Danish Ministry of the Environment
Environmental Protection Agency

Short-chain Polyfluoroalkyl Substances (PFAS)

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

Environmental project No. 1707, 2015

Title:

Short-chain Polyfluoroalkyl Substances (PFAS)

Editing:

Jesper Kjølholt [1]
Allan Astrup Jensen [2]
Marlies Warming [1]

1: COWI A/S
2: NIPSECT

Published by:

The Danish Environmental Protection Agency
Strandgade 29
1401 Copenhagen K
Denmark
www.mst.dk/english

Year:

2015

ISBN no.

978-87-93352-15-5

Contents

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 provided 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 Kjølholt, 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 (C_4, PFBS) and perfluorohexane sulfonic acid (C_6, 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 C_8-PFAS, there are hundreds of derivatives in use, for instance, phosphates and acrylates.

The short-chain PFAS, especially the C_6-substances such as 6:2 fluorotelomers, are used to about the same applications (impregnation, metal plating, fire-fighting foams, food packaging etc.) as the C_8-analogues; however, the C_8 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 (C_8).

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 C_3-perfluorcarbon chain is different and has a slower renal clearance than PFHxA (C_5), because PFBA seems not to be the substrates of the common transport protein Oatp1a1. In contradiction, PFBS with a C_4-perfluorocarbon chain seems not to be very bioaccumulative and has a much shorter half-life in the organism than PFHxS (C_6).

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 fluortelomer 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/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.

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 xenoestrogens 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 degradatation 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 Miljøstyrelsens 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 Miljøstyrelsens strategi for denne stofgruppe ved at tilvejebringe baggrundsdokumentation i forhold til mulige yderligere aktiviteter, herunder eventuel regulering.

Kortkædede PFAS'ers kemi og anvendelser
De vigtigste kortkædede perfluoralkylsulfonsyrer (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, fluorocarbonatomer kortere. Ligesom PFOS har de kortkædede alternativer hundredevis af forstadier, f.eks. mere komplekse molekyler som *N*-methyl-perfluorbutansulfonamidoethanol (MeFBSE) og *N*-methyl-perfluorhexansulfonamidoethylacrylat.

De vigtigste kortkædede alternativer blandt perfluorcarboxylsyrerne (PFCA'er), er perfluorobutansyre (PFBA) og perfluorohexansyre (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-analoger (imprægnering, metal plating, brandslukningsskum, emballage til fødevarer etc.), dog er C8optimale i forhold til overfladeaktive egenskaber med meget lave overfladespændinger og er derfor de foretrukne stoffer fra et teknologisk synspunkt.

Sundhedseffekter og eksponering af mennesker
Det er kendt fra dyreforsøg, at de undersøgte kortkædede polyfluoralkylerede stoffer (PFAS) absorberes næsten fuldstændigt oralt og ved inhalering, men at hudabsorption kan være ubetydelig. Både kort- og langkædede perfluoralkylerede syrer (PFAAs) anses at være metabolisk inaktive. De stærke CF-bindinger udelukker enhver almindelig nedbrydningsvej. Ethvert funktionelt derivat (precursor) vil gennem flere trin i sidste ende blive omdannet til den tilsvarende syre. Det er også tilfældet for fluortelomere og derivater heraf, som biotransformeres til PFCA'er af forskellig kædelængde gennem flere metaboliske trin, herunder mere toksiske metabolitter som aldehyder samt mættede og umættede carboxylsyrer., og en af metabolitterne, perfluorhexylethansyre (FHEA), er målt i menneskevæv.

Den gennemsnitlige halveringstid for elimination af PFAA fra blod afhænger både af selve det kemiske stof og af kønnet 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 forgrenede isomerer. I dyr er halveringstiderne ofte kortere hos hunner på grund af kønshormonafhængig forskel i udskillelsen fra nyrerne. Endvidere er halveringstider for PFAAs i serum dosisafhængig med længere halveringstid ved de lave koncentrationer, som er relevante for mennesker. Generelt er halveringstiden for PFAAs i blodet hos eksponerede gnavere timer eller få dage, i aber lidt længere, og i mennesker meget længere og ofte år.

Den primære udskillelsesvej 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 forsøgsdyr er, at udskillelsen af disse stoffer i mennesker er ubetydelig, fordi mennesker har den højeste andel af renal tubulær reabsorption (> 99%). Denne forskel mellem mennesker og forsøgsdyr gør det mere usikkert at bruge dyredata i vurderingen af risikoen for mennesker udsat for PFAA. Udskillelsesvejen er anderledes for fluortelomerer, 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-perfluorcarbonkæde anderledes og har en langsommere renal clearance end PFHxA (C5) fordi PFBA ikke synes at være substrater hørende til det fælles transportprotein Oatp1a1. I modsætning hertil synes PFBS med en C4-perfluorcarbonkæde ikke at være meget bioakkumulerende 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 cellemembranoverflader og fordeler 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 Spanienafslørede både individuelle forskelle mellem donorer og i vævs fordelingen af forskellige PFAS. De fandt relativt høje koncentrationer af kortkædede PFAS i humane væv, især PFBA, hvilket indikerer, at disse kemikalier opfører sig anderledes i mennesker end hos laboratoriedyr, 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.. Levertoksiciteten hos rotter medieres gennem peroxisomproliferation, og dets styrke stiger generelt med længden af fluorcarbonkæden indtil C9. Dog er PFHxS mere giftig end PFBS og PFOS.

Toksikokinetik 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 forekomst af kortkædede PFAS (særligt PFBA) i humant væv, herunder i menneskehjerner, er bekymrende og viser, at kortkædede PFAS og en fluorotelomermetabolit kan være meget mere bioakkumulerende i mennesker end det konkluderes baseret på studier med forsøgsdyr. Dette kan nedsætte sikkerheden af alternativerne.

Miljømæssige effekter og -eksponering
Perfluorerede carboxyl- og sulfonsyrer, herunder de kortkædede omdannes/nedbrydes stort set ikke i miljøet ved abiotiske reaktionsmekanismer sådan hydrolyse eller fotolyse i vand. Dog kan visse upolære PFASs, fx FTOHs, undergå indledende abiotisk 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. fluortelomeralkoholer/acrylater) kan undergå primær nedbrydning til den tilsvarende syre, men den meget persistente perfluorerede "hale" forbliver intakt.

PFCA og PFSA kan bioakkumulere i levende organismer i miljøet med de langkædede stoffer værende mere bioakkumulerende end de kortkædede. Da disse stoffer imidlertid er både hydrofobe og lipofobe, 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 snarere i væv med høj blodgennemstrømning end i fedtvæv. Precursorer, så som fluortelomere, formodes at være delvis ansvarlige for den observerede bioakkumulering af syrerne.

De kortkædede syrer har tendens til at være mere vandopløselige 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 sulfonsyrerne har tendens til at være mere giftige end de tilsvarende carboxylsyrer. 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 miljøeksponering 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 vandmiljøprøver, 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 fluortelomerer.

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 fjernelsesproces fra vandfasen for PFHxS (og syrere 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 fjerntliggende områder uden kendte, 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 toksikologiske 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 væv fra afdøde personer, bør bekræftes gennem undersøgelser foretaget af andre forskere og med prøver fra andre europæiske lande. I foreliggende biomoniteringsstudier 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' miljøegenskaber 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 miljøeksponering for de kortkædede carboxylsyrer (PFCA) og sulfonsyrer (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)[1]. 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[2].

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 sof 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.

---

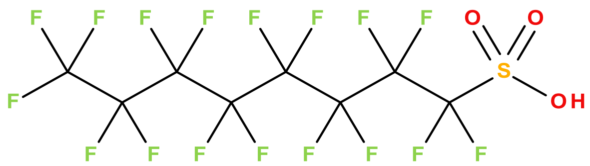
[1] http://www.mst.dk/English/Chemicals/assessment_of_chemicals/lous_list_undesirable_substances_2009/

[2] Can be downloaded here (in Danish): http://www.mst.dk/Virksomhed_og_myndighed/Kemikalier/Fokus+paa+saerlige+stoffer/LOUS_kortlaegning/2012-stofferne/2012stofstrategi.htm

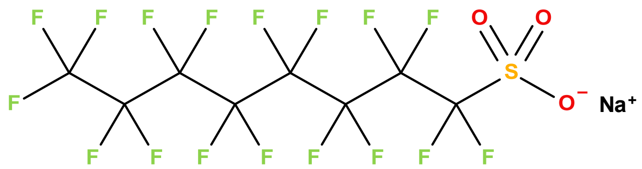
2. Chemistry and uses

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 (“C_8-chain”) and a sulfonic acid or sulfonate as the functional group (see formula):

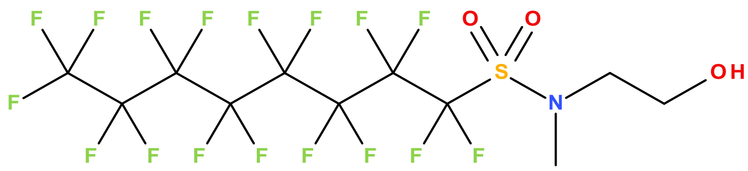


Perfluorooctane sulfonic acid (PFOS as acid)



Sodium perfluorooctane sulfonate (PFOS as salt)

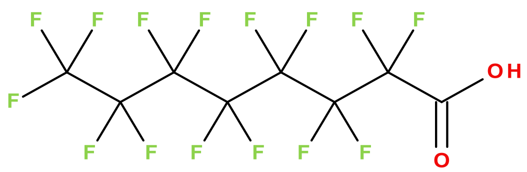
Besides its salts, PFOS has many other derivatives; the most important are *N*-substituted sulfonamides such as:



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.

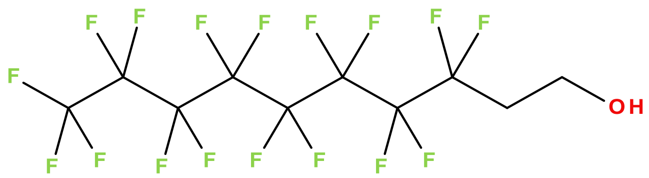
Another well-known “C_8-chain” compound is perfluorooctanoic acid (PFOA):



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).

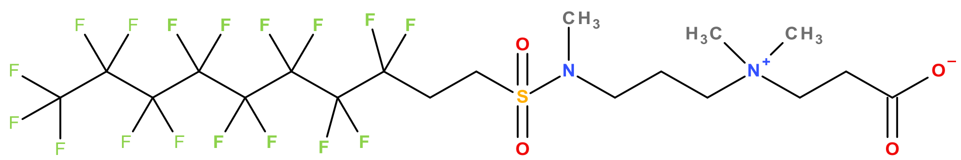
The third important group of C_8-fluorinated chemicals is 8:2 fluorotelomers. Fluorotelomers are *poly*fluoralkyl substances with a perfluorinated tail but the two first carbons have bonds to hydrogen instead of to fluorine. A reactive functional group may be attached, and this functional group and the non-fluorinated part of the alkyl chain can be degraded and metabolized, and in this way be precursors of *per*fluoroalkyl carboxylates. The most important 8:2 fluorotelomer is 8:2 fluorotelomer alcohol (1*H*,1*H*,2*H*,2*H*-perfluorodecanol, 8:2 FTOH):



8:2 Fluorotelomer alcohol (8:2 FTOH)

The ultimate degradation and metabolism of 8:2 FTOH is to PFOA (C_8) and perfluorononanoic acid (C_9, 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)sulfonylamino)-1-propanaminium

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

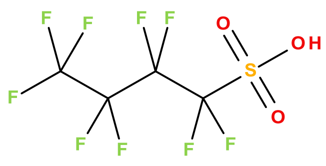
2.2 Short-chain alternatives to C8-polyfluoroalkylated substances

Major manufacturers of fluorinated chemicals in conjunction with global regulators have agreed to discontinue the manufacture of "C_8-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 C_8-PFAS and the other PFAS is the length of the fully fluorinated chain. Thus the examples of C_8-chemicals shown above will also exists as C_4- or C_6-analogues.

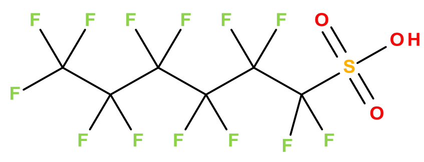
Already in 2005, a DEPA report about alternatives to PFOS and PFOA concluded that in most cases the alternatives to PFOS (and PFOA) related substances are other fluorinated chemicals with shorter chain length, such as C_6-fluorotelomers or perfluorobutane sulfonate (C_4, PFBS) (Poulsen *et al.* 2005). 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 (C_6 or shorter) or other classes of polyfluorinated substances, such as fluorotelomer alcohols (FTOH).

The most important short-chain perfluoroalkylsulfonic acids are perfluorobutane sulfonic acid (C_4, PFBS) and perfluorohexane sulfonic acid (C_6, PFHxS), which also exist as various salts. The only difference to PFOS is the four, respectively, two fluorocarbon shorter perfluorinated chain ("tail").

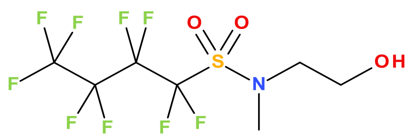


Perfluorobutane sulfonic acid (PFBS)

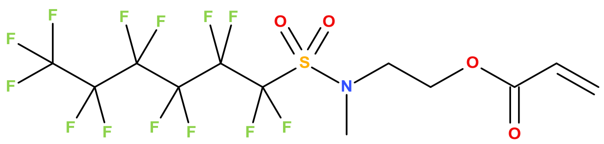


Perfluorohexane sulfonic acid (PFHxS)

Simliarly 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:

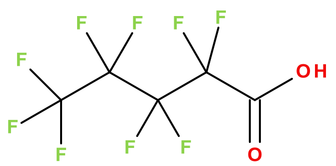


N-Methyl perfluorobutane sulfonamidoethanol

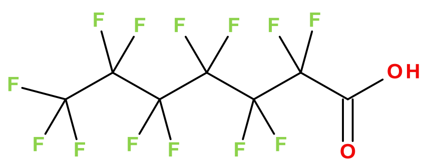


N-Methyl perfluorohexane sulfonamidoethyl acrylate

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

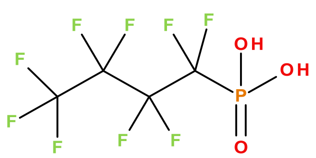


PFBA

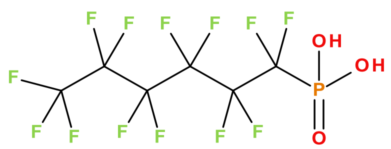


PFHxA

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

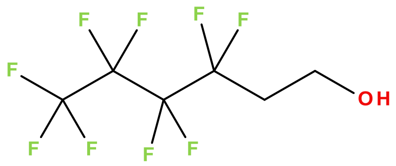


PFBPA

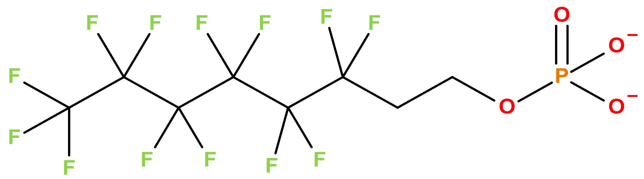


PFHxPA

The most important short-chain fluorotelomers are 2:4 FTOH and 6:2 FTOH, and as for the C_8-PFAS, there are hundreds of derivatives in use, for instance phosphates and acrylates. The structure of an alcohol and a phosphate are shown below:



4:2 Fluorotelomer alcohol (4:2 FTOH)



6:2 Fluorotelomer phosphate/mono[2-(perfluorohexyl)ethyl] phosphate

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 fluorotelomers. Since the agreement in 2006 with USEPA about phasing out C_8-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

[3] http://solutions.3m.com/wps/portal/3M/en_US/PFOS/PFOA/Information/phase-out-technologies/

[4] http://solutions.3m.com/3MContentRetrievalAPI/BlobServlet?locale=en_US&lmd=1120194514000&assetId=1114270648708&assetType=MMM_Image&blobAttribute=ImageFile

products.[5] The new DuPont™ Capstone® repellents and surfactants are based on short-chain chemistry that cannot break down to PFOA but to short-chain PFCAs. [6] 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.[7]

2.4 Recent uses of short-chain alternatives

In the following recent publications from the Stockholm Convention it is also stated that short-chain (C_4- and C_6-) fluorinated substances have substituted C_8-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.[8]
- "Technical paper on the identification and assessment on alternatives to the use of perfluorooctane sulfonic acid in open applications" with appendices in August 2012. Author: Stefan Posner, Sweden.[9]

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) (1*H*,1*H*,2*H*,2*H*-perfluorooctane sulfonic acid, H-PFOS). It is not fully fluorinated, but the C_6-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.

---

[5] http://www2.dupont.com/PFOA2/en_US/products/index.html
[6] http://www2.dupont.com/Capstone/en_US/assets/downloads/K-20614-3_Capstone_Stewardship_Detail_Brochure.pdf
[7] http://www2.dupont.com/Capstone/en_US/index.html
[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.)
- C_4-C_6 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).

PFAS substance	Mean concentrations ng/g w. w.				
	Liver	Bone	Brain	Lung	Kidney
PFBA	12.9	<LOD	13.5	304	464
PFBS	0.9	3.2	<LOD	17.8	8
PFPeA	1.4	0.8	<LOD	44.5	<LOD
PFHxA	11.5	35.6	18.0	50.1	5.6
PFHxS	4.6	1.8	3.2	8.1	20.8
Perfluorohexyl ethanoic acid (FHEA); metabolite of 6:2 FTOH	92.6	42.5	18.6	2.4	23.7
PFOA	13.6	60.2	<LOD	29.2	2.0
PFOS	102	<LOD	4.9	29.1	75.6

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 waxers is described. In a follow up study whole blood samples from 8 ski waxers 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 waxers 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 C_8-C_{11} 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).

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

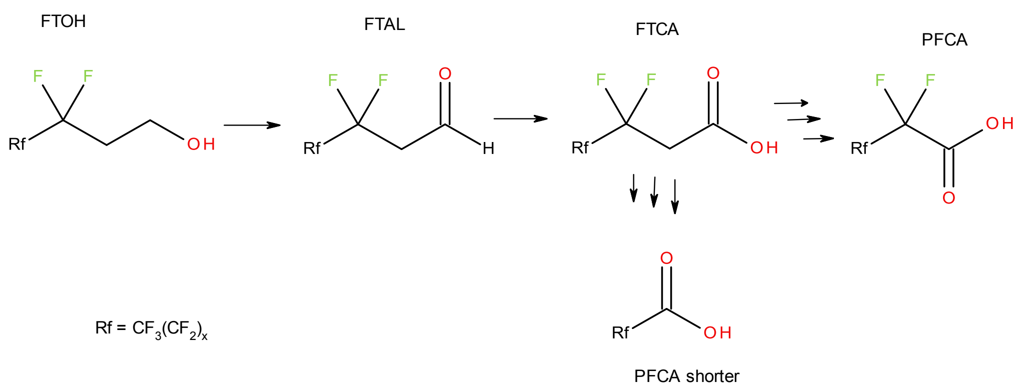
In human sera samples collected in 2009 in the USA the levels of 6:2 diPAPs were lower than in 2008 with max. 0.14 ng/mL (Lee and Mabury 2011). In addition, other surfactants (PFPiA) from food packaging, such as bis[perfluorohexyl] phosphinate (the C_4-analogue is in the CAS no. list above) were measured 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 mercaptoalkyl 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 fluorotelomers can be metabolized to PFCAs of various chain lengths, and already in 1981 the biotransformation of 8:2 FTOH via 2*H*,2*H*-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):



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 PFCAs 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 PFAA from the body is via kidneys in the urine. Renal clearance of PFCAs 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 PFAA renal elimination in rats are connected as the renal active secretion and reabsorption of PFAA 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 PFAA 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 C_6-perfluorocarbon chain bioaccumulates in the organism with a long half-life in the organism in the same way as PFOS; however PFBS with a C_4-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

Species	Substances							
	PFBS		PFHxS		PFBA		PFHxA	
	Male	Female	Male	Female	Male	Female	Male	Female
Rat	<4.5 days	<4 days	29 days	1 day	9 hours	2 hours	1.6 hours	0.6 hours
Mouse			30.5 days	24.8 days	5-16 hours	3 hours	1 hour	
Monkey	95 hours	83 hours	141 days	87 days	40 hours	41 hours	14-47 hours	
Human	24 days	46 days	8.5 years		72 hours	87 hours	32 days	

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 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 at 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 C_9. 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.

The effects of 18 PFASs on mRNA expression of selected genes in chicken embryo hepatocyte cultures *in vitro* have been studied (Hickey *et al.* 2009). The target genes were acyl-CoA oxidase (ACOX), a known PPARα target; liver fatty acid–binding protein (L-FABP), a transport protein known to bind PFASs; CYP1A4/5 and CYP4B1, regulators of xenobiotic metabolism; and HMG-CoA reductase and sterol regulatory element–binding protein 2 (SREBP2), important cholesterol metabolism genes. Of the short chain congeners PFHxS, PFHxA and PFPA induced CYP1A4 and/or CYP1A5 mRNA. The effects of PFHxA on CYP1A4/5 mRNAs and EROD activity were concentration-dependent. The EROD activity was, however, 50 000 times lower than that of dioxin.

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-EC_{50} dependence was clearly observed for PFCAs in an *in vitro* assay with human colon carcinoma (HCT116) cells. Estimated values of EC_{50} 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 (T_4) 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 3-4
COMPETITIVE BINDING TO TRANSTHYRETIN (WEISS ET AL. 2009).

Compound	IC_{50} nM	T_4 relative binding potency factor, (T_4 = 1)
PFHxA	8220	0.007
PFBS	19460	0.003
PFHxS	717	0.085
PFOS	940	0.065
PFOA	949	0.064

IC_{50} (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 thesechemicals.

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 perfluoroalkylated 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, C_4)

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 C_9. 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 sulfonyl 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 (C_4-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 sensitation. 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, C_6)

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 C_9. 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 and PFOS (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
PFAAs 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-thryonine (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 5 38,000 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) but not PFOS (GM: 8.40 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.

Reproductional 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 PFUnA 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 statistic 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, C_4)

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 lung 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 C_9, 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 perfluorooctanoate (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,C_6)

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 ^{14}C-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-live 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 waxers 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 C_9, 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 EC_{50} 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 9700 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 (BMD_{10} = 95% lower confidence limit of a dose resulting in a 10% increase in risk) to 13 mg PFHxA/kg b. w. per day.

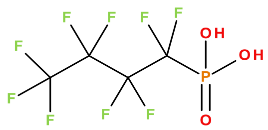
3.3.3 Perfluoroalkyl halogenides

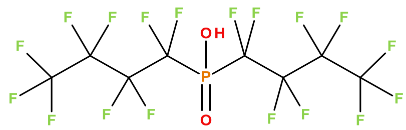
A reaction product between perfluorohexyl iodide (PFHxI, C_6) and 2-propen-1-ol is allowed in food packaging. Various polyfluorinated alkyl iodides have been studied for estrogenic activity in some *in vitro* test systems (Wang *et al.* 2012). The perfluorohexyl iodide and perfluorooctyl iodide (PFOI, C_8) 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 C_6-perfluoroalkyl iodides.

3.3.4 Perfluoroalkyl phosphor compounds

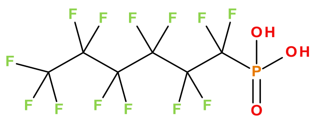
The mono- and di-substituted perfluorinated phosphonic acids (mono-PFPAs and di-PFPAs) belong to a new class of high production volume fluorinated surfactants used a. o. as wetting agent in waxes and coatings, and they have been used as defoaming additives to pesticides. Some of these chemicals are found occasionally in the environment and in human blood in Canada. A commercial wetting agent with the trade name Masurf-780 contained C_6, C_8, C_{10} and C_{12} substances (D'eon & Mabury, 2010).

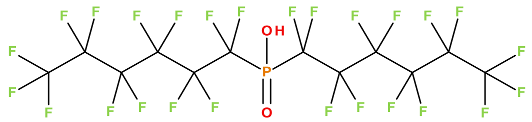
Examples:
Perfluorobutyl phosphinic acid/phosphinates and bis[perfluorobutyl] phosphinic acid/phosphinates (C_4):





Perfluorohexyl phosphonic acid/phosphonate and bis[perfluorohexyl] phosphinic acid/phosphinates (C_6):





In rats all these chemicals with C_6-C_{12} 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 phosphonate 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 C_4 compounds.

Masurf® FS-780 is a commercial mixture that contains C_{6-12}-perfluoroalkylphosphinic acid (PFPiA) derivatives (37% C_6/C_6-, 33% C_6/C_8- and 27% C_8/C_8 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 C_8 content.

A subchronic oral study in rats of a commercial FTOH mixture ($C_nF_{2n+1}CH_2CH_2OH$, 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 (Ladics *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, 1*H*,1*H*,2*H*-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, C_6)*

Since C_8-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 LD_{50} of 1.75 g/kg b. w. The dermal LD_{50} 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 without 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.

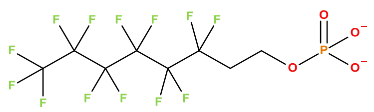
These derivatives can be metabolized in rodents to the 6:2 FTOH and later to the carboxylic acid (6:2 FTCA) and after many steps finally to PFHxA and to a little extent PFHpA (Butt et al 2010).

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 senzitisation 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.

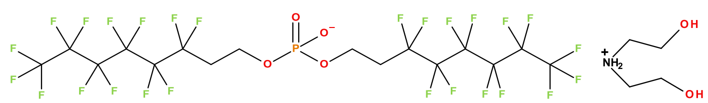
3.3.5.3 Polyfluoroalkyl phosphate esters (PAPs)

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).

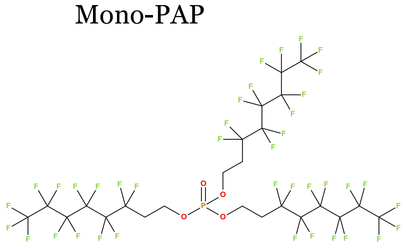
A mixture of diethanol-ammonium salts of fluorotelomer phosphates, where the C_6-fluoroalkyl content is 35%, and which also contains longer chain fluorotelomers, has the trade name Zonyl RP and is allowed in food packaging. 6:2 Fluorotelomer phosphate (1*H*,1*H*,2*H*,2*H*-perfluorooctyl (ortho)phosphate) and bis(6:2 fluortelomer) phosphate:



Mono-PAP



Di-PAP



Tri-PAP

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%).

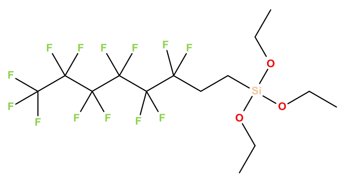
3.3.5.4 Silicium derivatives of PFAS

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.

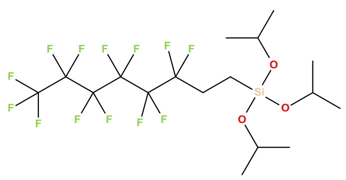
Some of these “magic” spray products discovered on the market in Denmark in 2010 were investigated for airway irritation, airway inflammation and lung damage in a mouse inhalation model (Nørgaard A *et al.* 2010). BALB/cJ mice were exposed for 60 min to the aerosolized product 3.3-60 mg/m^3 measured 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/m^3 ($2.1x10^6$ fine particles/cm^3) gave rise to significant increases of protein level in broncho- alveolar lavage fluid (BALF) and reduced body weight. Histological examination showed atelectasis, emphysema, and hemorrhages. A narrow interval between the no-effect-level (16.1 mg/m^3) and the lethal concentrations (18.4 mg/m^3) 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:

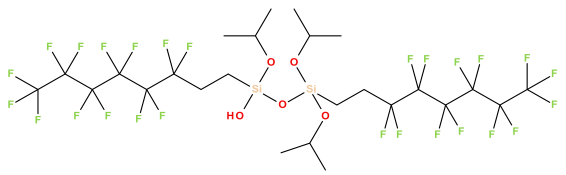
6:2 Fluorotelomer triethoxysilane (CAS 51851-37-7, 1*H*,1*H*,2*H*,2*H*-Perfluorooctyl triethoxysilane)



6:2-Fluorotelomer triisopropoxysilane (CAS no.?, 1*H*,1*H*,2*H*,2*H*-Perfluorooctyl triisopropoxysilane)



Di(6:2 fluorotelomer) monohydrolyzed disiloxane (CAS no.? Bis[1*H*,1*H*,2*H*,2*H*-perfluorooctyl] triisopropoxy hydroxy disiloxane)



3.4 Occurrence and exposure in relation to humans

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 C_8-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 in the diet. 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).

3.4.1 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/m

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/m^2) 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/m^2 textile were extracted (Becanova *et al.*, 2013).

In a children jacket the dominating PFAS was 6:2 FTOH and 19 µg/m^2 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).

Substance	Acronym	Concentrations of extracted PFAS from 5 impregnation agents µg/L
6:2 Fluorotelomer alcohol	6:2 FTOH	535 – 13.250
Perfluorobutanoate	PFBA	75-142
Perfluorohexanoate	PFHxA	23-25

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/m^3 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/dm^2 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/m^3. Individual PFAS concentrations were between 42 pg/m^3 (6:2 fluorotelomer acrylate, FTA) and 209 ng/m^3 (8:2 FTOH). Concentrations of total FTOHs ranged from 3.3 to 307 ng/m^3, and FTAs ranged from 0.2 to 152 ng/m^3. 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 3-6Table 3-6:

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

PFAS	4:2 FTOH	6:2 FTOH	6:2 FTA	MeFBSA	MeFBSE	Total FTOH
CAS no.	2043-47-2	647-42-7	17527-29-6	68298-12-4	34454-97-2	
Range (ng/m^3)	nd – 1.2	0.1 - 37	nd - 3.4	nd – 3.4	0.6 - 141	3.3 - 307

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/m3 with a mean of 240 ng/m3. Among the PFCAs, PFHxA (degradation product) was found in the highest levels that ranged from 57 to 14 000 ng/m3 with a mean of 4900 ng/m3. 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/m3, of 10:2 FTOH 370 ng/m3 and of 8:2 FTOH 92 000 ng/m3. 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/m3 with a geomean of 1320 pg/m3.

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).

PFAS	LOQ	Office dust (n=31) % detect	GM ng/g	Range	Home dust (n=30) % detect	GM ng/g	Range	Vehicle dust (n=13) % detect	GM ng/g	Range
PFOA	5	74	32.0	15-336	77	23.7	5-894	54	11.4	21-58
PFHxA	5	68	10.8	5-102	57	8.7	5-1380	54	5.9	5-18
PFPA	5	39	nr	5-28	33	nr	5-249	23	nr	7-18
PFBA	5	48	nr	5-148	90	13.9	5-999	85	11.5	5-240
PFOS	7	55	14.6	7-98	73	26.9	14-280	54	15.8	10-280
PFHxS	5	23	nr	5-19	40	nr	6-430	46	nr	5-108
PFBS	5	10	nr	8-12	3	nr	5-5	nr	- report	<5
6:2 FTOH	50	35	nr	90-2390	0	nr	<50	8	nr	2-243
8:2 FTOH	5	100	309	15-3390	57	10.8	9-136	69	11.3	8-82

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 " C_8 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 functuional 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 4-1
PHYSICO-CHEMICAL PROPERTIES OF SELECTED SHORT-CHAIN PFAS (AND PFOS, PFOA AND 8:2 FTOH FOR REFERENCE TO C_8)

Property	CAS	Water solubility (mg/L)	Mp/Bp (ºC)	Vapour pressure (Pa)	Log Pow	Log Koc
PFOS, perfluorooctane sulfonic acid	1763-23-1	519-570[3]		3.31×10^{-4}[3]	5.5-7.03[4]	2.57-3.3[4]
PFOA, perfluorooctanoic acid	335-67-1	3400 [5]		12.1 [5]	3.6[2]	2.11 [5]
PFHxS, perfluorohexane sulfonic acid	355-46-4	243.4[1]	190/452[1]	1.08×10^{-6}[1]	2.2[1]	3.36/2.14[1]
PFHxA, perfluorohexanoic acid	307-24-4	29.5 [5] <<29[6]		121 [5]	2.51[2] 3.12-3.26[6]	
PFHxA, perfluorohexanoate, sodium salt	2923-26-4	29.5[6]		~ 0 [6]	0.70[6]	
PFPeS, perfluoropentane sulfonic acid	2706-91-4					
PFPeA, perfluoropentanoic acid	2706-90-3	120 [5]			1.98[2]	
PFBS, perfluorobutane sulfonate, potassium salt	29420-49-3	4340[1]	188/447[1]	1.49×10^{-6}[1]	0.26[1]	2.25/1.07[1]
PFBA, perfluorobutanoic acid	375-22-4	447 [5]			1.43[2]	
8:2 FTOH, fluorotelomer alcohol	678-39-7	0.2 – 0.3 [5]		1.64 [5]	5.58 [5]	4.13 [5]
6:2 FTOH, fluorotelomer alcohol	647-42-7	19[3]		22.1 [5]	4.54 [5]	2.43 [5]
4:2 FTOH, fluorotelomer alcohol	2043-47-2	97[1]	-44/113[1]	1330[1]	3.07/3.30[1]	2.34/2.83[1]
6:2 FTS, fluorotelomer sulfonamide	27619-97-2				3.47-3.98[4]	
6:2 FTAC, fluorotelomer acrylate	17527-29-6	0.38[6]		44.3[6]	5.2[6]	

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 C_4-C_6 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 PFCAs 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 PFCAs 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 PFASs 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 perfluoroalkylated 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 sediment 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 perfluorbutane sulfonate (PFBS-K)I is expected.

Quinete *et al.* (2010) studied the degradability of some new substitutes for perfluorinated surfactants (PFBS, fluorosurfactant Zonyl, two fluroaliphatic 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 1 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 & Elllis (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 sharpbelly) in a Chinese lake and found PFOS to be the dominant perfluorinated acid (PFAA) accounting for 93-94% of the total content of PFAAs. Also other long chained PFAAs 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 PFAAs 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 PFAAs 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 PFASs. 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 K_{OC} 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 K_{OC}'s increased gradually up to around 5 (PFSAs were only included up to C8 (Log K_{OC} 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 probably due to biodegradation of percursors, 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 ubiquously 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-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 Antarctis (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 PFSAs 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) refered 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 testosteron 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 rewiewing 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 4-2
TOXICITY OF SHORT CHAIN PFAS TO FISH

Test substance		Organism	Endpoint	Test	Concentration	Reference
Abbr.	Cas no.				(mg/L)	
Perfluoroalkane sulfonic acids (PFSA) and their salts						
PFBS	375-73-5	Zebrafish larvae (*Danio rerio*)	EC50, embryo-toxicity	144 h	450	Ulhaq *et al.* 2013
PFBS-K	29420-49-3	Fathead minnow (*Pimephales promelas*)	LC50	96 h	1938	NICNAS, 2005
PFBS-K	29420-49-3	Bluegill sunfish (*Lepomis macrochirus*)	LC50	96 h	6452	NICNAS, 2005
Perfluorocarboxylic acids (PFCA)						
PFBA	375-22-4	Zebrafish larvae (*Danio rerio*)	EC50, embryo-toxicity	144 h	2200	Ulhaq *et al.* 2013

Test substance		Organism	Endpoint	Test	Concentration	Reference
Abbr.	Cas no.				(mg/L)	
PFPeA	2706-90-3	Fathead minnow (*P. promelas*)	LC50	96 h	32	Hoke *et al.*, 2012
PFHxA	307-24-4	Rainbow trout (*O. mykiss*)	LC50	96 h	>99.2	Hoke *et al.*, 2012
PFHxA	307-24-4	Rainbow trout (*O. mykiss*)	NOEC, reprod.	56 d	10.1	ENVIRON, 2014
Fluorotelomers						
6:2 FTOH	647-42-7	*Pimephales promelas*	LC50	96 h	4.84	ENVIRON, 2014
6:2 FTOH	647-42-7	*Danio rerio*	LOEC, testos-terone serum level in male fish	7 days	0.03	Liu *et al.* 2009
6:2 FTOH	647-42-7	*Danio rerio*	LOEC, estradiol serum level in female fish	7 days	0.3	Liu *et al.* 2009
6:2 FTAC	17527-29-6	*Oryzias latipes*	LC50	96 h	>0.306	ENVIRON, 2014
4:2 FT olefin	19430-93-4	*Danio rerio*	NOEC, mortality	96 h	≥ 1.86	ECHA, 2014

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 s 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. tentan*. 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 EC50 values are around or above 100 mg/L. The lowest effect concentration was observed for in an acute test with daphnids (LC50 of 29.6 mg 6:2 FTUCA/L).

TABLE 4-3
TOXICITY OF SHORT CHAIN PFAS TO INVERTEBRATES

Test substance		Organism	Endpoint	Test	Concentration*	Reference
Abbr.	Cas no.				(mg/L)	
Perfluoroalkane sulfonates (PFSA) and their salts						
PFBS-K	29420-49-3	*Daphnia magna*	EC50	48 h	2180	NICNAS, 2005
PFBS-K	29420-49-3	*Daphnia magna*	NOEC	21 d	502	NICNAS, 2005
Perfluorocarboxylic acids (PFCA) and their salts						
PFBA	375-22-4	*Daphnia magna*	LC50	48 h	>100	Hoke *et al.*, 2012
PFBA-K	2966-54-3	*Daphnia magna*	NOEC, reprod.	21 d	239	ECHA, 2014
PFPeA	2706-90-3	*Daphnia magna*	LC50	48 h	>112	Hoke *et al.*, 2012
PFHxA	307-24-4	*Daphnia magna*	LC50	48 h	>96.5	Hoke *et al.*, 2012
Saturated and unsaturated fluorotelomer carboxylic acids (FTCA and FTUCA)						
4:2 FTCA	7088789-7	*Daphnia magna*	LC50	48 h	>100	Hoke *et al.*, 2012
4:2 FTCA	7088789-7	Midge (*Chironomus tentans*)	LC50	10 d	>100	Hoke *et al.*, 2012
4:2 FTUCA	7088790-0	*Daphnia magna*	LC50	48 h	>100	Hoke *et al.*, 2012
4:2 FTUCA	7088790-0	Midge (*Chironomus tentans*)	LC50	10 d	>100	Hoke *et al.*, 2012
5:3 acid	914637-49-3	*Daphnia magna*	LC50	48 h	>103	Hoke *et al.*, 2012
6:2 FTCA	5382612-3	Midge (*Chironomus tentans*)	EC50	10 d	63.1	Ding and Peijnenburg, 2013
6:2 FTCA	5382612-3	Midge (*Chironomus tentans*)	LC50	10 d	75.2	Ding and Peijnenburg, 2013
6:2 FTCA	5382612-3	*Daphnia magna*	LC50	48 h	>97.5 >100b	Hoke *et al.*, 2012
6:2 FTCA	5382612-3	Midge (*Chironomus tentans*)	LC50	10 d	75.2	Hoke *et al.*, 2012
6:2 FTUCA	7088788-6	*Daphnia magna*	LC50	48 h	29.6 >100	Hoke *et al.*, 2012
6:2 FTUCA	7088788-6	Midge (*Chironomus tentans*)	LC50	10 d	>100	Hoke *et al.*, 2012

Test substance		Organism	Endpoint	Test	Concentration*	Reference
Abbr.	Cas no.				(mg/L)	
Fluorotelomer alcohols (FTOH) and acrylates (FTAC)						
6:2 FTOH	647-42-7	*Daphnia magna*	EC50	48 h	7.84	ENVIRON, 2014
6:2 FTOH	647-42-7	*Daphnia magna*	NOEC, reprod.	21 d	2.16	ENVIRON, 2014
6:2 FTAC	17527-29-6	*Daphnia magna*	EC50	48 h	>0.141	ENVIRON, 2014

* Some references cite several values from different sources.

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 lead 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 *Geitlerinema 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[12], 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.

[12] 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 (6:2FTCA, 8:2 FTCA, 6:2 FTUCA, 8:2 FTUCA, 5:3 acid[13], 7:3 acid[14], PFPeA, and PFDA) to the *Daphnia magna*, the green alga *Pseudokirchneriella subcapitata*, and fish (*Oncorhynchus 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

Test substance		Organism	Endpoint	Test	Concentration*	Reference
Abbr.	**Cas no.**				**(mg/L)**	
Perfluoroalkane sulfonates (PFSA) and their salts						
PFBS-K	29420-49-3	Algae (*Selenastrum capricornutum*)	EC50, biomass and growth	96 h	2347-5733 mg/L	NICNAS, 2005
Perfluorocarboxylic acids (PFCA)						
PFBA	375-22-4	Algae (*P. subcapitata)*	EC50, inhibition of photosynthesis	4.5 h	1.22 mM (261 mg/L)	Ding *et al.* 2012
PFPeA	2706-90-3	Algae (*P. subcapitata)*	ECb50 ErC50	72 h	81.7 99.2	Hoke *et al.*, 2012
PFHxA	307-24-4	Algae (*P. subcapitata)*	ECb50 ErC50	72 h	>100 >100	Hoke *et al.*, 2012
PFHxA	307-24-4	Algae (*G. amphibium*)	IC50, optical density	72 h	998.7	Ding and Peijnenburg, 2013
PFHxA	307-24-4	Algae (*S. subspicatus*)	ErC50 NOEC	72 h	86 50	ENVIRON, 2014
Saturated and unsaturated fluorotelomer carboxylic acids (FTCA and FTUCA)						
4:2 FTCA	7088789-7	Duck weed (*Lemna gibba)*	EC50, frond number	7 d	9.39	Ding and Peijnenburg, 2013
4:2 FTCA	7088789-7	Duck weed (*Lemna gibba)*	EC50, biomass	7 d	6.6	Hoke *et al.*, 2012
4:2 FTUCA	7088790-0	Duck weed (*Lemna gibba)*	EC50, frond number		6.64	Ding and Peijnenburg, 2013

[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

Test substance		Organism	Endpoint	Test	Concentration* (mg/L)	Reference
Abbr.	Cas no.					
4:2 FTUCA	7088790-0	Duck weed (*Lemna gibba)*	EC50, biomass	7 d	9.4	Hoke *et al.*, 2012
5:3 acid	914637-49-3	Algae (*P. subcapitata)*	EC50, biomass ErC50	72 h	22.5 53.3	Hoke *et al.*, 2012
6:2 FTCA	5382612-3	Duck weed (*Lemna gibba)*	EC50, frond number	7 d	1.29	Ding and Peijnenburg, 2013
6:2 FTCA	5382612-3	Duck weed (*Lemna gibba)*	EC50, biomass	7 d	1.3	Hoke *et al.*, 2012
6:2 FTCA	5382612-3	Algae (*P. subcapitata)*	ErC50, biomass	72 h	47.9 (>105)	Hoke *et al.*, 2012
6:2 FTUCA	7088788-6	Duck weed (*Lemna gibba)*	EC50, frond number	7 d	5.02	Ding and Peijnenburg, 2013
6:2 FTUCA	7088788-6	Duck weed (*Lemna gibba)*	EC50, biomass	7 d	10.4	Hoke *et al.*, 2012
6:2 FTUCA	7088788-6	Algae (*P. subcapitata)*	ErC50, biomass	72	28.5 (>84.5)	Hoke *et al.*, 2012
Fluorotelomer alcohols (FTOH)						
6:2 FTOH	647-42-7	Algae (*P. subcapitata)*	EC50, growth rate	72 h	4.52	ENVIRON, 2014
6:2 FTOH	647-42-7	Algae (*P. subcapitata)*	NOEC	72 h	0.62	ENVIRON, 2014
5H 4:1 FTOH	355-80-6	Algae (*P. subcapitata)*	EC50, inhibition of photosynthesis	4.5 h	4.85 mM (1125 mg/L)	Ding *et al.* 2012
PFAS acrylates						
6:2 FTAC	17527-29-6	Algae (*P. subcapitata)*	ErC50 NOEC	72 h 72 h	>0.022 >0.022	ENVIRON, 2014
C4 acrylate[1]	67584-55-8	Algae (*P. subcapitata)*	NOEC, growth rate	72 h	0.34	ECHA, 2014

* Some references cite several values from different sources.

1 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 inhibitation 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 micro-organisms.

TABLE 4-5
TOXICITY OF SHORT-CHAIN PFAS TO MICROORGANISMS

Test substance		Organism	Endpoint	Test	Concentration	Reference
Abbr.	Cas no.				(mg/L)	
Perfluoroalkane sulfonates (PFSA) and their salts						
PFBS-K	29420-49-3	Sewage microorganisms	EC50, inhibitory effects on respiration	3 h	> 1000	NICNAS, 2005
Perfluorocarboxylic acids (PFCA)						
PFHxA	307-24-4	*Vibrio fischeri*	EC50, bioluminescence inhibition	30 min	1340	Ding and Peijnenburg, 2013
Fluorotelomer alcohols (FTOH)						
4:2 FTOH	2043-47-2	*Tetrahymena thermophila* (ciliate protozoa)	EC50, population growth inhibition	24 h	276.1	Ding and Peijnenburg, 2013
6:2 FTOH	647-42-7	*Tetrahymena thermophila* (ciliate protozoa)	EC50, population growth inhibition	24 h	64.3	Ding and Peijnenburg, 2013

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.

TABLE 4-6
TOXICITY OF SHORT CHAIN PFAS TO BIRDS

Test substance		Organism	Endpoint	Test	Concentration	Reference
Abbr.	Cas no.					
PFBS	375-73-5	Bobwhite quail	LC50, acute effects	Acute dietary (OECD TG 205)	>10 000 mg/kg	NICNAS, 2005
PFBS	375-73-5	Bobwhite quail	NOEC, acute effects	Acute dietary (OECD TG 205)	3160 mg/kg	NICNAS, 2005
PFBS	375-73-5	Mallard duck	LC50, acute effects	Acute dietary (OECD TG 205)	>10 000 mg/kg	NICNAS, 2005
PFBS	375-73-5	Mallard duck	NOEC, acute effects	Acute dietary (OECD TG 205)	5620 mg/kg	NICNAS, 2005
PFBS	375-73-5	Bobwhite quail	NOEC, Reproduction	OECD 206,	900 mg/kg	NICNAS, 2005

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 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 bioavalailble for the earth worms. The EC50 values indicate a low or moderate toxicity to earth worms.

TABLE 4-7
TOXICITY OF SHORT CHAIN PFAS TO TERRESTRIAL INVERTEBRATES

Test substance		Organism	Endpoint	Test	Concentration	Reference
Abbr.	Cas no.					
6:2 FTS	27619-97-2	Earth worm (*Eisenia fetida*)	EC50, Number of cocoons	Acute (OECD 222)	566 mg/kg	NPCA, 2006
6:2 FTS	27619-97-2	Earth worm (*Eisenia fetida*)	EC50, Total weight of juvenile	Acute (OECD 222)	253 mg/kg	NPCA, 2006

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

Test substance		Organism	Endpoint	Test	Concentration (mg/L)	Reference
Abbr.	Cas no.					
PFAS acrylates						
C4 acrylate[1]	67584-55-8	Activated sludge of a predominantly domestic sewage	NOEC, respiration rate	3 h, OECD 209	1000 (nominal)	ECHA, 2014

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

4.2.2.4 Plants

The toxicity effects of seven PFAS (PFBA, 5H 4:1 FTOH, PFOA, PFNA, PFDA, PFUnA, and PFDoA) 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.

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

Test substance		Organism	Endpoint	Test	Concentration (mM)	Reference
Abbr.	Cas no.					
Perfluorocarboxylic acids (PFCA) and their salts						
PFBA	375-22-4	Lettuce (*L. sativa*)	EC50, root elongaton	4.5 h, acute	4.19 (897 mg/L)	Ding *et al.*, 2012
Fluorotelomer alcohols (FTOH)						
5H 4:1 FTOH	355-80-6	Lettuce (*L. sativa*)	EC50, root elongaton	4.5 h, acute	2.98 (691 mg/L)	Ding *et al.*, 2012

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 sligthly 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 perfluorocarboxylates (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 exhibitet 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. PFCAs 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 xenoestrogen 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
PBT ASSESSMENTS OF SHORT-CHAIN PFAS AVAILABLE FROM FULL REACH REGISTRATION DOSSIERS (ECHA, 2014).

Assessed substance		Persistence	Bioaccumulation	Toxicity
Abbr.	Cas no.			
Fluorotelomer olefins				
PFBE[1] (4:2 FT olefin)	19430-93-4	not P/vP	Not B/not vB based on Log Kow ≤ 4.5	Not T EC10 or NOEC ≥ 0.01 mg/L for marine / freshwater organisms (long-term toxicity)
PFAS acrylates				
C4 acrylate[2]	67584-55-8	**vP (and P)** based on 28-day biodegradation of 0% to 3% (OECD 301B) and T1/2 in freshwater > 60 days	Not B/not vB based on Log Kow ≤ 4.5	not T

Assessed substance		Persistence	Bioaccumulation	Toxicity
Abbr.	Cas no.			
6:2 FTMA	2144-53-8	Not P/ vP based on other biodegradability screening tests. However, some of the degradation products may be long-lived.	Not B/not vB based on BCF ≤ 2,000 L/kg	Not T EC10 or NOEC ≥ 0.01 mg/L for marine / freshwater organisms (long-term toxicity), does not meet CMR criteria, no other evidence of chronic toxicity
6:2 FTA	17527-29-6	Screening criteria not fulfilled	Not B/not vB based on: BCF ≤ 2,000 L/kg	Not T EC10 or NOEC ≥ 0.01 mg/L for marine / freshwater organisms (long-term toxicity), does not meet CMR criteria, no other evidence of chronic toxicity
PFAS amines				
PTBA[3]	311-89-7	**vP (and P)** 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[4]	355-04-4	Screening criteria not fulfilled	Not B/not vB (based on Log Kow ≤ 4.5)	Screening criteria not fulfilled

1 PFBE - 3,3,4,4,5,5,6,6,6-nonafluorohexene

2 C4 acrylate - 2-[methyl[(nonafluorobutyl)sulphonyl]amino]ethyl acrylate

3 PTBA - tris(perfluorobutyl)amine

4 PFMP - Perfluoro-2-methylpentane

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 PFSAs 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 rewiewed 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 af 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 municipial 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**).

Test substance	Concentration (ng/L)	Number of samples (>LOD/ total)	Origin	Source as indicated by references	Reference
Tap water					
PFBS	n.d.–26	22/28	Germany	Runoff from contaminated soil	Skutlarek *et al.* 2006
PFBA	n.d.-11	7/28	Germany	Runoff from contaminated soil	Skutlarek *et al.* 2006
PFPeA	n.d.-77	22/28	Germany	Runoff from contaminated soil	Skutlarek *et al.* 2006
PFHxA	n.d.-56	22/28	Germany	Runoff from contaminated soil	Skutlarek *et al.* 2006
PFOS	n.d.–22	11/28	Germany	Runoff from contaminated soil	Skutlarek *et al.* 2006
PFOA	n.d.–519	22/28	Germany	Runoff from contaminated soil	Skutlarek *et al.* 2006
WWTP influent					
PFHxS	n.d.-32.8	8/11	Denmark	-	Bossi *et al.*, 2008
PFOS	n.d.-10.1	10/11	Denmark	-	Bossi *et al.*, 2008
PFOA	n.d.-23.5	8/11	Denmark	-	Bossi *et al.*, 2008
WWTP effluent					
PFHxS	n.d.-2.7	5/11	Denmark	-	Bossi *et al.*, 2008
PFOS	n.d.-18.1	9/11	Denmark	-	Bossi *et al.*, 2008
PFOA	n.d.-24.4	10/11	Denmark	-	Bossi *et al.*, 2008
WWTP sludge (concentrations in ng/g dw)					
PFBS	0.54 – 0.64	3/8	Norway	from fire fighting training ground near Haugesund	Klif, 2010
PFHxS	0.2 – 6.7	5/8	Norway	from fire fighting training ground near Haugesund	Klif, 2010
6:2 FTS	6.5 - 379	5/8	Norway	from fire fighting training ground near Haugesund	Klif, 2010
PFHxS	0.4-10.7	-[2]	Denmark	-	Bossi *et al.*, 2008
PFOS	4.8-74.1	-[2]	Denmark	-	Bossi *et al.*, 2008
PFOA	0.7-19.7	-[2]	Denmark	-	Bossi *et al.*, 2008
Marine water (concentrations in pg/L)					
PFBS	n.d.-45	52	North AO[4]	Long-range transport with sea	Zhao *et al.*, 2012

Test substance	Concentration (ng/L)	Number of samples (>LOD/ total)	Origin	Source as indicated by references	Reference
				currents	
PFBS	n.d.-17	20	Middle AO4	Long-range transport with sea currents	Zhao *et al.*, 2012
PFBS	n.d.-13	39	South AO4	Long-range transport with sea currents	Zhao *et al.*, 2012
PFHxS	n.d.-39	52	North AO4	Long-range transport with sea currents	Zhao *et al.*, 2012
PFHxS	n.d.-14	20	Middle AO4	Long-range transport with sea currents	Zhao *et al.*, 2012
PFHxS	n.d.-17	39	South AO4	Long-range transport with sea currents	Zhao *et al.*, 2012
PFHxA	n.d.-88	52	North AO4	Long-range transport with sea currents	Zhao *et al.*, 2012
PFHxA	n.d.-38	20	Middle AO4	Long-range transport with sea currents	Zhao *et al.*, 2012
PFHxA	n.d.-26	39	South AO4	Long-range transport with sea currents	Zhao *et al.*, 2012
PFOS	n.d.-114	52	North AO4	Long-range transport with sea currents	Zhao *et al.*, 2012
PFOS	n.d.-77	20	Middle AO4	Long-range transport with sea currents	Zhao *et al.*, 2012
PFOS	n.d.-72	39	South AO4	Long-range transport with sea currents	Zhao *et al.*, 2012
PFOA	n.d.-209	52	North AO4	Long-range transport with sea currents	Zhao *et al.*, 2012
PFOA	n.d.-110	20	Middle AO4	Long-range transport with sea currents	Zhao *et al.*, 2012
PFOA	n.d.-62	39	South AO4	Long-range transport with sea currents	Zhao *et al.*, 2012
Sediment (concentrations in ng/g dw)					
PFBS	0.17	1/9	Langavatn Lake in Norway	Seepage from fire fighting training ground near Bergen	Klif, 2010
PFHxS	0.7 – 2.6	9/9	Langavatn Lake in Norway	Seepage from fire fighting training ground near Bergen	Klif, 2010
6:2 FTS	1.5 – 12	9/9	Langavatn Lake in Norway	Seepage from fire fighting training ground near Bergen	Klif, 2010
Surface water					

Test sub-stance	Concentration (ng/L)	Number of samples (>LOD/ total)	Origin	Source as indicated by references	Reference
PFBS	n.d.–71	4/29	Germany	Runoff from contaminated soil	Skutlarek *et al.* 2006
PFBA	n.d.-143	17/29	Germany	Runoff from contaminated soil	Skutlarek *et al.* 2006
PFPeA	n.d.-1638	22/29	Germany	Runoff from contaminated soil	Skutlarek *et al.* 2006
PFHxA	n.d.-1248	22/29	Germany	Runoff from contaminated soil	Skutlarek *et al.* 2006
PFOS	n.d.–193	20/29	Germany	Runoff from contaminated soil	Skutlarek *et al.* 2006
PFOA	n.d.–3640	24/29	Germany	Runoff from contaminated soil	Skutlarek *et al.* 2006
PFOS	n.d.–193	-	Germany	Various sources	Ahrens, 2011
PFOA	n.d.–3640		Germany	Various sources	Ahrens, 2011
PFBS	68 - 148	3/3	Norway	Fire fighting training ground near Bergen	Klif, 2010
PFBS	11 – 35	3/3	Norway	Fire fighting training ground near Haugesund	Klif, 2010
PFHxS	319 - 471	3/3	Norway	Fire fighting training ground near Bergen	Klif, 2010
PFHxS	33 – 48	3/3	Norway	Fire fighting training ground near Haugesund	Klif, 2010
Landfill effluent					
PFHxS	n.d-3.1	1/3	Denmark	Landfill	Bossi *et al*, 2008
PFOS	n.d–3.8	2/3	Denmark	Landfill	Bossi *et al*, 2008
PFOA	n.d–5.8	1/3	Denmark	Landfill	Bossi *et al*, 2008
PFBS	220 (<0.39–1356)	20	Germany	Treated and untreated landfill leachates	Busch *et al.*, 2010
PFHxS	22.2 (<0.24–178)	20	Germany	Treated and untreated landfill leachates	Busch *et al.*, 2010
PFBA	458 (<3.36–2968)	20	Germany	Treated and untreated landfill leachates	Busch *et al.*, 2010
PFHxA	234 (<0.37–2509)	20	Germany	Treated and untreated landfill leachates	Busch *et al.*, 2010
PFOS	30.9 (0.01–235)	20	Germany	Treated and untreated landfill leachates	Busch *et al.*, 2010
PFOA	145 (<0.40–926)	20	Germany	Treated and untreated landfill leachates	Busch *et al.*, 2010

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.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[15].

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.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).

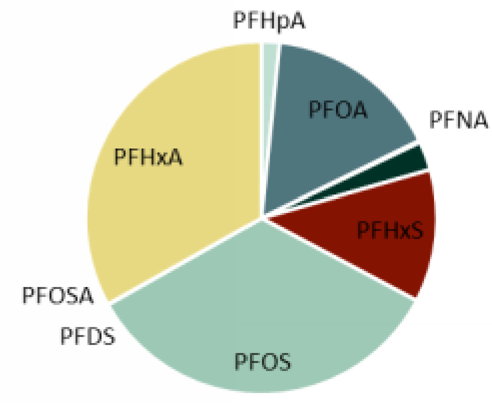


FIGURE 4.1
DISTRIBUTION OF PFAS FINDINGS IN GROUNDWATER SAMPLES FROM THE FIRE DRILL SITES (FROM TSITONAKI *ET AL.*, 2014).

---

[15] 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**).

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

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

(*Salmo trutta*). Concentrations of PFBS, PFPeA, PFHxA 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 4-13
PFAS CONCENTRATIONS IN BIOTA. DATA ON THE LONG-CHAIN PFAS-SUBSTANCES PFOS AND PFOA ARE INCLUDED IN THE TABLE FOR COMPARISON (IN **BOLD**).

Test substance	Species, organ	Concentration (ng/g ww)	No. of samples (>LOD/ total)	Origin	Reference
Marine fish					
PFBA	Herring, liver	0.23 - < 1.9	1/10[1]	Baltic Sea	IVL, 2009
PFBA	Perch, liver	< 1.5	0/5[1]	Baltic Sea	IVL, 2009
PFBA	Flounder, liver	< 0.4 – 1.0	1/7[1]	Baltic Sea	IVL, 2009
PFHxS	Herring, liver	< 0.1 – 0.57	7/10[1]	Baltic Sea	IVL, 2009
PFHxS	Perch, liver	< 0,07-0.20	2/5[1]	Baltic Sea	IVL, 2009
PFHxS	Flounder, liver	0.10 – 1.1	7/7[1]	Baltic Sea	IVL, 2009
PFHxS	Plaice, liver	<0.8	1[2]	Denmark, coastal waters	Bossi *et al.*, 2008
PFOS	Plaice, liver	156	1	Denmark, coastal waters	Bossi *et al.*, 2008
PFHxS	Flounder, liver	<0.8	2	Denmark, coastal waters	Bossi *et al.*, 2008
PFOS	Flounder, liver	9.5-25.4	2	Denmark, coastal waters	Bossi *et al.*, 2008
PFHxS	Eel, liver	<0.8 – 1.6	4	Denmark, coastal waters	Bossi *et al.*, 2008
PFOS	Eel, liver	13.1 – 54.3	4	Denmark, coastal waters	Bossi *et al.*, 2008
Freshwater fish					
PFHxS	Eel, liver	<0.8	7	Denmark, river or lake	Bossi *et al.*, 2008
PFOS	Eel, liver	13.7 – 70.1	7	Denmark, river or lake	Bossi *et al.*, 2008
PFHxS	Trout, liver	123 – 268	4	Langavatn Lake in Norway	KLIF, 2010

Test substance	Species, organ	Concentration (ng/g ww)	No. of samples (>LOD/ total)	Origin	Reference
				close to fire fighting training ground near Bergen	
PFOS	Trout, liver	2082 - 2532	4	Langavatn Lake in Norway close to fire fighting training ground near Bergen	KLIF, 2010
Crustaceans					
PFHxS	Crab	<0.1 – 0.46	4	Langavatn Lake in Norway close to fire fighting training ground near Bergen	KLIF, 2010
PFOS	Crab	0.8 – 4.9	4	Langavatn Lake in Norway close to fire fighting training ground near Bergen	KLIF, 2010
Birds					
PFHxA	Starling liver	< 0.15 – 0.25	8[3]	Mid and Southern Sweden	SW EPA, 2012
PFOS	Starling liver	1.89-6.73	8[3]	Mid and Southern Sweden	SW EPA, 2012
Mammals					
PFHxS	Otter, liver	6 (0-68)	93[4]	Sweden	SW EPA, 2012
PFOS	Otter, liver	1094 (21-8301)	93[4]	Sweden	SW EPA, 2012
PFBS	Grey seal, liver	< 0.006	20	Sweden	SW EPA, 2012
PFHxS	Grey seal, liver	0.7 (0.3-1.6)	20	Sweden	SW EPA, 2012
PFOS	Grey seal, liver	171 (89.6-490)	20	Sweden	SW EPA, 2012

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 Swedish otters sampled from 1972–2008.

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, 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 C_3-perfluorcarbon chain is different and has a slower renal clearance than PFHxA (C_5), because PFBA do not seem to be the substrates of the common transport protein Oatp1a1. In contradiction, PFBS with a C_4-perfluorocarbon chain seems not to be very bioaccumulative and has a much shorter half-life in the organism than PFHxS (C_6).

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 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 5-1
NOAEL VALUES OF SHORT-CHAIN PFAS IN RATS.

NOAEL mg/kg bw/d	PFBS	PFHxS	PFBA	PFHxA	6:2 FTOH
Male rat	60		6	50	5
Female rat	600	3	30	200	25

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 (T_4) 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 regurlarly 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 waxers 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 PFAAs 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 PFASs 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 thermophile,* 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 oberservation 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 degradatation 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 municipial 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 thyroidea 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 fluortelomer 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 biaccumulation 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 portential 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 compartements, 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 compartement (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

4:2 diPAP	4:2 Fluorotelomer phosphate diesters
4:2 FTOH	4:2 Fluorotelomer alcohol
6:2 diPAP	6:2 Fluorotelomer phosphate diesters
6:2 FTAC	6:2 Fluorotelomer acrylate
6:2 FTMAC	6:2 Fluorotelomer methacrylate
6:2 FTO	6:2 Fluorotelomer olefin
6:2 FTS	6:2 Fluorotelomer sulfonate
6:2 FTSA	6:2 Fluorotelomer sulfonic acid ()
6:2 monoPAP	6:2 Fluorotelomer phosphate monoester
8:2 diPAP	8:2 Fluorotelomer phosphate diesters
8:2 FTAL	8:2 Fluorotelomer aldehyde
8:2 FTCA	8:2 Fluorotelomer carboxylic acid
8:2 FTI	8:2 Fluorotelomer iodide
8:2 FTOH	8:2 Fluorotelomer alcohol
8:2 FTUOH	8:2 Unsaturated fluorotelomer alcohol
BCF	Bioconcentration factor
BMF	Biomagnification factor
C4-PFSAs	Perfluoroalkyl sulfonic acids with a chain length of four
C6/C6-PFPIA	Bis(perfluorohexyl) phosphinic acid
C6-PFSAs	Perfluoroalkyl sulfonic acids with a chain length of six
C8-PFPA	Perfluorooctyl phosphonic acid
CLP	Classification, Labelling and Packaging (Regulation)
C&L	Classification and Labelling
CMR	Carcinogenic, mutagenic or toxic to reproduction
diPAPS	polyfluoroalkyl-diester phosphates
d.l.	Detection limite
dw	dry weight
EC_n	Effect concentration where n % of the species tested show the effect
ErC	Effect concentration based on a rate (r), typically a growth rate
ECb	Effect concentration based on (algae) biomass
EFSA	European Food Safety Authority
EPA	Environmental Protection Agency
EtFOSAA	N-Ethyl perfluorooctane sulfonamidoacetic acid
FOSA	Perfluorooctane sulfonamide
FTCA	Fluorotelomer carboxylates
PTO	Fluorotelomer olefin
FTOH	Fluorotelomer alcohols
FTS	Fluorotelomer sulfonates
FTUCA	Fluorotelomer unsaturated carboxylic acids
KPFO	PFOA potassium salt
Kd	Soil/water distribution coefficient
LC	Lethal effect concentration
LOAEL	Lowest observable adverse effect level

LOUS	List of Undesirable Substances
MACeco:	Maximum Acceptable Concentration for ecosystems
monoPAP	polyfluoroalkyl-mono phosphates
NHANES	National Health and Nutrition Examination Survey (in the USA)
NOAEL	No observable adverse effect level
NOEC	No observable effect concentration
NOVANA	Danish national surveillance programme for the aquatic environment
MCF-7	Michigan Cancer Foundation – 7 breast cancer cell line
n:2 FTIs	n:2 Fluorotelomer iodides
n:2 FTOHs	n:2 Fluorotelomer alcohols
OECD	Organisation for Economic Co-operation and Development
OSPAR	Convention for the Protection of the Marine Environment of the North-East Atlantic
PAFs	Perfluoroalkanoyl fluorides
PAPs	Polyfluoroalkyl phosphoric acid esters
PASFs	Perfluoroalkane sulfonyl fluorides
PBSF	Perfluorobutane sulfonyl fluoride
PBT	Persistent, bioaccumulative and toxic (in the environment)
PFAA	Perfluoroalkyl acids
PFALs	Perfluoroalkyl aldehydes
PFAS	Entire group of perfluoroalkyl and polyfluoroalkyl substances
PFBA	Perfluorobutanoic acid
PFBS	Perfluorobutane sulfonic acid
PFCA	Perfluoroalkyl carboxylic acids
PFCA	Perfluoroalkyl carboxylates
PFCs	Collective designation of perfluoroalkyl substances, polyfluoroalkyl substances and side-chain fluorinated polymers
PFDA	Perfluorodecanoic acid
PFDoDA	Perfluorododecanoic acid
PFDS	Perfluorodecane sulfonic acid
PFHpA	Perfluoroheptanoic acid
PFHpS	Perfluoroheptane sulfonic acid
PFHxA	Perfluorohexanoic acid
PFHxI	Perfluorohexyl iodide
PFHxS	Perfluorohexane sulfonic acid
PFNA	Perfluorononanoic acid
PFOA	Perfluorooctanoic acid
PFODA	Perfluorooctadecanoic acid
PFOS	Perfluorooctane sulfonate
PFOS	Perfluorooctane sulfonic acid
PFOSA	Perfluorooctane sulphonamide
PFOSF	Perfluorooctane sulfonyl fluoride
PFPeA	Perfluoropentanoic acid
PFPeS	Perfluoropentane sulfonate
PFPeS	Perfluoropentane sulfonic acid
PFPA	Perfluoroalkyl phosphonic acids
PFPiA	Perfluoroalkyl phosphinic acids
PFSAs	Perfluoroalkyl sulfonic acids
PFSA	Perfluoroalkane sulfonates
PFTeDA	Perfluorotetradecanoic acid
PFUnDA	Perfluoroundecanoic acid = PFUnA
POF	Perfluorooctanoyl fluoride
POP	Persistent organic pollutants
POSF	Perfluorooctane sulfonyl fluoride

PPARα	Peroxisome proliferator-activated receptor-α
PTFE	Polytetrafluoroethylene
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals ((Regulation (EC) No 1907/2006)
ROS	Reactive oxygen species
SVHC	Substances of Very High Concern
SW EPA	Swedish Environmental Protection Agency
TDI	Tolerable daily intake
UNEP	The United Nations Environment Programme
UNIDO	The United Nations Industrial Development Organization
USEPA	United States Environmental Protection Agency
vPvB	Very persistent and very bioaccumulative
ww	Wet weight
WWTP	Waste water treatment plant

References

Human health references

Arbuckle TE, Kubwabo C, Walker M, Davis K, Lalonde K, Kosarac I, Wen SW, Arnold DL. Umbilical cord blood levels of perfluoroalkyl acids and polybrominated flame retardants. International Journal of Hygiene and Environmental Health 2013; 216: 184-195.

Axmon, Anna ; Axelsson, Jonatan ; Jakobsson, Kristina ; Lindh, Christian H. ; Jönsson, Bo A.G. Time trends between 1987 and 2007 for perfluoroalkyl acids in plasma from Swedish women. Chemosphere 102 (2014) 61–67.

Becanova J, Karaskova P, Klanova J. Perflurinated compounds (PFCs) in outdoor and indoor textile. Poster: 5th Int. Workshop on Per- and Polyfluorinated Alkyl Substances - PFAS. Helsingør, Oct. 27-29, 2013.

Beesoon S, Genuis SJ, Benskin JP, Martin JW. Exceptionally High Serum Concentrations of Perfluorohexanesulfonate in a Canadian Family are linked to Home Carpet Treatment Applications. Environ. Sci. Technol. 2012, 46 (23), 12960–12967.

Benskin JP, De Silva AO, Martin LJ, Arsenault G, McCrindle R, Riddell N, Mabury SA, Martin JW. Disposition of perfluorinated acid isomers in Sprague-Dawley rats; Part 1: Single dose. Environmental Toxicology and Chemistry 2009, 28, 542-554.

Bijland S, Rensen PC, Pieterman EJ, Maas AC, van der Hoorn JW, van Erk MJ, Havekes LM, Willems van Dijk K, Chang SC, Ehresman DJ, Butenhoff JL, Princen HM. Perfluoroalkyl sulfonates cause alkyl chain length-dependent hepatic steatosis and hypolipidemia mainly by impairing lipoprotein production in APOE*3-Leiden CETP mice. Toxicol Sci 2011; 123: 290-303.

Bischel HN, Macmanus-Spencer LA, Zhang C, Luthy RG. Strong associations of short-chain perfluoroalkyl acids with serum albumin and investigation of binding mechanisms. Environ Toxicol Chem 2011; 30: 2423-2430.

Bjork, J.A., Wallace, K.B. (2009). Structure-activity relationships and human relevance for perfluoroalkyl acid-induced transcriptional activation of peroxisome proliferation in liver cell cultures. Toxicol Sci, 111: 89-99.

Borg D, Håkansson H. 2012. Environmental and Health Risk Assessment of Perfluoroalkylated and Polyfluoroalkylated Substances (PFASs) in Sweden. Naturvårdsverket Rapport 6513.
[http://www.naturvardsverket.se/Documents/publikationer 6400/978-91-620-6513-3.pdf](http://www.naturvardsverket.se/Documents/publikationer6400/978-91-620-6513-3.pdf)

Brantsæter AL, Whitworth KW, Ydersbond TA, Haug LS, Haugen M, Knutsen HK, Thomsen C, Meltzer HM, Becher G, Sabaredzovic A, Hoppin JA, Eggesbø M, Longnecker MP. Determinants of plasma concentrations of perfluoroalkyl substances in pregnant Norwegian women. Environ Int 2013; 54: 74-84.

Buhrke T, Kibellus A, Lampen A. In vitro toxicological characterization of perfluorinated carboxylic acids with different carbon chain lengths. Toxicology Letters 2013; 218: 97-104.

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.

Butenhoff JL, Bjork JA, Chang SC, Ehresman DJ, Parker GA, Das K, Lau C, Lieder PH, van Otterdijk FM, Wallace KB. Toxicological evaluation of ammonium perfluorobutyrate in rats: twenty-eight-day and ninety-day oral gavage studies. Reprod Toxicol 2012; 33: 513-30.

Butenhoff JL, Chang SC, Ehresman DJ, York RG. Evaluation of potential reproductive and developmental toxicity of potassium perfluorohexanesulfonate in Sprague Dawley rats. Reprod Toxicol 2009; 27: 331-41.

Cassone CG, Vongphachan V, Chiu S, Williams KL, Letcher RJ, Pelletier E, Crump D, Kennedy SW. *In ovo* effects of perfluorohexane sulfonate and perfluorohexanoate on pipping success, development, mRNA expression, and thyroid hormone levels in chicken embryos. Toxicol. Sci. 127, 216 (2012).

Chang, S. C., Das, K., Ehresman, D. J., Ellefson, M. E., Gorman, G. S., Hart, J. A., Noker, P. E., Tan, Y. M., Lieder, P. H., Lau, C., Olsen, G. W., Butenhoff, J. L. (2008). Comparative pharmacokinetics of perfluorobutyrate in rats, mice, monkeys, and humans and relevance to human exposure via drinking water. Toxicol. Sci., 104, 40–53.

Chengelis, C.P., Kirkpatrick, J.B., Myers, N.R., Shinohara, M., Stetson, P.L., Sved, D.W., 2009a. Comparison of the toxicokinetic behavior of perfluorohexanoic acid (PFHxA) and nonafluorobutane-1-sulfonic acid (PFBS) in cynomolgus monkeys and rats. Reprod. Toxicol. 27, 400–406.

Chengelis, C.P., Kirkpatrick, J.B., Radovsky, A., Shinohara, M., (2009). A 90-day repeated dose oral (gavage) toxicity study of perfluorohexanoic acid (PFHxA) in rats (with functional observational battery and motor activity determinations). Reprod. Toxicol. 27: 342–351.

Corsini E, Sangiovanni E, Avogadro A, Galbiati V, Viviani B, Marinovich M, Galli CL, Dell'Agli M and Germolec DR, 2012. In vitro characterization of the immunotoxic potential of several perfluorinated compounds (PFCs). Toxicology and Applied Pharmacology, 258, 248-255.

D'eon J.C., Mabury S.A. (2011). Exploring indirect sources of human exposure to perfluoroalkyl carboxylates (PFCAs): evaluating uptake, elimination, and biotransformation of polyfluoroalkyl phosphate esters (PAPs) in the rat. Environmental Health Perspectives, 119: 344-350.

D'eon, J. C.; Crozier, P. W.; Furdui, V. I.; Reiner, E. J.; Libelo, E. L.; Mabury, S. A. Observation of a Commercial Fluorinated Material, the Polyfluoroalkyl Phosphoric Acid Diesters, in Human Sera, Wastewater Treatment Plant Sludge, and Paper Fibers. Environ. Sci. Technol. 2009, 43, 4589–4594.

D'eon, J.C., Mabury, S.A. (2007). Production of perfluorinated carboxylic acids (PFCAs) from the biotransformation of polyfluoroalkyl phosphate surfactants (PAPS): exploring routes of human contamination. Environ. Sci. Technol, 41: 4799–4805.

D'eon, J.C., Mabury, S.A. (2010). Uptake and elimination of perfluorinated phosphonic acids in the rat. Environmental Toxicology and Chemistry. 29(6): 1319–1329

Das, K., P. Rosen, B. Mitchell, C. R. Wood, B. D. Abbott, and C. Lau. Perfluorophosphonic acid activates peroxisome proliferator-activated receptor-alpha but not constitutive androstane receptor in the murine liver. Presented at Society of Toxicology (SOT) Annual Meeting, Washington, DC, March 06 - 10, 2011.

Das, K.P., Grey, B.E., Zehr, R.D., Wood, C.R., Butenhoff, J.L., Chang, S.C., Ehresman, D.J., Tan, Y.M., Lau, C. (2008). Effects of perfluorobutyrate exposure during pregnancy in the mouse. Toxicol Sci, 105: 173–181.

Dong GH, Tung KY, Tsai CH, Liu MM, Wang D, Liu W, Jin YH, Hsieh WS, Lee YL and Chen PC, 2013. Serum Polyfluoroalkyl Concentrations, Asthma Outcomes, and Immunological Markers in a Case-Control Study of Taiwanese Children. Environ Health Perspect 121: 507–513.

Dreyer, A, Neugebauer, F, Neuhaus, T, Selke, S. Emission of perfluoroalkyl substances (PFASs) from textiles. Paper, Dioxin 2014, Madrid August 31st - September 5th.

EFSA Panel on food contact materials, enzymes, flavourings and processing aids (CEF). Scientific Opinion on the safety evaluation of the substance, (perfluorobutyl)ethylene, CAS No. 19430-93-4, for use in food contact materials. EFSA Journal 2011; 9(2):2000.

Ehresman, D.J., Froehlich, J.W., Olsen, G.W., Chang, S.C., Butenhoff, J.L., 2007. Comparison of human whole blood, plasma, and serum matrices for the determination of perfluorooctanesulfonate (PFOS), perfluorooctanoate (PFOA), and other fluorochemicals. Environ. Res. 103, 176–184.

ENVIRON (2014). Assessment of POP Criteria for Specific Short-Chain perfluorinated Alkyl Substances. Report prepared for FluoroCouncil, Washington, DC. Project Number: 0134304A . ENVIRON International Corporation, Arlington, Virginia, January 2014.

Eriksen, K.T., Raaschou-Nielsen, O. , Sørensen, M., Roursgaard, M., Loft, S., Møller, P. (2010). Genotoxic potential of the perfluorinated chemicals PFOA, PFOS, PFBS, PFNA and PFHxA in human HepG2 cells. Mutat Res, 700: 39-43.

Fisher M, Arbuckle TE, Wade M, Haines DA. Do perfluoroalkyl substances affect metabolic function and plasma lipids? - Analysis of the 2007-2009, Canadian Health Measures Survey (CHMS) Cycle 1. Environ Res 2013; 121: 95-103.

Foreman, J.E., Chang, S.C., Ehresman, D.J., Butenhoff, J.L., Anderson, C.R., Palkar, P.S., Kang, B.H., Gonzalez, F.J., Peters, J.M., 2009. Differential hepatic effects of perfluorobutyrate mediated by mouse and human PPAR-alpha. Toxicological Sciences 110, 204–211.

Fraser AJ, Webster TF, Watkins DJ, Nelson JW, Stapleton HM, Calafat AM, Kato K, Shoeib M, Vieira VM, McClean MD. Polyfluorinated Compounds in Serum Linked to Indoor Air in Office Environments. Environmental Science & Technology, 2012; 46: 1209-1215.

Fraser AJ, Webster TF, Watkins DJ, Strynar MJ, Kato K, Calafat AM, Vieira VM, McClean MD. Polyfluorinated compounds in dust from homes, offices, and vehicles as predictors of concentrations in office workers' serum. Environ Int 2013; 60, 128–136.

Frisbee SJ, Brooks AP Jr, Maher A, Flensborg P, Arnold S, Fletcher T, *et al.* 2009. The C8 health project: design, methods, and participants. Environ Health Perspect 117:1873–1882.

Fromme H, Mosch C, Morowitz M, Alba-Alejandre I, Boehmer S, Kiranoglu M, Faber F, Hannibal I, Genzel-Boroviczény O, Koletzko B, Volkel W (2010). Pre-and postnatal exposure to perfluorinated compounds. Environ. Sci. Technol. 2010; 44: 7123-7129.

Fu JJ, Gao Y, Wang YW, Zhang AQ, Jiang GB. Temporal trends and estimated half-lives of perfluoroalkyl acids in fluorochemical workers in China. Paper, Dioxin 2014, Madrid August 31st - September 5th.

Fujii Y, Harada KH, Koizumi A. Occurrence of perfluorinated carboxylic acids (PFCAs) in personal care products and compounding agents. Chemosphere 93 (2013) 538–544.

Gannon, S.A., Johnson, T., Nabb, D.L., Serex, T.L., Buck, R.C., Loveless, S.E. (2011) Absorption, distribution, metabolism, and excretion of [1-14C]-perfluorohexanoate ([14C]-PFHx) in rats and mice. Toxicology, 283: 55-62.

Gao Y, Fu JJ, Wang T, Wang YW, Jiang GB. Levels, temporal trends and elimination of PFOS, PFOA and PFHxS isomers in occupational workers from a PFASs manufactory in China. Paper, Dioxin 2014, Madrid August 31st - September 5th.

Genuis S.J., Birkholz D., Ralitsch M., Thibault N.. Human detoxification of perfluorinated compounds. Public Health 124 (2010) 367–375.

Glynn A, Berger U, Bignert A, Ullah S, Aune M, Lignell S, Darnerud PO. Perfluorinated Alkyl Acids in Blood Serum from Primiparous Women in Sweden: Serial Sampling during Pregnancy and Nursing, And Temporal Trends 1996–2010. Environmental Science & Technology 2012; 46: 9071-9079.

Gorrochategui E, Pérez-Albaladejo E, Casas J, Lacorte S, Porte C. Perfluorinated chemicals: Differential toxicity, inhibition of aromatase activity and alteration of cellular lipids in human placental cells. Toxicology and Applied Pharmacology 277 (2014) 124–130.

Grandjean, P., Andersen, E.W., Budtz-Jørgensen, E., Nielsen, F., Mølbak, K., Weihe, P., Heilmann, C. (2012). Serum vaccine antibody concentrations in children exposed to perfluorinated compounds. Serum vaccine JAMA, 307: 391-397.

Greenpeace (2012). Chemistry for any weather. Greenpeace International.

Gump, B.B., Wu, Q., Dumas, A.K., Kannan, K. (2011). Perfluorochemical (PFC) Exposure in Children: Associations with Impaired Response Inhibition. Environ Sci Technol, 45: 8151–8159.

Gützkow KB, Haug LS, Thomsen C, Sabaredzovic A, Becher G, Brunborg G. Placental transfer of perfluorinated compounds is selective – A Norwegian Mother and Child sub-cohort study. Int J Hyg Environ Health. 2012; 215: 216-9.

Hagen, D.F., Belisle, J., Johnson, J.D., Venkateswarlu, P. (1981). Characterization of fluorinated metabolites by a gas chromatographic-helium microwave plasma detector – the biotransformation of 1H, 1H, 2H, 2H-perfluorodecanol to perfluorooctanoate. Anal Biochem, 118: 336-343.

Hamm MP, Cherry N, Chan E, Martin JW and Burstyn I, 2010. Maternal exposure to perfluorinated acids and fetal growth. Journal of Exposure Science and Environmental Epidemiology, 20, 589-597.

Han X, Nabb DL, Russell MH, Kennedy GL, Rickard RW. Renal elimination of perfluorocarboxylates (PFCAs). Chem Res Tox. 2012; 25: 35-46.

Harada K, Xu F, Ono K, Iijima T, Koizumi A. Effects of PFOS and PFOA on L-type Ca2+ currents in guinea-pig ventricular myocytes. Biochem Biophys Res Commun. 2005; 329: 487-94.

Harada, K., Inoue, K., Morikawa, A., Yoshinaga, T., Saito, N., and Koizumi, A. (2005) Renal clearance of perfluorooctane sulfonate and perfluorooctanoate in humans and their species-specific excretion. Environ. Res. 99, 253–261.

Hardell E, Kärrman A, van Bavel B, Bao J, Carlberg M, Hardell L. Case-control study on perfluorinated alkyl acids (PFAAs) and the risk of prostate cancer. Environ Int. 2014; 63: 35-39.

Herzke D, Posner S, Olsson E. (2009) Survey, screening and analyses of PFCs in consumer products. TA-2578/2009. Swerea/IVF Project report 09/47.

Hickey NJ, Crump D, Jones SP, Kennedy SW. Effects of 18 Perfluoroalkyl Compounds on mRNA Expression in Chicken Embryo Hepatocyte Cultures. Toxicological Sciences 111, 311–320 (2009).

Hoffman K, Webster TF, Weisskopf MG, Weinberg J, Vieira VM. 2010. Exposure to polyfluoroalkyl chemicals and attention deficit/hyperactivity disorder in U.S. children 12–15 years of age. Environ Health Perspect 118: 1762–1767.

Hu Wy, Jones PD, DeCoen W, King L, Fraker P, Newsted J, Giesy JP. Alterations in cell membrane properties caused by perfluorinated compounds. Comp Biochem Physiol C Toxicol Pharmacol. 2003; 135: 77-88.

Ikeda, T., Aiba, K., Fukuda, K., Tanaka, M. (1985). The indtion of peroxisome proliferation in rat liver by perfluorinated fatty acids, metabolically inert derivatives of fatty acids. J Biochem, 98: 475- 482.

Iwai H. Toxicokinetics of ammonium perfluorohexanoate. Drug Chem Toxicol. 2011; 34: 341-346

Iwai H, Hoberman AM. Oral (Gavage) Combined Developmental and Perinatal/Postnatal Reproduction Toxicity Study of Ammonium Salt of Perfluorinated Hexanoic Acid in Mice. Int J Toxicol. 2014; 33: 219-237

Jain RB. Association between thyroid profile and perfluoroalkyl acids: Data from NHANES 2007–2008. Environmental Research 126 (2013) 51–59.

Jensen AA, Poulsen PB, Bossi R. Survey and environmental/health assessment of fluorinated substances in impregnated consumer products and impregnating agents. Survey of Chemical Substances in Consumer Products, No. 99 2008, DEPA 2008.

Joensen, U.N., Bossi, R., Leffers, H., Jensen, A.A., Skakkebæk, N.E., Jørgensen, N. (2009). Do perfluoroalkyl compounds impair human semen quality? Environmental Health Perspectives, 117: 923–927.

Jones PD, Hu W, De Coen W, Newsted JL, Giesy JP. Binding of perfluorinated fatty acids to serum proteins. Environ Toxicol Chem. 2003; 22: 2639-2649.

Jönsson B, Axmon A, Lindh C, Hydbom AR, Axelsson J, Giwercman A, Bergman Å. Tidstrender för och halter av persistenta fluorerade, klorerade och bromerade organiska miljögifter i serum samt ftalater i urin hos unga svenska män – Resultat från den tredje uppföljningsundersökningen år 2009-2010. Rapport till Naturvårdsverket – 2010-11-19. Avdelningen för Arbets- och miljömedicin, Lunds Universitet, 221 85 Lund.

Kato, K.; Wong, L.-Y.; Jia, L. T.; Kuklenyik, Z.; Calafat, A. M. Trends in exposure to polyfluoroalkyl chemicals in the U.S. Population: 1999–2008. Environ. Sci. Technol. 2011, 45, 8037–8045.

Kim SK, Lee KT, Kang CS, Tao L, Kannan K, Kim KR, Kim CK, Lee JS, Park PS, Yoo YW, Ha JY, Shin YS and Lee JH, 2011. Distribution of perfluorochemicals between sera and milk from the same mothers and implications for prenatal and postnatal exposures. Environmental Pollution, 159, 169-174.

Kjeldsen LS, Bonefeld-Jørgensen EC. Perfluorinated compounds affect the function of sex hormone receptors. Environ Sci Pollut Res (2013) 20: 8031–8044.

Kleszczyński K, Gardzielewski P, Mulkiewicz E, Stepnowski P and Składanowski AC, 2007. Analysis of structure-cytotoxicity in vitro relationship (SAR) for perfluorinated carboxylic acids. Toxicology in Vitro, 21, 1206-1211.

Kudo, N., Bandai, N., Suzuki, E., Katakura, M., Kawashima, Y. (2000). Induction by perfluorinated fatty acids with different carbon length of peroxisomal oxidation in the liver of rats. Chem-Biol Interact, 124: 119.

Kudo, N., Katakura, M., Sato, Y., and Kawashima, Y. (2002) Sex hormone-regulated renal transport of perfluorooctanoic acid. Chem.-Biol. Interact. 139, 301–316.

Kudo, N., Suzuki, E., Katakura, M., Ohmori, K., Noshiro, R., Kawashima, Y. (2001). Comparison of the elimination between perfluorinated fatty acids with different carbon chain length in rats. Chem-Biol Interact, 134: 203-216.

Kärrman A, Ericson I, van Bavel B, Darnerud PO, Aune M, Glynn A, Lignell S and Lindstrom G, 2007. Exposure of perfluorinated chemicals through lactation: levels of matched human milk and serum and a temporal trend, 1996-2004, in Sweden. Environmental Health Perspectives, 115, 226-230.

Kärrman A, Harada KH, Inoue K, Takasuga T, Ohi E, Koizumi A. Relationship between dietary exposure and serum perfluorochemical (PFC) levels--a case study. Environ Int. 2009; 35: 712-717.

Ladics, G.S., Kennedy, G.L., O'Connor, J., Everds, N., Malley, L.A., Frame, S.R., Gannon, S., Jung, R., Roth, T., Iwai, H., Shin-ya, S. 90-day oral gavage toxicity study of 8-2 fluorotelomer alcohol in rats. Drug Chemical Toxicology 2008, 31, 189–216.

Ladics, G.S., Stadler, J.C., Makovec, G.T., Everds, N.E., Buck, R.C. Subchronic toxicity of a fluoroalkylethanol mixture in rats. Drug Chemical Toxicology 2005; 28: 135–158.

Langer V, Dreyer A, Ebinghaus R. (2010) Polyfluorinated compounds in residential and nonresidential indoor air. Environ Sci Technol 2010, 44:8075-8081.

Larsen ST, Dallot C, Larsen SW, Rose F, Poulsen SS, Nørgaard AW, Hansen JS, Sørli JB, Nielsen GD, Foged C. Mechanism of Action of Lung Damage Caused by a Nanofilm Spray Product. Toxicol. Sci. (2014) 140 (2): 436-444.

Lau C, Butenhoff JL, Rogers JM. The developmental toxicity of perfluoroalkyl acids and their derivatives. Toxicology and Applied Pharmacology Volume 198, 2004, 231–241.

Lau C, Anitole K, Hodes C, Lai D, Pfahles-Hutchens A, and Seed J. Perfluoroalkyl Acids: A Review of Monitoring and Toxicological Findings. Toxicol. Sci. (2007) 99 : 366-394.

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.

Lee, H., Mabury, S.A., 2011. A Pilot Survey of Legacy and Current Commercial Fluorinated Chemicals in Human Sera from United States Donors in 2009. Environmental science & technology 45, 8067–8074.

Liao, C.Y., Li, X.Y., Wu, B., Duan, S., Jiang, G.B. (2008). Acute enhancement of synaptic transmission and chronic inhibition of synaptogenesis induced by perfluorooctane sulfonate through mediation of voltage-dependent calcium channel. Environ. Sci. Technol., 42: 5335–5341.

Liao, C.Y., Wang, T., Cui, L., Zhou, Q., Duan, S., Jiang, G. (2009). Changes in synaptic transmission, calcium current, and neurite growth by perfluorinated compounds are dependent on the chain length and functional group. Environ Sci Technol, 43: 2099-2104.

Lieder, P.H., Chang, S.C., York, R.G., Butenhoff, J.L., 2009a. Toxicological evaluation of potassium perfluorobutanesulfonate in a 90-day oral gavage study with Sprague Dawley rats. Toxicology 255, 45–52.

Lieder, P.H., York, R.G., Hakes, D.C., Chang, S.C., Butenhoff, J.L. (2009). A two-generation oral gavage reproduction study with potassium perfluorobutanesulfonate (K+PFBS) in Sprague Dawley rats. Toxicology, 259: 33-45.

Lindeman B, Maass C, Duale N, Gützkow KB, Brunborg G, Andreassen A. Effects of per- and polyfluorinated compounds on adult rat testicular cells following in vitro exposure. Reproductive Toxicology 33 (2012) 531–537.

Long M, Ghisari M, Bonefeld-Jørgensen EC. Effects of perfluoroalkyl acids on the function of the thyroid hormone and the aryl hydrocarbon receptor. Environ Sci Pollut Res (2013) 20: 8045–8056.

Loveless, S.E., Slezak, B., Serex, T., Lewis, J., Mukerji, P., O'Connor, J.C., Donner, E.M., Frame, S.R., Korzeniowski, S.H., Buck, R.C., 2009. Toxicological evaluation of sodium perfluorohexanoate. Toxicology 264, 32–44.

Luebker, D.J., Case, M.T., York, R.G., Moore, J.A., Hansen, K.J., Butenhoff, J.L. (2005). Two generation reproduction and cross-foster studies of perfluorooctanesulfonate (PFOS) in rats. Toxicology, 215: 126–148.

Luebker, D.J., Hansen, K.J., Bass, N.M., Butenhoff, J.L., Seacat, A.M. (2002). Interactions of fluorochemicals with rat liver fatty-acid binding protein. Toxicology, 176: 175-185.

Maestri L, Negri S, Ferrari M, Ghittori S, Fabris F, Danesino P, Imbriani M. Determination of perfluorooctanoic acid and perfluorooctane sulfonate in human tissues by liquid chromatography/single quadropole mass spectrometry. Rapid Commun Mass Spectrom 2006; 20: 2728-2734.

Maisonet, M., Terrell, M.L., McGeehin, M.A., Christensen, K.Y., Holmes, A., Calafat, A.M., Marcus, M. (2012). Maternal concentrations of polyfluoroalkyl compounds during pregnancy and fetal and postnatal growth in British girls. Environ Health Perspect. 120(10):1432-1437.

Maras, M., Vanparys, C., Muylle, F., Robbens, J., Berger, U., Barber, J.L., Blust, R., De Coen, W. (2006). Estrogen-like properties of fluorotelomer alcohols as revealed by MCF-7 breast cancer cell proliferation. Environ Health Perspec, 114: 100-105.

Martin, J.W., Mabury, S.A., O'Brien, P.J. (2005). Metabolic products and pathways of fluorotelomer alcohols in isolated rat hepatocytes. Chem Biol Interact, 155: 165-180.

Mulkiewicz E, Jastorff B, Składanowski AC, Kleszczyński K and Stepnowski P, 2007. Evaluation of the acute toxicity of perfluorinated carboxylic acids using eukaryotic cell lines, bacteria and enzymatic assays. Environmental Toxicology and Pharmacology, 23, 279-285.

Naile JE, Wiseman S, Bachtold K, Jones PD, Giesy JP. Transcriptional effects of perfluorinated compounds in rat hepatoma cells. Chemosphere. 2012; 86: 270-277.

Nilsson, H., Karrman, A., Westberg, H., Rotander, A., Lindstrom, G., 2010b. A time trend study of significantly elevated perfluorocarboxylate levels in humans after using fluorinated ski wax. Environ. Sci. Technol. 44, 2150–2156.

Nilsson, H., Kärrman, A., Rotander, A., van Bavel, B., Lindström, G., Westberg, H., 2013. Biotransformation of fluorotelomer compound to perfluorocarboxylates in humans. Environ. Int. 51, 8–12.

Nilsson, H., Rotander, A., Van Bavel, B., Lindström, G., Westberg, H., 2010a. Inhalation exposure to fluorotelomer alcohols yield perfluorocarboxylates in human blood? Environ. Sci. Technol. 44, 7717–7722.

Nørgaard AW, Hansen JS, Sørli JB, Levin M, Wolkoff P, Nielsen GD, Larsen ST. Pulmonary Toxicity of Perfluorinated Silane-Based Nanofilm Spray Products: Solvent Dependency. Toxicol. Sci. (2014) 137: 179-188.

Nørgaard AW, Larsen ST, Hammer M, Poulsen SS, Jensen KA, Nielsen GD, Wolkoff P. Lung Damage in Mice after Inhalation of Nanofilm Spray Products: The Role of Perfluorination and Free Hydroxyl Groups. Toxicol. Sci. (2010) 116: 216-224.

Nørgaard AW. Mass spectrometric study of nanofilm products. Chemistry, exposure and health effects. PhD Thesis, University of Copenhagen, 2010.

Oldham ED, Xie W, Farnoud AM, Fiegel J, Lehmler HJ. Disruption of phosphatidylcholine monolayers and bilayers by perfluorobutane sulfonate. J Phys Chem B. 2012; 116: 9999-10007.

Olsen GW, Chang SC, Noker PE, Gorman GS, Ehresman DJ, Lieder PH, Butenhoff JL.A comparison of the pharmacokinetics of perfluorobutanesulfonate in rats, monkeys and humans. Toxicology 2009; 256: 65-74.

Olsen, G.W., Burris, J.M., Ehresman, D.J., Froehlich, J.W., Seacat, A.M., Butenhoff, J.L., Zobel, L. R. (2007). Half-life of serum elimination of perfluorooctanesulfonate, perfluorohexanesulfonate, and perfluorooctanoate in retired fluorochemical production workers. Environ Health Perspect, 115: 1298–1305.

Olsen, G.W., Chang, S.C., Noker, P.E., Gorman, G.S., Ehresman, D.J., Lieder, P.H., Butenhoff, J.L. (2009). A comparison of the pharmacokinetics of perfluorobutanesulfonate (PFBS) in rats, monkeys, and humans. Toxicology., 256: 65-74.

Pérez F, Nadal M, Navarro-Ortega A, Fàbrega F, Domingo JL, Barceló D, Farré M. Accumulation of perfluoroalkyl substances in human tissues. Environ Int. 2013; 59: 354-362.

Phillips, M. M. M., Dinglasan-Panlilio, M. J. A., Mabury, S. A., Solomon, K. R., and Sibley, P. K. (2007) Fluorotelomer acids are more toxic than perfluorinated acids. Environ. Sci. Technol. 41, 7159–7163.

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

Rand, A. A.; Mabury, S. A. 2012. In Vitro Interactions of Biological Nucleophiles with Fluorotelomer Unsaturated Acids and Aldehydes: Fate and Consequences. Env Sci & Technol 46:7398-7406.

Rand AA, Rooney JP, Butt CM, Meyer JN, Mabury SA. Cellular Toxicity Associated with Exposure to Perfluorinated Carboxylates (PFCAs) and their Metabolic Precursors. Chemical Research in Toxicology 2014; 27(1): 42-50.

Russell MH, Nilsson H, Buck RC. Elimination kinetics of perfluorohexanoic acid in humans and comparison with mouse, rat and monkey. Chemosphere 2013; 93: 2419-2425.

Schlummer M, Gruber L, Fiedler D, Kizlauskas M, Müller J. Detection of fluorotelomer alcohols in indoor environments and their relevance for human exposure. Environ Int 2013; 57–58: 42–49.

Seals R, Bartell SM, Steenland K. Accumulation and clearance of perfluorooctanoic acid (PFOA) in current and former residents of an exposed community. Environ Health Perspect. 2011; 119: 119-124.

Serex T, Anand S, Munley S, Donner EM, Frame SR, Buck RC, Loveless SE. Toxicological evaluation of 6:2 fluorotelomer alcohol. Toxicology 2014; 319: 1–9.

Slotkin TA, MacKillop EA, Meinick RL, Thayer KA and Seidler FJ, 2008. Developmental neurotoxicity of perfluorinated chemicals modeled in vitro. Environmental Health Perspectives, 116, 716-722.

Soto AM, Sonnenschein C, Chung KL, Fernandez MF, Olea N, Serrano FO. The E-SCREEN assay as a tool to identify estrogens: an update on estrogenic environmental pollutants. Environ Health Perspect. 1995 Oct;103 Suppl 7: 113-122.

Starling AP, Engel SM, Whitworth KW, Richardson DB, Stuebe AM, Daniels JL, Haug LS, Eggesbø M, Becher G, Sabaredzovic A, Thomsen C, Wilson RE, Travlos GS, Hoppin JA, Baird DD, Longnecker MP. Perfluoroalkyl substances and lipid concentrations in plasma during pregnancy among women in the Norwegian Mother and Child Cohort Study. Environ Int. 2014; 62: 104-112.

Stein CR, Savitz DA. Serum Perfluorinated Compound Concentration and Attention Deficit/Hyperactivity Disorder in Children 5–18 Years of Age. Environ Health Perspect 119: 1466–1471 (2011).

Sundström M, Chang SC, Noker PE, Gorman GS, Hart JA, Ehresman DJ, Bergman A, Butenhoff JL. Comparative pharmacokinetics of perfluorohexanesulfonate (PFHxS) in rats, mice, and monkeys. Reprod Toxicol. 2012; 33: 441-451.

Sundstrom, M; Ehresman, DJ; Bignert, 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.

Taylor KW, Hoffman K, Thayer KA, Daniels JL. 2014. Polyfluoroalkyl chemicals and menopause among women 20–65 years of age (NHANES). Environ Health Perspect 122:145–150.

Thomsen C, Haug LS, Sabaredzovic A, Gutzkow KB, Brunborg G, Becher G. Exposure of Norwegian infants to perfluorinated compounds. Dioxin 2010.

Trier X. Polyfluorinated surfactants in foode packaging of paper and board. PhD thesis, University of Copenhagen, 2011.

Upham, B.L., Deocampo, N.D., Wurl, B., Trosko, J.E. (1998). Inhibition of gap junctional intercellular communication by perfluorinated fatty acids is dependent on the chain length of the fluorinated tail. Int J Cancer, 78: 491-495.

Upham, B.L., Park, J.S., Babica, P., Sovadinova, I., Rummel, A.M., Trosko, J.E., Hirose, A., Hasegawa, R., Kanno, J., Sai, K. (2009). Structure-activity-dependent regulation of cell communication by perfluorinated fatty acids using in vivo and in vitro model systems. Environ Health Perspect, 117:545-551.

Vanden Heuvel, J. P., Kuslikis, B. I., Van Rafelghem, M. J., and Peterson, R. E. (1991) Tissue distribution, metabolism, and elimination of perfluorooctanoic acid in male and female rats. J. Biochem. Toxicol. 6, 83–92.

Vanden Heuvel, J.P. (1996). Perfluorodecanoic acid as a useful pharmacologic tool for the study of peroxisome proliferation. Gen Pharmacol, 27: 1123-1129.

Vanparys, C., Maras, M., Lenjou, M., Robbens, J., Van Bockstaele, D., Blust, R., De Coen, W. (2006). Flow cytometric cell cycle analysis allows for rapid screening of estrogenicity in MCF-7 breast cancer cells. Toxicology in Vitro, 20: 1238-1248.

Viberg H, Lee I and Eriksson P, 2013. Adult dose-dependent behavioral and cognitive disturbances after a single neonatal PFHxS dose. Toxicology, 304, 185-191.

Vongphachan, V., Cassone, C. G., Wu, D., Chiu, S., Crump, D., and Kennedy, S. W. (2011). Effects of perfluoroalkyl compounds on mRNA expression levels of thyroid hormone-responsive genes in primary cultures of avian neuronal cells. Toxicol. Sci. 120, 392–402.

Wang, C., Wang, T., Liu, W., Ruan, T., Zhou, Q., Liu, J., Zhang, A., Zhao, B., Jiang, G. (2012). The in vitro estrogenic activities of polyfluorinated iodine alkanes. Environ Health Perspect, 120: 119–125.

Washburn, S.T., Bingman, T.S., Braithwaite, S.K., Buck, R.C., Buxton, L.W., Clewell, H.J., Haroun, L.A., Kester, J.E., Rickard, R.W., Shipp, A.M., 2005. Exposure assessment and risk characterization for perfluorooctanoate in selected consumer articles. Environ Sci Technol 39, 3904-3910.

Weaver YM, Ehresman DJ, Butenhoff JL, Hagenbuch B (2010). Roles of rat renal organic anion transporters in transporting perfluorinated carboxylates with different chain lengths. Toxicol Sci. 113: 305-314.

Weiss, J.M., Andersson, P.L., Lamoree, M.H., Leonards, P.E., van Leeuwen, S.P., Hamers, T. (2009). Competitive binding of poly- and perfluorinated compounds to the thyroid hormone transport protein transthyretin. Toxicol Sci, 109: 206-216.

Wolf, C. J., Takacs, M. L., Schmid, J. E., Lau, C., and Abbott, B. D. (2008). Activation of mouse and human peroxisome proliferator-activated receptor alpha by perfluoroalkyl acids of different functional groups and chain lengths. Toxicol. Sci. 106, 162–171.

Wolf, C.J., Schmid, J.E., Lau, C., Abbott, B.D., 2012. Activation of mouse and human peroxisome proliferator-activated receptor-alpha (PPARalpha) by perfluoroalkyl acids (PFAAs): further investigation of C4-C12 compounds. Reprod Toxicol 33, 546–551.

Yang, C.H., Glover, K.P., Han, X., (2009). Organic anion transporting polypeptide (Oatp) 1a1-mediated perfluorooctanoate transport and evidence for a renal reabsorption mechanism of Oatp1a1 in renal elimination of perfluorocarboxylates in rats. Toxicol. Lett. 190, 163–171.

Yeung LW, Robinson SJ, Koschorreck J, Mabury SA. Part I. A Temporal Study of PFCAs and Their Precursors in Human Plasma from Two German Cities 1982–2009. Environ. Sci. Technol. 2013, 47, 3865–3874.

Zhao B, Hu GX, Chu Y, Jin X, Gong S, Akingbemi BT, Zhang Z, Zirkin BR and Ge RS, 2010. Inhibition of human and rat 3-beta-hydroxysteroid dehydrogenase and 17-beta-hydroxysteroid dehydrogenase 3 activities by perfluoroalkylated substances. Chemico-biological interactions, 188, 38-43.

Zhao B, Lian Q, Chu Y, Hardy DO, Li XK and Ge RS, 2011. The inhibition of human and rat 11β-hydroxysteroid dehydrogenase 2 by perfluoroalkylated substances. Journal of Steroid Biochemistry and Molecular Biology, 125, 143-147.

Environmental fate and effects references

Ahrens, L. (2011). Polyfluoroalkyl compounds in the aquatic environment: a review of their occurrence and fate. J. Environ. Monit., 2011, 13,20.

Bossi, R., Strand, J., Sortkjær, O., Larsen, M.M. (2008). Perfluoroalkyl compounds in Danish wastewater treatment plants and aquatic environments. Environment International 34 (2008) 443–450.

Busch, J., Ahrens, L., Sturm, R., Ebinghaus, R. (2010). Polyfluoroalkyl compounds in landfill leachates. Environmental Pollution 158 (2010) 1467–1471.

Butt, , C.M., Muir, D.C.G., Mabury, S.A. (2010). Biotransformation of the 8:2 fluortelomer acrylate in rainbow trout. 1. In vivo dietary exposure. Environmental Toxicology and Chemistry. Vol. 29. No. 12, pp. 2726-2735.

Castiglioni, S., Valsecchi, S., Polesello, S., Rusconi, M. (2014). Sources and fate of perfluorinated compounds in the aqueous environment and in drinking water of a highly urbanized and industrialized area in Italy. J. Hazard. Mater. (2014).

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

Compounds. *Critical Reviews in Environmental Science and Technology*, 43:598–678.

DMU (2007). PFAS og organotinforbindelser i punktkilder og det akvatiske miljø. NOVANA screeningsundersøgelse [PFAS and organotin compounds in the aquatic environment. NOVANA screening investigation.] Technical report no. 608, Danmarks Miljøundersøgelser, Aarhus University.

ECHA (European Chemicals Agency, 2014). Information on Chemicals - Registered substances. Accessed September 2014 at: echa.europa.eu/information-on-chemicals/registered-substances.

Ellis, D. A., Martin, J. W., De Silva, A. O., Mabury, S. A., Hurley, M. D., Sulbaek Andersen, M. P., & Wallington, T. J. (2004). Degradation of fluorotelomer alcohols: a likely atmospheric source of perfluorinated carboxylic acids. Environmental science & technology, 38(12), 3316-3321.

ENVIRON (2014). Assessment of POP Criteria for Specific Short-Chain Perfluorinated Alkyl Substances. Report prepared for FluoroCouncil, Washington, DC. Project Number: 0134304A . ENVIRON International Corporation, Arlington, Virginia, January 2014.

Hoke, R.A., Bouchelle, L.D., Ferrell, B.D., Buck, R.C. (2012). Comparative acute freshwater hazard assessment and preliminary PNEC development for eight fluorinated acids. *Chemosphere* 87 (2012) 725–733.

Iwai, H., Tsuda, N. (2011). Ecotox Findings for Ammonium Perfluorohexanoate. Conference Poster. Daikin Industries. Accessed November 2014 at: http://www.daikin.com/chm/csr/pdf/PFHxA/18)_PFHxA_E.pdf.

Jensen, A.A., Poulsen, P.B., Bossi, R. (2008). Kortlægning og miljø- og sundhedsmæssig vurdering af fluorforbindelser i imprægnerede produkter og imprægneringsmidler [Survey and environmental/health assessment of fluorinated substances in impregnated consumer products and impregnating agents]. Survey of Chemical Substances in Consumer Products, No. 99 2008, Danish Environmental Protetection Agency, Copemhagen.

KLIF (2010). Environmental screening of selected "new" brominated flame retardants and selected polyfluorinated compounds 2009. Rapport no. 1067/2010. Norwegian Climate and Pollution Agency (KLIF), Oslo.

Lassen, C. Jensen, A.A., Potrykus, A., Christensen, F., Kjølholt, J., Jeppesen, C.N., Mikkelsen, S.H., Innanen, S. (2013). Survey of PFOS, PFOA and other perfluoroalkyl and polyfluoroalkyl substances. Part of the LOUS-review. Environmental Project No. 1475, Danish Environmental Protetection Agency, Copemhagen.

Liu, C, Yu, L., Deng, J., Lam, P.K.S., Wu, R.S.S., Zhou, B. (2009). Waterborne exposure to fluorotelomer alcohol 6:2 FTOH alters plasma sex hormone and gene transcription in the hypothalamic–pituitary–gonadal (HPG) axis of zebrafish. *Aquatic Toxicology* 93 (2009) 131–137.

Martin, J.W., Mabury, S.A., Solomon, K.R., Muir, D.C.G. (2013). Progress towards understanding the bioaccumulation of perfluorinated alkyl acids. Environmental Toxicology and Chemistry. Vol. 32, No. 11, pp. 2421-2423.

NICNAS (2005). Potassium perfluorobutane sulfonate. Existing chemical hazard assessment report. Industrial Chemicals Notification and Assessment Scheme (NICNAS), Australia.

NPCA (Norwegian Pollution Control Authority) (2006). Økotoksikologiske effekter av PFOS, PFOA og 6:2 FTS på meitemark (Eisenia fetida) [Ecotoxicological effects of PFOS, PFOA and 6:2 FTS in earthworms]. Statens forurensningstilsyn (SFT), Norway.

Quinete, N., Orata, F., Maes, A., Gehron, M., Bauer, K. H., Moreira, I., & Wilken, R. D. (2010). Degradation studies of new substitutes for perfluorinated surfactants. Archives of environmental contamination and toxicology, 59(1), 20-30.

SW EPA (2012). Environmental and Health Risk Assessment of Perfluoroalkylated and Polyfluoroalkylated Substances (PFASs) in Sweden. Report 6513, Swedish Environmental Protection Agency, Stockholm.

Toxnet (2014). Hazardous Substances Data Bank (HSDB). Accessed November 2014 at: http://toxnet.nlm.nih.gov/newtoxnet/hsdb.htm.

Tsonaki, K., Jepsen, T.R., Larsen, T.H. (2014). Screeningsundersøgelse af udvalgte PFAS forbindelser som jord- og grundvandsforurening i forbindelse med punktkilder [Screening study of selected PFAS compounds as soil and groundwater contamination associated with point sources]. Environmental project 1600, 2014. Danish Environmental Protection Agency, Copenhagen.

Ulhaq, M. ,Örn, S., Carlsson, G., Morrison, D.A., Norrgren, L. (2013). Locomotor behavior in zebrafish (Danio rerio) larvae exposed to perfluoroalkyl acids. *Aquatic Toxicology* 144– 145 (2013) 332– 340.

UNEP (2012). Technical paper on the identification and assessment of alternatives to the use of perfluorooctane sulfonic acid in open applications. UNEP/POPS/POPRC.8/INF/17.

Webster, E. M., & Ellis, D. A. (2011). Equilibrium modeling: A pathway to understanding observed perfluorocarboxylic and perfluorosulfonic acid behavior. Environmental Toxicology and Chemistry, 30(10), 2229-2236.

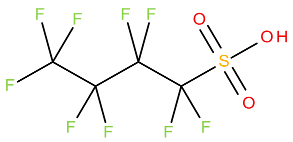
Zhao, Z., Xie, Z., Möller, A., Sturm, R., Tang, J., Zhang, G., & Ebinghaus, R. (2012). Distribution and long-range transport of polyfluoroalkyl substances in the Arctic, Atlantic Ocean and Antarctic coast. Environmental Pollution, 170, 71-77.

Zhou, Z., Liang, Y., Shi, Y., Xu, L., & Cai, Y. (2013). Occurrence and transport of perfluoroalkyl acids (PFAAs), including short-chain PFAAs in tangxun lake, China. Environmental science & technology, 47(16), 9249-9257.

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

PFBS and salts and halogenides:

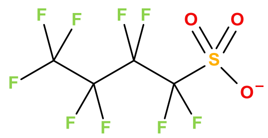
CAS 375-73-5 Perfluorobutane sulfonic acid, PFBS, Novec™

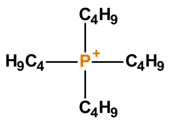


*CAS 29420-49-3 Potassium perfluorobutane sulfonate, PFBS-K

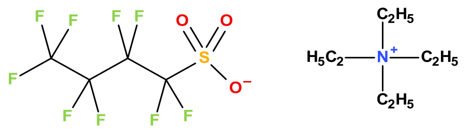
CAS 68259-10-9 Ammonium perfluorobutane sulfonate, used in photoresists

#CAS 220689-12-3 Tetrabutylphosphonium perfluorobutane sulfonate, Anti-Stat FC-1, wetting agent



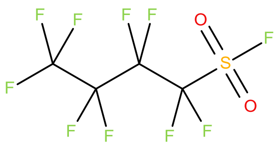


#CAS 25628-08-4 Tetraethylammonium perfluorobutane sulfonate



*CAS 70225-18-2 Bis(2-hydroxyethyl) ammonium perfluorobutane sulfonate

CAS 375-72-4 Perfluorobutane sulfonyl fluoride



CAS 90268-45-4 Perfluorobutane sulfonyl fluoride, branched

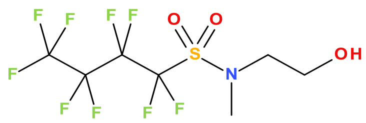
CAS 36913-91-4 Perfluorobutane sulfonic anhydride

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



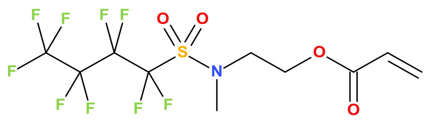
CAS 40630-65-7 *N*-Allyl perfluorobutane sulfonamide

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

CAS 68957-59-5	*N*-[3-(Dimethylamino)propyl)] perfluorobutane sulfonamide, hydro chloride
*CAS 53518-00-6 chloride,	Perfluorobutane sulfonamide, *N*-(*N'*,*N'*,*N'*-trimethyl propanaminium) used in AFFFs.
CAS 67939-95-1 iodide, used in	Perfluorobutane sulfonamide, *N*-(*N'*,*N'*,*N'*-trimethyl propanaminium) AFFFs.
CAS 70225-22-8 um)] sulfate, used	Di[Perfluorobutane sulfonamide *N*-(*N'*,*N'*,*N'*-trimethyl propanamini- in AFFFs.
CAS 67584-63-8	Perfluorobutane sulfonamide, *N*-ethyl-*N*-ethyl ethyl acetate
CAS 17329-79-2	Perfluorobutane sulfonamide, *N*-ethyl-*N*-ethyl acrylate
#*CAS 67584-55-8	Perfluorobutane sulfonamide, *N*-methyl-*N*-ethyl acrylate/*N*-Methyl perfluorobutane sulfonamidoethyl acrylate



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 67906-39-2	Perfluorobutane sulfonamide, *N*-methyl-*N*-butyl methacrylate
CAS 67939-89-3	Perfluorobutane sulfonamide, *N*-ethyl-*N*-ethyl dihydrogen phosphate
CAS 67939-91-7 PAP	Di[perfluorobutane sulfonamide *N*-ethyl]-*N*,*N'*-diethyl phosphate, Di-
CAS 68957-33-5	*N*-Ethyl-*N*-perfluorobutyl sulfonyl glycine
*CAS 67584-51-4	Potassium *N*-ethyl-*N*-perfluorobutyl sulfonyl glycinate
*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

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

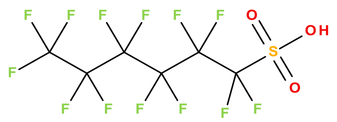
PFPS and derivatives:

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, hydro-chloride
*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 propanamini-um)] sulfate

*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

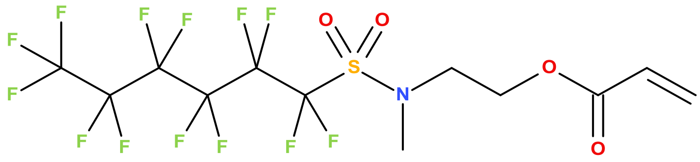


*CAS 3871-99-6	Potassium perfluorohexane sulfonate, PFHxS-K
CAS 68259-08-5	Ammonium perfluorohexane sulfonate, used in photoresists
*CAS 70225-16-0	Bis(2-hydroxyethyl)ammonium perfluorohexane sulfonate
CAS 55591-23-6	Perfluorohexane sulfonyl chloride

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'*-dimethyl-*N'*-hydroxyethyl-propanaminium), used in AFFFs.
CAS 38850-60-1	Perfluorohexane sulfonamide, *N*-sulfoxypropyl-*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'*-dimethyl-propanaminium), used in AFFFs.

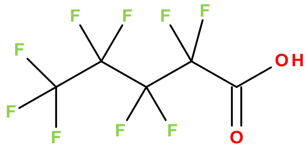
*CAS 52166-82-2	Perfluorohexane sulfonamide, *N-(N',N',N'*-trimethyl propanaminium) chloride, used in AFFFs.
*CAS 68957-58-4	Perfluorohexane sulfonamide *N-(N',N',N'*-trimethyl propanaminium) iodide, used in AFFFs and cleaning and disinfection
CAS 70248-52-1	Di[Perfluorohexane sulfonamide *N-(N',N',N'*-trimethyl propanaminium)] sulfate, used in AFFFs.
*CAS 67584-57-0	Perfluorohexane sulfonamide, *N*-methyl-*N*-ethyl acrylate



CAS 1893-52-3	Perfluorohexane sulfonamide, *N*-ethyl-*N*-ethyl acrylate
CAS 68227-98-5	Perfluorohexane sulfonamide, *N*-methyl-*N*-butyl acrylate
*CAS 67584-61-6	Perfluorohexane sulfonamide, *N*-methyl-*N*-ethyl methacrylate
CAS 67906-70-1	Perfluorohexane sulfonamide, *N*-ethyl-*N*-ethyl methacrylate
CAS 67939-61-1	Perfluorohexane sulfonamide, *N*-methyl-*N*-butyl methacrylate
CAS 67939-92-8	Di[perfluorohexane sulfonamide *N*-ethyl]-*N,N'*-diethyl phosphate, Di-PAP
CAS 68957-32-4	*N*-Ethyl-*N*-perfluorohexyl sulfonyl glycine
CAS 68957-53-9	Ethyl [*N*-ethyl-*N*-perfluorohexyl sulfonyl] glycinate
*CAS 67584-53-6	Potassium [*N*-ethyl-*N*-perfluorohexyl sulfonyl] glycinate
*CAS 68891-98-5	Chromium (III) [*N*-ethyl-*N*-perfluorohexyl sulfonyl] glycinate
CAS 68555-70-4	Sodium [*N*-ethyl-*N*-perfluorohexyl sulfonyl] glycinate
CAS 68299-21-8	Sodium (perfluorohexylsulfonyl)aminomethyl benzene sulfonate
CAS 67939-92-8	Di[perfluorohexane sulfonamide *N*-ethyl]-*N,N'*-diethyl phosphate, Di-PAP

PFBA salts and derivatives

CAS 3794-64-7[16]	Perfluorobutanoic acid, used to photographical film and chromatography additive for use in HPLC and LCMS applications.



CAS 375-22-4	Sodium perfluorobutyrate
CAS 356-27-4	Ethyl perfluorobutyrate

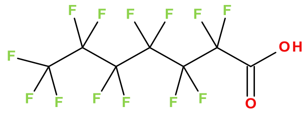
PFPA salts and derivatives

*CAS 2706-90-3	Perfluoropentanoic acid, PFPA
CAS 2706-89-0	Sodium perfluoropentanoate, PFPA
CAS 68259-11-0	Ammonium perfluoropentanoate, PFPA
CAS 68052-68-6	Ethylammonium perfluoroisopentadecanoate
CAS 375-62-2	Perfluoropentanoyl fluoride

[16] Red coloured substances not in the lists.

PFHxA salts and derivatives

*CAS 307-24-4	Perfluorohexanoic acid, PFHxA,



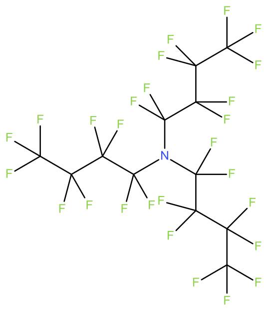
CAS 21615-47-4	Ammonium perfluorohexanoate, PFHxA
CAS 68015-84-9	Ethylammonium perfluoroisohexanoate
CAS 355-38-4	Perfluorohexanoyl fluoride
CAS 18017-31-7	Perfluoroisohexanoyl fluoride

Perfluoroalkyl iodides

CAS 423-39-2	Perfluorobutyl iodide, PFBI, chemical intermediate
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

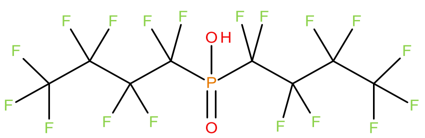
CAS 311-89-7	Tris(perfluorobutyl) amine, perfluorotributyl amine (PTBA), electronic fluids? 3M Fluorinated solvent compositions containing ozone, US patent 6372700 B1



CAS ?	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 C_{6-12} perfluoroalkyl-phosphonic acid (PFPA) derivatives.



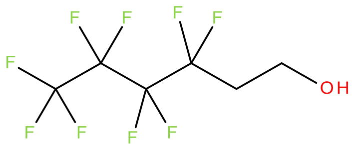
Alkyl perfluoroalkyl ethers

*CAS 297730-93-9	Ethyl perfluoroisoheptyl ether, Novec Engineered Fluid HFE 7500
#*CAS 163702-08-7	Methyl perfluoroisobutyl ether, 3M Novec Engineered Fluid HFE-7100 (Mixture/reaction mass with CAS 163702-07-6 = EC no. 422-270-2).

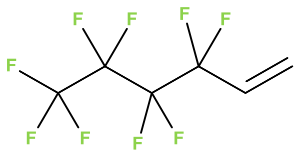
#*CAS 163702-07-6	Methyl perfluorobutyl ether, Cosmetic Fluid CF 61; 3M Novec Engi neered Fluid HFE-7100 (Mixture/reaction mass with CAS 163702-08-7 = EC no. 422-270-2)
#*CAS 163702-05-4	Ethyl perfluorobutyl ether (+ mixture/reaction mass with CAS 163702-06-5)
# CAS 163702-06-5	Ethyl perfluoroisobutyl ether (+ mixture/reaction mass with CAS 163702-05-4)

4:2 Fluorotelomers

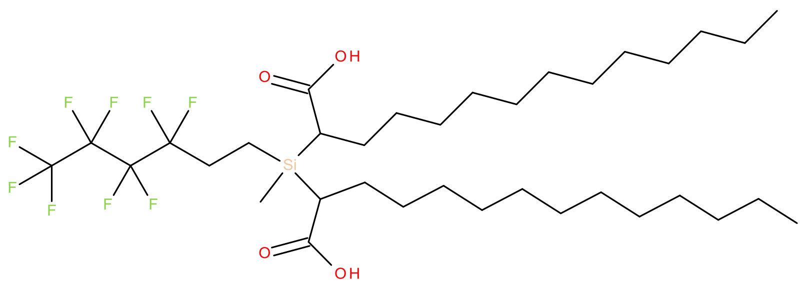
*CAS 2043-47-2	4:2 Fluorotelomer alcohol, 4:2 FTOH



CAS 2043-55-2	4:2 Fluorotelomer iodide, Zonyl™ PFBEI
#CAS 19430-93-4	4:2 Fluorotelomer olefin, Zonyl™ PFBE, (perfluorobutyl)ethylene, 1*H*,1*H*,2*H*-perfluoro-1-hexene, Capstone® 42-U , used in food contact materials, assessed by EFSA in 2011.



CAS 1799-84-4	4:2 Fluorotelomer acrylate
CAS 94094-26-5	4:2 Fluorotelomer [1,1'-di(tetradecanoic acid)] methyl silane/methyl (3,3,4,4,5,5,6,6,6- nonafluorohexyl)silylene dimyristate, drug intermediate

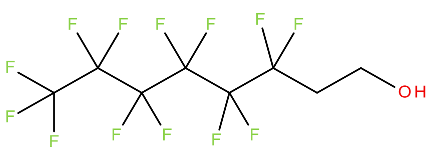


5:2 Fluorotelomers

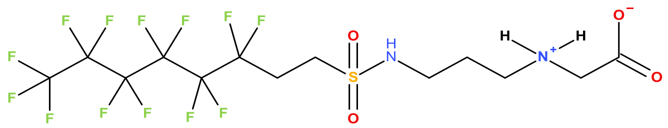
CAS 1682-31-1	5:2 Fluorotelomer iodide
CAS 65702-23-0	5:2 Fluorotelomer sulfonyl chloride

6:2 Fluorotelomers

*CAS 647-42-7	6:2 Fluorotelomer alcohol, 6:2 FTOH, Capstone™ 62-AL



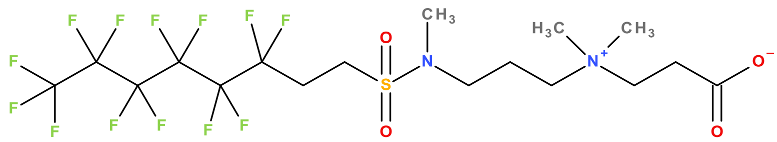
CAS 2043-57-4 | 6:2 Fluorotelomer iodide, Zonyl® TELB-LN, Capstone™ 62-I, Interme diate for surfactant/repellant production
CAS 26650-09-9 | 6:2 Fluorotelomer thiocyanate
*CAS 27619-97-2 | 6:2 Fluorotelomer sulfonic acid, Fumetrol®21 (for Cr hard metal plat ing), Forafac 1033
CAS 59587-38-1 | Potassium 6:2 fluorotelomer sulfonate, Zonyl 1176, wetting agent
*CAS 34455-29-3 | 6:2 Fluorotelomer sulfonamide, *N*-propanaminium *N'*-carboxymethyl, used in AFFFs.



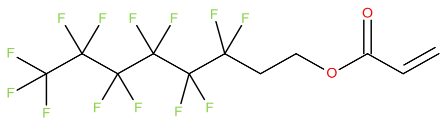
CAS 61798-69-4 | 6:2 Fluorotelomer sulfonamide, *N*-propanaminium *N'*-2-carboxyethyl, used in AFFFs.

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

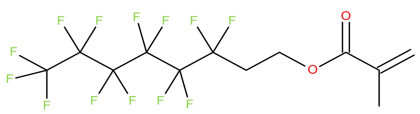
CAS 66008-72-8 | 6:2 Fluorotelomer sulfonamide, *N*-methyl-*N*-propanaminium *N',N'*-dimethyl *N'*-2-carboxyethyl, used in AFFFs.



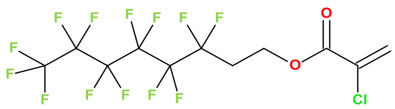
#*CAS 17527-29-6 | 6:2 Fluorotelomer acrylate, Zonyl® TA-N <5%



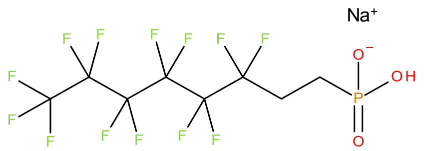
#*CAS 2144-53-8 | 6:2 Fluorotelomer methacrylate, Capstone™ 62-MA, chemical interme diate, monomer



#CAS 96383-55-0 | 6:2 Fluorotelomer 1-chloroacrylate



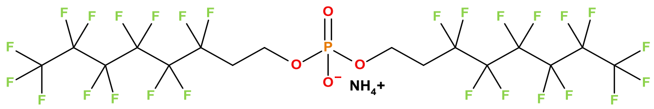
#CAS 1189052-95-6 Sodium 6:2 fluorotelomer phosphonate (used in cosmetics, function not reported):
http://ec.europa.eu/consumers/cosmetics/cosing/index.cfm?fuseaction=search.details&id=90057



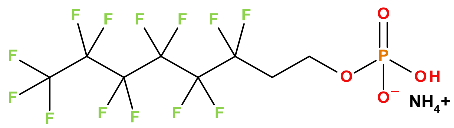
The analogue potassium salt (CAS 1224952-82-2) is not on the registration- or preregistration lists but it is also used in cosmetics (function not reported):
http://ec.europa.eu/consumers/cosmetics/cosing/index.cfm?fuseaction=search.details&id=88812

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



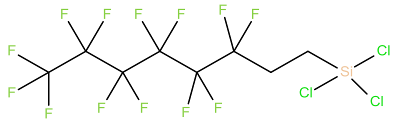
#CAS ? Ammonium mono[2-(perfluorohexyl)ethyl] hydrogen phosphate



Related substances <u>not</u> 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.

Danish Ministry of the Environment
Environmental Protection Agency

Strandgade 29
1401 Copenhagen K, Denmark
Tel.: (+45) 72 54 40 00

www.mst.dk