Concentrations in Adolescents Exposed to Perfluorinated Compounds. <a href="https://doi.org/10.1289/EHP275">https://doi.org/10.1289/EHP275</a> . « 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. » and « 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. »	Text has been amended.
ICC	110	Missing? In Timmermann et al 2017: The interaction between MMR vaccination and age-5 PFAS was significant for PFOA, PFNA, and PFDA in relation to asthma at ages 5 and 13 and for PFHxS in relation to asthma at age 5 (Table 2).	Text has been rewritten, however, wording was selected to focus on PFASs and not the MMR vaccine impact.
ICC	110	"..., but could be chance findings " -As stated by the authors.	Added.
ICC	115	Comment to Graves et al., 2012. - Shouldn't this be moved to the section of levels in biota?	Moved to section 2.3.1
ICC	123	Including humans	Added
ICC	Table 5	Include other Grandjean 2017 study? and Timmermanns et al., 2017	Added.
POPRC member 1 (Ms. Ingrid Hauzenberger)	4	In addition, releases due to use of aqueous film-forming foams (AFFFs) containing PFHxS and PFHxS-related compounds such as FHxSA <b>have occurred based on contamination with PFHxS especially in the vicinity of fire-fighting training areas as a result of the historical (and ongoing) use of PFHxS-containing foams...</b>	Some text has been added. But the text in red was not added due to the fact that FHxSA itself has been detected in the vicinity of fire-fighting training areas and not only through the detection of PFHxS itself. See section 2.2.2.
POPRC member 1	5	"5.3 - 35 years half-life"; This is an extreme value, it would be beneficial to have some more explanation also in the summary	No text has been added in the Executive summary but an explanation has been given in para 63.

Source of Comment	Para	Comments on the third draft of the risk profile on PFHxS, its salts and PFHxS-related compounds	Response
POPRC member 1	9	Comment to fertility index: Please substantiate this statement concerning fertility by detailed analyses of dose-response and statistical significance. Please note that the OECD T422 is a reproduction/developmental toxicity <b>screening</b> test, though more animals were used per dose level	Comment noted, text has been modified.
POPRC member 1	9	Comment to thyroid effects: Please state if the mechanistic information was derived from in-vitro systems	This sentence reflects results from both in vitro and in vivo. No change made to the text.
POPRC member 1	97	Comment to Butenhoff 2009: " absolute and relative liver weight in male rats and hepatocellular hypertrophy." Statistically significant at 3 mg/bw/d	Text has been amended.
POPRC member 1	98	Insert: "in transiently transfected COS1 cells"	Text has been amended.
POPRC member 1	98	Comment to Rosen 2017: The paper uses also Toxcast information indicating ERalpha binding of all four investigated PFAS (PFOS, PFHxS, PFOA, PFNA	Comment noted, however no change made to the text.
POPRC member 1	99	Is this the only study reporting hematopoietic effects? If yes, please state and include an interpretation of these effects and the magnitude to allow an interpretation	Text has been amended.
POPRC member 1	100	Also, female was dosed	Text has been amended.
POPRC member 1	100	Comment to "A LOAEL of 3 mg/kg bw/d was shown for hyperplasia of thyroid follicular epithelial cells." - Why didn't you select the NOAEL? It should be mentioned that the authors did not report NOAEL or LOAEL values in the publication	Wording amended. Since some incidence of mild alterations were observed in the control group, a LOAEL seems more appropriate.
POPRC member 1	100	Comment to " PFHxS did also dose-dependently inhibit triiodothyronine (T3)-dependent cell growth in vitro from 10 <sup>-8</sup> Molar (Long et al., 2013)." -This sentence should be improved to better reflect the findings from this investigation: Because the basic mechanism of the decrease of GH3cell proliferation compared to solvent control is not clear probably it is better to report the competitive effect of PFHxS with T3: e.g. « In the T-screen assay PFHxS competitively decreased the T3-induced proliferation of GH3 cells at lower concentrations but increased cell proliferation at higher concentrations"	Text has been amended.
POPRC member 1	101	Comment to litter size: - Please add that clear dose-response relationship was lacking	Text has been added.
POPRC member 1	102	Please see my previous comment on fertility in the executive summary	Comment noted. Text amended.
POPRC member 1	102	Please note that the study authors concluded in de Witt, 2015 and Lee and Viberg, 2013 that this effect occurred at the highest dose.	Text has been edited
POPRC member 1	102	Levels of several proteins important in the brain growth spurt <b>indicative of normal brain development and cognitive function</b> were affected 24 h after exposure, and taurine levels in <b>the cerebral cortex</b>	Details have been included.
POPRC member 1	104	Endocrine <b>modalities</b> <del>disrupting activity</del> has have been <del>observed</del> <b>investigated</b>	Text was amended.
POPRC member 1	104	Cf. Rosen et al. ERalpha ?	Rosen et al 2017 was not included due to references used for estrogen receptor antagonists did not include PFHxS,

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			However, reference to Kjeldsen and Bonefeld-Jørgensen 2013 is valid.
POPRC member 1	108	Please insert : Rapazzo et al. (2017) could not reach a conclusion based on the systematic review of epidemiological literature on thyroid studies due to limited studies and variability in responses for PFAS. <a href="https://www.ncbi.nlm.nih.gov/pubmed/28654008">https://www.ncbi.nlm.nih.gov/pubmed/28654008</a>	Text not added due to conclusion based on PFAS and do not explicitly mention PFHxS. There are also very limited number of studies for thyroid effects in children, as this review only looked at studies prenatal and children data.
POPRC member 1	109	You might consider the findings from the following paper in this section: Vuong AM, Yolton K, Webster GM, Sjodin A, Calafat AM, Braun JM, et al. 2016. Prenatal polybrominated diphenyl ether and perfluoroalkyl substance exposures and executive function in school-age children. Environmental research 147:556-564. Cohort, United States, n = 256 No associations between PFHxS and neurodevelopmental outcomes	Study included.
POPRC member 1	110	Comment on Grannum et al., 2013 -Please check if the association was adjusted for potential confounders	This study had thorough analysis of confounders, however they were kept in the multivariate analysis if they contributed. From the article: "Poisson regression analyses were used for health outcomes consisting of count data (number of episodes of common cold), otherwise logistic or linear regression analyses were applied on binary and continuous health outcomes, respectively. Multivariate regression analyses were performed when the p-value was $\leq 0.1$ in bivariate analyses between the different health outcomes and the concentration of PFAS. Potential confounding variables were extracted from BraMat and MoBa questionnaires (~15th and 30th week of gestation and ~6 months after delivery; Version 5 of the quality-controlled data files) and the Medical Birth Registry of Norway. The criterion for inclusion of potential confounding factors in the multivariate regression analysis was $p \leq 0.25$ in the bivariate analysis between the confounding variable in question and both PFAS concentrations and health outcomes. Variables found to be potential confounders were older siblings, previous breastfeeding (number of months with breastfeeding of older siblings), maternal and paternal allergy, paternal asthma, maternal education, gross income of the household, birth season, child's gender, and/or child's age at the 3-year follow-up (for vaccination responses and allergen-specific IgE only). Older siblings and previous breastfeeding were highly correlated ( $r=0.82$ ). Therefore, in analyses where 41 of these variables were shown to be potential confounders, only previous breastfeeding was included in the multivariate model. Additional variables initially evaluated for

Source of Comment	Para	Comments on the third draft of the risk profile on PFHxS, its salts and PFHxS-related compounds	Response
			confounding effects were: APGAR score after 1 min, passive smoking for the child, child's age when starting at a day-care centre, breastfeeding of the index child, maternal asthma, maternal body mass index (BMI; before pregnancy), maternal age at the time of delivery, maternal passive smoking during pregnancy, and maternal smoking during the last 3 months before pregnancy. For all regression models, a manual backward deletion method was used, starting with all included variables in the model. At each deletion step, the least significant confounding variable was manually removed until only statistically significant ( $p \leq 0.05$ ) variables remained in the model. For logistic regression analyses, Hosmer-Lemeshow test, Cook's D, and residuals were used to investigate the robustness of the models, whereas for Poisson and linear regression analyses, Cook's D, and residuals were used."
POPRC member 1	110	You may also consider Humblet et al. (2014), that reported no associations with asthma for PFHxS in a cross-sectional study in the United States (n = 1877). <a href="https://www.ncbi.nlm.nih.gov/pubmed/24905661">https://www.ncbi.nlm.nih.gov/pubmed/24905661</a>	Study included.
POPRC member 1	110	Please insert: Grandjean et al., 2012, observed odds ratios <b>in a well conducted cohort study</b> of 1.78	Added
POPRC member 1	120	concerning on-going production?	Text edited.
POPRC member 1	122	.. in numerous <b>environmental</b> matrixes	Text edited.
POPRC member 1	122	... persistent to <del>environmental and biological</del> <b>abiotic and biotic</b> degradation.	Text edited.
POPRC member 1	Table 5	and <b>may impair</b> neuro development.	Text inserted.
POPRC member 1	Table 5	... NOAELs of <del>0.3</del> <b>1</b> mg/kg bw/	Text edited.
POPRC member 1	Table 5	Please see my previous comments to litter size and fertility index	Text was edited.
POPRC member 1	Table 5	Comment to epidemiology studies on thyroid hormones: - Please reflect here that positive and negative associations were observed	Wording has been modified.
POPRC member 1	Table 5	Delete Chen et al 2011	Done.
POPRC member 2 (Mr. Martien Janssen)	General	Thanks to the drafters for a good piece of work. Almost 20 pages of literature indicates that a lot of work has been done. Together with PFOS and PFOA, PFHxS is one of the perfluorinated substance most measured and together with those two it shows the highest environmental concentration. Kato et al (2015), chapter 3 in DeWitt (2015) Toxicological Effects of Perfluoroalkyl and Polyfluoroalkyl Substances provides a nice overview of the concentrations of these three substances in the General population. It also shows the relative abundance of these three substances in serum, which coincides with the production volumes. PFOS production was probably	Comment noted. Measurements reflecting the amount of PFHxS in AFFF from the publications mentioned in the text has been added in para 34 (AFFFs for firefighting). Regarding book chapters Kato et al 2015 and DeWitt et al 2015 we were not able to retain these before the submission dead line of the risk profile. If relevant information is contained in these chapters they may be added at POPRC14.

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		<p>10-20 times larger than PFHxS production, at least when I compare the amount in para 29 with the 3M production volumes for PFOS which were between 3500 and 4500 tonnes a year in the 90s. I would recommend making use of the work mentioned above and indicate that PFHxS concentrations are often a factor of 10 lower than PFOS and in the same range as PFOA to put the current state of play around PFHxS in perspective.</p> <p>For quite some applications there are hardly any data. For a number of applications, it is not clear whether PFHxS has been applied on purpose, or whether it is present as an impurity (I expect that that is the case in firefighting foam). Where data are available, e.g. the fire fighting foams, use such data and provide them, try to indicate the amounts and to draw a conclusion.</p>	
POPRC member 2	29	Interesting to note that production of PFOS was about 3500 – 4500 tonnes per year in that period, see: UNEP-CHW-SUBM-GUID-TGsPOPsWastes-PFOS-UNEPChemicals-RefJunHuangChina-201310.English	Comment noted.
POPRC member 2	AFFF	See also data submitted during the EU PFHxS public opinion by Mineraloelwirtschaftsverband, Industry or trade association, Germany <a href="https://echa.europa.eu/documents/10162/d8329daf-93ea-4358-a70a-80b2960ad1a2">https://echa.europa.eu/documents/10162/d8329daf-93ea-4358-a70a-80b2960ad1a2</a>	Comment noted. Submission is in German.
POPRC member 2	34	I think Olsen et al 2005 should be cited more correctly. Olsen does not say that PFHxS was used, but that PFOS was used and that PFHxS was formed in the production of PFOS. Olsen further remarks: « These fluorochemical residuals were typically present at a concentration of < 1% in the final commercialized products ». When I look at the measurements, e.g. in Backe et al 2013, it is often much less than 1%.	<p>Text has been edited to reflect Olsen et al 2005 correctly; "3M produced PFHS as a building block for compounds incorporated in fire-fighting foams."</p> <p>Regarding comment on the "1% in the final..." the comment has been noted but information was not given in the third draft of the risk profile. However, measured amounts of PFHxS in AFFF from the referenced papers have now been added to the text and from these numbers is it indicated that the content is &gt; 1%. However, we would not consider these 'residuals', they are the intended concentrations in the manufactured products. Intended levels can be up to 5% but can be down around 0.5%</p>
POPRC member 2	34	"with measurements of legacy AFFF formulations" Please provide these measurements and have also a look at Backe et al 2013 which provides data on five 3M foams from 1989 to 2001. Yes, they do contain PFHxS, however concentrations are about 1/10th of the PFOS ones.	<p>The text has been edited because "measurements of legacy..." did not necessarily mean that PFHxS concentration was analysed (in all these papers referenced), rather it meant that PFHxS-related compounds had been identified. See new text.</p> <p>Measurements from the publications have been provided in the text.</p>
POPRC member 2	Other potential use	The Netherlands submitted information on emissions to water by Agfa-Gevaert which suggest that PFHxS has been used there as well.	Text added.
POPRC member 2	52	Wang et al 2014 does not report on the biotic degradation to PFHxS.	<p>There was a mistake in the reference list, the correct Wang et al 2014 is now cited.</p> <p>Wang Z, Cousins IT, Scheringer M, Buck RC, Hungerbühler K (2014). Global emission inventories for C4-C14 perfluoroalkyl carboxylic acid (PFCA)</p>

Source of Comment	Para	Comments on the third draft of the risk profile on PFHxS, its salts and PFHxS-related compounds	Response
			homologues from 1951 to 2030, part II: the remaining pieces of the puzzle. Environ Int. 2014 69:166-76.
POPRC member 2	52	The subtitle of the report from the Norwegian Environment Agency is « Literature study and theoretical assessment of abiotic degradation pathways leading to PFBS and PFHxS”. This suggest that the report does not contain any statement on biotic degradation. Further the report states: «The overall objective of the present project is to summarize relevant information available in the open literature to provide an overall assessment of relevant precursors including possible grouping, and to evaluate possible routes to provide documentation, where missing, on the potential of abiotic degradation resulting in PFBS and PFHxS. » Please delete the reference to the Norwegian Environment Agency 2017.	Text has been edited and reference moved (not deleted) to better reflect the text in para 52.
POPRC member 2	55	"Detection of PFHxS precursors is in line with what has been detected for precursors of PFBS and PFOS in other matrixes” What do the authors try to say here?	Text have been modified. The sentence was meant to reflect data from Allred et al., 2014
POPRC member 2	62	"which is the longest of all PFASs for which data are available." This depend on which PFAS have been studied. Better refer to PFOS and PFOA.	No changes made. We are referring to the half-life for PFHxS which has by far the highest half-life of any PFAS where data are presently available.
POPRC member 2	94	Comment to Lou et al., 2013. -Why is this effect attributed to the impurity of PFHxS and not to the PFOS? If there is no good explanation remove the text.	Text has been amended to clarify that observed effects should be anticipated to be a result of PFOS exposure. However, information on the PFHxS presence is still relevant to mention.
POPRC member 2	95	This is a scientific document. The last sentence is pure speculation unless a clear read across explanation is provided. Please skip the paragraph.	Sentence has been removed and paragraph has been rewritten.
POPRC member 2	96	Comment to bird studies: - Are these realistic exposure amounts?	No, however, the effect on gene expression was observed in avian primary neuronal culture in concentration range 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)
POPRC member 3 (Ms. Tamara Kukharcyk)	8	PFDS	Edited.
POPRC member 3	44	To add the ref. Ahrens et al., 2015 in the sentence: " 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)." Ahrens, L., Norstrom, K., Viktor, T., Cousins, A.P., Josefsson, S., 2015. Stockholm Arlanda Airport as a source of per- and polyfluoroalkyl substances to water, sediment and fish. Chemosphere 129, 33-38.	Reference added.

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POPRC member 4 (Mr. Andreas Buser)	Table 2	The asterisk note in Table 2 does not match the pKa as there are always neutral and ionic forms involved. Hence, the asterisk in the pKa row of the table needs to be removed.	Changes made.
POPRC member 4	Table 2	In Table 2, I suggest changing “Water solubility for PFHxSK” to read “Water solubility”. Accordingly, “1.4 g/L (20–25°C)” may be changed to read “1.4 g/L (PFHxSK, 20–25 °C)”. Like that it matches the second value that was estimated for the non-dissociated form of PFHxS (i.e. not PFHxSK).	Changes made.