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Helsinki, 11 February 2019

Substance name: 3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl acrylate
EC number: 241-527-8
CAS number: 17527-29-6
Date of Latest submission(s) considered[1]: 21 March 2017
Decision/annotation number: (SEV-D-XXXXXXXXXX-XX-XX/F)
Addressees: Registrant(s)[2] of 3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl acrylate

DECISION ON SUBSTANCE EVALUATION

1. Requested information

Based on Article 46(1) of Regulation (EC) No 1907/2006 (the 'REACH Regulation'), you are requested to submit the following information:

1.1 a **fish sexual development test** (FSDT); test method: OECD 234, as specified in Appendix 1 using the metabolite/transformation product 6:2 fluorotelomer alcohol (6:2 FTOH, 3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctan-1-ol, EC number: 211-477-1, CAS number: 647-42-7)

1.2 an **amphibian metamorphosis assay** (AMA); test method: OECD 231, as specified in Appendix 1 using the metabolite/transformation product perfluorohexanoic acid (PFHxA, undecafluorohexanoic acid, EC number: 206-196-6, CAS number: 307-24-4)

1.3 **further information on uses and environmental release estimations** for the registered substance, as specified in Appendix 1

You have to provide an update of the registration dossier(s) containing the requested information, including robust study summaries and, where relevant, an update of the Chemical Safety Report by **18 August 2020**. The deadline takes into account the time that you, the Registrant(s), may need to agree which of the registrant(s) will perform the required tests.

The reasons of this decision are set out in Appendix 1.

The procedural history is described in Appendix 2.

Further information, observations and technical guidance as appropriate are provided in Appendix 3.

Appendix 4 contains a list of registration numbers for the addressees of this decision.

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[1] This decision is based on the registration dossier(s) at the end of the 12 month evaluation period

[2] The terms Registrant(s), dossier(s) or registration(s) are used throughout the decision, irrespective of the number of registrants addressed by the decision.

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This appendix is confidential and not included in the public version of this decision.

2. Who performs the testing

The tests under 1.1 and 1.2 are also required in the separate substance evaluation decision for EC 218-407-9, 3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl methacrylate, following substance evaluation of this substance. Therefore, the addressees of this decision are required to coordinate with the addressees of the decision on EC 218-407-9.

Based on Article 53 of the REACH Regulation, you are requested to inform ECHA who will carry out the study/ies on behalf of all Registrant(s) within 90 days. Instructions on how to do this are provided in Appendix 3.

3. Appeal

This decision can be appealed to the Board of Appeal of ECHA within three months of its notification. An appeal, together with the grounds thereof, shall be submitted to ECHA in writing. An appeal has suspensive effect and is subject to a fee. Further details are described under http://echa.europa.eu/regulations/appeals

Authorised[3] by Christel Schilliger-Musset, Director of Hazard Assessment

[3] As this is an electronic document, it is not physically signed. This communication has been approved according to ECHA's internal decision-approval process.

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Appendix 1: Reasons

Based on the evaluation of all relevant information submitted on 3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl acrylate (6:2 fluorotelomeracrylate, 6:2 FTA) and other relevant available information, ECHA concludes that further information is required in order to enable the evaluating Member State Competent Authority (MSCA) to complete the evaluation of whether the substance constitutes a risk to human health and the environment.

The evaluating MSCA will subsequently review the information submitted by you and evaluate if further information should be requested in another decision to clarify the concern, according to Article 46(3) of REACH.

It is noted that in August 2018 the German MSCA prepared a proposal for identification of a Substance of Very High Concern (SVHC) for PFHxA, (EC 206-196-6, CAS 307-24-4) and its ammonium salt (ammonium undecafluorohexanoate, EC 244-479-6, CAS 21615-47-4). The proposal is for SVHC identification according to Article 57(f) of REACH and addresses separate concerns to the ED concerns addressed in this decision.

In this decision, an OECD 231 test is requested on PFHxA to clarify the specific concern for endocrine disruption via the HPT axis as a metabolite of the registered substance 6:2 FTA. More certainty on the long-term effects of PFHxA is needed to better describe the risk. This would help to further specify relevant regulatory risk management measures.

General considerations

For 6:2 fluorotelomeracrylate (6:2 FTA), no data on endocrine disrupting properties are available. Benninghoff et al. (2011) assessed the *in vitro* binding properties of 8:2 FTA, which is a longer-chain homologue of the structurally related compound 6:2 FTMA, to trout hepatic estrogen receptor (ER) up to 1mM finding no binding in a competitive assay with estradiol (E2). Therefore, the **concern on 6:2 FTA endocrine properties was not substantiated**.

Concerns for endocrine disruption have been identified for metabolites/transformation products of 6:2 FTA: 6:2 fluorotelomer alcohol (6:2 FTOH; 3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctan-1-ol; EC number: 211-477-1; CAS number: 647-42-7) and perfluorohexanoic acid (PFHxA; undecafluorohexanoic acid; EC number: 206-196-6; CAS number: 307-24-4).

It is noted that 6:2 FTOH is registered under REACH as a transported isolated intermediate. The evaluating MSCA has reviewed the information available in these registration dossiers and in the open literature for the purposes of this substance evaluation.

The following chapters give evidence to justify the formation of 6:2 FTOH and PFHxA from the evaluated substance 6:2 FTA in the environment and in organisms and their occurrence in the environment is shown.

Environmental degradation of 6:2 FTA to 6:2 FTOH and PFHxA

6:2 FTA is not readily biodegradable. No simulation tests are available. Nevertheless, the microbial transformation of the structurally similar substance 8:2 FTA (two more CF_2-groups) was investigated in aerobic soil (Royer et al., 2015). 8:2 FTA was hydrolysed at

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the ester linkage with formation of 8:2 FTOH. 8:2 FTOH was further degraded to PFOA, which was the main stable transformation product at the end of the study (formation of PFOA: 8 mol% in 105 days). After 105 days approximately 50 mol% of intermediates and stable transformation products were observed.

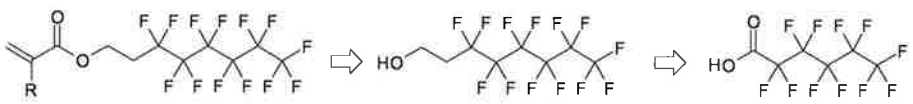
There are no indications showing differences in the transformation pathway of 8:2 FTA compared to 6:2 FTA. In analogy to the formation of 8:2 FTOH and PFOA from 8:2 FTA, for 6:2 FTA formation of PFHxA via 6:2 FTOH is expected. A number of studies on degradation of 6:2 FTOH show formation of PFHxA and other short-chain perfluoroalkyl carboxylic acids (PFCAs) as stable transformation products. Degradation pathway is the same as suggested for the degradation of 8:2 FTOH and subsequent formation of PFOA.

In a flow through soil incubation system dosed with [^{14}C] 6:2 FTOH, 4.5% PFHxA was formed after 84 days (Liu et al., 2010b). In a further study the authors investigated the aerobic biodegradation of 6:2 FTOH in a closed soil system and in mixed bacterial culture (activated sludge from an industrial wastewater treatment plant mixed with nutrient medium) (Liu et al., 2010c). 8.1% PFHxA was formed after 180 days in the soil system and 5% PFHxA after 90 days in the mixed bacterial culture, respectively. The aerobic biotransformation of 6:2 FTOH in activated sludge of two domestic waste water treatment plants showed formation of PFHxA with 11 mol% within two months (Zhao et al., 2013b). In an aerobic river sediment system similar biotransformation products as in soil and activated sludge were detected (e.g. 8.4 mol% PFHxA after 100 days) (Zhao et al., 2013a). Compared with the results of aerobic degradation studies, the formation of PFHxA was much slower in anaerobic digester sludge. In two studies performed under methanogenic conditions 0.2 mol% PFHxA and 0.4 mol% PFHxA were detected after 90 and 176 days, respectively (Zhang et al., 2013).

At the end of above mentioned studies up to 45% intermediates were detected. With increasing time, those intermediates will be further degraded to PFHxA and other persistent short-chain PFCAs.

PFHxA itself is likely to be persistent based on the general stability of organic fluorine compounds and read-across to the structurally similar substance PFOA, which is already identified as P and vP (European Chemicals Agency (2015)).

Thus, based on the available studies and information in the registration dossiers the proposed degradation pathway is the following (shown for both 6:2 FTA and 6:2 FTMA):



Metabolic degradation of 6:2 FTA to 6:2 FTOH

No studies are available documenting the metabolic degradation of 6:2 FTA in aquatic organism. The only *in vivo* fish study is investigating metabolic products of 8:2 FTA (Butt et al., 2010). In this study, trouts were administered with 8:2 FTA via diet. The parent, suspected intermediates and terminal metabolites were monitored in liver, blood, kidney, bile, and faeces during the 5-day uptake and 8-day elimination phases. Very low levels of the 8:2 FTA were detected in the internal tissues and faeces, suggesting that the 8:2

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FTA was rapidly biotransformed in the gut or liver. Similarly, low concentrations of the 8:2 FTOH were accumulated in the fish tissues, although high concentrations were measured in faeces. In liver and kidney, a low but constant level of FTA and FTOH could be measured during the uptake phase. The 8:2 fluorotelomer carboxylic acid (FTCA) was formed in the highest concentration. The 8:2 fluorotelomer unsaturated carboxylic acid (FTUCA) and 7:3 FTCA were also accumulated in high levels, at levels approximately 10-fold lower than the 8:2 FTCA. Both the 7:3 FTCA and PFOA showed increasing levels throughout the uptake phase and into the initial stages of the elimination phase, indicating continued formation through precursors still present in the body. Furthermore, PFNA was also detected in small amounts. The following simplified metabolic pathway can be taken from these results representing also the internal concentrations (in liver/ kidney given in ng/g wet weight) during the uptake phase:

8:2 FTA (5/25) → 8:2FTOH (300/60) → 8:2 FTCA (1000/1000), 7:3 FTCA (100/100), 8:2 FTUCA (50/100) →→→ * PFOA (80/100), PFNA (1/1)

*Beta-like oxidation: 8:2 FTUCA→7:3 β-keto acid → 7:2 ketone→ PFOA.
*Alpha-oxidation: 8:2 FTCA→PFOA

The formation of 8:2 FTA metabolites takes place within few hours and reaches the saturated state in few days (4-5 days).

Due to the structural similarities between perfluoroalkyl substances (PFASs) homologues of different fluorinated chain length, similar metabolic pathway can be postulated for C_6 homologues. These results suggest that while the assessment of endocrine effects of FTAs might not be relevant, their degradation products might be of concern.

Further *in vitro* studies are available for 8:2 FTOH, which have been discussed in the proposal[4] for harmonised classification and labelling of 8:2 FTOH. According to the RAC opinion[5], methodical flaws of these studies do not allow a quantitative assessment of 8:2 FTOH metabolism and a comparison between tested organism (rats, mice, fish and humans). However, an *in vivo* formation of PFOA from 8:2 FTOH was accepted by RAC.

Monitoring data showing exposure of the environment with PFHxA and 6:2 FTOH

Several studies show the ubiquitous exposure of the environment with PFHxA whereby no natural sources for PFHxA are known. PFHxA occurs for example in the low ng/L range in the North Sea (Ahrens et al., 2009) as well in remote surface waters like the Canadian Arctic Oceans (Benskin et al., 2012). Also in drinking water ((Gellrich et al., 2013) (Llorca et al., 2012a) (Haug et al., 2010) (Ullah et al., 2011)) and biota ((Klein et al., 2016) (Llorca et al., 2012b) (Falk et al., 2012) (Fang et al., 2014)) PFHxA was detected. 6:2 FTOH can be found in the atmosphere of urban as well as rural areas ((Jahnke et al., 2007) (Barber et al., 2007)).
Overall, the occurrence of these substances in the environment is showing their relevance.

[4] CLH report: Proposal for Harmonised Classification and Labelling Based on Regulation (EC) No 1272/2008 (CLP Regulation), Annex VI, Part 2 (20.03.2012)
[5] Committee for Risk Assessment: Opinion proposing harmonised classification and labelling at EU level of 8:2 Fluorotelomer alcohol (8:2 FTOH)EC number: 211-648-0CAS number: 678-39-7 CLH-O-0000002460-84-03/F Adopted 06 March 2013.

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What is the possible regulatory outcome

The new information is needed to decide on whether or not the substance should be considered as a substance of very high concern (SVHC) due to its potential endocrine disrupting effects with respect to the environment. If so, further risk management measures might be needed for the registered substance and the relevant metabolites/transformation products.

Request 1.1: Fish sexual development (FSDT) test according to OECD TG 234 to assess environmental estrogenic properties of 6:2 FTOH

The concerns identified

In vitro and *in vivo* studies show an estrogenic mode of action for 6:2 FTOH. These data indicate that **6:2 FTOH interacts with one of the main endocrine axes, the hypothalamus-pituitary-gonadal (HPG) axis** and thus might be an endocrine disruptor**:**

- Benninghoff et al. (2011) - Klimisch reliability 2
  Method in vitro: an ER competitive binding assay was conducted by incubating liver cytosols from E_2 exposed trout in the presence of [3H]-estradiol and increasing concentrations of 6:2 FTOH (10^{-7}-10^{-3} M) for 24h.
  Results in vitro: 6:2 FTOH exhibited no response in the tested concentration ranges.
  Method in vivo: The same study investigated the *in vivo* VTG (vitellogenin) induction in blood plasma of juvenile trout prior to reproductive development (genetic sex was not determined in this study) in a subchronic dietary exposure (14d) to 250 ppm 6:2 FTOH. VTG was determined using ELISA (Enzyme Linked Immunosorbent Assay).
  Results in vivo: 6:2 FTOH exhibited an 8-fold increase VTG induction compared to the control.

- Ishibashi et al. (2007) - Klimisch reliability 2
  Method: estrogenic effects of 6:2 FTOH in a concentration range of 0.01-1000 µM were assessed during 4h exposure using a yeast two-hybrid assay with human ERα or ERβ and coactivator TIF2 using β-galactosidase as reporter.
  Results: Interaction was visible starting at 0.1 µM; EC_{10} for ERα and ERβ were 2.3 and 4.1 µM, respectively. These results show a possible stimulation of human ER mediated target gene transcription by 6:2 FTOH, thus giving an indication for estrogenic mode of action.

- Ishibashi et al. (2008) - Klimisch reliability 2
  Method in vitro: estrogenic effects of 6:2 FTOH in a concentration range of 0.01-1000 µM were assessed during 4h exposure using a yeast two-hybrid assay with *Medaka* ERα and coactivator TIF2 using β-galactosidase as reporter.
  Results in vitro: the authors reported a concentration-dependent interaction between *Medaka* ERα and coactivator TIF2 for 6:2 FTOH showing a possible stimulation of *Medaka* ER mediated target gene transcription, thus giving an indication for estrogenic mode of action. Effects of 6:2 FTOH (EC_{10} = 0.26 µM) started at 0.1 µM and 6:2 FTOH had a 0.16% affinity, compared to the positive control E2 (EC_{10} = 410 pM).
  Method in vivo: In the same study, *in vivo* estrogenic effects were also assessed by exposing adult *Medaka* to 6:2 FTOH treated water (nominal concentration of

0.01, 0.1, 1, 10 and 100 µM) over three days for hepatic VTG analysis and 8h for gene expression analysis of ERα, ERβ, VTGI and VTGII. VTG analysis was performed using ELISA, gene expression analysis was conducted with qPCR (quantitative polymerase chain reaction).
Results in vivo: 6:2 FTOH caused a concentration-dependent induction of VTG and hepatosomatic index (HSI) in male *Medaka*. Significant changes were seen starting at 1 µM 6:2 FTOH regarding VTG levels, and 10 µM regarding HSI, respectively. In addition, supporting an estrogenic mode of action, a significant increase in gene expression induction exhibited by 6:2 FTOH for ERα, and for two VTG genes, but not for ERβ was observed. Concentration-dependent gene expression changes were seen for ERα only, starting at 10 µM.

- Liu et al. (2007)- Klimisch reliability 2
Method: VTG induction exhibited by 6:2 FTOH was assayed in primary cultured hepatocytes of freshwater male tilapia and compared with that of known estrogenic compounds. Time-course (0-96h with 14µM 6:2 FTOH) and dose dependent (48h with 1.4-54 µM 6:2 FTOH) VTG induction were assessed using single-compound-exposure. Binary exposures (0.22-22 µM 6:2 FTOH) to E2 or tamoxifen (anti-estrogen, selective estrogen-receptor modulator) were investigated to elucidate ER-mediated effects. Hepatocyte viability was determined by comparing mitochondrial MTT activity. A non-competitive ELISA was employed to determine the VTG production.
Results: Hepatocyte cell viability was unchanged in all treatment groups compared to controls. Significant VTG induction took place after 12h (1.4×10^{-5} M 6:2 FTOH), and the VTG production increased further after 96h of exposure. A concentration-dependent induction of VTG was observed in E2, 4-nonylphenol (4-NP) and 6:2 FTOH-treated cells. The estimated 48h EC_{50} values for E_2, 4-NP and 6:2 FTOH were 0.47 µM, 7.1 µM and 28 µM, respectively. Reduction of VTG induction could be observed when 30 µM 6:2 FTOH was applied in combination with 10 µM tamoxifen meaning that 6:2 FTOH presumably exhibits its effect via the ER directly or an involved co-factor. Interestingly, 6:2 FTOH showed also anti-estrogenic effects (IC_{50}=1.1 µM) when applied in combination with E2. This might be explained by a competitive binding of 6:2 FTOH and E2 to the same receptor site but with 6:2 FTOH showing a lower potential for receptor activation. Thus, 6:2 FTOH can show estrogenic effects in male fish where the background level of E2 is low and a more anti-estrogenic effect in female fish by its competitive binding to the ER proteins.

- Liu et al. (2009) - Klimisch reliability 2
Method: An *in vivo* study was conducted by Liu et al. (2009) using adult zebrafish exposed to 0.03, 0.3 and 3.0 mg/l (0.08, 0.8 and 8.2 µM) 6:2 FTOH for 7 days. Effects on plasma sex hormone levels and gene expression of selected genes of the HPG axis were measured in liver, gonad and brain. Sex hormones were measured using ELISA, gene expression was analysed with qPCR.
Results: Exposure to 6:2 FTOH significantly increased plasma E2 and testosterone (T) levels in both males and females (LOEC 0.08 and 0.8 µM, respectively). Furthermore, the ratio of T/E2 was reduced in females while increased in males (LOEC 0.08 and 0.8 µM, respectively). As supporting data in females, the increase of E2 was accompanied by upregulated hepatic VTG (VTG1 and VTG3, LOEC 0.08 µM), downregulation of gonad ERα and ERβ (LOEC 0.8 and 0.08 µM, respectively) and upregulation of the brain activin and activin receptor (putative mediator of gonadotropin-induced oocyte maturation, LOEC 8.2 µM) gene

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expression. In males, the elevation of the T level is consistent with supporting data from gene expression analysis. Here the altered regulation of some enzymes playing a role in the steroid biosynthesis (CYP17 and CYP19A). In males, gonadal CYP19B, ERα, ERβ, GnRH2 and FSH were upregulated (LOEC 0.08, 0.08, 0.8, 8.2 and 0.08, respectively), while hepatic VTG showed a concentration-dependent decreasing upregulation with increasing concentration (LOEC 0.08).

- Maras et al. (2006) - Klimisch reliability 2
  Method: Maras et al. (2006) investigated estrogen-like properties of 6:2 FTOH using a combination of three *in vitro* assays: E-screen assay using MCF-7 breast cancer cells (incubation for 6d to 0.1-30µM 6:2 FTOH, analysis of proliferation with CyQuant assay), cell cycle analysis (incubation for 24h to 0.3-30µM 6:2 FTOH, cell cycle distribution and apoptosis were analysed with flow cytometer), and gene expression analysis using qPCR of estrogen-responsive biomarker genes exposed over 48h to 30µM 6:2 FTOH (trefoil factor 1, progesterone receptor, ER, ERBB2 and PDZK1).
  Results: By means of an E-screen assay, the authors detected the proliferation-promoting capacity of 10 µM 6:2 FTOH. Exposure to 6:2 FTOH stimulated resting MCF-7 cells to re-enter the synthesis phase of the cell cycle. Furthermore, similar to E2 and 4-NP 6:2 FTOH induced the expression of some estrogen responsive genes, although showing lower but relevant fold induction changes. Based on this latter finding, the authors hypothesised different estrogenic mode of action of 6:2 FTOH compared to that of E2.

In your comments on the draft decision, you argued that the *in vivo* environmental studies with 6:2 FTOH are of low quality/reliability and have a number of shortcomings. Responses to all these points are provided below:

The use of high DMSO levels (~0.01%) within aquatic toxicity experiments:

You comment that carrier solvents (e.g., DMSO) are commonly used in aquatic testing with 6:2 FTOH. High concentrations of DMSO or ethanol have been shown to alter enzymatic rates, as well as potential for increasing the uptake of chemicals into aquatic biota (Hutchinson, 2006).

ECHA recognises this concern. The OECD Guidance Document No. 23 on aquatic toxicity testing of difficult substances and mixtures recommends the use of maximum 100 µl/L (i.e. 0.01%) solvent (OECD, 2000). Indeed, there are studies available in the open literature showing that even such low levels of solvents might have toxic /teratogenic effect on fish (Verma and Rana, 2009) or they might influence the toxicokinetic or toxicodynamic properties of the test substance or even act as modulator of estrogen receptor isoforms and xenoestrogen biomarker responses (Mortensen and Arukwe, 2006). Therefore, ECHA is also of the opinion that solvent concentrations should be kept as low as possible.

Regarding the *in vivo* studies used in the assessment, only Ishibashi et al. (2008) used 0.01% DMSO. Benninghoff et al. (2011) applied maximal 0.5 ppm (i.e. 0.0005%) DMSO for dissolution of 6:2 FTOH, which was added directly to the oil portion of the custom trout diet. Liu et al. (2009) used 0.0025% DMSO both in control and exposure groups, which is close to the one recommended by Hutchinson et al. (2006). Therefore, the scientific findings supporting the concern for endocrine disruption in fish remains.

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Analytical measurement of 6:2 FTOH:

It is recognised that in all of the studies used to assess estrogenic properties of 6:2 FTOH, only nominal concentrations are given and no analytical measurement was performed. Therefore, the derived LOEC values might over- or underestimate the effect of 6:2 FTOH. Since these studies were used to support the estrogenic mode of action of 6:2 FTOH, for which a concentration dependent change of certain estrogen sensitive biomarkers might be satisfactory (showing monotonic trends), and no conclusion on potency was driven, there is no reason not to take into account these studies. Certainly, analytical confirmation of the test substance might help to interpret correctly the test results, therefore analytical measurements shall be conducted in the requested FSDT study as required by the OECD TG 234. It should be also taken into account that using nominal concentrations of weakly soluble substances normally leads to an underestimation of effects, i.e. that the real NOEC values might be even lower than expected.

Concentration levels of 6:2 FTOH in the studies vs. in the environment:

You commented that the exposure concentrations that altered VTG levels and other estrogenic signals (i.e. plasma hormone levels, mRNA expression) were well above environmentally relevant concentrations (i.e. ng/L) so it is unknown what these signals represent from a risk perspective. Mahmoud et al. (2009) did not detect 6:2 FTOH in multiple surface water samples collected in Japan. The authors reported a detection limit of 0.5 ng/L for 6:2 FTOH.

Sensitivity of wildlife species might be different than that of laboratory organisms and test conditions cannot completely mirror environmental conditions. Furthermore, environmental concentrations might rise in the future, given the phase out of long-chain PFASs and the corresponding increase in the use of the C6 fluorochemistry. Therefore, the FSDT should be conducted with concentrations (below the level of systemic toxicity) in which positive results regarding ED effects can be expected based on previous testing, independently from the current level of environmental concentrations.

Positive control in aquatic toxicity studies:

You noted that a positive control was not included in any of the aquatic toxicity studies. While not specifically prescribed in an OECD protocol, in your view a positive control is essential in an endocrine study investigating a defined mode of action (MoA) as it provides a quality check on the experiment that was conducted.

ECHA notes that the OECD TG 234 does not require to use a positive control. For the verification of non-standard test protocols, the use of a positive control is definitely useful.

ECHA notes that the following studies which are summarised above did in fact use a positive control: Benninghoff et al. (2011): E2, EE_2 and 4-NP in the *in vitro* study, E2 in the *in vivo* study; Ishibashi et al. (2007): E2; Ishibashi et al. (2008): E2 in the *in vitro* study; Liu et al. (2007): E2 and 4-NP; Maras et al. (2006): E2 and 4-NP.

Only two of the studies assessed did not use a positive control: Ishibashi et al. (2008): no positive control in the *in vivo* study; Liu et al. (2009): no positive control.

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Lack of GLP certified studies:

You commented that none of the studies cited complied with Good Laboratory Practices (GLP). Given the studies did not follow GLP, in your view it cannot be concluded that these studies are of sufficient quality.

ECHA considers that for the assessment of endocrine disrupting properties, all available studies should be taken into account. When evaluating these studies, their relevance and reliability should be assessed and documented. Certainly, studies according to internationally accepted test guidelines conducted under strict GLP certified conditions have the highest reliability. However, the GLP standard is not mandatory to classify a study as relevant and reliable. Indeed, studies used in the substance evaluation for assessing ED properties, have all Klimisch reliability of 2, due to the applied non-standard protocols and the missing analytical measurement of the test substance. The requested FSDT should verify the findings on the MoA of 6:2 FTOH and provide information on adverse effects of the test substance.

More information is available on ED properties of **other FTOH homologues**:

- Similarly to 6:2 FTOH, 8:2 FTOH caused a concentration-dependent induction of VTG and increase in the HSI in male *Medakas*. There was also a significant increase in gene expression induction for ERα, and for two VTG genes, but not for ERβ Ishibashi et al. (2008).
- Impairment of reproduction has been shown for 8:2 FTOH: disruption of sex hormone biosynthesis (increased T and E_2 levels in females, decreased T and increased E_2 levels in males) and impaired reproduction in adult zebrafish (poor sperm and egg quantity and quality), ultimately resulting in decreased hatching rates in the offspring (Liu et al., 2010a).

In your comments on the draft decision, you raise concerns about a proposed read-across to 8:2 FTOH since it is much more toxic to fish than 6:2 FTOH. However, no read-across has been performed between 6:2 FTOH and 8:2 FTOH for ecotoxicity. Data on 8:2 FTOH is taken into account as supporting information when degradability or metabolism of 6:2 FTOH was assessed or when endocrine disrupting properties of 6:2 FTOH were evaluated. None of these studies report on systemic toxicity of 8:2 FTOH.

Summary of the concern

In summary, available studies listed at level 2 and 3 of the "OECD conceptual framework and standardised test guidelines for evaluating chemicals for endocrine disruption" (OECD guidance document No. 150) show that 6:2 FTOH interacts with the HPG axis both *in vitro* and *in vivo*: four (out of five) *in vitro* studies report on 6:2 FTOH estrogenic activity in µM concentrations. This is supported by three *in vivo* studies finding concentration-dependent influences on biomarkers indicating an estrogenic mode of action: induction of VTG and HSI or increased sex hormone concentrations and altered estrogen signalling pathway related gene expression changes observed starting at low µM concentrations of 6:2 FTOH.

Why new information is needed

The above data show a concern for 6:2 FTOH due to interaction with the endocrine system in fish. The data presented above clearly indicate an estrogenic mode of action

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but are not sufficient to conclude on population relevant adverse effects and hence to decide on whether 6:2 FTOH is an endocrine disruptor in the environment or not. In order to analyse whether the observed estrogenic mode of action of 6:2 FTOH results in adverse effects, an aquatic test, which includes population relevant adverse endpoints is requested.

The results of the requested FSDT (OECD TG 234) will be used to evaluate whether 6:2 FTOH meets the WHO definition for endocrine disruptors and the criteria given in REACH Article 57 (f). Since the FSDT gives information both on endocrine mode of action and endocrine mediated adverse effects, the test is adequate to conclude on the endocrine disrupting properties of 6:2 FTOH.

In your comments on the draft decision, you cite other studies, including ToxCAST results, showing that no concerns on interaction with thyroid hormone signaling or androgen pathway could be identified. Similarly, some of the *in vitro* studies assessed to investigate interactions with estrogen hormone signaling showed either positive or negative results. In ECHA's view, the *in vivo* data support the estrogenic MoA shown by some *in vitro* assays and further testing is necessary to conclude on the hypothesised estrogenic MoA of 6:2 FTOH and to assess whether this MoA can trigger endocrine related adverse effects in fish. This is best to conduct in one test, which can deliver answer to both questions (adverse effects and a biologically plausible link to an endocrine mediated pathway of these effects). This can be provided, as stated within the OECD Guidance 150 document, by the requested FSDT.

Considerations on the test method and testing strategy

A Fish Sexual Development test, OECD TG 234 shall be performed. The test material, 6:2 FTOH, is commercially available at reasonable costs as it is used as analytical standard; so this request does not require any additional work on substance synthesis. The solubility of 6:2 FTOH (18.8 mg/L=52µM measured by Ding and Peijnenburg (2013)) allows a water borne exposure. Taking into account the solubility of 6:2 FTOH and the available results on its endocrine properties at least four test concentrations shall be set. The spacing of the concentrations shall be as described in OECD TG 234 using the water solubility (50µM) as the maximum test concentration. However, in response to a proposal for amendment, it is recommended to use five concentrations to increase the probability to derive a more precise NOEC/LOEC or ECx to be used for further risk management considerations.

In your comments you noted the comprehensive review of Hutchinson (2006) which recommended a maximal solvent concentration that was 5x less than that prescribed by the OECD (2000) (i.e. 0.01%) for endocrine related studies. The evaluating MSCA agreed and considered that, if used, the solvent concentrations for the OECD TG 234 shall be kept as low as possible. It shall not exceed the concentration of 0.01% v/v but the maximal level might be kept preferably at 0.002% v/v to avoid interaction of the solvent with endocrine signalling or the toxicodynamic/toxicokinetic processes. Separate control and solvent control is needed to clarify that the used solvent concentration does not have any endocrine disrupting effects. Thus, it is requested to use a control and a solvent control in parallel.

Since estrogenic activity has already been determined using Japanese medaka (*Oryzias latipes*) and zebrafish (*Danio rerio*), the FSDT shall be conducted with one of these two species. If medaka is chosen, this test shall include genetic sex determination to

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increase the statistical power of the test result on sex ratio, as well as reporting of any change of the secondary sex characteristics.

You shall submit the full study report for the information requirement 1.1. Considering the complexity of the case, access to all available information (implemented method, raw data collected, interpretations and calculations, consideration of uncertainties, argumentation, etc.) is needed. This will allow the evaluating MSCA to fully assess the provided information, including the statistical analysis, and to efficiently clarify the concern for endocrine disruption in fish by 6:2 FTOH.

Furthermore, it has been investigated whether or not a sequential testing considering the requests 1.1 and 1.2 might be reasonable. Test 1.1 covers estrogenic effects and the related adverse effects of 6:2 FTOH on the HPG axis, while test 1.2 addresses effects of PFHxA on the HPT axis, a sequential testing seem to be not reasonable for these Endpoints.

Alternative approaches and Proportionality of the request

In order to decide whether or not 6:2 FTOH is an endocrine disruptor according to Art. 57 (f) of REACH, a test is needed which includes information on endocrine mode of action, as well as robust adverse effect endpoints. Beside the FSDT only two types of fish tests provide such data: the fish short-term reproduction assay (OECD 229) or the 21-d fish assay (OECD 230) and fish full life cycle studies: Fish Lifecycle Toxicity Test (USEPA OPPTS 850.1500) or the Medaka Extended One Generation Reproduction Test (OECD 240)).

In your comments on the draft decision, you proposed to conduct as a first step an OECD 229 fish short-term reproduction assay before a higher tiered study such as OECD 234. In your view, the OECD 229 will not only provide dose-response data on fecundity and VTG alterations, but also histopathological data to "ground" any biomarker finding (e.g. VTG). ECHA considers that the available *in vitro* and *in vivo data* are sufficient to conclude on the endocrine modes of action of 6:2 FTOH. Additionally, the available *in vivo* data provide sufficient information to set an adequate concentration range for further, higher tier testing. Hence, no further level 3 testing is considered to be necessary and a level 4 assay is requested to conclude on adverse, population relevant effects evoked by the endocrine activity of 6:2 FTOH. Furthermore, since the OECD 229 test only uses adult fish, sensitive juvenile lifestages are not covered by this screening assay, but are included into the FSDT protocol.

A fish full life cycle or multi-generation test would be robust enough and would include all sensitive life stages. However, with regard to an estrogenic mode of action the evaluating MSCA considers, that there is scientific evidence that sexual development is an endpoint responding sensitive to estrogens and therefore, a test covering life stages at which sexual development takes place is considered sufficient to detect estrogenic mode of action mediated endocrine disruption. Thus, a full life cycle test or a multi-generation test seem to be not proportionate. In conclusion, the FSDT is considered to be the most proportionate request to clarify the concern. The FSDT serves as a higher tier test, which is placed at level 4 of the OECD ED conceptual framework for providing test data on (anti)estrogen and (anti)androgen mode of action and data on its plausible link to related serious (adverse) effects on fish sexual development. Therefore, the request for a FSDT is suitable and necessary to obtain the information needed.

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Conclusion

Therefore, based on the substance evaluation and pursuant to Article 46(1) of the REACH Regulation, ECHA concludes that you are required to carry out the following study using 6:2 FTOH, a metabolite/transformation product of the registered substance: Fish sexual development test; test method: OECD 234, as specified above.

Request 1.2: Amphibian metamorphosis assay (AMA) according to the OECD TG 231 to assess potential thyroid disrupting properties of PFHxA.

The concerns identified

Available *in vitro* and *in vivo* data indicate that the metabolite/transformation product PFHxA might affect the endocrine system via interference with the hypothalamus-pituitary-thyroid (HPT) axis by interacting with the thyroid hormone signalling.

Regarding **interaction of PFHxA with the HPT axis** four *in vitro* assays of OECD CF level 2 are available:

- Ren et al. (2015) - Klimisch reliability 2
  Method: using GH3 rat pituitary cancer cells a T-screen assay was performed to test for thyroid hormone dependent cell proliferation in order to identify thyroid hormone receptor active compounds. The competitive binding of 200-500000 nM PFHxA to the human TR ligand binding domain was tested in presence of fluorescein tagged T_3.
  Results: PFHxA exhibited very low binding (0.06%) in comparison with T_3. PFHxA showed no agonistic or antagonistic activity in the T-screen assay in the concentrations tested (5-500 µM and 15 µM).

- Naile et al. (2012) - Klimisch reliability 2
  Method: Rat H4IIE hepatoma cells were exposed for 72 h to 0.1-100 µM PFHxA and changes in mRNA abundance of thyroid-, cholesterol- and lipoprotein related genes were quantified by qPCR. Regarding thyroid-related genes PAX and HEX expression playing a role in thyroid development were tested. Cell viability was assessed visually.
  Results: The cell viability was not affected by the treatment. An upregulation of the gene expression could be observed for PFHxA starting at 0.1µM, although not in a concentration-dependent way. In your comments you argue that: "*while the in vitro studies described by Weiss et al. (2009) and Naile et al. (2012) were suggested as providing evidence of thyroid activity, these studies do not provide dose-dependent observations or observations that PFHxA is a strong agonist/antagonist (< 1% of T4 binding affinity). In a series of in vitro assays by Ren et al. (2015; 2016), no relevant binding interaction with thyroid receptor was demonstrated (Appendix B, Table 4).*" In response, to provide a concern for thyroidal activity of PFHxA neither strict dose-dependency nor potency should be considered as contradicting factors. There still remains a concern on the *in vitro* screening level that needs to be clarified further. In addition it should be mentioned here that Ren et al. (2016) did not investigate the binding of PFHxA to the thyroid receptor (TR) but to the TTR protein. The authors conclude that there is a weak binding potential of PFHxA to the TR which might be of concern for highly exposed workers. The data do not allow an assessment of e.g. amphibian species known to be more sensitive to thyroid active substances in general.

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- Vongphachan et al. (2011) - Klimisch reliability 2
  Method: A gene expression assay was performed on avian embryonic neuronal cells of domestic chicken and herring gull investigating key genes in the thyroid hormone pathway (iodothyronine 5'-deiodinase 2 and 3 –D2/D3, transthyretin –TTR, neurogranin –RC3, octamer motif-binding factor –Oct-1, and myelin basic protein –MBP). Primary cultures of chicken embryonic neuronal cells and herring gull embryonic neuronal cells were prepared from the cerebral cortices of day 11 or 14 embryos, respectively. PFHxA was administered at concentrations of 0.01, 0.1, 1, 3, 10, and 50µM (the latter was applied only for chicken neuronal cells) over 24h. Cell viability was estimated using the Calcein-AM assay. After RNA isolation and cDNA synthesis, qPCR was performed to investigate gene expression changes. In chicken cells, expression of genes of D2, D3, TTR, RC3, Oct-1, in herring gull cells, genes of D2, RC3, Oct-1 were investigated. As positive control for the gene expression analyses, T_3 was used.
  Results: PFHxA decreased the cell viability in concentrations > 10µM, therefore this was the highest applied concentration in the definitive test. PFHxA altered significantly the expression of MBP (LOEC 10µM), D2 (LOEC 10µM) and D3 (LOEC 3µM) genes in chicken embryonic neuronal cells, although for D3 not in a concentration-dependent way (for MBP and D2 only the highest tested concentration exhibited significant expression changes). For the rest of the genes, no changes in gene expression were seen. The positive control, T_3 exhibited gene expression induction for D2, RC3 (LOEC 3nM) but not for TTR, D3, Oct-1 and MBP. In herring gull embryonic neuronal cells changes were seen only for Oct-1 expression following PFHxA exposure (LOEC 3 µM). The positive control T_3 was effective for RC3 (LOEC 300 nM) but not for D2 and Oct-1. In your comments you argue that: "*the in vitro study by Vongphachan et al. (2011) was cited as providing evidence of a potential thyroid related effect. Unfortunately, the results of this study provide no insight into the potential for a thyroid related effect associated with PFHxA as the observed responses were not dose related and only occurred at extremely high concentrations (Appendix B, Table 4). In addition, the results were not observed in a second bird cell line.*" In response, the maximum tested concentration in the definitive gene expression assay was 10µM and effects on genes related to the thyroidal pathway were detected on the same level or below. As also mentioned above the absence of a clear dose-dependency of effects cannot remove the concern on the *in vitro* screening level.

- Weiss et al. (2009) - Klimisch reliability 2
  Method: using radiolabelled ^{125}I-labeled T_4 the competitive binding of PFHxA with T_4 to the human TTR was assessed for a concentration range of 10-10000 nM.
  Results: PFHxA exhibited 0.7% of activity of T_4 with IC_{50} of 8220 nM (IC_{50} of T_4 = 61 nM) showing a concentration-dependent inhibition of T_4 bound to TTR. Using a fluorescence labelled T4 competitive binding assay Ren et al. (2016) found a comparable binding affinity of PFHxA to the TTR protein.

In summary, the available *in vitro* assays conducted with PFHxA give rise to the concern that PFHxA might interact with the HPT axis showing interferences with TH synthesis, transport, bioactivation, action and metabolism. Given that no data are available for aquatic species, this concern should be further investigated.

In your comments on the draft decision, you comment that important studies with PFHxA (listed in Appendix B of your comments; ToxCast/Tox21 results, Ren et al. 2016 and Cassone et al. 2012) were missed during the evaluation which clearly show no

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endocrine disruption of the thyroid therefore a request for a study is not substantiated. It is acknowledged that there are studies which show no or only weak thyroid effects. However, their existence does not invalidate those studies giving a rise to the concern that PFHxA might interact with the HPT axis and this concern still needs to be clarified.

In your response to a proposal for amendment you state that there are further studies summarised in Borghoff et al. (2018) that have not been addressed in the draft decision and do not provide evidence for endocrine effects. We acknowledge that there are further studies not addressed in our response above (Frey et al. 2010, Kim et al. 2015 and Li et al. 2017) cited by Borghoff et al. However, the evidence provided within these studies does not remove the concern for PFHxA acting via the HPT axis as an ED substance in the environment. For example, in the bird study performed by Frey et al. only adult animal were exposed and there were no parameters investigated allowing a conclusion whether or not the observed effects are mediated via an ED mode of action. The Li et al. study provides human epidemiological data, which are inconclusive on HPT effects of PFHxA, but shows that there are some HPT related parameters changed in humans exposed to PFHxA. Finally, a FETAX like study performed by Kim et al. shows developmental and teratogenic effects of PFHxA. However, within this study no HPT indicative parameters have been investigated.

Why new information is needed

Based on the information described above, ECHA has identified a concern for possible endocrine disrupting properties of the metabolite/transformation product PFHxA in vertebrate non-mammalian wildlife species as there is a concern for PFHxA affecting thyroid hormone signalling. The data presented above are not sufficient to draw a definite conclusion on the possible modes of action and whether or not they result in adverse effects. In order to identify whether PFHxA is an endocrine disrupting substance an amphibian metamorphosis assay (AMA, OECD TG 231) is requested.

In your comments on the original draft decision requesting a LAGDA (OECD 241) study, you comment that the request for a LAGDA study for PFHxA is premature given that altered thyroid activity has not been documented *in vivo* for PFHxA. In your view, given the similarity of toxicant targets across species and the lack of thyroid specific responses in rodent assays ([redacted], 2005; Loveless et al., 2009; Chengelis et al., 2009; Iwai et al. 2014, Klaunig et al., 2015), one would not expect a dose-dependent thyroid related PFHxA response in an aquatic vertebrate. You proposed to conduct an OECD 231 AMA test first to provide guidance if conduct of the OECD 241 LAGDA test becomes necessary. You commented that OECD 231 would also provide additional data if a weight of evidence evaluation becomes necessary.

ECHA considers that, based on the available *in vitro* studies – although they are showing no or low thyroid disrupting activity of PFHxA – it cannot be excluded that PFHxA has a thyroid disrupting mode of action. In this respect, it is unclear to which extent data from gene expression studies can be used to draw conclusions regarding the existence of a mode or action (or its absence), since specific guidance on how to interpret such results is still missing. However, ECHA considers that changes in gene expression patterns can be used as supporting information in a weight of evidence approach.

Regarding *in vivo* assays, no studies of PFHxA are available using aquatic organisms. Indeed, it can be acknowledged that some endocrine mechanisms are evolutionarily conserved between aquatic vertebrates and mammals. However, extrapolation of study

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results between these taxonomic groups should be conducted carefully due to physiological differences and differences in exposure (i.e. via diet or water) leading to differences in sensitivity. Thus, while it is acknowledged that *in vivo* rat studies conducted with PFHxA do not report on thyroid disruption related endocrine effects (although in the study of Loveless et al. (2009) minimal hypertrophy of thyroid follicular epithelium was present in male and female rats in the 500 mg/kg bw/d group. The effects were reversible after 90 days of recovery but not following 30 days of recovery), aquatic tests with fish species using higher PFCA homologues showed both thyroid disrupting mode of action related and adverse effects. Therefore based on a proposal for amendment and in accordance with the OECD Conceptual Framework for Testing and Assessment of Endocrine Disrupters, an AMA test is requested to further clarify the environmental ED concern for PFHxA.

Considerations on the test method and testing strategy

An amphibian metamorphosis assay (AMA, OECD TG 231) is requested to clarify the interference of PFHxA with the HPT axis. The test material, PFHxA, is commercially available at reasonable costs as it is used as analytical standard; so this request does not require any additional work on substances synthesis. Solubility of PFHxA (29.5 mg/L=93µM estimated by Ding and Peijnenburg (2013)) allows a water borne exposure. The use of solvents is allowed in the test, however, it should be kept as low as possible. It should not exceed the concentration of 0.01% v/v but the maximal level might be kept preferably at 0.002% v/v to avoid interaction of the solvent with endocrine signalling or the toxicodynamic/toxicokinetic processes. You shall submit the full study report for the information requirement 1.2. Considering the complexity of the case, access to all available information (implemented method, raw data collected, interpretations and calculations, consideration of uncertainties, argumentation, etc.) is needed. This will allow the evaluating MSCA to fully assess the provided information, including statistical analysis, and to efficiently clarify the concern for endocrine disruption in vertebrate non-mammalian wildlife species by PFHxA. Furthermore, it has been investigated whether or not a sequential testing considering the requests 1.1 and 1.2 might be reasonable. Test 1.1 covers estrogenic effects and the related adverse effects of 6:2 FTOH on the HPG axis, while test 1.2 addresses effects of PFHxA on the HPT axis, a sequential testing seem to be not reasonable for these endpoints.

Alternative approaches and Proportionality of the request

As alternatives, *in vitro* studies could be used to clarify the potential interference with the HPT axis further. However, the available data report on different molecular initiating actions (interferences with TH synthesis, transport, bioactivation, action and metabolism). Thus, such *in vitro* testing would require several assays, while an *in vivo* assessment would integrate the effects of the different molecular initiating actions given the autoregulatory feedback loop of the HPT axis (it is known, that many thyroid disruptors ultimately affect thyroid hormone levels and cause a compensatory regulation of genes coding for proteins involved in hormone synthesis, which leads to altered plasma concentration of T_3/T_4 or histological changes of the thyroid follicles (e.g. (Brown et al., 2004)). Furthermore, *in vitro* testing might be hampered as no guidelines for standardised *in vitro* tests for assessing interactions with the HPT axis are available.

Regarding test organisms, amphibians should be used as they are particularly sensitive to thyroid disruptors given the metamorphosis is mainly driven by the HPT axis. For that

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purpose, AMA (Amphibian Metamorphosis Assay) according to OECD TG 231 or LAGDA according to OECD TG 241 would be adequate.

Conclusion

Therefore, based on the substance evaluation and pursuant to Article 46(1) of the REACH Regulation, ECHA concludes that you are required to carry out the following study using PFHxA, the metabolite/transformation product of the registered substance: Amphibian metamorphosis assay; test method: OECD 231 as specified above.

Request 1.3: Further information on uses and environmental release estimations

The concerns identified

As described above, the registered substance subject to this decision does degrade in the environment, forming PFHxA and 6:2 FTOH. Both PFHxA and 6:2 FTOH can be found in the environment, whereby no natural sources are known (see chapter on general considerations). Sources for the release into the environment have to be identified.

In your comments on the draft decision, you mentioned that fluorotelomer-based products have included 6:2 homologues since they began manufacture in the early 1970s (Kissa, 2001; Rao et al., 1994) and that present findings in the environment are not only result of a recent shift to production of short-chain 6:2 fluorotelomer-based products but also of historical manufacture and use. It is noted that the present findings are not only a result of the shift to the production of 6:2 fluorotelomer-based products. Nevertheless, it is important to identify the sources for the current releases into the environment.

Why information is needed

The registered substance is used as a monomer or intermediate to make polymers or other substances. There is a concern that the registered substance and/or the transformation products 6:2 FTOH and PFHxA can be present in these polymers/substances. They could then leach out leading to emissions to the environment. Both PFHxA and 6:2 FTOH can be found in the environment, whereby no natural sources are known (see chapter on general considerations). Sources for the release into the environment have to be identified but only a few registrants of the substance consider environmental emissions from all lifecycle stages in their chemical safety assessments.

Overall, ECHA's concern is that the available data in the registration dossiers are insufficient to be confident that the environmental risks from the registered substance and its transformation products 6:2 FTOH and PFHxA are adequately managed. ECHA considers it important to gather additional information on use pattern (i.e. life cycle, sources and use volumes) and emissions to ensure that risk management measures (if needed) can be appropriately targeted by both the registrant(s) (in their own supply chain) and the regulatory authorities (e.g. a restriction might be warranted if a risk is identified from multiple sources). Whilst worst case assumptions about releases and tonnages could be made by the regulatory authorities, it is likely that there would still be a need to refine the information before deciding on the most appropriate risk management measure(s). Therefore further information is needed.

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As stated in the registration dossiers, the substance may be used as a monomer for polymerisation and/or as an intermediate to manufacture substances other than polymers. In the registration dossiers, emission scenarios are given for manufacturing of the substance as well as use as intermediate and in polymerisation. For analysing risk management options to address above described concerns on PFHxA and 6:2 FTOH (transformation products of 6:2 FTA), it is necessary to have knowledge about the uses and releases of 6:2 FTA into the environment during its whole life cycle. This knowledge is of relevance because emissions of 6:2 FTA are at the same time a source for PFHxA and 6:2 FTOH (see chapter: Degradation of the substance in the environment).

For fluorinated polymers – the polymer formed out of the substance is also a fluorinated polymer – some information is available on uses and emissions from the public literature. For example textiles is one of the use areas of fluorinated polymers (European Chemicals Agency, 2015). Textiles are also mentioned by some registrants as one of the product categories for use of the substance in polymerisation. Fluorinated polymers are used for making textiles water-, dirt- and stain repellent (Lacasse and Baumann, 2004). When extracting such textiles, e.g. outdoor textiles, non-polymeric fluorinated substances, beyond others PFHxA and 6:2 FTOH, can be found (Greenpeace International, 2016; Gremmel et al., 2016; Kotthoff et al., 2015). Textiles release these substances into air during use as well as into water during washing (Knepper et al., 2014). It is not clear whether the non-polymeric fluorinated constituents, like PFHxA and 6:2 FTOH, are (a) originally present in the polymer, (b) result from the degradation of other non-polymeric fluorinated constituents also in the polymer or (c) result from the degradation of the polymeric constituents themselves.

Several studies investigated the degradation of fluorinated polymers in soil, especially acrylate based polymers (C8-based instead of C6-based as given by the substance). Half-lives ranged from 8 year to > 2000 years (Rankin et al., 2014; Russell et al., 2008; Washington et al., 2009; Washington and Jenkins, 2015). All studies show the formation of non-polymeric PFASs whereby it can mostly not be excluded that parts of this are coming from unreacted monomers and their degradation. Modelled data indicate much shorter half-lives with 170 – 270 years in marine systems and < 1 year in landfills (calculated with SPARC) (Rayne and Forest, 2010). One of those studies is also mentioned in a few registrations for the substance. This information is confidential for the specific registrants.

Specification of the information need

Overall, studies show that fluorinated polymers are a source of non-polymeric PFASs into the environment. Only a few registrants of the substance address these above described issues from the general literature in their registration. As none of the aspects described on a general basis in the literature is addressed in the registrations in detail, it cannot be excluded that emissions of 6:2 FTA occur out of the polymer.

Therefore, for the use of the substance in polymerisation:

(i) it needs to be quantified what amount (%w/w) unreacted monomer 6:2 FTA, as well as unbound transformation products such as 6:2 FTOH and PFHxA is typically present in the types of polymers (polymers that manufactured from 6:2 FTA, including homo- and copolymers)manufactured from 6:2 FTA in your in-house supply chain.

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(ii) it needs to be quantified what amount (%w/w) of 6:2 FTA (unreacted monomer), 6:2 FTOH and PFHxA (unbound transformation products) can typically be released and leached out of the types of polymers manufactured from 6:2 FTA in your in-house supply chain. This investigation has to specifically seek unreacted monomers and the two specific transformation products of the monomer: 6:2 FTOH and PFHxA in the polymer (prior to application in any consumer or industrial products). In case residue analysis has already been conducted for the polymer, experimental details (e.g. study documentation, test guidelines followed, experimental conditions) and exact results should be given for each respective study. Identification and quantification of volatile transformation products (e.g. FTOH, PFHxA) might be performed using the purge and trap method (using preferably XAD cartridges for the sample collection after at least two days of purging) coupled with gas chromatography-mass spectrometry analysis as specified by Dinglasan-Panlilio et al., 2006 or using organic solvent extraction with sonication as given by Gremmel et al., 2016 for volatile PFASs and XAD cartridges for sample collection. Non-volatile transformation products might be assessed using acetone/acetonitrile extraction of the polymer with sonication followed by liquid chromatography-tandem mass spectrometry as specified by Gremmel et al., 2016. Given no guideline exists for this specific assessment, other similar methods can also be accepted. In order to prove the adequacy of other methods, sufficient experimental details shall be provided.

As regards information requests (i) and (ii) above, the information is necessary to evaluate the amount of 6:2 FTA (unreacted monomer), 6:2 FTOH and PFHxA (unbound transformation products) released to the environmental compartments during the whole life cycle of the types of polymers manufactured from 6:2 FTA and to conduct an appropriate exposure- and risk assessment. If these data are commercially sensitive, they can be provided separately by each registrant or by the way of using an independent third party. If you are unable to gather suitable representative data for any part of the life cycle of 6:2 FTA, you shall base your assessment of that life cycle stage on a reasonable worst case assumption (with a proper justification for instance demonstrating the most important emission pathway)

If these quantifications show that 6:2 FTA as a monomer in the manufacturing of polymers leads to the release of 6:2 FTA as such or in the form of structures corresponding to its transformation products (i.e. 6:2 FTOH and PFHxA) are released into the environment you have to provide:

(iii) Representative exposure scenarios need to be given for the release of 6:2 FTA, 6:2 FTOH and PFHxA from the various polymer types, covering each life cycle step for your in-house supply chain, including their use in articles, or a justification why for these uses exposure scenarios do not apply. This information will be used to identify potential sources of 6:2 FTA, 6:2 FTOH and PFHxA to the environment to ensure that risk management measures (if needed) can be appropriately targeted.

If you cannot provide the information as you do not conduct polymerisation, you shall provide an explanation of this in your updated registration dossier.

For the uses of 6:2 FTA as an intermediate to manufacture substances other than polymers:

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(iv) You have to provide information on the identity of the substances that are manufactured from 6:2 FTA for the in-house supply chain together with a comprehensible description of the technical process used. It is acknowledged that the in-house process may be different to those of other processes by downstream users but this information is readily available to the Registrants and will help to estimate the emissions from use of 6:2 FTA as an intermediate. This information is currently not available from the chemical safety reports.

Finally, the registration dossiers contain inconsistencies on whether and, if yes, in which amounts manufacturing of 6:2 FTA is taking place within the EU. Therefore:

(v) The annual tonnage of 6:2 FTA produced within the EU and/or imported into the EU need to be consistently quantified. This is to allow the evaluating MSCA to estimate the emissions arising from the production of 6:2 FTA in the EU, and the associated potential risks.

As regards information requests (iii) to (v) above, the information, if commercially sensitive, can be provided separately by each registrant or by the way of using an independent third party. If you are unable to gather suitable representative data for these parts of the life cycle of 6:2 FTA, you shall base your assessment of the specific life cycle stage on a reasonable worst case assumption (with a proper justification for instance demonstrating the most important emission pathway).

Alternative approaches and Proportionality of the request

In accordance with Articles 10(b) and 14(1) of the REACH Regulation, the registration must contain a chemical safety report (CSR) which documents the chemical safety assessment (CSA) conducted in accordance with Article 14(2) to (7) and with Annex I to the REACH Regulation.

Annex I, Section 5 of the REACH Regulation requires the Registrant to generate exposure scenarios and exposure estimations for the registered substance. The exposure assessment shall consider all stages of the life-cycle of the substance resulting from the manufacture and identified uses and shall cover any exposures that may relate to the identified hazards.

Pursuant to Annex I, Section 5.2.1 of the REACH Regulation, the exposure shall be estimated for each exposure scenario developed. The exposure estimation entails three elements: emission estimation, assessment of chemical fate and pathways and estimation of exposure levels. Emission estimation shall be performed under the assumption that the risk management measures (RMMs) and the operational conditions (OCs) described in the exposure scenarios (ES) have been implemented

Annex I, Section 6 of the REACH Regulation requires the Registrant to characterise the risk for each exposure scenario and to consider the human population (exposed as workers, consumer or indirectly via the environment and if relevant a combination thereof) and the environmental spheres for which exposure to the substance is known or reasonable foreseeable, under the assumption that the risk management measures described under exposure scenario in Section 5 of the same Annex have been implemented. In addition, the overall environmental risk caused by the substance shall be reviewed by integrating the results for the overall releases, emissions and losses from all sources to all environmental compartments.

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With regard to the scope of the required exposure assessment, as stated above and in accordance with Annex I, section 5.0., it has to cover all hazards that have been identified according to sections 1 to 4 of Annex I of REACH Regulation.

ECHA observes that the registered substance has a self-classification as STOT RE 2 and is thus fulfilling the criteria set out in Article 14(4) of the REACH Regulation for exposure assessment. Consequently, you are required to conduct an exposure assessment including the generation of exposure scenarios and a risk characterisation in the chemical safety assessment covering both human health and the environment. This assessment not only has to cover the assessment of exposure and related risks for humans and environment directly resulting from the use as such but also indirect routes of exposure. This refers to the different environmental compartments but also to the people as such who are not users of the substance (exposure pathway "man via the environment"). In addition part D of the Guidance on Chemical Safety Assessment under REACH (version 2.0; August 2016) states that exposure assessment may also be required in case that no classification results from the tests for aquatic toxicity, but adverse effects were observed at concentrations below the concentration limits of the standard OECD test guidelines for acute aquatic toxicity.

In addition, according to *ECHA's Guidance on information requirements and chemical safety assessment (version 3.0, February 2016), Chapter R.16, Section R-16.1.3. if "transformation products (or degradation products" or "metabolites") are stable and/or toxic they should be taken into account in the environmental assessment."*

Therefore, pursuant to Article 46 of the REACH Regulation, you are requested to provide further information on uses of 6:2 FTA and related releases into the environment covering the information request (i) to (v) above.

The information is needed because ECHA cannot make its own worst case assumptions on the basis of the data available in the registration dossiers. These serve as a starting point for identification of relevant routes of emissions of 6:2 FTA or the transformation products FTOH and PFHxA which are potential SVHC substances. This information is needed for follow-up considerations whether a regulatory action is needed for these potential non-threshold substances or if releases result from other sources/uses that are not covered within the identified uses of the registration.

In your comments you argue that there is no legal basis to request for information to be obtained through analysis of 6:2 FTA, 6:2 FTOH and PFHxA as residue or impurity which are (believed) to be degraded from polymer and/or assessment of such degradation itself, since the information on the registered monomer, i.e. 6:2 FTA, shall be sufficient under the REACH Regulation. You cite the Judgment of the Court (Grand Chamber) of 7 July 2009 (C-558/07 – S.P.C.M. and Others).

However, information request 1.3 as specified above in points (i)-(v) is in line with the REACH Regulation.

More specifically, the Board of Appeal of ECHA has confirmed (Decision of the Board of Appeal, 6 June 2018, SI Group UK Ltd et al v ECHA, A-006/2016) that Article 2(9) of REACH in conjunction with Article 46 of REACH must be interpreted as meaning that ECHA has the power to request information on the presence of a monomer in polymers as an unreacted impurity after polymerisation, or as a degradation product of those polymers, pursuant to the substance evaluation of a monomer. This information can be

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requested from the registrants of the monomer substance as there is no reason why they cannot provide the requested information on polymers that they supply themselves.

As the 'monomer substance' continues to exist in the polymer, environmental exposure towards that polymer is at the same time potential exposure to the 'monomer substance'.

In reply to your comments on the draft decision, ECHA has further specified the information requests (i) to (v) above.

Regarding to your concerns on competition law and possibly commercially sensitive data, ECHA points out that the information listed in points (i) to (v) above, if commercially sensitive, can be provided separately by each Registrant or by the way of using an independent third party. Therefore, there is leeway for you as how to provide the requested information without violating competition law and commercially sensitive information. Please refer to the ECHA Guidance on Data sharing, Version 3.1, January 2017, Section 7.3.3 in particular as an example of using a trustee for carrying out of CSA/CSR duties or sending sensitive individual information to the authorities.

Therefore, the specified information can be required under substance evaluation.

In response to the requests for environmental exposure and risk assessment in the draft decision, you stated that "*As such, emissions to the environment from the historic manufacture and use of fluorotelomer-based products has included 6:2 FTOH, 6:2 FTMAC, 6:2 FTAC and PFHxA. Therefore, present day environmental monitoring data in many matrices reflects largely historical emissions. The present findings are not only the result of a recent shift to production of short-chain 6:2 fluorotelomer-based products. Manufacturers and users have aligned on best practices to minimize environmental releases from present-day use*". Just because the registration dossier does not contain comprehensible information on operational conditions related to the releases to the environment ECHA is not able to evaluate what are the "best practices" to minimise emissions and whether these represent techniques that are commonly used within the EU.

Conclusion

Therefore, based on the substance evaluation and pursuant to Article 46(1) of the REACH Regulation, ECHA concludes that you are required to provide the following information on the registered substance subject to this decision: Further information on uses and environmental release estimations (see (i)-(v)).

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Abbreviations

4-NP	4-nonylphenol
AMA	Amphibian metamorphosis assay
BOD	Biochemical oxygen demand
CoRAP	Community Rolling Action Plan
DMSO	Dimethylsulphoxide
E2	Estradiol
EC_{50}	Half maximal effect concentration
ED	Endocrine disruptor
EE2	Ethinylestradiol
ELISA	Enzyme linked immunosorbent assay
ER	Estrogen receptor
FT	Fluorotelomer compounds
	6:2 FTOH 6:2-Fluorotelomer alcohol
	8:2 FTOH 8:2-Fluorotelomer alcohol

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	6:2 FTA	6:2 Fluorotelomer acrylate
	8:2 FTA	8:2 Fluorotelomer acrylate
	6:2 FTMA	6:2 Fluorotelomer methacrylate
	FTUCA	Fluorotelomer unsaturated acid
	FTCA	Fluorotelomer carboxylate
FSDT	Fish sexual development test	
GSI	Gonadosomatic index	
HPG	Hypothalamus-pituitary-gonadal	
HPT	Hypothalamus-pituitary-thyroid	
HSI	Hepatosomatic index	
IC_{50}	Half maximal inhibitory concentration	
LAGDA	Larval amphibian growth and development assay	
LOEC	Lowest observed effect concentration	
MBP	Myelin basic protein	
MoA	Mode of action	
MTT	3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide	
NIS	Sodium iodide symporter	
NOEC	No observed effect concentration	
Oct-1	Octamer motif-binding factor	
OECD	Organisation for Economic Co-operation and Development	
PBT	Persistent, bioaccumulative and toxic	
PFASs	Per- and polyfluorinated alkyl substances	
PFCA	Perfluoroalkyl carboxylic acids	
	PFBA	Perfluorobutanoic acid
	PFPeA	Perfluoropentanoic acid
	PFHxA	Perfluorohexanoic acid
	PFOA	Perfluorooctanoic acid
	PFNA	Perfluorononanoic acid
	PFDA	Perfluorodecanoic acid
	PFTrDA	Perfluorotridecanoic acid
qPCR	Quantitative polymerase chain reaction	
RC3	Neurogranin	
RMOA	Risk management option analysis	
SVHC	Substances of Very High Concern	
T	Testosterone	
T_3	Triiodothyronine	
T_4	Thyroxin	
TG	Test guideline	
TH	Thyroid hormone	
TR	Thyroid receptor	
TTR	Transtyretin	
VTG	Vitellogenin	
vPvB	Very persistent, very bioaccumulative	

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Appendix 2: Procedural history

On the basis of an opinion of the ECHA Member State Committee and due to initial grounds for concern relating to potential endocrine disruptor, suspected PBT/vPvB, other (high mobility in the environment), wide dispersive use and exposure of the environment, 3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl methacrylate CAS No 2144-53-8 (EC No 218-407-9) was included in the Community rolling action plan (CoRAP) for substance evaluation to be evaluated in 2016. The updated CoRAP was published on the ECHA website on 22 March 2016. The Competent Authority of Germany (hereafter called the evaluating MSCA) was appointed to carry out the evaluation.

Pursuant to Article 45(4) of the REACH Regulation the evaluating MSCA carried out the evaluation of the above substance based on the information in your registration(s) and other relevant and available information.

The evaluating MSCA considered that further information was required to clarify the following concerns:

- potential endocrine disruptor
- wide dispersive use
- exposure of the environment

Therefore, it prepared a draft decision pursuant to Article 46(1) of the REACH Regulation to request further information. It submitted the draft decision to ECHA on 20 March 2017.

The decision making followed the procedure of Articles 50 and 52 of the REACH Regulation.

ECHA notified you of the draft decision and invited you and the other Registrant(s) to provide comments.

Registrant(s)' commenting phase

ECHA received comments from you and forwarded them to the evaluating MSCA without delay.

The evaluating MSCA took into account the comments from the Registrant and they are reflected in the Reasons (Appendix 1). The requested information was not changed in response to the submitted comments.

Proposals for amendment by other MSCAs and ECHA and referral to Member State Committee

The evaluating MSCA notified the draft decision to the Competent Authorities of the other Member States and ECHA for proposal(s) for amendment.

Subsequently, the evaluating MSCA received proposal(s) for amendment to the draft decision and modified the draft decision. They are reflected in the reasons (Appendix 1).

ECHA referred the draft decision, together with your comments, to the Member State Committee.

ECHA invited you to comment on the proposed amendment(s).

Your comments on the proposed amendment(s) were taken into account by the Member State Committee. Some of these comments referred to SVHC identification of PFHxA which are not relevant for this decision.

MSC agreement seeking stage

The Member State Committee reached a unanimous agreement on the draft decision during its MSC-62 meeting and ECHA took the decision according to Article 52(2) and 51(6) of the REACH Regulation.

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Appendix 3: Further information, observations and technical guidance

1. This decision does not imply that the information provided by you in the registration(s) is in compliance with the REACH requirements. The decision neither prevents ECHA from initiating compliance checks on your dossier(s) at a later stage, nor does it prevent a subsequent decision under the current substance evaluation or a new substance evaluation process once the present substance evaluation has been completed.

2. Failure to comply with the request(s) in this decision, or to fulfil otherwise the information requirement(s) with a valid and documented adaptation, will result in a notification to the enforcement authorities of your Member State.

3. In relation to the required experimental study/ies, the test materials to use are specified under Section 1. Requested information.

4. In relation to the experimental stud(y/ies) the legal text foresees the sharing of information and costs between Registrant(s) (Article 53 of the REACH Regulation). You are therefore required to make every effort to reach an agreement regarding each experimental study for every endpoint as to who is to carry out the study on behalf of the other Registrant(s) and to inform ECHA accordingly within 90 days from the date of this decision under Article 53(1) of the REACH Regulation. This information should be submitted to ECHA using the following form stating the decision number above at:
https://comments.echa.europa.eu/comments_cms/SEDraftDecisionComments.aspx

   Further advice can be found at:
http://echa.europa.eu/regulations/reach/registration/data-sharing. If ECHA is not informed of such agreement within 90 days, it will designate one of the Registrants to perform the stud(y/ies) on behalf of all of them.