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FluoroCouncil
Global Industry Council for FluoroTechnology

FluoroCouncil's response to the SVHC proposal for PFHxA

Contents

1. Executive summary

Germany submitted a proposal to list undecafluorohexanoic acid (also known as perfluorohexanoic acid, or "PFHxA") as Substance of Very High Concern (SVHC) according to Article 57(f) of Regulation (EC) No 1907/2006 (REACH).

In effect, Germany's opinion is that PFHxA should be identified as a SVHC due its persistence, mobility in the aquatic environment, long-range transport potential, potential to enrich in plants, remediation challenges, and "high uncertainty" regarding toxicity.

However, as this response document aims to demonstrate, there is ample evidence to specifically evaluate PFHxA's toxicity, environmental persistence, occurrence, fate and related risks. **These data do not support the listing of PFHxA as SVHC**.

Available PFHxA-specific toxicity information is sufficient to assess human health hazards from chronic exposure. Studies demonstrate that PFHxA is not carcinogenic, mutagenic, endocrine disrupting, or toxic for reproduction, and that toxicity data are sufficient to derive safe thresholds.

Empirical data on PFHxA in the environment and in human serum from biomonitoring studies are consistent and support a conclusion with high confidence that PFHxA is either unlikely to be present or is present at very low levels in the general population.

Recent advances in remediation technologies, including ion exchange resins and membrane filtration, have resulted in full-scale water treatment technologies able to effectively and efficiently remove short-chain perfluoroalkyl acids (PFAAs), including PFHxA, from groundwater and drinking water. In addition, the ongoing efforts to minimize emissions along the value chain do not support the assumption that C6 levels will significantly increase in the environment as a consequence of the substitution from C8 to C6 fluorotelomers.

The proposal by Germany regarding exposure fails to demonstrate, even in an approximate manner, at what rate accumulation in the environment could supposedly take place, if any, and whether or not and in what time framework, the resulting level could create any harm to human health.

It should be highlighted, furthermore, that this SVHC proposal is unprecedented. While the scope of the Equivalent Level of Concern (ELoC) is not clear, whether it relates to CMR and PBT/vPvB or only to PBT/vPvB (cf. page 5 of the dossier), it is the first time that a SVHC proposal includes a concern about mobility in the water compartment, and more generally, that ELoC is claimed for environmental effects other than endocrine disruption (which is specifically mentioned in Article 57(f)).

However, unlike for human health, criteria to assess environmental effects in comparison with those of PBT/vPvB substances do not exist. We therefore call for **an objective, transparent policy discussion on ELoC criteria for environmental effects, before it can be considered as a valid basis for SVHC identification**. Failure to properly implement the ELoC principle would **create a precedent and result in legal uncertainty** that could impact a large number of substances and sectors of the European economy.

2. Toxicological data for PFHxA demonstrates low human health and environmental hazard

Epidemiological studies and a full suite of standard laboratory assays are available for PFHxA, including:

- Four epidemiology studies of children and adults (Dong et al. 2013; Fan et al. 2014; Zhou et al. 2016; Li et al. 2017)
- Two-year rodent cancer bioassay (Klaunig 2015)
- DNA mutation and genotoxicity *in vitro* assays (NTP 2018; Loveless 2009; Eriksen 2010)
- Chronic systemic toxicity rodent bioassay (Klaunig 2015)
- Reproductive/Developmental rodent bioassays (Loveless 2009; Iwai and Hoberman 2014; Iwai et al. 2018 (in review))
- Sub-chronic systemic toxicity bioassays (Loveless 2009; Chengelis 2009a; Iwai and Hoberman 2014; Iwai et al. 2018 (in review); NTP 2018)
- Analysis of endocrine disruption (Behr 2018; Borghoff 2018)
- High-throughput molecular *in vitro* assays (USEPA Tox21)
- Toxicokinetic assays in rats, mice, microminipigs, monkeys and humans (many, examples include Chengelis 2009b; Iwai 2011; Russell 2013, 2015; Nilsson 2010, 2013; Fujii 2014; Guruge 2015; Gannon 2011, 2016)

2.1 Available human data do not show a strong association between PFHxA exposure and any human health disease.

Dong et al. 2013 investigated the relationship between serum levels of 11 perfluorinated compounds, including PFHxA, and levels of immunological markers (e.g., IgE, absolute eosinophil counts, eosinophilic cationic protein) in asthmatic Taiwanese children (N=231) and nonasthmatic controls (N=225). No association between serum PFHxA levels and immunological markers or asthma outcomes were detected. Zhou et al. (2016) investigated the relationship between serum levels of nine PFAS and sex hormone levels (e.g., testosterone and estradiol) in Taiwanese teenagers (N=225). A negative association between serum PFHxA and testosterone levels was identified in Taiwanese boys, however, the authors note that puberty indicators and diurnal cyclicity, both of which can influence sex hormone levels, were not accounted for in the study analysis. A study of the general population in China (N=202) found that exposure to PFHxA was positively associated with two biomarkers of thyroid autoimmune disease – thyroglobulin antibody (TGAb) and thyroid microsomal antibody (TMAb) – but not TSH, free T4, or T3 (Li et al. 2017). This positive finding is inconsistent with evidence from rat studies of thyroid effects following exposure to PFHxA (Loveless 2009, Iwai 2014). Furthermore, the study authors did not statistically control for the multiple PFAS exposures in their analyses; PFOS and PFOA accounted for approximately 70 - 90% of the total sum of blood PFAS in the Li et al. (2017) cohort. A study conducted using the C8 Health Study cohort investigated the relationship between serum levels of 10 PFAS and Gilbert syndrome (GS; genetic disorder characterized by hyperbilirubinemia) (Fan et al. 2014). Statistically significant differences in geometric serum PFHxA levels were noted for individuals who expressed the GS phenotype (both men and women). However, genetic testing was not part of the classification criteria, indicating that it is likely that some individuals in the control group were misclassified.

Overall, the epidemiology studies provide some evidence of statistical associations between serum PFHxA levels and testosterone (Zhou et al. 2016), thyroid antibody markers (Li et al. 2017), and Gilbert Syndrome (Fan et al. 2014). However, all identified studies are cross-sectional in nature (can only be used to identify associations, not causal relationships), had other methodological weaknesses, and individuals had co-exposures to other PFAS that were not controlled for in analyses. **Therefore, the available human literature to date does not show a strong association between PFHxA exposure and any human health disease.**

2.2 PFHxA does not exhibit carcinogenicity, mutagenicity, or genotoxicity

PFHxA was not carcinogenic and has not exhibited any DNA mutation or genotoxic effects in several studies (NTP 2018, Klaunig 2015, Loveless 2009, Nobels 2010). A chronic rat cancer bioassay found no increase in neoplasms in any organ of male or female rats exposed to high levels of PFHxA (up to 200 mg/kg-day) for 104-weeks (Klaunig et al. 2015). The genotoxicity of PFHxA has been investigated *in vitro* (Eriksen et al. 2010; Burke et al. 2013; Loveless et al. 2009; NTP 2018), and all results were negative. PFHxA has also been evaluated for mutagenicity in the bacterial reverse mutation (Ames) assay according to OECD Guideline 471 (Burke et al. 2013; Loveless et al. 2009; NTP 2018). None of these studies found PFHxA to be mutagenic in *Salmonella typhimurium* (TA98, TA100, TA1535, TAA1537) or *Escherichia coli* (WP2uvrA, pKM101). Loveless et al. (2009) also tested PFHxA in the chromosomal aberration assay in accordance with OECD Guideline 473 and found no chromosomal damage in human peripheral blood lymphocytes exposed to activated (S9 activation system) or non-activated PFHxA. In general agreement with this, NTP (2018) found no chromosomal aberrations in red blood cells harvested from female Harlan SD rats orally (gavage) exposed to PFHxA (doses ranged from 31.3 to 500.0 mg/kg). Burke et al. (2013) conducted an *in vitro* micronucleus test with V79-cells in accordance with OECD Guideline 487 and found that PFHxA did not induce micronuclei formation. **Combined, there is strong evidence to conclude that PFHxA is not carcinogenic, mutagenic, or genotoxic.**

2.3 PFHxA is not an endocrine disruptor.

The dossier refers to in vitro data supported by in vivo fish data on homologues, with the conclusion that not enough evidence is available to conclude on the endocrine effects for PFHxA in the environment. (p. 73).

On this, a comprehensive weight-of-evidence review of both *in vitro* and *in vivo* studies evaluating PFHxA activity across endocrine pathways shows that PFHxA is not bioactive in estrogen, androgen, aromatase or thyroid receptor signaling pathways (Borghoff et al. 2018) and studies have shown that PFHxA does not act as an estrogen or androgen receptor agonist or antagonist at environmentally relevant levels (Behr 2018).

Additionally, PFHxA showed no bioactivity in any of U.S. Environmental Protection Agency ToxCast/Tox21 high-throughput screening assays pertaining to androgen receptor, aromatase activity, estrogen receptor, or thyroid receptor (USEPA 2017).

Based on the lack of evidence for endocrine disruption by PFHxA in both *in vivo* mammalian and non-mammalian models, as well as the overall lack of endocrine bioactivity in *in vitro* studies, PFHxA is not an endocrine disruptor.

2.4 PFHxA does not exhibit adverse effects on reproduction or development

The reproductive and developmental toxicity of PFHxA has been investigated in mammalian (Iwai et al. 2018 (in review); Iwai & Hoberman 2014; Loveless et al. 2009) and non-mammalian models (ECHA

2015; Frey et al. 2010). PFHxA has not demonstrated any adverse reproductive or developmental effects in mice or rats, as evident by several OECD guideline studies. PFHxA exposure did not cause any developmental effects in rats (Loveless 2009). A mouse study indicated some potential developmental concerns due to low incidences of increased stillbirths, pup death at postnatal days 1 to 4, and effects on the eye (Iwai 2014). However, when the full concurrent controls are included and when historical controls from the same mouse strain and lab are evaluated, it is clear that the low incidence of stillbirths is unrelated to PFHxA exposure [Iwai et al. 2018 (in review)]. No signs of male reproductive toxicity and no changes in uterus weight were reported in a recent 28-day subchronic rat study (NTP, 2018). Several in vivo guideline studies using non-mammalian models have also been conducted to assess the reproductive toxicity of PFHxA. No adverse effects on fertility or fecundity were observed in medaka (ECHA 2015), and no PFHxA-related effects on multiple reproductive parameters were reported for bobwhite quail (Frey et al. 2010). **Collectively, results from in vivo mammalian and non-mammalian studies indicate that PFHxA is not a reproductive or developmental toxicant.**

2.5 Toxicology data are sufficient to derive a human health-based chronic toxicity value for PFHxA

The currently available database for PFHxA is quite standard for environmental chemicals. Effects noted from high level exposure (more than 100 mg/kg) to PFHxA in subchronic and chronic noncancer rodent bioassays include liver, thyroid, kidney and hematologic effects (Loveless 2009, Chengelis 2009, Iwai 2014), with the lowest no-observed-adverse effect level (NOAEL) of 30 mg/kg-day from the chronic rat study (Klaunig 2015). **The French agency for food safety, environment and labor, ANSES derived a toxicity value for PFHxA** based on kidney effects from the chronic rodent study (Klaunig 2015), which was deemed protective of all other potential health endpoints of concern (ANSES 2017). Given the extremely quick elimination of PFHxA from all species tested, the agency applied the standard allometric scaling based on body weights to convert the rodent administered dose to the human equivalent dose. This methodology has been shown to be appropriate for PFHxA specifically (Russell 2013). The agency also applied standard uncertainty factors to account for variability in humans and database uncertainty. **The final PFHxA oral chronic toxicity value is 0.32 mg/kg-day**.

Compared to the most stringent toxicity value for PFOA derived by the United States Environmental Protection Agency (USEPA 2016) (i.e., an oral reference dose of 0.00002 mg/kg-day), the comparable toxicity value for PFHxA is four orders of magnitude greater. Furthermore, when this toxicity value is applied to the standard USEPA drinking water health advisory calculation, the result is a drinking water health advisory of 2.2 mg/L (2.2 x10^6 parts per trillion (ppt)), which is almost 32,000 times higher than the USEPA health advisory for PFOA of 70 ppt[1]). **This finding underscores the importance of evaluating PFHxA data rather than extrapolating findings from PFOA or other PFAAs.**

The derived-no-effect-level (DNEL), equivalent to an RfD, presented in the PFHxA Annex XV document (p. 77) is highly questionable and unsuitable for use in assessing human health. It is not clear why the ANSES value was not presented. ANSES used the chronic rat study (Klaunig 2015) rather than 90 day Chengelis et al. 2009 study. A chronic exposure study is the most appropriate toxicity study for assessing human-health effects from potential long term exposure. Moreoever, the no-observed adverse effect level (NOAEL) of 10 mg/kg-day was selected as the starting point for the DNEL-derivation,

[1] USEPA (2016) did not use the standard drinking water exposure parameters when deriving the health advisory for PFOA. Their critical effect for PFOA was a developmental endpoint; they used a drinking water intake rate for lactating women rather than standard adult parameters.

however statistically significant adverse effects (i.e. minor changes in relative liver and kidney weights) were only seen at the highest dose group (200 mg/kg-day), which means that the mid-dose group, 50 mg/kg-day, should be defined as the NOAEL. Lastly, the "assessment factors" applied (4 for allometric scaling, 2.5 for toxicodynamics, 10 for intraspecies differences, and 2 to extrapolate from subchronic to chronic) are not justified and appear highly uncertain. Even with these apparent technical deficiencies, the DNEL for PFHxA presented in the Annex XV report is 2500 times greater than the most stringent RfD available for PFOA (USEPA 21016). After a comprehensive review of the collective evidence, the potential for human health risks from PFHxA exposure at relevant levels is low. When the collective toxicological data are reviewed, the conclusion can be reached that PFHxA would "not [be] considered to cause serious damage to health" (NICNAS 2017, p.11).

2.6 PFHxA exhibits low toxicity for the environment

As stated in the SVHC proposal, **no adverse effects have been observed** in the various tests conducted on ecotoxicity for algae, daphnia and fish covering acute as well as chronic toxicity (p. 68). Further, it is stated that "studies on aquatic organisms show no effects at environmentally relevant concentrations of PFHxA" (p. 73). The dossier raises potential concerns with respect to exposure to mixtures in the long-term, but fails to provide any evidence. With respect to endocrine disrupting effects, **the dossier has not analysed many available studies, both in vivo and vitro, which are referred to above in the document, and which suggest no endocrine activity.**

3. Absence of mobility criteria, no bioaccumulation and very slow degradation

3.1 PFHxA is characterized as (very) mobile without clear criteria for mobility

The SVHC proposals concludes that "PFHxA is mobile in the aquatic environment" (p. 33) without giving clear and consistent criteria of the mobility concept. Is it the ability to reach groundwater via bank filtration? Is it the ability to pass water filtration membrane for drinking water production? Is it the ability to cover long distances? Is it based on intrinsic properties of PFHxA or based on the results of water monitoring (i.e. exposure considerations)?

No intrinsic cut-off criterion is given, except log Koc cut-off values of 4 for mobility (M) and 3 for high mobility (vM), which are merely based on Germany's proposal on PMT/vPvM as ELoC to PBT/vPvB. This proposal is dated from November 2017 and is far to reach an agreement within the EU. Furthermore, the dossier submitter contradicts itself as it claims "*the technical guidance documents of REACH define a range of log Koc = 3.0 to 4.0 as threshold when a substance can be considered to have high potential for adsorption*" and at the same time considers that substance log Koc in the 3-4 range should be considered mobile. According to ECHA's guidance on information requirements and chemical safety assessment, chapter R.7b (v4.0; June 2017; p.146; first paragraph), substances with "*log Koc > 3*" are considered "*strongly adsorbing*". Therefore, it is scientifically irrelevant to consider substances with log Koc just below 3 as very mobile. In addition, a log Koc value of 3.6 for PFHxA as found in one study would make PFHxA not mobile according the criterion set out in ECHA's guidance chapter R.7b. In addition, Wang et al. (2011) give a log Kow of 4.06, which does not even fulfill Germany's own M criterion.

Thus, it is unclear how the dossier submitter comes to the conclusion that PFHxA is "very mobile" (p. 6). **A clear definition of mobility should be provided so that any line of evidence can be confronted to the definition.**

Finally, while the dossier does not clearly refer to the concepts of PMT or vPvM as proposed by the German Federal Environment Agency (UBA), the mobility aspect is of particular importance in this respect. ELoC to PBT is not applicable to PFHxA since PFHxA does not meet the T classification criteria and can therefore not be regarded as PMT. Similarly, if PFHxA is not vM, this would not support an ELoC to vPvB.

3.2 PFHxA is not bioaccumulative.

The carbon-fluorine bonds contribute to the extreme stability of PFHxA, and as discussed previously, PFHxA has relatively higher solubility in water which may result in higher mobility in soil. However, these properties are not predictive of the bioaccumulation potential of PFHxA. PFHxA is rapidly eliminated in humans and other mammals. PFHxA is nearly completely eliminated from the serum of mice, rats, and monkeys 24 hours after dosing (Chengelis et al., 2009b; Iwai 2011), suggesting that no bioaccumulation is occurring. The estimated human half-life of PFHxA is approximately 32 days, compared with 3-5 years for PFOA (Gannon 2011; Russell 2013). Furthermore, Russell et al. (2013) note no apparent trend of bioaccumulation in professional ski wax technicians occupationally exposed to PFHxA over four years. The consistent low-level FOD and low levels in human serum, as discussed above, provide further lines of evidence that PFHxA does not bioaccumulate in humans or mammals. PFHxA also does not bioaccumulate in fish (Martin 2003a, 2003b). Most studies suggest PFHxA does not bioaccumulate, or has weak bioaccumulative properties in earthworms (Moshfeghi 2015; Zhao et al., 2013; Zhu et al., 2019); published biota-sediment accumulation factors for PFHxA are <1, suggesting PFHxA is not bioaccumulative. **In summary, these studies support the conclusion that PFHxA is not bioaccumulative in humans, mammals, aquatic organisms or low sediment-dwelling invertebrates.** This conclusion is consistent with the biological mechanisms of PFHxA tissue distribution and elimination kinetics, discussed below. Moreover, this conclusion is important with respect to the concern reflected in the dossier that "PFHxA is taken up in plants" (p. 48). The large body of evidence available on the non-bioaccumulation of PFHxA tends to dispute the statement that "the enrichment in plants might lead to an enrichment in other organisms" (p. 48). Further it questions if, for a not-bioaccumulative substance, this should be regarded as of "high concern" (p. 48).

3.3 PFHxA does not have as high a binding affinity for proteins as long-chain PFAAs, as demonstrated by numerous protein binding assays.

Protein rich body compartments such as the liver, kidney, and blood are the primary tissues for the retention of long-chain PFAAs such as PFOA and PFOS (Jones 2013). This is due to the high non-covalent binding affinity of long-chain PFAAs to serum proteins such as serum albumin (Bischel 2010). Furthermore, the extensive renal tubular reabsorption of long-chain PFAAs is mediated by high affinity binding to the organic anion transport proteins (OATs) located within the proximal tubular cell membranes (Yang 2010; Han 2011). A wide range of association constants and affinity parameters have been reported for PFAAs and serum albumin and OATs. Specifically, all studies have shown that the carbon-chain length and functional group directly influence the protein binding capacity; binding affinity is highest for PFAAs having at least eight carbon atoms.

- Serum protein binding – PFHxA with a carbon chain length of six has a reduced protein binding affinity (Han 2011; Fuji 2015). Using a fluorescence model for binding, Herbert et al. 2010 demonstrate that PFHxA does not appear to bind to the human serum albumin protein in the same manner as long-chain PFAAs.
- Liver protein binding – PFAA binding to liver proteins such as the liver fatty acid binding protein (FABP) is thought to be important for tissue distribution and liver effects (Ng and Hungerbuhler 2013; Zhang 2009; Han 2003). However, PFHxA has shown no binding affinity to the human

liver FABP in several studies (Sheng 2016; Zhang 2013), further demonstrated a marked difference between long chain PFAA protein binding and PFHxA.

In summary, there are multiple biological mechanisms that help to explain the observed low bioaccumulation potential of PFHxA. **Unlike longer-chain PFAAs, PFHxA does not tend to accumulate as a bound fraction to protein in blood serum or the liver, nor is PFHxA likely to be reabsorped in the proximal tublar cell membranes of the kidney**, **as PFHxA has been shown to be rapidly eliminated in every mammalian species tested to date.**

3.4 PFHxA is rapidly eliminated from all mammals.

Renal elimination is the most significant route of elimination and a determining factor for PFAA-specific internal body concentrations/exposure and long elimination half-lives. Because PFAAs vary in their protein binding affinities, as discussed above, the elimination kinetics and bioaccumulation of PFAAs in mammalian systems is directly related to the fluorinated carbon chain length, functional group, and associated protein binding (Conder 2008; Han 2011).

PFHxA is nearly 100% eliminated within the first day after dosing in rodents (Gannon 2011). The elimination half-lives of PFHxA are reported as 0.5 to 1.7 hours in rats and 2.4 to 5.3 hours in monkeys (reviewed in Han 2011). The elimination kinetics for PFHxA have also been analyzed in humans (a cohort of professional ski was technicians), and the apparent half-life estimated at approximately 32 days (Russell 2013; note that this was not a formal pharmacokinetic study). The half-lives of PFHxA in mice, rats, monkeys and humans are proportional to body weight, with no significant differences observed between males and females, suggesting similar elimination mechanisms (Russell 2013), and therefore, less inter-species extrapolation uncertainty compared with long-chain PFAAs.

3.5 Very slow degradation from C6 fluorinated polymers

Recent degradation tests on a C6 methacrylate-based fluorinated polymers have shown **very slow degradation in soil under aerobic and anaerobic conditions, under a: $t_{1/2}$ ca. 3,000 years** (Archroma, 2017). Both test protocols have been approved by the US EPA. These data contribute to lowering the risk of exposure to PFHxA from the use of C6 fluorinated polymers.

4. Exposure is, and will likely remain low for PFHxA

4.1 Detection of PFHxA in the environment is generally low, and infrequent

While the dossier refers to several studies reporting findings of PFHxA (p. 29), it should be highlighted that in general, PFHxA has a low frequency of detection (FOD) and is detected at low levels in most studies that have investigated its occurrence in ground water (GW), surface water (SW), and drinking water (DW) at sites not associated with an identified point-source contamination. Gellrich et al (2013) investigated the occurrence of various PFAAs, including PFHxA, in tap water, untreated water, bottled water, and spring water across Germany. PFHxA was generally not detected, with the exception of low concentrations (median: 2.0 ng/L; maximum: 6.4 ng/L) in 23% of tap water samples.

In another study, Skultlarek et al (2006) measured the occurrence of various PFAAs in DW within and outside of the Ruhr area of Germany. Outside of the Ruhr area, PFHxA occurred at a very low frequency (6.3%) and concentration (≤ 9 ng/L) in DW. As stated in the SVHC Proposal, concentrations of PFHxA in tap water range are below the German guide value for drinking water (Trinkwasserleitwert) of 6 µg/l. (p.31)

PFHxA has been infrequently detected at low concentrations in snow, sediment, and seawater in remote locations. It is still not well understood if these detections were a result of direct emission or degradation of PFHxA precursors or both (reviewed in Environ 2014, Rankin et al. 2016).

Occurrence studies consistently demonstrate that PFHxA is simply not found at a high frequency or at high levels within the environment. Some environmental (and human) monitoring programs has been discontinued for this reason.

Occurrence of PFHxA in different water sources (concentration units are µg/L).

Sample Type	Location	Year	N	FOD	Min	Median	Mean	Max	Reference
SW Rhine river & tributaries	Germany	2006	38	32%	<LOQ	-	-	77	Skultlarek et al. 2006
SW Ruhr	Germany	2006	29	76%	<LOQ	-	-	1,248	Skultlarek et al. 2006
SW Moehne river & tributaries	Germany	2006	12	67%	<LOQ	-	-	3,040	Skultlarek et al. 2006
DW Ruhr	Germany	2006	28	75%	<LOQ	-	-	56	Skultlarek et al. 2006
DW outside of Ruhr	Germany	2006	16	6.3%	<LOQ	-	-	9	Skultlarek et al. 2006
TW	Germany		26	23%	< 1	2.0	-	6.4	Gellrich et al. 2013
Untreated water	Germany		14	0%	< 1	< 1	< 1	< 1	Gellrich et al. 2013
BW	Germany		119	0%	< 1	< 1	< 1	< 1	Gellrich et al. 2013
Spring water	Germany		18	0%	< 1	< 1	< 1	< 1	Gellrich et al. 2013
GW[2]	USA	2014	149	94%	<LOQ	820	-	120,000	Anderson et al. 2016, 2019
BW = bottled water; DW = drinking water; FOD = frequency of detection; GW = groundwater; LOQ = limit of quantitation; mean = arithmetic mean; N = sample size; NJ = New Jersey; SW = surface water; TW = tap water; "-" = not reported									

4.2 PFHxA has a low frequency of detection in humans and, when detected, the range of concentrations is low relative to the detection limits.

Biomonitoring surveys consistently demonstrate that PFHxA is infrequently detected in human serum in the general population, particularly compared with most other PFAAs (Frisbee et al. 2009; New Zealand Ministry of Health 2013; Olsen et al. 2017; Lee et al. 2017; Health Candada 2013; Japan Ministry of the Environment 2016; Li et al. 2017; Ingelido et al. 2018; Karman et al. 2006; Falandysz et al. 2006; First Nations Biomonitoring Initiative, 2013). Karrman et al. (2006) detected PFHxA in only 8%

of serum samples (N=66) in a biomonitoring study in Sweden, while Ingelido et al. (2018) detected PFHxA in ~20% of serum samples (N= 507) in Italy. In contrast, PFOA was detected in 100% of samples in both biomonitoring studies. In the First Nations Biomonitoring Initiative (2013), PFHxA was always below the detection limit. Some biomonitoring studies in Europe have detected PFHxA at higher frequencies, for example, Falandysz et al. (2006) detected PFHxA in 80% of serum samples collected in Poland (N=60); however, the mean serum concentration was low (0.03 ng/mL; max = 0.24 ng/mL), compared to mean serum PFOA levels (3.3 ng/mL; max = 8.7 ng/mL) (Falandysz et al. 2006). Furthermore, recent analysis conducted by the United States Centers for Disease Control and Prevention to develop standard methods for detecting short-chain PFAAs in urine reveal that PFHxA is also not detected in preliminary evaluations of the general United States adult population (Kato et al. 2018, Calafat 2018). Although preliminary, the lack of PFHxA detections in urine is striking, given that urine has reliably served as an important media for detecting other non-biologically persistent pollutants, such as phthalates. The preliminary results in the United States are consistent with a urinary biomonitoring study in South Korea in which the FOD for PFHxA ranged from 5-11% in child and adult urine samples (Kim et al. 2014). Collectively, the available biomonitoring data provide another line of evidence that PFHxA exposure to the general human population is low and PFHxA does not bioaccumulate over time.

PFAS such as long-chain PFOA and PFOS are frequently detected in breast milk, however, fewer studies have investigated the presence of PFHxA in breast milk. Studies of populations in France and Spain demonstrate that PFHxA is detected in 10% or less of the breast milk samples, at concentrations less than 100 ng/mL (Kadar et al. 2011; Antignac et al. 2013' Cariou et al. 2015; Lorenzo et al. 2016). In two studies conducted in Korea, the FOD ranged from 40% to 71% and the maximum PFHxA concentration was 250 ng/L (Kang et al. 2016; Lee et al. 2018), compared to PFOA which was detected in 88 to 99% of samples at a maximum concentration of 657 ng/L. The low FOD and PFHxA levels detected are consistent with the biomonitoring results for human serum and urine discussed previously.

The data available to date clearly demonstrate that there continues to be a low FOD and magnitude of PFHxA throughout the general global population (i.e., absent site-specific environmental contamination). Low detection levels and rates of PFHxA in human serum, urine, and breast milk indicate that human exposure to PFHxA is limited, likely also influenced by rapid elimination kinetics (see discussion below). Additionally, the fact that PFHxA is thus far rarely detected in urine further suggests that human exposure to PFHxA, if and when it occurs, is not of sufficient magnitude, frequency, and/or duration to be retained or to accumulate in tissues.

4.3 There are multiple full-scale treatment technologies available to remove PFHxA from water

Unlike what is claimed in the SVHC dossier, according to which "for the current state of technology it can be concluded that it is very difficult, or even impossible, to remove PFHxA from (waste) water or from the environment" (p. 53), **proven full scale water treatment technologies are currently available for the removal of PFHxA from water**. These technologies include in particular ion exchange resins and membrane filtration. These ex situ treatment technologies have been applied to drinking water supplies, groundwater remediation, and industrial wastewater treatment.

Ion Exchange Resins

Ion exchange resins are an established treatment technology for many common contaminants in both municipal drinking water and groundwater, including sulfate, chromate, nitrate, chloride, and perchlorate. Full scale ion exchange resin systems engineered to treat PFAS impacted water are currently in operation in Australia and the United States (ITRC 2018). The resins utilize both adsorption

and ion exchange, which effectively remove long and short-chained PFAS compounds by attraction of both the polar and non-polar properties of PFAS compounds (ECT2 2018a). Ion exchange resins designed to selectively remove PFAS are not subject to the same degree of fouling as carbon-based sorbents (ITRC 2018).

Ion exchange resins are designed to be regenerable or disposed of after breakthrough of target compounds (single use). Resin regeneration is typically performed within the ion exchange treatment vessel, and results in a highly concentrated regenerant waste that requires further treatment and disposal. Currently available literature regarding PFAS removal has focused on regenerable ion exchange resins, however, single use resins are gaining traction in the remedial market as they have lower initial capital costs and the used resin can be disposed of by incineration (ITRC 2018).

The regenerable ion exchange resin Sorbix LC1 was designed to treat an array of PFAS compounds, specifically short-chain PFAS, and is currently in use in multiple full-scale ion exchange groundwater treatment plants in Australia and the United States (ECT2 2018a,b). United States-based company Emerging Compounds Treatment Technologies (ECT2) developed designed, fabricated, and oversaw the installation of ion exchange resin groundwater treatment plants at two separate Australian Government Department of Defence (Defence) sites formerly used for fire-fighting training (ECT2 2018a,b). The two Australian plants have a similar design to one another: each are capable of operating at 192 liters per minute (50 gallons per minute), and each contain two vessels filled with Sorbix A3F resin followed by polish vessels containing Sorbix LC1 (ECT2 2018a,b). Influent PFAS concentrations range from 1-120 µg/L and both plants have demonstrated removal of three regulated target PFAS compounds, including short-chain PFAS perfluorohexane sulfonic acid (PFHxS), below reportable limits of 10 parts per trillion (ppt) (ECT2 2018 a,b; Defence 2018). ECT2 is currently building a second, larger PFAS removal and resin regeneration system capable of treating 750 liters per minute (200 gallons per minute) at an identified source area on one of the Defence sites (ECT2 2018a).

Additional commercially available ion exchange resins have demonstrated short-chain PFAS removal at the bench scale. Purolite Purofine® PFA694E is a single use resin being marketed for point of entry and point of use systems for removal of both long and short-chain PFAS (Purolite 2018). Bench-scale results from treatment of municipal well water with PFA694E showed 100% removal of PFHxA, reducing concentrations below 1 part per trillion, as compared with less than 10% by a bituminous granular activated carbon sorbent (Purolite 2018). Separately, bench-scale experiments tested the removal efficacy of PFHxA from synthetic and fluorochemical plant wastewater using five different commercially available Purolite resins; Purolite resin BA103 was found to have the highest PFHxA adsorption capacity of the five tested resins, with removal rates ranging from 101-320 mg/g/hour (Karnwadee 2015).

Membrane Filtration

Two commercially available membrane filtration technologies, reverse osmosis and nanofiltration, have demonstrated effective removal of PFAS regardless of chain length (Dickenson 2016). In each of these technologies, impacted water is forced via high pressure through a filter membrane with a high contact area, producing a high concentration rejectate while allowing the treated filtrate to pass through. Dickenson and Higgins (2016) evaluated fifteen full-scale water treatment systems and concluded reverse osmosis was the most effective PFAS treatment method evaluated in the study: reverse osmosis systems at two California potable reuse treatment plants demonstrated removal of all PFAS analyzed, including PFHxA, to below reportable quantities (less than 0.50 ng/L for PFHxA) (Dickenson 2016). Additionally, reverse osmosis techniques have been designed for household under

sink and residential well water PFAS treatment with removal rates greater than 90% for PFHxA (AWWA 2016).

It is to be noted that though full-scale implementation of nanofiltration has not yet been demonstrated for PFAS removal, commercially available nanofiltration membrane systems could evolve to be just as effective as reverse osmosis (ITRC 2018). Nanofiltration was shown to reject PFHxA at greater than 95% removal rates in bench scale testing of the Dow FILMTECTM NF270, NF200, and NF90 membranes (Steinle-Darling 2008) and field pilot-scale testing of two NF270 membranes in series at a Swedish drinking water treatment plant (Lindegren 2015).

Water treatment technologies capable of complete destruction of PFHxA are in development and may eventually evolve to commercial full-scale applications.

Current commercially available treatment technologies (e.g. ion exchange resin, membrane filtration) do not destroy PFAS but rather concentrate PFAS in the spent media, rejectate water, or regenerant solution. Ongoing research is being performed to develop advanced chemical oxidation techniques that are capable of complete PFAS destruction. AECOM (2018) developed the DE-FLUOROTM electrochemical oxidation technology, a proprietary electrode capable of PFHxA destruction. The manufacturer is currently identifying trial sites for the treatment of groundwater and commercialization of this technology is underway (AECOM 2018). Heat activated persulfate chemical oxidation has shown promise at the bench scale for PFAS destruction in waters impacted by fire-fighting foams: at the start of the experiments PFHxA concentrations increased due to precursor degradation, but ultimately PFHxA further degraded and eventually mineralized (Bruton 2017).

Combinations of remedial technologies into treatment trains show potential to be an efficient method for removal of a wide array of PFAS from water.

The development of a treatment technology that can effectively treat the full suite of PFAS, including precursors, has been challenging given the varying physical and chemical characteristics within this class of compounds. However, available scientific and product literature highlight the possibility of combining remedial technologies in treatment trains for the efficient removal of a wide array of PFAS compounds, including short-chain PFAS such as PFHxA, from impacted waters.

Recent research has demonstrated the potential for electrochemical oxidation technologies to effectively treat highly-concentrated PFAS waste streams generated during remediation, such as the rejectate from membrane filtration or ion-exchange regenerant waste.

Bench-scale testing for the electrochemical oxidation technology DE-FLUOROTM demonstrated a 99.66% removal rate of PFHxA from ozone oxidation treatment effluent (AECOM 2018).

Separately, Soriano et al. (2017) performed a series of bench scale experiments to remove and degrade PFHxA from industrial process waters using a combination of nanofiltration and electrochemical oxidation.

Initial PFHxA concentrations ranged from 60 – 200 mg/L: under a range of operating pressures, they found that the Dow FILMTECTM NF270 membrane rejected PFHxA at a rate of 96.6 – 99.4%.

The nanofiltration step concentrated PFHxA in the rejectate solution to 870 mg/L, which was then subjected to electrochemical degradation to reduce PFHxA by 98% (Soriano 2017).

Some companies are specifically marketing their remedial technologies for use in treatment trains for comprehensive PFAS removal.

At an Australian demonstration treatment plant for a former fire-fighting training facility, Evocra verified the efficacy of its patented ozofractionation column technology combined with sorbent polishing steps (Evoqua 2017). The ozofractionation columns were effective at removing PFOA and PFOS and precursors from influent wastewater, and subsequent polishing steps with engineered sorbent removed PFHxA and other residual PFAS.

The overall PFHxA removal rate in the combined ozofractionation and sorbent treatment train was 99.8%, reducing influent wastewater PFHxA from 5.16 µg/L to 0.0114 µg/L (Evocra 2017).

Given the reduced toxicity of PFHxA as compared to long-chain PFAS, future PFHxA treatment goals based on toxicity data may be magnitudes higher (i.e., parts per billion (ppb)) than those currently in place for long-chain PFAS (i.e., ppt). PFHxA standards and guidance values in the ppb range would be more practicable and achievable for emerging treatment technologies discussed in the sections above.

4.4 Best practices along the value chain

The assumption that exposures to PFHxA are likely to increase due to the phase out of long-chain perfluoroalkyl acids (PFAAs) is unsubstantiated by any data. Short-chain fluorotelomers have been used within the fluorotechnology market since the 1970's. They have also been present as unintentional fraction in historic long-chain products. The source of the detected levels, which remain infrequent and low, cannot be directly attributed to the shift to C6 products.

The assumption of increasing levels, a fortiori to levels that would represent a concern for human health or the environment, are inconsistent with present-day industry manufacture, use, and **improved best management practices.**

In fact, the manufacturing of fluorochemicals and customer usage have both become more efficient, thus limiting environmental releases and potential future contamination levels.

The leading producers of FluoroTechnology, represented within the FluoroCouncil, are committed to sound environmental stewardship of fluorotechnology. The FluoroCouncil has been actively working with downstream sectors, including Fire Fighting Foams and Textile, to develop Best Management Practices that ensure that PFAS-based products are only used when necessary and only at levels that are necessary, that minimize the waste and emissions related to manufacture and product use, and that manufacturers and users dispose of all chemicals and PFAS-based products properly.

A revision of the BREF/BAT document for the Textile sector is ongoing. Strict requirements to minimize emissions of fluorinated substances are being developed, including closed loop water management to avoid discharges to water.

In addition, there has been a public and well-documented shift from fluorinated surfactants and repellants over the past several years.

This significant shift has resulted in decreased usage based on company reports (IKEA, M&S, Patagonia, KEEN, etc). Additionally, the dramatic change in fire-fighting training practices in the U.S. and Australian Departments of Defense, and elsewhere, have significantly decreased potential future contamination by orders of magnitude.

In summary, the improvements within the various manufacturing processes, the significant changes in the fire-fighting foam industry, and the shift away from fluorinated repellants for low performing applications, are expected to result in reduced environmental levels of PFAS, including PFHxA, on a continuing basis over the next several years.

5. Precedent setting in applying the ELoC

5.1 Absence of agreed upon criteria for ELoC for environmental concerns

It is the first time that a SVHC proposal includes a concern about mobility in the water compartment, and more generally, that a ELoC is claimed for environmental effects other than endocrine disruption. Nonetheless, unlike for human health, no criteria for applying EloC have been developed for environmental effects.

The criteria for equivalent level of concern to CMR substances for human health effects were developed to assess SVHC proposals for certain sensitizing substances. At the time, a process of consultation within the relevant committees of REACH, including in CARACAL, was followed. This resulted in a publication by ECHA of a document listing the relevant criteria.

A similar process has not been conducted for persistent and mobile substances. Unlike for bioaccumulation, mobility criteria are not defined in REACH. Further work is needed to determine the conditions according to which persistent and mobile substances may represent an equivalent level of concern to a vPvB substance in terms of adverse effects.

5.2 Any SVHC proposal based on ELoC should fulfil the conditions set by the European Court of Justice

The concept of ELoC has been subject to a ruling of the European Court of Justice (Case C 323/15 P) in which the Court defined **two cumulative conditions** for its application: first, it must be probable that the hazards arising from the substance's intrinsic properties have **serious effects** on human health or the environment. Second, there must be **scientific evidence that these effects give rise to an equivalent level of concern to those of CMR, PBT or vPvB substances**. With respect the first condition on the severity of effects, it should not be considered as fulfilled for substances which have a well-documented low environmental and/or human toxicity. As for the second condition set by the ECJ, any use of the ELoC route should include a scientific assessment of the risk of exposure and its related adverse effects. A SVHC proposal based only on assumptions of increasing concentrations in the long-term without consideration of the available data and the reasonable conditions of use that would allow for a better risk quantification, should not be regarded as in line with the ECJ ruling.

5.3 Further considerations disproving the ELoC

Not only has PFHxA low hazards with continually low detection limits, which under reasonably expected conditions of use do not provide evidence of any long-term risk, but it does not meet the "other factors" that the ECJ has identified as being relevant in the assessment of an ELoC under SVHC. In particular, the ECJ insists that Authorisation must be necessary to control the risks resulting from the substance at stake. In the case of PFHxA, the RMOA conducted by the German UBA concluded that the Restriction process, not the Authorisation process, was the most appropriate regulatory process under REACH. Furthermore, in the case of PFHxA, a SVHC listing will not allow for identification of the substance in articles, which is often given as an argument for SVHC identification. Due to its extremely low degradation from polymers, PFHxA may only be found in concentrations in articles much below the threshold of 0,1% w/w.

Another important consideration relates to the main concern identified which relates to drinking water. **SVHC identification does not address concerns with respect to the protection of drinking water**. In contrast, water legislation, but also other sectoral regulations (plant protection products, biocides,

industrial emissions directive), provide tailored tools for substances representing a risk for water contamination.
Furthermore, the SVHC identification induces other obligations not related to improve water protection. It could lead to unnecessary market deselection of products and their uses causing an unwanted collateral damage to users and industry. This would **not be in line with the EU Better Regulation Agenda** which aims for targeted regulation that goes no further than required, to achieve the necessary objectives.
Last but not least, substances with persistence and mobility as intrinsic properties cover a large number of chemicals. Already 167 REACH registered substances have been identified by the German Environmental Agency (UBA) on the basis of these properties (UBA, 2018).

More generally, we hold the view that more tailored approaches, based on a risk assessment, may have to be considered for substances with these properties.

6. Conclusions on SVHC based on an equivalent level of concern to CMR, PBT, vPvB

In summary, the Annex XV proposal for identifying PFHxA as a substance of very high concern does not correctly present the available data on PFHxA, which collectively demonstrate low risks. PFHxA is not ubiquitous in the environment – environmental detections are infrequent and at low concentrations and human exposure is infrequent and at low levels. It has not been demonstrated that PFHxA levels are increasing in the environment or in humans. PFHxA can be efficiently removed from water. PFHxA is not carcinogenic, mutagenic, or a reproduction or developmental toxicant. PFHxA does not have endocrine disrupting properties. Finally, there is no evidence that exposure to PFHxA at levels expected for the general population would result in serious effects to human health or the environment.

Based on the information summarized in this document, the following can be concluded based on the scientific evidence regarding potential exposure and toxicity from PFHxA in the environment:

1. PFHxA is not carcinogenic, mutagenic or toxic for reproduction, nor does it exhibit endocrine disrupting properties or any evidence of serious effects to human health or the environment.
2. Large margins of safety using the published derived Reference Dose
3. PFHxA does not exhibit potential to bioaccumulate in fish, wildlife or humans, nor to biomagnify in the food chain.
4. The levels of PFHxA in the environment and in human serum are extremely low and there is no documented temporal evidence that they are increasing.
5. Soil biodegradation studies on C6 fluorotelomer side-chain polymers provide a degradation half-life of thousands of years
6. Current use patterns, trends, emission controls and best practices will help keep both presence and exposure low
7. Ion exchange resins and membrane filtration are two demonstrated full-scale water treatment technologies currently available for the removal of PFHxA. Water treatment technologies capable of complete destruction of PFHxA are in development and may eventually evolve to commercial full-scale applications.

Furthermore, there is a need for a broad policy discussion on how to apply the concept of ELoC with respect to environmental concerns, and whether SVHC is an appropriate tool for concerns about water. This policy process should be completed before any SVHC proposal is considered for adoption within the ECHA Member State Committee.

In conclusion, the data and additional considerations reflected in this document do not support the listing of PFHxA as a substance of very high concern.

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Annex II: Information on uses

The main applications of short-chain perfluorinated substances include high performance textiles, carpeting, paints and coatings, firefighting foams, electronics, food packaging, as well as building and construction. C6 chemicals are also used as polymerisation aids in the production of certain fluoropolymers and fluoroelastomers.

Non-fluorinated alternatives may be used in applications requiring limited performance (water-repellency and water-based stains only, fire fighter training and extinguishing of some Class B fires), but not in high reliability, durable, safety applications, where often a combination of the unique properties (oil repellency and oil-based stain prevention; film-formation) of short-chain PFASs is required. For sectors requiring such combinations, the absence of C6 products could affect product performance and safety, and lead to a higher carbon footprint throughout the product's life cycle.

The substitution from C8 – to C6-based products was the result of years of research, customer re-qualifications, work with governmental agencies, and significant investments.

Substitution is part of innovation and as such is a permanent effort of leading industry members which have already successfully honoured their commitment to U.S. EPA to phase out the production and use PFOA and PFOA related compounds.

Nonetheless, as stated above, substitution to non-fluorinated substances is currently possible only for some specific performance applications. To the best of our knowledge no non-fluorinated polymerization aids alternatives are available, while fluoropolymers and fluoroelastomers are critical for key sectors of the European economy.

Finally, C6 perfluorinated substances are key in supporting the transition from C8 chemicals globally. A restriction on C6 fluorotelomers, and short-chain fluorinated substances more generally, would slow down that transition process in Europe. It would also discourage any efforts in this direction in emerging economies.

Overview of main applications of C6 FluoroTechnology

Industry	**Application**	**Property**	**Benefit**	**Fluoro-Technology Used**
Performance textiles and carpeting	Interior textiles of cars/ aircrafts	Water, Oil, Stain, Soil Protection	Improved cleanability, longer fabric life lowering overall maintenance costs	Fluorinated polymer
	Outdoor apparel and equipment	Water, Oil, Stain, Soil Protection	Durable, lifesaving protection in severe environments, longer useful garment life	Fluorinated polymer
	Professional protective textile	Durable, high water and oil (solvent) repellency. Chemical resistance	Life protection in severe environments, protection against hazardous chemicals, protection against water and liquids in a (fuel) fire.	Fluorinated polymer

	Non-Woven (Medical)	IPA repellency (alcohol); repellency to blood, urine and other body fluids	Prevention for medical work wear for the operating theatre; protection of hospital staff; departmental, ward and surgical clothing for nurses, nursing staff and doctors	Fluorinated polymer
	Non-woven (automotive)	Water- and oil repellency; Resistance to liquid chemicals (Battery), Diesel- and Gasoline; Heat resistance	Protection of components in the motor area; insulation	Fluorinated polymer
	Carpets/ home textile	Water, oil, stain, soil protection, reduced dirt pickup	Easy clean, longer useful life	Fluorinated polymer
Food packaging		Oil and grease resistance	Enabling paper packaging for pet food, microwave popcorn, quick service restaurant, meals. Reduces potential for burns from hot oil migration through the packaging or wrap. Maintains aesthetics and integrity of packaging material	Fluorinated polymer
Electronics	Semi-conductors (etching and resist materials, cleaning fluids)	Wetting and leveling to control and improved chemical etching. High purity, pure drying cleaners	Ability to manufacture semi-conductors	Fluorinated surfactant
Fire-fighting foams	Airports, oil fields, fuel storage, military applications	High efficiency oxygen starvation, faster extinguishment times, better burnback resistance	Quicker extinguishing of fires, resulting in saved lives, reduced asset losses; fire-fighter safety	Fluorinated surfactant

Building and construction	Paints, building materials protection	Wetting, levelling, mold-releasing, anti-fouling	Longer useful lifetime, lower repainting interval, reduced paint waste from recoat preparation	Fluorinated surfactant
Polymerisation aid in the production of fluoropolymers and fluoroelastomers	Automotive, Aerospace, Power and Chemical sectors, Electronics, Medical devices	Very high thermal and chemical resistance, resilience (fluoroelastomers)	Reduced fuel consumption, reduced emissions, high reliability equipment, longer life time	C6 chemicals