Short-chain Polyfluoroalkyl Substances (PFAS)

A literature review of information on human health effects and environmental fate and effect aspects of short-chain PFAS

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Editing: Jesper Kjølholt 1
          Allan Astrup Jensen 2
          Marlies Warming 1

1: COWI A/S
2: NIPSECT

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Contents

Preface ...................................................................................................................... 5
Summary and Conclusion ....................................................................................... 7
Sammendrag og konklusion .................................................................................. 11

1. Introduction .......................................................................................................... 15
   1.1 Background and scope ................................................................................. 15
   1.2 Objective ...................................................................................................... 15

2. Chemistry and uses .............................................................................................. 17
   2.1 Background about polyfluoroalkylated substances (PFAS) ....................... 17
   2.2 Short-chain alternatives to C8-polyfluoroalkylated substances .............. 18
   2.3 Developments in industry ........................................................................... 20
   2.4 Recent uses of short-chain alternatives ..................................................... 21
       2.4.1 Impregnation .................................................................................. 21
       2.4.2 Fire-fighting foams ......................................................................... 21
       2.4.3 Metal plating ............................................................................... 21
       2.4.4 Oil production .............................................................................. 21
       2.4.5 Food packaging ........................................................................... 21
   2.5 Substances included in this study ................................................................. 22

3. Human health effects ........................................................................................... 23
   3.1 General aspects of toxicokinetics and metabolism .................................... 23
       3.1.1 Uptake and distribution .................................................................. 23
       3.1.2 Levels in human blood .................................................................... 24
       3.1.3 Metabolism/biotransformation ....................................................... 26
       3.1.4 Excretion/elimination from the body .............................................. 27
       3.1.5 Blood serum elimination half-lives ................................................. 27
       3.1.6 Fetal and lactational transfer ......................................................... 28
   3.2 Toxicological mechanisms ............................................................................ 28
       3.2.1 Peroxisome proliferation ................................................................ 28
       3.2.2 Effects on cell membranes ............................................................. 29
       3.2.3 Effect on lipids ............................................................................. 29
       3.2.4 Cytotoxicity ............................................................................... 29
       3.2.5 Neurotoxicity ............................................................................. 30
       3.2.6 Endocrine disruption .................................................................... 30
   3.3 Toxic effects of single PFAS ......................................................................... 30
       3.3.1 Perfluoroalkane sulfonic acids/sulfonates (PFSA) ......................... 31
       3.3.2 Perfluoroalkanoic acids/perfluoralkanoates, perfluorocarboxylic acid/perfluorocarboxylates (PFCA) ......................................................... 36
       3.3.3 Perfluorooalkyl halogenides ............................................................ 39
       3.3.4 Perfluorooalkyl phosphor compounds ........................................... 39
       3.3.5 Fluorotelomers and derivatives ....................................................... 40
   3.4 Occurrence and exposure in relation to humans .......................................... 45
       3.4.1 Occurrence in products .................................................................. 45
       3.4.2 PFAS in indoor air and workplace air ............................................. 46
4. Environmental fate and effects ..............................................49
  4.1 Environmental behaviour and fate .....................................49
     4.1.1 Physico-chemical properties of environmental relevance ....49
     4.1.2 Abiotic transformation and degradation .......................50
     4.1.3 Biotransformation and degradation ..............................50
     4.1.4 Bioaccumulation ..................................................51
     4.1.5 Sorption, mobility and distribution .............................51
     4.1.6 Long-range atmospheric and marine transport ...............52
  4.2 Environmental effects ..................................................52
     4.2.1 Toxicity to aquatic organisms ...................................53
     4.2.2 Toxicity to terrestrial organisms ...............................59
  4.3 Environmental fate and effects of single PFAS ....................61
     4.3.1 Perfluoroalkane sulfonic acids/sulfonates (PFSA) ..........61
     4.3.2 Perfluoroalkanoic acids/perfluoroalkanoates, perfluorocarboxylic acids and
          perfluorocarboxylates (PFCA) ....................................62
     4.3.3 Perfluoroalkyl halogenides ....................................63
     4.3.4 Perfluoroalkyl phosphor compounds ............................63
     4.3.5 Fluorotelomers ....................................................63
  4.4 PBT assessment .........................................................64
  4.5 Environmental occurrence and exposure ............................65
     4.5.1 Aquatic environment ..............................................65
     4.5.2 Terrestrial environment .........................................70
     4.5.3 Biota ...............................................................71
     4.5.4 Atmospheric environment .......................................73

5. Summary and conclusions ................................................75
  5.1 Human health effects and exposure ..................................75
     5.1.1 Human health effects ............................................75
     5.1.2 Exposure of humans ..............................................76
  5.2 Environmental fate and effects ......................................76
     5.2.1 Environmental fate ...............................................76
     5.2.2 Environmental effects ..........................................77
     5.2.3 Environmental occurrence and exposure .......................77
  5.3 Short-chain PFAS as alternatives to PFOS/PFOA .................78
     5.3.1 Human health aspects ............................................78
     5.3.2 Environmental aspects ...........................................78
  5.4 Data gaps ...............................................................79
     5.4.1 Human health effects (including exposure) ...................79
     5.4.2 Environmental aspects (including exposure) ..................79

Abbreviations and acronyms ...............................................81

References .............................................................................85

Appendix 1: List of substances considered to be "short-chain PFAS"........97
Preface

A survey of PFOS, PFOA and other perfluoroalkyl and polyfluoroalkyl substances (here collectively referred to as PFAS) were undertaken in 2012 as part of the surveys of the Danish EPA of the 40 substances/substance groups on the Agency’s List of Undesirable Substances (LOUS). On the basis of the survey, the Danish EPA developed three strategy papers (Danish EPA, 2013) addressing the following issues:

- risk management of PFOS and PFOS substances;
- risk management of PFOA and PFOA substances; and
- risk management of other perfluorinated substances.

The strategy papers note that there is a general lack of published data on the properties of the alternatives to the PFAS of most concern, partly because the data usually are protected by trade secrets, partly because most of the scientific research have focused on a few polyfluorinated substances such as PFOS and PFOA; historically the substances of most concern.

In order to obtain further information on alternatives to the PFAS of most concern and to PFAS in general, the Danish EPA have launched two reviews:

- This literature review of environmental and health properties of short-chain PFAS;
- A study on non-fluorinated alternatives to PFAS-based impregnation agents for textiles.

The objective of this study is:

- To provide an updated overview of the human health and environmental fate and effects aspects of short-chain polyfluorinated substances introduced as alternatives to PFOS/PFOA and other long-chain PFAS;
- To support the Danish EPA’s strategy on this substance group by providing background documentation in relation to further activities, including possible regulation.

The project has been carried out by COWI A/S with NIPSECT as subcontractor in the period July-December 2014 and was followed by a steering group consisting of:

- Louise Grave-Larsen, Danish Environmental Protection Agency
- Jesper Kjølholm, COWI A/S
- Allan Astrup Jensen, NIPSECT
Summary and Conclusion

This report has been prepared to support part of the Danish EPA's strategy on “other perfluorinated substances” (i.e. other than PFOS and PFOA). In the strategy it is, among others, stated that an overview of uses and applications, exposure and impact on human health and the environment should be established, and a need for more information on short-chain PFAS as possible alternatives to the long-chained was identified.

Hence, the objectives of this study have been to review the open literature on these subjects for short-chain PFAS and assess the possible impacts of these substances on human health and the environment in comparison to long-chain PFAS and thereby supporting the Danish EPA's strategy on this substance group by providing background documentation in relation to further activities, including possible regulation.

Chemistry and uses of short-chain PFAS
The most important short-chain perfluoroalkyl sulfonic acids are perfluorobutane sulfonic acid (C₄, PFBS) and perfluorohexane sulfonic acid (C₆, PFHxS), which also exist as various salts. The only difference to PFOS is the four, respectively two, fluorocarbon shorter perfluorinated chain (“tail”). Similarly to PFOS the short-chain alternatives have hundreds of precursors such as e.g. the more complex molecules N-Methyl perfluorobutane sulfonamidoethanol (MeFBSE) and N-methyl perfluorohexane sulfonamidoethyl acrylate.

The most important short-chain alternatives among the perfluorocarboxylic acids (PFCAs), are perfluorobutanoic acid (PFBA) and perfluorohexanoic acid (PFHxA) and their precursors: the short-chain fluorotelomers such as 4:2 FTOH and 6:2 FTOH, and as for the C₈-PFAS, there are hundreds of derivatives in use, for instance, phosphates and acrylates.

The short-chain PFAS, especially the C₆-substances such as 6:2 fluorotelomers, are used to about the same applications (impregnation, metal plating, fire-fighting foams, food packaging etc.) as the C₈-analogues; however, the C₆ has optimal surfactant properties with very low surface tensions and therefore may be the preferable substances from a technological point of view.

Human health effects and exposure
It is known from animal studies that the studied short chain polyfluoroalkylated substances (PFAS) are almost completely absorbed orally and by inhalation but that skin absorption may be negligible. Both short- and long-chain perfluoroalkyl acids (PFAAs) are considered being metabolically inert. The strong C-F bonds exclude any normal degradation pathway. Any functional derivative (precursor) will through several steps ultimately be transformed to the acids. That is also the case for fluorotelomers and derivatives hereof, which are biotransformed into PFCAs of different chain length through several metabolic steps, including aldehydes and saturated and unsaturated carboxylic acids. These metabolites are more toxic than the parent compounds, and one of these metabolites: perfluorohexyl ethanoic acid (FHEA) was measured in various tissues from deceased people.

The mean blood elimination half-lives for PFAAs depend on the chemical substance and animal species and its sex. Generally, the blood half-lives of PFAAs are longer for sulfonates than for carboxylates, half-lives increase with chain length for carboxylates, and are shorter for branched isomers, and in animals they are often shorter in females due to the sex hormone dependent difference in renal clearance. Further, the serum half-lives of PFAAs are dose-dependent with longer half-lives for the lower concentrations relevant for humans. The general blood elimination half-lives of PFAAs in exposed rodents were hours or few days, in monkeys a little longer and in humans much longer and often years. The blood elimination half-lives of PFAAs decrease generally with shorter chain length. An exemption is PFHxS (C6), which has a longer half-life in humans than PFOA and PFOS (C₈).
The primary route of elimination of PFAA from the body is with the urine via the kidneys. Presence of membrane transport proteins and reabsorption of PFAA in the kidneys is the fundamental mechanism responsible for renal elimination of these substances, which also influences their plasma half-lives. A main reason for the long plasma half-life of PFAAs in humans compared to experimental animals is that the excretion of PFAAs in humans is insignificant, because humans have the highest percentage of renal tubular reabsorption (>99%). That difference between humans and experimental animals makes it more uncertain to use animal data in human risk assessment of PFAAs. Elimination is different for fluorotelomers, which are mainly eliminated from the body via faeces.

Longer chain length PFAAs tend to have longer renal elimination half-lives in rats. However, PFBA with a C₅-perfluorcarbon chain is different and has a slower renal clearance than PFHxA (C₃), because PFBA seems not to be the substrates of the common transport protein Oatp1a1. In contradiction, PFBS with a C₅-perfluorocarbon chain seems not to be very bioaccumulative and has a much shorter half-life in the organism than PFHxS (C₆).

PFASs have contrary to most other persistent organic pollutants (POPs) a low affinity to lipids but bind to proteins, and in the blood PFAS are bound to serum proteins, mainly albumin. PFASs are mainly associated to cell membrane surfaces and mainly distributed in plasma and in well-perfused tissues such as the lung, liver, kidney and spleen but also in the bone, testes and brain. That was illustrated in a recent study from Spain where analysis of autopsy tissues revealed both individual differences between donors and in the tissue distribution of the PFAS. The relatively high concentrations of short-chain PFAS in human tissues, especially PFBA, indicate that these chemicals behave differently in humans than in laboratory animals.

In animal experiments the acute toxicity of short-chain PFAS is low. After repeated exposure, large doses of short-chain PFAS may damage the liver and kidneys. In rats PFHxS is the most toxic short-chain PFAS, followed by 6:2-FTOH, PFBA, PFHxA and PFBS. In general, PFAS are more toxic in males than females having a higher elimination rate. The liver toxicity in rats is mediated through peroxisome proliferation, and its potency generally increases with the fluorocarbon chain length until C₉. However, PFHxS is much more liver toxic than PFBS and PFOS.

The toxicokinetics and toxicity in humans for short-chain PFAS are mainly investigated for PFHxS, and it seems to be close to that of PFOS. Thus PFHxS may not be a good alternative. For the other short-chain PFAS it may be different but the available data is insufficient for a final evaluation.

The high presence of short-chain PFAS in human tissue, including brain from deceased people, especially PFBA, is worrying and it shows that the short-chain PFAS and a fluorotelomer metabolite may be much more bioaccumulative in humans, than the studies with experimental animals conclude. That may compromise the safety of the alternatives.

**Environmental effects and exposure**

Perfluorinated carboxylic and sulfonic acids, including the short-chained, are not transformed/degraded by abiotic reaction mechanisms such hydrolysis or photolysis in water to any appreciable extent. However, some neutral PFASs, e.g. FTOHs, can undergo initial abiotic transformation in the atmosphere by OH-initiated oxidation pathways but only to (persistent) perfluoroalkylated substances. Likewise, perfluorinated acids are not biodegradable in water or soil while PFAS with other functional groups (e.g. telomer alcohols/acylates) may undergo primary degradation to the corresponding acid/salt, however leaving the highly persistent perfluorinated backbone intact.

PFCAs and PFSAs can bioaccumulate in living organisms in the environment with the long-chained substances being more bioaccumulative than the short-chained. However, because these substances are both hydrophobic and lipophobic they do not follow the typical pattern of partitioning into fatty tissues followed by accumulation but tend to bind to proteins and therefore are present rather in highly perfused tissues than in lipid tissue. Precursors such as fluorotelomers may be partially responsible for the observed bioaccumulation of the acids.
The shorter chain length acids tend to be more soluble in water and have a lower potential for sorption to particles than the long-chain analogues. Thereby, they have a higher potential for aqueous long-transport. Precursors like FTOHs, on the other hand, will mainly be transported over long distances via the atmosphere.

With regard to environmental effects, PFOS/PFOA and other long-chain PFAS are generally more toxic than the short-chain analogues and the sulfonic acids tend to be more toxic than the corresponding carboxylic acids. However, the toxicity of short-chain PFAS is not thoroughly studied or well described, in particular with regard to log term effects, and there are examples of exceptions to the general picture. FTOHs have been shown to be xenoeštrogens causing effects down to 0.03 mg/L, and 6:2 FTOH to be more potent than 8:2 FTOH.

The available environmental exposure studies are mainly concerned with the aquatic environment, and data exist for surface water, drinking water, ground water, marine water, as well as WWTP influents, effluents, and sludge in Denmark and other European countries. Most data are for PFOS, PFOA and other long-chain PFAS but some data are available for short-chain compounds such as PFBS, PFHxS, PFBA, PFPeA, and PFHxA, which are also detected in many aquatic samples, often in concentrations ranging from levels similar to those of PFOS or PFOA to about an order of magnitude lower. The presence of the shorter chain compounds in the environment may be explained by substitution of long chained compounds with shorter chain alternatives as well as by degradation of fluorotelomers.

WWTP mass flow studies showed similar or higher PFCAs and PFSA concentrations in the effluent than in the influent, indicating that conventional WWTPs do not effectively remove PFAS in from wastewater effluents. However, sorption to sewage sludge has been shown to be a removal process from the water phase for PFHxS.

In the Atlantic Ocean, the concentrations of PFAS are considerably higher in the North Atlantic Ocean compared to the Middle and South Atlantic Ocean. The ΣPFAS concentrations decreased from 2007 to 2010 in the North and Middle Atlantic Ocean mainly due to decreasing concentrations of PFOA/PFOS while short-chain PFAS such as PFBS, PFHxA and PFHxS did not show such trend. PFAS have also been detected in remote areas without obvious sources, such as the Greenland Sea, where PFBS, PFHxA and PFHxS were among the 5 most frequently detected compounds.

**Data gaps**

As mentioned above there is a general lack of toxicological information regarding the short-chain PFAS other than PFHxS. Specifically for 4:2 FTOH and PFPeS/PFPeA there is virtually no available health-related information. Further, the Spanish study showing worrying high levels of short-chain PFAS in all tissues from deceased persons has to be confirmed by similar studies by other scientists and with samples from other European countries. The biomonitoring studies already executed have not identified any high levels of short-chain PFAS in the blood from the general population, thus the high levels in organs is a mystery to be solved.

Overall, environmental fate and effects data on PFAS are primarily available for PFOS/PFOA and some of the longer chain PFAS while the properties of the short-chain PFAS to a large extent are estimated based on read-across. Thus, there is a general lack of specific experimental data on short-chain PFAS. Also, the environmentally relevant physico-chemical data identified appear somewhat inconsistent and confusing. A consistent set of data produced by the same standard methods would be valuable.

Internationally, environmental exposure data are available for mainly short chain carboxylic (PFCA) and sulfonic acids (PFSA), but not for other PFAS. With respect to the Danish situation, data on PFOS, PFOA and PFHxS are available for some relevant point sources (WWTP influents, effluents and sludge; landfill effluents) and for marine biota while data on shorter chain PFAS are not available. Further, Danish surface water data are virtually absent.
Sammendrag og konklusion

Denne rapport er udarbejdet som led i Miljøstyrrelsens strategi for "andre perfluorerede stoffer" (dvs. andre end PFOS og PFOA). I strategien indgår blandt andet, at der bør etableres bedre oversigt over stoffernes anvendelser og funktioner samt eksponering og indvirkning på menneskers sundhed og miljøet. Desuden er et behov for mere information om kortkædede PFAS som mulige alternativer til de langkædede PFAS identificeret.

Formålet med denne undersøgelse har derfor været at gennemgå den tilgængelige litteratur om disse emner for kortkædede PFAS og vurdere de mulige virkninger af disse stoffer på menneskers sundhed og miljøet i forhold til langkædede PFAS og dermed bidrage til Miljøstyrrelsens strategi for denne stofgruppe ved at tilvejebringe baggrundsdokumentation i forhold til mulige yderligere aktiviteter, herunder eventuel regulering.

Kortkædede PFAS’s kemi og anvendelser
De vigtigste kortkædede perfluorkylsulfonsyrer (PFSA’er) er perfluorbutansulfonsyre (C4, PFBS) og perfluorhexansulfonsyre (C6, PFHxS), der også eksisterer som forskellige salte. Den eneste forskel ift. PFOS er den kortere perfluorerede kæde ("hale"), som er fire, henholdsvis to, fluorcarbonatomer kortere. Ligesom PFOS har de kortkædede alternativer hundredevis af forstadi, f.eks. mere komplekse molekyler som N-methyl-perfluorbutansulfonamidoethanol (MeFBSE) og N-methyl-perfluorhexansulfonamidothylacrylat.

De vigtigste kortkædede alternativer blandt perfluorcarboxylsyrerne (PFCA’er), er perfluorbutansyre (PFBA) og perfluorhexansyre (PFHxA) og deres precursorer, dvs. kortkædede fluortelomerer såsom 4:2 FTOH og 6:2 FTOH, og lige som for C8-PFAS er der hundredevis af derivater i brug, f.eks. phosphater og acrylater.

De kortkædede PFAS, især C6-stoffer som 6:2 fluortelomerer, anvendes til omtrent de samme applikationer som deres C8-analoser (imprægnering, metal plating, brandslukningsskum, emballage til fødevarer etc.), dog er C8-optimale i forhold til overfladeaktive egenskaber med meget lave overladespændinger og er derfor de foretrukne stoffer fra et teknologisk synspunkt.

Sundhedseffekter og eksponering af mennesker

Den gennemsnitlige halveringstid for elimination af PFAS fra blod afhænger både af selve det kemiske stof og af kunnet af de undersøgte dyr. Halveringstiden for elimination af PFAA fra blodet falder generelt med kortere kædelængde. En undtagelse er PFHxS (C6), som har en længere halveringstid hos mennesker end PFOA og PFOS (C8). Halveringstiderne for PFAA i blod er længere for sulfonater end for carboxylatermens den er falder for forgrønede isomerer. I dyr er halveringstiderne ofte kortere hos huner på grund af kunshormonafhængig forskel i udkillelsen fra nyerne. Endvidere er halveringstider for PFAS i serum dosisafhængig med længere halveringstid ved de lave koncentrationer, som er relevante for mennesker. Generelt er halveringstiden for PFAS i blodet hos eksponerede gnaver timer eller få dage, i alber lidt længere, og i mennesker meget længere og ofte år.
Den primære udskillesesvej for PFAA er med urinen. Tilstedeværelse af membrantransportproteiner og reabsorption af PFAA i nyrerne er den grundlæggende mekanisme bag renal udskillelse af disse stoffer, hvilket også påvirker deres plasmahalveringstider. En væsentlig årsag til den lange plasmahalveringstid af PFAAs hos mennesker i forhold til forøgelsedyr er, at udskillelsen af disse stoffer i mennesker er ubetydelig, fordi mennesker har den højeste andel af renal tubuler reabsorption (> 99%). Denne forskel mellem mennesker og forøgelsedyr gør det mere usikkert at bruge dyredata i vurderingen af risikoen for mennesker udsat for PFAA. Udskillesesvejen er anderledes for fluoromeler, der hovedsagelig elimineres fra kroppen via fæces.

Hos rotter har de langkædede PFAA en tendens til at have længere renal halveringstid. Dog er PFBA med en C3-perfluoralkylkæde anderledes og har en langsommere renal clearance end PFHxS (C5) fordi PFBA ikke synes at være substrater hørende til det fælles transportprotein Oatp1a1. I modsætning hertil synes PFBS med en C4-perfluoralkylkæde ikke at være meget bioakumulerende og har en meget kortere halveringstid i organismen end PFHxS (C6).

PFASs har i modsætning til de fleste andre persistente organiske miljøgifte (POP) en lav affinitet til lipider, men binder sig til proteiner, og i blodet er PFAS bundet til serumproteiner, primært albumin. PFASs er hovedsageligt knyttet til celledemembranoverflader og fordelser sig fortrinsvis i plasma og i væv med høj blodgennemstrømning, såsom lunge, lever, nyrer og milt, men også i knogler, testikler og hjerne.

En nylig analyse af væv fra obduktioner fra Spanienslæderede både individuelle forskelle mellem donorer og i vævs fordelingen af forskellige PFAS. De fundte relativt høje koncentrationer af kortkædede PFAS i humane væv, især PFBA, hvilket indikerer, at disse kemikalier opfører sig anderledes i mennesker end hos laboratorydyr, hvor de korte former ikke ophobes i samme grad.

I dyreforsøg er den akutte toksicitet af kortkædede PFAS fundet at være lav. Efter gentagne eksponering kan høje doser af kortkædede PFAS beskadige leveren og nyrerne. Hos rotter er PFHxS er den mest giftige kortkædede PFAS, efterfulgt af 6:2-FTOH, PFBA, PFHxA og PFBS. Leverhaptokineten hos rotter medieres gennem p-hemiproliferation, og dets styrke stiger generelt med længden af fluoralkylkæden indtil C9. Dog er PFHxS mere giftig end PFBS og PFOS.

Toxikokinetik og toksicitet for kortkædede PFAS hos mennesker er primært undersøgt for PFHxS og synes at være tæt på den for PFOS. Således er PFHxS muligvis ikke et godt alternativ til PFOS. For de andre kortkædede PFAS kan det være anderledes, men de tilgængelige data er utilstrækkelige til en endelig vurdering.

Den høje forkomst af kortkædede PFAS (særligt PFBA) i humant væv, herunder i menneskehjernen, er bekymrende og viser, at kortkædede PFAS og en fluorotrolomermetabolit kan være meget mere bioakumulerende i mennesker end det konklueres baseret på studier med forøgelsedyr. Dette kan nedsætte sikkerheden af alternativerne.

**Miljømæssige effekter og -eksponering**

Perfluorerede carbonyl- og sulfonsyrer, herunder de kortkædede omdannes/nedbrydes stort set ikke i miljøet ved biotiske reaktionsmekanismer sådan hydrolyse eller fotolyse i vand. Dog kan visse upolære PFASs, fx FTOHs, undergå indledende biotisk omdannelse i atmosfæren, men kun til de persistente perfluoralkylstoffer.. Ligeledes er perfluorerede syrer ikke biologisk nedbrydelige i vand eller jord, mens PFAS med andre funktionelle grupper (f.eks. fluorotrolomeralcoholer/acrylater) kan undergå primær nedbrydning til den tilsvarende syre, men den meget persistente perfluorerede "hale" forbliver intakt.

PFCA og PFSA kan bioakumulere i levende organismer i miljøet med de langkædede stoffer værende mere bioakumulerende end de kortkædede. Da disse stoffer imidlertid er både hydrofobe og lipofohe, følger de ikke det typiske mønster for fordeling i fedtvæv efterfulgt af ophobning, men synes i højere grad at bindes til proteiner og findes derfor snævere i væv med høj blodgennemstrømning end i fedtvæv. Precursorer, så som fluorotrolomere, formodes at være delvis ansvarlige for den observerede bioakumulering af syrerne.
De kortkædede syrer har tendens til at være mere vandoploselige og have et lavere potentiale for binding til partikler end de langkædede analoger og har derved også et større potentiale for vandbåren langtransport. Precursorer som FTOH vil på den anden side hovedsagelig blive langtransporteret via luften.

Med hensyn til de miljømæssige effekter er PFOS, PFOA og andre langkædede PFAS generelt mere giftige end de kortkædede analoger, og sulfonsyrenes har tendens til at være mere giftige end de tilsvarende carboxylyser. Imidlertid er giftigheden af de kortkædede PFAS ikke velbeskrevet, specielt hvad angår kroniske effekter, og der findes også eksempler på undtagelser fra det generelle billede. Der er indikationer fra studier med fisk på, at kortkædede FTOH kan have større hormonforstyrrende potentiale end de langkædede FTOHs. Således har FTOH vist sig at have østrogen effekt på niveauer ned til 0,03 mg/L, og her er 6:2 FTOH mere potent end 8:2 FTOH.

De foreliggende undersøgelser af miljøkspansion vedrører navnlig vandmiljøet, og der findes data for fersk og marint overfladevand, drikkevand, grundvand, indløb til og udløb fra renseanlæg samt slam både i Danmark og andre europæiske lande. De fleste data er for PFOS, PFOA og andre langkædede PFAS, men der findes også nogle data for kortkædede forbindelser såsom PFBS, PFHxS, PFBA, PFPeA og PFHxA. De kortkædede former er påvist i mange vandmiljøprover, typisk i koncentrationer mellem dem, som PFOS eller PFOA findes i, og ned til omkring en størrelsesorden lavere. Tilstedeværelsen af de kortkædede forbindelser miljøet kan forklares ved substitution af langkædede forbindelser med alternativer med kortere fluorerede kæder samt ved nedbrydning af fluorotelomerer.

Massebalancestudier på renseanlæg har vist tilsvarende eller højere koncentrationer af PFCA og PFSA i udløbene fra renseanlæggene end i tilløbene, hvilket indikerer, at traditionelle renseanlæg ikke er særlig effektive mht. at fjerne PFAS fra vandfasen. Dette gælder især de kortkædede former, mens sorption til slam er påvist at være en relevant fjerneløsproces fra vandfasen for PFHxS (og syre med længere fluorkæder).

I Atlanterhavet er koncentrationerne af PFAS fundet at være betydeligt højere i Nordatlanten end i Midtatlanten og det sydlige Atlanterhav. Den samlede koncentration af PFAS-forbindelser faldt fra 2007 til 2010 både i Nord- og Midtatlanten. Faldet skyldes især lavere niveauer af PFOS og PFOA, mens der ikke ses nogen nedadgående trend i niveauerne af kortkædede forbindelser som PFBS, PFHxA og PFHxS. PFAS er også blevet påvist i fjernliggende områder uden kende, lokale kilder, som f.eks. Grønlandshavet, hvor PFBS, PFHxA og PFHxS er blandt de fem hyppigst fundne stoffer.

**Manglende viden**

Som nævnt ovenfor er der en generel mangel på toxikologiske oplysninger om andre kortkædede PFAS end PFHxS. Specifikt for 4:2-FTOH og PFPeS/PFPeA findes der næsten ingen tilgængelige sundhedsrelaterede oplysninger. En spansk undersøgelse, der har vist bekymrende høje niveauer af kortkædede PFAS i alle slags vev fra afdøde personer, bør bekræftes gennem undersøgelser foretaget af andre forskere og med prøver fra andre europæiske lande. I foreliggende biomonitoringsstudier er der ikke identificeret høje niveauer af kortkædede PFAS i blodet fra den generelle befolkning. Derfor er de høje niveauer i organer stadig uforklarlige.

Samlet set vedrører de tilgængelige data om effekter af PFAS i miljøet data primært PFOS, PFOA og nogle af de længerekædede PFAS, mens de kortkædede PFAS' miljøgenskaber i stor udstrækning er estimeret ved read-across. Der er således en generel mangel på specifikke forsøgsdata for kortkædede PFAS. Også de identificerede, miljømæssigt relevante fysisk-kemiske data fremstår som usystematiske og forvirrende. Tilvejebringelse af et sammenhængende sæt af data produceret efter anerkendte standardmetoder ville være værdifuldt.

Internationalt findes der primært data om miljøkspansion for de kortkædede carboxylyser (PFCA) og sulfonsyren (PFSA), men ikke for andre PFAS. Med hensyn til den danske situation er der tilgængelige oplysninger om PFOS, PFOA og PFHxS for et antal relevante punktkilder (indløb til og udløb fra renseanlæg, slam, udløb fra deponier samt for marin biota), mens data om kortkædede PFAS er ikke identificeret. Endvidere er data om PFAS i overfladevand i Danmark stort set ikke eksisterende.
1. Introduction

1.1 Background and scope
PFOA (perfluorooctanoic acid) and PFOS (perfluorooctane sulfonic acid) compounds are included in the Danish EPA List of Undesirable Substances (LOUS). The reason for including the PFOA and PFOS is that they are very persistent, have been measured in the blood of humans and wildlife and are toxic to animals. PFOA, PFOS and other related perfluoroalkyl and polyfluoroalkyl substances have been subject to a Danish “LOUS” survey to provide basis for an assessment of whether there is a need for further information generation, regulation and/or other risk reduction measures (Lassen et al., 2013).

Based on this report, the Danish EPA has on 31 May 2013 issued three strategies for risk management of PFOS and PFOS substances, PFOA and PFOA substances and other perfluorinated substances, respectively. As part of the Danish EPA strategy on “other perfluorinated substances” (i.e. other than PFOS and PFOA compounds), but not directly related to the LOUS follow-up activities, a need was identified for an overview of uses/applications, exposure throughout the life cycles, as well as the impact on human health and the environment of short-chained PFAS as these substances increasingly are being introduced as alternatives to the long-chain PFAS in a variety of applications.

1.2 Objective
The objective of the project is to provide the Danish EPA with the best possible overview of the human health and environmental fate and effects aspects of the short-chain polyfluorinated substances, which are being introduced as alternatives to PFOS/PFOA and other long-chain PFAS in an increasing number of application areas.

The overview should support the Danish EPA’s strategy on this substance group by providing background documentation in relation to further activities, including possible regulation.

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2. Can be downloaded here (in Danish): http://www.mst.dk/Virksomhed_op_mynighed/Kemikalier/Fokus+paa+saelege+stofter/LOUS_kortlaegning/2012-stofferne/2012stofstrategi.htm
2. Chemistry and uses

2.1 Background about polyfluoroalkylated substances (PFAS)
Perfluorooctane sulfonic acid (PFOS) is the best known polyfluoroalkylated substance (PFAS), and it has a linear perfluoroalkyl chain of 8 carbon atoms (“C₈-chain”) and a sulfonic acid or sulfonate as the functional group (see formula):

Perfluorooctane sulfonic acid (PFOS as acid)

Sodium perfluorooctane sulfonate (PFOS as salt)

Besides its salts, PFOS has many other derivatives; the most important are N-substituted sulfonamides such as:

N-Methyl perfluorooctane sulfonamidoethanol, MeFOSE

PFOS is a very stable molecule which is not degraded in nature or metabolized in organisms. However, MeFOSE and other derivatives are finally degraded and metabolized to PFOS; they are PFOS-precursors.

Another well-known “C₈-chain” compound is perfluorooctanoic acid (PFOA):
The perfluorinated chain in PFOA is a link shorter than for PFOS because the carboxylic acid carbon is part of the general chain. PFOA is the most important perfluorocarboxylic acid (PFCA), and it forms also various salts and functional derivatives. PFOA is stable and not degradable in the environment or in organisms but the derivatives may degrade to PFOA. A PFOA ammonium salt was previously used for manufacturing fluoropolymers such as Teflon® and has been found as traces in various products of fluoropolymers, such as coated non-stick kitchenware (Washburn et al. 2005).

The third important group of C₈-fluorinated chemicals is 8:2 fluorotelomers. Fluorotelomers are polyfluoralkyl substances with a perfluorinated tail but the two first carbons have bonds to hydrogen instead of to fluorine. A reactive functional group may be attached, and this functional group and the non-fluorinated part of the alkyl chain can be degraded and metabolized, and in this way be precursors of perfluoroalkyl carboxylates. The most important 8:2 fluorotelomer is 8:2 fluorotelomer alcohol (1H,1H,2H,2H-perfluorodecanol, 8:2 FTOH):

![8:2 Fluorotelomer alcohol (8:2 FTOH)]

The ultimate degradation and metabolism of 8:2 FTOH is to PFOA (C₈) and perfluorononanoic acid (C₉, PFNA). The functional group in a fluorotelomer molecule can instead of an alcohol for example be an acryl ester, a phosphate or a substituted sulfonamide.

An example of a telomere with a complex bulky functional group is 8:2 fluorotelomer sulfonamide betaine, which is used in fire-fighting foams for fires at oil rigs, oil terminals and airports:

![N-(2-Carboxyethyl)-N,N-dimethyl-3-((1H,1H,2H,2H-tetrahydroperfluorodecyl)sulfonylamo)-1-propanaminium]

However, there are hundreds other derivatives of C₈-polyfluoroalkylated substances (PFAS).

### 2.2 Short-chain alternatives to C₈-polyfluoroalkylated substances

Major manufacturers of fluorinated chemicals in conjunction with global regulators have agreed to discontinue the manufacture of “C₈-chain” fluorinated products discussed above before 2015, and instead they manufacture analogue “short-chain” fluorinated substances as alternatives supposed to be less hazardous as discussed in the following section. The only difference between C₈-PFAS and the other PFAS is the length of the fully fluorinated chain. Thus the examples of C₈-chemicals shown above will also exists as C₄⁺ or C₆⁻-analogues.

Already in 2005, a DEPA report about alternatives to PFOS and PFOA concluded that in most cases the alternatives to PFOS (and PFOA) related substances are other fluorinated chemicals with shorter chain length, such as C₆-fluorotelomers or perfluorobutane sulfonate (C₆, PFBS) (Poulsen et al. 2005). These chemicals fall also under the larger chemical family called polyfluoroalkyl substances (PFAS). The reason for this continuous use of fluorinated compounds is that polyfluorinated surfactants have superior surface-active properties compared to other and less expensive surfactants.
Similarly, in a later DEPA report from 2008 (Jensen et al. 2008) about fluorinated substances in impregnated consumer products and impregnating agents it was also concluded that the use of fluorinated substances had shifted towards either perfluorinated substances with a shorter chain length (C₆ or shorter) or other classes of polyfluorinated substances, such as fluorotelomer alcohols (FTOH).

The most important short-chain perfluoroalkylsulfonic acids are perfluorobutane sulfonic acid (C₄, PFBS) and perfluorohexane sulfonic acid (C₆, PFHxS), which also exist as various salts. The only difference to PFOS is the four, respectively, two fluorocarbon shorter perfluorinated chain (“tail”).

Similarly to PFOS the short-chain alternatives have hundreds of derivatives as more complex molecules such as: N-Methyl perfluorobutane sulfonamidoethanol (MeFBSE) and N-methyl perfluorohexane sulfonamidoethyl acrylate:

The most important short-chain alternatives among the perfluorocarboxylic acids (PFCAs), are perfluorobutanoic acid (PFBA) and perfluorohexanoic acid (PFHxA) and their derivatives:

However, also perfluorobutyl- and perfluorohexyl phosphonate and their derivatives are used:

The most important short-chain fluorotelomers are 2:4 FTOH and 6:2 FTOH, and as for the C₈-PFAS, there are hundreds of derivatives in use, for instance phosphates and acrylates. The structure of an alcohol and a phosphate are shown below:
2.3 Developments in industry

The 3M Company, the previous producer of PFOS and Scotchgard™ products with PFOS derivatives, decided in May 2000 to phase out its PFOA, PFOS and PFOS-related products. For PFOS this phase-out was completed in 2002 and in 2008 for PFOA.³

3M is now using PFBS derivatives;⁴ however, on their Scotchgard website (www.scotchgard.com) the chemical identities and exact percentages of the fluorochemicals they use are not mentioned but considered a trade secret, thus it is not possible to control their claims.

Examples:

- “Scotchgard™ Fabric Protector” repels liquids and blocks stain for apparel and upholstery; keeps classic canvas sneakers looking newer longer. Contains <3 % of a “Fluorochemical Urethane” (chemical identity and exact percentage is a trade secret).

- “Scotchgard™ Fabric & Upholstery Cleaner” leaves behind Scotchgard™ Protector anti-soiling agents to protect against future resoiling. No MSDS and info about content but it must contain a fluorochemical.

- “Scotchgard™ Oxy Carpet & Fabric Spot & Stain Remover”. A unique 2-in-1 cleaner with built-in “Scotchgard™ Protector” eliminates tough stains and prevents resoiling. No MSDS and info about content but it must contain a fluorochemical.

- “Scotchgard™ Carpet & Rug Protector” protects your carpet from spills, stains and dirt soiling. Contains 3-7 % of a “Fluorochemical Urethane” (chemical identity and exact percentage is a trade secret).

- “Scotchgard™ Auto Interior Fabric Protector” Repels oil and water, blocks stains, protects against soiling and gives a powerful barrier causes liquids to bead up on the fabric surface for easy cleanup. Contain <3 % of a “Fluorochemical Urethane” (chemical identity and exact percentage is a trade secret).

- “Scotchgard™ OXY Auto Spot & Stain Remover.” Unique 2-in-1 cleaner with genuine Scotchgard™ Protector helps protect against future resoiling. No MSDS and info about content but it must contain a fluorochemical.

- “Scotchgard™ Tile Stone and Grout Penetrating Sealer” protect your tile bathroom floor from moisture and mildew. Contain 5-7% of a “Fluorochemical Urethane” (chemical identity and exact percentage is a trade secret).

Another large producer of fluorinated chemical products is DuPont, which mainly produced and used fluortelomers. Since the agreement in 2006 with USEPA about phasing out C₈-chemistry (completed in 2008), DuPont has phased-out their PFOA and 8:2 fluortelomer products and substituted them with 4:2/6:2 FTOH derived

⁴ http://solutions.3m.com/3MContentRetrievalAPI/BlobServlet?locale=en_US&lmd=1120194514000&assetId=1114270648708&assetType=MMM_Image&blobAttribute=ImageFile
The new DuPont™ Capstone® repellents and surfactants are based on short-chain chemistry that cannot break down to PFOS but to short-chain PFCAs. In the technical information/MSDS there is no exact information about what fluorinated chemicals are actually used but products are commercially available for home furnishings, fire-fighting foams, fluorosurfactants, and other end uses.

2.4 Recent uses of short-chain alternatives
In the following recent publications from the Stockholm Convention it is also stated that short-chain (C₄- and C₆-) fluorinated substances have substituted C₈-fluorinated substances:

- Guidance on alternatives to perfluorooctane sulfonic acid, its salts, perfluorooctane sulfonyl fluoride and their related chemicals. The first version from 2010 was drafted by Allan Astrup Jensen. The latest update by the secretariat was from November 2013.

In the following the developments for some important use areas are summarized based on these two publications.

2.4.1 Impregnation
Fluorinated finishes/impregnations are known to deliver durable and effective oil, water, and dirt repellence to textiles, leather, carpet, apparel, and upholstery. Historically, fluorinated polymers based on PFOS at up to 2 wt % or 8:2 fluorotelomer-based polymers have been used. Alternatives are fluorinated polymers based on PFBS and 4:2/6:2 FTOH-based polymers but exact chemicals used are not public information.

2.4.2 Fire-fighting foams
Over the last several years, manufacturers of aqueous film forming foams AFFF have been replacing long-chain fluorosurfactants based on perfluorooctane sulfonate (PFOS) derivatives/precursors or 8:2 FTOH (precursor of PFOA) with shorter-chain fluorosurfactants based on perfluorobutane sulfonate (PFBS) and perfluorohexane sulfonic acid (PFHxS) derivatives/precursors or derivatives of 6:2 FTOH, which is a precursor of PFHxA.

2.4.3 Metal plating
The most common substitute for PFOS in hard metal plating has been 6:2-Fluorotelomer sulfonate (6:2 FTS) (1H,1H,2H,2H-perfluorooctane sulfonic acid, H-PFOS). It is not fully fluorinated, but the C₆-perfluorinated tail is persistent, and the chemical is a precursor of perfluorinated carboxylic acids as PFHxA.

2.4.4 Oil production
PFOS derivatives are/have been used in some parts of the world as surfactants in oil well stimulation to recover oil trapped in small pores between rock particles to improve the wells productivity. The main two types of operations are acidization matrix and hydraulic fracturing. Alternatives fluorosurfactants to PFOS derivatives are PFBS derivatives, 6:2 fluorotelomers, and perfluoroalkyl amines, acids, amino acids, and thioether acids.

2.4.5 Food packaging
Fluorinated surfactants have been used for grease repellence to food contact papers paper products for long time, originally perfluorooctyl sulfonamidoethanol-based phosphates. Fluorotelomer thiol-based phosphates and polymers followed. Alternatives to the long-chain substances are PFBS derivatives and 4:2/6:2 fluorotelomer derivatives.

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8 UNEP/POPS/POPRC.9/INF/11/Rev.1
9 UNEP/POPS/POPRC.8/INF/17
2.5 **Substances included in this study**

Short-chain polyfluoroalkyl substances (PFAS) includes in this report mainly:

- The parent perfluorobutane sulfonate (PFBS), perfluoropentane sulfonate (PFPeS), and perfluorohexane sulfonate (PFHxS), their alkali/ammonium salts and acid halogenides e.g. PFBSF.
- Other PFBS, PFPeS and PFHxS functional derivatives/precursors, e.g. N-substituted sulfonamides such as FBSE.
- The parent perfluorobutanoic acid (PFBA), perfluoropentanoic acid (PFPeA), and perfluorohexanoic acid (PFHxA), their alkali/ammonium salts.
- Functional derivatives/precursors of PFBA, PFPeA, PFHxA, such as esters.
- Other PFCA precursors: 4:2 fluorotelomers and 6:2 fluorotelomers with various functional derivatives (halides, alcohols, sulfonates, amides, phosphates, esters etc.)
- C₄-C₆ Perfluoroalkyl alkyl ethers.

In 2011, these substance groups comprised about 140 CAS no. on the SPIN list and the preregistration list in REACH. The list of substances comprised by the term "short term PFAS", and thereby in principle by this report, is included as Appendix 1 to this report. Substances with REACH registration are indicated by a hash tag (#). The SPIN chemicals are indicated with an asterisk (*). These lists should not be considered complete. During the report work there appeared some evidence for usage and occurrences of not listed short-chain PFAS.

The majority of chemicals on the lists are chemical intermediates for production of other chemicals. Although it is documented above that the content of PFAS in commercial products is confidential information, it is seen in the extensive list below that there are a few known uses, probably as substitutes for longer chain homologues. That is in fire-fighting foams, in cosmetics, in inks, in food packaging, in metal plating, and for impregnation of textiles etc.
3. **Human health effects**

3.1 **General aspects of toxicokinetics and metabolism**

3.1.1 **Uptake and distribution**

It is known from animal studies that perfluoroalkylated substances (PFAS) are almost completely absorbed orally and by inhalation but that skin absorption is negligible; specifically, the oral absorption of perfluorohexanoate (PFHxA) in rats and mice was rapid and complete (Gannon et al. 2011).

Also rather complete oral absorption rates have also been demonstrated for perfluorobutanoic acid (PFBA) (Chang et al. 2008) and perfluorobutane sulfonic acid (PFBS) (Olsen et al. 2009). For PFHxS the oral absorption of two branched isomers (impurities) in rats was 30% lower than for the linear main isomer (Benskin et al. 2009).

Perfluoroalkylated substances (PFAS) have contrary to most other persistent organic pollutants (POPs) a low affinity to lipids but bind to proteins (Jones et al. 2003). PFAS is mainly associated to cell membrane surfaces and is mainly distributed in plasma and in well-perfused tissues such as the liver, kidney and spleen but also in the testes and brain (van den Heuvel et al. 1991). The longer the fluoroalkyl chain the more of the compound accumulates in the liver of male rats (Kudo et al. 2001).

A human post-mortem study showed highest levels of PFOS in liver, blood, lungs and kidneys and highest levels of PFOA in lungs, kidneys, liver and blood (Maestri et al., 2006).

In a recent more detailed study, the concentrations of 21 PFASs were analyzed in 99 samples of autopsy tissues (brain, liver, lung, bone, and kidney) from subjects who had been living in Tarragona (Catalonia, Spain). The occurrence of PFASs was confirmed in all human tissues but the concentration pattern differed between tissues, individuals and substances (Perez et al. 2013). Although PFAS accumulation followed particular trends depending on the specific tissue, some similarities were found. In kidney and lung, perfluorobutanoic acid (PFBA) was the most frequent compound, and found at the highest concentrations (median values: 263 and 807 ng/g in kidney and lung, respectively). In liver and brain, perfluorohexanoic acid (PFHxA) showed the maximum levels (median: 68.3 and 141 ng/g, respectively), while perfluorooctanoic acid (PFOA) was dominating in bone (median: 20.9 ng/g). Lung tissues accumulated the highest concentration of PFAS. However, perfluorooctane sulfonic acid (PFOS) and perfluorooctanoic acid (PFOA) were more prevalent in liver and bone, respectively. The high levels of perfluorohexyl ethanoic acid (FHEA), a metabolite of 6:2 FTOH, in some organs of some individuals were surprising and show that the metabolism of PFAS in humans must be different from metabolism in rodents. This needs to be taken into consideration in relation to risk assessment based on studies in rat where other metabolites dominate (discussed later). The high levels of the short chain PFAS are worrying and in contradiction to the claims from industry that there is no significant bioaccumulation by these PFAS. Some data for for the content of short chain PFAS in five organs and PFOA/PFOS as references are shown in Table 3.1.
### TABLE 3.1
DISTRIBUTION OF SHORT CHAIN PFAS IN 5 AUTOPSY TISSUES FROM 20 HUMAN INDIVIDUALS OF TARRAGONA, SPAIN (PEREZ ET AL. 2013).

<table>
<thead>
<tr>
<th>PFAS substance</th>
<th>Mean concentrations ng/g w. w.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Liver</td>
</tr>
<tr>
<td>PFBA</td>
<td>12.9</td>
</tr>
<tr>
<td>PFBS</td>
<td>0.9</td>
</tr>
<tr>
<td>PFPeA</td>
<td>1.4</td>
</tr>
<tr>
<td>PFHxA</td>
<td>11.5</td>
</tr>
<tr>
<td>PFHxS</td>
<td>4.6</td>
</tr>
<tr>
<td>Perfluorohexyl ethanoic acid (FHEA); metabolite of 6:2 FTOH</td>
<td>92.6</td>
</tr>
<tr>
<td>PFOA</td>
<td>13.6</td>
</tr>
<tr>
<td>PFOS</td>
<td>102</td>
</tr>
</tbody>
</table>

LOD = Limit of detection

In the blood PFAS are almost completely bound to serum albumin and transported around in the body in that way but the binding affinities vary among PFAS, animal species and binding sites (Bischel et al. 2011). PFCAs mimic fatty acids, and specifically PFHxA is attached to a different binding site on serum albumin compared to PFOA; however, PFOA is more strongly bound, and 5-6 PFOA molecules can interact with each albumin molecule (D’eon and Mabury 2010).

#### 3.1.2 Levels in human blood

In most studies of human biomonitoring of environmental exposures the levels of PFHxA in blood serum/plasma have either not been included or have been near or below the limit of quantification at levels of 0.05-0.10 ng/mL or 40-400 times lower than for PFOS and PFOA (Russell et al. 2013). At the typical pH in in human blood PFHxA is supposed to exist in a dissociated anionic form.

The concentrations of PFAS in human whole blood are approximately half of the serum/plasma levels. The levels in serum and plasma are about the same (Ehresman et al. 2007). In the blood from 18 volunteers employed by 3M Company, a producer of polyfluorochemicals, serum concentrations of PFBS ranged from <5-25 ng/mL and <5-75 ng/mL for PFHxS. Levels of PFOS and PFOA were 10-100 times higher (Ehresman et al. 2007).

In case of community exposure near industrial sources a mean level of about 1 ng PFHxA/mL was measured (Frisbee et al. 2009).

In a later section of this report (3.4.2) the high workplace air exposure to PFAS by World Cup professional ski waxes is described. In a follow up study whole blood samples from 8 ski waxes the median of PFOA was 112 ng/mL compared to 2.7 ng/mL in an unexposed control group (Nilsson et al. 2010b). PFHxS (0.3-4.3 ng/mL) was found in 93% of the 57 blood samples. Low levels of PFBA (<0.08-0.68 ng/mL), PFPeA (<0.06-0.14 ng/mL), and PFBS (<0.02-0.04 ng/mL) were found in 35, 10, and 7 samples, respectively. PFHxA (<0.07-12 ng/mL) was only observed in samples collected during the exposed period from December 2007 to March 2008, and PFHxA was not found over the detection limit in samples collected during the unexposed months. Levels of PFHxA in ski waxes blood peaked with 0.65-15 ng/mL in the ski season and rapidly declined to near the limit of quantification in the spring and summer – and no long-term bioaccumulation in blood.

In a follow up study with 11 male skiwax technicians (includes 3 new participants) average levels of short chain congeners were: PFHxA (1.9 ng/mL), PFPA (0.14 ng/mL), and PFBA (1.8 ng/mL) in comparison with PFOA (130
ng/mL). In addition, the fluorotelomer acid 5:3 FTCA (1.9 ng/mL) and the unsaturated fluorotelomer acids 6:2 FTUCA (0.03 ng/mL) were measured in the blood (Nilsson et al. 2013).

Data from the US National Health and Nutrition Examination Survey (NHANES) 1999-2008 including 7876 serum samples showed declining levels of PFOS since 1999-2000 from 30 to 13 ng/mL, but in the same period levels of PFOA and PFHxS were rather stable at levels of 4-5 ng/mL and 2 ng/mL, respectively (Kato et al. 2011).

In another study from the US, serum levels of PFBS, PFPeA and PFHxA were mostly below the quantification limit. PFHxS was determined in levels of 2.25 ng/mL in 2000 and 1.34 ng/mL in 2010 and declined with 40% from 2000-2010 but it was less than the decline for PFOS and PFOA (Olsen et al. 2012).

In Canada 100 umbilical cord blood samples from 2005-2008 were analyzed for the main PFASs. PFHxS was measured in 77% of the samples in levels up to 9.6 ng/mL and with a median of 0.5 ng/mL (Arbuckle et al. 2012). The median for PFOS was 10 times higher. PFHxS contaminant levels were significantly positively associated with lower gravida (p = 0.007), and smoking during pregnancy (p = 0.015). In a Norwegian study previous pregnancies and breastfeeding duration also was associated with lower PFAS and specifically PFHxS levels (Brantsæter et al. 2013).

Levels of some PFASs in serum of Swedish males at the age of 18 (n=50) in samples from 2009–2010 have been measured, and specifically PFHxS levels in the range of 0.38–2.5 ng/ml with a median of 0.78 ng/mL. These levels were about a tenth of the PFOS levels (Jönsson et al. 2010; Borg and Håkansson, 2012).

In most studies the levels of PFOS and PFOA in human blood are declining, and levels of the shorter and longer chain congeners are increasing. In Sweden levels of PFBS and PFHxS in blood serum from pregnant women have increased 11% and 8.3% per year respectively from 1996-2010 (Glynn et al. 2012) while during the same period the concentrations of PFOS and PFOS decreased 8.4% and 3.1% per year, respectively.

In another Swedish study with 80 women, levels of PFOA, PFOS and PFHxS in blood plasma peaked around year 2000 and decreased thereafter, PFHxS less than the other substances, from a median of 0.98 ng/mL to 0.82 ng/mL. The levels of longer chain congeners continued to increase after year 2000 (Axmon et al. 2014).

In blood from some office workers in Boston exposed to FTOHs. PFHxA was not detectable but PFHxS reached 0.2-13 ng/mL with a geomean of 1.5 ng/mL (Fraser et al. 2012).

A family of 4:2 through 10:2 fluorotelomer-based phosphate surfactants used in food packaging, the polyfluoroalkyl phosphate diesters (diPAPs), - precursors of PFCAs - have a.o. been discovered at μg/L concentrations in human sera samples from the Midwestern USA (D'eon et al 2009). Serum samples from 2004-2005 contained 4.5 ng diPAPs/mL with 6:2 diPAPs as the dominating congener at about 2 ng/mL. That was at the same concentration levels as for C₈-C₁₁ PFCAs. In the samples from 2008 the levels of 6:2 diPAPs were lower with a mean of 0.6 ng/mL.

Also in Germany a series of PFCAs and of 4:2 and 6:2 diPAPs were determined in human blood plasma (Yeung et al. 2013). Concentrations of PFCAs were measured in 420 samples while concentrations of diPAPs were measured in 320 samples. All samples had detectable concentrations of PFHpA , PFOA PFNA PFDA and). Approximately 80% of the samples had detectable concentrations of PFTrA and about 40% of the samples had detectable levels of 4:2/4:2-diPAP and 6:2/6:2-diPAP. Approximately 30% of the samples had detectable levels of 8:2/8:2-diPAP, fewer than 20% of the samples had detectable levels of 4:2/6:2-diPAP and 6:2/8:2-diPAP and fewer than 10% of the samples had detectable levels of PFHxA (see Table 3-2).
### TABLE 3.2
PFAS IN HUMAN BLOOD PLASMA FROM GERMANY (YEUNG ET AL. 2013).

<table>
<thead>
<tr>
<th>PFAS</th>
<th>Percent samples with PFAS levels &gt; LOD</th>
<th>Range of concentrations in plasma (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFHpA</td>
<td>100</td>
<td>0.0191 − 2.24</td>
</tr>
<tr>
<td>PFOA</td>
<td>100</td>
<td>0.092 − 39.4</td>
</tr>
<tr>
<td>PFNA</td>
<td>100</td>
<td>0.200 − 2.70</td>
</tr>
<tr>
<td>PFDA</td>
<td>100</td>
<td>0.020 − 0.880</td>
</tr>
<tr>
<td>PFUnA</td>
<td>100</td>
<td>0.003 − 0.555</td>
</tr>
<tr>
<td>PFTrA</td>
<td>80</td>
<td>&lt;0.005 − 0.0484</td>
</tr>
<tr>
<td>4:2/4:2-diPAP</td>
<td>40</td>
<td>&lt;0.0007 − 0.0948</td>
</tr>
<tr>
<td>6:2/6:2-diPAP</td>
<td>40</td>
<td>&lt;0.0002 − 0.687</td>
</tr>
<tr>
<td>8:2/8:2-diPAP</td>
<td>30</td>
<td>&lt;0.0010 − 0.285</td>
</tr>
<tr>
<td>4:2/6:2-diPAP</td>
<td>&lt;20</td>
<td>&lt;0.0007 − 2.38</td>
</tr>
<tr>
<td>6:2/8:2-diPAP</td>
<td>&lt;20</td>
<td>&lt;0.0002 − 0.113</td>
</tr>
<tr>
<td>PFHxA</td>
<td>&lt;10</td>
<td>&lt;0.005 − 0.0998</td>
</tr>
</tbody>
</table>

In human sera samples collected in 2009 in the USA the levels of 6:2 diPAPs were lower than in 2008 with max. 0.14 ng/mL (Lee and Mabury 2011). In addition, other surfactants (PFPIa) from food packaging, such as bis[perfluorohexyl] phosphinate (the C₄-analogue is in the CAS no. list above) were measured in low levels (<0.1 ng/mL) together with 6:2 FTS, PFBA, PFPA, PFHxA, and PFBS. The levels of PFHxS were just over 1 ng/mL and only PFOS (4-12 ng/mL) and PFOA (2 ng/mL) were higher. The 6:2 fluorotelomer mercaptopalkyl phosphate diester (6:2 FTMAP), which is also used in food packaging, for example for microwave popcorn, was not found.

#### 3.1.3 Metabolism/biotransformation

Both short- and long-chain perfluoroalkyl acids (PFAAs) are considered being metabolically inert. The strong C-F bonds exclude any normal degradation pathway. Any functional derivative (precursor) will ultimately be transformed to the acids. PFHxA was not metabolized in rat or mouse hepatocytes, nor were any metabolites observed after oral dosing in either rodent species (Gannon et al. 2011).

Also fluorotelomer can be metabolized to PFCAs of various chain lengths, and already in 1981 the biotransformation of 8:2 FTOH via 2H₂H-perfluoro ecanoic acid (a FTCA) into PFOA was shown in rats (Hagen et al. 1981).

The general pathways are shown in the following simplified scheme (adopted from Martin et al. 2005):

![Diagram showing the biotransformation of perfluoroalkyl acids](image-url)
In this way 4:2 FTOH can be metabolized to PFBA and PFPeA, and 6:2 FTOH to PFHxA and PFHpA. However, many other and more reactive metabolites (unsaturated aldehydes and acids) are formed in test systems (Rand and Mabury 2012). The amounts of free PFCA formed seem to be small. Regarding 6:2 FTOH the metabolic yield of PFHxA in mammalian systems was estimated to <1% (Russell et al. 2013).

3.1.4 Excretion/elimination from the body
The primary route of elimination of PFCA from the body is via kidneys in the urine. Renal clearance of PFCA is a sum of three processes involving glomerular filtration, renal tubular secretion, and renal tubular reabsorption. It depends on chain length, species and gender. Females have much less reabsorption of PFCA and thus a much higher renal clearance than males. Since it was showed that PFOA was less toxic to female rats compared to males, sex hormones have been identified as a major factor in determining renal clearance of PFOA. Castration of male rats greatly increased PFOA renal elimination. Administration of 17β-estradiol to castrated males brought PFOA urinary elimination to the level of females, whereas testosterone treatment of castrated males reduced PFOA elimination to the same level as that in intact males (Han et al. 2011).

The roles of sex hormones and the rates of PFNA renal elimination in rats are connected as the renal active secretion and reabsorption of PFCA are mediated via specific transport proteins such as the organic anion transporting polypeptide 1a1 (Oatp 1a1). This is located in the membranes of the proximal tubular cells, and the sexdependent renal clearance differences have all been attributed to the reabsorption mechanism mediated by rat renal Oatp1a1 transport proteins (Kudo et al. 2001; 2002; Yang et al. 2009; Weaver et al. 2010).

Transport via membrane transport proteins and reabsorption appears to be the fundamental mechanism responsible for the observation of chain length-dependent renal clearance of PFCA in rodents i.e., longer chain length perfluorocarboxylates tend to have longer elimination half-lives in rats (Kudo et al. 2001). However, PFBA is different and has a slower clearance than PFHxA, and PFBA seems not to be the substrates of Oatp1a1 (Yang et al. 2009).

PFHxS with a C6-perfluorocarbon chain bioaccumulates in the organism with a long half-life in the organism in the same way as PFOS; however PFBS with a C4-perfluorocarbon chain seems not to be bioaccumulative and has a shorter half-life in the organism.

In a human case cholestyramine was successful in detoxification through increased gastrointestinal elimination of perfluorinated chemicals in a person highly exposed to PFHxS from carpets in the home (Genuis et al. 2010; Beeson et al. 2012). Blood PFHxS serum levels declined from 60 ng/g to 47 ng/g after 20 weeks treatment.

3.1.5 Blood serum elimination half-lives
The mean blood elimination half-lives for PFASs depend on the chemical substance and animal species and its sex. Generally, the blood half-lives of PFASs are longer for sulfonates than for carboxylates, they increase with chain length for carboxylates, and they are shorter for branched isomers. They are often shorter in females, mainly due to a sex-specific difference in renal clearance with females more actively excreting these materials via the kidney than males. The half-lives of PFAS are dose-dependent with longer half-lives for lower concentrations relevant for humans (Seals et al. 2011). The general elimination half-lives of PFAS in exposed rodents were hours or few days, in monkeys a little longer, and in humans very long. The actual reason for the long PFOA plasma half-life in humans is that humans have the highest percentage of renal tubular reabsorption (>99%) (Harada et al. 2005). The actual serum half-lives for the short chain PFAS is discussed later for each substance but Table 3-3 contains an overview.

A selection of the published data on serum elimination half-lives in different species are shown in Table 3-3.
TABLE 3-3
OVERVIEW OF SOME SERUM ELIMINATION HALF-LIVES OF SHORT CHAIN PFAS

<table>
<thead>
<tr>
<th>Species</th>
<th>PFBS Male</th>
<th>PFBS Female</th>
<th>PFHxS Male</th>
<th>PFHxS Female</th>
<th>PFBA Male</th>
<th>PFBA Female</th>
<th>PFHxA Male</th>
<th>PFHxA Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rat</td>
<td>&lt;4.5 days</td>
<td>&lt;4 days</td>
<td>29 days</td>
<td>1 day</td>
<td>9 hours</td>
<td>2 hours</td>
<td>1.6 hours</td>
<td>0.6 hours</td>
</tr>
<tr>
<td>Mouse</td>
<td>30.5 days</td>
<td>24.8 days</td>
<td>5-16 hours</td>
<td>3 hours</td>
<td>2 hours</td>
<td>1 hour</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monkey</td>
<td>95 hours</td>
<td>83 hours</td>
<td>141 days</td>
<td>87 hours</td>
<td>40 hours</td>
<td>41 hours</td>
<td>14-47 hours</td>
<td></td>
</tr>
<tr>
<td>Human</td>
<td>24 days</td>
<td>46 days</td>
<td>8.5 years</td>
<td>72 hours</td>
<td>87 hours</td>
<td>32 days</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

3.1.6 Fetal and lactational transfer

In Norway the human maternal and fetal levels of up to seven PFAS were significantly correlated. The relative proportion of PFHxS was higher than that of PFOS in cord blood compared to maternal blood. This indicated that the chain length of the fluorinated compound was an important determinant for placental passage, and that shorter chain PFASs were transferred relatively more (Thomsen et al. 2010). That was confirmed in a later study where 19 PFAS were analysed in maternal and cord plasma (Gützkow et al. 2012). The median PFAS concentrations (ng/mL) in cord blood were between 30% and 79% of the maternal concentrations. In maternal samples, the median of PFNA was slightly higher than for PFHxS, while the opposite was seen in cord plasma, with a two-fold higher PFHxS concentration compared to PFNA. The ratio between cord concentration (0.23 ng/mL) and maternal concentrations (0.34 ng/mL) of PFHxS was about 0.67.

Lactational transfer of PFAS is limited and breast milk concentrations are a few % of the maternal blood concentration (Fromme et al. 2010).

PFHxS was detected in 100 % of maternal serum samples (n = 44; 0.55 ng/mL) and cord blood samples (n = 43; 0.34 ng/mL) whereas no correlations were observed in the paired maternal serum (0.89 ng/mL) and human milk samples (7.2 pg/mL) taken from the women in South Korea (Kim et al., 2011).

All human milk samples collected between 1996 and 2004 and analysed in an early study from Sweden contained PFOS (mean 0.2 ng/mL) and PFHxS (mean 0.085 ng/mL). The total PFAS mean concentration was 0.34 ng/mL (Kärman et al. 2007). The total PFAS concentration in maternal serum was 32 ng/mL, 100-fold higher than breast milk, thus on average milk levels are about 1% of serum levels. Specifically regarding PFHxS the mean level in the serum was 4.7 ng/mL and breast milk about 2% hereof.

A study of pooled Swedish breast milk samples from 1972-2008 observed a clear time trend with increasing levels of PFOS and PFOA until about year 2000 and decreasing levels therefrom. The levels of PFHxS were about ten times lower (5-25 pg/mL), and the decrease was not so clear. Other short-chain congeners were not analyzed (Sundström et al. 2011).

3.2 Toxicological mechanisms

3.2.1 Peroxisome proliferation

Many PFAS are highly potent peroxisome proliferators in rodent livers and affect mitochondrial, microsomal, and cytosolic enzymes and proteins involved in lipid metabolism (Ikeda et al. 1985; Van den Heuvel 1996; Upham et. al. 1998; Kudo et al. 2000). The liver fatty acid–binding protein (L-FABP) is a transport protein known to bind PFAS (Luebker et al., 2002).
The liver toxicity and peroxisome proliferation potency in rats depends on the carbon chain length. PFCA activated both mouse and human PPARα in a concentration dependent fashion, and activation of PPARα by PFCA was positively correlated with carbon chain length, up to C9. PPARα activity was higher in response to carboxylates compared to sulfonates. Activation of mouse PPARα was generally higher compared to that of human PPARα (Wolf et al. 2008). The relative activity increased from PFBS < PFOS < PFHxS < PFBA < PFHxA < PFOA. In a recent study also PFPeA was also shown to be a weak peroxisome proliferator in mice and human cells in potency between PFBA and PFHxA (Wolf et al. 2013).

3.2.2 Effects on cell membranes
Another general impact of PFAS is alterations in cell membrane properties, and the mechanisms of toxicity may involve partitioning into lipid bilayers. Actually (PFBS) disrupted different model phosphatidylcholine (PC) lipid assemblies indicating a potential for PFBS to be a human toxicant (Oldham et al. 2012). However, the effects of PFBS were not as pronounced as those seen with longer chain PFAS.

In a study of fish leucocytes PFOS at a lowest effect concentration 5-15 mg/L decreased the membrane fluidity and increased the permeability of the cell membrane but PFBS and PFHxS had no effect at these concentrations (Hu et al. 2003).

3.2.3 Effect on lipids
This study investigated the mechanism underlying the effect of some PFASs, including PFBS and PFHxS, on lipid- and lipoprotein metabolism (Bijland et al. 2011). Mice were fed a diet with PFBS (30 mg/kg/day) and PFHxS (6 mg/kg/day) for 4–6 weeks. Whereas PFBS modestly reduced only plasma triglycerides, PFHxS markedly reduced plasma triglycerides, total cholesterol and very low- and high-density lipoproteins, mainly by impairing lipoprotein production. In addition, PFHxS increased liver weight and hepatic triglyceride content. Hepatic gene expression profiling data indicated that these effects were the combined result of peroxisome proliferator–activated receptor alpha and pregnane X receptor activation. The potency of PFAS to affect lipoprotein metabolism increased with increasing alkyl chain length.

3.2.4 Cytotoxicity
The cytotoxicity of eight PFASs, including PFBA, PFHxA, PFBS, and PFHxS was assessed in the human placental choriocarcinoma cell line JEG-3 (Gorrochategui et al. 2014). Only the long chain PFAS (PFOS, PFDoA, PFNA, PFOA) showed significant cytotoxicity but it was showed that PFBS (+ PFOS and PFOA) acted as aromatase inhibitors in placental cells. This inhibitory effect of the short chain PFBS was considered particularly important, because it is often considered a safe substitute of PFOS. It was also observed that exposure of JEG-3 cells to a mixture of the eight PFASs (0.6 μM each) altered/increased cellular lipid pattern (up to 3.4-fold) at concentrations well below those that generate toxicity.

A study compared the effects of 10 PFASs (PFBS, PFHxS, PFOS, PFBA, PFPeA, PFHA, PFOA, PFNA, PFUnA and PFDoA) on mRNA abundance of 7 genes related to processes known to be affected by PFOS, such as fatty acid and cholesterol synthesis, and thyroid development (Naile et al. 2012). Rat H4IIE hepatoma cells were exposed, and changes in mRNA abundance were quantified by real-time PCR. Significant changes in mRNA abundance were observed. The effects on individual target genes caused by the shorter chain chemicals differed significantly from effects on genes caused by PFOS or PFOA, and that differences could not simply be attributed to chain-length or functional group. These differences could mean that these short chain chemicals do not act through the same mechanisms as the more studied PFOS and PFOA.
A chain-length-EC50 dependence was clearly observed for PFCAs in an *in vitro* assay with human colon carcinoma (HCT116) cells. Estimated values of EC50 decreased with elongation of fluorocarbon chain from PFHxA > PFHpA > PFOA > PFNA etc. The cytotoxicity was rather low but intensified after longer exposure (72 h) (Kleszczynski *et al.* 2007).

### 3.2.5 Neurotoxicity

The developmental neurotoxicity of 4 perfluorinated chemicals, including PFBS, was modeled *in vitro* in undifferentiated and differentiating PC12 cells, a standard *in vitro* model for neuronal development used to characterize neurotoxicity. Inhibition of DNA synthesis, deficits in cell numbers and growth, oxidative stress, reduced cell viability, and shifts in differentiation toward or away from the dopamine (DA) and acetylcholine (ACh) neurotransmitter phenotypes were assessed. In general, the rank order of adverse effects was PFOSA > PFOS > PFBS ≈ PFOA. However, the various agents differed in their underlying mechanisms and specific outcomes. Specifically, PFBS suppressed differentiation of both the ACh and DA phenotypes (Slotkin *et al.*, 2008). These findings indicated that all perfluorinated chemicals are not the same with regard to their impact on neurodevelopment and that it is unlikely that there is one simple, shared mechanism by which they all produce their effects.

### 3.2.6 Endocrine disruption

In many PFAS toxicology studies decreased thyroid hormone levels are observed. The mechanism is a competitive binding to the thyroid hormone plasma transport protein transthyretin (TTR) that will alter/decrease the free thyroxine (T4) in blood. This competitive binding capacity of some poly- and perfluorinated compounds was studied by Weiss *et al.* (2009) with a radio-ligand-binding assay. The binding potency of the fluorinated chemicals was 12-300 times lower than for thyroxine itself and decreased in the order: PFHxS > PFOS/PFOA > PFHxA > PFBS. PFBA and FTOHs had no effect in that assay.

In Table 3.4 some of the data on the competitive binding to transthyretin for the short-chain congeners are shown together with some long-chain congeners for comparison.

<table>
<thead>
<tr>
<th>Compound</th>
<th>IC50 nM</th>
<th>T4 relative binding potency factor, (T4 = 1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFHxA</td>
<td>8220</td>
<td>0.007</td>
</tr>
<tr>
<td>PFBS</td>
<td>19460</td>
<td>0.003</td>
</tr>
<tr>
<td>PFHxS</td>
<td>717</td>
<td>0.085</td>
</tr>
<tr>
<td>PFOS</td>
<td>940</td>
<td>0.065</td>
</tr>
<tr>
<td>PFOA</td>
<td>949</td>
<td>0.064</td>
</tr>
</tbody>
</table>

IC50 (nM) = conc. at 50% inhibition

### 3.3 Toxic effects of single PFAS

While PFOS, PFOA and perfluorohexansulfonic acid (PFHxS) have been extensively studied, replacement chemicals, such as perfluorobutanesulfonate (PFBS), perfluorobutyric acid (PFBA) and perfluorohexanoic acid (PFHxA), have not been well characterized. Perfluoropentane sulfonic acid (PFPeS) and perfluoropentanoic acid (PFPeA) are not discussed separately in the following, because there is virtually no public available health data on these chemicals.

Despite the relative lack of data available on the short-chain PFASs it has often been assumed that they will cause similar or lesser effects than PFOS. A recent extensive literature study of the oral toxicity of various perfluoroal-
kylated substances (PFASs), their precursors and potential replacements in experimental animals and humans has been commissioned by EFSA (Bull et al. 2014).

3.3.1 Perfluoroalkane sulfonic acids/sulfonates (PFSA)

3.3.1.1 Perfluorobutane sulfonate (PFBS, C₄)

Toxicokinetics

The toxicokinetics of perfluorobutane sulfonate (PFBS) has been compared between rats, monkeys and humans (Olsen et al. 2009). In rats the serum elimination half-lives after intravenous injection of 30 mg PFBS/kg b. w. were 4.51±2.22 hours in males and 3.96±0.21 hours in females. However, the renal clearance – the major body elimination route - was 4 times greater in female than male rats. In monkeys exposed to a lower intravenous dose of 10 mg PFBS/kg b. w. the serum elimination half-lives were 95.2±27.1 hour in males and 83.2±41.9 hours in females. In some workers with a lower than the animals but long-term exposure to PFBS as potassium salt, the mean serum elimination half-life of PFBS was determined to be 25.8 days in humans. However, that doesn’t mean that the substance is excreted, because analysis of Spanish human autopsy tissues revealed that the highest concentration of PFBS was found in lung tissues, however, PFBS also accumulated in liver, kidney and bone but not in brain (Perez et al. 2013).

The 20 times longer half-life of PFBS in monkeys than in rats determined in the study above was not seen in another study, in which the serum elimination half-life of PFBS in monkeys following a single intravenous dose of 10 mg PFBS/kg b. w. were 8 hours in females and 15 hours in males (Chengelis et al 2009a). Male monkeys appeared to have higher exposure and a longer serum elimination half-life than female monkeys. In this study a similar exposure of rats resulted in half-lives for PFBS of 0.64 hours in females and 2.1 hours in males, also different from the study above. The half-lives for urinary elimination were 2.4 and 3.1 hours respectively.

Animal toxicity

The liver toxicity and peroxisome proliferation potency of PFAS in rats increase with the carbon chain length until C₉. PFBS is much less liver toxic than PFOS but large doses may damage the liver, kidneys and blood. The doses of PFBS required to produce similar increases in the enzyme hepatic acyl CoA oxidase activity (a measure of liver proliferation) was about 50 times higher than those of PFOS and PFHxS (Lau et al 2007). PFBS had also a relatively low PPARα activity in the liver (Wolf et al. 2008).

The sub-chronic toxicity of potassium perfluorobutane sulfonate (PFBS) has been studied in rats at doses of 60, 200, and 600 mg/kg b. w. per day for 90 days (Lieder et al. 2009). No treatment-related mortality, bodyweight, or neurological effects were noted. Red blood cell counts, hemoglobin, and hematocrit values were reduced in males receiving 200 and 600 mg/kg b. w. per day. The NOAEL for the male rat was 60 mg/kg per day based on hematological effects. The NOAEL for the female rat in this study was 600 mg/kg b. w. per day (highest dose tested). Potassium perfluorobutane sulfonate (PFBS-K) has in one study been assessed for developmental and reproductive effects in rats at maternal doses until 1 mg/kg/day. No adverse effect on embryo/fetal development was noted, and no significant alterations were observed in a two-generation study (Lau et al. 2004).

In a two-generation reproduction study with the potassium salt of PFBS, parental-generation (P) rats were dosed orally by gavage with 0, 30, 100, 300 and 1000 mg PFBS/kg b. w. per day for 10 weeks prior to and through mating (males and females), as well as during gestation and lactation (females only). First generation (F1) pups were dosed similarly, beginning at weaning. Second generation (F2) pups were not directly dosed but potentially exposed to PFBS through placental transfer and nursing, and the study was terminated 3 weeks after their birth. In the two high doses increased liver weight and some effect on the kidneys were observed. NOAEL for the parental generations was 100 mg/kg bw/day (Lieder et al. 2009).

For comparison the NOAEL value in rats for PFOS was 0.1 mg/kg b. w. per day or 1000 times lower (Luebker et al. 2005).

Toxicological mechanisms
The mechanisms of toxicity may involve partitioning into lipid bilayers. PFBS disrupted different model phosphatidylcholine lipid assemblies indicating a potential for PFBS to alter cell membrane properties (Oldham et al. 2012). However, the effects of PFBS were not as pronounced as those seen with longer chain PFAS.

Another toxicity mechanism may be an effect on lipid metabolism, as PFBS modestly reduced plasma triglycerides in a study with mice (Bijland et al. 2011).

PFBS like PFOS and PFOA acted as an aromatase inhibitor in placental cells (Gorrochategui et al. 2014). This inhibitory effect of the short chain PFBS was considered particularly important, because it is often considered a safe substitute of PFOS.

Many PFASs, especially PFOA and PFOS, may generate reactive oxygen species’ (ROS) and induce oxidative DNA damage in human HepG2 cells. PFBS did not show activity in this test (Eriksen et al. 2010).

The potassium salt of PFBS had no effect on 3-β-hydroxysteroid dehydrogenase and 17-β-hydroxysteroid dehydrogenase 3 activity in human or rat testes microsomes, even at high concentrations (Zhao et al. 2010). PFOS was a potent inhibitor of both human and rat 11β-hydroxysteroid dehydrogenase 2 (HSD2) activities PFBS minimally inhibited 11β-HSD2 in human and rat kidney microsomes. The potency of inhibition declined with the length of the carbon chain: PFOS > PFOA > PFHxS > PFBS (Zhao et al., 2011).

Corsini et al. (2012) made an in vitro characterization of the immunotoxic potential of several perfluorinated compounds, including PFBS. Cells of the human promyelocytic cell line THP-1 were incubated with PFBS (0.1-10 µg/mL) in the presence of lipopolysaccharide (LPS) or phytohemagglutinin (PHA) in order to examine the effects on the inflammatory cytokine response. PFBS inhibited the release of the tumor necrosis factor-α (TNF-α) and interleukin (IL) IL-10, but IL-6 and interferon-γ (IFN-γ) were unaffected. In THP-1 cells, PFBS also inhibited the protein NF-κB activation by inhibiting LPS-induced phosphorylation of P65, necessary for NF-κB transcription, and prevented I-κB kinase degradation. PPAR-α was not activated (Corsini et al., 2012).

Effects in humans and guideline
In a study from Taiwan PFAS serum levels including of PFBS were reported to be significantly higher in children with asthma compared to children without asthma (Dong et al. 2013).

The Minnesota Department of Health (The 3M industry produces PFBS in this state) has developed a subchronic reference dose for PFBS of 0.0042 mg/kg b. w. per day based on a NOAEL value of 60 mg/kg b. w. per day in a 90 days rat study (Leider et al. 2009). The mean human half-life was estimated to 28 days. A half-life adjustment factor of 142 was used for extrapolation to a human equivalent dose of 0.42 mg/kg b. w. per day. Based on that they also developed a subchronic health based guidance for groundwater of 9 µg PFBS/L (MDH Web Publication, September 25, 2009).

PFBS derivatives
The PFBS derivative perfluorobutane sulfonyle fluoride (FBSF) is the basic reagent for production of PFBS. It is more reactive than PFBS, and it is self-classified in REACH as acute toxic and as a skin- and eye irritant.

N-Methyl perfluorobutane sulfonamide ethyl acrylate (C4-acrylate, CAS 67584-55-8) is an important derivative/precursor of PFBS used as an industrial intermediate. This substance has a relatively low acute toxicity but it is an eye irritant and may cause skin sensitisation. It has a short half-life in rats but eventual metabolites formed have not been investigated (data from REACH pre-registration).

3.3.1.2 Perfluorohexane sulfonate (PFHxS, C6)
Toxicokinetics
The toxicokinetics of the potassium salt of PFHxS after a single intravenous exposure (10 mg/kg b. w.) was compared in rats, mice and monkeys (Sundström et al. 2012). Urine was the major route of excretion in male and female rats, and mean daily fecal excretion was <0.5% of administered dose at all times. Within 96 hours females
excreted 28% of a dose in urine. Males excreted only about 6–7% of a dose in urine and had very much higher levels of PFHxS in blood and liver. The excretion increased with the dose. The mean serum elimination half-lives in male and female rats were calculated to 6.83 days and 1.83±0.26 days, respectively. These values are not likely to be reliable due to the short duration (24 hours). A comparison between intravenous- and oral exposures showed a PFHxS bioavailability of about 50%. After 10 weeks the mean serum elimination half-lives in male rats was calculated to about 29 days. In females the levels of PFHxS in the blood after 10 weeks were too low to quantify. In mice given oral doses of 20 mg PFHxS-K/kg body weight the mean serum elimination half-lives in males and females were 30.5 and 24.8 days, respectively, and not so different as for rats. Elimination in urine dominated also in mice but it was less than for rats. After 24 hours <3% of a dose was recovered in urine. In monkeys, PFHxS was much more long-lived in the blood with mean serum elimination half-lives for females and males of 87±27 days versus 141±30 days, respectively; however, this difference was not statistically significant. Less than 0.1 % of a dose was determined in the urine, thus renal elimination was very slow in monkeys.

In rats the serum depuration half-life of linear PFHxS was 15.9 days, while the half-lives for two branched isomers (impurities) were 3–7 days (Benskins et al. 2009). In the same study the half-life of linear PFOS was about the double, and the half-life of linear PFOA was 15% lower than PFHxS.

In retired workers from the fluorochemical producing industry serum half-lives for PFHxS (perfluorohexane sulfonate) were 7.3–8.5 years or about twice the half-lives for PFOS and PFOA (Olsen et al. 2007). Thus, the half-life for PFHxS in rats is, like for other PFAS, much shorter than in humans. However, the half-life of PFHxS is shorter in rats than the half-life (40 days) of PFOS in rats.

The long residence time of PFHxS in human blood may explain the relatively low organ concentrations of this chemical compared to other PFASs measured in Spanish autopsy tissues. The highest concentration of PFHxS was found in the kidneys but 20 times lower compared to PFBA (Perez et al. 2013).

In a recent study of Chinese workers the estimated median half-life for PFHxS was 13.8 years in males and 7.2 years in females. The half-lives in females were also shorter with regard to PFOA and PFOS, and thus the sex difference seen in animals is also observed in humans. The difference was explained by a lower female reabsorption in the kidneys and a comparable excretion with menstruation blood (Fu et al. 2014). In the Chinese workers the PFAS concentrations were extremely high with PFHxS at 1763 ng/mL. The branched isomers showed a faster renal clearance than the linear – also for PFHxS (Gao et al. 2014).

Toxicity in animals

The liver toxicity and peroxisome proliferation potency in rats of PFAS increase with the carbon chain length until C9. PFHxS is much more liver toxic than PFBS and PFOS. PFHxS was about 50 times more potent inducer of the enzyme hepatic acyl CoA oxidase activity (a measure of liver proliferation) than PFBS (Lau et al 2007). PFHxS had also a higher PPARα activity in the liver than PFBS (Wolf et al. 2008).

The potential reproductive and developmental toxicity of perfluorohexane sulfonate (PFHxS) was studied in a study with rats dosed by gavage at 0.3, 1, 3, and 10 mg/kg/d 14 days prior to co-habitation, during cohabitation, and until the day before sacrifice (21 days of lactation or presumed gestation day 25 (if not pregnant) for females and minimum of 42 days of treatment for males). Offspring were not dosed by gavage but were exposed by placental transfer in utero and potentially exposed via milk. At all doses reductions in serum total cholesterol and other biochemical changes in the blood but no reproductive or developmental effects were observed, and there were no treatment-related effects in dams or offspring (Butenhoff et al. 2009a). Thus, in this rodent study the metabolism of lipids was affected at a daily exposure for 0.3 mg/kg b. w., and liver damage was observed after exposure to 3 mg/kg b. w. per day (NOAEL = 1 mg/kg per day). A NOAEL of 10 mg/kg b. w. per day (highest concentration tested) for effects on the reproduction was determined for PFHxS.

Other studies have determined neurotoxicity in pups. Following treatment of 10 days (the peak of the brain growth spurt) old NMRI mouse pups with a single oral-oral gavage dose of the potassium salt of PFHxS (0, 0.61, 6.1 or 9.2 mg/kg b. w.), animals in the highest dose group exhibited dose–response related and long-lasting
changes in both spontaneous and nicotine-induced behavior as adults (Viberg et al., 2013). In a follow-up study by the authors it was shown that after 24 hours the neuroprotein levels were altered in the highly exposed mice, e.g. calcium/calmodulin-dependent kinase II (CaMKII), growth-associated protein-43 (GAP-43), synaptophysin and tau proteins, which are essential for normal brain development in mice. This was measured for both males and females, in hippocampus and cerebral cortex. There were also altered levels of neuroproteins in adult male mice explaining the results in the previous publication. These results suggest that PFHxS may act as a developmental neurotoxicant, and the effects are similar to that of PFOS and PFOA (Lee and Viberg 2013).

Toxicological mechanisms
PFAs are substances attracted to surfaces, which can partition into model bilayers and cell membranes, where they cause changes in membrane structure, properties and function. An increased fluidity may change cell membrane surface potential and enhance calcium channels with the result of increased intracellular Ca^{2+} (Harada et al. 2005; Liao et al. 2008). PFOS is the most active membrane disturber but in cultured hippocampal neurons, PFHxS was also active (Liao et al. 2009).

A typical effect of the longer-chain PFAs is inhibition of the gap junction intercellular communication, which is the major pathway of intracellular signal transduction, and it is thus important for normal cell growth and function. Defects in this communication may lead to teratogenesis, neuropathy, infertility, diabetes, autoimmune disorders, cancer, and other diseases (Upham et al. 2009). Among the short chain PFAS, only PFHxS may induce this effect.

PFHxS (and PFOS and PFOA) acts as a 17β-Estradiol (ER) agonist in vitro and enhanced significantly the E2-induced estrogen receptor (ER) response in human MVLN breast cancer cells (Kjeldsen et al. 2013).

PFHxS possess in vitro endocrine disrupting potential by interfering with functions of thyroid hormone in a system assessing the proliferation of the 3,3',5-triiodo-L-thyronine (T3)-dependent rat pituitary GH3 cells using the T-screen assay and the effect on the Aryl hydrocarbon Receptor (AhR) transactivation in the AhR-luciferase reporter gene bioassay (Long et al. 2013). In a test system measuring the competitive binding capacity of various PFAs to the thyroid hormone plasma transport protein transthyretin (TTR) the potency of PFHxS was higher than all other tested PFAS’s, including PFOS and PFOA (Weiss et al. 2009).

There is some evidence to suggest that PFAAs can impact essential endocrine pathways and neurodevelopment in birds and other animals. In a study by Vongphachan et al. (2011), PFHxS altered significantly the messenger RNA (mRNA) expression of thyroid hormone (TH)–responsive transcripts in chicken embryonic neuronal (CEN) cells in vitro.

In a later study, the same research group successfully validated previous in vitro results concerning the modulation of TH-responsive genes and identified adverse effects associated with TH homeostasis in response to PFHxS treatment. They determined in ovo effects of PFHxS exposure (maximum dose 538,000 ng/g egg) on embryonic death, developmental endpoints, tissue accumulation, mRNA expression in liver and cerebral cortex, and plasma TH levels (Cassone et al. 2012). Pipping success was reduced to 63% at the highest dose of PFHxS. PFHxS exposure decreased tarsus length and embryo mass. PFHxS accumulated in the three tissue compartments analyzed as follows: yolk sac > liver > cerebral cortex. Type II and type III 5−deiodinases (D2 and D3) and cytochrome P450 3A37 mRNA levels were induced in liver tissue of chicken embryos exposed to PFHxS, whereas D2, neurogranin (RC3), and octamer motif binding factor 1 mRNA levels were up-regulated in cerebral cortex. Plasma thyroxine levels were reduced in a concentration-dependent manner following PFHxS exposure.

Effects of PFHxS in humans
There are many population studies, where exposure to PFAS has been associated to various adverse effects. Most studies have measured the most abundant PFOS and PFOA in blood serum but some studies have included for instance PFHxS which occurs in lower concentration than PFOS and PFOA. However, it is normally impossible to isolate the specific contributive effect of PFHxS but as a worst case assumption, the PFAS may be considered having additive effects.
Effects on the metabolism of lipids

The effect of PFAS on the metabolism of lipids in rodents has also been observed in humans. A 2007-2009 Canadian health measures survey found a significant association between PFHxS (GM: 2.18 mg/L) and PFOA (GM: 2.46 mg/L) levels and total cholesterol (TC), low-density lipoprotein cholesterol (LDL), total cholesterol/high density lipoprotein cholesterol ratio (TC/HDL) and non-HDL cholesterol as well as an elevated odds of high cholesterol (Fisher et al. 2013). The concentration of PFHxS in this study was relatively high for a reference population.

In the Norwegian Mother and Child Cohort Study in 2003–2004 plasma concentrations of 7 PFAS were positively associated with HDL cholesterol, and specifically PFOS but not PFHxS was positively associated with total cholesterol in this sample of pregnant Norwegian women (Starling et al. 2014). The median concentrations of PFOS and PFHxS were 13 ng/mL and 0.6 ng/mL, respectively.

Reproductive effects

A study of a large cohort from Avon in the UK with prenatal blood concentration (medians) of 19.2 ng/mL PFOS, 3.7 ng/mL PFOA and 1.6 ng/mL PFHxS showed that the most exposed mothers from the upper tertile gave birth to girls weighing 140 gram less than for the less exposed but at 20 months the girls with high PFOS exposure weighed 580 gram more (Maisonet et al. 2012). In a study from Canada there was no significant effect of PFAS on birth weight. The blood levels were, however, somewhat lower with medians of 7.8, 1.5 and 0.97 ng/mL for PFOS, PFOA and PFHxS, respectively (Hamm et al. 2010).

That may not be a problem of the mother alone, because another Danish study found that high levels of perfluorinated acids (PFAAs) (medians: 24.5 ng PFOS/mL, 4.9 ng PFOA/mL and 6.6 ng PFHxS/mL) in blood serum were associated with fewer normal sperm cells in normal young men included in the study (Joensen et al. 2009).

After adjusting for age, race/ethnicity, education, ever smoking, and parity, women with higher levels of PFAS had still earlier menopause than did women with the lowest PFAS levels (Taylor et al. 2014). Specifically, a monotonic association with PFHxS was observed: The hazard ratio (HR) was 1.42 (95% CI: 1.08, 1.87) for serum concentrations in tertile 2 versus tertile 1, and 1.70 (95% CI: 1.36, 2.12) for tertile 3 versus tertile 1.

Endocrine disruption

Data from National Health and Nutrition Examination Survey (NHANES) for the years 2007–2008 were used to evaluate the effect of PFOS, PFOA, PFNA, PFDA, PFHxS, and 2-(N-methyl-perfluorooctane sulfonamide) acetic acid on the levels of six thyroid function variables (Jain et al. 2013). Levels of triiodothyronine were found to increase with the levels of PFOA (p=0.01), and total thyroxine levels were found to increase with increase in PFHxS levels (p<0.01).

Effects on the immune system

An investigation of children aged 5 and 7 years from Faroe Island in the Atlantic showed that commonly prevalent exposures to PFOS, PFOA, PFHxS, PFNA and PFDA measured in blood serum were associated with lower antibody responses to childhood immunizations (vaccinations) and an increased risk of antibody concentrations below the level needed to provide long-term protection against diphtheria and tetanus (Grandjean et al. 2012). In a study from Taiwan PFAS serum levels including of PFHxS were reported to be significantly higher in children with asthma compared to children without asthma (Dong et al. 2013).

Children behavior

Data from the NHANES 1999-2004 and the C8-Health Project in the USA surveys showed positive association between some serum PFAA levels and attention deficit-hyperactivity disorder (ADHD) in children (Hoffman et al. 2010; Stein and Savitz 2011). The later study found a specific association with ADHD and PFHxS blood levels. The prevalence of ADHD plus medication increased with perfluorohexane sulfonate (PFHxS) levels, with an adjusted odds ratio of 1.59 (95% confidence interval, 1.21–2.08) comparing the highest quartile of exposure to the lowest. Higher blood levels of PFOS, PFNA, PFDA, PFHxS and PFOSA (but not PFOA) were associated with significantly shorter “Impaired Response Inhibition” (IRT) during the “differential reinforcement of low rates of responding”
(DRL) tasks measuring children’s impulsivity (Gump et al. 2011). PFHxS was the second most abundant in the blood with a mean blood concentrations of about 6 ng/mL. The mean concentration of PFOs was higher and about 10 ng/mL, and the mean concentration of PFOA was about 3 ng/mL.

Cancer
In Sweden a case-control study on PFAS and prostate cancer was conducted. PFOS, PFHxS, PFOA, PFNA, PFDA and PFU were analysed in the whole blood of 200 cases and 186 controls both groups with median age 67 (Hardell et al. 2014). Cases had higher mean and median levels than controls but the differences were not statistically significant. Regards PFHxS cases had a mean concentration of 1.1 ng/mL and controls had a mean 0.94 ng/mL. Because it is whole blood, the concentration are about half of serum concentrations.

3.3.2 Perfluoroalkanoic acids/perfluoroalkanoates, perfluorocarboxylic acid/perfluorocarboxylates (PFCA)
The toxicity of perfluorinated carboxylic acids (PFCA) with a carbon chain length ranging from four to twelve carbon atoms has been studied and compared in some in vitro test systems (Buhrke et al. 2013). The cytotoxicity was examined by using the human hepatocarcinoma cell line HepG2 as an in vitro model for human hepatocytes; there was a positive correlation between the carbon chain length of the respective PFCA and its cytotoxicity. In this test PFBA and PFHxA had respectively a 20-fold and 8-fold lower cytotoxicity than PFOA. All PFCA under investigation were negative in two independent genotoxicity assays (Ames test and the micronucleus assay). The homologous PFCA compounds also had the capacity to activate human PPARα. The compounds with a mid-chain length such as PFHpA and PFOA had the highest potential for PPARα activation, whereas PFCA with shorter and with longer carbon chain length showed a lower potential for PPARα activation.

3.3.2.1 Perfluorobutanoic acid (PFBA, C4)
Toxicokinetics
PFBA is predominantly excreted in the urine. In a study with male and female rats, 51-90 % and 101-112 % of PFBA was excreted in urine within 24 hours, respectively, but only 0-3 % was excreted in the feces. In mice, 65-68 % was excreted in urine by female mice after 24 hours compared with approximately 35 % in male mice. 4-11 % was excreted in feces by both sexes. In monkeys, 41 and 46 % of the administered dose of PFBA was excreted in urine by male and females, respectively (Chang et al. 2008).

The serum elimination half-lives of PFBA in rats given 30 mg/kg b. w. in drinking water were 9 hours for males and 1.76 hours for females (Chang et al. 2008). If PFBA was administered intravenously the half-lives were a little shorter (6 and 1 hours). For mice given oral doses of PFBA as the ammonium salt the half-lives were 5-16 hours for males and about 3 hours for females. For monkeys given 10 mg PFBA/kg b. w. intravenous the half-lives were 40 hours for males and 41 hours for females. For humans the half-lives were about 72 and 87 hours for males and females, respectively. The last values were determined in workers and after a PFBA drinking water pollution incident in Minnesota, where levels were 1-2 µg PFBA/L.

The relatively short residence time in the blood doesn’t mean that PFBA is quickly excreted in humans. Analysis of Spanish autopsy tissues revealed that the highest concentrations of most PFAS were found in lungs tissues, and that the short-chain PFBA surprisingly had the highest concentration, which was 100 times higher than for e.g. PFOS. Also in the kidneys PFBA had the highest concentration of all, and that was six times higher than the concentration of PFOS. PFBA was also measured in the liver and brain (Perez et al. 2013). Thus, PFBA seems to behave differently in humans compared to experimental animals.

Animal toxicity
The liver toxicity and peroxisome proliferation potency in rats of PFAS increase with the carbon chain length until C9, and the activity was higher in response to carboxylates compared to sulfonates. PFBA can cause peroxisome proliferation, induction of peroxisomal fatty acid oxidation and hepatomegaly, suggesting that PFBA activates the
nuclear receptor, peroxisome proliferator–activated-receptor-α (PPAR-α) in mice and humans (Foreman et al. 2009). PFBA has a slighter effect on indicators of peroxisome proliferation than PFOA (Ikeda et al. 1985). PFBA had also a slighter effect than PFHxA but had a higher PPARα activity in the liver than PFBS, PFHxS and PFOS (Wolf et al. 2008).

PFBA has been tested in a 90 days gavage study with rats (Bjork and Wallace 2009). At the highest dose (30 mg/kg bw/day) there was an increase in liver weight and reduced thyroid hormone in males. In that study PFBA was surprisingly more toxic than PFHxA but five times less toxic than PFOA.

In another study sequential 28-day and 90-day oral toxicity studies have been performed in male and female rats with ammonium perfluorobutanoate/perfluorobutyrate (PFBA) at doses up to 150 mg/kg/day in males and 30 mg/kg/day in females, and ammonium perfluoroctanoate (PFOA) was used as a comparator at a dose of 30 mg/kg/day in the 28-days study (Butenhoff et al. 2012). Female rats were unaffected by PFBA with the no-observable-adverse-effect-levels (NOAELs) >150 mg PFBA/kg/day in the 28-day study and >30 mg PFBA/kg/day in the 90 days study. Effects in males included: increased liver weight, slight to minimal hepatocellular hypertrophy; decreased serum total cholesterol; and reduced serum thyroxin. The NOAEL for males was 6 mg PFBA/kg/day in both the short- and long-term study. A comparative dosing with 30 mg/kg/day PFOA resulted in increased incidence of clinical signs of toxicity (e.g. hunched posture), increased liver weight in females as well as males, and a major (75%) reduction in body weight of males. Thus, the relative response of rats to dosing with PFBA as compared to PFOA was considered by the authors to be the result of both the more rapid toxicokinetic clearance in rodents and lesser toxicodynamic potency of PFBA.

Another study exposing pregnant mice to PFBA in doses of 35, 175 and 350 mg/kg bw/day showed maternal liver effects at the two high doses but no significant effects on the offspring (Das et al. 2008). Thus PFBA has lower developmental toxicity than PFOA.

### 3.3.2.2 Perfluorohexanoic acid and salts (PFHxA,C₆)

#### Toxicokinetics in animals

The oral absorption of PFHxA in rats and mice was rapid and complete; 100% of an oral dose was eliminated in the urine within 24 hours demonstrating that PFHxA was readily absorbed and bioavailability approaches 100% (Gannon et al. 2011). Serum elimination half-lives in this study were of 1.6 hours in males and 0.6 hours in females rats.

The serum elimination half-life of PFHxA following a single intravenous dose of 10 mg PFHxA/kg b. w. was 0.4-1 hours in female and male rats, respectively (Chengelis et al. 2009a). After long-term oral administration of PFHxA the blood elimination half-lives in rats were a little longer at 2.2-2.8 hours, and the half-lives for urinary excretion were 1.9-3.1 hours. In this rat study PFHxA cleared much more rapidly than PFBS.

In another study mice and rats were exposed by gavage to one dose or multiple doses for 14 days of 50 mg/kg b. w. of the ammonium salt of PFHxA ¹⁴C-labelled (Iwai 2011). The major route of elimination was via the urine (up to 90% of dose). The renal elimination was a little slower in mice compared to rats. A plasma elimination half-life of about 1 hour was calculated.

The terminal serum elimination half-life of PFHxA in monkeys following a single intravenous dose of 10 mg PFHxA/kg b. w. was 2-5 hours, and there were no clear gender difference (Chengelis et al 2009a). However, after long-term oral administration the half-lives of PFHxA were longer at 14-47 hours. In this study PFHxA cleared more rapidly than PFBS.

In the blood PFHxA is attached to a different binding site on serum albumin than PFOA; however, PFOA is bound stronger, and 5-6 PFOA molecules can interact with each albumin molecule (D’eon and Mabury 2010).

#### Toxicokinetics and distribution in humans
Analysis of Spanish human autopsy tissues revealed that the highest concentrations of most PFAS, including PFHxA, were found in lung tissues but the highest PFAS in the brain was PFHxA. PFOS concentration in the brain was less than a third of that (Perez et al. 2013). Thus the body half-life of PFHxA seems to be much longer in humans than in experimental animals.

In most studies of human biomonitoring of environmental exposures the levels of PFHxA in blood serum/plasma have either not been included or have been near or below the limit of quantification levels of 0.05-0.10 ng/mL or 40-400 times lower than for PFOS and PFOA (Russell et al. 2013). However, in case of community exposure near industrial sources a mean level of about 1 ng PFHxA/mL was measured (Frisbee et al. 2009).

In whole blood (approx. half of the serum/plasma levels) from ski waxes PFHxA had the highest concentrations (up to 12 ng/l) during the season of all PFAS. In addition, the fluorotelomer acid 5:3 FTCA (1.9 ng/mL) and the unsaturated fluorotelomer acids 6:2 FTUCA (0.03 ng/mL) were measured in the blood (Nilsson et al. 2013). This seems to indicate that the exposure had been to 6:2 FTOH derivatives.

The toxicokinetics of perfluorohexanoic acid (PFHxA) has recently been evaluated in human ski waxers (Russell et al. 2013). The decline in blood levels after the ski season was used to determine the apparent human blood elimination half-life to 14-29 days with a geomean of 32 days. These calculations assume that PFHxA is eliminated from the body, when it leaves the blood, however, in stead PFHxA may be distributed to various organs as it was measured in liver, kidney, bone and brain from some autopsy samples from Spain (Perez et al. 2013).

Animal toxicity
The liver toxicity and peroxisome proliferation potency in rats of PFAS increase with the carbon chain length until C9, and the activity was higher in response to carboxylates compared to sulfonates. PFHxA can cause peroxisome proliferation and had a higher PPARα activity in the liver than PFBS, PFHxS, PFOS and PFBA but lower than PFOA (Wolf et al. 2008).

The acute toxicity of the sodium salt of perfluorohexanoic acid (PFHxA) is considered low with a rat oral LD50 > 1,750 mg/kg bw. PFHxA was tested in a 90-days sub-chronic toxicity gavage study with rats. It was not a reproductive or neurobehavioral toxicant at 500 mg/kg bw/day. NOAEL for developmental toxicity was determined at 100 mg/kg bw/day. The NOAEL based on liver effects and blood parameter was determined at 20 mg/kg bw/day (Loveless et al. 2009). NOAELs for PFHxA were 3-30 times higher than values for PFOA.

In another 90-day rat study with gavage (10, 50 and 200 mg/kg PFHxA in water) body weight gain was decreased in all dose groups in males and in the two higher dose groups in females (Chengelis et al. 2009b). No effects were noted in the functional observation battery (FOB) or motor activity evaluations conducted in the current study. Minimal liver enlargement (hepatocellular hypertrophy) and higher liver weights occurred in males, and the NOAELs based on liver effects were estimated at 50 mg/kg bw/day and 200 mg/kg bw/day for male and female rats, respectively. These NOAELs were up to 30 times higher than for PFOA.

The reproductive oral toxicity of the ammonium salt of PFHxA in pregnant female mice was investigated by Iwai and Hoberman (2014). PFHxA was administered once daily from gestation day 6 through 18 in doses up to 500 mg/kg b. w. The maternal and reproductive no observable adverse effect level (NOAEL) of PFHxA ammonium salt was 100 mg/kg/d.

In a not yet published 24-month oral rat study NOAELs of 15 mg/kg bw/day for males and 30 mg/kg bw/day for females were identified based on non-neoplastic systemic toxicity observed in the highest dose groups (ENVIRON 2014).

Toxicity mechanisms
Many PFASs, especially PFOA and PFOS, may generate reactive oxygen species’ (ROS) and induce oxidative DNA damage in human HepG2 cells but perfluorohexanoic acid (PFHxA) did not show activity in that test (Eriksen et al. 2010).
PFHxA was neither mutagenic in the Ames test nor induced chromosome aberrations in human lymphocytes (Loveless et al. 2009).

Mulkiewicz et al. (2007) evaluated the acute cytotoxicity of among others PFHxA in several in vitro assays using eukaryotic cell lines, bacteria and enzymatic assays. The toxicity was in general low and increased with chain length, and the toxicity of PFHxA was about ten times lower than PFOA.

In an in vitro assay with human colon carcinoma (HCT116) cells estimated values of EC50 decreased with elongation of fluorocarbon chain from PFHxA > PFHpA > PFOA > PFNA etc. The cytotoxicity was rather low but intensified after longer exposure (72 h) (Kleszczynski et al. 2007). Again a study showing stronger effect by the substance with the shortest chain.

There is some evidence to suggest that perfluoroalkyl acids (PFAA’s) can impact essential endocrine pathways and neurodevelopment in birds and other animals. In a study by Vongphachan et al. (2011), PFHxA altered the messenger RNA (mRNA) expression of thyroid hormone (TH)–responsive transcripts in chicken embryonic neuronal (CEN) cells.

In a later study, the same research group determined in ovo effects of PFHxA exposure (maximum dose 5,970 ng/g egg) on embryonic death, developmental endpoints, tissue accumulation, mRNA expression in liver and cerebral cortex, and plasma TH levels. PFHxA accumulated in the three tissue compartments analyzed as follows: yolk sac > liver > cerebral cortex (Cassone et al. 2012).

**Human effects**

One human study examined the association between PFHxA exposure and childhood asthma. The study reported no difference in serum levels (median = 0.2 ng/mL) in children aged 10-15 years with (n = 231) or without (n = 225) asthma, and no dose-response trend (Dong et al., 2013).

Russell et al. (2013) calculated the benchmark dose (BMD10 = 95% lower confidence limit of a dose resulting in a 10% increase in risk) to 13 mg PFHxA/kg b. w. per day.

### 3.3.3 Perfluoroalkyl halogenides

A reaction product between perfluorohexyl iodide (PFHxI, C6) and 2-propen-1-ol is allowed in food packaging. Various polyfluorinated alkyl iodides have been studied for estrogenic activity in some in vitro test systems (Wang *et al.* 2012). The perfluorohexyl iodide and perfluoroocetyl iodide (PFOI, C8) were the only tested substances promoting the proliferation of MCF-7 cells, inducing luciferase activity in MVLN cells, and up-regulated the expression of two estrogen-responsive genes, TFF1 and EGR3. All tested substances showed some estrogenic effects but the optimal chain length for stronger estrogenic effect was C6-perfluoroalkyl iodides.

### 3.3.4 Perfluoroalkyl phosphor compounds

The mono- and di-substituted perfluorinated phosphonic acids (mono-PFPAs and di-PFPAs) belong to a new class of high production volume fluorinated surfactants used a. o. as wetting agent in waxes and coatings, and they have been used as defoaming additives to pesticides. Some of these chemicals are found occasionally in the environment and in human blood in Canada. A commercial wetting agent with the trade name Masurf-780 contained C6, C8, C10, and C12 substances (D’eon & Mabury, 2010).
Examples:

Perfluorobutyl phosphinic acid/phosphinates and bis[perfluorobutyl] phosphinic acid/phosphinates (C₄):

Perfluorohexyl phosphonic acid/phosphonate and bis[perfluorohexyl] phosphinic acid/phosphinates (C₆):

In rats all these chemicals with C₆-C₁₂ fluoroalkyl chains were absorbed from the gut and into the blood stream a little slower than PFCAs and the absorption decreases with chain length and di-PFPAs less than mono-PFPAs. The blood half-lives of perfluorohexyl phosphate were one day for males and 1.6 days for females. The half-lives were 1.8-2.3 days for the bis-compound, and among the studied substances the half-lives increased with the length of the fluoroalkyl chain. The renal clearance was much slower, and for the mono-PFPAs it decreased with increasing chain length. The di-PFPAs were not excreted in the urine at all. The fecal excretion was lower than 10%. Preliminary data indicates that these chemicals are long-lived in humans (D’Eon & Mabury, 2010). No info in that paper about the C₄ compounds.

Masurf® FS-780 is a commercial mixture that contains C₆-C₁₂-perfluoroalkylphosphinic acid (PFPiA) derivatives (37% C₆/C₆-, 33% C₈/C₈- and 27% C₁₀/C₁₀ PFPiA). This mixture has been tested and shown to activate the peroxisome proliferator-activated-receptor-α (PPARα) in mice. It is shown that PFPiAs are liver toxic and cause liver enlargement through activation of PPARα (Das et al. 2011).

3.3.5 Fluorotelomers and derivatives

It is mentioned earlier under biotransformation that fluorotelomer based compounds yields saturated and unsaturated fluorotelomer aldehydes (FTALs and FTUALs, respectively) and carboxylic acids (FTCAs and FTUCAs, respectively) as intermediate metabolites that subsequently transform to perfluorinated carboxylic acids (PFCAs). Studies have demonstrated that the FTCAs and FTUCAs are 1 to 5 orders of magnitude more toxic than PFCAs after exposure to aquatic organisms (Philips et al. 2007). Additionally, FTUALs have demonstrated reactivity with proteins, which may be associated with toxicity through the inhibition of protein function. In a test with human liver epithelial (THLE-2) cells the toxicity increased with chain length for all PFCAs and precursors. The relative toxicity also increased from FTUALs ≥ FTALs > FTUCAs > FTCAs > PFCAs. For FTUALs and FTALs – the most toxic precursors – the toxicity was surprisingly enhanced at shorter chain length (6:2 compared with 8:2) and indicates that the shift to shorter chain length compounds has brought unexpected challenges through the increased toxicity of the FTUALs (Rand et al. 2014).

Commercial fluorotelomer products are mainly mixtures with different chain length. For example, the well-known product Zonyl™ BA contains about 2% 6:2 FTOH, 34% 8:2 FTOH, 34% 10:2 FTOH, 20% 12:2 FTOH, and the rest longer chain fluorotelomers. Similar Zonyl™ TA-N contains about 51% 8:2 fluorotelomer acrylate, 26% 10:2 fluorotelomer acrylate, 2% 6:2 fluorotelomer acrylate and 12% of other fluorotelomer acrylates (DuPont data sheet). This product is to be phased out because it high Cs content.

A subchronic oral study in rats of a commercial FTOH mixture (CₙF₂ₙ₊₁CH₂CH₂OH, where n = 6, 8, 10, 12) at doses of 0, 25, 100 and 250 mg/kg/day showed effects from fluorosis on teeth to elevated liver and kidney weights and thyroid follicular hypertrophy, with a no observed adverse effect level (NOAEL) of 25 mg/kg b. w. per day (Ladics et al. 2005). In a similar subchronic oral dosing study of one of the main ingredients, 8:2 FTOH (99.2%
purity], the subchronic NOAEL was lower at 5 mg/kg b. w. per day based on liver necrosis in male rats at 25 mg/kg b. w. per day (Ladies et al. 2008).

A CLH Report with a proposal for "Harmonized classification and labelling" of 8:2 FTOH has been presented by Norway in June 2010 but no such report exists for 4:2 FTOH and 6:2 FTOH.

There are some polymers based on short-chain fluorotelomers, which are in industrial use, e.g. methacrylate polymers assessed by ENVIRON (2014). Their conclusion was that the polymer molecules were too large to cross biological barriers, thus having low toxicity and not fulfilling the REACH criterion for toxicity to human health.

3.3.5.1 4:2 Fluorotelomer alcohol (4:2 FTOH) and derivatives
No health information about 4:2 FTOH but it is supposed to degrade/metabolize into PFBA and at smaller degree into PFPA.

4:2 Fluorotelomer olefin, (Zonyl™ PFBE, (perfluorobutyl)ethylene, 1H,1H,2H-perfluoro-1-hexene ) is a highly volatile substance with a boiling point of 59°C. It is used in as a co-monomer up to 0.1% w/w in the polymerization process of fluoropolymers such as polytetrafluoroethylene (PTFE) that are processed at high temperature such as sintering and used as food contact materials. The production range 10 000-500 000 pound in the US, thus there is a great potential for workplace exposures. The 8-hr-Time-Weighted-Averaged (TWA) is 100 ppm (cit. from HSBD online, substance no. 7917).

PFBE was assessed by EFSA (2011). Animal studies were not taken into account but the substance was not genotoxic in various in vitro test systems with bacteria, mouse lymphoma cells and Chinese hamster ovary cells, and EFSA’s CEF Panel concluded that there was no safety concern for the consumer from such low concentration use. In consideration of its chemical structure with a supposedly reactive double bond, the EFSA assessment may be premature. PFBE resembles the strong human carcinogen vinyl chloride by having a perfluorobutyl group instead of a chlorine atom. Therefore, the lack of long-term animal bioassays is worrying.

In a 2-week inhalation study with male and female rats exposed 6 hours/day, 5 days/week at 0, 500, 5000, or 50,000 ppm to PFBE vapor. Exposed animals did not show any clinical signs of toxicity during or after the exposure period. The most exposed animals had some changes in blood chemistry, excreted 5 times more fluoride and liver and kidney were enlarged. Males were more sensitive to the effects. The no-observed-adverse-effect level (NOAEL) for this study was 500 ppm in PFBE-exposed male and female rats (cit. from HSBD online).

In another similar inhalation study male and female rats were exposed 6 hours/day for 28 consecutive days at 400, 2000, or 10,000 ppm PFBE vapor. In the 10,000 ppm-exposed group d minor effects were observe, including slight liver changes. The NOAEL for this study was 2000 ppm (cit. from HSBD online).

Developmental or reproductive toxicity was studied in pregnant rats exposed 6 hours/day to PFBE at 0, 1,000, or 70,000 ppm on days 6 to 15 of gestation. The 1000-ppm exposure did not cause any compound-related effects. Body weight gains in rats exposed to 70,000 ppm were significantly decreased (about 30%) during the exposure period. Mean food consumption in this group was lower than in controls during exposure and post exposure periods. No other adverse maternal effects were observed. No increase in malformation rate was observed in the treated groups during the fetal external or skeletal evaluations. (cit. from HSBD online). NOAEL was 1000 ppm but the study design included a large jump in dose levels.

In a MSDS for the undiluted substance the following hazard statements have been suggested for PFBE:10

- H225 Highly flammable liquid and vapour
- H315 Causes skin irritation
- H319 Causes serious eye irritation
- H335 May cause respiratory irritation

10 www.fluorochem.co.uk
3.3.5.2 6:2 Fluorotelomer alcohol (6:2 FTOH, C₆)

Since C₆-chemicals are being phased-out by industry for most uses, 6:2FTOH will be a key raw material used as an intermediate in the production of very many technically important polyfluorinated substances.

In rodents, predominant metabolites of 6:2 FTOH measured in plasma were the intermediates: 6:2 FTCA and 6:2 FTUCA and the terminal metabolites: 5:3 polyfluorinated carboxylic acid and the perfluorinated carboxylic acids (PFBA, PFHxA, and PFHpA). At high exposures, the 5:3 acids were the most prominent, while PFCAs and 6:2 FTCA were barely detectable (ENVIRON 2014).

In humans, perfluorohexyl ethanoic acid (FHEA) seems to be an important and persistent metabolite of 6:2 FTOH, because relatively high levels were measured in liver, kidney, bone and brain from some autopsy samples from Spain (Perez et al. 2013). It shows that the metabolism of PFAS in humans must be different from metabolism in rodents, where other metabolites dominate.

In the REACH regulation 6:2 FTOH is self-classified as acute toxic in Group 4, which corresponds to an oral rat LD₅₀ of 1.75 g/kg b. w. The dermal LD₅₀ was >5000 mg/kg. Erythema, but no edema, was observed in one rabbit only at the 60-min evaluation in a dermal irritation study (Serex et al., 2014).

In a 90-day subchronic study, 6:2 FTOH was administered to rats by oral gavage (0, 5, 25, 125,250 mg/kg b. w. per day). Mortality was observed at 125 and 250 mg/kg b. w. per day; deaths in the two highest dosed groups of animals occurred after approximately three weeks of dosing and continued sporadically. The deaths were attributed to kidney degeneration and necrosis. Clinical observations in these dose-groups included urine-stained abdominal fur, excess salivation, dehydration, coldness to touch, ungroomed coat, and hunched posture. Dental effects included whitened teeth and an increased incidence in missing/broken/ misaligned incisors. Increased liver weights were observed in males at 25 mg/kg/day and above, and in females at 125 mg/kg/day and above, accompanied by increases in various blood serum chemistries. No effects on mortality or clinical signs were observed at 5 mg/kg/day in male rats and 25 mg/kg/day female rats. The NOAEL in the subchronic study was 5 mg/kg b. w. per day based on hematology and liver effects (Serex et al., 2014). The results of this 90-day study with 6:2 FTOH were comparable to those results found in rats after a 28-day inhalation exposure to 6:2 FTOH, where a NOAEL of 35 mg/kg/day was determined, assuming 100% absorption.

Martin et al. (2005) found no increased cell death in rat hepatocytes in vitro after exposure to 6:2 FTOH at concentrations up to 200µM for 4 h.

The toxicity of 6:2 FTOH was also studied in adult rat testicular cells in vitro (Lindeman et al. 2012). No significant increase in oxidative DNA damage and no induction of DNA single strand breaks were measured. Further, no cytotoxic effect on cell membrane integrity and no significant alteration of expression levels of the P-gp protein and the Oat2 gene were found.

There was neither indication of mutagenic nor genotoxic activity by 6:2 FTOH in the Ames test with Salmonella bacteria, neither in a chromosome aberration test with human blood lymphocytes, nor it was mutagenic in a Mouse Lymphoma Assay (Serex et al. 2014).

However, in contradiction to PFOS or PFOA the two fluorotelomer alcohols 6:2 FTOH and 8:2 FTOH, induce cell proliferation in an E-screen assay with MCF-7 breast cancer cells and up-regulates the estrogenic receptor (Maras et al. 2006; Vanparys et al. 2006). Their estrogenic effect potency was half of 4-nonylphenol but 20,000 times lower than 17β-estradiol.

In the health assessment of 6:2 FTOH by ENVIRON (2014) internal laboratory reports on toxicological studies are used instead of available publications in scientific journals used for this assessment.

Some derivatives of 6:2 FTOH are very important as reactive intermediates in production of various fluorinated substances, including polymers. Copolymers with 6:2 FTA or 6:2 FTMA and some acrylates/methacrylates with-
out fluorine are allowed in food packaging. 6:2 fluorotelomer iodide (perfluorohexyl ethyl iodide) is the main component (85%) of the commercial intermediate product Capstone™ 62-1 by DuPont™ for product ion of repellents and surfactants.

Four fluorotelomer derivatives have been self-classified as eye- and skin irritants in REACH. Those are:

- 6:2 Fluorotelomer iodide
- 6:2 Fluorotelomer sulfonyl chloride
- 6:2 Fluorotelomer acrylate (6:2 FTAC)
- 6:2 Fluorotelomer methacrylate (6:2 FTMAC)

Their acute toxicity was considered insignificant but there is no study with repeated exposures.

These derivatives can be metabolized in rodents to the 6:2 FTOH and later to the carboxylic acid (6:2 FTCA) and after many steps finally to PFHxA and to a little extent PFHpA (Butt et al 2010).

ENVIRON (2014) has made health assessment of 6:2 FTAC and 6:2 FTMAC and refers to oral LD50’s in rats and mice of 2,000 to 5,000 mg/kg. A weak skin irritation but no skin sensitisation were observed. However, both substances were weak but reversible eye irritants. Oral exposure of 6:2 FTAC for 28 days to ≥ 25 mg/kg bw/day resulted in increased kidney weight. The NOAEL value was 5 mg/kg bw/day. In a similar study 6:2 FTMAC had effects on incisors (foreteeths) and organ weights (liver, kidney) with the same NOAEL of 5 mg/kg bw/day. No genotoxic effects in bacteria and mammalian cells were identified for any of the substances.

### Polyfluoroalkyl phosphate esters (PAPs)

A class of fluorotelomer-based commercial products with high potential for human exposure is the polyfluoroalkyl phosphate esters (PAPs). Commercial PAP formulations contain a mixture of fluorinated chain lengths as well as phosphate mono-, di- and tri-esters (Begley et al. 2008). PAPs are used to greaseproof food-contact paper and cardboard, and it has been discovered that these fluorochemicals can migrate into the food (Trier 2011). DiPAPs have been measured in human serum from the US (D’eon et al. 2009).

A mixture of diethanol-ammonium salts of fluorotelomer phosphates, where the C₆-fluoroalkyl content is 35%, and which also contains longer chain fluorotelomers, has the trade name Zonyl RP and is allowed in food packaging. 6:2 Fluorotelomer phosphate (1H,1H,2H,2H-perfluorooctyl (ortho)phosphate) and bis(6:2 fluortelomer) phosphate:

![Mono-PAP](image1)

![Di-PAP](image2)

![Tri-PAP](image3)

The uptake, elimination, and biotransformation of mono- and di-PAPs of various chain lengths have been studied in rats (D’eon and Mabury, 2007; 2011). Among these were 4:2 and 6:2 fluorotelomer mono- and di-esters studied in the second paper. The uptake and bioavailability of 4:2 and 6:2 di-esters were almost complete and much larger than for 8:2 and 10:2 di-esters. Mono-esters were not observed in the blood but PFCA degradation products were. MonoPAPs are supposedly/thought to be hydrolyzed into FTOHs and phosphoric acid in the gut.
Elimination half-lives from blood after gavage exposure were 2 days for 4:2 diPAP and 3.9 days for 6:2 diPAP and increased with chain lengths. The only compound found in the urine was 4:2 diPAP glucuronide and 4:2 diPAP sulfate but it was still not a major route of elimination since it could only account for 0.03% of the dose administered. Also after 24 hours feces levels only accounted for 1% of gavage dose for 6:2 monoPAP, 3% for 4:2 diPAP and 9% for 6:2 diPAP. The excretion in Feces increased by time and 48 hours after gavage 21% of 4:2 diPAP and 65% of 6:2 diPAP was eliminated in feces.

Elimination kinetics of the metabolites PFBA and PFHxA in the blood was significant slower after diPAP administration than after monoPAP. After diPAP exposure were observed serum half-lives of 3.3±1.2 days for PFBA and 1.8±0.5 days for PFHxA, while from MonoPAP dosing the half-lives were shorter (0.5 and 0.2 days).

Biotransformation to the PFCAs was observed for both monoPAPs and diPAPs congeners. The biotransformation was lowest for 4:2 diPAPs (0.5%) and increased with chain length with 6:2 diPAPs (1%) and 8:2 diPAPs (9%).

3.3.5.4 Silicium derivatives of PFAS

Some nanofilm spray products based on 6:2 fluorotelomer silanes or –siloxanes are new types of surface coatings with non-stick properties when applied to surfaces such as bathroom tiles, floors, windows and textiles.

Some of these “magic” spray products discovered on the market in Denmark in 2010 were investigated for airway irritation, airway inflammation and lung damage in a mouse inhalation model (Nørgaard A et al. 2010). BALB/cJ mice were exposed for 60 min to the aerosolized product 3.3–60 mg/m³ measured in the breathing zone of the mice. Chemical analysis showed that the products besides fluorotelomer trialkoxysilanes contained hydroxylates and condensates of these. Exposure to the spray products induced a concentration-dependent decrease of the tidal volume lasting for at least 1 day. Exposure concentrations above 16.1 mg/m³ (2.1x10⁶ fine particles/cm³) gave rise to significant increases of protein level in broncho-alveolar lavage fluid (BALF) and reduced body weight. Histological examination showed atelectasis, emphysema, and hemorphages. A narrow interval between the no-effect-level (16.1 mg/m³) and the lethal concentrations (18.4 mg/m³) was observed. A similar substance without fluorine had no effect in the test system. A hydroxy group increased the effects.

In a later study the toxicological mechanism was studied (Larsen et al. 2014). The toxic effect of the waterproofing spray product included interaction with the pulmonary surfactants. More specifically, the active film-forming components in the spray product, perfluorinated siloxanes, inhibited the function of the lung surfactant due to non-covalent interaction with surfactant protein B, a component which is crucial for the stability and persistence of the lung surfactant film during respiration. The toxicity also depends on the solvent (Nørgaard et al. 2014). Some names and formulas for the active substances include:

6:2 Fluorotelomer triethoxysilane (CAS 51851-37-7, 1H,1H,2H,2H-Perfluoroctyl triethoxysilane)

6:2-Fluorotelomer triisopropoxysilane (CAS no., 1H,1H,2H,2H-Perfluoroctyl triisopropoxyxilane)

Di(6:2 fluorotelomer) monohydrolyzed disiloxane (CAS no. Bis[1H,1H,2H,2H-perfluoroctyl] triisoproxy hydroxy disiloxane)
Previously, the short-chain PFAS often occurred as contaminants or minor constituents in the longer-chain analogues used but recently the use of short-chain PFAS has increased as substitutes for C₈-PFAS. Still, it remains largely unclear whether ingestion of contaminated food and water, inhalation of indoor and ambient air, ingestion of indoor dust, or direct contact with PFC-containing consumer products is the largest contributor to human body burdens of PFCs (Fraser et al. 2013). In addition there may be workplace exposures. It probably depends on the circumstances which exposure is most important. In a study from Japan of matched daily diet and serum samples, only PFOS and PFOA were detectable. It was calculated that in the mega city Osaka only about 23% of the serum PFAS levels came from the diet, while it in a small rural city almost 100% of the PFAS came from the diet (Kärman et al. 2009).

### Occurrence in products

In older studies 6:2 FTOH was found in less textile products for children than 8:2 FTOH and 10:2 FTOH, and generally in lower concentrations, and specifically 4:2 FTOH was below the detections limit in all studies.

In a recent study (Dreyer et al. 2014) comprising 16 samples from outdoor jackets and gloves, all samples contained PFAS. The perfluoroalkyl acid which was quantified most often (14 of 16 samples) was PFOA, followed by PFHxA (13 of 16 samples) and PFBA/PFDA (10 of 16 samples). Concentration for individual PFASs were usually between 0.1 and 11 μg/m³.

FTOHs and FTAs (acrylates) were observed in all samples investigated. Concentrations of volatile PFAS were up to a factor of 100 higher (10 – 1200 μg/m²) than concentrations of the perfluoroalkyl acids. FTOHs were found at highest concentrations with 6:2 FTOH being the predominant compound in most samples, followed by 8:2 FTOH.

All outdoor jackets in the study emitted volatile PFAS at room temperature implying that such products are important PFAS sources, particularly for indoor air environments. Similar to the product PFAS contents, emission rates varied strongly between samples and compounds. Emission rates were highest for 6:2 FTOH (up to 9200 ng 6:2 FTOH/d). Emission rates published previously were in the same order of magnitude, however with maximum emissions observed for 8:2 FTOH.

In 10 mixed textile samples 2-16 μg PFHxA/m² textile were extracted (Becanova et al., 2013).

In a children jacket the dominating PFAS was 6:2 FTOH and 19 μg/m² was extracted (Greenpeace 2012).

In an older Norwegian study (Herzke et al. 2009) of impregnation agents the dominating PFASs were 6:2 FTOH, PFBA and PFHxA (see Table 3-5). The concentrations of the following short-chain substances were below the detection limit in all agents: 6:2 FT(U)CA, 6:2 FTS, PFPS, PFHxS, and 4:2 FTOH.
TABLE 3-5
SHORT-CHAIN PFAS IN FIVE IMPREGNATION AGENTS (HERZKE ET AL., 2009).

<table>
<thead>
<tr>
<th>Substance</th>
<th>Acronym</th>
<th>Concentrations of extracted PFAS from 5 impregnation agents µg/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>6:2 Fluorotelomer alcohol</td>
<td>6:2 FTOH</td>
<td>535 – 13,250</td>
</tr>
<tr>
<td>Perfluorobutanoate</td>
<td>PFBA</td>
<td>75-142</td>
</tr>
<tr>
<td>Perfluorohexanoate</td>
<td>PFHxA</td>
<td>23-25</td>
</tr>
</tbody>
</table>

Some polyfluoroalkyl phosphate esters (PAPs) are used in the production of ingredients in some Personal Care Products/cosmetics, including foundation, manicure, lip rouge and sun cream. The PAPs are degraded into PFCAs, and these acids can be determined in commercial products. For PFHxA concentrations of up to 2.1 mg/kg was measured in cosmetics on the market (Fujii et al. 2013).

3.4.2 PFAS in indoor air and workplace air

In closed rooms, where PFAS-impregnated clothes are stored, relatively high indoor air concentrations of PFAS, especially fluorotelomers, have been measured as two studies from Germany have revealed.

In one study 11 indoor air sampling sites characterized by the presence of materials with fluorinated surface treatments were selected. A carpet shop and two conference rooms were influenced by treated carpets. Other sites (a car and three shops selling sports/outdoor clothes) were influenced by impregnated textiles, and the rest of the sites were a shop for soccer equipment, a kitchen and two metal workshops (Schlummer et al., 2013). The highest levels were measured in shops selling outdoor clothing with air levels up to 47, 286 and 58 ng/m³ of 6:2, 8:2 and 10:2 FTOH (4:2 FTOH was not detected in any sample), respectively, indicating outdoor textiles to be a relevant source of FTOH in indoor workplace environments. Total amounts of FTOH in materials of outdoor textiles accounted for <0.8–7.6, 12.1–180.9 and 4.65–105.7 µg/dm² for 6:2, 8:2 and 10:2 FTOHs, respectively. Emission from selected textiles revealed FTOH emission rates of up to 494 ng/h. FTOH concentrations in impregnation sprays ranged from <LOD to 725 mg/kg. Calculations showed that the indoor exposures the staff had of PFAS were of the same magnitude as their PFAS food intakes.

In another German study indoor air samples were taken from 16 locations: 2 residential houses, 2 furniture shops, 1 carpet shop, 2 stores selling outdoor equipment, 2 printing shops, 2 auto lacquers, 1 car shop, 1 powder coating workshop, and an electroplater (Langer et al., 2010). Total PFAS indoor air concentrations ranged from 8.2 to 458 ng/m³. Individual PFAS concentrations were between 42 pg/m³ (6:2 fluorotelomer acrylate, FTA) and 209 ng/m³ (8:2 FTOH). Concentrations of total FTOHs ranged from 3.3 to 307 ng/m³, and FTAs ranged from 0.2 to 152 ng/m³. In addition some PFOS and PFBS precursors (N-Methyl perfluorobutane sulfonamide, MeFBSA; N-Methyl perfluorobutane sulfonamidoethanol, MeFBSE) were measured especially in the carpet shop. The highest total-PFAS concentrations and FTA concentrations were detected in two stores selling outdoor equipment, one furniture shop, and one carpet shop. The range of average concentrations of the short chain congeners in indoor air are specified in Table 3-6:

TABLE 3-6
RANGE OF AVERAGE CONCENTRATIONS OF THE SHORT CHAIN CONGENERS IN INDOOR AIR (LANGER ET AL. 2010).

<table>
<thead>
<tr>
<th>PFAS</th>
<th>4:2 FTOH</th>
<th>6:2 FTOH</th>
<th>6:2 FTA</th>
<th>MeFBSA</th>
<th>MeFBSE</th>
<th>Total FTOH</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAS no.</td>
<td>2043-47-2</td>
<td>647-42-7</td>
<td>17527-29-6</td>
<td>68298-12-4</td>
<td>34454-97-2</td>
<td></td>
</tr>
<tr>
<td>Range (ng/m³)</td>
<td>nd – 1.2</td>
<td>0.1 - 37</td>
<td>nd - 3.4</td>
<td>nd – 3.4</td>
<td>0.6 - 141</td>
<td>3.3 - 307</td>
</tr>
</tbody>
</table>

nd: not detected
Indoor air concentrations were several orders of magnitude higher than published outdoor air concentrations, indicating indoor air environments as sources for PFAS to the ambient atmosphere.

Skiwax technicians in the skiing World Cup are highly exposed to various perfluoroalkyl acids (PFAA’s) and their precursors. The most dominating compound in air samples in the breathing zone of 8 technicians was 8:2 FTOH but also short chain congeners were measured. Air concentrations of 6:2 FTOH ranged between <1.3 to 2400 ng/m$^3$ with a mean of 240 ng/m$^3$. Among the PFCAs, PFHxA (degradation product) was found in the highest levels that ranged from 57 to 14 000 ng/m$^3$ with a mean of 4900 ng/m$^3$. The perfluoroalkane sulfonates PFBS and PFHxS were present at levels close to detection limit if at all (Nilsson et al. 2010a). Continued exposure contributed to 50-fold elevated blood levels in ski technicians compared to the general population (See later).

In a follow-up study with 11 ski wax technicians the average air level of 6:2 FTOH was 280 ng/m$^3$, of 10:2 FTOH 370 ng/m$^3$ and of 8:2 FTOH 92 000 ng/m$^3$. FTOHs could not be detected in blood. Instead the technicians had elevated whole blood levels of some metabolites (Nilsson et al. 2013).

In 30 US offices various PFAS was measured in the air. The measured FTOH concentrations in the indoor air in these offices did significantly predict the serum PFCA concentrations measured in people working in these offices (Fraser et al. 2012). Level of 6:2 FTOH ranged <LOD-11 000 pg/m$^3$ with a geomean of 1320 pg/m$^3$.

In a follow up study of the same group PFAS was measured in dust from homes, offices, and vehicles as predictors of PFAS concentrations in office workers’ serum (Fraser et al. 2013). The highest geometric mean concentration in office dust was for 8:2 FTOH (309 ng/g), while PFOS was highest in homes (26.9 ng/g) and vehicles (15.8 ng/g). Overall, offices had the highest PFAS concentrations, particularly for longer-chain carboxylic acids and FTOHs. Perfluorobutyrate was prevalent in homes and vehicles, but not offices. In Table 3-7 is shown the results for the short-chain PFAS together with PFOA, PFOS and 8:2 FTOH.

### Table 3-7
**PFAS IN OFFICE, HOME AND VEHICLE DUST (FRASER ET AL. 2013).**

<table>
<thead>
<tr>
<th>PFAS</th>
<th>LOQ</th>
<th>Office dust (n=31)</th>
<th>Range</th>
<th>Home dust (n=30)</th>
<th>Range</th>
<th>Vehicle dust (n=13)</th>
<th>GM ng/g</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>% detect</td>
<td>GM ng/g</td>
<td></td>
<td>% detect</td>
<td>GM ng/g</td>
<td></td>
<td>% detect</td>
</tr>
<tr>
<td>PFOA</td>
<td>5</td>
<td>74</td>
<td>32.0</td>
<td>15-336</td>
<td>77</td>
<td>23.7</td>
<td>5-894</td>
<td>54</td>
</tr>
<tr>
<td>PFHxA</td>
<td>5</td>
<td>68</td>
<td>10.8</td>
<td>5-102</td>
<td>57</td>
<td>8.7</td>
<td>5-1380</td>
<td>54</td>
</tr>
<tr>
<td>PFPA</td>
<td>5</td>
<td>39</td>
<td>nr</td>
<td>5-28</td>
<td>33</td>
<td>nr</td>
<td>5-249</td>
<td>23</td>
</tr>
<tr>
<td>PFBA</td>
<td>5</td>
<td>48</td>
<td>nr</td>
<td>5-148</td>
<td>90</td>
<td>13.9</td>
<td>5-999</td>
<td>85</td>
</tr>
<tr>
<td>PFOS</td>
<td>7</td>
<td>55</td>
<td>14.6</td>
<td>7-98</td>
<td>73</td>
<td>26.9</td>
<td>14-280</td>
<td>54</td>
</tr>
<tr>
<td>PFHxS</td>
<td>5</td>
<td>23</td>
<td>nr</td>
<td>5-19</td>
<td>40</td>
<td>nr</td>
<td>6-130</td>
<td>46</td>
</tr>
<tr>
<td>PFBS</td>
<td>5</td>
<td>10</td>
<td>nr</td>
<td>8-12</td>
<td>3</td>
<td>nr</td>
<td>5-5</td>
<td>nr</td>
</tr>
<tr>
<td>6:2 FTOH</td>
<td>50</td>
<td>35</td>
<td>nr</td>
<td>90-2390</td>
<td>0</td>
<td>nr</td>
<td>&lt;50</td>
<td>8</td>
</tr>
<tr>
<td>8:2 FTOH</td>
<td>5</td>
<td>100</td>
<td>309</td>
<td>15-3390</td>
<td>57</td>
<td>10.8</td>
<td>9-136</td>
<td>69</td>
</tr>
</tbody>
</table>

*nr = not reported*

PFOA serum concentrations in this study were not associated with PFAS dust levels after adjusting for PFAS concentrations in office air. Dust concentrations of most PFAS are higher in offices than in homes and vehicles.
4. Environmental fate and effects

4.1 Environmental behaviour and fate

4.1.1 Physico-chemical properties of environmental relevance

Some environmentally relevant physico-chemical properties of selected short-chain PFAS are listed in Table 4-1 along with the corresponding data for PFOS PFOA and 8:2 FTOH (as "Cs reference substances").

Among the PFASs, PFCAs and PFSAs are strong acids with estimated pKa’s estimated to be near zero for PFCAs and around -1 for PFSAs, which implies that they will be present in the ionic form under normal environmental conditions. The perfluoralkyl chain is one of the most hydrophobic molecular fragments possible and, similarly, the anionic/acid functional groups are some of the most hydrophilic functional groups known. These acids are therefore likely to be transported substantially in the environment by water surfaces (e.g. by dispersion on water surfaces, sorption to clouds and rain droplets) (KLIF, 2010), while the less soluble, more volatile FTOHs are more likely to be transported via air (Ellis et al., 2004; Ahrens, 2011).

<table>
<thead>
<tr>
<th>Property</th>
<th>CAS</th>
<th>Water solubility (mg/L)</th>
<th>Mp/Bp (ºC)</th>
<th>Vapour pressure (Pa)</th>
<th>Log Pow</th>
<th>Log Koc</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFOS, perfluorooctane sulfonic acid</td>
<td>1763-23-1</td>
<td>519-570</td>
<td>3.31x10^{-4}</td>
<td>5.5-7.03</td>
<td>2.57-3.3</td>
<td></td>
</tr>
<tr>
<td>PFOA, perfluorooctanoic acid</td>
<td>335-67-1</td>
<td>3400</td>
<td>12.1</td>
<td>3.6</td>
<td>2.11</td>
<td></td>
</tr>
<tr>
<td>PFHxS, perfluorohexane sulfonic acid</td>
<td>355-46-4</td>
<td>243.4</td>
<td>1.08x10^{-6}</td>
<td>2.2</td>
<td>3.36/2.14</td>
<td></td>
</tr>
<tr>
<td>PFHxA, perfluorohexanoic acid</td>
<td>307-24-4</td>
<td>29.5</td>
<td>121</td>
<td>2.51</td>
<td>3.12-3.26</td>
<td></td>
</tr>
<tr>
<td>PFHxA, perfluorohexanoate, sodium salt</td>
<td>2923-26-4</td>
<td>29.5</td>
<td>~0</td>
<td>0.70</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PFPeS, perfluoropentane sulfonic acid</td>
<td>2706-91-4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PFPeA, perfluoropentanoic acid</td>
<td>2706-90-3</td>
<td>120</td>
<td></td>
<td>1.98</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PFBS, perfluorobutane sulfonate, potassium salt</td>
<td>29420-49-3</td>
<td>434.0</td>
<td>1.49x10^{-6}</td>
<td>0.26</td>
<td>2.25/1.07</td>
<td></td>
</tr>
<tr>
<td>PFBA, perfluorobutanoic acid</td>
<td>375-22-4</td>
<td>447</td>
<td></td>
<td>1.43</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8:2 FTOH, fluorotelomer alcohol</td>
<td>678-39-7</td>
<td>0.2-0.3</td>
<td>1.64</td>
<td>5.58</td>
<td>4.13</td>
<td></td>
</tr>
<tr>
<td>6:2 FTOH, fluorotelomer alcohol</td>
<td>647-42-7</td>
<td>19</td>
<td>22.1</td>
<td>4.54</td>
<td>2.43</td>
<td></td>
</tr>
<tr>
<td>4:2 FTOH, fluorotelomer alcohol</td>
<td>2043-47-2</td>
<td>97</td>
<td>-44/113</td>
<td>1330</td>
<td>3.07/3.30</td>
<td>2.34/2.83</td>
</tr>
<tr>
<td>6:2 FTS, fluorotelomer sulfonamide</td>
<td>27619-97-2</td>
<td>44.3</td>
<td>3.47-3.98</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6:2 FTAC, fluorotelomer acrylate</td>
<td>17527-29-6</td>
<td>0.38</td>
<td>44.3</td>
<td>5.2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1 UNEP, 2012 (annex 1) 2 Iwai & Tsuda, 2011 3 Jensen et al., 2008 4 KLIF, 2010 5 Ding & Peijnenburg, 2013 6 ENVIRON, 2014
4.1.2 Abiotic transformation and degradation

According to the LOUS review of a range of PFASs including some C4-C6 substances (Lassen et al., 2013), perfluorinated substances are not transformed/degraded by hydrolysis or photolysis in water to any appreciable extent. Thus, half-lives of several years have estimated for PFOS (most studied single PFAS) and related substances, i.e. long-chained PFSAs.

Similarly, the HSDB database (Toxnet, 2014) states for perfluorobutyl ethylene that the substance "is not expected to undergo hydrolysis in the environment due to the lack of functional groups that hydrolyze under environmental conditions" and, further, it "does not contain chromophores that absorb at wavelengths > 290 nm, and therefore is not expected to be susceptible to direct photolysis by sunlight".

Ionic PFASs, like PFCs and PFSAs, are very persistent in the environment due to the strong bonding between carbon and fluorine (Ahrens, 2011). Neutral PFASs (e.g. FTOHs) are less persistent than the PFSAs and PFCAs and can undergo initial transformation by hydrolysis, photolysis and biodegradation (Ahrens, 2011).

In a review of potassium perfluorobutane sulfonate (PFBS-K), NICNAS (2005) concluded that hydrolysis and photolysis are both unlikely to occur.

Smog chamber experiments reported by Ellis et al. (2004) have shown that FTOHs (4:2, 6:2 and 8:2 FTOH were tested) can degrade by OH-initiated oxidation pathways, with the intermediates FTCAs and FTUCAs, to a homologous series of PFCA in the atmosphere, and a lifetime of approximately 20 days for the FTOHs was estimated. Ellis et al. (2004) therefore conclude that atmospheric degradation of FTOHs is likely to contribute to the widespread dissemination of PFCAs as the pattern of PFCAs yielded from FTOHs could account for the distinct contamination profile of PFCAs observed in arctic animals.

4.1.3 Biotransformation and degradation

Perfluorinated acids are not biodegradable neither under aerobic nor under aerobic environmental conditions in water or soil (Lassen et al., 2013). PFAS with other functional groups may undergo primary degradation but the perfluorinated backbone remains intact and is highly persistent. Most of the available data on transformation/degradation of PFASs is based on studies with PFOS and PFOA (and a few more long-chain PFASs) but many of the findings appear to relate more generally to PFAS and can therefore be extrapolated to similar perfluorinated substances with shorter chain-lengths.

Jensen et al. (2008) refer studies of the aerobic biodegradation of the fluorotelomer alcohol 8:2 FTOH showing a half-life of about 1 day and 85% degradation within a week. However, the degradation was not complete; fluorotelomer acids and PFOA were identified as the degradation products. It is concluded that in general the perfluoralkylated acids/salts are very stable under environmental conditions but may undergo initial transformation under extreme laboratory conditions, however only leading to persistent fluorinated metabolites. Functional derivatives such as substituted sulfonamides and fluorotelomer alcohols will undergo primary degradation in the environment and be transformed to the basic corresponding acids/salts (that will persist) (Jensen et al., 2008).

In a review undertaken by ENVIRON (2014) for FluoroCouncil, results of studies in soil and sediments are presented for 6:2 FTOH demonstrating primary biodegradation with half-lives of less than 2 days. Transformation products such as e.g. PFHxA did, however, not degrade appreciably within half a year.

According to NICNAS (2005), no biodegradation of potassium perfluorobutane sulfonate (PFBS-K) is expected.

Quinete et al. (2010) studied the degradability of some new substitutes for perfluorinated surfactants (PFBS, fluorosurfactant Zonyl, two fluoroaliphatic esters (NOVEC FC-4430 and NOVEC FC-4432) and 10-(trifluoromethoxy)-decane -1- sulfonate) for traditional perfluorinated surfactants (PFOS, PFOA) by testing them, among others, in two traditional OECD ready biodegradability screening tests, the manometric respirometry test (OECD 301F) and the closed-bottle test (OECD 301D) with River Rhine water as inoculum. While PFBS did not show any significant biodegradation over the 28 day duration of the tests, fluorosurfactant Zonyl biodegraded 13%
in the OECD 301F test and 47% in OECD 301D, the two NOVEC products degraded 25-28% and 19-22%, respectively, in the same two tests and 10-(trifluoromethoxy)-decane sulfonate degraded 40% in OECD 301F and >80% in OECD 301D (all results in % of ThOD). Thus, the latter substance was readily biodegradable in the OECD 301D test while the other substitutes showed inherent biodegradability (at the best) except PFBS, which did not degrade at all.

4.1.4 Bioaccumulation

Lassen et al. (2013) mention in the LOUS review of long and short-chain PFAS that because PFOS is both hydrophobic and lipophobic it does not follow the typical pattern of partitioning into fatty tissues followed by accumulation, but tends to bind to proteins and therefore is present rather in highly perfused tissues than in lipid tissue. It is also mentioned by Lassen et al. (2013) that the bioaccumulation of PFOS and other PFAS is higher in the marine environment than in soil. These findings are believed to be valid also for the short-chain perfluorinated carboxylic and sulfonic acids and their salts. According to a number of reports (e.g. Ellis et al. (2004), Butt et al. (2010), Martin et al. (2013)), the acids are not very bioaccumulative in themselves but precursors such as fluorotelomer alcohols and acrylates accumulate and are subsequently transformed in the organs of animals to the corresponding acids, which are retained in the body.

Webster & Ellis (2011) modelled BCF in fish for perfluorocarboxylic acids as a function of the carbon chain length based on experimentally determined BCF values for rainbow trout (carcass, liver and blood). Based on data for C8-C14 perfluorocarboxylic acids they postulated a linear relationship between Log BCF and number of carbons in the chain (from C12 and downwards to C6), most convincing for whole carcass and for liver. Log BCFs were extrapolated down to C6 for which in both cases a Log BCF of approximately -1 was determined (i.e. BCF about 0.1). For C12 the Log BCF in carcass was about approx. 5 while in liver it was about 4.5.

Zhou et al. (2013) studied some PFCAs and PFSAs in muscle tissue of two fish species (crucian carp and sharpsbely) in a Chinese lake and found PFOS to be the dominant perfluorinated acid (PFAA) accounting for 93-94% of the total content of PFAs. Also other long chained PFAs were detected in the fish while PFBA and PFBS were detected only in low concentrations and PFPeA, PFHxA and PFHpA were all below the detection limits. This was in contrast to the findings in the water phase where the short-chained PFAs occurred at much higher concentrations than the long-chained. The Log BCFs of the C4-C7 carboxylic and sulfonic acids were all found to be below 1 thus indicating little bioaccumulation potential of these substances in fish. Log BCF (fish) for C11-C13 PFAs ranged in contrast to this from 4.3 to 5.1.

Ding and Peijnenburg (2013) provide in their review the following conclusions on bioaccumulation of PFAS:

- Bioconcentration and bioaccumulation of perfluorinated acids are directly related to the length of each compound’s fluorinated carbon chain
- PFSA are more bioaccumulative than PFCA of the same fluorinated carbon chain length
- Short chain PFCA (with seven fluorinated carbons or less) are not considered bioaccumulative according to the regulatory criteria of 1000–5000 L/kg
- Short chain PFCA (with seven fluorinated carbons or less) have low biomagnification potential in food webs

4.1.5 Sorption, mobility and distribution

Ahrens (2011) refers findings of marine sediment studies in Japan demonstrating that the perfluorocarbon chain length and the functional group were the dominating parameters influencing the partitioning of PFAS. Thus, short chain PFCAs (C <7) were exclusively found in the dissolved phase while long chain PFCAs (C ≥7), PFSAs, EtFOSAA and PFOSA appeared to bind more strongly to particles. As a consequence the short chain PFCAs are considered to have a higher potential for aqueous long-range transport.

Zhou et al. (2013) studied sediments of a Chinese lake and determined carbon normalized sorption constants for a range of PFCAs and PFSAs (perfluoroalkyl lengths from 3 to 12). They found that up to and including C7 the Log KOC did not change much but was approx. in the range from 2 to 2.5 for all investigated substances (PFCAs as well as PFSAs). However, for C8-C12 carboxylic acids the Log KOC increased gradually up to around 5 (PFSAs were only included up to C8 (Log KOC approx. 3.7)). Zhou et al. (2013) found that this was reflected in the levels in the
surface water of the lake where levels of PFOS and PFOA decreased much more rapidly with distance from an industrial discharge point than did the shorter-chained PFBS and PFBA.

Castiglioni et al. (2014) studied a range of PFAS including a number of short-chain PFAS in a river catchment in northern Italy with local industrial and general urban contamination sources, including wastewater treatment plants (WWTPs). The overall conclusion with regard to WWTPs was that the investigated substances, which included PFOS, PFOA and short-chain PFAS such as PFBA, PFPeA, PFHxA, PFBS and PFHxS, were poorly removed in all six WWTPs studied. PFOA loads in the effluents were always higher than in the influents due to biodegradation of precursors, such as fluorotelomer substances during the activated sludge treatment.

4.1.6 Long-range atmospheric and marine transport

It is well established from a number of monitoring studies undertaken throughout the world that PFASs occur ubiquitously in air, water, soil and biota (including humans), even in remote areas such as the Arctic (summarised e.g. by Lassen et al., 2013). The ionic PFASs such as the carboxylic and sulfonic acids (PFCAs and PFSAs) are considered to undergo long-range transport mainly via the aquatic environment (Ahrens, 2011), not least via the oceanic currents while atmospheric long-range transport have been postulated to involve mainly the neutral PFASs such as the precursors known as fluorotelomer alcohols (FTOHs). These have properties ensuring sufficient residence time in the atmosphere for long-range transport while at the same time being sufficiently reactive to be transformed by various oxidation reactions into the corresponding carboxylic acids and/or other products including other fluorotelomer species (Ellis et al., 2004).

Recently, Zhao at al. (2012) published a study in which partly a number of marine samples were taken along the East coast of Greenland and partly along a transect in the Atlantic Ocean starting at the western end of the English Channel and extending almost to Antarctica (to approx. 70° S). Along the East coast of Greenland, total PFAS concentrations were typically in the 150-250 pg/L range of which PFOA was the most important single substance but shorter chain PFAS such as PFBS, PFHxA and PFHxS were also present. The short-chain PFASs accounted in the samples taken relatively close to the coast for about 50% of the total amount of PFAS, while PFOS was more dominant in other samples taken further at sea in the direction of Svalbard. Thus, also the short-chain PFASs apparently have potential for long-range transport with water to remote areas. However, the part of the study conducted along the Atlantic transect showed steadily decreasing content of PFAS in the water samples in a southern direction from the English Channel (> 500 pg/L) towards the Equator (< 100 pg/L). South of the Equator, PFASs were hardly detectable in the samples. See section 4.5.1 for more details and data on the study by Zhao et al. (2012).

In a recent review by ENVIRON (2014), several monitoring results demonstrating the presence of 6:2 FTOH in remote environments are presented. Also the presence of PFHxA, a transformation product of 6:2 FTOH, in remote areas is documented thus indicating a long-range transport potential of this substance as well.

4.2 Environmental effects

The following sections give an overview of the available toxicity data on aquatic and terrestrial organisms. Data were retrieved from literature search on reports on PFAS, search on primary articles and reviews on scientific article databases (PubMed, Web of Science and Google Scholar) and registration data available at ECHAs homepage. Because of the very sparse results with respect to terrestrial toxicity data, the US Ecotox database was also used in the search for terrestrial data. 11

Most sources consider the toxicity of several PFAS, including both short chain and longer chain PFAS. Therefore, the study conclusions are commonly based on the whole range of investigated substances. However, the tables with the toxicity data display only effect concentrations of short chain PFAS.

11 http://cfpub.epa.gov/ecotox/
4.2.1 Toxicity to aquatic organisms

4.2.1.1 Marine mammals

No toxicity studies with short-chain PFAS on marine mammals have been identified.

4.2.1.2 Fish

Toxicity data for fish are available for a number of short-chain PFAS. The results are summarised in Table 4-2.

Ulhaq et al. (2013) evaluated the behavioural effects of seven structurally different PFAS (i.e. trifluoroacetic acid, PFBA, PFOA, PFNA, PFDA, PFBS and PFOS) in zebrafish larvae. As indicated by the difference in EC50 values for PFBS and PFBA, they concluded that the PFAS with sulfonic groups have a larger potential to affect zebrafish larvae. Chain length was the other determining toxicity factor, rendering longer chain compounds more toxic than short chain compounds.

Liu et al. (2009) referred to a number of in vitro toxicity studies showing estrogenic activities of FTOH and they also demonstrated endocrine disrupting effects of 6:2 FTOH in zebra fish exposed to 0.03, 0.3 and 3.0 mg/L 6:2 FTOH for 7 days, whereafter the effects on plasma sex hormone levels and selected gene expression were measured. The lowest observable effect occurred in male fish of the lowest exposure group (0.03 mg/L) with respect to testosterone serum levels, while for most of the other endpoints significant effects were only observed in the higher exposure groups. The authors concluded that waterborne exposure of 6:2 FTOH altered plasma levels of testosterone and estradiol, as well as gene expression profiles of the hypothalamic–pituitary–gonadal axis and liver, but they also noted that long-term exposure of environmental relevant concentration of FTOH on effects on fish reproduction needed further investigation. They observed that 6:2 FTOH was a stronger xenoestrogen than 8:2 FTOH.

Hoke et al. (2012) evaluated the acute toxicity of eight fluorinated acids to daphnids, green alga, rainbow trout, and fathead minnow by their own performed toxicity tests and by reviewing the results from a few other studies. They determined a 50 % mortality effect concentration of 32 mg/L for exposure of fathead minnow to PFPeA. It may be surprising that the EC50 for PFPeA (32 mg/L) is lower than for PFHxA (>99.2 mg/L, Table 4-2), however, given species differences and calculation methods, these two EC50 values do not allow for conclusion on toxicity differences.

The available fish toxicity data indicate that short chain PFAS are of moderate to low acute toxicity for fish, while prolonged acute exposures (7 days) can lead to altered effects at very low concentrations (< 0.1 mg/L).

<table>
<thead>
<tr>
<th>Test substance</th>
<th>Organism</th>
<th>Endpoint</th>
<th>Test Concentration (mg/L)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perfluoroalkane sulfonic acids (PFSA) and their salts</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PFBS</td>
<td>Zebrafish larvae (Danio rerio)</td>
<td>EC50, embryotoxicity</td>
<td>144 h</td>
<td>450</td>
</tr>
<tr>
<td>PFBS-K</td>
<td>Fathead minnow (Pimephales promelas)</td>
<td>LC50</td>
<td>96 h</td>
<td>1938</td>
</tr>
<tr>
<td>PFBS-K</td>
<td>Bluegill sunfish (Lepomis macrochirus)</td>
<td>LC50</td>
<td>96 h</td>
<td>6452</td>
</tr>
<tr>
<td>Perfluorocarboxylic acids (PFCA)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PFBA</td>
<td>Zebrafish larvae (Danio rerio)</td>
<td>EC50, embryotoxicity</td>
<td>144 h</td>
<td>2200</td>
</tr>
</tbody>
</table>

TABLE 4-2 TOXICITY OF SHORT CHAIN PFAS TO FISH
<table>
<thead>
<tr>
<th>Test substance</th>
<th>Organism</th>
<th>Endpoint</th>
<th>Test</th>
<th>Concentration (mg/L)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFPeA</td>
<td>Fathead minnow (<em>P. promelas</em>)</td>
<td>LC$_{50}$</td>
<td>96 h</td>
<td>32</td>
<td>Hoke <em>et al.</em>, 2012</td>
</tr>
<tr>
<td>PFHxA</td>
<td>Rainbow trout (<em>O. mykiss</em>)</td>
<td>LC$_{50}$</td>
<td>96 h</td>
<td>&gt;99.2</td>
<td>Hoke <em>et al.</em>, 2012</td>
</tr>
<tr>
<td>PFHxA</td>
<td>Rainbow trout (<em>O. mykiss</em>)</td>
<td>NOEC, reprod.</td>
<td>56 d</td>
<td>10.1</td>
<td>ENVIRON, 2014</td>
</tr>
</tbody>
</table>

### Fluorotelomers

<table>
<thead>
<tr>
<th>Compound</th>
<th>Cas no.</th>
<th>Organism</th>
<th>Endpoint</th>
<th>Test</th>
<th>Concentration (mg/L)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>6:2 FTOH</td>
<td>647-42-7</td>
<td><em>Pimephales promelas</em></td>
<td>LC$_{50}$</td>
<td>96 h</td>
<td>4.84</td>
<td>ENVIRON, 2014</td>
</tr>
<tr>
<td>6:2 FTOH</td>
<td>647-42-7</td>
<td><em>Danio rerio</em></td>
<td>LOEC, testosterone serum level in male fish</td>
<td>7 days</td>
<td>0.03</td>
<td>Liu <em>et al.</em>, 2009</td>
</tr>
<tr>
<td>6:2 FTOH</td>
<td>647-42-7</td>
<td><em>Danio rerio</em></td>
<td>LOEC, estradiol serum level in female fish</td>
<td>7 days</td>
<td>0.3</td>
<td>Liu <em>et al.</em>, 2009</td>
</tr>
<tr>
<td>6:2 FTAC</td>
<td>17527-29-6</td>
<td><em>Oryzias latipes</em></td>
<td>LC$_{50}$</td>
<td>96 h</td>
<td>&gt;0.306</td>
<td>ENVIRON, 2014</td>
</tr>
<tr>
<td>4:2 FT olefin</td>
<td>19430-93-4</td>
<td><em>Danio rerio</em></td>
<td>NOEC, mortality</td>
<td>96 h</td>
<td>≥ 1.86</td>
<td>ECHA, 2014</td>
</tr>
</tbody>
</table>

### 4.2.1.3 Invertebrates

Aquatic toxicity data are available for the crustacean *Daphnia magna* and the midge *Chironomus tentans*. Data on other invertebrates, such as molluscs, was not identified.

Ding and Peijnenburg (2013) summarise a large number of aquatic toxicity studies with in a review on physico-chemical properties and aquatic toxicity of poly- and perfluorinated compounds. Most of the studies are concerned with longer chain PFAS, but 7 of the reviewed studies do also include short chain PFAS.

A study (cited as Phillips *et al.* 2007) tested toxicity of FTCA and FTUCA on *Daphnia magna* (48 hr) and on the midge *C. tentans*. The results showed that toxicity increased with increasing chain length and that the saturated forms of the fluorotelomer carboxylic acids were usually more toxic than their unsaturated counterparts (Ding and Peijnenburg, 2013).

However, comparing the available data on short-chain PFAS as presented in Table 4-3, the values do not seem to allow for a conclusion on toxicity differences between the saturated and unsaturated forms of the fluorotelomer carboxylic acids. The data do neither allow for a conclusion on toxicity differences between the acids and the salts.

Generally, short chain PFAS appear to have low toxicity on aquatic invertebrates, as most EC$_{50}$ values are around or above 100 mg/L. The lowest effect concentration was observed for in an acute test with daphnids (LC$_{50}$ of 29.6 mg 6:2 FTUCA/L).
TABLE 4-3
TOXICITY OF SHORT CHAIN PFAS TO INVERTEBRATES

<table>
<thead>
<tr>
<th>Test substance</th>
<th>Organism</th>
<th>Endpoint</th>
<th>Test</th>
<th>Concentration* (mg/L)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abbr.</td>
<td>Cas no.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perfluoroalkane sulfonates (PFSA) and their salts</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PFBS-K</td>
<td>29420-49-3</td>
<td>Daphnia magna</td>
<td>EC50</td>
<td>48 h</td>
<td>2180</td>
</tr>
<tr>
<td>PFBS-K</td>
<td>29420-49-3</td>
<td>Daphnia magna</td>
<td>NOEC</td>
<td>21 d</td>
<td>502</td>
</tr>
<tr>
<td>Perfluorocarboxylic acids (PFCA) and their salts</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PFBA</td>
<td>375-22-4</td>
<td>Daphnia magna</td>
<td>LC50</td>
<td>48 h</td>
<td>&gt;100</td>
</tr>
<tr>
<td>PFBA-K</td>
<td>2966-54-3</td>
<td>Daphnia magna</td>
<td>NOEC, reproduc.</td>
<td>21 d</td>
<td>239</td>
</tr>
<tr>
<td>PFPeA</td>
<td>2706-90-3</td>
<td>Daphnia magna</td>
<td>LC50</td>
<td>48 h</td>
<td>&gt;112</td>
</tr>
<tr>
<td>PFHxA</td>
<td>307-24-4</td>
<td>Daphnia magna</td>
<td>LC50</td>
<td>48 h</td>
<td>&gt;96.5</td>
</tr>
<tr>
<td>Saturated and unsaturated fluorotelomer carboxylic acids (FTCA and FTUCA)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4:2 FTCA</td>
<td>7088789-7</td>
<td>Daphnia magna</td>
<td>LC50</td>
<td>48 h</td>
<td>&gt;100</td>
</tr>
<tr>
<td>4:2 FTCA</td>
<td>7088789-7</td>
<td>Midge (Chironomus tentans)</td>
<td>LC50</td>
<td>10 d</td>
<td>&gt;100</td>
</tr>
<tr>
<td>4:2 FTUCA</td>
<td>7088790-0</td>
<td>Daphnia magna</td>
<td>LC50</td>
<td>48 h</td>
<td>&gt;100</td>
</tr>
<tr>
<td>4:2 FTUCA</td>
<td>7088790-0</td>
<td>Midge (Chironomus tentans)</td>
<td>LC50</td>
<td>10 d</td>
<td>&gt;100</td>
</tr>
<tr>
<td>5:3 acid</td>
<td>914637-49-3</td>
<td>Daphnia magna</td>
<td>LC50</td>
<td>48 h</td>
<td>&gt;103</td>
</tr>
<tr>
<td>6:2 FTCA</td>
<td>5382612-3</td>
<td>Midge (Chironomus tentans)</td>
<td>EC50</td>
<td>10 d</td>
<td>63.1</td>
</tr>
<tr>
<td>6:2 FTCA</td>
<td>5382612-3</td>
<td>Midge (Chironomus tentans)</td>
<td>LC50</td>
<td>10 d</td>
<td>75.2</td>
</tr>
<tr>
<td>6:2 FTCA</td>
<td>5382612-3</td>
<td>Daphnia magna</td>
<td>LC50</td>
<td>48 h</td>
<td>&gt;97.5</td>
</tr>
<tr>
<td>6:2 FTCA</td>
<td>5382612-3</td>
<td>Midge (Chironomus tentans)</td>
<td>LC50</td>
<td>10 d</td>
<td>75.2</td>
</tr>
<tr>
<td>6:2 FTUCA</td>
<td>7088788-6</td>
<td>Daphnia magna</td>
<td>LC50</td>
<td>48 h</td>
<td>29.6</td>
</tr>
<tr>
<td>6:2 FTUCA</td>
<td>7088788-6</td>
<td>Midge (Chironomus tentans)</td>
<td>LC50</td>
<td>10 d</td>
<td>&gt;100</td>
</tr>
</tbody>
</table>
4.2.1.4 *Algae and aquatic plants*

Ding and Peijnenburg (2013) cite three studies on algae toxicity including short chain PFAS in their review. The main results are summarised in Table 4-4 and the following paragraphs.

Only a single review citing results on the sulfonate PFBS-K was identified (NICNAS, 2005). The short chain PFAS showed to be practically non-toxic to algae with effects concentrations > 1000 mg/L.

The toxicity of saturated and unsaturated fluorotelomer carboxylic acids (FTCA and FTUCA) with a chain length of 4–8 has been investigated on the floating macrophyte *Lemna gibba*. Toxicity increased with increasing chain length and the saturated acids were usually more toxic than the unsaturated acids. *L. gibba* was more sensitive to the short chain telomer acids than *Daphnia magna* and *Chironomus tentans*. In addition, the study authors pointed out that the fluorotelomer carboxylic acids, as precursors of PFCAs, were more toxic than the PFCAs themselves (Ding and Peijnenburg, 2013).

Another study cited by Ding and Peijnenburg (2013) tested the toxicity of PFBS, PFHxS, PFOS, PFHxA, PFOA, PFDoA, and PFTeA on the freshwater green alga *Scenedesmus obliquus*. They found that PFOS, PFDoA, and PFTeA inhibited algal growth in a concentration-dependent manner while PFBS, PFHxA, and PFOA did not inhibit the algal growth within the range of concentrations tested (range not indicated). This leads to the conclusion that both carbon chain length and nature of the acid group influenced the toxicity of PFAS with toxicity increasing with increasing carbon chain length for compounds belonging to the same class.

The 72-hr toxicity (optical density) of PFHxA, PFHpA, PFOA, and PFNA was tested on three representative marine algae in the Baltic Sea, the green alga *Chlorella vulgaris*, the diatom *Skeletonema marinoi*, and the blue-green alga *Gtillerinema amphibium*. The blue-green alga and diatom showed to be far more sensitive to PFCAs than the green alga, which was explained on the basis of differences in the cell wall structure. Furthermore, a good linear correlation between the log EC50 values and chain length as well as between the log EC50 values and logKow predicted by EPI Suite v4.0. was found (Ding and Peijnenburg, 2013). The reviewers do, however, note that micelle formation in the higher concentration ranges (up to 50 mM) could have biased the results.

Ding *et al.* (2012) investigated the photosynthesis effects of seven PFAS (PFBA, 5H 4:1 FTOH, PFOA, PFNA, PFDA, PFUnA, and PFDoA) on green algae. The results yielded a good relationship between effect concentrations and chain length, apart from PFBA. The actual EC50 of 1.22 mM was 5.7 lower than the EC50 that could be predicted from the relationship. The authors presume that increased acidification of the test solution (the pKa of PFBA is 0.39 and thus lower than the other PFAS investigated) contributed to the toxicity effects, warranting additional information.

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**Table 4-4**

<table>
<thead>
<tr>
<th>Test substance</th>
<th>Organism</th>
<th>Endpoint</th>
<th>Test</th>
<th>Concentration* (mg/L)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluorotelomer alcohols (FTOH) and acrylates (FTAC)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6:2 FTOH</td>
<td>Daphnia magna</td>
<td>EC50</td>
<td>48 h</td>
<td>7.84</td>
<td>ENVIRO, 2014</td>
</tr>
<tr>
<td>6:2 FTOH</td>
<td>Daphnia magna</td>
<td>NOEC, repro.</td>
<td>21 d</td>
<td>2.16</td>
<td>ENVIRO, 2014</td>
</tr>
<tr>
<td>6:2 FTAC</td>
<td>Daphnia magna</td>
<td>EC50</td>
<td>48 h</td>
<td>&gt;0.141</td>
<td>ENVIRO, 2014</td>
</tr>
</tbody>
</table>

* Some references cite several values from different sources.

2,2,3,3,4,4,5,5-Octafluoro-1-pentanol, Cas no. 355-80-6
Hoke et al. (2012) investigated short-term toxicity of eight fluorinated acids (6:2 FTCA, 8:2 FTCA, 6:2 FTUCA, 8:2 FTUCA, 5:3 acid, 7:3 acid, PFPeA, and PFDA) to the Daphnia magna, the green alga Pseudokirchneriella subcapitata, and fish (Onchorhynchus mykiss or Pimephales promelas) as well as compared their own results to effect concentrations determined in another study on the duckweed Lemna gibba. L. gibba showed to be the most sensitive of the tested organisms. They also conclude that the toxicity of PFAS increases with the length of the fluorinated carbon chain. Moreover, their results supports the hypothesis that FTCA are typically more toxic to aquatic organisms than the corresponding PFCA. One hypothesis proposed for the increased toxicity of the FTCA and FTUCA, 7:3 acid and 5:3 acid relative to the corresponding PFCA is that they are metabolized with subsequent release of hydrogen fluoride leading to toxicity effects of F or pH depression in the test medium. However, Hoke et al. (2012) reject this hypothesis based on considerations of HF concentrations being too low to cause such effects.

The derived effect concentrations from the mentioned studies are summarised in Table 4-4. The lowest EC50 was identified for duckweed at a concentration of 1.29 mg 6:2 FTCA/L. This concentration level is supported by the outcome of other tests, which show effect concentrations in the same range.

**TABLE 4-4**

**TOXICITY OF SHORT CHAIN PFAS TO ALGAE**

<table>
<thead>
<tr>
<th>Test substance</th>
<th>Organism</th>
<th>Endpoint</th>
<th>Test</th>
<th>Concentration* (mg/L)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Perfluoroalkane sulfonates (PFSA) and their salts</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PFBS-K</td>
<td>29420-49-3</td>
<td>Algae (<em>Selanastrum capricornutum</em>)</td>
<td>EC50, biomass and growth</td>
<td>96 h</td>
<td>2347-5733 mg/L</td>
</tr>
<tr>
<td><strong>Perfluorocarboxylic acids (PFCA)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PFBA</td>
<td>375-22-4</td>
<td>Algae (<em>P. subcapitata</em>)</td>
<td>EC50, inhibition of photosynthesis</td>
<td>4.5 h</td>
<td>1.22 mM (261 mg/L)</td>
</tr>
<tr>
<td>PFPeA</td>
<td>2706-90-3</td>
<td>Algae (<em>P. subcapitata</em>)</td>
<td>EC50</td>
<td>72 h</td>
<td>81.7</td>
</tr>
<tr>
<td>PFHxA</td>
<td>307-24-4</td>
<td>Algae (<em>P. subcapitata</em>)</td>
<td>Ec50</td>
<td>72 h</td>
<td>&gt;100</td>
</tr>
<tr>
<td>PFHxA</td>
<td>307-24-4</td>
<td>Algae (<em>G. amphibium</em>)</td>
<td>IC50, optical density</td>
<td>72 h</td>
<td>998.7</td>
</tr>
<tr>
<td>PFHxA</td>
<td>307-24-4</td>
<td>Algae (<em>S. subspicatus</em>)</td>
<td>ErC50 NOEC</td>
<td>72 h</td>
<td>86</td>
</tr>
<tr>
<td><strong>Saturated and unsaturated fluorotelomer carboxylic acids (FTCA and FTUCA)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4:2 FTCA</td>
<td>7088789-7</td>
<td>Duck weed (<em>Lemna gibba</em>)</td>
<td>EC50, frond number</td>
<td>7 d</td>
<td>9.39</td>
</tr>
<tr>
<td>4:2 FTCA</td>
<td>7088789-7</td>
<td>Duck weed (<em>Lemna gibba</em>)</td>
<td>EC50, biomass</td>
<td>7 d</td>
<td>6.6</td>
</tr>
<tr>
<td>4:2 FTUCA</td>
<td>7088790-0</td>
<td>Duck weed (<em>Lemna gibba</em>)</td>
<td>EC50, frond number</td>
<td>6.64</td>
<td></td>
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</tbody>
</table>

13 $2H,2H,3H,3H$-undecafluoro octanoic acid (5:3 acid), Cas no. 914637-49-3
14 $2H,2H,3H,3H$-pentadecafluoro decanoic acid (7:3 acid), Cas no. 812-70-4
<table>
<thead>
<tr>
<th>Test substance</th>
<th>Organism</th>
<th>Endpoint</th>
<th>Test</th>
<th>Concentration* (mg/L)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>4:2 FTUCA</td>
<td>Duck weed (Lemna gibba)</td>
<td>EC50, biomass</td>
<td>7 d</td>
<td>9.4</td>
<td>Hoke et al., 2012</td>
</tr>
<tr>
<td>5:3 acid</td>
<td>Algae (P. subcapitata)</td>
<td>EC50, biomass</td>
<td>72 h</td>
<td>22.5</td>
<td>Hoke et al., 2012</td>
</tr>
<tr>
<td>6:2 FTCA</td>
<td>Duck weed (Lemna gibba)</td>
<td>EC50, frond number</td>
<td>7 d</td>
<td>1.29</td>
<td>Ding and Peijnenburg, 2013</td>
</tr>
<tr>
<td>6:2 FTCA</td>
<td>Duck weed (Lemna gibba)</td>
<td>EC50, biomass</td>
<td>7 d</td>
<td>1.3</td>
<td>Hoke et al., 2012</td>
</tr>
<tr>
<td>6:2 FTCA</td>
<td>Algae (P. subcapitata)</td>
<td>ErC50, biomass</td>
<td>72 h</td>
<td>47.9</td>
<td>Hoke et al., 2012</td>
</tr>
<tr>
<td>6:2 FTUCA</td>
<td>Duck weed (Lemna gibba)</td>
<td>EC50, frond number</td>
<td>7 d</td>
<td>5.02</td>
<td>Ding and Peijnenburg, 2013</td>
</tr>
<tr>
<td>6:2 FTUCA</td>
<td>Duck weed (Lemna gibba)</td>
<td>EC50, biomass</td>
<td>7 d</td>
<td>10.4</td>
<td>Hoke et al., 2012</td>
</tr>
<tr>
<td>6:2 FTUCA</td>
<td>Algae (P. subcapitata)</td>
<td>ErC50, biomass</td>
<td>72 h</td>
<td>28.5</td>
<td>Hoke et al., 2012</td>
</tr>
<tr>
<td>Fluorotelomer alcohols (FTOH)</td>
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<td></td>
</tr>
<tr>
<td>6:2 FTOH</td>
<td>Algae (P. subcapitata)</td>
<td>EC50, growth rate</td>
<td>72 h</td>
<td>4.52</td>
<td>ENVIRON, 2014</td>
</tr>
<tr>
<td>6:2 FTOH</td>
<td>Algae (P. subcapitata)</td>
<td>NOEC</td>
<td>72 h</td>
<td>0.62</td>
<td>ENVIRON, 2014</td>
</tr>
<tr>
<td>5H 4:1 FTOH</td>
<td>Algae (P. subcapitata)</td>
<td>EC50, inhibition of photosynthesis</td>
<td>4.5 h</td>
<td>4.85 mM (1125 mg/L)</td>
<td>Ding et al. 2012</td>
</tr>
<tr>
<td>PFAS acrylates</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6:2 FTAC</td>
<td>Algae (P. subcapitata)</td>
<td>ErC50</td>
<td>72 h</td>
<td>&gt;0.022</td>
<td>ENVIRON, 2014</td>
</tr>
<tr>
<td>C4 acrylate†</td>
<td>Algae (P. subcapitata)</td>
<td>NOEC, growth rate</td>
<td>72 h</td>
<td>0.34</td>
<td>ECHA, 2014</td>
</tr>
</tbody>
</table>

* Some references cite several values from different sources.
† IUPAC Name: 2-[(methyl[(nonafluorobutyl)sulfonyl]amino)ethyl]acrylate.

4.2.1.5 Microorganisms
In the review on aquatic toxicity, Ding and Peijnenburg (2013) refer to two studies on short chain PFAS with microorganisms.

In one of the studies cited, the population growth impairment potential of four FTOH (chain length from 4:2 to 10:2) on the protozoa Tetrahymena thermophila was investigated. The results revealed that no growth inhibition effect was found for 8:2 FTOH and 10:2 FTOH. However, 4:2 FTOH inhibited the population growth with a 24-hr EC50 of 276.1 mg/L, whereas 6:2 FTOH had a lower 24-hr EC50 of 64.3 mg/L (see Table 4-5). The higher toxicity
of the shorter FTOH is presumably related to the mode of action, which includes macronucleus destruction (for 6:2 FTOH), while direct membrane damage has not been detectable. The test were performed in both open and closed systems, and the authors suggested that tests in closed system are more reliable for testing these volatile compounds.

The other study tested the acute toxicity of PFHxA, PFHpA, PFOA, PFNA, and PFDA on the marine bacterium *Vibrio fischeri*. It was found that bioluminescence inhibition was was increased with increasing chain length rendering PFHxA as the least toxic compound with an EC50 of 1340 mg/L.

The data indicate that FTOH are potentially more toxic then the PFCA with respect to microorganisms.

The PFBS-K review by NICNAS (2005) cites one study concluding that PFBS-K is not inhibitory to sewage microorganisms.

**TABLE 4-5**

<table>
<thead>
<tr>
<th>Test substance</th>
<th>Organism</th>
<th>Endpoint</th>
<th>Test</th>
<th>Concentration (mg/L)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perfluoroalkane sulfonates (PFSA) and their salts</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PFBS-K</td>
<td>29420-49-3</td>
<td>Sewage microorganisms</td>
<td>EC50, inhibitory effects on respiration</td>
<td>3 h</td>
<td>&gt; 1000</td>
</tr>
<tr>
<td>Perfluorocarboxylic acids (PFCA)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PFHxA</td>
<td>307-24-4</td>
<td><em>Vibrio fischeri</em></td>
<td>EC50, bioluminescence inhibition</td>
<td>30 min</td>
<td>1340</td>
</tr>
<tr>
<td>Fluorotelomer alcohols (FTOH)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>4:2 FTOH</td>
<td>2043-47-2</td>
<td>Tetrahymena thermophila (ciliate protozoa)</td>
<td>EC50, population growth inhibition</td>
<td>24 h</td>
<td>276.1</td>
</tr>
<tr>
<td>6:2 FTOH</td>
<td>647-42-7</td>
<td>Tetrahymena thermophila (ciliate protozoa)</td>
<td>EC50, population growth inhibition</td>
<td>24 h</td>
<td>64.3</td>
</tr>
</tbody>
</table>

### 4.2.2 Toxicity to terrestrial organisms

Very limited data on terrestrial organisms have been available. With respect to mammals and food-web-effects, no toxicity data could be identified at all.

#### 4.2.2.1 Birds

An acute dietary study as well as a reproduction study with birds is cited in the NICNAS (2005) review on PFBS-K. Generally, the acute effects investigated were not treatment-related in the two bird species (see Table 4-6). For both species the dietary LC50 value was determined to be >10000 ppm, the highest concentration tested. For the bobwhite quail the NOEC was considered to be 3160 ppm due to the reduction in body weight gain in the 5620 and 10000 mg/kg dose group, while for the mallard the NOEC was 5620 mg/kg due to the reduction in body weight gain only at 10 000 mg/kg. With respect to the reproduction study, it was concluded that the no-observed-effect concentration for northern bobwhite exposed to PFBS in the diet was 900 ppm, the highest concentration tested. The results indicate a very low ecotoxicity for PFBS to birds.
### 4.2.2.2 Invertebrates

The Norwegian Pollution Control Authority (NPCA) performed tests in earthworms (*Eisenia fetida*) with three PFAS; PFOS, PFOA and 6:2 fluorotelomer sulfonate (6:2 FTS) in order to increase the limited knowledge of effects on terrestrial organisms with importance to soil function and food web (NPCA, 2006). 6:2 FTS was less toxic to earthworms than PFOS and PFOA, and harmful effects on reproduction were not observed until soil concentration of 6:2 FTS exceeded 30 mg/kg (EC10 for total weight of juvenile). The authors noted, however, that due to problems of solubilising the substance in water, it was unsure to what extent 6:2 FTS was actually bioavailable for the earth worms. The EC50 values indicate a low or moderate toxicity to earth worms.

### 4.2.2.3 Soil microorganisms and microbial processes

A NOEC of 1000 mg/L was the only data identified for terrestrial microorganisms. The value indicates that at least the C4 acrylate is a short chain PFAS with low microorganism toxicity.
### TABLE 4-8
TOXICITY OF SHORT CHAIN PFAS TO SOIL AND SEWAGE MICROORGANISMS

<table>
<thead>
<tr>
<th>Test substance</th>
<th>Organism</th>
<th>Endpoint</th>
<th>Test</th>
<th>Concentration (mg/L)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PFAS acrylates</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C₄ acrylate&lt;br&gt;¹</td>
<td>67584-55-8</td>
<td>Activated sludge of a predominantly domestic sewage</td>
<td>NOEC, respiration rate</td>
<td>3 h, OECD 209</td>
<td>1000 (nominal)</td>
</tr>
</tbody>
</table>

¹ IUPAC Name: 2-[(methyl[(nonafluorobutyl)sulfonyl]amino)ethyl acrylate

### TABLE 4-9
TOXICITY OF SHORT CHAIN PFAS TO TERRESTRIAL PLANTS

<table>
<thead>
<tr>
<th>Test substance</th>
<th>Organism</th>
<th>Endpoint</th>
<th>Test</th>
<th>Concentration (mM)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Perfluorocarboxylic acids (PFCA) and their salts</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PFBA</td>
<td>375-22-4</td>
<td>Lettuce (L. sativa)</td>
<td>EC₅₀, root elongation</td>
<td>4.5 h, acute</td>
<td>4.19 (897 mg/L)</td>
</tr>
<tr>
<td><strong>Fluorotelomer alcohols (FTOH)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5H 4:1 FTOH</td>
<td>355-80-6</td>
<td>Lettuce (L. sativa)</td>
<td>EC₅₀, root elongation</td>
<td>4.5 h, acute</td>
<td>2.98 (691 mg/L)</td>
</tr>
</tbody>
</table>

### 4.2.2.4 Plants

The toxicity effects of seven PFAS (PFBA, 5H 4:1 FTOH, PFOA, PFNA, PFDA, PFUnA, and PFDaA) on root elongation of lettuce (*Lactuca sativa*) was investigated along with the photosynthesis effect of the same PFAS on green algae. The authors concluded that for both species, there was a good relationship between effect concentrations and fluorinated carbon-chain length (Ding et al., 2012). The EC₅₀ values (Table 4-9) indicate moderate to low toxicity of PFBA and 5H 4:1 FTOH on lettuce.

### 4.3 Environmental fate and effects of single PFAS

The environmental fate and effects of the single short chain PFAS are summarised in the following paragraphs based on the information available i.e. including information based on read-across. The section is structured identically to the corresponding section in Chapter 3 on toxic effects of single PFAS (section 3.3) and uses for convenience the same headings. However, it should be noted that much less data are available about the environmental aspects of the short-chained PFAS are available than data on human health effects and therefore specific information on a number of substances described in section 3.3 is not necessarily included in the sub-sections of this section.

#### 4.3.1 Perfluoroalkane sulfonic acids/sulfonates (PFSA)

**4.3.1.1 PFBS**

Hydrolysis and photolysis of PFBS were concluded to be unlikely to occur (read-across from the potassium salt of PFBS). No biodegradation of the compound was observed. PFBS was, like other PFAS, poorly removed in WWTPs. The Log BCFs of the C₄-C₇ sulfonic acids were found to be below 1 thus indicating little bioaccumulation potential of these substances in fish.

The lowest effect concentration for PFBS was an EC₅₀ (144 h) on embryotoxicity of 450 mg/L in an study with zebra fish. The toxicity results generally indicate a very low ecotoxicity for PFBS to birds (NOEC for reproduction
of 900 mg/kg), algae (EC50 for biomass of 2347 mg/L), invertebrates (NOEC for chronic toxicity in daphnids 502 mg/L), fish (EC50 for embryotoxicity 450 mg/L), and sewage organisms (EC50 on respiration > 1000 mg/L).

### 4.3.1.2 PFPeS

Fate data on PFPeS have not been identified. Based on the read-across approach, conclusions applying to the fate of PFBS can be anticipated to be valid for PFPeS as well. Thus, the compound is not expected to undergo hydrolysis or photolysis, and no biodegradation is expected. The substance was, like other PFAS, poorly removed in WWTPs. The Log BCFs of the C4-C7 sulfonic acids were found to be below 1 thus indicating little bioaccumulation potential of these substances in fish.

Toxicity data on PFPeS have not been available. Considering the conclusions on chain length and presence of functional groups of PFAS, it can be expected that PFPeS shows slightly increased toxicity compared to PFBS, as well as increased toxicity compared to PFPeA.

### 4.3.1.3 PFHxS

Fate data on PFHxS are very sparsely. Based on the read-across approach, conclusions applying to the fate of PFBS can be anticipated to be valid for PFHxS as well. Thus, the compound is not expected to undergo hydrolysis or photolysis, and no biodegradation is expected. The substance was, like other PFAS, found to be poorly removed in WWTPs. In one study, the Log BCFs of the C4-C7 sulfonic acids were all found to be below 1 in fish thus indicating little bioaccumulation potential of these substances in this organism group in contrast to long-chain (C11-C13) PFSAs.

Toxicity data on PFHxS have not been available. Considering the conclusions on chain length and presence of functional groups of PFAS, it can be expected that PFHxS shows increased toxicity compared to PFBS, as well as increased toxicity compared to PFHxA.

### 4.3.2 Perfluoroalkanoic acids/perfluoroalkanoates, perfluorocarboxylic acids and perfluoro-carboxylates (PFCA)

#### 4.3.2.1 PFBA

Fate data on PFBA are sparse. PFCAs are degradation products of other PFAS and are not transformed/degraded by hydrolysis or photolysis in water to any appreciable extent. They are neither biodegradable under aerobic or anaerobic environmental conditions in water or soil. These conclusions have been derived for longer chain PFCAs, but are also expected to be valid for short-chain PFCAs such as PFBA. PFBA has been shown to be poorly removed in WWTPs.

The log BCFs of the C4-C7 carboxylic acids were found to be below 1 thus indicating little bioaccumulation potential of these substances in fish. Short chain PFCA are not considered bioaccumulative according to the regulatory criteria of 1000–5000 L/kg.

The lowest effect concentration identified was an LC50 > 100 in a immobilisation study with daphnids. Generally, the substance shows low ecotoxicity with effect concentrations of 2200 mg/L (fish EC50, embryotoxicity, 144 h), 239 mg/L (PFBA-K, Daphnia magna, NOEC for reproduction, 21 d), 261 mg/L (algae EC50, inhibition on photosynthesis, 4.5 h, and 897 mg/L (lettuce EC50, root elongation, 4.5 h).

#### 4.3.2.2 PFPeA

Fate data on PFPeA are sparse. PFCAs are degradation products of other PFAS and are not transformed/degraded by hydrolysis or photolysis in water to any appreciable extent. They are neither biodegradable under aerobic or anaerobic environmental conditions in water or soil. These conclusions have been derived for longer-chain PFCAs, but are also expected to be valid for short chain PFCAs such as PFPeA. PFPeA has been shown to be poorly removed in WWTPs.
The log BCFs of the C4-C7 carboxylic acids were found to be below 1 thus indicating little bioaccumulation potential of these substances in fish. Short chain PFCA are not considered bioaccumulative according to the regulatory criteria of 1000–5000 L/kg.

With respect to toxicity, a 50 % mortality effect concentration of 32 mg/L was determined for fish (fathead minnow, acute test) as the lowest effect concentration. Other species exhibit corresponding susceptibility with EC50 concentrations ranging from 81.7 mg/L (algae, biomass, 72h) to >112 mg/L (daphnids, immobilisation, 48 h).

4.3.2.3 PFHxA
Fate data on PFHxA are sparse. PFCA are degradation products of other PFASs and are not transformed/degraded by hydrolysis or photolysis in water to any appreciable extent. They are neither biodegradable under aerobic or anaerobic environmental conditions in water or soil. These conclusions have been derived for longer chain PFCAs but are also expected to be valid for short-chain PFCAs such as PFHxA. PFHxA has been shown to be poorly removed in WWTPs.

The log BCFs of the C4-C7 carboxylic acids were found to be below 1 thus indicating little bioaccumulation potential of these substances in fish. Short chain PFCAs are not considered bioaccumulative according to the regulatory criteria of 1000–5000 L/kg.

Toxicity tests with rainbow trout, *Daphnia magna*, and the alga (*P. subcapitata*) showed corresponding 50 % effect concentrations of >100 mg/L. Other algae (*S. marinoi* and *G. amphibium*) as well as a marine bacterium were less susceptible to PFHxA with effect concentrations ranging from 998.7 – 1482 mg/L.

4.3.3 Perfluoroalkyl halogenides
No data on fate and toxicity of short chain perfluoroalkyl halogenides have been identified. The general rule of increased toxicity of PFAS with increasing chain length is presumably also valid for the halogenides.

4.3.4 Perfluoroalkyl phosphor compounds
No data on fate and toxicity of short chain perfluoroalkyl phosphor compounds have been identified. The general rule of increased toxicity of PFAS with increasing chain length is presumably also valid for the phosphor compounds.

4.3.5 Fluorotelomers
4.3.5.1 4:2 FTOH
The short-chain 4:2 FTOH can via an intermediate degrade to PFBA in the atmosphere. A lifetime of approximately 20 days was estimated for 4:2, 6:2 and 8:2 FTOH.

Aerobic biodegradation of the fluorotelomer alcohol 8:2 FTOH, showing a half-life of about 1 day and 85 % degradation within a week, has been demonstrated. Degradation was not complete; telomere acids and PFOA were identified as the degradation products. Corresponding pathways do most likely apply to 4:2 FTOH and degradation will lead to the formation of PFBA.

A number of in *vitro* toxicity studies show estrogenic activities of FTOH, but no information is provided whether these effects do also apply for 4:2 FTOH, being the shortest of the FTOH. However, 6:2 FTOH was found to be a stronger xenoestrogen than 8:2 FTOH. Since the mechanisms of estrogenic activity of the FTOH are not known and an increased bioavailability of 4:2 FTOH compared to 6:2 FTOH can be expected due to its physical-chemical properties, it cannot be excluded that 4:2 FTOH is a strong xenoestrogen, too, or even a stronger xenoestrogen than 6:2 FTOH. The lowest observable effect following 6:2 FTOH exposure occurred in male fish group at a concentration of 0.03 mg/L.

The only toxicity study identified for 4:2 FTOH is with a ciliate protozoa, revealing a EC50 concentration of 276.1 mg/L for population growth inhibition.
4.3.5.2 6:2 FTOH
The short chain 6:2 FTOH can via an intermediate degrade to PFHxA in the atmosphere. A lifetime of approximately 20 days was estimated for 4:2, 6:2 and 8:2 FTOH.

Aerobic biodegradation of the fluorotelomer alcohol 8:2 FTOH, showing a half-life of about 1 day and 85 % degradation within a week, has been demonstrated. Degradation was not complete; telomer acids and PFOA were identified as degradation products. Corresponding pathways do most likely apply to 6:2 FTOH and degradation will lead to the formation of PFHxA.

The estrogenic activity of FTOH have been demonstrated in a number of in vitro toxicity studies and also endocrine disrupting effects have been observed for 6:2 FTOH in zebra fish. 6:2 FTOH was found to be a stronger xenosterogen than 8:2 FTOH. The lowest observable effect of 6:2 FTOH occurred in male fish at a concentration of 0.03 mg/L, while in female fish, the lowest effect concentration was 0.3 mg/L. A toxicity study with a ciliate protozoa revealed an EC50 value of 64.3 mg/L for population growth inhibition.

4.4 PBT assessment
For several of the short-chain PFAS registered with full registration dossiers on ECHAs homepage, a full or partial PBT assessment is available. The PBT conclusions are presented in Table 4-10.

Generally, the substances are evaluated by the registrants as not meeting the REACH PBT criteria. Only the C4 acrylate (CAS no. 67584-55-8) and the perfluoroalkyl amine PTBA (CAS no. 311-89-7) are recognized to be very persistent substances. It is believed that this general conclusion by the registrant is reached because of the primary degradation these substances can undergo. This, however, only leads to generation of transformation products with an intact perfluorinated backbone, which has been shown to be highly persistent in the environment. Hence, the authors of this report do not consider these substances to be truly biodegradable.

With regard to bioaccumulation there are indications (as described in section 3.1.1) that humans and maybe other higher mammals can accumulate PFAS in organs via a different mechanism than traditional uptake in lipid tissue. Therefore, a B/vB assessment based exclusively on Log Pow considerations may not be sufficient for an evaluation of the bioaccumulation potential of the short-chain PFAS.

### Table 4-10
<table>
<thead>
<tr>
<th>Assessed substance</th>
<th>Persistence</th>
<th>Bioaccumulation</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fluorotelomer olefins</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PFBE&lt;sup&gt;1&lt;/sup&gt; (4:2 FT olefin)</td>
<td>19430-93-4</td>
<td>not P/vP</td>
<td>Not B/not vB based on Log Kow ≤ 4.5</td>
</tr>
<tr>
<td>PFAS acrylates</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C4 acrylate&lt;sup&gt;1&lt;/sup&gt;</td>
<td>67584-55-8</td>
<td>vP (and P) based on 28-day biodegradation of 0% to 3% (OECD 301B) and T1/2 in freshwater &gt; 60 days</td>
<td>Not T or NOEC ≥ 0.01 mg/L for marine / freshwater organisms (long-term toxicity)</td>
</tr>
</tbody>
</table>

<sup>1</sup> PBT criteria based on Log Pow

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64
### Assessed substance

<table>
<thead>
<tr>
<th>Assessed substance</th>
<th>Persistence</th>
<th>Bioaccumulation</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Abbr.</strong></td>
<td><strong>Cas no.</strong></td>
<td><strong>Persistence</strong></td>
<td><strong>Bioaccumulation</strong></td>
</tr>
<tr>
<td>6:2 FTMA</td>
<td>2144-53-8</td>
<td>Not P/ vP based on other biodegradability screening tests. However, some of the degradation products may be long-lived.</td>
<td>Not B/not vB based on BCF ≥ 2,000 L/kg</td>
</tr>
<tr>
<td>6:2 FTA</td>
<td>17527-29-6</td>
<td>Screening criteria not fulfilled</td>
<td>Not B/not vB based on: BCF ≥ 2,000 L/kg</td>
</tr>
</tbody>
</table>

**PFAS amines**

| PTBA<sup>3</sup> | 311-89-7 | vP (and P) <br>Remark: This substance is very persistent in the atmosphere but won’t be present in the aquatic or terrestrial environments. | not B/vB | Screening criteria not fulfilled |

**Perfluoroalkanes**

| PFMP<sup>4</sup> | 355-04-4 | Screening criteria not fulfilled | Not B/not vB (based on Log Kow ≤ 4.5) | Screening criteria not fulfilled |

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### 4.5 Environmental occurrence and exposure

PFAS can enter the environment during product manufacturing processes, supply chains, product use, and disposal of various industrial and consumer products (Ahrens, 2007).

### 4.5.1 Aquatic environment

Eight recent studies comprising both reviews, reports and primary articles, have been identified for description of the presence of short-chain PFAS in the aquatic environment. The available data present results for surface water, drinking water, marine water, as well as WWTP influents, effluents and sludge (Table 4-11). For the sake of comparison, the well investigated compounds PFOA and PFOS are often included in the table. Many of studies refer to findings linked to specific contaminations, thus presenting very high environmental concentrations. Freshwater concentrations are usually in the ng – µg/L range, while marine concentration are considerably lower i.e. in the pg/L range.

Ahrens (2011) reviewed the occurrence and fate of 40 PFASs in the aquatic environment. He states that PFAS are ubiquitously found in the aqueous environment with concentrations usually ranging from pg to ng/L for individual compounds. Sources of PFAS in the aqueous environment can be generally grouped into point sources such as...
industrial or municipal wastewater treatment plants (WWTPs) and landfill leachates, and non-point sources such as dry or wet atmospheric deposition, soil or street surface runoff (Ahrens, 2011).

Ahrens (2011) notes that WWTP mass flow studies have shown similar or higher PFCAs and PFSA concentrations in the effluent than in the influent, indicating that conventional WWTPs are probably not effective for removal of ionic PFAS and that biodegradation of precursors may lead to increasing concentrations of PFCAs and PFASs in the effluent. This observation is supported by the results of monitoring of PFOA and PFOS concentrations in Danish WWTP influents (up to 23.5 and 10.1 ng/L, respectively) and effluents (up to 24.4 and 18.1 ng/L, respectively) by Bossi et al. (2008). With respect to PFHxS, the concentration in the effluent was lower. However, substantial amounts of PFHxS where found in sewage sludge, indicating that the compound was removed from the water phase by sorption (Bossi et al., 2008).

In the studies reviewed by Ahrens (2011), PFAS concentrations in WWTP effluents were about 5–10 times higher than in river water samples. Major contaminants in WWTP effluents were PFBS, PFOS and the C4–C9 PFCAs with no large seasonal variations. The high concentrations of PFBS (compared to PFOS) may be surprising, but might stem from the substitution of the C8-based compounds by C4-based compounds after the voluntary phase-out of PFOS-based production by several companies in Germany (Ahrens, 2011).

High PFAS concentrations were also found in drinking water in the Ruhr area, Germany, with a maximum concentration of 598 ng/L for the sum of 7 short- and long-chain PFAS. Drinking water in this area is (partly) derived from river water. The main contaminant was PFOA (up to 519 ng/L), but PFBA, PFPeA, PFHxA, and PFBS were also detected in concentrations of up to 11, 77, 56, and 26 ng/L, respectively. The high concentrations originated from PFAS contaminated soil, documenting that PFAS contaminated soil has the potential to contaminate groundwater (Skutlarek et al., 2006; Ahrens et al. 2011). Skutlarek et al. (2006) analysed also tap water from regions in Germany without obvious point sources of PFAS, which for the majority of samples (13 out of a total of 16) resulted in concentrations below the detection limit. The sum of PFAS did not exceed 27 ng/L in any of the three positive samples. The NOVANA screening investigation by DMU (2007) summarises PFAS concentrations in the Danish aquatic environment, including influents, effluents and sludge from WWTPs, as well as industrial effluents and percolates. Industrial waste water effluents from Denmark showed highly varying concentrations of PFAS (e.g. PFHxS 0.2-18.8 ng/L and PFOS <1.5-1115 ng/L). But also municipal WWTP effluents were estimated to have the potential of contributing significantly to environmental PFAS exposure in Denmark (DMU, 2007). More details on the study results are provided by Bossi et al. (2008), which is also cited in Table 10.

In 2009, the Norwegian Climate and Pollution Agency carried out a screening of selected PFASs including PFBS and PFHxS in environmental samples (soil, sediment, water, and biota) in order to assess whether the investigated compounds give rise to environmental concern or not. Both PFBS and PFHxS were detected in water samples taken from seepage water from a fire fighting training ground at Flesland airport near Bergen (KLIF, 2010).

Two of the identified environmental exposure studies analysed the presence of PFAS in landfill leachates (Bossi et al., 2008; Busch et al., 2010). In the study on Danish landfills, concentrations of PFOS, PFOA, and PFHxS were comparable (Bossi et al., 2008). Busch et al. (2010) documented significantly increased concentrations of short-chain PFAS compared to the longer chain PFAS in both treated (activated carbon, biological treatment, nanofiltration, reverse osmosis, wet air oxidation) and untreated effluents. No plausible explanation was found for this difference, but may be explained by different usage of PFAS, different regulation, and different treatment processes of the landfill leachates. The results also documented that biological treatment was the least efficient removal method for PFAS (Busch et al. 2010).

Zhao et al. (2012) analysed seawater samples from the Greenland Sea and Atlantic Ocean for PFBS, PFHxS, PFOS, PFPeA, PFHxA, PFOA, PFNA, PFDA, PFUnA, and PFDoA. In the Greenland Sea, the PFAS concentrations ranged from 45 to 280 pg/L, and five most frequently detected compounds were PFOA, PFHxS, PFHxA, PFOS, and PFBS. The presence of PFAS was linked to release of PFAS from melted ice and snow. The short chain PFAS, i.e. PFBS,
PFHxS and PFHxA, were quantified in 24%, 88%, and 56% of all samples in the Greenland Sea. This result could be attributed to the shift of usage from C8 to C4-C6 PFAS after the phase-out of PFOS and PFOA (Zhao et al., 2012).

Elevated levels of PFAS were detected in the North Atlantic Ocean with the concentrations ranging from 130 to 650 pg/L for the sum of PFAS. In the Atlantic Ocean, the PFAS concentration decreased from 2007 to 2010 (Zhao et al., 2012).

**TABLE 4.11**
PFAS CONCENTRATIONS IN THE AQUATIC ENVIRONMENT. DATA ON THE LONG-CHAIN PFAS-SUBSTANCES PFOS AND PFOA ARE INCLUDED IN THE TABLE FOR COMPARISON/REFERENCE UNDER EACH OF THE AQUATIC SUB-MEDIA (IN **BOLD**).

<table>
<thead>
<tr>
<th>Test substance</th>
<th>Concentration (ng/L)</th>
<th>Number of samples (&gt;LOD/ total)</th>
<th>Origin</th>
<th>Source as indicated by references</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tap water</strong></td>
<td></td>
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<td></td>
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</tr>
<tr>
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<td>n.d.–26</td>
<td>22/28</td>
<td>Germany</td>
<td>Runoff from contaminated soil</td>
<td>Skutlarek et al. 2006</td>
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<tr>
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<td>n.d.-11</td>
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<td>Germany</td>
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<td>Skutlarek et al. 2006</td>
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<td>PFHxA</td>
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<td>22/28</td>
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<td>Runoff from contaminated soil</td>
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<td>11/28</td>
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<td>Runoff from contaminated soil</td>
<td>Skutlarek et al. 2006</td>
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<td><strong>WWTP influent</strong></td>
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<td>-</td>
<td>Bossi et al., 2008</td>
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<td>-</td>
<td>Bossi et al., 2008</td>
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<td>-</td>
<td>Bossi et al., 2008</td>
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<td><strong>WWTP effluent</strong></td>
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<td>-</td>
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<td>-</td>
<td>Bossi et al., 2008</td>
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<td>-</td>
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<td><strong>WWTP sludge (concentrations in ng/g dw)</strong></td>
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<td>0.34 – 0.64</td>
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<td>from fire fighting training ground near Haugesund</td>
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<td>Norway</td>
<td>from fire fighting training ground near Haugesund</td>
<td>Kliif, 2010</td>
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<tr>
<td>6:2 FTS</td>
<td>6.5 - 379</td>
<td>5/8</td>
<td>Norway</td>
<td>from fire fighting training ground near Haugesund</td>
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<td><strong>Marine water (concentrations in pg/L)</strong></td>
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<td>52</td>
<td>North AO</td>
<td>Long-range transport with sea</td>
<td>Zhao et al., 2012</td>
</tr>
</tbody>
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67
<table>
<thead>
<tr>
<th>Test substance</th>
<th>Concentration (ng/L)</th>
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<th>Origin</th>
<th>Source as indicated by references</th>
<th>Reference</th>
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<td>PFHxA</td>
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<td>Zhao et al., 2012</td>
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</tr>
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</table>

Sediment (concentrations in ng/g dw)

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<th>Source as indicated by references</th>
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<td>Seepage from fire fighting training ground near Bergen</td>
<td>Klif, 2010</td>
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<td>PFHxS</td>
<td>0.7 – 2.6</td>
<td>9/9</td>
<td>Langavatn Lake in Norway</td>
<td>Seepage from fire fighting training ground near Bergen</td>
<td>Klif, 2010</td>
</tr>
<tr>
<td>6:2 FTS</td>
<td>1.5 – 12</td>
<td>9/9</td>
<td>Langavatn Lake in Norway</td>
<td>Seepage from fire fighting training ground near Bergen</td>
<td>Klif, 2010</td>
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<tr>
<td>PFBS</td>
<td>n.d.–71</td>
<td>4/29</td>
<td>Germany</td>
<td>Runoff from contaminated soil</td>
<td>Skutlarek et al. 2006</td>
</tr>
<tr>
<td>PFBA</td>
<td>n.d.–143</td>
<td>17/29</td>
<td>Germany</td>
<td>Runoff from contaminated soil</td>
<td>Skutlarek et al. 2006</td>
</tr>
<tr>
<td>PFPeA</td>
<td>n.d.–1638</td>
<td>22/29</td>
<td>Germany</td>
<td>Runoff from contaminated soil</td>
<td>Skutlarek et al. 2006</td>
</tr>
<tr>
<td>PFHxA</td>
<td>n.d.–1248</td>
<td>22/29</td>
<td>Germany</td>
<td>Runoff from contaminated soil</td>
<td>Skutlarek et al. 2006</td>
</tr>
<tr>
<td>PFOS</td>
<td>n.d.–193</td>
<td>20/29</td>
<td>Germany</td>
<td>Runoff from contaminated soil</td>
<td>Skutlarek et al. 2006</td>
</tr>
<tr>
<td>PFOA</td>
<td>n.d.–3640</td>
<td>24/29</td>
<td>Germany</td>
<td>Runoff from contaminated soil</td>
<td>Skutlarek et al. 2006</td>
</tr>
<tr>
<td>PFOS</td>
<td>n.d.–193</td>
<td>-</td>
<td>Germany</td>
<td>Various sources</td>
<td>Ahrens, 2011</td>
</tr>
<tr>
<td>PFOA</td>
<td>n.d.–3640</td>
<td></td>
<td>Germany</td>
<td>Various sources</td>
<td>Ahrens, 2011</td>
</tr>
<tr>
<td>PFBS</td>
<td>68 – 148</td>
<td>3/3</td>
<td>Norway</td>
<td>Fire fighting training ground</td>
<td>Klif, 2010</td>
</tr>
<tr>
<td>PFBS</td>
<td>11 – 35</td>
<td>3/3</td>
<td>Norway</td>
<td>Fire fighting training ground</td>
<td>Klif, 2010</td>
</tr>
<tr>
<td>PFHxS</td>
<td>319 – 471</td>
<td>3/3</td>
<td>Norway</td>
<td>Fire fighting training ground</td>
<td>Klif, 2010</td>
</tr>
<tr>
<td>PFHxS</td>
<td>33 – 48</td>
<td>3/3</td>
<td>Norway</td>
<td>Fire fighting training ground</td>
<td>Klif, 2010</td>
</tr>
</tbody>
</table>

**Landfill effluent**

<table>
<thead>
<tr>
<th>Test substance</th>
<th>Concentration (ng/L)</th>
<th>Number of samples (&lt;LOD/ total)</th>
<th>Origin</th>
<th>Source as indicated by references</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFHxS</td>
<td>n.d–3.1</td>
<td>1/3</td>
<td>Denmark</td>
<td>Landfill</td>
<td>Bossi et al, 2008</td>
</tr>
<tr>
<td>PFOS</td>
<td>n.d–3.8</td>
<td>2/3</td>
<td>Denmark</td>
<td>Landfill</td>
<td>Bossi et al, 2008</td>
</tr>
<tr>
<td>PFOA</td>
<td>n.d–5.8</td>
<td>1/3</td>
<td>Denmark</td>
<td>Landfill</td>
<td>Bossi et al, 2008</td>
</tr>
<tr>
<td>PFBS</td>
<td>220 (&lt;0.39 – 1356)</td>
<td>20</td>
<td>Germany</td>
<td>Treated and untreated landfill leachates</td>
<td>Busch et al., 2010</td>
</tr>
<tr>
<td>PFHxS</td>
<td>22.2 (&lt;0.24 – 178)</td>
<td>20</td>
<td>Germany</td>
<td>Treated and untreated landfill leachates</td>
<td>Busch et al., 2010</td>
</tr>
<tr>
<td>PFBA</td>
<td>458 (&lt;3.36 – 2968)</td>
<td>20</td>
<td>Germany</td>
<td>Treated and untreated landfill leachates</td>
<td>Busch et al., 2010</td>
</tr>
<tr>
<td>PFHxA</td>
<td>234 (&lt;0.37 – 2509)</td>
<td>20</td>
<td>Germany</td>
<td>Treated and untreated landfill leachates</td>
<td>Busch et al., 2010</td>
</tr>
<tr>
<td>PFOS</td>
<td>30.9 (0.01 – 235)</td>
<td>20</td>
<td>Germany</td>
<td>Treated and untreated landfill leachates</td>
<td>Busch et al., 2010</td>
</tr>
<tr>
<td>PFOA</td>
<td>145 (&lt;0.40 – 926)</td>
<td>20</td>
<td>Germany</td>
<td>Treated and untreated landfill leachates</td>
<td>Busch et al., 2010</td>
</tr>
</tbody>
</table>

1 Median concentration (min. – maks. concentration)  
2 Sludge samples were taken from the same six WWTP as influent and effluent samples by Bossi et al. (2008) but details (total number of samples, number of samples > LOD) on sludge sampling are not provided.  
3 Mean concentration (min. – maks. concentration)  
4 AO – Atlantic Ocean
4.5.2 **Terrestrial environment**

Compared to the aquatic environment, much less data exist on the exposure of the terrestrial environment to PFAS. Table 4-12 presents the result on soil and groundwater concentrations from a Norwegian and Danish study, respectively.

The Danish screening study (Tsitonaki *et al.*, 2014) investigated PFOS, PFOA and 7 other PFAS (PFHpA, PFNA, PFBS, PFHxS, PFDS, PFOSA, PFHxA) in a total of 39 groundwater samples from point-contaminated sites, amongst others fire training facilities and chromium plating industrial sites. The results were compared to the German recommended maximum level in drinking water.

The project results were summarised as follows:

“PFAS were detected in 5 out of 8 fire drill sites. The level varies from a few to several thousand ng/l. The quality of the site investigations varied and investigations had a character of screening. 4 of the sites are considered well-studied (several wells in the source area). At two of these sites PFAS levels were above or close to 100 ng/l, while at the other 2 levels of more than 1000 ng/l were detected (sum of 9 PFAS compounds). In the remaining 4 sites, where the site investigations’ quality is considered less robust, no PFAS were detected, with the exception of one site, at which little over 100 ng/l was found. It is noted that the concentration level of PFAS in fire training grounds was generally above 100 ng/l, the drinking water limit value recommended for the sum of PFOS and PFOA in Germany. … A high concentration of PFAS compounds of approx. 1500 ng/l (of which PFOS + PFOA amounts to 1130 ng/l) in one sample taken was found at the investigated carpet industry. It … The screening investigations in this project did not find high levels of PFAS in landfills, chromium plating sites and paint manufacturers” (Tsitonaki *et al.*, 2014).

The highest concentrations found at the investigated sites were usually made up of PFOS or PFOA (up to 62,000 ng/L and 33,000 ng/L), but also PFBS, PFHxS, and PFHxA were measured in very high concentrations in some samples (up to 2,300, 14,000, and 63,000 ng/L) (Tsitonaki *et al.*, 2014). The average distribution of the compounds found at the fire training facilities is shown in Figure 4.1. The high concentration of PFHxA originated probably from the degradation of fluorotelomers. The authors emphasize that the findings are not in drinking water, but in groundwater under contaminated sites (Tsitonaki *et al.*, 2014).

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**FIGURE 4.1**

DISTRIBUTION OF PFAS FINDINGS IN GROUNDWATER SAMPLES FROM THE FIRE DRILL SITES (FROM TSITONAKI ET AL., 2014).

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55 There are no set threshold values for the content of PFAS in groundwater / drinking water in Denmark. Norway has set a provisional guideline of 100 ng/g dry matter for PFOS in soil. In Germany, there is a recommendation of a maximum of 100 ng/L for the sum of PFOA/PFOS in drinking water. In the United States there is a preliminary requirement of 200 ng/L for PFOS and 400 ng/L for PFOA drinking water. The least conservative values are found in the UK, where there is a recommendation of a maximum acceptable level of 300 ng/L for PFOS and 10,000 ng/L for PFOA in drinking water (Tsitonaki *et al.*, 2014).
The Norwegian Climate and Pollution Agency screened selected PFASs including the short-chain PFASs PFBS, PFHxS and 6:2 FTS in environmental samples (soil, sediment, water, and biota) in order to assess whether the investigated compounds give rise to environmental concern or not (KLIF, 2010). The three short-chain PFASs were detected in soil samples taken with increasing distance (0–200) from a fire fighting training ground at Flesland airport near Bergen (KLIF, 2010). The maximum concentrations were typically measured at 10 – 30 m distance from the training platform, and PFAS were usually at concentrations below 1 % of the maximum concentrations at a distance of 200 m from the platform.

### TABLE 4.12
PFAS CONCENTRATIONS IN THE TERRESTRIAL ENVIRONMENT AND GROUNDWATER. DATA ON THE LONG-CHAIN PFAS-SUBSTANCES PFOS AND PFOA ARE INCLUDED IN THE TABLE FOR COMPARISON (IN **BOLD**).

<table>
<thead>
<tr>
<th>Test substance</th>
<th>Concentration</th>
<th>Number of samples (&gt;LOD/total)</th>
<th>Origin</th>
<th>Source as indicated by the reference</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Soil (ng/g dw)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PFBS</td>
<td>n.d – 1.8</td>
<td>6/10</td>
<td>Norway</td>
<td>Fire fighting training ground at Flesland airport</td>
<td>Klif, 2010</td>
</tr>
<tr>
<td>PFHxS</td>
<td>0.12 – 21</td>
<td>10/10</td>
<td>Norway</td>
<td>Fire fighting training ground at Flesland airport</td>
<td>Klif, 2010</td>
</tr>
<tr>
<td>PFHxA</td>
<td>0.18 - 18.5</td>
<td>10/10</td>
<td>Norway</td>
<td>Fire fighting training ground at Flesland airport</td>
<td>Klif, 2010</td>
</tr>
<tr>
<td>6:2 FTS</td>
<td>0.84 – 2101</td>
<td>10/10</td>
<td>Norway</td>
<td>Fire fighting training ground at Flesland airport</td>
<td>Klif, 2010</td>
</tr>
<tr>
<td><strong>Groundwater (ng/L)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PFBS</td>
<td>n.d.-2,300</td>
<td>25/39</td>
<td>Denmark</td>
<td>Point source contamination</td>
<td>Tsitonaki et al., 2014</td>
</tr>
<tr>
<td>PFHxS</td>
<td>n.d.-14,000</td>
<td>26/39</td>
<td>Denmark</td>
<td>Point source contamination</td>
<td>Tsitonaki et al., 2014</td>
</tr>
<tr>
<td>PFHxA</td>
<td>n.d.-63,000</td>
<td>27/39</td>
<td>Denmark</td>
<td>Point source contamination</td>
<td>Tsitonaki et al., 2014</td>
</tr>
<tr>
<td>PFOS</td>
<td>n.d.-62,000</td>
<td>26/39</td>
<td>Denmark</td>
<td>Point source contamination</td>
<td>Tsitonaki et al., 2014</td>
</tr>
<tr>
<td>PFOA</td>
<td>n.d.-33,000</td>
<td>27/39</td>
<td>Denmark</td>
<td>Point source contamination</td>
<td>Tsitonaki et al., 2014</td>
</tr>
</tbody>
</table>

#### 4.5.3 Biota
The findings of four studies presenting concentrations of PFAS in biota have been summarised in Table 4.13 and ranged from below detection to 1.9 and 1.1 ng/g ww for PFBA and PFHxS, respectively. With regard to the short chain PFAS, the results did not allow for any conclusions on species differences.

Bossi et al. (2008) analysed fish from marine, lake and river sediments. For the marine samples, each sample consisted of a pool of 10 individual fish from 7 different sampling sites, for the freshwater samples, each sample consisted of a pool of 5 individual fish from 8 sampling sites. Moreover, mussels were collected at the marine sampling sites, but all concentrations were below detection limit. PFOS and PFOA were the predominant PFAS found in the fish livers, with concentrations being 1 – 2 orders of magnitude larger than concentrations of PFHxS. The same analytical results are used in the NOVANA screening publication by DMU (2007). The authors conclude, that the findings from sediments, mussels and fish reflect the high biomagnification potential of PFAS (DMU, 2007).

The Norwegian Climate and Pollution Agency screened selected PFASs including the short-chain PFASs PFBS, PFHxS, PFPeA, PFHxA and 6:2 FTS in sea mussels (*Mytilus edulis*), crabs (*Cancer pagurus*), and trout liver.
Concentrations of PFBS, PFPcA, PFHxS, and 6:2 FTS were below the detection and/or quantification limits in all samples. PFHxS could be quantified in crab and trout liver, with trout liver concentrations being considerably higher than in crab. For comparison, PFOS concentrations were about 1 order of magnitude larger than concentrations of PFHxS (KLIF, 2010).

The Swedish EPA reviewed a number of studies on PFAS exposure of humans and environment (SW EPA, 2012). Within the National Swedish Contaminant Monitoring Programme in Terrestrial Biota, pooled liver samples (n=10/sample) of starling from eight locations in mid- and southern Sweden were collected during 2006 and analysed for PFAS, hereunder the short chain PFAS PFBS, PFHxS, and PFHxA. The results showed that PFOS was the dominant PFAS. PFBS was under the detection limit in all samples, while PFHxA was measured in low concentrations (up to 0.25 ng/g ww). Information on PFHxS is missing in the review (SW EPA, 2012).

Tissue levels of PFAS in Swedish peregrine falcon eggs sampled in 2006 from a breeding area in south-western Sweden were analysed for the sulfonates PFBS, PFHxS, PFOS and PFDS, and 10 perfluorinated carboxylates with PFHxA being the only short-chain PFCA. PFOS was the dominant PFAS. Based on the slope of temporal increase/decrease from 2000–2007, most concentrations of most PFCAs as well as PFHxS are decreasing. PFBS and PFHxA could not be detected in any of the samples from 2006 (SW EPA, 2012).

Hepatic concentrations of 10 PFAS, including PFHxS, in Swedish otter were analysed. The concentration of PFOS exceeded the concentration PFHxS by 2-3 orders of magnitude. The same applies for liver samples of grey seal (SW EPA, 2012).

<table>
<thead>
<tr>
<th>Test substance</th>
<th>Species, organ</th>
<th>Concentration (ng/g ww)</th>
<th>No. of samples (&gt;LOD/ total)</th>
<th>Origin</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marine fish</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PFBA</td>
<td>Herring, liver</td>
<td>0.23 - &lt; 1.9</td>
<td>1/10&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Baltic Sea</td>
<td>IVL, 2009</td>
</tr>
<tr>
<td>PFBA</td>
<td>Perch, liver</td>
<td>&lt; 1.5</td>
<td>0/5&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Baltic Sea</td>
<td>IVL, 2009</td>
</tr>
<tr>
<td>PFBA</td>
<td>Flounder, liver</td>
<td>&lt; 0.4 – 1.0</td>
<td>1/7&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Baltic Sea</td>
<td>IVL, 2009</td>
</tr>
<tr>
<td>PFHxS</td>
<td>Herring, liver</td>
<td>&lt; 0.1 – 0.57</td>
<td>7/10&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Baltic Sea</td>
<td>IVL, 2009</td>
</tr>
<tr>
<td>PFHxS</td>
<td>Perch, liver</td>
<td>&lt; 0.07-0.20</td>
<td>2/5&lt;sup&gt;1&lt;/sup&gt;</td>
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<td>IVL, 2009</td>
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<td>Flounder, liver</td>
<td>0.10 – 1.1</td>
<td>7/7&lt;sup&gt;1&lt;/sup&gt;</td>
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<td>IVL, 2009</td>
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<td>Plaice, liver</td>
<td>&lt;0.8</td>
<td>1&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Denmark, coastal waters</td>
<td>Bossi et al., 2008</td>
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<tr>
<td>PFOS</td>
<td>Plaice, liver</td>
<td>156</td>
<td>1</td>
<td>Denmark, coastal waters</td>
<td>Bossi et al., 2008</td>
</tr>
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<td>&lt;0.8</td>
<td>2</td>
<td>Denmark, coastal waters</td>
<td>Bossi et al., 2008</td>
</tr>
<tr>
<td>PFOS</td>
<td>Flounder, liver</td>
<td>9.5-25.4</td>
<td>2</td>
<td>Denmark, coastal waters</td>
<td>Bossi et al., 2008</td>
</tr>
<tr>
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<td>Eel, liver</td>
<td>&lt;0.8 – 1.6</td>
<td>4</td>
<td>Denmark, coastal waters</td>
<td>Bossi et al., 2008</td>
</tr>
<tr>
<td>PFOS</td>
<td>Eel, liver</td>
<td>13.1 – 54.3</td>
<td>4</td>
<td>Denmark, coastal waters</td>
<td>Bossi et al., 2008</td>
</tr>
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<td>Freshwater fish</td>
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</tr>
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<td>PFHxS</td>
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<td>&lt;0.8</td>
<td>7</td>
<td>Denmark, river or lake</td>
<td>Bossi et al., 2008</td>
</tr>
<tr>
<td>PFOS</td>
<td>Eel, liver</td>
<td>13.7 – 70.1</td>
<td>7</td>
<td>Denmark, river or lake</td>
<td>Bossi et al., 2008</td>
</tr>
<tr>
<td>PFHxS</td>
<td>Trout, liver</td>
<td>123 – 268</td>
<td>4</td>
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<td>KLIF, 2010</td>
</tr>
<tr>
<td>Test substance</td>
<td>Species, organ</td>
<td>Concentration (ng/g ww)</td>
<td>No. of samples (&gt;LOD/ total)</td>
<td>Origin</td>
<td>Reference</td>
</tr>
<tr>
<td>----------------</td>
<td>---------------</td>
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<td>-----------------------------</td>
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<td>-----------</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>close to fire fighting training ground near Bergen</td>
<td></td>
</tr>
<tr>
<td>PFOS</td>
<td>Trout, liver</td>
<td>2082 - 2532</td>
<td>4</td>
<td>Langavatn Lake in Norway close to fire fighting training ground near Bergen</td>
<td>KLIF, 2010</td>
</tr>
<tr>
<td>Crustaceans</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>PFHxS</td>
<td>Crab</td>
<td>&lt;0.1 – 0.46</td>
<td>4</td>
<td>Langavatn Lake in Norway close to fire fighting training ground near Bergen</td>
<td>KLIF, 2010</td>
</tr>
<tr>
<td>PFOS</td>
<td>Crab</td>
<td>0.8 – 4.9</td>
<td>4</td>
<td>Langavatn Lake in Norway close to fire fighting training ground near Bergen</td>
<td>KLIF, 2010</td>
</tr>
<tr>
<td>Birds</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PFHxA</td>
<td>Starling liver</td>
<td>&lt;0.15 – 0.25</td>
<td>8</td>
<td>Mid and Southern Sweden</td>
<td>SW EPA, 2012</td>
</tr>
<tr>
<td>PFOS</td>
<td>Starling liver</td>
<td>1.89-6.73</td>
<td>8</td>
<td>Mid and Southern Sweden</td>
<td>SW EPA, 2012</td>
</tr>
<tr>
<td>Mammals</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>PFHxS</td>
<td>Otter, liver</td>
<td>6 (0-68)</td>
<td>93</td>
<td>Sweden</td>
<td>SW EPA, 2012</td>
</tr>
<tr>
<td>PFOS</td>
<td>Otter, liver</td>
<td>1094 (21-8301)</td>
<td>93</td>
<td>Sweden</td>
<td>SW EPA, 2012</td>
</tr>
<tr>
<td>PFBS</td>
<td>Grey seal, liver</td>
<td>&lt; 0.006</td>
<td>20</td>
<td>Sweden</td>
<td>SW EPA, 2012</td>
</tr>
<tr>
<td>PFHxS</td>
<td>Grey seal, liver</td>
<td>0.7 (0.3-1.6)</td>
<td>20</td>
<td>Sweden</td>
<td>SW EPA, 2012</td>
</tr>
<tr>
<td>PFOS</td>
<td>Grey seal, liver</td>
<td>171 (89.6-490)</td>
<td>20</td>
<td>Sweden</td>
<td>SW EPA, 2012</td>
</tr>
</tbody>
</table>

1 Number of samples above quantification limit/ total number of samples
2 Number of pooled samples, each consisting of 10 (marine) or 5 (freshwater) individual fish.
3 Number of pooled samples, each consisting of 10 individual birds.

4.5.4 **Atmospheric environment**

No monitoring data identified. However, some PFAS (e.g. FTOHs) are relatively volatile and are, primarily based on theoretical considerations and controlled experiments, believed to undergo long-range atmospheric transport and transformation contributing to the exposure of the environment to PFAS even in remote regions (e.g. the Arctic).
5. Summary and conclusions

5.1 Human health effects and exposure

5.1.1 Human health effects

It is known from animal studies that the studied short chain polyfluoroalkylated substances (PFAS) are almost completely absorbed orally and by inhalation but that skin absorption may be negligible. Both short- and long-chain perfluoroalkyl acids (PFAAs) are considered being metabolically inert. The strong C-F bonds exclude any normal degradation pathway. Any functional derivative (precursor) will through several steps ultimately be transformed to the acids. That is also the case for fluorotelomers and derivatives hereof, which are biotransformed into PFCAs of different chain length through several metabolic steps, including aldehydes and saturated and unsaturated carboxylic acids. These metabolites are more toxic than the parent compounds, and one of these metabolites: perfluorohexyl ethanoic acid (FHEA) was measured in various tissues from deceased people.

The mean blood elimination half-lives for PFAAs depend on the chemical substance and animal species and its sex. The blood elimination half-lives of PFAAs decrease with shorter chain length. An exemption is PFHxS (C6), which has a longer half-life in humans than PFOA and PFOS (C8). Generally, the blood half-lives of PFAAs are longer for sulfonates than for carboxylates, half-lives increase with chain length for carboxylates, and are shorter for branched isomers, and in animals they are often shorter in females due to the sex hormone dependent difference in renal clearance. Further, the serum half-lives of PFAAs are dose-dependent with longer half-lives for the lower concentrations relevant for humans. The general blood elimination half-lives of PFAAs in exposed rodents were hours or few days, in monkeys a little longer and in humans much longer and often years.

The primary route of elimination of PFAA from the body is with the urine via the kidneys. Presence of membrane transport proteins and reabsorption of PFAA in the kidneys are the fundamental mechanism responsible for renal elimination of these substances, which also influences their plasma half-lives. A main reason for the long plasma half-life of PFAAs in humans compared to experimental animals is, that the excretion of these substances in humans is insignificant, because humans have the highest percentage of renal tubular reabsorption (>99%). This difference between humans and experimental animals makes it more uncertain to use animal data in human risk assessment of PFAAs. Elimination is different for fluorotelomers, which are mainly eliminated from the body via faeces.

Longer chain length PFAAs tend to have longer renal elimination half-lives in rats. However, PFBA with a C₄-perfluorocarbon chain is different and has a slower renal clearance than PFHxA (C₅), because PFBA do not seem to be the substrates of the common transport protein Oatp1a1. In contradiction, PFBS with a C₄-perfluorocarbon chain seems not to be very bioaccumulative and has a much shorter half-life in the organism than PFHxS (C₅).

PFAs have contrary to most other persistent organic pollutants (POPs) a low affinity to lipids but bind to proteins, and in the blood PFAS are bound to serum proteins, mainly albumin. PFASs are mainly associated to cell membrane surfaces and mainly distributed in plasma and in well-perfused tissues such as the lung, liver, kidney and spleen but also in the bone, testes and brain. That was illustrated in a recent study from Spain where analysis of autopsy tissues revealed both individual differences between donors and in the tissue distribution of the PFAS. The relatively high concentrations of short-chain PFAS in human tissues, especially PFBA, indicate that these chemicals behave differently in humans than in laboratory animals.

In animal experiments the acute toxicity of short-chain PFAS is low. After repeated exposure, large doses of short-chain PFAS may damage the liver and kidneys. In rats PFHxS is the most toxic short-chain PFAS, followed by 6:2-FTOH, PFBA, PFHxA and PFBS. In general, PFAS are more toxic in males than females having a higher elimina-
tion rate. The liver toxicity in rats is mediated through peroxisome proliferation, and its potency generally increases with the fluorocarbon chain length until C9. However, PFHxS is much more liver toxic than PFBS and PFOS.

The few existing data on fluorotelomers shows different toxicokinetics compared to PFAAs, and their intermediary metabolites (aldehydes, unsaturated acids) do have more severe toxicities, and the metabolites of the shorter 6:2 FTOH were more toxic than 8:2 FTOH. Some telomer acrylates are skin and eye irritating.

In Table 5.1 is shown a summary of the estimated no-adverse-effect-levels (NOAELs) for some short-chain PFAS studied in rats. The NOAEL value for 6:2-FTOH is 10 times lower than for it ultimate metabolite, PFHxA.

<table>
<thead>
<tr>
<th>NOAEL mg/kg bw/d</th>
<th>PFBS</th>
<th>PFHxS</th>
<th>PFBA</th>
<th>PFHxA</th>
<th>6:2 FTOH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male rat</td>
<td>60</td>
<td>6</td>
<td>50</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Female rat</td>
<td>600</td>
<td>3</td>
<td>30</td>
<td>200</td>
<td>25</td>
</tr>
</tbody>
</table>

In various animal and in vitro studies PFAS have shown effects on thyroidea hormones and decreased the levels. The mechanism may be a competitive binding to the thyroid hormone plasma transport protein transthyretin (TTR) that will alter/decrease the free thyroxine (T4) in blood. Of the short-chain PFAS only PFHxS and 6:2 FTOH seem to be potent endocrine disruptors.

In human population studies it is difficult to assess effects of the single PFAS, since most populations are exposed to a mixture of PFAS, in which PFOA and/or PFOS dominate, and where levels of most short-chain PFAS often are below the quantitation limit. However, there are studies showing associations between PFHxS and effects on lipid metabolism, fertility, thyroidea hormones, asthma, and children’s behaviour.

5.1.2 Exposure of humans
In human monitoring studies background levels of most short-chain PFASs are below the quantitation limit. Only PFHxS is regularly determined with typical medians of 0.5-1.5 ng/mL or about ten times lower than PFOS. In contradiction to PFOS, levels of PFHxS and PFBS seem to increase in recent years.

Exposure near industrial sources and occupational exposures may result in very much higher levels. In blood samples from professional ski waxes relatively high levels of PFOA, PFHxA, PFBA and some meatbolites were measured.

In some studies from USA and Germany low concentrations of some 4:2 and 6:2 fluorotelomer-based phosphate surfactants used in food packaging have been measured in human blood.

5.2 Environmental fate and effects
5.2.1 Environmental fate
Perfluorinated carboxylic and sulfonic acids (PFAAs), including the short-chained, are not transformed/degraded by abiotic reaction mechanisms such hydrolysis or photolysis in water to any appreciable extent. However, some neutral PFASs, e.g. FTOHs, can undergo initial abiotic transformation in the atmosphere by OH-initiated oxidation pathways but only to perfluoroalkylated substances.

Likewise, perfluorinated acids are not biodegradable neither under aerobic nor under aerobic environmental conditions in water or soil while PFAS with other functional groups (e.g. telomere alcohols and acrylates) may undergo primary degradation to the corresponding acid/salt, however leaving the highly persistent perfluorinated backbone intact.
PFCAs and PFSAs can bioaccumulate in living organisms in the environment with the long-chained substances being more bioaccumulative than the short-chained. However, because these substances are both hydrophobic and lipophobic they do not follow the typical pattern of partitioning into fatty tissues followed by accumulation but tend to bind to proteins and therefore are present rather in highly perfused tissues than in lipid tissue. Precursors such as fluorotelomers may be partially responsible for the observed bioaccumulation of the acids.

Japanese studies have demonstrated that the perfluorocarbon length and functional groups are the dominating parameters influencing the partitioning of PFASs. Thus, the short-chain PFCAs (C <7) were exclusively found in the dissolved phase while long-chain PFCAs and PFSAs (C ≥7) appeared to bind more strongly to particles. As a consequence, the short chain PFAs are considered to have a higher potential for aqueous long-range transport. It has been shown, e.g. in Italian studies, that these substances are only poorly removed from the water phase during wastewater treatment and, hence, they are to a large extent released to surface waters with the treated WWTP effluents.

Ionic PFASs such as PFCAs and PFSAs are considered to undergo long-range transport mainly via the aquatic environment, not least via the oceanic currents while atmospheric long-transport have been postulated to involve mainly the neutral PFAs including precursors such as FTOHs. These have properties ensuring sufficient residence time in the atmosphere for long-range transport while at the same time being sufficiently reactive to be transformed by various oxidation reactions into carboxylic acids or aldehydes etc.

5.2.2 Environmental effects
Several studies note that the toxicity of short chain PFAS as well as their long-term effects and mixture toxicity with other PFAS is not well described and need further investigation (e.g. Ding et al., 2012; Liu et al., 2009). Generally, toxicity of PFAS increases with increasing fluorocarbon chain length. Exceptions from this, however, can been observed, e.g. in the case of growth inhibition of the protozoa *Tetrahymena thermophila*, which was more susceptible to short chain FTOH. Moreover, most studies show that FTCA are typically more toxic to aquatic organisms than the corresponding PFCA, however, the mechanism behind this observation is not understood. A few studies do also suggest that the saturated FTCA are more toxic than the unsaturated FTCA. PFAS with sulfonic groups have a larger potential to affect zebrafish larvae than the carboxylic acids.

In the acute aquatic toxicity studies, duckweed (*Lemna gibba*) showed to be more sensitive to the short chain PFAS than *Daphnia magna*, the midge *Chironomus tentans*, the green alga *Pseudokirchneriella subcapitata*, and fish (*Oncorhynchus mykiss* or *Pimephales promelas*) with a growth related EC50 of 1.29 mg 6:2 FTCA/L. EC50 values for the other aquatic organisms ranged from 22.5 mg/L (green algae, 5:3 acid) to 2200 mg/L (zebra fish, PFBA).

Endocrine disrupting effects of FTOH have been demonstrated in zebra fish (*Danio regio*) at very low concentrations (down to 0.03 mg/L) and 6:2 FTOH was shown to be more a potent xenoestrogen than the longer chain 8:2 FTOH.

In summary, chain length is a determining toxicity factor, in general rendering longer chain compounds more toxic than short chain compounds. The presence of functional groups further determines the toxicity mechanisms and toxic potential of short chain PFAS, which can lead to exceptions from the general picture.

5.2.3 Environmental occurrence and exposure
Most environmental exposure studies are concerned with the aquatic environment, and data exist for surface water, drinking water, ground water, marine water, as well as WWTP influents, effluents, and sludge in Denmark and other European countries. PFAS are ubiquitously found in the aqueous environment and freshwater concentration are usually in the ng – mg/L range depending on contamination source, while marine concentration are considerably lower in the pg/L range. PFOS and PFOA are usually found in the highest concentrations in the aquatic environment (up to 18.1 and 24.4, respectively, in Danish WWTP effluents), but the short-chain compounds PFBS, PFHxS, PFBA, PFPeA, and PFHxA were also detected in many aquatic samples, often in concentrations ranging from levels similar to those of PFOS or PFOA to about an order of magnitude lower. The presence of
the shorter chain compounds in the environment may be explained by substitution of long chained compounds with shorter chain alternatives, as well as by degradation of fluorotelomers.

WWTP mass flow studies showed similar or higher PFCAs and PFSA concentrations in the effluent than in the influent, indicating that conventional WWTPs do not seem to be effective in removing PFAS from the water phase. In particular the short-chained PFAS appear to remain in the water phase while sorption to sewage sludge has been shown to be a process for removal from the water phase for PFHxS as well as for long-chain PFAS.

High concentrations of PFAS, including some short-chain PFAS, found in groundwater samples in Denmark and Norway usually originated from PFAS contaminated soil, documenting that PFAS contaminated soil has the potential to contaminate groundwater.

Industrial waste water effluents from Denmark showed highly varying concentrations of PFAS (e.g. PFHxS 0.2-18.8 ng/L and PFOS <1,5-1115 ng/L), but also municipal WWTP effluents were estimated to have the potential of contributing significantly to environmental PFAS exposure in Denmark (DMU, 2007).

In the Atlantic Ocean, the concentrations of PFAS are considerably higher in the North Atlantic Ocean compared to the Middle and South Atlantic Ocean. The ΣPFAS concentrations decreased from 2007 to 2010 in the North and Middle Atlantic Ocean as a result mainly of decreasing concentrations of PFOA/PFOS while short-chain substances such as PFBS, PFHxA and PFHxS did not show such trend. PFAS have also been detected in remote areas without obvious sources, such as the Greenland Sea, where PFBS, PFHxA and PFHxS were among the 5 most frequently detected compounds.

5.3 Short-chain PFAS as alternatives to PFOS/PFOA

5.3.1 Human health aspects

Short-chain PFAS have different properties and have to be evaluated individually. In most instances, however, longer chain PFAS such as PFOS (C8) are the most toxic PFAS in animals but some studies show that PFHxS comes close with regard to liver toxicity. The present knowledge indicates that the other short chain PFAS generally are less toxic in animals. However, there are individual differences e.g. both PFBA and 6:2 FTOH were more toxic than PFBS and PFHxA. In one assay FTOHs seem to be more potent estrogens than the PFAAs. In another assay FTOH and PFBA had no effect on thyroid hormones but PFBS and PFHxA had. However, the potencies were much less than for PFOS/PFOA.

The toxicokinetics and toxicity in humans for short-chain PFAS are mainly investigated for PFHxS, and that substance has rather similar properties as PFOS. Thus PFHxS may not be a good alternative. The other short-chain PFAS seem to be less toxic than PFOS/PFOA but the available data is insufficient for a final evaluation. The high presence of short-chain PFAS, especially PFBA, in human tissue including brain from deceased people is worrying, and it shows that the short-chain PFAS and a fluorotelomer metabolite may be much more bioaccumulative in humans than the studies with experimental animals conclude.

5.3.2 Environmental aspects

Short-chain PFAS are similar to their long-chain analogues in the sense that ultimately their transformation in the environment will lead to the corresponding acids with persistent perfluorinated "tails". However, the shorter chain length acids tend to be more soluble in water and have a lower potential for sorption to particles than the long-chain analogues. Thereby, they have a higher potential for aqueous long-transport. On the other hand, the bioaccumulation potential of short-chain PFAAs is lower than that of long-chain PFAAs with PFSAs being more bioaccumulative than the corresponding PFCAs.

With regard to environmental effects, PFOS/PFOA and other long-chain PFAS are generally more toxic than the short-chain analogues. However, the toxicity of short-chain PFAS is not thoroughly studied or well described and there are examples of exceptions to the general picture. There are indications that short-chain FTOHs may have higher endocrine disrupting potential than the long-chain FTOHs.
5.4 Data gaps

5.4.1 Human health effects (including exposure)
As mentioned above there is a general lack of toxicological information regarding the short-chain PFAS other than PFHxS. Especially for 4:2 FTOH and PFPeS/PFPeA there is virtually no available health-related information. Further, the Spanish study showing worrying high levels of short-chain PFAS in all tissues from deceased persons has to be confirmed by similar studies by other scientists and with samples from other European countries. The Nordic countries could initiate such studies. The biomonitoring studies already executed have not identified any high levels of short-chain PFAS in the blood from the general population, thus the high levels in organs determined in the Spanish study have to be confirmed.

5.4.2 Environmental aspects (including exposure)
Overall, environmental fate and effects data on PFAS are primarily available for PFOS/PFOA and some of the longer chain PFAS while the properties of the short-chain PFAS to a large extent are estimated based on read-across. Thus, there is a general lack of experimental data specifically for short-chain PFAS. Also, the environmentally relevant physico-chemical data identified appear somewhat confusing (e.g. do they refer to the acid or a salt) and not fully reliable. A consistent set of data produced by the same standard methods would be valuable.

International environmental exposure data are available for mainly short chain carboxylic (PFCA) and sulfonic acids (PFSA), but not for other short-chain PFAS. Commonly, measurements have been taken in environmental compartments, where knowledge about a specific contamination source was present. Therefore, contamination levels caused by specific point sources are relatively well described with respect to PFCA and PFSA, while knowledge on more diffuse contamination is more sparse.

With respect to the Danish situation, data on PFOS, PFOA and PFHxS from the aquatic compartment (WWTP influents, effluents and sludge; landfill effluents) and marine biota are available but data on shorter chain PFAS are not available. Further, Danish surface water data are virtually absent.
### Abbreviations and acronyms

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>4:2 diPAP</td>
<td>4:2 Fluorotelomer phosphate diesters</td>
</tr>
<tr>
<td>4:2 FTOH</td>
<td>4:2 Fluorotelomer alcohol</td>
</tr>
<tr>
<td>6:2 diPAP</td>
<td>6:2 Fluorotelomer phosphate diesters</td>
</tr>
<tr>
<td>6:2 FTAC</td>
<td>6:2 Fluorotelomer acrylate</td>
</tr>
<tr>
<td>6:2 FTMAC</td>
<td>6:2 Fluorotelomer methacrylate</td>
</tr>
<tr>
<td>6:2 FTO</td>
<td>6:2 Fluorotelomer olefin</td>
</tr>
<tr>
<td>6:2 FTS</td>
<td>6:2 Fluorotelomer sulfonate</td>
</tr>
<tr>
<td>6:2 FTSA</td>
<td>6:2 Fluorotelomer sulfonic acid ()</td>
</tr>
<tr>
<td>6:2 monoPAP</td>
<td>6:2 Fluorotelomer phosphate monoester</td>
</tr>
<tr>
<td>8:2 diPAP</td>
<td>8:2 Fluorotelomer phosphate diesters</td>
</tr>
<tr>
<td>8:2 FTAL</td>
<td>8:2 Fluorotelomer aldehyde</td>
</tr>
<tr>
<td>8:2 FTCA</td>
<td>8:2 Fluorotelomer carboxylic acid</td>
</tr>
<tr>
<td>8:2 FTI</td>
<td>8:2 Fluorotelomer iodide</td>
</tr>
<tr>
<td>8:2 FTOH</td>
<td>8:2 Fluorotelomer alcohol</td>
</tr>
<tr>
<td>8:2 FTUOH</td>
<td>8:2 Unsaturated fluorotelomer alcohol</td>
</tr>
<tr>
<td>BCF</td>
<td>Bioconcentration factor</td>
</tr>
<tr>
<td>BMF</td>
<td>Biomagnification factor</td>
</tr>
<tr>
<td>C4-PFSAs</td>
<td>Perfluoroalkyl sulfonic acids with a chain length of four</td>
</tr>
<tr>
<td>C6/C6-PFPIA</td>
<td>Bis(perfluorohexyl) phosphinic acid</td>
</tr>
<tr>
<td>C6-PFSAs</td>
<td>Perfluoroalkyl sulfonic acids with a chain length of six</td>
</tr>
<tr>
<td>C8-PFPA</td>
<td>Perfluoroctyl phosphonic acid</td>
</tr>
<tr>
<td>CLP</td>
<td>Classification, Labelling and Packaging (Regulation)</td>
</tr>
<tr>
<td>C&amp;L</td>
<td>Classification and Labelling</td>
</tr>
<tr>
<td>CMR</td>
<td>Carcinogenic, mutagenic or toxic to reproduction</td>
</tr>
<tr>
<td>diPAPS</td>
<td>Polyfluoroalkyl-diester phosphates</td>
</tr>
<tr>
<td>d.l.</td>
<td>Detection limite</td>
</tr>
<tr>
<td>dw</td>
<td>dry weight</td>
</tr>
<tr>
<td>ECₙ</td>
<td>Effect concentration where n % of the species tested show the effect</td>
</tr>
<tr>
<td>ErC</td>
<td>Effect concentration based on a rate (r), typically a growth rate</td>
</tr>
<tr>
<td>ECB</td>
<td>Effect concentration based on (algae) biomass</td>
</tr>
<tr>
<td>EFSA</td>
<td>European Food Safety Authority</td>
</tr>
<tr>
<td>EPA</td>
<td>Environmental Protection Agency</td>
</tr>
<tr>
<td>EtFOSAA</td>
<td>N-Ethyl perfluoroctane sulfonamidoacetic acid</td>
</tr>
<tr>
<td>FOSA</td>
<td>Perfluoroctane sulfonamide</td>
</tr>
<tr>
<td>FTCA</td>
<td>Fluorotelomer carboxylates</td>
</tr>
<tr>
<td>PTO</td>
<td>Fluorotelomer olefin</td>
</tr>
<tr>
<td>FTOH</td>
<td>Fluorotelomer alcohols</td>
</tr>
<tr>
<td>FTS</td>
<td>Fluorotelomer sulfonates</td>
</tr>
<tr>
<td>FTUCA</td>
<td>Fluorotelomer unsaturated carboxylic acids</td>
</tr>
<tr>
<td>KPFO</td>
<td>PFOA potassium salt</td>
</tr>
<tr>
<td>Kd</td>
<td>Soil/water distribution coefficient</td>
</tr>
<tr>
<td>LC</td>
<td>Lethal effect concentration</td>
</tr>
<tr>
<td>LOAEL</td>
<td>Lowest observable adverse effect level</td>
</tr>
<tr>
<td>Term</td>
<td>Definition</td>
</tr>
<tr>
<td>--------------------</td>
<td>---------------------------------------------------------------------------</td>
</tr>
<tr>
<td>LOUS</td>
<td>List of Undesirable Substances</td>
</tr>
<tr>
<td>MACeco</td>
<td>Maximum Acceptable Concentration for ecosystems</td>
</tr>
<tr>
<td>monoPAP</td>
<td>polyfluoroalkyl-mono phosphates</td>
</tr>
<tr>
<td>NHANES</td>
<td>National Health and Nutrition Examination Survey (in the USA)</td>
</tr>
<tr>
<td>NOAEL</td>
<td>No observable adverse effect level</td>
</tr>
<tr>
<td>NOEC</td>
<td>No observable effect concentration</td>
</tr>
<tr>
<td>NOVANA</td>
<td>Danish national surveillance programme for the aquatic environment</td>
</tr>
<tr>
<td>MCF-7</td>
<td>Michigan Cancer Foundation – 7 breast cancer cell line</td>
</tr>
<tr>
<td>n:2 FTIss</td>
<td>n:2 Fluorotelomer iodides</td>
</tr>
<tr>
<td>n:2 FTOHs</td>
<td>n:2 Fluorotelomer alcohols</td>
</tr>
<tr>
<td>OECD</td>
<td>Organisation for Economic Co-operation and Development</td>
</tr>
<tr>
<td>OSPAR</td>
<td>Convention for the Protection of the Marine Environment of the North-East Atlantic</td>
</tr>
<tr>
<td>PAFs</td>
<td>Perfluoroalkanoyl fluorides</td>
</tr>
<tr>
<td>PAPs</td>
<td>Polyfluoroalkyl phosphoric acid esters</td>
</tr>
<tr>
<td>PASFs</td>
<td>Perfluoroalkane sulfonyl fluorides</td>
</tr>
<tr>
<td>PBSF</td>
<td>Perfluorobutane sulfonyl fluoride</td>
</tr>
<tr>
<td>PBT</td>
<td>Persistent, bioaccumulative and toxic (in the environment)</td>
</tr>
<tr>
<td>PF AA</td>
<td>Perfluoroalkyl acids</td>
</tr>
<tr>
<td>PFAs</td>
<td>Perfluoroalkyl aldehydes</td>
</tr>
<tr>
<td>PFAS</td>
<td>Entire group of perfluoroalkyl and polyfluoroalkyl substances</td>
</tr>
<tr>
<td>PFBA</td>
<td>Perfluorobutanoic acid</td>
</tr>
<tr>
<td>PFBS</td>
<td>Perfluorobutane sulfonic acid</td>
</tr>
<tr>
<td>PFCA</td>
<td>Perfluoroalkyl carboxylic acids</td>
</tr>
<tr>
<td>PFCA</td>
<td>Perfluoroalkyl carboxylates</td>
</tr>
<tr>
<td>PFCs</td>
<td>Collective designation of perfluoroalkyl substances, polyfluoroalkyl substances and side-chain fluorinated polymers</td>
</tr>
<tr>
<td>PFDA</td>
<td>Perfluorodecanoic acid</td>
</tr>
<tr>
<td>PFDODA</td>
<td>Perfluorododecanoic acid</td>
</tr>
<tr>
<td>PFDS</td>
<td>Perfluorodecanesulfonic acid</td>
</tr>
<tr>
<td>PFHpA</td>
<td>Perfluoroheptanoic acid</td>
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<td>PFHpS</td>
<td>Perfluoroheptane sulfonic acid</td>
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<td>PFHXA</td>
<td>Perfluorohexanoic acid</td>
</tr>
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<td>PFHxI</td>
<td>Perfluorohexyl iodide</td>
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<td>PFHxS</td>
<td>Perfluorohexane sulfonic acid</td>
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<td>Perfluorononanoic acid</td>
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<td>PFOA</td>
<td>Perfluoroctanoic acid</td>
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<td>PFODA</td>
<td>Perfluorooctadecanoic acid</td>
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<td>PFOS</td>
<td>Perfluorooctane sulfonate</td>
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<td>PFOS</td>
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<td>Perfluorooctane sulphonamide</td>
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<tr>
<td>PFOSF</td>
<td>Perfluorooctane sulfonyl fluoride</td>
</tr>
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<td>PFPeA</td>
<td>Perfluoropentanoic acid</td>
</tr>
<tr>
<td>PFPeS</td>
<td>Perfluoropentane sulfonate</td>
</tr>
<tr>
<td>PFPeS</td>
<td>Perfluoropentane sulfonic acid</td>
</tr>
<tr>
<td>PPFA</td>
<td>Perfluoroalkyl phosphoric acids</td>
</tr>
<tr>
<td>PF PLA</td>
<td>Perfluoroalkyl phosphinic acids</td>
</tr>
<tr>
<td>PF SAs</td>
<td>Perfluoroalkyl sulfonic acids</td>
</tr>
<tr>
<td>PF SA</td>
<td>Perfluoroalkane sulfonates</td>
</tr>
<tr>
<td>PFTeDA</td>
<td>Perfluorotetradecanoic acid</td>
</tr>
<tr>
<td>PFUnDA</td>
<td>Perfluoroundecanoic acid = PFUnA</td>
</tr>
<tr>
<td>POF</td>
<td>Perfluorooctanoyl fluoride</td>
</tr>
<tr>
<td>POP</td>
<td>Persistent organic pollutants</td>
</tr>
<tr>
<td>POSF</td>
<td>Perfluorooctane sulfonyl fluoride</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
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</tr>
<tr>
<td>PPARα</td>
<td>Peroxisome proliferator-activated receptor-α</td>
</tr>
<tr>
<td>PTFE</td>
<td>Polytetrafluoroethylene</td>
</tr>
<tr>
<td>ROS</td>
<td>Reactive oxygen species</td>
</tr>
<tr>
<td>SVHC</td>
<td>Substances of Very High Concern</td>
</tr>
<tr>
<td>SW EPA</td>
<td>Swedish Environmental Protection Agency</td>
</tr>
<tr>
<td>TDI</td>
<td>Tolerable daily intake</td>
</tr>
<tr>
<td>UNEP</td>
<td>The United Nations Environment Programme</td>
</tr>
<tr>
<td>UNIDO</td>
<td>The United Nations Industrial Development Organization</td>
</tr>
<tr>
<td>USEPA</td>
<td>United States Environmental Protection Agency</td>
</tr>
<tr>
<td>vPvB</td>
<td>Very persistent and very bioaccumulative</td>
</tr>
<tr>
<td>ww</td>
<td>Wet weight</td>
</tr>
<tr>
<td>WWTP</td>
<td>Waste water treatment plant</td>
</tr>
</tbody>
</table>
Human health references


Bull S, Burnett K, Vassaux K, Ashdown L, Brown T, Rushton L. Extensive literature search and provision of summaries of studies related to the oral toxicity of perfluoroalkylated substances (PFASs), their precursors and potential replacements in experimental animals and humans Area 1: Data on toxicokinetics (absorption, distribution,
metabolism, excretion) in in vitro studies, experimental animals and humans Area 2: Data on toxicity in experimental animals Area 3: Data on observations in human. EFSA supporting publication 2014: EN-572.


Lee I, Viberg H. A single neonatal exposure to perfluorohexane sulfonate (PFHxS) affects the levels of important neuroproteins in the developing mouse brain. NeuroToxicology 37 (2013) 190–196.


Poulsen PB, Jensen AA, Wallström E. More environmentally friendly alternatives to PFOS-compounds and PFOA. DEPA Environmental Project No. 1013, 2005.


Sundstrom, M; Ehresman, DJ; Biglert, A; Butenhoff, JL; Olsen, GW; Chang, SC; Bergman, A. A temporal trend study (1972-2008) of perfluorooctanesulfonate, perfluorohexanesulfonate, and perfluorooctanoate in pooled human milk samples from Stockholm, Sweden. Environment International 2011; 37: 178-183.


Environmental fate and effects references


Ding and Peijnenburg (2013). Physicochemical Properties and Aquatic Toxicity of Poly- and Perfluorinated


Appendix 1:  List of substances considered to be "short-chain PFAS"

**PFBS and salts and halogenides:**

CAS 375-73-5  Perfluorobutane sulfonic acid, PFBS, Novec™

![Perfluorobutane sulfonic acid](image1)

*CAS 29420-49-3  Potassium perfluorobutane sulfonate, PFBS-K
CAS 68259-10-9  Ammonium perfluorobutane sulfonate, used in photoresists
#CAS 220689-12-3  Tetrabutylphosphonium perfluorobutane sulfonate, Anti-Stat FC-1, wetting agent

#CAS 25628-08-4  Tetraethylammonium perfluorobutane sulfonate

![Tetraethylammonium perfluorobutane sulfonate](image2)

*CAS 70225-18-2  Bis(2-hydroxyethyl) ammonium perfluorobutane sulfonate
CAS 375-72-4  Perfluorobutane sulfonyl fluoride

![Perfluorobutane sulfonyl fluoride](image3)

CAS 90268-45-4  Perfluorobutane sulfonyl fluoride, branched
CAS 36913-91-4  Perfluorobutane sulfonic anhydride

**PFBS derivatives**

CAS 68298-12-4  N-Methyl perfluorobutane sulfonamide, MeFBSA
*CAS 34449-89-3  N-Ethyl-N-(2-hydroxyethyl) perfluorobutane sulfonamide
*CAS 34454-97-2  N-(2-Hydroxyethyl)-N-methyl perfluorobutane sulfonamide/N-Methyl perfluorobutane sulfonamidoethanol, MeFBSE

![N-Allyl perfluorobutane sulfonamide](image4)

CAS 40630-65-7  N-Allyl perfluorobutane sulfonamide
CAS 34455-00-0  N,N-Bis(2-hydroxyethyl) perfluorobutane sulfonamide
CAS 812-94-2  N-(4-Hydroxybutyl)-N-methyl perfluorobutane sulfonamide
CAS 68555-77-1  N-[3-(Dimethylamino)propyl] perfluorobutane sulfonamide
**PFPS and derivatives:**

CAS 68298-13-5  N-Methyl perfluoropentane sulfonamide
CAS 335-97-7  N-Allyl perfluoropentane sulfonamide
*CAS 68555-74-8  N-(2-Hydroxyethyl)-N-methyl perfluoropentane sulfonamide
*CAS 68555-72-6  N-Ethyl-N-(2-hydroxyethyl) perfluoropentane sulfonamide
CAS 68239-72-5  N-(4-Hydroxybutyl)-N-methyl perfluoropentane sulfonamide
CAS 68555-78-2  N-[3-(Dimethylamino)propyl] perfluoropentane sulfonamide
CAS 68957-60-8  N-[3-(Dimethylamino)propyl] perfluoropentane sulfonamide, hydrochloride
*CAS 68957-55-1  Perfluoropentane sulfonamide N-(N',N',N'-trimethyl propanaminium) chloride
*CAS 68957-57-3  Perfluoropentane sulfonamide N-(N',N',N'-trimethyl propanaminium) iodide
CAS 70225-24-0  Di[Perfluoropentane sulfonamide N-(N',N',N'-trimethyl propanaminium)] sulfate

**PFPS, salts and halogenides:**

*CAS 3872-25-1  Potassium perfluoropentane sulfonate, PFPS-K
CAS 68259-09-6  Ammonium perfluoropentane sulfonate
*CAS 70225-17-1  Bis(2-hydroxyethyl) ammonium perfluoropentane sulfonate
CAS 375-81-5  Perfluoropentane sulfonyl fluoride

**PFPS, salts and halogenides:**

CAS 1492-87-1  Perfluorobutane sulfonamide, N-methyl-N-butyl acrylate
*CAS 67584-59-2  Perfluorobutane sulfonamide, N-methyl-N-ethyl methacrylate
CAS 67939-33-7  Perfluorobutane sulfonamide, N-ethyl-N-ethyl methacrylate
CAS 67936-9-2  Perfluorobutane sulfonamide, N-methyl-N-butyl methacrylate
CAS 67939-89-3  Perfluorobutane sulfonamide, N-ethyl-N-ethyl dihydrogen phosphate
CAS 67939-91-7  Di[perfluorobutane sulfonamide N-ethyl]-N,N'-diethyl phosphate, DiPAP
CAS 68957-33-5  N-Ethyl-N-perfluorobutyl sulfonamidoethyl acrylate
*CAS 67584-51-4  Potassium N-ethyl-N-perfluorobutyl sulfonamidoethyl acrylate
*CAS 68900-97-0  Chromium (III) N-ethyl-N-perfluorobutyl sulfonyl glycinate
CAS 68555-68-0  Sodium N-ethyl-N-perfluorobutyl sulfonyl glycinate
CAS 68299-19-4  Sodium (perfluorobutylsulfonyl)aminomethyl benzene sulfonate
CAS 67939-89-3  Perfluorobutane sulfonamide, N-ethyl-N-ethyl dihydrogen phosphate, MonoPAP
PFHxS derivatives:

CAS 67584-56-9 Perfluoropentane sulfonamide, \( N\)-methyl-\( N\)-ethyl acrylate

CAS 68298-06-6 Perfluoropentane sulfonamide \( N\)-ethyl-\( N\)-ethyl acrylate

CAS 68227-99-6 Perfluoropentane sulfonamide, \( N\)-methyl-\( N\)-butyl acrylate

*CAS 67584-60-5 Perfluoropentane sulfonamide, \( N\)-methyl-\( N\)-ethyl methacrylate

CAS 67906-73-4 Perfluoropentane sulfonamide, \( N\)-ethyl-\( N\)-ethyl methacrylate

CAS 67906-40-5 Perfluoropentane sulfonamide, \( N\)-methyl-\( N\)-butyl methacrylate

CAS 67939-90-6 Perfluoropentane sulfonamide \( N\)-ethyl-\( N\)-ethyl dihydrogen phosphate, MonoPAP

CAS 67939-87-1 Di[perfluoropentane sulfonamide \( N\)-ethyl]-\( N\),\( N\)-diethyl phosphate, DiPAP

CAS 68957-31-3 \( N\)-Ethyl-\( N\)-perfluoropentyl sulfonyl glycine

CAS 68555-79-3 Ethyl [\( N\)-ethyl-\( N\)-perfluoropentyl sulfonyl] glycinate

*CAS 67584-52-5 Potassium [\( N\)-ethyl-\( N\)-perfluoropentyl sulfonyl] glycinate

*CAS 68891-99-6 Chromium (III) \( N\)-ethyl-\( N\)-perfluoropentyl sulfonyl glycinate

CAS 68555-69-1 Sodium \( N\)-ethyl-\( N\)-perfluoropentyl sulfonyl glycinate

CAS 68299-20-7 Sodium (perfluoropentylsulfonyl)aminomethyl benzene sulfonate

CAS 67939-90-6 [Perfluoropentane sulfonamide-\( N\)-ethyl]-\( N\)-ethyl dihydrogen phosphate MonoPAP

CAS 67939-87-1 Di[perfluoropentane sulfonamide \( N\)-ethyl]-\( N\),\( N\)-diethyl phosphate, DiPAP.

PFHxS salts and halogenides:

CAS 355-46-4 Perfluorohexane sulfonic acid, PFHxS

*CAS 3871-99-6 Potassium perfluorohexane sulfonate, PFHxS-K

CAS 70225-16-0 Ammonium perfluorohexane sulfonate, used in photoresists

*CAS 70225-16-0 Bis(2-hydroxyethyl)ammonium perfluorohexane sulfonate

CAS 55591-23-6 Perfluorohexane sulfonyl chloride

PFHxS derivatives:

CAS 68259-15-4 \( N\)-Methyl perfluorohexane sulfonamide

CAS 67584-48-9 \( N\)-Allyl perfluorohexane sulfonamide

*CAS 68555-75-9 \( N\)-(2-Hydroxyethyl)-\( N\)-methyl perfluorohexane sulfonamide

*CAS 34455-03-3 \( N\)-Ethyl-\( N\)-(2-hydroxyethyl) perfluorohexane sulfonamide

CAS 85665-64-1 \( N\)-(2-Hydroxyethyl)-\( N\)-propyl perfluorohexane sulfonamide

CAS 68239-74-7 \( N\)-(4-Hydroxybutyl)-\( N\)-methyl perfluorohexane sulfonamide

CAS 50598-28-2 \( N\)-[3-(Dimethylamino)propyl] perfluorohexane sulfonamide

CAS 68957-61-9 \( N\)-[3-(Dimethylamino)propyl)] perfluorohexane sulfonamide, hydrochloride

CAS 38850-52-1 Perfluorohexane sulfonamide, \( N\)-carboxymethyl-\( N\)-(\( N\)\( N\)\( N\)-trimethyl-propanaminium), used in AFFFs.

*CAS 38850-58-7 Perfluorohexane sulfonamide, \( N\)-sulfoxypropyl-\( N\)-(\( N\)\( N\)\( N\)-dimethyl-\( N\)-hydroxyethyl-propanaminium), used in AFFFs.

CAS 38850-60-1 Perfluorohexane sulfonamide, \( N\)-sulfoxypropyl-\( N\)-(\( N\)\( N\)\( N\)-dimethyl-propanaminium), used in AFFFs.

*CAS 52166-82-2 Perfluorohexane sulfonamide, \( N\)-(\( N\)\( N\)\( N\)-trimethyl propanaminium) chloride, used in AFFFs.

CAS 38850-60-1 Perfluorohexane sulfonamide, \( N\)-sulfoxypropyl-\( N\)-(\( N\)\( N\)\( N\)-dimethyl-propanaminium), used in AFFFs.
Perfluorohexane sulfonamide, N-(N',N',N'-trimethyl propanaminium) chloride, used in AFFFs.

Perfluorohexane sulfonamide N-(N',N',N'-trimethyl propanaminium) iodide, used in AFFFs and cleaning and disinfection.

Di[Perfluorohexane sulfonamide N-(N',N',N'-trimethyl propanaminium)] sulfate, used in AFFFs.

Perfluorohexane sulfonamide, N-methyl-N-ethyl acrylate

Perfluorohexane sulfonamide, N-ethyl-N-ethyl acrylate

Perfluorohexane sulfonamide, N-methyl-N-butyl acrylate

Perfluorohexane sulfonamide, N-ethyl-N-ethyl methacrylate

Perfluorohexane sulfonamide, N-methyl-N-butyl methacrylate

Di[perfluorohexane sulfonamide N-ethyl]-N,N'-diethyl phosphate, Di-PAP

N-Ethyl-N-perfluorohexyl sulfonyl glycine

Ethyl [N-ethyl-N-perfluorohexyl sulfonyl] glycinate

Potassium [N-ethyl-N-perfluorohexyl sulfonyl] glycinate

Chromium (III) [N-ethyl-N-perfluorohexyl sulfonyl] glycinate

Sodium [N-ethyl-N-perfluorohexyl sulfonyl] glycinate

Sodium (perfluorohexylsulfonyl)aminomethyl benzene sulfonate

Di[perfluorohexane sulfonamide N-ethyl]-N,N'-diethyl phosphate, Di-PAP

Perfluorobutanoic acid, used to photographic film and chromatography additive for use in HPLC and LCMS applications.

Sodium perfluorobutyrate

Ethyl perfluorobutyrate

Perfluoropentanoic acid, PFPA

Sodium perfluoropentanoate, PFPA

Ammonium perfluoropentanoate, PFPA

Ethylammonium perfluoroisopentadecanoate

Perfluorpentanoyl fluoride

Red coloured substances not in the lists.
PFHxA salts and derivatives
*CAS 307-24-4 Perfluorohexanoic acid, PFHxA,

Ammonium perfluorohexanoate, PFHxA
CAS 21615-47-4

Ethylammonium perfluorohexanoate
CAS 68015-84-9

Perfluorohexanoyl fluoride
CAS 18017-31-7

Perfluorohexyl iodide, C6
CAS 375-50-8 1,4-diiodoperfluorobutane
CAS 375-80-4 1,6-Diiodoperfluorohexane

Ammonium perfluorohexanoate, PFHxA
CAS 638-79-9 Perfluoropentyl iodide, C5
CAS 355-43-1 Perfluorohexyl iodide, C6
CAS 375-50-8 1,4-diiodoperfluorobutane
CAS 375-80-4 1,6-Diiodoperfluorohexane

Perfluoroalkyl amines
CAS 311-89-7 Tris(perfluorobutyl) amine, perfluorotributyl amine (PTBA), electronic fluids? 3M Fluorinated solvent compositions containing ozone, US patent 6372700 B1

Perfluorodibutylisobutyl amine
CAS 338-84-1 Perfluorotripentyl amine

Perfluoroalkyl phosphorous compounds
#CAS 52299-25-9 Bis(perfluorobutyl) phosphinic acid, PFBPiA, Masurf® FS-780 is an anionic fluorosurfactant mixture that contains C6-12 perfluoroalkyl-phosphonic acid (PFPA) derivatives.

Alkyl perfluoroalkyl ethers
*CAS 297730-93-9 Ethyl perfluorooctadecyl ether, Novec Engineered Fluid HFE 7500
#CAS 163702-08-7 Methyl perfluorooctadecyl ether, 3M Novec Engineered Fluid HFE-7100 (Mixture/reaction mass with CAS 163702-07-6 = EC no. 422-270-2).
Methyl perfluorobutyl ether, Cosmetic Fluid CF 61; 3M Novec Engineered Fluid HFE-7100 (Mixture/reaction mass with CAS 163702-08-7 = EC no. 422-270-2)

Ethyl perfluorobutyl ether (+ mixture/reaction mass with CAS 163702-06-5)

Ethyl perfluoroisobutyl ether (+ mixture/reaction mass with CAS 163702-05-4)

4:2 Fluorotelomers

4:2 Fluorotelomer alcohol, 4:2 FTOH

4:2 Fluorotelomer iodide, Zonyl™ PFBEI

4:2 Fluorotelomer olefin, Zonyl™ PFBE, (perfluorobutyl)ethylene, 1H,1H,2H-perfluoro-1-hexene, Capstone® 42-U, used in food contact materials, assessed by EFSA in 2011.

4:2 Fluorotelomer acrylate

4:2 Fluorotelomer [1,1’-di(tetradecanoic acid)] methyl silane/methyl (3,3,4,4,5,5,6,6,6-nonfluorohexyl)silylene dimyristate, drug intermediate

5:2 Fluorotelomers

5:2 Fluorotelomer iodide

5:2 Fluorotelomer sulfonyl chloride

6:2 Fluorotelomers

6:2 Fluorotelomer alcohol, 6:2 FTOH, Capstone™ 62-AL

CAS 26650-09-9  6:2 Fluorotelomer thiocyanate

*CAS 27619-97-2  6:2 Fluorotelomer sulfonic acid, Fumetrol®21 (for Cr hard metal plating), Forafac 1033

CAS 59587-38-1  Potassium 6:2 fluorotelomer sulfonate, Zonyl 1176, wetting agent

*CAS 34453-29-3  6:2 Fluorotelomer sulfonamide, N-propanaminium N'-carboxymethyl, used in AFFFs.

CAS 61798-69-4  6:2 Fluorotelomer sulfonamide, N-propanaminium N'-2-carboxyethyl, used in AFFFs.

CAS 66008-71-7  6:2 Fluorotelomer sulfonamide, N-methyl N-propanaminium N',N'-dimethyl N'-carboxymethyl, used in AFFFs.

CAS 66008-72-8  6:2 Fluorotelomer sulfonamide, N-methyl-N-propanaminium N',N'-dimethyl N'-2-carboxyethyl, used in AFFFs.

#CAS 17527-29-6  6:2 Fluorotelomer acrylate, Zonyl® TA-N <5%

#CAS 2144-53-8  6:2 Fluorotelomer methacrylate, Capstone™ 62-MA, chemical intermediate, monomer

#CAS 96383-55-0  6:2 Fluorotelomer 1-chloroacrylate
#CAS 1189052-95-6 Sodium 6:2 fluorotelomer phosphonate (used in cosmetics, function not reported):

The analogue potassium salt (CAS 1224952-82-2) is not on the registration- or preregistration lists but it is also used in cosmetics (function not reported):

Reaction mass of mixed 6:2 fluorotelomer ammonium phosphates, 6:2 monoPAP, surfactants, ECHA info by read across to 6:2 FTOH:
http://apps.echa.europa.eu/registered/data/dossiers/DISS-b2c96a85-1cdf-414d-e044-00144f67d031/AGGR-17aa94bb-198a-4f19-b541-1aa7b6710a86_DISS-b2c96a85-1cdf-414d-e044-00144f67d031.html#AGGR-17aa94bb-198a-4f19-b541-1aa7b6710a86

Possible composition:
#CAS 1764-95-0 Ammonium bis(2-(perfluorohexyl)ethyl) phosphate, used in inks

Related substances not on the lists:
CAS ? Diammonium [2-(perfluorohexyl)ethyl] phosphate, used in inks
CAS ? Sodium bis[2-(perfluorohexyl)ethyl] phosphate
CAS 57678-01-0 Mono[2-(perfluorohexyl)ethyl] dihydrogen phosphate
CAS 57677-95-9 Bis[2-(perfluorohexyl)ethyl] hydrogen phosphate
CAS? 6:2 Fluorotelomer mercaptoalkyl phosphate diester (6:2 FTMAP), used in food pack ageing.

*CAS 78560-45-9 6:2 Fluorotelomer trichlorosilane
**Short-chain Polyfluoroalkyl Substances (PFAS)**

This literature search provides an overview of the human health and environmental fate and effects aspects of the short-chain polyfluorinated substances, which are being introduced as alternatives to PFOS/PFOA and other long-chain PFAS in an increasing number of application areas.

Denne litteraturgennemgang har undersøgt tilgængelige studier af kortkædede polyfluorinerede stoffer, for at give et overblik over mulige miljø og sundhedseffekter af de stoffer der anvendes som alternativer til PFOS/PFOA og andre langkædede PFAS-stoffer.