Environmental and Health Risk Assessment of Perfluoroalkylated and Polyfluoroalkylated Substances (PFASs) in Sweden

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Förord

Denna är rapport är resultatet från en forskningsutredning som finansierats av Naturvårdsverkets miljöforskningsanslag.

Syftet med projektet var att ta fram information och ny kunskap gällande möjliga miljö- och hälsorisker av perfluoralkylerade och polyfluoralkylerade ämnen (PFAS) i Sverige.

PFAS en stor grupp av industriellt framställda kemikalier som förekommer utbrett i miljön och i människor globalt. Utmärkande för denna grupp av kemikalier är deras extrema motståndskraft mot kemisk och biologisk nedbrytning.

En sammanställning av exponeringsdata för olika PFAS i den svenska befolkningen samt en bedömning av möjliga hälsorisker förknippade med dessa saknas. Det fanns därför ett behov av en samlad kunskapsöversikt över miljö- och hälsorisker för PFAS baserad på svenska miljöövervakningsdata och tillgängliga effektdata.

Arbetet har utförts av doktorand Daniel Borg vid Institutet för Miljömedicin (IMM), Karolinska Institutet, i samarbete med Professor Helen Håkansson (IMM) samt Docent Bert-Ove Lund och Professor Nils-Gunnar Lindquist vid Kemikalieinspektionen.

Författarna svarar för innehållet i rapporten. Rapportens innehåll har genom Naturvårdsverkets initiativ och hantering granskats och kommenterats av oberoende experter inför färdigställandet.

Kontaktpersoner på Naturvårdsverket har varit Britta Hedlund och Tove Hammarberg.

Naturvårdsverket, augusti 2012.

Preface

This report presents the outcome of a project funded by the Swedish Environmental Protection Agency´s Environmental Research Grant.

The purpose of the project was to present new information and knowledge about possible environmental- and health risks of perfluoroalkylated and polyfluoroalkylated substances (PFASs) in the Swedish population and in Swedish biota.

PFASs is a large group of synthetically manufactured chemicals that during the last decade has emerged as a new group of contaminants with widespread global presence in the environment and in humans. Characteristic for this group of compounds is an extreme resistance towards chemical and biological degradation.

Concerning human health, a collection of exposure data for PFASs in the Swedish population is lacking as well as an assessment of possible health risks. There was therefore a need of an overview of environmental and health risks of PFASs based on Swedish monitoring data and available toxicity data.

The work was carried out by PhD student Daniel Borg at the Institute of Environmental Medicine (IMM), Karolinska Institutet, in cooperation with Professor Helen Håkansson (IMM) and Associate Professor Bert-Ove Lund as well as Professor Nils-Gunnar Lindquist at the Swedish Chemicals Agency.

The authors are responsible for the contents of the report. On the initiative and management by the Swedish EPA, the report has been reviewed and commented on by independent experts before completion.

Contact persons at the Swedish EPA have been Britta Hedlund and Tove Hammarberg.

Abbreviations

6:2 FTSA	6:2 Fluorotelomer sulfonate
AF	Assessment factor
HÄMI	The Swedish Health-Related Environmental Monitoring Programme
BMD	Benchmark Dose
BMDL	Benchmark dose at the lower 95% confidence interval
BMCL	Benchmark concentration at the lower 95% confidence interval
DNEL	Derived No-effect-level
EtFOSA	N-ethyl perfluorooctanesulfonamide
LOAEL	Lowest Observed Adversed Effect Level
GD	Gestational day
LOD	Limit of detection
LOQ	Limit of quantification
MOE	Margin of Exposure
NOAEL	No Observed Adversed Effect Level
NOEC	No Observed Effect Concentration
PFASs	A collective term for all perfluoroalkylated and polyfluoroalkylated substances
PFOS-related compounds	A collective term for all precursor compounds that can be degraded to PFOS
PFBS	Perfluorobutane sulfonate
PFHxS	Perfluorohexane sulfonate
PFHpS	Perfluoroheptane sulfonate
PFOS	Perfluorooctane sulfonate
PFOSi	Perfluorooctane sulfinate
PFOSA	Perfluorooctane sulfonamide
PFDS	Perfluorodecane sulfonate
PFBA	Perfluorobutanoate
PFPeA	Perfluoropentanoate
PFHxA	Perfluorohexanoate
PFHpA	Perfluoroheptanoate
PFOA	Perfluorooctanoate
PFNA	Perfluorononanoate
PFDA	Perfluorodecanoate
PFUnDA	Perfluoroundecanoate
PFDoDA	Perfluorododecanoate
PFTrDA	Perfluorotridecanoate
PFTeDA	Perfluorotetradecanoate
PFPeDA	Perfluoropentadecanoate
PFHxDA	Perfluorohexadecanoate
PND	Postnatal day
POD	Point(s) of departure
Ppb	Parts per billion
Ppm	Parts per million
RCR	Risk characterization ratio
w.w.	wet weight

Contents

Sammanfattning

Denna rapport sammanfattar resultatet av ett projekt för att ta fram information och ny kunskap gällande möjliga miljö- och hälsorisker av perfluoralkylerade och polyfluoralkylerade ämnen (PFAS) i Sverige. Projektet har utförts i form av en riskbedömning, bestående av en exponeringsbedömning med svenska monitoringdata för 23 utvalda PFAS i människor, däggdjur, fågel och fisk, en farobedömning med toxikologiska data på däggdjur, fågel och fisk för de utvalda ämnena och en riskkaraktärisering för människa, däggdjur, fågel och fisk. Detta är den första hälso- och miljöriskbedömningen som undersöker ett stort antal PFAS, individuellt och i kombination.

I den hälsorelaterade exponeringsbedömningen valdes två populationer ut – människor exponerade indirekt via miljön (dvs. allmänbefolkningen) och en yrkesexponerad grupp – professionella skidvallare. Exponeringsdata i form av PFAS-halter i blod och serum användes. Resultatet visade att de undersökta PFAS-kongenerna förekom i serum i låga ppb-halter (ng/ml) i allmänbefolkningen. I en liten subpopulation av allmänbefolkningen som ätit kontaminerad fisk kunde högre ppb-halter av PFOS uppmätas. I den yrkesexponerade gruppen förekom avsevärt högre koncentrationer av vissa kongener, t ex PFNA och PFOA som uppmätts i höga ppb- eller låga ppm- halter (µg/ml), ca 125 och 200 gånger högre än i den allmänna befolkningen. Tidstrendstudier i den allmänna befolkningen visade att halterna av PFOS, PFDS, PFOSA och PFOA i serum förefaller minska, medan halterna av PFBS, PFHxS, PFNA, PFDA och PFUnDA istället förefaller öka.

I den hälsorelaterade farobedömningen användes främst data och slutsatser från redan existerande faro- eller riskbedömningar, som kompletterades med nytillkomna eller andra relevanta data. Två toxikologiska endpoints som identifierades som gemensamma för PFAS användes: 1) levertoxicitet, och 2) reproduktions/utvecklingstoxicitet. För kongener som saknade toxikologiska data eller interndoser gjordes en ”read-across”, dvs. extrapolering av data, till den närmaste mest potenta kongenern för respektive endpoint. Andra toxikologiska endpoints som uppvisade lägre effektnivåer än lever- eller reproduktionstoxicitet beaktades också. Resultatet av farobedömningen visade att de olika PFAS-kongenerna var relativt lika avseende deras potens för lever- och reproduktionstoxicitet, med utgångspunkter (på engelska ”point-of-departure”) på 4–89 µg/ml serum respektive 4–> 60 µg/ml serum. Användbara toxikologiska data med interndoser fanns tillgängliga för 4 av 15 kongener i allmänbefolkningen och 5 av 17 kongener för de yrkesexponerade. För några kongener kunde ytterligare toxikologiska endpoints identifieras (immuntoxicitet, påverkan på bröstkörtelutveckling, fetma) vid väldigt låga effektnivåer – vid eller under nuvarande exponeringsnivåer för allmänbefolkningen. Epidemiologiska studier visade motstridiga resultat.

Riskkaraktäriseringen visade inte på någon risk[1] för lever- eller reproduktionstoxicitet i allmänbefolkningen, vare sig för enskilda kongener eller i kombination. I den subpopulation som ätit kontaminerad fisk kunde däremot en risk för levertoxicitet påvisas baserat på uppmätta PFOS-halter. För de yrkesexponerade skidvallarna kunde en risk för levertoxicitet identifieras, baserat på enskilda kongener och i kombination, samt för reproduktionstoxicitet baserat på den samlade PFAS-exponeringen. Det bör dock understrykas att denna grupp omfattar ett mycket begränsat antal människor i Sverige.

I den miljörelaterade exponeringsbedömningen valdes 5 arter/grupper ut med följande vävnadsmatriser: 1) säl (lever), 2) utter (lever), 3) fågel (ägg), 4) marin fisk (lever) och 5) högexponerad sötvattensfisk (muskel), baserat på förekomsten av PFAS i dessa arter. Alla dessa finns i, eller är kopplade till, den akvatiska miljön och visar på hur PFAS sprids till miljön. I de terrestra arter som granskades var halterna av PFAS signifikant lägre. PFOS var den dominerande kongenern i alla arter och kunde uppmätas i låga ppm-nivåer eller höga ppb-nivåer i säl och utter, fågelägg och högexponerad sötvattensfisk, och i låga ppb-nivåer i marin fisk. I säl och utter kunde en nedåtgående trend för halter av sulfonater och en ökande trend för halter av karboxylater urskiljas. I ägg från pilgrimsfalk var alla uppmätta kongener långkedjiga och en tidstrendstudie visade att nivåer av sulfonater var oförändrade eller nedåtgående, och att karboxylater med en kedjelängd av 11–15 kol minskar, men att PFNA och PFDA ökar. I marin fisk innehåll alla detekterade kongener sex eller fler kol för sulfonater, och nio eller fler kol för karboxylater, vilket troligen återspeglar den högre biokoncentrationsfaktorn (BCF) för långkedjiga kongener. PFAS-halterna var betydligt högre i högexponerad sötvattensfisk än i marin fisk.

I den miljörelaterade farobedömningen användes för säl och utter samma toxikologiska endpoints och utgångspunkter som i den hälsorelaterade farobedömningen, baserat på deras gemensamma toxikologiska dataunderlag, men med skillnad i de specifika kongener som undersökts samt att halter i lever användes som interdos istället för serum. Användbara toxikologiska data med interndoser i lever var tillgängliga för 4 av 17 kongener, varav data för övriga kongener behövde extrapoleras. För fågel togs enbart data från reproduktionstoxicitetsstudier med interndoser uppmätta i ägg i beaktande, vilka fanns tillgängliga för 5 av 15 kongener, varav de övriga behövde extrapoleras. Få relevanta studier på reproduktionstoxicitet av PFAS i fågel fanns tillgängliga, och i dessa kunde endast effekter påvisas för PFOS. Dataunderlaget på PFAS i fågel kan därför anses osäkert med avseende på toxiska effekter, effektnivåer och de extrapoleringar som gjorts. För fisk så fanns data tillgängliga för 5 av 17 kongener och toxiska effektnivåer och utgångspunkter bör betraktas som högst osäkra beroende på att olika typer av studier, arter, och endpoints har

[1] Med ”risk” (engelska ”concern”) avses inte att det idag nödvändigtvis finns hälso- eller miljöproblem pga. av kemikalien, men visar på en otillräcklig marginal mellan nuvarande exponeringsnivåer och toxiska effektnivåer samt att en ytterligare förfining av riskbedömningen och/eller förebyggande åtgärder för att reducera exponeringen kan vara nödvändigt (se avsnitt 1.2.3).

använts, vilket gör dem väldigt svåra att jämföra mellan olika kongener. Dessa extrapoleringar är därför högst osäkra.

Resultatet av riskkaraktäriseringen för säl och utter visade på risk för levertoxicitet och reproduktionstoxicitet för enskilda kongener och/eller i kombination. Det bör poängteras att slutsatser gällande säl och utter är baserade på genomsnittsnivåer av PFAS vid den sista tidpunkten i tidstrendstudier, och att nivåerna kan vara högre på individnivå, vilket skulle resultera i lägre säkerhetsmarginaler. För reproduktionstoxicitet i fågel kunde en risk påvisas, där de högsta halterna i pilgrimsfalksägg (provtagna 2006) översteg de halter i ägg där en studie visat toxiska effekter, och där den genomsnittliga halten var nära de toxiska effektnivåerna. Det kan därför inte uteslutas att halterna av PFOS i dessa ägg kan ge upphov skadliga effekter. För marin och högexponerad sötvattensfisk indikerar tillgängliga data ingen risk för skadliga effekter. Det bör dock tydliggöras att data för fisk, monitoring såväl som toxicitetsdata och dess extrapoleringar är förknippade med en hög grad av osäkerhet p.g.a. brister i dataunderlaget.

Summary

This report summarizes the outcome of a project to present new information and knowledge about possible environmental- and health risks of perfluoroalkylated and polyfluoroalkylated substances (PFASs) in the Swedish population and in Swedish biota. The project was carried out as a risk assessment, consisting of an exposure assessment with Swedish biomonitoring data for 23 PFASs measured in humans, mammals, birds and fish, a hazard assessment with toxicological data from studies on mammals, birds and fish for the selected compounds and a risk characterization for humans, mammals, birds and fish. This is the first environmental and health risk assessment investigating a large number of PFASs, individually and in combination.

In the human exposure assessment, two populations were identified and selected – individuals exposed indirectly via the environment (i.e. the general population) and an occupationally exposed subpopulation – professional ski waxers. The exposure data used consisted of PFASs levels in blood and serum. The result showed that PFAS congeners were found at low ppb (ng/ml) concentrations in serum in the general population. In a small subpopulation eating contaminated fish, PFOS was found at higher ppb concentrations. In the occupationally exposed, the levels of some congeners were significantly higher than in the average population, i.e. PFNA and PFOA reaching high ppb and low ppm (µg/ml) levels in serum, being approximately 125 and 200 times higher than in the general population. Temporal trend studies in the general population showed that the levels of PFOS, PFDS, PFOSA and PFOA seem to decrease, whereas, the levels of PFBS, PFHxS, PFNA, PFDA and PFUnDA in serum seem to increase.

In the human hazard assessment, toxicity data and conclusions were primarily based on already existing hazard- and/or risk assessments and supplemented with additional published toxicological data of relevance. Two toxicological endpoints common for PFASs were identified and selected: 1) hepatotoxicity and 2) reproductive toxicity. For congeners lacking toxicological data or internal dose measurements a read-across was performed to the closest most potent congener for the respective endpoint. In addition, other endpoints showing lower effect levels were also considered. The result showed that the PFAS congeners were relatively similar with regard to their hepatotoxic and reproductive toxic properties, with points of departure (PODs) ranging from 4–89 µg/ml serum and 4–> 60 µg/ml, respectively. However, relevant toxicological data with internal doses were available for 4 of 15 congeners in the general population and for 5 of 17 in the occupationally exposed. For some congeners, other endpoints were identified at very low doses (e.g. immunotoxicity, impaired mammary gland development, obesity), similar to or below current human exposure levels. Epidemiological studies on PFASs showed inconsistent results.

The risk characterization did not indicated any cause for concern[2] for hepatotoxicity or reproductive toxicity in the general population, neither for congeners assessed individually nor in combination. PFOS levels in the subpopulation that consumed contaminated fish were, or were close to, being of concern. For the occupationally exposed ski waxers a cause for concern was identified for hepatotoxicity based on single and combined PFAS exposure, as well as for reproductive toxicity based on combined PFAS exposure. It should be noted, that this group comprises a very limited number of people in Sweden.

In the environmental exposure assessment, five species/subgroups with corresponding tissues were identified and selected: 1) seals (liver), 2) otters (liver), 3) birds (eggs), 4) marine fish (liver), and 5) highly exposed freshwater fish (muscle) based on the presence of PFASs in these species. All of these are present in or connected to the aquatic environment, demonstrating how PFASs enter the food chain via this route. In contrast, PFASs-levels were significantly lower in the terrestrial species examined. PFOS was the dominant congener in all species, often present at levels one to three orders of magnitude higher than the other congeners, and found at low ppm (µg/g) or high ppb (ng/g) levels in seals and otters, bird's eggs and highly exposed freshwater fish, and at low ppb levels in marine fish. In seals and otters, there was a tendency for levels of sulfonates to decrease and carboxylates to increase. In peregrine falcon eggs, all PFASs detected were long chain congeners and temporal trends showed that the levels of sulfonates were either unchanged or decreasing. For carboxylates, the levels of congeners with 11–15 carbons were decreasing, but increasing for PFNA and PFDA. In marine fish, all congeners detected contained six or more carbons for sulfonates and nine or more for carboxylates, likely reflecting the higher bioconcentration factor (BCF) for the long chain congeners. In highly exposed freshwater fish, PFASs levels were significantly higher than in marine fish.

In the environmental hazard assessment, hepatotoxicity and reproductive toxicity were assessed for seals and otters, and the PODs were derived from the same toxicological database as for the human hazard assessment but with hepatic concentrations used as internal dose. Toxicological data with hepatic PFASs-levels were available for 4 of 17 congeners assessed; thus data for the other congeners had to be extrapolated. For birds, only data from reproductive toxicity studies with PFASs-levels in eggs were considered, which was available for 5 of 15 congeners, and data for the other congeners had to be extrapolated. Few relevant studies on the reproductive toxicity of PFASs in birds were available, with effects being shown only for PFOS, hence the data can be considered uncertain with regard to effects and effect levels, and consequently, the extrapolations were uncertain. For fish, toxicological data were

[2] "Concern" does not necessarily mean that a threat to human health and/or the environment exists, but show that there is an inadequate margin between current exposure levels and toxic effect levels, and that further refinement of the risk assessment and/or preventative measures to reduce the exposure levels may be needed (see section 1.2.3).

available for 5 of 17 congeners but are highly uncertain due to different species, study durations and endpoints used in the different studies.

The result of the environmental risk characterization indicated a cause for concern for seals and otters for hepatotoxicity and reproductive toxicity, for either individual congeners and/or all congeners combined. It should be noted that the conclusions regarding seals and otters are based on the average PFASs-levels at the latest time-point in temporal studies, and that the levels can be higher on an individual basis, which would result in lower safety margins than presented herein. For reproductive toxicity in birds, a cause for concern was indicated for PFOS where the highest level in peregrine falcons eggs (sampled in 2006) exceeded the toxic effect level identified in one study and where the average PFOS level is close to the toxic effect level. Thus, it cannot be excluded that these levels of PFOS in the eggs could give rise to adverse effects. For marine as well as freshwater fish, the available data do not indicate any cause for concern, even in waters contaminated by PFOS. However, it should be noted that the data for fish, monitoring as well as toxicity data, were subject to highly uncertain extrapolations.

1. Introduction

1.1 Perfluoroalkylated and polyfluoroalkylated substances (PFASs)

Perfluoroalkylated and polyfluoroalkylated substances (PFASs) are a large family of man-made highly fluorinated organic chemicals that has been used since the 1950s as components of and precursors for surfactants and surface protectors for industrial and consumer applications. During the last decade, PFASs has been found globally in humans, wildlife and in the environment and recognized as highly persistent environmental contaminants. Initially, most attention were given to perfluorooctane sulfonate (PFOS) and perfluorooctanoate (PFOA), two common PFASs in biota and also the most studied with regard to toxicity and ecotoxicity. Lately, more attention have been given also to other PFASs, however risk assessments for the vast majority of these are lacking.

1.1.1 Physicochemical and biological properties

PFASs are characterized by a partly (poly) or fully (per) fluorinated carbon chain, typically four to fifteen carbons long, and with a functional group at the end. The most common groups of PFASs measured and detected in humans and biota are perfluorinated sulfonates and carboxylates (Figure 1). Due to the strength of the carbon-fluorine bond, PFASs are extremely resistant towards thermal, chemical and biological degradation (Järnberg et al., 2006). In addition, the fluorinated carbon chain is both oil-and water repellent, making PFASs useful in many industrial and consumer applications. However, their resistance to degradation also renders them persistent in the environment. Perfluorinated sulfonates and carboxylates are considered stable end-stage products that will not degrade under any environmental circumstances. However, they can be generated from the transformation of polyfluorinated precursor molecules containing the same "backbone" structure, e.g. fluorotelomers (Dinglasan et al., 2004). Perfluorinated sulfonates and carboxylates

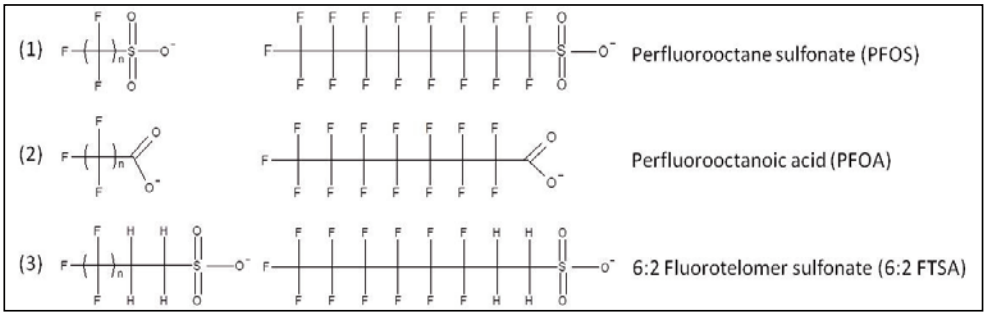


Figure 1. Schematic chemical structures of perfluorinated sulfonates (1), carboxylates (2) and fluorotelomer alcohols (3), including perfluorooctane sulfonate (PFOS), perfluorooctanoate (PFOA) and 6:2 FTSA.

are strong acids and present mostly in their non-volatile acid forms in the environment and in biota. Fluorotelomers (e.g. fluorotelomer alcohols, Figure 1), on the other hand, are volatile and can be transported in the atmosphere (reviewed in Houde et al., 2006).

In the environment, PFASs have the potential to bioaccumulate in fish, with the bioconcentration factor (BCF) being proportional to carbon chain length, at least up to 11 carbons (Martin et al., 2003a). PFASs also have a potential for biomagnification in food chains, as shown by the highest levels found in top predators such as polar bear, mink, otter and seal (Giesy and Kannan, 2001, Kannan et al., 2002; 2005, Kelly et al., 2009). In contrast to classical persistent organic contaminants, e.g. chlorinated and brominated compounds, PFASs does not distribute to fatty tissues in living organisms, but to proteins such as albumin in liver, plasma and eggs, and fatty acid binding proteins in cells (Kannan, et al., 2005, Kerstner-Wood et al., 2004, Luebker et al., 2002).

1.1.2 Nomenclature

Individual PFAS congeners are named according to the number of carbons on the alkyl chain and the functional group, e.g. the four carbon chain with a sulfonate group is named perfluorobutane sulfonate (PFBS). There are three main classes of PFAS that are included in this report: perfluorinated sulfonates, perfluorinated carboxylates and fluorotelomers. For a full list of the compounds assessed in this report, their CAS-number and chemical structure see Table 1.

For many years, there has not been a consistent terminology for perfluoroalkylated substances. Different and sometimes overlapping abbreviations have been used. Recently, Buck et al. (2011) proposed a terminology and classification scheme for perfluoroalkylated and polyfluoroalkylated substances, which will also be used herein, e.g.:

- PFASs – Perfluoroalkylated and polyfluoroalkylated substances (singular PFAS).
- PFAA – Perfluoroalkylated Acid.
- PFSA – Perfluoroalkylated sulfonic acid.
- PFCA – Perfluoroalkylated carboxylic acid.
- Long-chain PFASs – PFSAs with ≥ 6 carbons and PFCAs with ≥ 8 carbons, as originally defined by the Organization for Economic Co-operation and Development (OECD, 2012).
- Homologues – Different PFASs sharing the same functional group, e.g. PFSAs, PFCAs.

1.1.3 Uses and regulations

PFASs have been widely used as components of and precursors for surfactants and surface protectors in industrial applications and consumer products, such as impregnating agents for clothing and textiles, as coatings for paper and packaging, in waxes and cleaning agents, insecticides, fire-fighting foams and hydraulic fluids in airplanes (3M, 2000; Kissa, 2001).

By 2002, the largest producer of PFOS and PFOS-related compounds (all precursor compounds that can be degraded to PFOS) discontinued its production of these substances (OECD, 2005). Since then, other risk-reducing measures have also been taken within e.g. the European Union (EU) and the United Nations (UN) to reduce the use of PFOS. PFOS and PFOS-related compounds was prohibited from use in chemical products and articles within the EU in 2008 (EU, 2006) and were in 2009 included in the Stockholm Convention on Persistent Organic Pollutants (UNEP, 2009) as well as in the Convention on Long-Range Transboundary Air Pollution (CLRTAP)(UNECE, 2009), resulting in restrictions on their use. Although PFOS is still produced elsewhere (UNEP, 2008), these measures has led to a markedly decreased use of PFOS (KemI, 2006). To replace PFOS, several manufacturers have moved towards the use of other per- or highly fluorinated compounds, such as fluorotelomers and shorter alkyl chain sulfonates, such as PFBS, sharing similar technical properties as PFOS (KemI, 2006; 2009). There are no restrictions on the use of other PFASs in the EU than PFOS and PFOS-related compounds, though PFOA are kept under review for ongoing risk assessment activities (EU, 2006).

1.1.4 Sources of PFASs in the Swedish environment

There is and has not been any production of PFASs in Sweden (KemI, 2006). PFASs detected in the Swedish environment is likely a result of release from industrial use of these chemicals, from consumer use of products containing PFASs, from leakage from waste disposals and landfills as well as from sewage treatment plants effluents. Aqueous fire-fighting foams (AFFF) have been pointed out as a significant point-source of PFOS and other PFASs (Järnberg et al., 2006, Moody et al., 2003). Also, atmospheric import of volatile precursor molecules, e.g. fluorotelomer alcohols that can be degraded to PFCAs (Ellis et al. 2004), is likely (Järnberg et al., 2006).

1.1.5 Sources of human exposure to PFASs

The most significant sources of PFASs for the general population are thought to be food, including drinking water, as well as inhalation of household dust (D'Hollander et al., 2010). Of these, diet has been proposed to be the major exposure route for several PFASs, particularly fish and seafood (Haug et al., 2010), and where the diet may account for as much as 99% and 84% of the total PFOS and PFOA intake, respectively, though dust may also constitute a major source on an individual basis (Haug et al., 2011). For infants, breast milk is the major source to PFASs (Haug et al., 2011), in addition to placental transfer of these chemicals during pregnancy (Kim et al., 2011), and may equal the dietary PFASs intake in adults (Thomsen et al., 2010). Occupationally exposed individuals are highly exposed as compared to the general population, likely through inhalation and/or ingestion of aerosols and dust containing PFASs (ATDSR, 2009). The highest levels of PFASs have been measured in individuals working in production facilities of PFASs (KemI, 2004). The most highly occupationally exposed population in Sweden

are likely professional ski waxers for which the highest levels in this report are presented, due to the presence of PFASs in gliding waxes. No other highly exposed subpopulations have been identified in Sweden.

1.1.6 Guidance values

There are no legal limit values for PFASs in Sweden or in the EU. However, to protect human health, limit values have been proposed by the Swedish Environmental Protection Agency (EPA) for PFOS in Sweden of 0.35–1 µg/l in drinking water, and 6 µg/g in food (Naturvårdsverket, 2008). In a risk assessment of PFOS and PFOA, the European Food Safety Authority (EFSA) derived tolerable daily intake (TDI) values for PFOS and PFOA of 0.15 and 1.5 µg/kg bw/day (EFSA, 2008). Other European authorities have provided recommendations for maximum intake of PFASs in food and water. The United Kingdom (UK) Food Standards Agency's Committe on Toxicity of Chemicals in Food, Consumer Products and the Environment recommended TDI values for PFOS and PFOA of 0.3 and 3 µg/kg bw/day (COT, 2006a;b). The German Federal Institute for Risk Assessment (BfR) suggested a TDI value of 0.1 µg/kg bw/day for PFOS (German BfR, 2006). In drinking water, the UK's Drinking Water Inspectorate (DWI) recommends no higher levels than 0.3 µg/l of PFOS or PFOA (DWI, 2009) and the German Federal Environment Agency (German UBA) no higher level than 0.1 µg/l of PFOS and PFOA together (German UBA 2006).

For the environment, limit values of PFOS of 30 and 3 µg/l have been proposed by the Swedish EPA for limnic and marine waters, respectively, and 6 µg/g wet weight (w.w.) in biota to protect predatory animals and humans (Naturvårdsverket, 2008). Recently, within the EU Water Framework Directive (2000/60/EC), environmental quality standard values for PFOS and its derivatives was proposed at 0.65 ng/l (annual average) and 36 µg/l (maximum acceptable concentration) in inland surface waters, 0.13 (annual average) and 7.2 µg/l (maximum acceptable concentration) in marine water, and 9.1 µg/kg w.w. in fish (EU, 2012)[3].

1.1.7 Biomonitoring of PFASs in Sweden

THE SWEDISH ENVIRONMENTAL MONITORING PROGRAMME

The Swedish national environmental monitoring programme is coordinated by the Swedish EPA, and consists of 10 different areas, of which "Toxic substances coordination" constitutes one. This area includes screening/monitoring of metals and organic pollutants and an environmental specimen bank at the Swedish Museum of Natural history, Stockholm, in which analyses on compounds can be performed. Data host for this programme is the Swedish Environmental Research Institute, IVL, Stockholm, Sweden. PFASs was first included in the screening during 2001–2003 (Naturvårdsverket, 2005), and

[3] Added subsequent to the last literature search in August, 2011.

were then, based on being identified as a group of concern, adopted into the regular environmental monitoring.

THE SWEDISH HEALTH-RELATED ENVIRONMENTAL MONITORING PROGRAMME (HÄMI)

Included in the Swedish national environmental monitoring programme is the Health-related Environmental Monitoring Programme (HÄMI). HÄMI started 1993 with the purpose to monitor health effects that may be related to environmental factors, including estimation of human exposure to hazardous substances by analysing human blood, breast milk and urine. Data host is the Institute of Environmental Medicine (IMM), Karolinska Institutet, Solna, Sweden.

1.2 Approach of the risk assessment

This risk assessment is for the human health part conducted in accordance with the EU's chemicals legislation REACH terminology and guidelines (European Chemicals Agency (ECHA), 2012). The environmental part will not be conducted according to REACH guidelines, but instead use a combination of a margin of exposure (MOE) approach for all species together with the risk characterization ratio (RCR) approach used within REACH (see descriptions below) for mammals, based on the unconventional approach herein to apply biomonitoring data in wildlife species as a measure of exposure.

1.2.1 Exposure assessment

For the health-related exposure assessment, biomonitoring data from the Swedish population is used (blood and serum levels of PFASs), to be compared to toxicological effect levels. Evaluation of external exposure data of PFASs, such as oral intake via food and drinking water, or exposure via inhalation or dermal contact is not covered within the scope of this project. For the environmental exposure assessment, tissue levels of PFASs are used for mammals, fish and birds. Data for the health-related as well as the environmental exposure assessment have been collected from HÄMI and the Swedish environmental monitoring programme, from national and international reports, from the scientific literature and via contact with individual researchers. Publications from 2004 until August 2011 have been included in this report, subsequent to the previous risk assessment on PFOS by KemI (KemI, 2004). Studies are presented in chronological order based on the time-point of collection of samples for the study.

The exposure data used for the risk characterization will consist of exposure levels of PFASs in blood/serum or tissues from the latest time-point in a temporal study or from a sample in a snapshot study taken no earlier than 2006, on the basis that samples ≥ 5 years old are considered out of date for this assessment. Temporal trend evaluations have been based on levels from 2000 and onwards. Where available, the highest levels from selected key

studies and the highest levels of the latest time-points in temporal trend studies, respectively, have been used in order for the assessment to be conservative. The advantage of using serum and tissue levels of PFASs as opposed to external exposure is that these internal concentrations represent an integrated exposure for the respective PFAS congeners, irrespective of the source, e.g. precursor molecules that can be metabolized to e.g. PFOS and PFOA. Also, using serum and tissue levels eliminates uncertain extrapolations of external dose-response relationships between species and from animals to humans due to large differences in kinetics.

For the assessment of human health, two exposure groups are considered:

1. Individuals exposed indirectly via the environment (i.e. the general population).
2. Occupationally exposed individuals (professional ski waxers).

For the environmental assessment, five subgroups are evaluated:

1. Seals (liver).
2. Otters (liver.
3. Birds (eggs).
4. Marine fish (liver).
5. Highly exposed freshwater fish (muscle).

1.2.2 Hazard assessment

For the human and the environmental hazard assessment of the 23 individual PFAS congeners included in this project, toxicity data and conclusions will primarily be used from already existing hazard- and/or risk assessments and supplemented with additional published data of relevance, i.e., studies showing lower effect levels or other relevant information. This is a pragmatic approach needed in order to cover all substances within the time-frame of the project. The supplementary data are derived from literature searches in Pubmed. For congeners lacking toxicological information or internal dose measurements, a read-across to the closest most potent congener for the respective endpoint will be performed.

In the human hazard assessment, all PFAS congeners included in the human exposure assessment will be assessed. Also, congeners that have been identified in mammals in the environmental exposure assessment will be included in the human hazard assessment part, since toxicity data from mammals are used for both humans and mammals.

For the environmental hazard assessment, all compounds identified in the exposure assessment for mammals, birds and fish will be included. For birds, levels in eggs in toxicity studies will be used for comparison to PFASs levels in eggs in the exposure assessment. For fish, tissue levels of the respective PFASs in the exposure assessment will be used for comparison to tissue levels in toxicity studies. If no tissue levels are available from the critical toxicity study, an estimation of tissue concentration will be made based on extrapolation from serum to tissue levels or on the bioconcentration factor (BCF) of the compound, if available.

Points of departure (PODs) will be identified in the toxicological data sets, i.e. No-Observed-Adverse-Effect-Levels (NOAELs), Lowest-Observed-Adverse-Effect-Levels (LOAELs), No-observed-effect concentrations (NOECs) or Benchmark dose (BMD) levels. Internal dose-metrics (levels in serum, liver, eggs, muscle) at critical effect levels will be used. From the PODs, a "safe" exposure level will be derived by the use of appropriate assessment factors (AFs) resulting in endpoint-specific Derived-No-Effect-Levels (DNELs):

DNEL = POD (e.g. NOAEL, LOAEL, BMD)/AFs

For further information on the methodology to derive DNELs, see guidance documents from ECHA (ECHA 2010, 2011).

1.2.3 Risk characterization

For the assessment of risks to human health, the risk characterization will be conducted for all individual congeners by deriving risk characterization ratios (RCRs), i.e. comparing DNELs with exposure levels for the respective PFASs to evaluate whether there exists a risk or not:

RCR = Exposure/DNEL. Ratio < 1 = risk is of no/minor concern, ratio of > 1 = risk is of concern

For further information on the methodology to derive RCRs, see guidance documents from ECHA (ECHA, 2008).

In addition, a cumulative risk characterization and evaluation will be performed for all congeners combined. This is accomplished by addition of the respective RCR values for individual PFAS congeners:

$RCR_{Cumulative} = \sum RCR_X + RCR_Y + RCR_Z...$; Ratio < 1 = risk is of no/minor concern, ratio of > 1 = risk is of concern

This method to sum the RCR values is justified by the structural, physico-chemical and toxicological similarities between the PFAS congeners. However, different types of toxicity studies have been used herein (long-term, short-term etc.) and "read-across" extrapolations performed, all adding uncertainties. These uncertainties are compensated for by applying different assessment factors before calculating the RCRs for the individual congeners. When adding the RCR values in the cumulative evaluation, these uncertainties are taken into account in the individual RCR values. A similar approach has been used by e.g. the Danish Environmental Protection Agency (Danish EPA) in a cumulative health risk assessment of phthalates (Danish EPA, 2011).

For the environmental risk assessment, a margin of exposure approach (MOE) will be used for all species assessed.

MOE = POD/exposure. For this assessment a MOE of 100 is considered sufficient.

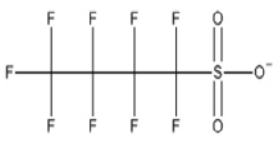
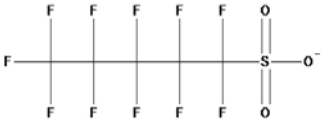
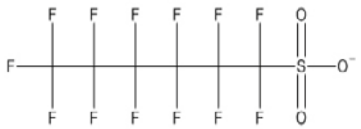
In addition, for mammals, a cumulative risk characterization will be performed using the same REACH-methodology as for human health, in order to allow for a comparison of RCR values to the human situation. This latter approach is not, however, suitable for birds and fish in this assessment based on that different endpoints are being used in the evaluation of toxicological data for these species and due to large uncertainties in extrapolations of toxicological data for these species.

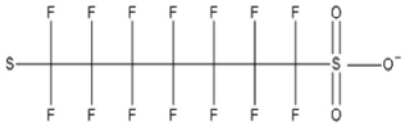
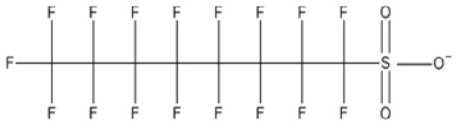
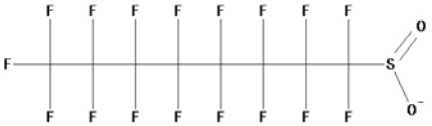
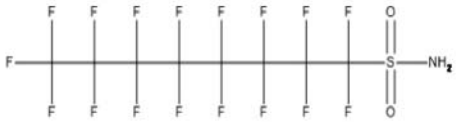
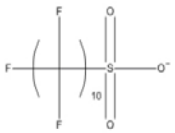
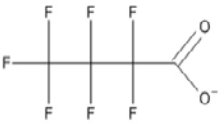
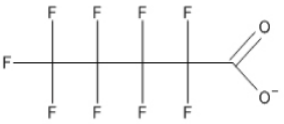
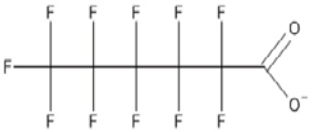
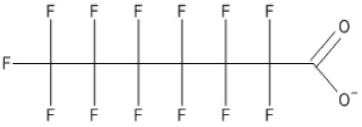
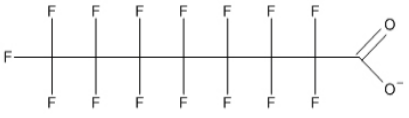
For both the human health and the environmental risk assessment, a RCR of > 1 and a MOE of ≤ 100, respectively, indicate that risks are of concern. The expression "concern" does not necessarily mean that there is a threat to human health and/or the environment, but rather shows that there is an inadequate margin between current exposure levels and toxic effect levels, and that preventative measures may be needed in order to reduce the exposure levels. Also, further refinement of the assessment can be done, for instance by improving the hazard assessment to obtain a more comprehensive database and/or by improving the exposure assessment (ECHA, 2009).

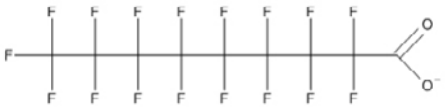
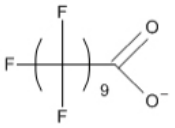
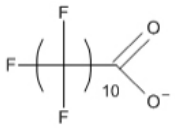
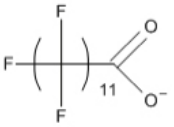
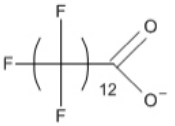
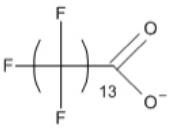
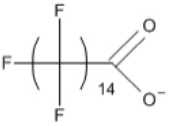
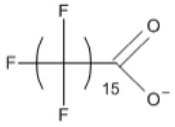
1.3 Selection of compounds

The PFASs assessed in this report consist of the congeners that have been studied within the Swedish Health-Related Environmental Monitoring Programme (HÄMI) and the Swedish Environmental Monitoring Programme as well as within individual research projects and reported to be present in the blood of the Swedish population and in Swedish biota. For a full list of the compounds, their CAS-number and their chemical structure see Table 1.

Table 1. PFASs covered within this project and their acronyms, CAS-number and structure.

Acronym	Substance name	CAS-number[a]	Structure
PFBS	Perfluorobutane sulfonate	45187-15-3 75-22-4 (acid) 375-73-5 (potassium salt)	
PFPS	Perfluoropentane sulfonate	2706-91-4 (acid) 3872-25-1 (potassium salt)	
PFHxS	Perfluorohexane sulfonate	108427-53-8 355-46-4 (acid) 3871-99-6 (potassium salt)	

Acronym	Substance name	CAS-numbera	Structure
PFHpS	Perfluoroheptane sulfonate	375-92-8 (acid) 60270-55-5 (potassium salt) 68259-07-4 (ammonium salt)	
PFOS	Perfluorooctane sulfonate	45298-90-6 1763-23-1 (acid) 2795-39-3 (potassium salt) 4021-47-0 (sodium salt) 29081-56-9 (ammonium salt)	
PFOSi	Perfluorooctane sulfinate	647-29-0 (acid)	
PFOSA	Perfluorooctane sulfonamide	754-91-6	
EtFOSA	N-ethyl perfluorooctane sulfonamide	4151-50-2	
PFDS	Perfluorodecane sulfonate	126105-34-8 335-77-3 (acid) 2806-16-8 (potassium salt) 67906-42-7 (ammonium salt)	
PFBA	Perfluorobutanoate	45048-62-2 375-22-4 (acid) 2218-54-4 (sodium salt) 10495-86-0 (ammonium salt)	
PFPeA	Perfluoropentanoate	45167-47-3 2706-90-3 (acid) 68259-11-0 (ammonium salt)	
PFHxA	Perfluorohexanoate	92612-52-7 307-24-4 (acid) 2923-26-4 (sodium salt) 21615-47-4 (ammonium salt)	
PFHpA	Perfluoroheptanoate	120885-29-2 375-85-9 (acid) 20109-59-5 (sodium salt) 6130-43-4 (ammonium salt)	
PFOA	Perfluoroctanoate	45285-51-6 335-67-1 (acid) 2395-00-8 (potassium salt) 335-95-5 (sodium salt) 3825-26-1 (ammonium salt)	

Acronym	Substance name	CAS-numbera	Structure
PFNA	Perfluorononanoate	72007-68-2 375-95-1 (acid) 21049-39-8 (sodium salt) 4149-60-4 (ammonium salt)	
PFDA	Perfluorodecanoate	73829-36-4 335-76-2 (acid) 3108-42-7 (ammonium salt)	
PFUnDA	Perfluoroundecanoate	196859-54-8 2058-94-8 (acid) 4234-23-5 (ammonium salt)	
PFDoDA	Perfluorododecanoate	171978-95-3 307-55-1 (acid)	
PFTrDA	Perfluorotridecanoate	862374-87-6 72629-94-8 (acid)	
PFTeDA	Perfluorotetradecanoate	365971-87-5 376-06-7 (acid)	
PFPeDA	Perfluoropentadecanoate	1214264-29-5 141074-63-7 (acid)	
PFHxDA	Perfluorohexadecanoate	1214264-30-8 67905-19-5 (acid)	
6:2 FTSA	1,1,2,2-Tetrahydroper-fluorooctanesulfonate	425670-75-3 27619-97-2 (acid)	

[a] = adopted from Buck et al. (2011)

2. Human exposure

There are a number of biomonitoring studies where blood or serum/plasma levels of PFASs have been measured in the Swedish population and that are included herein. Most commonly, serum levels are measured and used for comparisons between studies. A ratio of 1:1 between serum and plasma levels for PFOS, PFOA and PFHxS has been shown (Ehresman et al., 2007) and levels in these two matrices are therefore directly comparable to each other, whereas a ratio of approximately 2:1 exists for serum or plasma to whole blood for the same PFAASs. Consequently, whole blood levels of these PFASs can be multiplied by a factor of 2 to give their corresponding serum levels, and it can be assumed that this is the case also for other PFAAs, based on their similar physicochemical properties. The non-charged congener PFOSA was however shown to distribute to a greater extent to whole blood than to plasma (Kärrman et al., 2006). Levels of different PFASs in breast milk were shown to be approximately 1–12% of their corresponding serum levels (Kärrman et al., 2007; Table 5).

2.1 Indirect exposure via the environment – Snapshot studies

2.1.1 Samples taken before 2006 (not considered for risk characterization)

Glynn et al. (2008) performed a study where levels of PFOS, PFOA and PFNA were analysed in mothers from Uppsala and their neonates. Blood samples were drawn during 1996–1999 from 19 primipara pregnant women during the first trimester, the third trimester and after three weeks and three months post-delivery, respectively, as well as in cord blood. The result showed that the levels of PFOS in maternal serum as well as in cord blood were highest among the congeners analysed, followed by PFOA and PFNA (Table 2). The levels in cord blood as compared to maternal serum were lower for all compounds (after conversion to serum levels), however to various extents, indicating a difference in the rates of placental transfer between the congeners.

Table 2. Levels of PFOS, PFOA and PFNA in serum from pregnant and nursing women and in cord blood sampled during 1996–1999. The results are presented as medians (range). Source. Glynn et al. (2008).

Congener	Pregnancy (ng/g serum)		Delivery (ng/g blood)	Nursing (ng/g serum)	
	1st trimester	3rd trimester	Cord blood	3 weeks	3 months
PFOS	33 (18–53)	32 (14–44)	5.6 (2.5–8.4)	29 (13–51)	29 (17–42)
PFOA	4.4 (2.5–11)	3.7 (2.0–7.5)	1.4 (0.66–2.3)	3.5 (1.4–7.3)	3.1 (1.4–5.4)
PFNA	0.78 (0.36–1.1)	0.52 (0.2–1.1)	< 0.16 (< 0.16–0.25)	0.43 (0.27–0.85)	0.44 (0.19–0.98)

Berglund et al. (2004) analysed blood for PFOS and PFOA sampled during 1997–2000 from 108 women (19–56 years, median age 40 years) with high fish consumption from different parts of Sweden. The results showed that the level of PFOS was on average 18 ng/ml whole blood and 2.0 ng/ml for PFOA (Table 3).

Table 3. Geometric mean levels of PFOS and PFOA in whole blood samples (ng/ml) of Swedish women with high fish consumption (n=108) 1997–2000. Source: Berglund et al. (2004).

Congener	Mean	Range
PFOS	18	3.0–67
PFOA	2.0	0.40–4.8

Kärrman et al. (2006) determined the levels of 12 PFASs – PFBS, PFHxS, PFOS, PFOSA, PFDS, PFHxA, PFOA, PFNA, PFDA, PFUnDA, PFDoDA and PFTeDA in whole blood sampled 1997–2000 in 47 males (age 19–46) and their mothers (age 47–75) primarily from southern Sweden. Overall, PFOS was detected at the highest mean concentrations (16 ng/ml), followed by PFOSA, PFOA and PFHxS (Table 4). These PFASs were detected in all samples. PFHxDA, PFNA, PFDS, PFDA, and PFUnDA were not detected in all samples and at levels close to the detection limit. PFDoDA and PFTeDA could only be identified but not quantified and PFBS was not detected at all.

Table 4. Geometric mean levels of detected PFASs in whole blood (ng/ml) in Swedish males and females sampled 1997–2000. Source: Kärrman et al. (2006).

Sex	N	Whole blood	PFOS	PFOSA	PFOA	PFHxS	PFNA	PFUnDA
All	66	Mean	16	3.0	2.4	1.5	0.3	0.1
		Range	1.7–37.0	0.4–22.9	0.5–12.4	0.4–28.4	< 0.1–1.9	< 0.1–0.7
Males	40	Mean	17	3.2	2.6	1.9	0.2	0.1
		Range	1.7–37.0	0.8–22.9	0.5–12.4	0.4–28.4	< 0.1–1.9	< 0.1–0.6
Females	26	Mean	16	2.6	2.1	1.1	0.3	0.1
		Range	4.6–32.8	0.4–9.5	0.8–4.1	0.4–2.5	< 0.1–1.0	< 0.1–0.7
Sex	**N**	**Whole blood**	**PFDA**	**PFHxA**	**PFDS**	**PFDoDA**	**PFTeDA**	**PFBS**
All	66	Mean	0.1	–	–	< 0.1	< 0.1	< 2
		Range	< 0.1–0.6	< 0.1–1.6	< 0.1–4.5	< 0.1	< 0.1	< 2
Males	40	Mean	0.1	–	–	< 0.1	< 0.1	< 2
		Range	< 0.1–0.5	< 0.1–1.1	< 0.1–2.4	< 0.1	< 0.1	< 2
Females	26	Mean	0.1	–	–	< 0.1	< 0.1	< 2
		Range	< 0.1–0.6	< 0.1–1.6	< 0.1–4.5	< 0.1	< 0.1	< 2

Kärrman et al. (2007) analysed matched breast milk and serum samples from 12 primipara women in different Swedish regions during 2004 for 13 PFASs – PFBS, PFHxS, PFOS, PFDS, PFHxA, PFHpA, PFOA, PFNA, PFDA, PFUnDA, PFDoDA, PFOSA and tetrahydro-PFOS (not included in this risk assessment). The results showed that eight PFASs could be detected in the serum samples, with PFOS showing the highest mean serum concentration followed by PFHxS,

PFOA, PFNA, PFDA, PFUnDA and PFOSA (Table 5). PFDS was detected in only one serum sample. Of the eight PFASs found in the serum samples, five were detected in the matched milk samples. PFOS and PFHxS were detected in all the matched breast milk samples. PFOSA and PFNA were detected in eight and two milk samples, respectively, and PFOA in one sample. The mean ratios between milk and serum (M:S) concentrations were 0.01:1 for PFOS, 0.02:1 for PFHxS, and 0.07:1 for PFOSA. The M:S ratios for PFOA and PFNA were uncertain because of that only one and two milk samples contained levels above the detection limit. There were significant correlations between levels of PFOS and PFHxS in serum and breast milk.

Table 5. Levels of PFASs (ng/ml) in matched milk and serum samples from 12 Swedish women in 2004. Source: Kärrman et al. (2007).

Serum	PFOS	PFHxS	PFOA	PFNA	PFDA	PFUnDA	PFOSA
N > LOD	12	12	12	12	12	12	9
Mean	20.7	4.7	3.8	0.80	0.53	0.40	0.24
Range	8.2–48	1.8–11.8	2.4–5.3	0.43–2.5	0.27–1.8	0.20–1.5	< 0.10–0.49
Milk	**PFOS**	**PFHxS**	**PFOA**	**PFNA**	**PFDA**	**PFUnDA**	**PFOSA**
N > LOD	12	12	1	2	–	–	8
Mean	0.201	0.085	–	0.017	–	–	0.013
Range	0.06–0.47	0.03–0.17	< 0.21–0.49	< 0.005–0.02	< 0.008	< 0.005	< 0.007–0.03
M:S ratio	0.01:1	0.02:1	0.12:1	0.01:1	–	–	0.07:1

2.1.2 Samples taken after 2006 (considered for risk characterization)

Ericson et al. (2008) measured the levels of 12 PFASs – PFBS, PFHxS, PFOS, PFHxA, PFHpA, PFOA, PFNA, PFDA, PFUnDA, PFDoDA, PFTeDA and 6:2 FTSA in whole blood samples collected in 2007 from nine individuals, four males and five females between the ages 19–65 in Örebro. In total, six individual PFASs were detected, the dominant being PFOS, with a mean concentration of 5.9 ng/ml, followed by PFOA, PFHxS, PFNA, PFDA and PFUnDA (Table 6). PFBS, 6:2 FTSA, PFHxA, PFHpA, PFDoDA and PFTeDA were all under their limits of detection.

Table 6. Geometric mean PFASs levels in blood (ng/ml) from Swedish men and women (n = 9) sampled 2007. Source: Ericson et al. (2008).

Congener	Mean	Range
PFOS	5.9	2.8–13.2
PFOA	1.3	< 0.58–2.2
PFHxS	0.51	0.14–0.89
PFNA	0.40	0.19–0.68
PFDA	0.21	< 0.12–0.35
PFUnDA	0.17	0.06–0.29
6:2 FTSA	< 1.82	–
PFHpA	< 0.12	–
PFHxA	< 0.11	–
PFTeDA	< 0.04	–
PFDoDA	< 0.03	–
PFBS	< 0.012	–

Hovgard et al. (2009) measured in 2009 the levels of PFOS in blood serum of persons living close to the popular sport fishing lakes Ingsjöarna, where elevated levels of PFOS have been detected in the water as well as in fish, likely due to runoff from the nearby airport Landvetter where fire-fighting foam containing PFOS has been used. Individuals were divided into three groups based on their feeding habits: A) individuals that had consumed fish from the area, B) individuals that had not consumed fish from the area but other kind of fish, and C) individuals that do not, or rarely, consume fish. The results showed that individuals in group A had the highest levels of PFOS in serum with a mean/median of 43/23 ng/ml serum, followed by group B and C (Table 7).

Table 7. Levels of PFOS in blood serum (ng/ml) of people living close to the lakes Ingsjöarna sampled 2009. Source: Hovgard et al. (2009).

Group	N	Mean/median	Range
A	13	45/23	3.0–204
B	8	31/20	8.5–83
C	8	12/13	3.9–17

Jönsson et al. (2010) analysed during 2009–2010 the levels of PFHxS, PFOS, PFOA, PFNA, PFDA and PFUnDA in serum samples from 50 males at the age of 18 recruiting for military. The results showed that PFOS was the dominant PFAS with a median level of 6.9 ng/ml serum, followed by PFOA, PFNA, PFHxS, PFDA and PFUnDA (Table 8).

Table 8. Levels of PFASs in serum (ng/ml) of Swedish males at the age of 18 (n=50) sampled 2009–2010. Source. Jönsson et al. (2010).

Congener	Median	Range
PFOS	6.9	3.7–19
PFOA	1.9	1.2–3.3
PFNA	0.96	0.49–2.6
PFHxS	0.78	0.38–2.5
PFDA	0.41	0.14–0.65
PFUnDA	< 0.1	< 0.1–0.83

2.2 Indirect exposure via the environment – Temporal trend studies

2.2.1 Samples taken before 2006 (not considered for risk characterization)

Kärrman et al. (2007) analysed pooled milk samples (25–90 women/year) from different regions in Sweden sampled 1996–2004, for 13 PFASs – PFBS, PFHxS, PFOS, PFDS, PFHxA, PFHpA, PFOA, PFNA, PFDA, PFUnDA PFDoDA, PFOSA and tetrahydro-PFOS (not included in this risk assessment). The result showed that PFOS was detected at the highest levels followed by PFHxS and PFNA. The temporal trend show a possible decline in the levels of PFOS and PFHxS after 2002 (Figure 2), though it cannot be excluded that the decline is due to regional differences.

2.2.2 Samples taken after 2006 (considered for risk characterization)

Jönsson et al. (2009) analysed the levels of PFHxS, PFOS, PFOA, PFNA and PFOSA in 80 plasma samples (n = 1–15/group) from females in Lund with an average age of 48 years, taken between 1987 and 2007 and stored in a bio bank. The levels of PFOS were highest of the compounds tested during that time-period, followed by PFOA, PFHxS and PFNA (Table 9). The levels of PFOSA were below LOD for all samples. Although difficult to draw firm conclusions due to small number of samples at some time-points, the authors concluded that over the whole time-period the levels of PFOS was decreasing, the levels of PFNA and PFHxS increasing, and that no temporal trend could be observed for PFOA. However considering the temporal trends from 2000 onwards, no increasing trend for PFHxS can be identified for that time-period.

Table 9. Mean levels of PFOS, PFOA, PFNA and PFHxS in (ng/ml) plasma sampled in females from Lund between 1987 and 2007. Source: Jönsson et al (2009).

Year	N	PFOS		PFOA		PFHxS		PFNA	
		Mean	Range	Mean	Range	Mean	Range	Mean	Range
1987	3	14.4	8.3–21.8	2.5	1.8–3.0	0.49	0.28–0.90	0.26	0.15–0.32
1988	8	17.8	8.6–25.8	3.7	1.2–6.9	0.66	0.41–0.89	0.29	0.17–0.37
1989	9	17.4	11.1–25.0	2.7	1.5–4.2	0.70	0.49–1.5	0.25	0.11–0.40
1990	4	19.1	10.7–32.3	2.3	1.6–4.1	0.83	0.44–1.3	0.36	< 0.10–0.64
1991	1	11.4	N.A.	1.7	N.A.	0.36	N.A.	0.22	N.A
1993	1	18.5	N.A.	4.9	N.A.	0.99	N.A.	0.28	N.A.
1994	2	20.9	20.1–21.6	3.9	3.7–4.1	1.52	1.1–1.9	0.35	0.31–0.38
1995	4	23.2	15.7–33.0	5.0	3.7–7.2	0.68	0.52–0.82	0.32	0.20–0.47
1996	8	20.5	11.1–36.7	3.9	2.3–6.3	0.99	0.52–1.7	0.37	0.22–0.56
1997	3	15.2	10.0–18.2	3.7	2.8–5.3	1.29	0.73–2.3	0.37	0.34–0.39
1998	1	35.5	N.A.	5.5	N.A.	1.93	N.A.	0.89	N.A.
1999	2	17.3	16.8–17.9	2.5	1.9–3.1	0.80	0.49–1.1	0.22	< 0.10–0.43
2000	8	19.0	10.2–27.6	3.3	1.4–5.1	1.30	0.65–2.6	0.37	0.24–0.54
2001	1	12.1	N.A.	2.2	N.A.	0.71	N.A.	0.36	N.A.
2006	15	13.1	3.7–27.5	2.7	1.2–4.7	0.85	0.16–1.5	0.71	0.42–1.6
2007	10	11.5	4.1–20.0	3.1	1.3–5.2	1.25	0.33–2.4	0.88	0.30–1.4
Mean	80	16.7	3.7–36.7	3.2	1.2–7.2	0.94	0.16–2.6	0.47	< 0.10–1.6

N.A. = Not applicable.

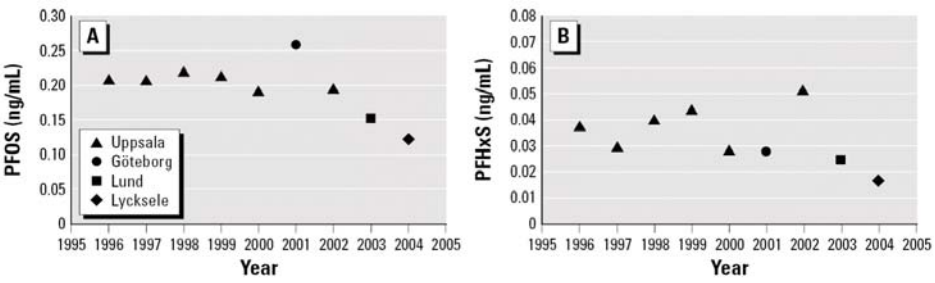


Figure 2. Temporal trend for PFOS (A) and PFHxS (B) in human composite milk samples from different regions in Sweden 1996–2004. Source: Kärrman et al. (2007).

Sundström et al. (2011a) measured the concentrations of PFOS, PFHxS and PFOA in pooled human milk samples (n = 18–116) obtained from mothers in Stockholm between 1972 and 2008. The results showed that PFOS was the predominant PFAS, followed by PFOA and PFHxS (Figure 3). All three analytes showed statistically significant increasing trends from 1972 to 2000, with concentrations reaching a plateau in the 1990s. PFOS and PFOA showed statistically significant decreasing trends from 2001 to 2008. In 2008, the concentrations of PFOS, PFOA and PFHxS were 0.075 ng/ml, 0.074 ng/ml and 0.014 ng/ml, respectively.

Glynn et al. (2011) investigated temporal trends of nine perfluorinated carboxylates (PFHxA, PFHpA, PFOA, PFNA, PFDA, PFUnDA, PFDoDA, PFTrDA, PFTeDA), four sulfonates (PFBS, PFHxS, PFOS, PFDS) and PFOSA in pooled blood serum from nursing primipara women in Uppsala between 1996 and 2010. The result showed that PFOS, PFHxS and PFOA were the dominant PFAS in the samples (Table 10). There were diverging temporal trends of the studied PFASs, with some congeners showing increasing levels during the study period, whereas others showed decreasing or unchanged levels (Figure 4). The authors concluded that increasing trends was observed for PFBS, PFHxS, PFNA and PFDA, whereas decreasing trends was observed for PFOS, PFDS, PFOSA and PFOA. No significant increasing or decreasing trends were observed for PFHpA and PFUnDA. The levels of PFHxA, PFDoDA, PFTrDA and PFTeDA were all below their respective LODs.

For a summary of the human biomonitoring data for the respective congeners in serum that are used for risk characterization and trend analysis of individuals exposed indirectly via the environment see Table 11. For a summary of breast milk data see Table 12.

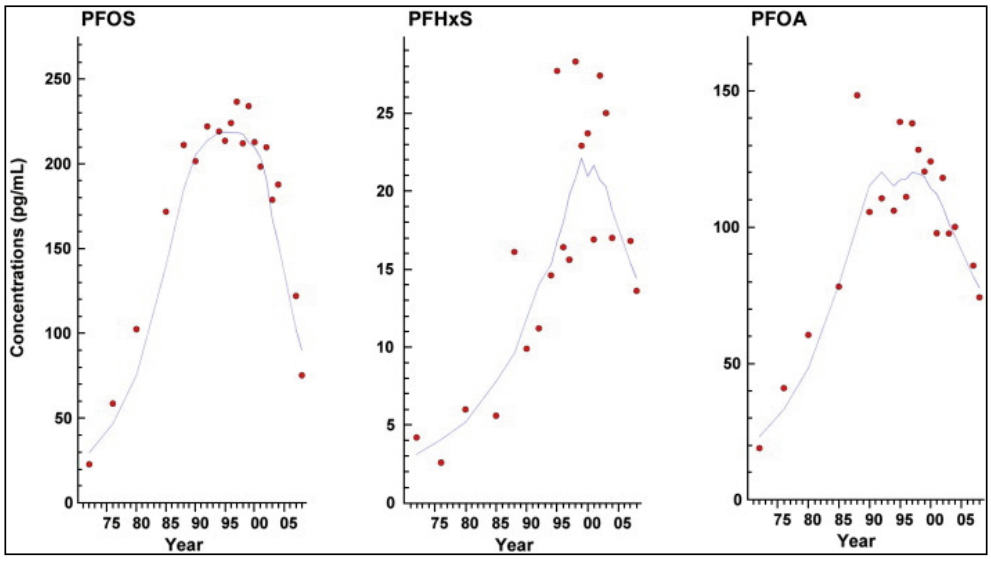


Figure 3. Time-trend of PFOS, PFHxS, and PFOA concentration (pg/mL) in human milk from mothers in Stockholm. Source: Sundström et al. (2011).

Table 10. Range of PFASs concentrations (ng/g fresh weight) in 36 pooled samples of serum from first-time mothers in Uppsala. Source: Glynn et al. (2011).

Year	N	PFBS	PFHxS	PFOS	PFDS	FOSA	PFHpA	PFOA	PFNA	PFDA	PFUnDA
1996	3	< 0.013–0.021	1.7–2.5	22.7–27.3	0.042–0.26	0.51–0.79	0.075–0.084	2.2–2.9	0.41–0.54	0.18–0.24	0.18–0.23
1997	3	< 0.013–0.029	1.6–2.4	20.3–24.8	0.09–0.15	0.44–0.61	0.080–0.11	2.3–3.1	0.28–0.47	0.25–0.26	0.17–0.29
1998	3	< 0.0130.019	1.2–2.2	20.2–23.1	0.021–0.17	0.41–0.51	0.073–0.14	2.2–2.7	0.42–0.47	0.22–0.25	0.18–0.24
1999	3	< 0.013–0.013	1.8–3.0	20.0–23.0	0.020–0.046	0.51–0.58	0.056–0.12	2.4–3.1	0.33–0.43	0.15–0.19	0.16–0.29
2000	2	< 0.013–0.018	2.5–3.1	18.7–22.0	0.048–0.052	0.36–0.44	0.063–0.094	2.5–2.7	0.38–0.41	0.19–0.19	0.22–0.22
2001	1	0.017	2.0	28.1	0.057	0.57	0.11	3.1	0.65	0.29	0.35
2002	3	< 0.013–0.025	2.3–3.1	17.0–23.2	0.037–0.064	0.19–0.30	0.079–0.13	2.2–3.0	0.38–0.53	0.20–0.30	0.25–0.30
2004	3	< 0.013–0.029	1.9–3.9	13.6–16.6	0.037–0.052	0.07–0.21	0.097–0.107	2.1–2.2	0.46–0.53	0.29–0.33	0.20–0.33
2006	3	0.033–0.069	3.3–5.4	10.7–16.5	0.025–0.043	< 0.040–0.10	0.080–0.093	1.7–2.1	0.45–0.61	0.27–0.31	0.19–0.26
2007	3	0.026–0.037	3.3–4.8	8.8–18.3	0.022–0.057	0.056–0.078	0.064–0.090	1.4–2.4	0.54–0.81	0.22–0.32	0.20–0.27
2008	3	0.052–0.065	4.0–5.2	9.3–11.1	0.021–0.039	< 0.040–0.049	0.058–0.11	1.7–2.6	0.53–0.92	0.21–0.43	0.23–0.29
2009	3	0.054–0.094	4.2–6.2	6.6–7.5	0.024–0.037	< 0.040	0.080–0.12	1.6–2.1	0.74–0.80	0.29–0.39	0.29–0.31
2010	3	0.074–0.108	5.6–8.5	5.0–6.4	0.011–0.035	< 0.040	0.084–0.14	1.6–2.2	0.62–1.0	0.31–0.48	0.21–0.35

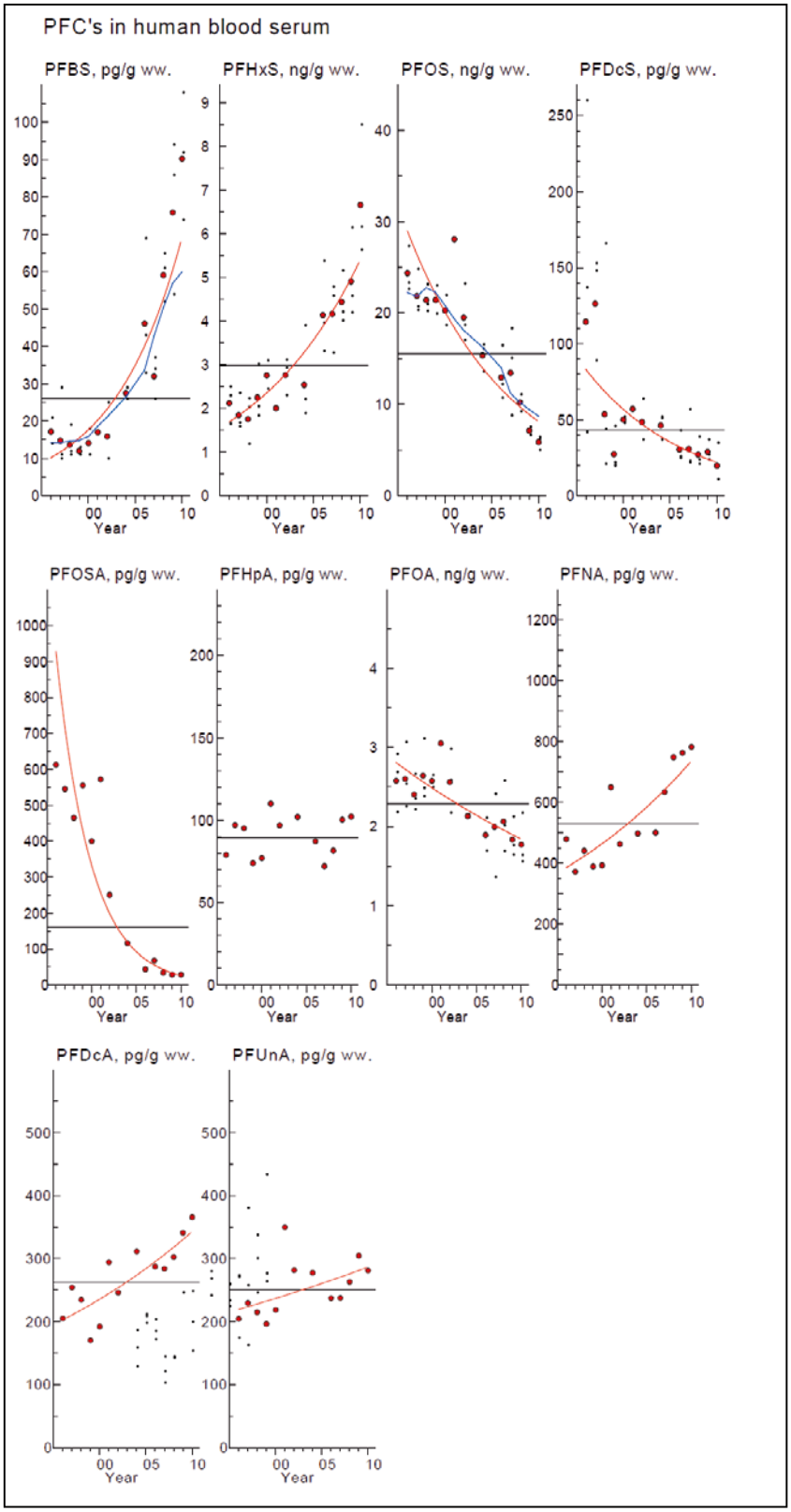


Figure 4. Concentrations of perfluorinated alkyl sulfonates in pooled samples (N=36) of blood serum from first-time mothers in Uppsala sampled between 1996 and 2010. The bigger red dots represent the geometric means for the pooled samples for each year and the black horizontal lines the geometric mean for the respec-tive series. The red regression lines show significant linear trends for log-normal PFAS data. A running mean smoother (blue line) shows significant non-linear trend components. Source: Glynn et al. (2011).

Table 11. Summary table of Swedish human serum biomonitoring data from key studies that will be used for the risk characterization of individuals exposed indirectly via the environment (letters marked in bold), or for temporal trend analysis based on levels from 2000 and onwards. Selected levels represent the highest levels at the latest time-point in a temporal study and/or from a sample being no more than 5 years old.

Congener	Serum level (ng/ml)	Sampling year	Population	Reference	Temporal trend analysis	
					Trend	Conclusion
PFBS	**0.108**	2010	Nursing mothers	Glynn et al., 2011	↑	Levels increasing
PFHxS	**8.50**	2010	Nursing mothers	Glynn et al., 2011	↑	Levels increasing
PFOS	**27.5**	2006	General population	Jönsson et al., 2009	↓	Levels decreasing
	6.44	2010	Nursing mothers	Glynn et al., 2011	↓	
	204	2009	Highly exposed	Hovgard et al., 2009	N.A.	
PFOSA	**< 0.040**	2010	Nursing mothers	Glynn et al., 2011	↓	Levels decreasing
PFDS	**0.035**	2010	Nursing mothers	Glynn et al., 2011	↓	Levels decreasing
PFHxA	**< 0.22**[a]	2007	General population	Ericson et al., 2008	N.A.	–
PFHpA	**0.135**	2010	Nursing mothers	Glynn et al., 2011	↔	Levels unchanged
PFOA	**5.2**	2007	General population	Jönsson et al., 2009	↔	Levels decreasing
	2.17	2010	Nursing mothers	Glynn et al., 2011	↓	
PFNA	**2.6**	2009–2010	General population	Jönsson et al., 2010	N.A.	Levels increasing
	1.0	2010	Nursing mothers	Glynn et al., 2011	↑	
PFDA	**0.70**[a]	2007	General population	Ericson et al., 2008	N.A.	Levels increasing
	0.482	2010	Nursing mothers	Glynn et al., 2011	↑	
PFUnDA	**0.83**	2009–2010	General population	Jönsson et al., 2010	N.A.	Levels unchanged
	0.353	2010	Nursing mothers	Glynn et al., 2011	↔	
PFDoDA	**< 0.03**	2007	General population	Ericson et al., 2008	N.A.	–
PFTrDA	**< 0.15**	2010	Nursing mothers	Glynn et al., 2011	N.A.	–
PFTeDA	**< 0.04**	2007	General population	Ericson et al., 2008	N.A.	–
6:2 FTSA	**< 1.82**	2007	General population	Ericson et al., 2008	N.A.	–

[a]=converted from whole blood to serum levels using a factor of 2 according to Ehresman et al (2007). N.A. = Not available.

Table 12. Summary table of Swedish human breast milk biomonitoring data and temporal trends.

Congener	Level in breast milk (pg/ml)	Sampling year	Reference	Population	Temporal trend analysis	
					Trend	Conclusion
PFHxS	0.014	2008	Sundström et al., 2011	Nursing mothers	↓	Levels decreasing
PFOS	0.075	2008	Sundström et al., 2011	Nursing mothers	↓	Levels decreasing
PFOA	0.074	2008	Sundström et al., 2011	Nursing mothers	↓	Levels decreasing

2.3 Occupational exposure

Nilsson et al. (2010) performed a study during 2007–2008 on eight Swedish and international ski waxing technician's exposure to PFASs from fluorinated wax fumes. The technicians were employed by the Swedish and the US national cross-country ski teams and applied fluorinated ski wax for approximately 30 hours/week. Levels of eight perfluorocarboxylates – PFBA, PFPeA, PFHxA, PFHpA, PFOA PFNA, PFDA and PFUnDA, and three perfluorosul-

fonates – PFBS, PFHxS, and PFOS, were analysed in monthly whole blood samples before the season, during the season, and during a 5 month post-season period. The result showed that among the PFASs detected in all samples, PFOA was detected at highest levels, followed by PFNA, PFOS, PFDA, and PFUnDA (Table 13). Among the PFASs, not detected in all samples, PFHpA was detected at highest levels, followed by PFHxA, PFHxS, PFBA, PFPeA and PFBS. Significant correlations were found between the number of working years and levels of perfluorocarboxylates, but no correlations were found for perfluorosulfonates.

Table 13. Levels of PFASs in whole blood samples (ng/ml) from Swedish and international ski waxing technicians during 2007–2008. Source: Nilsson et al. (2010).

Congener	**PFOA**	**PFDA**	**PFNA**	**PFOS**	**PFUnDA**	**PFHpA**
Range	4.8–535	0.87–24	0.86–163	0.28–27	0.11–2.8	< 0.37–20
Congener	**PFHxS**	**PFBA**	**PFHxA**	**PFPeA**	**PFBS**	
Range	< 0.30–4.3	< 0.08–1.1	< 0.07–12	< 0.06–0.14	< 0.02–0.04	

For a summary of the human biomonitoring data for the respective congeners in serum that is used for risk characterization of occupationally exposed individuals see Table 14.

Table 14. Summary table of Swedish human serum biomonitoring data from key studies that will be used for the risk characterization of occupationally exposed individuals based on Nilsson et al. (2010). For those congeners where no serum measurements were available, values from people exposed indirectly via the environment have been used (Table 11).

Congener	**Serum level (ng/ml)**	**Sampling year**	**Reference**
PFBS	5.6[a]	2007–2008	Nilsson et al., 2010
PFHxS	8.6[a]	2007–2008	Nilsson et al., 2010
PFOS	54[a]	2010	Nilsson et al., 2010
PFOSA	< 0.040[b]	2010	Glynn et al., 2011
PFDS	0.035[b]	2010	Glynn et al., 2011
PFBA	2.2[a]	2007–2008	Nilsson et al., 2010
PFPeA	0.28[a]	2007–2008	Nilsson et al., 2010
PFHxA	24[a]	2007–2008	Nilsson et al., 2010
PFHpA	40[a]	2007–2008	Nilsson et al., 2010
PFOA	1070[a]	2007–2008	Nilsson et al., 2010
PFNA	326[a]	2007–2008	Nilsson et al., 2010
PFDA	48[a]	2007–2008	Nilsson et al., 2010
PFUnDA	5.6[a]	2007–2008	Nilsson et al., 2010
PFDoDA	< 0.03[b]	2007	Ericson et al., 2008
PFTrDA	< 0.15[b]	2007	Ericson et al., 2008
PFTeDA	< 0.04[b]	2007	Ericson et al., 2008
6:2 FTSA	< 1.82[b]	2007	Ericson et al., 2008

[a] = converted from whole blood to serum levels using a factor of 2 according to Ehresman et al. (2007).

[b] = Value taken from Table 11.

2.4 Exposure assessment results/discussion

For individuals exposed indirectly via the environment (the general population), the exposure assessment showed that PFAS congeners in serum were found at low ppb (ng/ml) concentrations. In one study, PFOS was found at higher ppb concentrations in a small population eating fish from a PFOS-contaminated lake. This supports the proposal of food, in particular fish, being a major source of exposure. PFOS has for a long period been the dominating congener in human serum; however it shows a decreasing trend and was in one study (Glynn et al., 2011) exceeded by higher levels of PFHxS.

In the occupationally exposed population, professional ski-waxers, the levels of some congeners were significantly higher than in the average population, i.e. the carboxylates PFNA and PFOA being approximately 125 and 200 times higher and reaching high ppb as well as ppm (µg/ml) levels in serum. This is likely due to that PFASs are constituents of gliding waxes (Nilsson et al., 2010), and in particular perfluorinated carboxylates, for which a correlation between serum levels and the number of working years was found, and support the proposal of inhalation being a major route of occupational exposure. No correlations were found between the number of working years and levels of perfluorinated sulfonates, indicating other sources of exposure for these homologues.

In the general population, the levels of PFOS, PFDS, PFOSA and PFOA seem to decrease. This is likely a result of the phase-out of PFOS-related production in 2002 by the major manufacturer (3M, 2011) and by the on-going phase-out of PFOA by some manufacturers (U.S. EPA, 2010). In contrast, the levels of PFBS, PFNA, PFDA and PFUnDA in serum seem to increase. The increase in PFBS is likely due to that it has been introduced as a replacement product for six- and eight carbon analogs (Ehresman et al., 2007). For PFHxS, a clear temporal increase in serum levels was observed in one study (Glynn et al., 2011), whereas unchanged serum levels (Jönsson et al., 2010) or decreasing levels in breast milk was observed (Sundström et al., 2011). The reason for the increase in PFHxS in women from Uppsala as opposed to the decrease in the other two studies has not been established, but could be a result of the elevated levels of PFHxS that has been detected in the municipal water in Uppsala (Glynn, 2012)[4]. The increasing levels of the long chain carboxylates, PFNA, PFDA and PFUnDA as opposed to the decreasing or unchanged levels of the short chain carboxylates could be due to a shift in the use towards long chain perfluorocarboxylates. For other congeners it was not possible to determine the temporal trend due to either unchanged levels such as for PFHpA, because of the lack of temporal trend data, or because the levels were < LOD.

[4] Added subsequent to the last literature search in August, 2011.

3. Environmental exposure

3.1 Snapshot studies

3.1.1 Samples taken before 2006 (not considered for risk characterization)

Within the Swedish Environmental Monitoring Screening Programme, levels of PFOS and PFOA were studied in muscle of perch at 23 different locations during 2000–2002 (Naturvårdsverket, 2005). The result showed that the concentrations of PFOS ranged from 1.2–41 ng/g wet weight (w.w.), and that a spatial trend could be observed, with higher levels in urban areas and lower levels in rural areas. PFOA could not be detected in any sample.

In a screening study on PFASs in the Nordic environment, levels of three perfluorinated sulfonates – PFHxS, PFOS and PFDS, and four carboxylates – PFHxA, PFHpA, PFOA and PFNA as well as PFOSA was measured in livers of Swedish grey seals, cod, and freshwater perch sampled in 2003 (Kallenborn et al., 2004). The result showed that PFOS, PFOSA and PFNA could be detected in all samples, with PFOS being the dominant congener in all species (Table 15). The levels of almost all congeners were higher in the grey seals, likely a result of the bioaccumulative properties of these compounds.

Table 15. Range of concentrations of PFASs in livers (ng/g w.w.) of Swedish perch, cod and grey seals sampled in 2003. Source: Kallenborn et al. (2004).

Species	PFOS	PFNA	PFOSA	PFHxA	PFHxS	PFOA	PFHpA	PFDS
Perch (n=4)	169–432	0.23–6.3	0.6–6.1	0.62–1.08	< 0.4–1.4	< 0.6	≤ 0.3	< 1.4–3.6
Cod (n=8)	6.4–62	0.47–18	0.41–6.1	< 0.5	< 0.4	< 0.6	< 0.3	< 1.4
Grey seal (n=3)	331–537	29–36	7.5–15	0.48–0.62	0.67–2.0	0.6–1.8	< 0.3	9–13

Holmström et al (2008) investigated tissue concentrations of PFASs in guillemots from the Baltic Sea. In total, 11 perfluorinated carboxylates – PFHxA, PFHpA, PFOA, PFNA, PFDA, PFUnDA, PFDoDA, PFTrDA, PFTeDA, PFPeDA and PFHxDA, four perfluorinated sulfonates – PFBS, PFHxS, PFOS, PFDS as well as PFOSA were determined in egg, liver, kidneys and muscle of adult guillemot and in liver from chicks, all sampled in 1989. Also, whole herring homogenates from 2005 were analysed, since herring constitute a large part of the guillemot's diet. The results showed that PFOS was the predominant congener, followed by PFTrDA and PFUnDA (Table 16). The median concentration of PFOS was highest in eggs, followed by chick liver, adult kidneys, liver and muscle. Relatively low levels of PFOS were found in herring. Some PFASs showed higher concentrations in eggs than in the female livers. The ratio of levels in egg/female liver, increased with increasing PFAS chain length.

Table 16. Median concentration (ng/g w.w.) and range in samples of guillemot (sampled 1989) and whole herring (Sampled 2005) from the Baltic Sea. Source. Holmström et al. (2008).

Compound		Adult muscle (n=8)	Adult kidney (n=10)	Adult liver (n=10)	Chick liver (n=10)	Egg (n=8)	Herring (n=10)
PFOS	Median	14	127	121	309	325	2.3
	Range	9.8–17	92–183	91–150	185–322	243–432	1.7–2.8
PFTrDA	Median	1.3	7.8	7.1	15	11	0.50
	Range	1.0–1.9	5.9–14	3.9–15)	7.8–32	8.8–14	< 0.28–0.94 (8/10)
PFUnDA	Median	0.63	5.0	12	12	12	0.46
	Range	0.33–1.2	3.7–7.8	6.6–28	7.1–25	7.6–13	0.27–0.94
PFDoDA	Median	0.53	2.6	3.4	4.0	3.6	< 0.24
	Range	< 0.13–0.77 (6/8)	1.7–3.0	2.1–8.5	2.3–8.3	2.7–4.1	< 0.24–0.28 (1/10)
PFDA	Median	0.44	2.4	3.5	4.7	2.0	0.31
	Range	0.31–0.61	1.6–4.2	2.4–8.5	2.4–12	1.7–2.6	< 0.28–0.41 (8/10)
PFNA	Median	0.24	3.3	2.8	3.2	1.1	0.57
	Range	0.17–0.42	1.2–5.7	1.3–5.8	0.96–4.7	0.76–1.8	0.34–0.74
PFTeDA	Median	< 0.26	1.3	< 0.40	2.3	0.94	< 0.68
	Range	< 0.26–0.57 (4/8)	< 0.11–2.9 (8/10)	< 0.40–0.86 (2/13)	1.8–3.7	0.31–2.5	
PFPeDA	Median	< 0.32	< 0.30	< 0.84	< 0.22	0.33	< 1.7
	Range		< 0.30–1.9 (4/10)		< 0.22–4.1 (5/10)	0.19–0.96	
PFHxS	Median	< 0.32	0.53	< 3.5	< 3.7	1.5	< 0.06
	Range		0.12–0.78			1.2–1.8	
PFDS	Median	< 0.22	< 0.11	< 0.20	2.5	2.3	< 0.10
	Range		< 0.11–0.87 (1/10)	< 0.20–43 (6/13)	1.1–4.5	1.9–2.7	
PFOSA	Median	< 0.16	0.53	< 0.13	0.79	0.86	0.23
	Range		< 0.04–0.94 (7/10)		0.47–1.6	0.61–1.1	0.12–0.41
PFBS	Median	< 0.87	< 0.10	< 0.19	< 0.06	< 0.15	< 0.07
PFHxA	Median	< 1.0	< 0.51	< 1.9	< 1.3	< 0.75	< 1.4
PFHpA	Median	< 2.2	< 1.5	< 4.5	< 4.4	< 0.72	< 1.1
PFOA	Median	< 0.60	< 1.2	< 2.2	< 0.76	< 0.99	< 1.4
PFHxDA	Median	< 0.38	< 0.26	< 0.40	< 0.18	< 0.21	Not analysed

In 2005, within the Swedish National Screening Programme levels of PFBS, PFHxS, PFOS, PFDS, PFBA, PFHxA, PFHpA, PFOA, PFNA, PFDA, PFUnDA, PFOSA and 6:2 FTSA were analysed in muscles of in total four perch from three lakes with background exposure close to Göteborg and Stockholm, as well as from Västra Ingsjön, a lake close to Landvetter Airport where PFASs are suspected to be released (Woldegiorgis et al., 2006). The result showed that PFOS was detected in all fish, ranging between 1.2–1.4 ng/g w.w. in the lakes with background exposure, and 98 ng/g w.w. in Västra Ingsjön. Except for the presence of PFOSA in the sample from Västra Ingsjön (2.4 ng/g w.w.). all other congeners were below their limits of detection.

Within the National Swedish Contaminant Monitoring Programme in Terrestrial Biota, muscle of moose and reindeer were collected during 1986–2005 and 1987–2006, respectively, and analysed for PFASs (Danielsson et al., 2008). In total, four perfluorinated sulfonates – PFBS, PFHxS, PFOS and PFDS, seven carboxylates – PFBA, PFHxA, PFHpA, PFOA, PFNA, PFDA and PFUnDA as well as PFOSA and 6:2 FTSA were investigated. The result showed that all PFASs were below LOQ, though PFOS, PFOSA and PFOA could be detected during some single years.

3.1.2 Samples taken after 2006 (considered for risk characterization)

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 analysed for PFASs (Odsjö et al., 2008). In total, four perfluorinated sulfonates – PFBS, PFHxS, PFOS and PFDS, 10 carboxylates – PFHxA, PFHpA, PFOA, PFNA, PFDA, PFUnDA, PFDoDA, PFTrDA, PFTeDA and PFPeDA as well as PFOSA were investigated. The result showed that PFOS was the dominant congener with an average and maximum concentration of 3.5 and 6.7 ng/g w.w., respectively (Table 17). PFNA, PFUnDA and PFTrDA were detected at average concentrations of approximately 0.6 ng/g w.w., followed by PFDoDA with an average level of 0.3 ng/g w.w. The levels of PFHpA, PFOA, PFDA, PFTeDA, PFPeDA, PFBS and PFDS were all under their limit of detection.

Table 17. Range of concentrations of PFASs in starling livers (ng/g w.w.) from various locations in Sweden sampled in 2006. Source: Odsjö et al. (2008).

PFHxA	PFNA	PFUnDA	PFDoDA	PFTrDA	PFOS	PFOSA
< 0.15–0.25	< 0.30–0.84	0.44–1.03	0.08–0.60	< 0.15–0.73	1.89–6.73	< 0.03–0.08

Within the National Swedish Contaminant Monitoring Programme in Fresh Water Biota, the levels of 15 PFASs were analysed in pooled liver samples of pike, arctic char and perch (n=10/sample) from 32 Swedish lakes from all parts of Sweden during 2007–2008 (Gustavsson et al., 2010). The PFASs analysed were PFHxA, PFHpA, PFOA, PFNA, PFDA, PFUnDA, PFDoDA, PFTrDA, PFTeDA, PFPeDA, PFBS, PFHxS, PFOS, PFDS and PFOSA.

The result showed that PFOS were found in all lakes and at the highest concentrations. Also, PFTrDA were found in all lakes, PFNA in 30 of the lakes and PFOSA and PFOA only in concentrations exceeding the detection limit on three and two locations, respectively (Figure 5). The other compounds were below their respective LODs. For PFOS and PFTrDA, a pattern of increasing concentrations from north to south was found, with the highest measured concentration being 168 and 17.4 ng/g w.w., respectively. No general pattern was observed for the three other compounds presented here.

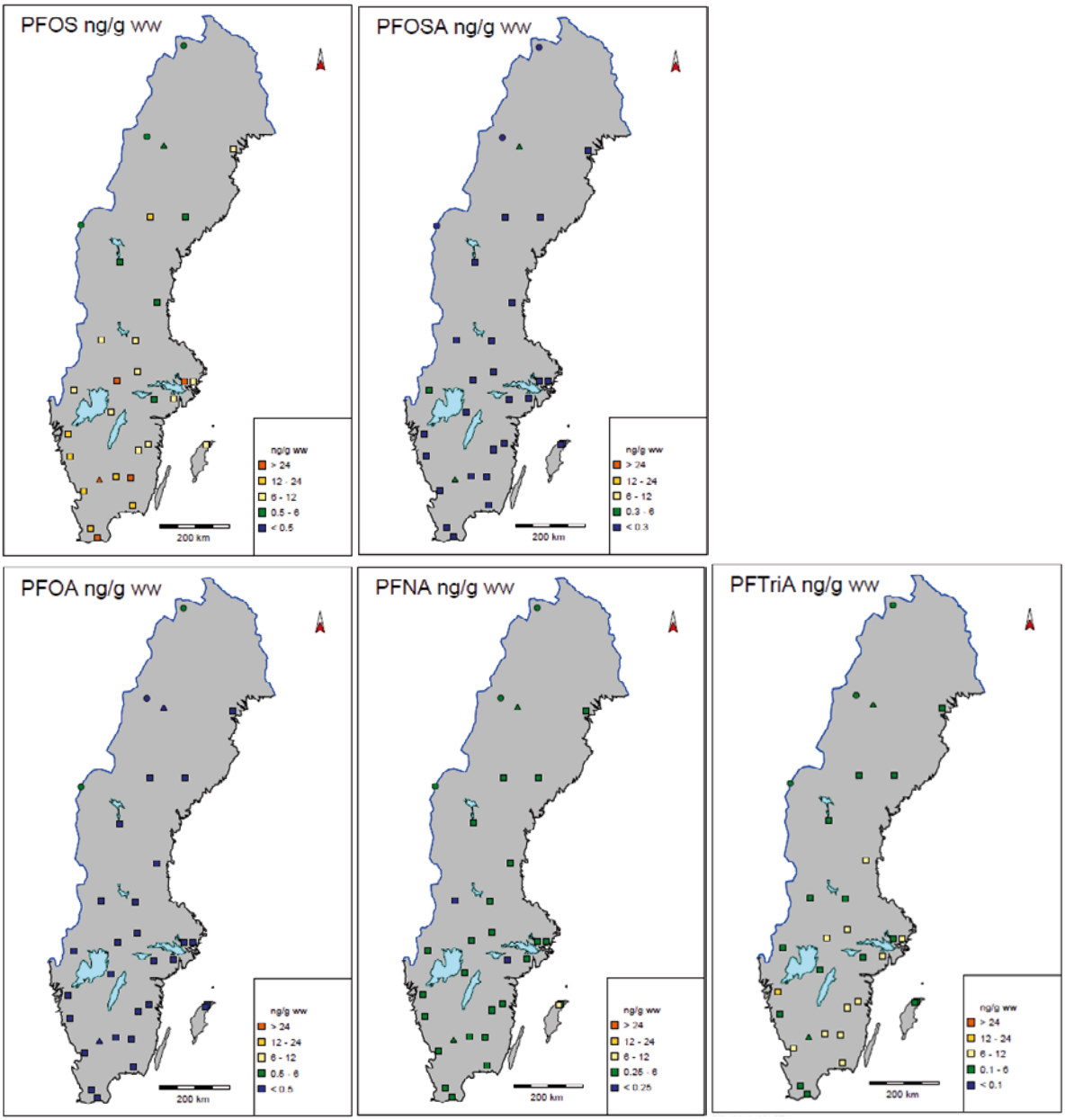


Figure 5. Spatial variation of PFOS, PFOSA, PFOA, PFNA and PFTrDA (PFTriA). The squares represents the concentration interval of average measured concentrations in fish liver between 2007-2008 from lakes within the Swedish national monitoring programme. ■ = Perch • = Char ▲= Pike. Source. Gustavsson et al. (2010).

Holmström et al (2010) examined the tissue levels of PFASs in Swedish peregrine falcon eggs sampled in 2006 from a breeding area in south-western Sweden. In total, four perfluorinated sulfonates – PFBS, PFHxS, PFOS and PFDS, 10 perfluorinated carboxylates – PFHxA, PFHpA, PFOA, PFNA, PFDA, PFUnDA, PFDoDA, PFTrDA, PFTeDA and PFPeDA as well as PFOSA were analysed. The result showed that PFOS was the dominant congener, followed by PFTrDA and PFUnDA (Table 18). PFHxA, PFHpA, PFOA, PFBS and PFOSA were all under their limits of detection.

Table 18. Tissue levels of PFASs in Swedish peregrine falcon eggs (ng/g w.w.) collected 2006 (n=10). Source: Holmström et al (2010).

Congener	Mean	Range
PFOS	83	40–220
PFTrDA	7.3	4.0–14
PFUnDA	4.2	2.0–9.7
PFDoDA	3.2	1.3–5.6
PFDA	3.1	1.0–9.6
PFTeDA	2.7	1.5–4.9
PFNA	1.6	0.97–2.3
PFHxS	0.8	0.52–1.9
PFDS	0.66	0.31–2.3
PFPeDA	0.57	0.24–1.1
PFOA	< 2.2	–
PFHpA	< 1.4	–
PFHxA	< 0.6	–
PFOSA	< 0.1	–
PFBS	< 0.08	–

Within the RE-PATH project (Risks and Effects of the dispersion of PFASs on Aquatic, Terrestrial, and Human populations in the vicinity of International Airport), muscle of perch and roach were sampled during 2009 for analysis of in total 11 PFASs – PFBS, PFHxS, PFOS, PFDS, PFHxA, PFHpA, PFOA, PFNA, PFDA and PFUnDA (Woldegiorgis et al., 2010). Three lakes in connection to Landvetter Airport (Lilla Issjön, closest to the airport; V:a Ingsjön, downstream Lilla Issjön; and Sandsjön, background) and in two lakes in connection to Arlanda Airport (Halmsjön, close to the airport; and Valloxen, background) were selected. The result showed that PFOS was by far the predominant congener found, with levels approximately 100x higher in perch in the lakes close to the respective airports (up to 988 ng/g w.w.), as compared to perch in the reference lakes, (Table 19). In contrast, the levels of most other congeners were relatively low. In addition, one perch was dissected for investigation of the distribution of PFAS to different tissues. The result showed that the e.g. levels of PFOS were 15 and 12 times higher in liver and blood, respectively, as compared to muscle tissue (Table 20).

Table 19. Concentrations of PFASs in muscle of perch and roach (ng/g w.w.) sampled in the vicinity of Landvetter and Arlanda Airports in 2009. Source: (Woldegiorgis et al., 2010).

Landvetter	Species	PFOS	PFOSA	PFDS	PFUnDA	PFDA	PFHxS	PFHxA	PFNA	PFOA	PFBS	PFHpA
Lilla Issjön	Perch (n=3–6)	217–324	16.9–20.3	1.1–1.5	0.2–0.3	0.1–0.2	0.2–0.3	< 0.02–0.7	< 0.10	≤ 0.02	< 0.20	< 0.001
V:a Ingsjön	Perch (n=3–6)	31.0–45.5	1.0–1.7	0.1–0.3	0.5–0.6	0.2–0.3	< 0.06–0.08	< 0.04–0.2	0.008–0.03	< 0.02	< 0.20	< 0.001
	Roach (n=2)	20.1–24.0	1.5–1.8	0.3	0.6–1.1	0.2	< 0.06	< 0.04	0.006–0.007	< 0.02	< 0.20	< 0.001
Sandsjön (reference)	Perch (n=3–6)	1.8–4.1	< 0.01–0.02	< 0.05	0.3–0.5	0.2–0.3	< 0.10	≤ 0.2	< 0.10	< 0.02	< 0.02	< 0.001
	Roach (n=3)	1.3–4.0	< 0.005–0.09	< 0.06	0.1–0.4	0.02–0.3	< 0.06–0.02	< 0.002–0.4	< 0.10–0.2	< 0.02–0.003	< 0.02	< 0.001
Arlanda												
Halmsjön	Perch (n=4–9)	266–988	2.1–3.1	0.08–0.7	0.3–0.8	1.2–2.6	0.3–0.9	< 0.002–4.8	0.06–0.1	< 0.001–4.3	< 0.20	< 0.001
	Roach (n=3)	76–239	1.1–1.4	< 0.06–0.2	0.1–0.3	0.1–0.6	0.4–1.0	< 0.050–0.3	< 0.10	< 0.10	< 0.20	< 0.02
Valloxen (Reference)	Perch (n=4–8)	3.2–5.9	< 0.01–0.05	< 0.06	0.08–0.3	0.04–0.2	< 0.020	< 0.050–0.4	< 0.10	< 0.10	< 0.20	< 0.02
	Roach (n=3)	1.8–2.4	< 0.005–0.3	< 0.06	0.05–0.1	0.008–0.1	< 0.010	< 0.050–1.2	< 0.10	< 0.10	< 0.20	< 0.02

Table 20. Distribution of PFASs in heart+blood (ng/g w.w.), muscle (ng/g w.w) and liver (ng/g w.w.), respectively, in one perch collected in Halmsjön close to Arlanda airport in 2009. Source: (Woldegiorgis et al., 2010).

Tissue	PFOS	PFOSA	PFDS	PFUnDA	PFDA	PFHxS	PFHxA	PFNA	PFOA	PFBS	PFHpA
Heart+Blood	6472	18.1	1.9	7.0	11.5	7.0	< 0.05	< 0.1	< 0.1	< 0.2	< 0.02
Muscle	490–528	1.0–1.5	0.4–0.6	0.5–0.6	0.9–1.1	1.2–1.4	< 0.05	< 0.1	< 0.1	< 0.2	< 0.02
Liver	8098.8	50.6	2.3	11.7	20.9	13.6	< 0.05	< 0.1	< 0.1	< 0.2	< 0.02
Ratio heart+blood/muscle	12.3–13.2	12.1–18.1	3.2–4.8	11.7–14	10.5–12.8	5.0–5.8	–	–	–	–	–
Ratio liver/heart+blood	1.25	2.80	1.21	1.67	1.82	1.94	–	–	–	–	–
Ratio liver/muscle	15.3–16.5	33.7–50.6	3.8–5.8	19.5–23.4	19–23.2	9.7–11.3	–	–	–	–	–

Within the National Swedish Contaminant Monitoring Programme in Marine Biota, levels of 16 PFASs have been assessed and reported from 2005–2009 in pooled herring livers (n=10–12) from different sample locations in Sweden – four sulfonates – PFBS, PFHxS, PFOS and PFDS, 10 carboxylates – PFHxA, PFHpA, PFOA, PFNA, PFDA, PFUnDA, PFDoDA, PFTrDA, PFTeDA, PFPeDA as well as PFOSA and 6:2 FTSA (Bignert et al., 2008; 2009; 2010; 2011). Changes in sample locations have been made during the years, and the results therefore need to be interpreted with caution with regard to spatial variations in concentrations, which may be dependent on local discharges. Out of the 16 PFASs analysed, seven could be measured at levels above the limit of quantification (LOQ) – PFHxS, PFOS, PFOSA, PFNA, PFDA, PFUnDA and PFTrDA, whereas the levels of nine of the compounds could not be determined – PFHxA, PFHpA, PFOA, PFDoDA, PFTeDA, PFPeDA, PFBS, PFDS, and 6:2 FTSA. In 2005–2006, PFOSA was detected at the highest concentration followed by PFOS (Table 21) (Bignert et al., 2008). The reason for the higher concentration of PFOSA, detected in southern Sweden, was proposed to be due to a current source in the North Sea. The levels of perfluorinated sulfonates were in general higher in southern Sweden than in northern Sweden, believed to be due to the higher population density, whereas the levels of carboxylates in general were more homogenous, believed to be due to, at least partly, indirect formation from volatile precursor molecules (e.g. fluorotelomers). During the years 2007–2009, PFOS was detected at the highest concentrations followed by PFOSA (Table 21) (Bignert et al., 2009; 2010; 2011). Based on the few years of sampling, temporal trends were considered too early to interpret (Bignert et al., 2011). The spatial distribution from 2009 is shown in Figure 6.

Table 21. Maximum concentrations (ng/g w.w.) of PFASs in pooled herring liver (n=10–12/sample) sampled during 2005–2009 at various locations within the National Swedish Contaminant Monitoring Programme in Marine Biota. Source: Bignert et al. (2008; 2009; 2010; 2011).

Year	PFOS	PFOSA	PFTrDA	PFUnDA	PFNA	PFDA	PFHxS
2005–2006	7.9	14.2	2.2	2.6	2.6	3.9	0.2
2007	25.6	9.7	5.2	4.6	5.6	3.7	2.2
2008	19.0	6.8	5.2	4.6	3.3	3.3	2.2
2009	18.7	7.1	3.3	3.0	2.9	2.1	1.3

During 2008 and 2009, a screening study for the Helsinki Commission (HELCOM) was carried out, "Screening study on occurrence of hazardous substances in the eastern Baltic Sea", in which liver of one flounder and one herring at one location in southern Sweden were analysed for 13 PFASs – 6:2 FTSA, PFOSA, PFBS, PFHxS, PFOS, PFDS, PFBA, PFHxA, PFHpA, PFOA, PFNA, PFDA, PFUnDA (Lilja et al., 2009). The result showed that the only detectable congeners were PFHxS, PFOS, PFNA and PFUnDA, which showed concentrations of 0.25 and 0.57, 8.9 and 12, 3.3 and 3.8, and 0.88 and 0.94 ng/g w.w. in the flounder and herring, respectively.

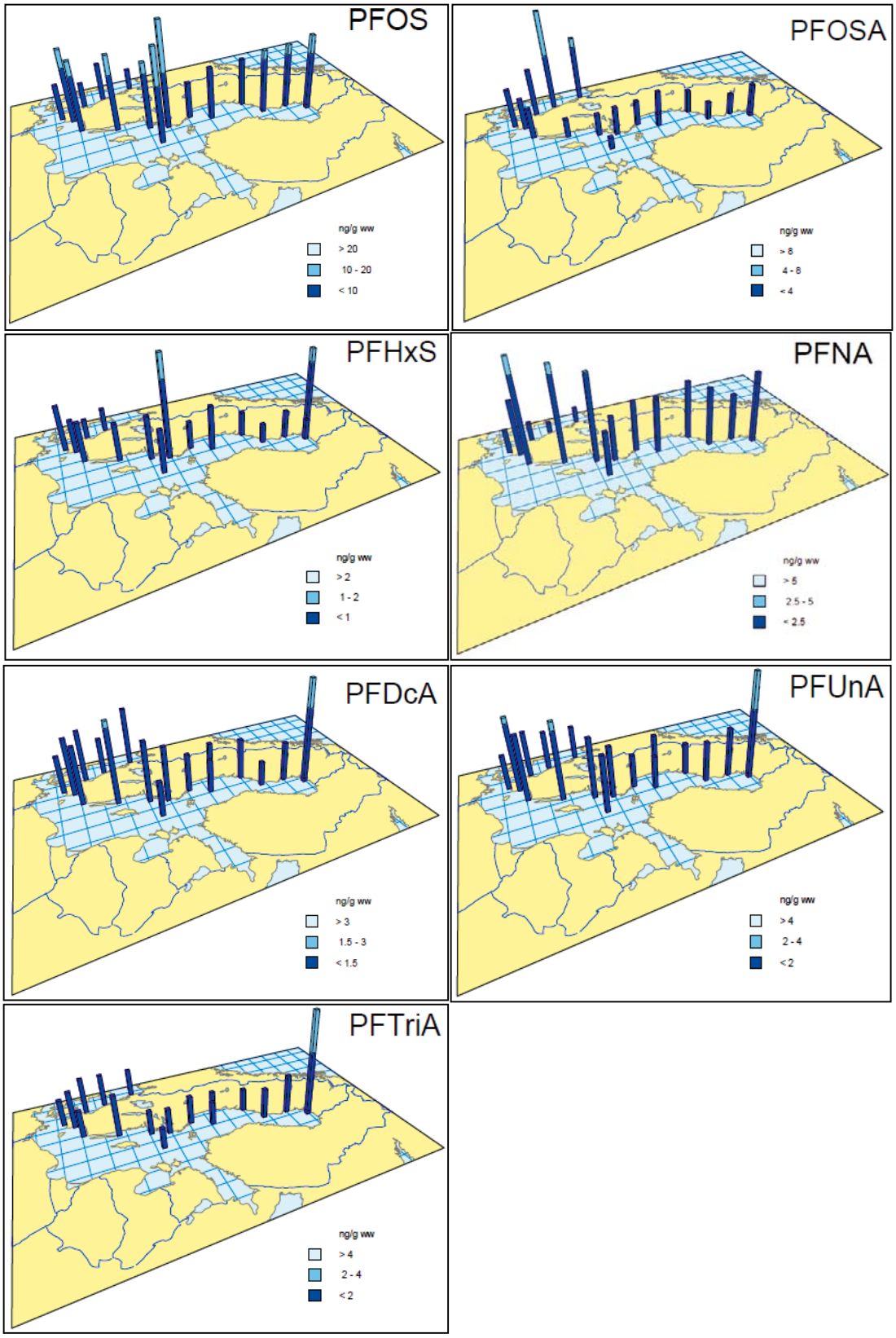


Figure 6. Spatial variation of PFOS, PFOSA, PFHxS, PFNA, PFDA (PFDcA), PFUnDA (PFUnA), and PFTrDA (PFTriA) in pooled herring liver samples (n=12/sample) collected during 2007–2008. Source: Bignert et al. (2011).

In 2011, muscle of perch were sampled and analysed for PFOS and PFOA in two lakes in the vicinity of Malmö Airport (WSP Environmental, 2011). In the two lakes, mean PFOS levels of 218 ng/g w.w. (n=3, range 129–279 ng/g w.w.) and 49.7 ng/g w.w. (n=3, range 36.6–57.7 ng/g w.w.), respectively, was detected. PFOA could not be detected in any sample.

3.2 Temporal trend studies

3.2.1 Samples taken before 2006 (not considered for risk characterization)

Holmström et al. (2005) performed a temporal trend study investigating the concentrations of PFOS and PFOA in guillemot eggs from the Baltic Sea during the years 1968–2003. The results showed that the levels of PFOS increased 30-fold during the time period, from 25 ng/g w.w. in 1968 to 614 ng/g w.w. in 2003, with an annual increase between 7–11% (Figure 7). A peak level was observed in 1999 (1023 ng/g wet weight), followed by decreasing levels until 2002. The levels of PFOA were below the limit of detection (3 ng/g wet weight) in all samples.

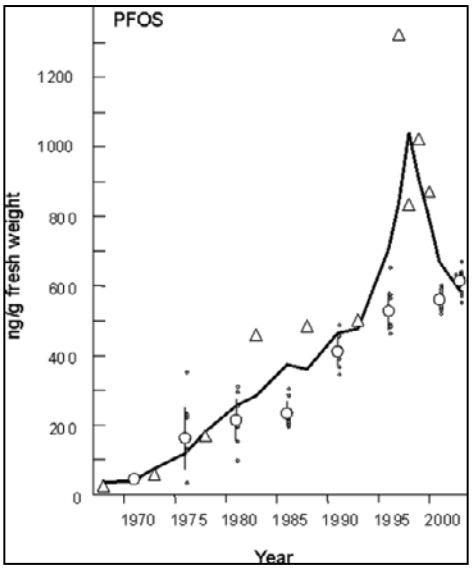


Figure 7. Temporal trend in PFOS concentrations in guillemot eggs from the Baltic Sea, 1968–2003. Arithmetic mean values (circles), values from pooled samples of 8 individuals (triangles), and values from the individual eggs (dots) are shown. The error bars represent 95% confidence interval of the arithmetic mean values. The line illustrates a three-point running mean smoother ($p < 0.001$). Source: Holmström et al. (2005).

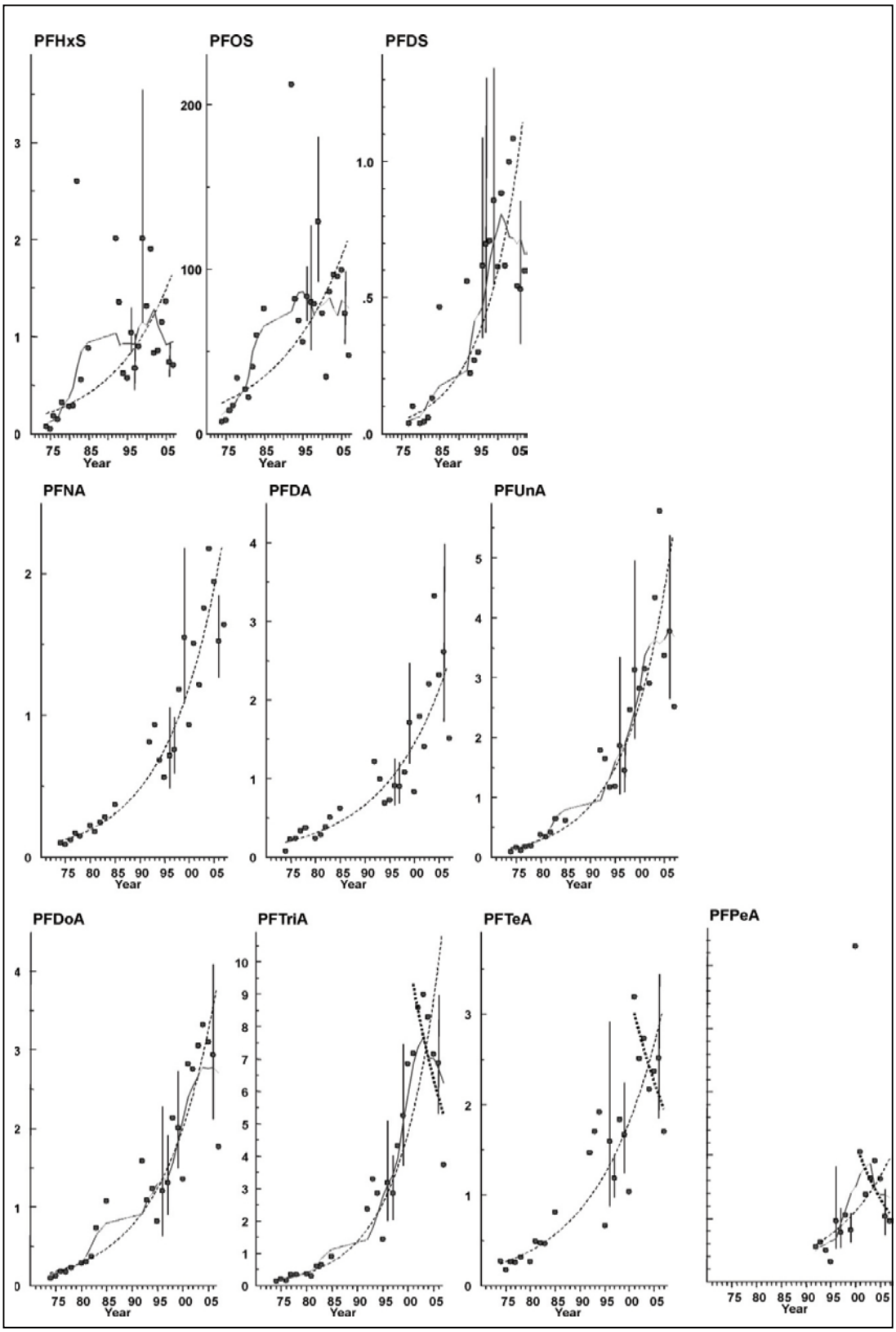


Figure 8. Temporal trends of PFHxS, PFOS, PFDS and PFCAs of chain lengths C9–C15 in Swedish peregrine falcon eggs collected between 1974 and 2007. Concentrations are given in ng/g w.w. and error bars represent 95% confidence intervals of the geometric mean. Log-linear regression (dashed line, 1974–2007), Log-linear regression (dotted line, 2000–2007, drawn when statistically significant) and a seven point running mean smoother (line) are shown. Source: Holmström et al., 2010.

3.2.2 Samples taken after 2006 (considered for risk characterization)

Holmström et al (2010) examined PFASs levels in Swedish peregrine falcon eggs collected between 1974 and 2007 from a breeding area in south-western Sweden. In total, four perfluorinated sulfonates – PFBS, PFHxS, PFOS and PFDS, 10 perfluorinated carboxylates – PFHxA, PFHpA, PFOA, PFNA, PFDA, PFUnDA, PFDoDA, PFTrDA, PFTeDA and PFPeDA as well as PFOSA were analysed. The results showed that PFOS was the predominant congener (83 ng/g w.w. in 2006), followed by PFTrDA (7.2 ng/g w.w.) and PFUnDA (4.2 ng/g w.w.). The authors report, based on the slope of temporal increase/decrease from 2000–2007, that PFNA, PFDA and PFOS are increasing and that PFUnDA, PFDoDA, PFTrDA, PFTeDA, PFPeDA, PFHxS and PFDS are decreasing (Figure 8). PFBS, PFHxA, PFHpA and PFOA could not be detected, and PFOSA only in a few samples. This temporal trend in the terrestrial peregrine falcon is different from the trend observed in the marine guillemot and indicates potential differences with regard to their exposure.

Roos et al (2009) investigated the levels of PFASs in Swedish otters collected 1972–2008. Hepatic concentrations of in total three perfluorinated sulfonates – PFHxS, PFOS and PFDS, seven carboxylates – PFOA, PFNA, PFDA, PFUnDA, PFDoDA, PFTrDA and PFTeDA as well as PFOSA was analysed. The results showed that PFOS was the dominating PFAS, followed by PFDA and PFUnDA (Table 22). The temporal trends analysis showed that some PFAS show a tendency to decrease during recent years (PFUnDA, PFDoDA, PFTrDA, PFOS and PFDS), while show a tendency to decrease (PFOA and PFNA) (Figure 9).

Table 22. Hepatic concentrations of PFASs (ng/g w.w.) in Swedish otters sampled 1972–2008 (n=93).Source: Roos et al (2009).

Congener	Mean	Range
PFOS	1094	21–8301
PFOSA	72	2–478
PFDA	85	0–360
PFUnDA	78	0.7–302
PFNA	75	0–280
PFDoDA	17	0–112
PFDS	8	0–101
PFTrDA	23	0–98
PFHxS	6	0–68
PFOA	9	0.2–58
PFTeDA	5	0–48

Kratzer et al. (2011) investigated temporal trends of PFASs in grey seal livers from the Baltic Sea sampled 1969–2008. In total 43 individual PFASs were investigated, covering perfluorinated sulfonates, sulfinates, phosphonates, carboxylates, fluorotelomer carboxylates, fluorotelomers unsaturated carboxylates, sulfonamides and sulfonamidoethanols. Out of these 43 individual PFASs, 17 could be detected – PFBS, PFPS, PFHxS, PFHpS, PFOS,

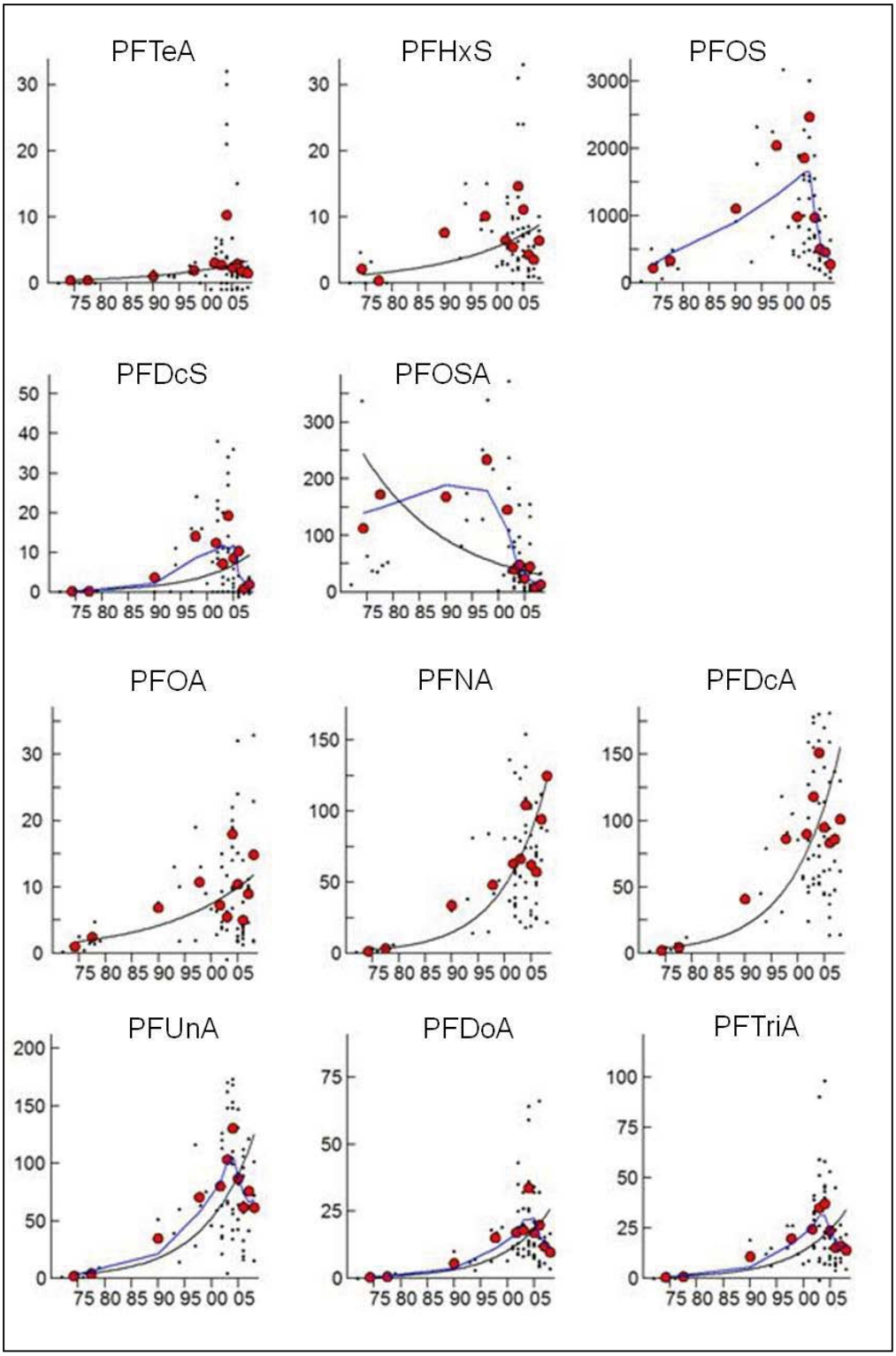


Figure 9. Concentrations of individual PFASs in otter liver (ng/g w.w.). Red circles represent annual geometric means. Black solid lines show the result of linear regression on log-transformed annual means. A running smoothers is drawn in blue if significant. Source: Roos et al., 2009.

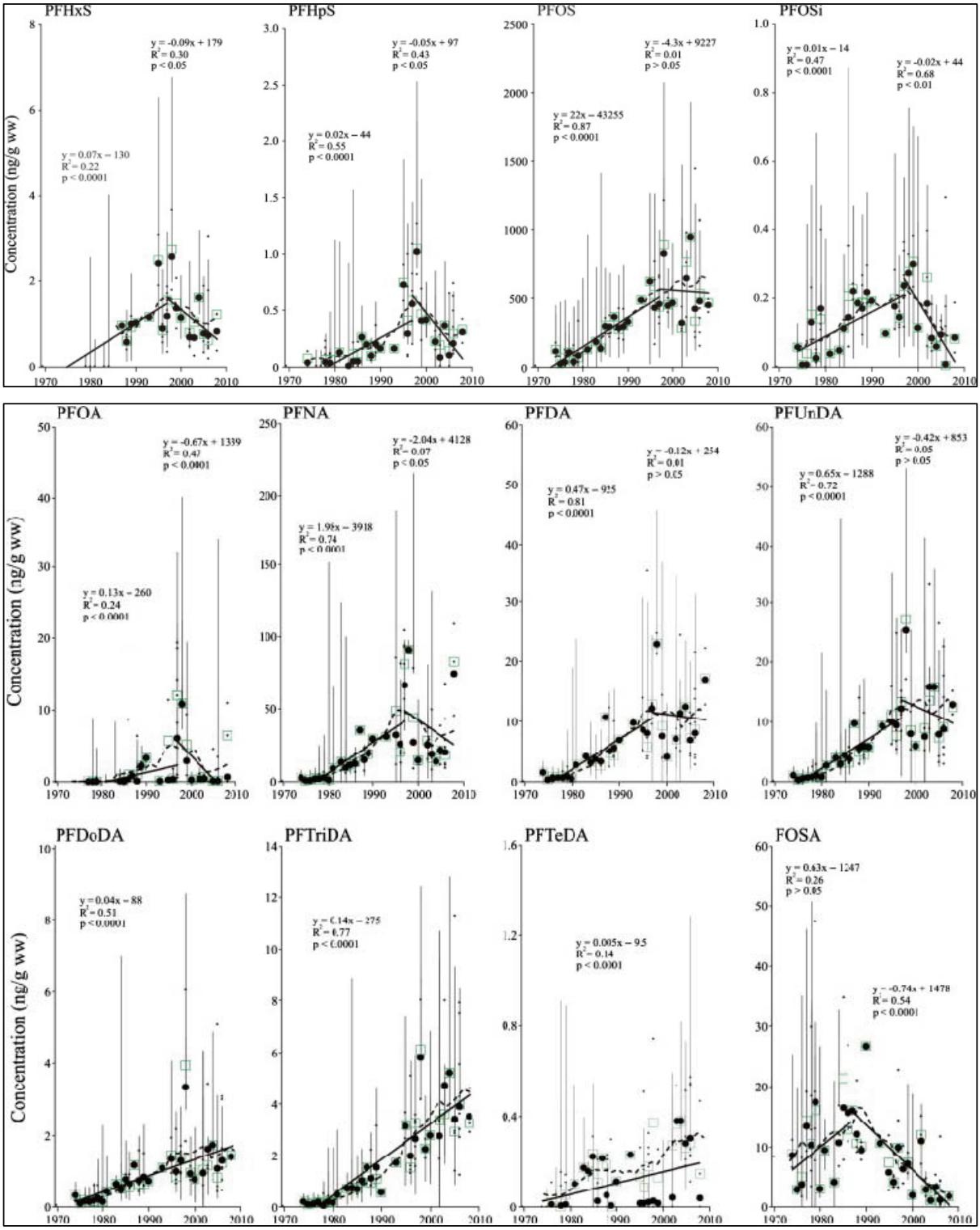


Figure 10. Temporal trends of PFASs in grey seal livers from the Baltic Sea, 1969–2008. The plots display the geometric means (cir-cles) and the median (green squares) together with the individual analysis (small dots), the 95% confidence intervals of the geometric means, and a seven-point running mean smoother (dashed line). Source: Kratzer et al. (2011).

PFOSi, PFDS, PFOSA, PFHpA, PFOA, PFNA, PFDA, PFUnDA, PFDoDA, PFTrDA, PFTeDA and EtFOSA. PFOS was the predominant compound found (9.57–1444 ng/g w.w.) followed by perfluorononanoate (PFNA, 0.47–109 ng/g w.w.). Based on log-linear regression of concentrations 1998–2008 it was estimated that the levels of PFHxS, PFHpS, PFOS, PFOSi, PFOA, PFNA, PFDA, PFUnDA and PFOSA are decreasing, whereas the levels of PFDoDA, PFTrDA and PFTeDA are increasing (Figure 10).

Roos et al (2011) investigated the levels of PFASs in livers of grey seal (n=20) collected in the Baltic Sea during 2005–2009. In total, 12 PFASs was analysed – PFBS, PFHxS, PFOS, PFDS, PFOSA, PFNA, PFDA, PFUnDA, PFDoDA, PFTrDA, PFTeDA and PFPeDA. The result showed that PFOS was the dominant congener (mean level 171 ng/g w.w.) followed by PFNA (mean level 43.3 ng/g w.w.) (Table 23).

Table 23. Levels of PFASs in liver of grey seals (ng/g) collected in the Baltic Sea during 2005–2009 (n=20). Source: Roos et al (2011).

Congener	Mean	Range
PFOS	171	89.6–490
PFNA	43.3	15.4–97.5
PFDA	14.5	5.0–56.6
PFUnDA	15.5	4.9–52.7
PFTrDA	7.9	2.5–24.6
PFDoDA	2.4	0.8–9.0
PFTeDA	1.7	0.5–5.8
PFOSA	2.4	0.3–5.4
PFPeDA	0.8	0.2–2.6
PFDS	0.4	0.1–1.9
PFHxS	0.7	0.3–1.6
PFBS	< 0.006	–

For a summary of the monitoring data in biota for the respective congeners that will be used for the environmental risk characterization see Table 24, Table 25, Table 26, Table 27 and Table 28, respectively. Based on the data available, exposure data to be used in the risk characterization are summarized for:

1. Seals (liver).
2. Otters (liver).
3. Birds (Peregrine falcons – eggs).
4. Marine fish (Herring – liver).
5. Highly exposed freshwater fish (perch – muscle).

Table 24. Summary table of Swedish environmental biomonitoring data from that will be used for the risk characterization (marked in bold) and/or for temporal trend analysis in seals (based on levels from 2000 onwards).

Congener	Level (ng/g w.w.)	Sampling year	Species & matrix	Reference	Temporal trend analysis	
					Trend	Conclusion
PFBS	**< 0.006**	2008	Grey seal, liver	Kratzer et al., 2011	N.A.	–
PFPS	**0.1**	2008	Grey seal, liver	Kratzer et al., 2011	N.A.	–
PFHxS	**1.2**	2008	Grey seal, liver	Kratzer et al., 2011	↓	Decreasing
PFHpS	**0.4**	2008	Grey seal, liver	Kratzer et al., 2011	↓	Decreasing
PFOS	**494**	2008	Grey seal, liver	Kratzer et al., 2011	↔	No increase/decrease
PFOSA	**2.3**	2008	Grey seal, liver	Kratzer et al., 2011	↔	No increase/decrease
PFOSi	**0.2**	2008	Grey seal, liver	Kratzer et al., 2011	↓	Decreasing
EtFOSA	**0.7**	2008	Grey seal, liver	Kratzer et al., 2011	N.A.	–
PFDS	**0.2**	2008	Grey seal, liver	Kratzer et al., 2011	N.A.	–
PFHpA	**0.04**	2008	Grey seal, liver	Kratzer et al., 2011	N.A.	–
PFOA	**11**	2008	Grey seal, liver	Kratzer et al., 2011	↔	No increase/decrease
PFNA	**109**	2008	Grey seal, liver	Kratzer et al., 2011	↔	No increase/decrease
PFDA	**22**	2008	Grey seal, liver	Kratzer et al., 2011	↑	Increasing
PFUnDA	**15**	2008	Grey seal, liver	Kratzer et al., 2011	↑	Increasing
PFDoDA	**1.5**	2008	Grey seal, liver	Kratzer et al., 2011	↑	Increasing
PFTrDA	4.6	2008	Grey seal, liver	Kratzer et al., 2011	↑	Increasing
	24.6	2005–2009	Grey seal, liver	Roos et al., 2011	–	–
PFTeDA	0.5	2008	Grey seal, liver	Kratzer et al., 2011	↔	Unchanged
	5.8	2005–2009	Grey seal, liver	Roos et al., 2011	–	–

N.A. = Not available.

Table 25. Summary table of Swedish environmental biomonitoring data from that will be used for the risk characterization and/or for temporal trend analysis in otters (based on levels from 2000).

Congener	Levela (ng/g w.w.)	Sampling year	Reference	Species & matrix	Temporal trend analysis	
					Trend	Conclusion
PFHxS	5	2008	Roos et al., 2009	Otter, liver	↔	No increase/decrease
PFOS	280	2008	Roos et al., 2009	Otter, liver	↓	Decreasing
PFOSA	30	2008	Roos et al., 2009	Otter, liver	↓	Decreasing
PFDS	2	2008	Roos et al., 2009	Otter, liver	↓	Decreasing
PFOA	15	2008	Roos et al., 2009	Otter, liver	↑	Increasing
PFNA	125	2008	Roos et al., 2009	Otter, liver	↑	Increasing
PFDA	100	2008	Roos et al., 2009	Otter, liver	↑	Increasing
PFUnDA	75	2008	Roos et al., 2009	Otter, liver	↓	Decreasing
PFDoDA	10	2008	Roos et al., 2009	Otter, liver	↓	Decreasing
PFTrDA	13	2008	Roos et al., 2009	Otter liver	↓	Decreasing
PFTeDA	1.5	2008	Roos et al., 2009	Otter liver	↓	Decreasing

[a] = Estimated from Figure 9.

Table 26. Summary table of Swedish environmental biomonitoring data from key studies on birds that will be used for the risk characterization and/or temporal trend analysis.

Congener	Level (ng/g w.w.)	Sampling year	Species & matrix	Reference	Temporal trend analysis	
					Trend	Conclusion
PFBS	< 0.08	2006	Peregrine Falcon, eggs	Holmström et al., 2010	N.A.	–
PFHxS	1.9	2006	Peregrine Falcon, eggs	Holmström et al., 2010	↓	Decreasing
PFOS	220	2006	Peregrine Falcon, eggs	Holmström et al., 2010	↑	Increasing
PFOSA	< 0.1	2006	Peregrine Falcon, eggs	Holmström et al., 2010	N.A.	–
PFDS	2.3	2006	Peregrine Falcon, eggs	Holmström et al., 2010	↓	Decreasing
PFHxA	< 0.6	2006	Peregrine Falcon, eggs	Holmström et al., 2010	N.A.	–
PFHpA	< 1.4	2006	Peregrine Falcon, eggs	Holmström et al., 2010	N.A.	–
PFOA	< 2.2	2006	Peregrine Falcon, eggs	Holmström et al., 2010	N.A.	–
PFNA	2.3	2006	Peregrine Falcon, eggs	Holmström et al., 2010	↑	Increasing
PFDA	9.6	2006	Peregrine Falcon, eggs	Holmström et al., 2010	↑	Increasing
PFUnDA	9.7	2006	Peregrine Falcon, eggs	Holmström et al., 2010	↓	Decreasing
PFDoDA	5.6	2006	Peregrine Falcon, eggs	Holmström et al., 2010	↓	Decreasing
PFTrDA	14	2006	Peregrine Falcon, eggs	Holmström et al., 2010	↓	Decreasing
PFTeDA	4.9	2006	Peregrine Falcon, eggs	Holmström et al., 2010	↓	Decreasing
PFPeDA	1.1	2006	Peregrine Falcon, eggs	Holmström et al., 2010	↓	Decreasing

N.A. = Not available.

Table 27. Summary table of Swedish environmental biomonitoring data from key studies on fish that will be used for the risk characterization of Baltic herring.

Congener	Level (ng/g w.w.)	Sampling year	Species & matrix	Reference
PFBS	< 0.6	2005–2009	Herring, liver	Bignert et al., 2008–2011
PFHxS	1.3	2009	Herring, liver	Bignert et al., 2008–2011
PFOS	18.7	2009	Herring, liver	Bignert et al., 2008–2011
PFOSA	7.1	2009	Herring, liver	Bignert et al., 2008–2011
PFDS	< 0.6	2005–2009	Herring, liver	Bignert et al., 2008–2011
PFBA	< 0.6	2008–2009	Flounder, herring, liver	Lilja et al., 2009
PFHxA	< 0.6	2005–2009	Herring, liver	Bignert et al., 2008–2011
PFHpA	< 0.6	2005–2009	Herring, liver	Bignert et al., 2008–2011
PFOA	< 0.6	2005–2009	Herring, liver	Bignert et al., 2008–2011
PFNA	2.9	2009	Herring, liver	Bignert et al., 2008–2011
PFDA	2.1	2009	Herring, liver	Bignert et al., 2008–2011
PFUnDA	3.0	2009	Herring, liver	Bignert et al., 2008–2011
PFDoDA	< 0.6	2005–2009	Herring, liver	Bignert et al., 2008–2011
PFTrDA	3.3	2009	Herring, liver	Bignert et al., 2008–2011
PFTeDA	< 0.6	2005–2009	Herring, liver	Bignert et al., 2008–2011
PFPeDA	< 0.6	2005–2009	Herring, liver	Bignert et al., 2008–2011
6:2 FTSA	< 0.6	2005–2009	Herring, liver	Bignert et al., 2008–2011

Table 28. Summary table of Swedish environmental biomonitoring data from key studies on fish that will be used for the risk characterization of highly exposed freshwater fish. Levels in muscle is converted to levels in liver for comparison to effect levels from the hazard assessment

Congener	Level (ng/g w.w.)		Sampling year	Species	Reference
	Muscle	Liver[a]			
PFBS	< 0.20	< 0.20	2009	Freshwater perch – highly exposed	Woldegiorgis et al., 2010
PFHxS	1.0	11.3	2009	Freshwater perch – highly exposed	Woldegiorgis et al., 2010
PFOS (Contaminated lake)	988	16 300	2009	Freshwater perch – highly exposed	Woldegiorgis et al., 2010
PFOS (Reference lake)	5.9	97	2009	Freshwater perch	Woldegiorgis et al., 2010
PFOSA	20.3	1 030	2009	Freshwater perch – highly exposed	Woldegiorgis et al., 2010
PFDS	1.5	8.7	2009	Freshwater perch – highly exposed	Woldegiorgis et al., 2010
PFBA	< 4.4	< 4.4	2005	Freshwater perch – highly exposed	Woldegiorgis et al., 2006
PFHxA	14.8	14.8	2009	Freshwater perch – highly exposed	Woldegiorgis et al., 2010
PFHpA	< 0.02	< 0.02	2009	Freshwater perch – highly exposed	Woldegiorgis et al., 2010
PFOA	4.3	4.3	2009	Freshwater perch – highly exposed	Woldegiorgis et al., 2010
PFNA	0.1	0.1	2009	Freshwater perch – highly exposed	Woldegiorgis et al., 2010
PFDA	2.6	60.3	2009	Freshwater perch – highly exposed	Woldegiorgis et al., 2010
PFUnDA	1.1	25.7	2009	Freshwater perch – highly exposed	Woldegiorgis et al., 2010

[a] = Converted using the upper range of the congener-specific liver-to-muscle ratios in Table 20. For the congeners lacking liver-to-muscle ratios a 1:1 ratio has been assumed which is considered conservative.

3.3 Discussion/Conclusion

The environmental exposure assessment shows that PFASs was present in all the species and matrices that will be used for the environmental risk characterization – seals, otters, peregrine falcon's eggs, herring and freshwater perch. These species are present in or connected to the aquatic environment, and illustrates how PFASs enter the food chain via this route. On the opposite, the levels of PFASs were significantly lower in terrestrial species. No PFASs congeners could be quantified in moose and reindeer, though a few congeners could be detected during some single years. Some PFAS congeners could be detected and quantified in livers of starling.

PFOS was the by far dominant congener in all species, found at ppm and high ppb levels in seals and otters, bird's eggs and highly exposed fish, and at low ppb levels in Baltic herring. PFOS was often present at one up to three orders of magnitude higher levels than for the other congeners.

In seals and otters, there was a tendency for levels of sulfonates to decrease, and a tendency for carboxylates to increase.

In peregrine falcon eggs, all PFASs detected represented the longer carbon chains. The temporal trend for sulfonates was either unchanged or decreasing, and for carboxylates the levels of congeners with 11–15 carbons were decreasing, but increasing for PFNA and PFDA.

In Baltic herring, all congeners found in liver contained six or more carbons for sulfonates, and nine or more carbons for carboxylates. This likely reflects the BCF potential of these compounds, which was shown to be proportional to the length of the carbon chain (Martin et al., 2003a), where sulfonates shorter than six carbons and carboxylates shorter than seven carbons are considered not to bioconcentrate in fish. The lack of PFOA indicates that exposure to this congener likely was low. In contrast, in highly exposed perch, ten out of twelve measured congeners were detected. The levels were also significantly higher, but due to that the fish were sampled in lakes being contaminated by PFASs-containing run-offs from nearby airports, these fish represent the "worst-case".

4. Human Hazard Assessment

4.1 Toxicokinetics of PFASs

4.1.1 Absorption

In rodents, PFOS and PFOA are well absorbed orally, > 95% and > 93%, respectively, within 24 hours (Gibson and Johnson, 1979; Johnson et al., 1979a). Also, 100% of PFHxA, 51–112% of PFBA and 69–74% of PFBS were recovered in urine of rats following single or repeated oral dosing (Chang et al., 2008, Gannon et al., 2011; Olsen et al., 2009) indicating high oral uptakes. Comparable absorption data for other congeners were not found, but can be assumed to be high based on their similar physicochemical properties. Quantitative studies on inhalatory or dermal absorption are lacking, though toxicity studies on PFOS and PFOA using these exposure routes show qualitatively similar toxicological profiles as for the oral route, demonstrating absorption (Kennedy et al., 2004 and OECD, 2002). No human data on PFASs absorption was found.

4.1.2 Distribution

PFASs are found at high levels in liver and serum. Hundley et al. (2006) found PFOA at highest levels in liver, blood and kidneys of rats and in liver and blood of mice after oral dosing. Vanden Heuvel et al. (1991a, b) showed that PFOA and PFDA were present at highest levels in liver, plasma and kidneys in rats after intraperitoneal (i.p) administration. PFOS has shown similar distribution, with highest levels in liver, plasma/blood, lungs and kidneys following i.p dosing in rats (Johnson et al., 1979b) and oral administration in mice (Bogdanska et al., 2011), though also other tissues have been shown to contain high concentrations, such as skin and bone (bone marrow) (Bogdanska et al., 2011). These findings are confirmed in a human post-mortem study showing 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 both animals and humans, PFASs are transferred to the fetus via the placenta and to the offspring via breast milk (ATDSR, 2009).

The characteristic distribution of PFASs to liver and serum is, at least partly, due to high affinity to proteins. PFOS, PFOA and PFHxS were > 99.7% bound to human albumin at physiological concentrations and > 97.3% bound to rat and monkey albumin (Kerstner-Wood et al., 2003). Also, PFBS, PFHxS, PFOS, PFPeA, PFHxA, PFHpA, PFOA, PFNA, PFDA and PFUnDA were highly bound to bovine serum albumin (Bischel et al., 2011). PFOS and PFOA bind to fatty-acid binding protein (FABP) in liver, an abundant intracellular lipid-carrier protein (Luebker et al., 2002), which may explain their high distribution to the liver.

A 1:1 ratio between human serum and plasma levels of PFOS, PFOA and PFHxS have been shown (Ehresman et al., 2007), and levels in these matrices are therefore directly comparable. Also, the ratio for serum to whole blood

was 2:1, equal to the volume displacement by red blood cells. Thus, whole blood levels of these PFAAs can be doubled to obtain corresponding serum levels, and this can be assumed also for other PFAAs based on their similar physicochemical properties. In contrast, the non-charged congener PFOSA was shown to distribute to a greater extent to whole blood than to plasma (Kärrman et al., 2006). Correlations between levels of PFAS in serum and breast milk have been shown, with levels of PFOS, PFNA, PFHxS, PFOSA and PFOA in breast milk being about 1%, 2%, 7% and 12%, respectively, of that in serum (Kärrman et al., 2007, Fromme et al., 2010, Kim et al., 2011). Kim et al. (2011) found the concentrations of PFHxS and PFOA to be 0.8% and 2.5%, respectively, of that in maternal serum.

4.1.3 Metabolism

No metabolism has been shown for perfluorinated sulfonic or carboxylic acids. Studies on the metabolism of PFOS, PFOA and PFDS in rats have shown that they are excreted without forming any metabolites or conjugates (OECD, 2002; U.S. EPA, 2005; Vanden Heuvel et al., 1991b). Perfluorinated sulfonates and carboxylates are thus believed to represent stable metabolic end-stage products. However, certain precursor PFASs have in rodents been shown to transform to various extents into their perfluorinated sulfonate or carboxylate "backbone structure", e.g. PFOSA and N-ethyl perfluorooctane sulfonamidoethanol (N-etFOSE, not covered herein) into PFOS, and 8:2 fluorotelomer alcohol (not covered herein) into PFOA and PFNA (3M, 2003; Seacat and Luebker, 2000; Henderson and Smith, 2007).

4.1.4 Excretion

The major elimination route of PFASs is renal elimination, and to a smaller extent biliary and fecal excretion (Han et al., in press). Elimination rates of PFASs in rodents, monkeys and humans vary substantially between different congeners, animal species and gender (Table 29). In general, the rate of elimination from serum 1) increases with decreasing carbon chain length, 2) occur more rapidly in rats > mice > non-human primates > humans, 3) is faster for carboxylates than the corresponding sulfonates, and 4) show pronounced gender differences within certain species (e.g., faster elimination in female rodents) (Lau et al., 2007). The reason for the species and gender differences in elimination rates are believed to be due to active renal reabsorption via renal organic anion transporters which are expressed differentially between species and sex and for which PFASs has shown to be substrates (Han et al., in press; Kudo et al., 2002; Weaver et al., 2010).

Table 29. Serum half-lives of PFASs congeners in different species (including humans).

Congener	Rat	Mouse	Monkey	Human	References
PFBS	0.6–4.0h (♀) 2.1–4.5h (♂)	NA	15h–3.5d (♀) 8.1h–4d (♂)	46d (♀) 24d (♂)	Chengelis et al., 2009a; Olsen et al., 2009
PFHxS	1d (♀) 30d (♂)	25–27d (♀) 28–31d (♂)	87d (♀) 141d (♂)	8.5y	Olsen et al., 2007; Sundström et al., 2011
PFOS	62–71d (♀) 38–41d (♂)	30–38d (♀) 36–43d (♂)	110d (♀) 132d (♂)	5.4y	Chang et al., 2011; Olsen et al., 2007,
PFBA	1–2h (♀) 6–9h (♂)	3h (♀) 5–16h (♂)	1.7d (♂, ♀)	3.6d (♀) 3.0d (♂)	Chang et al., 2008
PFHxA	0.4–1.2h (♀) 1.0–2.4h (♂)	N.A.	2.4h (♀) 5.3h (♂)	N.A.	Chengelis et al., 2009a; Ohmori et al., 2003, Gannon et al., 2011
PFOA	2–4h (♀) 4–6d (♂)	17d (♀) 19d (♂)	33d (♀) 21d (♂)	3.8y	Butenhoff et al., 2004b; Kemper and Jepson 2003, Lau et al., 2007; Ohmori et al., 2003; Olsen et al., 2007
PFNA	1–2d (♀) 30–31d (♂)	26–68d(♀) 34–69d (♂)	NA	NA	Ohmori et al., 2003; Tatum-Gibbs et al., 2011
PFDA	59d (♀) 40d (♂)	NA	NA	NA	Ohmori et al., 2003

h = hours, d = days, y = years, N.A.= not available.

4.2 Toxicity

The different PFAS congeners included herein have in toxicological studies shown similar toxicological profiles, which likely is due to their structural similarities.

4.2.1 Acute toxicity, corrosivity/sensitization, genotoxicity

PFOS, PFOA and PFBS show low to moderate acute toxicity following oral or inhalatory exposure (EFSA, 2008; NICNAS, 2005; OECD, 2002). Further, they are irritating to the eyes, likely due to their surface acting and strongly acidic properties, but not to the skin and are not considered to be genotoxic.

4.2.2 Subacute, subchronic and chronic toxicity (incl. carcinogenicity)

Repeated-dose toxicity studies in rodents and monkeys show that liver is the main target organ for PFASs. The hepatotoxicity is manifested as hepatocellular hypertrophy (enlargement of liver cells), increased liver weight, hepatocellular vacuolation, pigmentation and necrosis. Also, PFOS and PFOA cause liver tumours in rodents, likely via non-genotoxic mechanisms (Lau et al., 2007). Other common toxic effects by PFASs are (reviewed in Lau et al., 2007):

- Decreased body weight.
- Effects on lipid metabolism – decreased serum cholesterol and serum triglycerides.
- Effects on thyroid hormone levels – decreased triiodothyronine (T3) and thyroxine (T4).
- Immunotoxicity (atrophy of thymus and spleen, suppressed antibody responses).

4.2.3 Reproductive toxicity

PFASs have shown to possess reproductive toxic properties. Commonly observed effects in the offspring following in utero exposure include (reviewed in Lau et al,. 2007):

- Reduced fetal/neonatal body weight and reduced body-weight gain in pups.
- Reduced perinatal/neonatal viability (including mortality).
- Structural malformations (at high doses also affecting the dams).

In addition, PFOS and PFOA have shown other reproductive toxic effects such as delayed sexual maturation, impaired mammary gland development and developmental neurotoxicity (Lau et al., 2004; Onischchenko et al., 2011, White et al., 2007). Accordingly, PFOS and PFOA are proposed to be classified as reproductive toxicants within the EU (Klif, 2010).

As for many toxicants, the toxicity of PFASs are correlated to their body burden, i.e. rapidly excreted congeners require higher doses than slowly excreted congeners to produce the same magnitude of effect (Lau et al., 2007). For compounds with half-lives of only a few hours (e.g. PFBA in female rats and mice), steady-state and toxic levels may not be reached with one daily

dosing. Hence it is important to consider the kinetics of the congener when interpreting toxicological data on PFASs, in particular for species with rapid elimination, such as female rats. When comparing toxic effect levels between species, a measure of body burden can preferably be used rather than administered dose, of which serum levels is easy to apply.

4.2.4 Mode of action

The mode of action for PFASs is not well known. However, their toxicity and mode of action can partly be attributed to their structure. PFASs are often referred to as ”perfluorinated fatty acids” due to their structural analogy to endogenous fatty acids. They are also treated as fatty acids by the body, such as being transported via albumin in blood and being intracellularly bound to fatty acid binding proteins (FABP). Also, as endogenous fatty acids, PFASs have been shown to be ligands to the peroxisome-proliferator activated receptor alpha (PPAR-α) (Vanden Heuvel et al., 2006; Wolf et al., 2008a), a nuclear receptor and regulator of lipid metabolism (Berger and Moller, 2002). Compounds that bind PPAR-α induce proliferation of peroxisomes (hence called “peroxisome proliferators”) which, in turn, leads to catabolism of fatty acids and cholesterol (Peters et al., 2005) via e.g. peroxisomal β-oxidation, particularly in the liver which is the main organ for storage and mobilization of lipids (Lee et al., 2003). Peroxisome proliferators induce hepatocellular hypertrophy and increased liver weight by e.g. increasing the number and size of peroxisomes in the liver (Holden and Tugwood, 1999), which have been observed in rodents (Maronpot et al., 2010) as well as monkeys (Hoivik et al., 2004). Peroxisome proliferators are associated with liver tumours in rodents (Moronpot et al., 2010), however this effect is not observed in humans or non-human primates and liver tumours in rodents by peroxisome proliferators are therefore not considered relevant to humans (Peters et al., 2005). Though PFASs have been shown to bind PPAR-α and induce effects similar to peroxisome proliferators (e.g. hepatocellular hypertrophy and increased liver weight), PFOS have been shown to do so without affecting markers for peroxisome proliferation in rodents and non-human primates, indicating that other mechanisms of action are involved (Reviewed in Lau et al., 2007). This is supported by findings of Yang et al. (2002) and Wolf et al. (2008b) showing that hepatotoxicity occur also in PPAR-α knockout mice following exposure to PFOA, but not after exposure to the prototypic PPAR-α-ligand WY 14,643, suggesting that the effects of PFOA are independent of PPAR-α. The cytoplasmic vacuoles were suggested to consist of PFOA (Wolf et al., 2008b). Also, reproductive/developmental toxicity studies have shown that neonatal mortality in mice following *in utero* exposure to PFOA and PFNA (Abbott et al., 2007; Wolf et al., 2010) are dependent on PPAR-α, but independent on PPAR-α for PFOS (Abbott et al., 2009), indicating involvement of non-PPAR-α-related mechanisms. Also, activation of other nuclear receptors than PPAR-α by PFAS have been shown, such as the constitutive androstane receptor (CAR) and pregnenolone X receptor (PXR) (Andersen et al., 2008), adding more complexity into the issue of the mechanism of action of PFASs.

Regarding different potencies of PFASs to induce their effects, Kudo et al. (2000, 2003, 2006) showed that increased liver weight and peroxisomal β-oxidation in rodents following PFASs exposure is not correlated to the length of the carbon chain, but to the hepatic concentration of the congener itself. With regard to PPAR-α activation, Wolf et al. (2008a) showed in vitro that PFASs, in general, induce increasing activity of PPAR-α with increasing chain lengths and that perfluorinated carboxylates are stronger activators of PPAR-α than perfluorinated sulfonates.

In conclusion, though some of the effects by PFASs are likely mediated via PPAR-α, strong evidence exist that other mechanisms are also involved in e.g. hepatotoxicity and reproductive toxicity. These effects can therefore be considered to be of human relevance.

4.3 Points of departure for individual PFAS congeners

4.3.1 Availability and selection of data

There are large differences in the amount of toxicological data available for different PFASs. The far most studied and assessed congeners are PFOS and PFOA. PFOS has been reviewed by e.g. the OECD, The Swedish Chemicals Agency (KemI), The European Food Safety Authority (EFSA), The United Nations (UN) conventions for persistent organic pollutants – The Stockholm convention and the LRTAP convention, as well as by other national and international authorities and organizations. PFOA has been reviewed by e.g. EFSA, The United States Environmental Protection Agency (U.S. EPA) and by German authorities and industry in a Chemical Safety Report (CSR) within REACH (German UBA, 2009). For other congeners only a few assessment exists, and for the majority of the compounds there is also a shortage of toxicological/ecotoxicological data in the open literature.

All congeners that were identified in blood of the Swedish population and part of the human exposure assessment (Table 11 and Table 14) are part of the hazard assessment. Also, congeners that were identified in seals and otters and that will be used in the environmental risk characterization for these species (Table 24) is included here. Since PFASs generally show hepatotoxicity and reproductive toxicity, points of departure (PODs) from the hazard assessment to the risk characterization will focus on hepatotoxicity and reproductive toxicity, but any other identified relevant effect, if occurring at a lower effect level than hepatotoxicity and reproductive toxicity will also be included. The PODs in the human hazard assessment represent No-Observed-Adverse-Effect-Levels (NOAELs), Lowest-Observed-Adverse-Effect-Levels (LOAELs) or Benchmark dose (BMD) levels. Internal dose-metrics (levels in serum or liver) at critical effect levels will be used and are derived from the same sex from which the POD was derived. For congeners lacking toxicological information or internal dose measurements, a read-across to the closest most potent congener for the respective endpoint is performed.

4.3.2 Points of departure for individual PFAS congeners

PFBS

In 2005, a hazard assessment of PFBS was carried out by the Australian National Industrial Chemicals and Assessment Scheme (NICNAS, 2005). Among the studies examined, the most sensitive endpoints were identified in a two-generation reproductive/developmental toxicity study in rats orally dosed with 0, 30, 100, 300 or 1000 mg/kg bw/day PFBS for 10 weeks prior to and during mating (males and females) and during gestation and lactation (females) (Argus Research, 2003; Lieder et al., 2009a). The lowest NOAEL in the study was 100 mg/kg bw/day based on increased liver weight and/or histopathological changes of the liver and kidneys in parent animals and F_1 offspring at 300 mg/kg bw/day. Terminal body weights in F_1 offspring were reduced at 1000 mg/kg bw/day, giving a NOAEL of 300 mg/kg bw/day for this effect. No PFBS serum levels were measured in the animals.

In 2009, the U.S. Agency for Toxic Substances and Disease Registry (ATSDR) completed a draft toxicological profile report of 13 different PFASs, including PFBS, based on PFASs that have been measured in serum in a representative U.S. population during 2003–2004 (ATDSR, 2009). Only one study on PFBS was included in the report, a 28-day oral gavage study in rats administered 0, 100, 300, or 900 mg/kg bw/day PFBS (3M, 2001). NOAEL was set to 300 mg/kg bw/day based on significant increased absolute and relative liver and/or kidney weights in males and females at the higher dose. No PFBS serum levels were measured.

In 2011, the U.S. Minnesota Department of Health (MDH) performed a risk assessment of PFBS (MDH, 2011a). The most sensitive endpoint identified and used as POD was hematological effects (decreased hemoglobin and hematocrit) at 60 mg/kg bw/day in a 90-day oral toxicity study in rats (Lieder et al., 2009b; see below).

Additional scientific publications of interest

Lieder et al. (2009b) presented data from a 90-day oral gavage toxicity study in rats dosed with 0, 60, 200 or 600 mg/kg bw/day PFBS. The same dataset was reviewed by NICNAS (NICNAS, 2005), however in this publication the authors derive a lower NOAEL of 60 mg/kg bw/day PFBS, based on hematological effects (decreased red blood cell count, hematocrit, and hemoglobin).

Points of departure

Based on the data presented above, the selected points of departure for PFBS are:

- Hepatotoxicity (rat, subchronic exposure, NOAEL, increased liver weight,): 100 mg/kg bw/day.
- Reproductive toxicity (rat, NOAEL, reduced F_1 bodyweight): 300 mg/kg bw/day.
- Other endpoint (rat, subchronic exposure): Hematological effects: 60 mg/kg bw/day.

Due to lack of internal dose measurements, data on PFHxS will instead be used.

PFPS

No assessments or relevant scientific publications on the toxicity of PFPS were found.

Points of Departure

Due to the lack of toxicity data on PFPS, data on PFHxS will be used.

PFHxS

In 2009, ATSDR completed a draft toxicological profile of 13 different PFASs including PFHxS (ATDSR, 2009). One study for PFHxS was available for review, a reproductive/developmental toxicity study in male and female rats dosed with 0, 0.3, 1, 3, or 10 mg/kg bw/day PFHxS by oral gavage for 14 days before and during cohabituation and until PND 21 (females) or for 42 days (males) (Hoberman and York 2003). No reproductive/developmental or maternal toxicity endpoints were affected. However, PFHxS induced hematological alterations (decreased hemoglobin) in male rats starting at 0.3 mg/kg/day and liver and thyroid effects at 3 mg/kg bw/day, hence a LOAEL for hematological alterations was set to 0.3 mg/kg bw/day, and a NOAEL for liver and thyroid effects to 1 mg/kg bw/day. No serum levels of PFHxS were presented.

Additional scientific publications

Butenhoff et al. (2009) presented the same dataset for PFHxS that was reviewed by ATDSR (ATDSR, 2009) and presented above. The authors concluded that there were no treatment-related effects in dams or offspring at any dose. In males, reductions in serum cholesterol occurred at all doses, and hepatocellular hypertrophy and increased relative liver weight was observed at 3 and 10 mg/kg bw/day. At GD 21, the mean serum level of PFHxS at the highest dose, 10 mg/kg bw/day was 60 µg/ml, and the mean hepatic level 17 µg/g. After 42 days of dosing, the mean serum level of PFHxS in males at 0.3 and 1.0 mg/kg bw/day were 44 and 89 µg/ml, and mean hepatic levels 44 and 150 µg/g, respectively.

Points of Departure

Based on the data presented above, the selected points of departure for PFHxS are:

- Hepatotoxicity (rat, subacute exposure, NOAEL, hepatocellular hypertrophy/increased liver weight): 1 mg/kg bw/day, 89 µg/ml serum, 150 µg/g liver.
- Reproductive toxicity (rat, no effects): > 10 mg/kg bw/day, > 60 µg/ml serum, > 17 µg/g liver.
- Other endpoint (rat, subacute exposure, LOAEL): Hematological effects at 0.3 mg/kg bw/day, 44 µg/ml serum, 44 µg/g liver.

PFHpS

No assessments or relevant scientific publications on the toxicity of PFHpS were found.

Points of Departure

Due to the lack of toxicity data on PFHpS, data from PFOS will be used.

PFOS

In 2002, a hazard assessment of PFOS was carried by OECD (OECD, 2002) in which PFOS was classified as persistent, bioaccumulative and toxic to mammalian species. Of the studies reviewed, a lowest NOAEL was obtained in a 2-year chronic toxicity study (3M, 2002) where rats were administered PFOS via the diet at doses 0, 0.5, 2, 5 or 20 ppm. NOAEL was set to 0.5 ppm (equivalent to 0.025 mg/kg bw/day) based on hepatotoxicity at the higher dose. Corresponding serum and hepatic levels are presented in Table 30.

Table 30. Concentrations of PFOS in serum and liver for different time-points at NOAEL (0.5ppm/0.025mg/kg bw/day) in a 2-year chronic toxicity study (3M, 2002).

Time-point	Sex	Serum (µg/ml)	Liver (µg/g w.w.)
Week 4	Male	0.907 ± 0.0619	11.0 ± 2.31
	Female	1.61 ± 0.207	8.71 ± 0.552
Week 14	Male	4.04 ± 0.801	23.8 ± 3.45
	Female	6.96 ± 0.993	19.2 ± 3.77
Week 105	Male	1.31 ± 1.30	7.83 ± 7.34
	Female	4.35 ± 2.78	12.9 ± 6.81

In 2003, the 3M Company performed a health risk assessment of PFOS (3M, 2003). Two PODs were used from the hazard assessment for the risk characterization, hepatotoxicity and reproductive toxicity. For hepatotoxicity, a study on male and female Cynomolgus monkeys orally exposed to PFOS for 182 days at the doses 0, 0.03, 0.15 or 0.75 mg/kg bw/day was chosen (Seacat et al., 2002). Effects occurred only in the highest dose group and included increased liver weight, decreased body weight, lowered serum cholesterol, triiodothyronine (T3) and estradiol as well as mortality. NOAEL was 0.15 mg/kg bw/day and corresponded to serum levels of PFOS of 67 and 83 µg/ml and hepatic levels of 70 and 59 µg/g in females and males, respectively. For reproductive toxicity a two-generation reproductive/developmental toxicity study in rats dosed with PFOS via gavage at the doses 0, 0.1, 0.4, 1.6 or 3.2 mg/kg bw/day was chosen (Christian et al., 1999). NOAEL in this study was set to 0.4 mg/kg bw/day based on decreased viability in the second generation (F_2). However, as POD, a 5% decrease in body-weight gain in F_2 rat pups in a separate toxicokinetic study (3M, 2003) using the same dose levels of PFOS was used, and the corresponding PFOS mean serum level of *31 µg/ml* in dams before gestation and at gestational day 21, as determined by benchmark dose (BMD) modeling. Similarly, the PFOS concentration in liver at the end of gestation was 74 µg/g.

In 2004, The Swedish Chemicals Agency (KemI) carried out a health risk assessment of PFOS (KemI, 2004). From the hazard assessment, two PODs were used in the risk characterization, hepatotoxicity and reproductive toxicity. For hepatotoxicity (hepatocellular hypertrophy), a NOAEL of 0.025 mg/kg bw/day was used, based on liver toxicity (hepatocellular hypertrophy) in male rats in the same chronic toxicity study as reviewed by OECD above (3M, 2002). Though hepatocellular hypertrophy often is considered an adaptive and reversible response, the increasing severity of the effect at higher doses (vacuolization, necrosis) and that PFOS has a long half-life in humans was taken into account. The corresponding lowest serum and hepatic levels in the male and female rats at NOAEL after 14 weeks, 4.04 µg/ml and 19.2 µg/g, respectively (Table 30), were identified as the most suitable time point for the PODs. For reproductive toxicity, the two-generation reproductive/developmental toxicity study in rats dosed with PFOS via gavage at the doses 0, 0.1, 0.4, 1.6 or 3.2 mg/kg bw/day was chosen (Christian et al., 1999). NOAEL in this study was set to 0.1 mg/kg bw/day based on decreased viability (increased mortality, decreased body weight gain) in the second generation (F_2) and two serum levels were chosen for the risk characterization, 10.3 and 4.9 µg/ml, measured in female rats before and at the end of gestation, respectively. Corresponding hepatic PFOS levels were 23.4 and 9.2 µg/g.

In 2008, The EFSA Scientific Panel on Contaminants in the Food Chain (CONTAM) completed a health risk assessment of PFOS (EFSA, 2008). One POD from the hazard assessment was used for the risk characterization; a lowest NOAEL at 0.03 mg/kg bw/day from the subchronic study on male and female Cynomolgus monkeys orally dosed with PFOS at the doses 0, 0.03, 0.15 or 0.75 mg/kg bw/day (Seacat et al., 2002). The NOAEL was based on lowered levels of high-density lipoproteins (HDL) in females, lowered levels of triiodothyronine (T3) in males and females, and increased thyroid stimulating hormone (TSH) in males at the higher dose. The corresponding serum and hepatic levels at 0.03 mg/kg bw/day at the end of the study that were used as a PODs were 15.8 and 13.2 µg/ml and 17.3 and 22.8 µg/g in males and females, respectively.

In 2008, the MDH performed a risk assessment of PFOS (MDH, 2009a). Of the studies examined, a BMDL of 35 µg/ml serum was used as POD, based on decreased HDL decreased T3 and increased TSH in a subchronic study in Cynomolgus monkeys (Seacat et al. (2002)).

In 2009, ATSDR completed a draft toxicological profile of 13 different PFASs, where PFOS was included (ATDSR, 2009). Of the studies examined, a lowest NOAEL was derived from a 2-year chronic toxicity study, where rats were fed a diet providing approximately 0, 0.03, 0.1, 0.4, or 1.5 mg/kg/day PFOS (3M, 2002). A NOAEL of 0.03 mg/kg bw/day was identified based on liver toxicity at higher doses (cystic hepatocellular degeneration; centrilobular hepatocytic hypertrophy, eosinophilic granules and vacuolation). The corresponding serum levels at NOAEL are shown in Table 30.

In 2009, the U.S. EPA performed a risk assessment of PFOS (U.S. EPA, 2009). The critical study selected was a subchronic study in Cynomolgus monkeys orally dosed with PFOS at the doses 0, 0.03, 0.15 or 0.75 mg/kg bw/day (Seacat et al., 2002) and the POD was set to 0.03 mg/kg bw/day based on increased levels of TSH in males, reduced T3 levels in males and females and reduced HDL levels in females (Seacat et al., 2002).

In 2010, the National Institute for Public Health and the Environment (RIVM) in the Netherlands derived national limit values for PFOS, following an accidental large spill of PFOS at Schiphol Airport, Amsterdam (Moermond et al., 2010). For a human limit value, conclusions from the EFSA health risk assessment of PFOS (EFSA, 2008) were adopted, i.e. using a NOAEL of 0.03 mg/kg bw/day from a subchronic study on Cynomolgus monkeys (Seacat et al., 2002).

Additional scientific publications of interest

Peden-Adams et al. (2008) investigated the effects of PFOS on immunotoxicological parameters in male and female mice exposed orally for 28 days to 0, 0.166, 1.66, 3.31, 16.6, 33.1 or 166 µg/kg bw/day PFOS. NOAEL in the study was 0.166 µg/kg bw/day, based on reduced IgM response to an antigen at the higher dose 1.66 µg/kg bw/day (LOAEL). The corresponding serum level of PFOS at NOAEL was 17.8 ng/ml. No PFOS levels were measured in liver.

Points of Departure

Based on the data presented above, the selected points of departure for PFOS are:

- Hepatotoxicity (rat, chronic exposure, NOAEL, hepatocellular hypertrophy): 0.025 mg/kg bw/day, 4.04 µg/ml serum, 19.2 µg/g liver.
- Reproductive toxicity (rat, decreased F_2 viability, NOAEL): 0.1 mg/kg bw/day, 4.9 µg/ml, 9.2 µg/g liver.
- Other endpoint: Immunotoxicity (mouse, subacute exposure, NOAEL): 0.166 µg/kg bw/day, 17.8 ng/ml serum.

PFOSi

No assessments or relevant scientific publications on the toxicity of PFOSi were found.

Points of Departure

Due to the lack of toxicity data on PFOSi, data from PFOS will be used.

PFOSA

In the ATSDR PFASs assessment (ATSDR, 2009) only one study on PFOSA was reviewed, a toxicokinetic study where a single dose of 5 mg/kg PFOSA was given to rats that were subsequently sampled at day 1, 5 and 29 (Seacat and Luebker, 2002). No compound-related effects were observed on body- or liver weights. The serum levels of PFOSA were 0.31 and 0.06 µg/ml after

1 and 4 days respectively. However, serum levels of PFOS, also measured, were 8.2 and 8.6 µg/ml after 1 and 4 days, respectively, indicating substantial metabolism of PFOSA to PFOS.

Points of Departure
Due to little toxicity data on PFOSA and the extensive metabolism to PFOS, data on PFOS will be used for the risk characterization.

EtFOSA
No assessments or scientific publications on the toxicity of EtFOSA were found.

Additional scientific publications of interest
A number of toxicity studies on the structurally very similar congener, N-ethyl perfluorooctanesulfonamidoethanol (N-EtFOSE) are available Among these, a lowest NOAEL was set in a two-generation reproductive toxicity study in rats exposed to 0, 1, 5, 10 or 15 mg/kg bw/day (reviewed in Lau et al., 2004). Postnatal survival of the F_1 generation pups was significantly reduced in the 10 and 15 mg/kg bw/day dose groups and weight gain deficits were evident among the survivors. The number of dams in the F_1 generation with stillborn pups or neonatal mortality and reduced weight gain in the F_2-generation was slightly, though not significantly, increased at 5 mg/kg bw/day. There were no significant adverse effects at 1 mg/kg/day. No serum levels of N-EtFOSE were presented.

Xie et al (2009) investigated the effects of N-EtFOSE on biochemical parameters in female rats receiving intraperitoneal injections for 5 days/week at the dose 5 mg/kg over three weeks. The results showed that N-EtFOSE caused a significant decrease in body weight gain and increased relative liver weight over the time-course of the study. The corresponding level of N-EtFOSE in serum was 0.177 µg/ml, however due to the extensive metabolism of N-EtFOSE to PFOS, this serum level is not considered appropriate as point of departure. Levels in liver were not available. LOAEL in this study can be calculated to approximately 4 mg/kg bw/day, however the intraperitoneal route of administration can be questioned.

Points of Departure
Based on the lack of serum measurements for the reproductive toxicity study, as well as an extensive metabolism of N-EtFOSE to PFOS, data on PFOS will be used for the risk characterization.

PFDS
No assessments or relevant scientific publications on the toxicity of PFDS were found.

Points of Departure
Due to the lack of toxicity data on PFDS, data from PFOS will be used

PFBA

PFBA was included in the ATSDR draft assessment of 13 different PFASs (ATSDR, 2009). Of the studies reviewed, a lowest and identical NOAEL was observed in two studies, one 28-day and one 90-day study in rats dosed via gavage with 0, 6, 30 or 150 and 0, 1.2, 6 or 30 mg/kg bw/day PFBA, respectively (van Otterdiijk et al., 2007a, 2007b; Butenhoff et al., 2011). The NOAEL of 6 mg/kg bw/day observed for both studies was based on e.g. increased liver weight, hepatocellular hypertrophy and decreased serum cholesterol in male rats. The corresponding serum levels of PFBA at NOAEL in the males were 25 and 14 µg/ml in the 28-day and 90-day studies, respectively. Similarly, the corresponding hepatic levels of PFBA were 7.5 and 3.1 µg/g liver in the 28-day and 90-day studies, respectively.

In 2011, the MDH performed a risk assessment of PFBA (MDH, 2011b). The most sensitive endpoint identified and used as POD was 10% decreased serum cholesterol observed at a BMDL of 3.01 mg/kg bw/day in a 28-day oral gavage study in rats (Butenhoff el al., 2011).

Additional scientific publications of interest

In a developmental toxicity study where PFBA was administered orally by gavage to pregnant mice during GDs 1–17 at the doses 0, 35, 175 or 350 mg/kg bw/day, the most sensitive response, a delay in eye opening occurred in the pups already at the lowest dose, 35 mg/kg bw/day (Das et al. 2008). Hence, no NOAEL could be established for this effect. The corresponding serum level at LOAEL in pregnant dams were 3.8 µg/ml. Incidence of full litter loss was significantly increased at 350 mg/kg bw/day, giving a NOAEL of 175 mg/kg bw/day for this effect, with corresponding serum and hepatic PFBA levels of 4.4 µg/ml and 1.6 µg/g, respectively. It should be noted that the serum samples in this study were drawn 24h after the previous PFBA administration and, given the half-life of 3h in female mice (Chang et al., 2008), very little of the compound would remain in serum. Thus, using this serum level is very conservative.

Points of Departure

Based on the data presented above, the selected points of departure for PFBA are:

- Hepatotoxicity (rat, subchronic exposure, NOAEL, hepatocellular hypertrophy/increased liver weight): 6 mg/kg bw/day, 14 µg/ml serum and 3.1 µg/g liver.
- Reproductive toxicity (mouse, full litter loss, NOAEL): 175 mg/kg bw/day, 4.4 µg/ml serum and 1.6 µg/g liver.
- Other endpoint: Decreased serum cholesterol (rat, subacute exposure, BMDL): 3.01 mg/kg bw/day.

PFPeA

No assessments or relevant scientific publications on the toxicity of PFPeA were found.

Points of Departure
Due to the lack of toxicity data on PFPeA, data from PFOA will be used.

PFHxA
No assessments of PFHxA were found.

Additional scientific publications
A number of scientific publications presenting acute, subchronic, developmental/reproductive toxicity data on PFHxA are available (Chengelis et al., 2009b; Kudo et al., 2006; Loveless et al., 2009). Among these studies, a lowest NOAEL for hepatotoxicity of 20 mg/kg bw/day can be derived based on hepatocellular hypertrophy and increased liver weight at 100 mg/kg bw/day in a 90-day oral subchronic toxicity study in rats (Loveless et al., 2009). For reproductive/developmental toxicity, the authors derive a lowest NOAEL of 20 and 100 mg/kg bw/day for weight loss in male parental rats and reduced F_1 pup birth weights and body weight gain (Loveless et al., 2009), respectively. The lowest NOAEL observed in these studies were nasal lesions, estimated to occur at 13 and 21 mg/kg bw/day, based on BMD modeling, however these effects were considered to be due to the acidic properties of the compound in combination with the oral route of administration. No PFHxA levels in serum or liver were available from these studies.

Points of Departure
Based on the data presented above, the selected points of departure for PFHxA are:

- Hepatotoxicity (rat, subchronic exposure, NOAEL, hepatocellular hypertrophy/increased liver weight): 20 mg/kg bw/day.
- Reproductive toxicity (rat, reduced F_1 body weights, NOAEL): 100 mg/kg bw/day.

Due to lack of internal dose measurements, data from PFOA will instead be used for the risk characterization.

PFHpA
No assessments of PFHpA were found.

Additional scientific publications
Kudo et al. (2006) reported a NOAEL of 20 mg/kg for acute toxicity in mice receiving a single intraperitoneal dose, based on increased liver weight at the higher dose 50 mg/kg.

Points of Departure
Toxicity data for PFHpA was not considered sufficient for use in the risk characterization. Therefore toxicity data on PFOA will be used.

PFOA

In 2005, the Unites States Environmental Protection Agency (U.S. EPA) completed a draft risk assessment of PFOA (U.S. EPA, 2005). Several PODs were chosen from the hazard assessment for the risk characterization, based on studies in non-human primates, adult rats, and rat developmental toxicity studies. Though being a sensitive endpoint, hepatotoxicity was not considered relevant to humans and used in the risk characterization, due to the proposed mode-of-action via PPAR-α. The lowest POD was generated in a two-generation reproductive toxicity study in rats dosed with PFOA orally at the doses 0, 1, 3, 10 or 30 mg/kg bw/day (Butenhoff et al., 2004a); where a LOAEL was identified at the lowest dose of 1 mg/kg bw/day for decreased body weight in F_1 males. Consequently, no NOAEL was established. No serum levels were available at LOAEL, but a serum concentration of 13 µg/ml was estimated in F_0 dams at the higher dose 3 mg/kg bw/day based on a separate pharmacokinetic study (Mylchreest et al., 2003). However, it was also noted that female rats may not be a good model for extrapolation to humans due to the rapid elimination rate, where some effects may not be detected that could occur in species with longer half-lives, such as humans.

In 2007, OECD completed a hazard assessment report of PFOA (OECD, 2007). The lowest NOAEL was identified in a developmental toxicity study in CD-1 mice where the dams were given 0, 1, 3, 5, 10, 20, or 40 mg/kg bw/day PFOA via gavage during gestational days (GD) 1–17 (Lau et al., 2006). The NOAEL of 1 mg/kg bw/day was based on decreased pup body weight at PND23. BMD modeling in the results, with 5% response level, resulted in a BMDL of 0.86 mg/kg bw/day. No serum or hepatic levels of PFOA were presented at BMDL.

In 2008, The EFSA Scientific Panel on Contaminants in the Food Chain (CONTAM) completed a risk assessment of PFOA (EFSA, 2008). One POD was brought from the hazard assessment to the risk characterization. From a subchronic study in male rats dosed with PFOA via the diet at levels equivalent to 0, 0.06, 0.64, 1.94 and 6.4 mg/kg bw/day (Perkins et al., 2004), the Panel derived a lowest NOAEL of 0.06 mg/kg bw/day, based on hepatocellular hypertrophy and increased liver weight at the higher dose (0.64 mg/kg bw/day). Though these pathological changes often are classified as adaptive and reversible, their possible involvement in e.g. tumor promotion and/or changes in drug-metabolizing enzyme activities was taken into account as well as that reversibility is of limited importance for compounds with a persistency and long half-life as PFOA. The corresponding serum PFOA level at NOAEL, that in the risk characterization was compared with human serum PFOA levels, was 7.1 µg/ml. However, higher NOAELs were reported for hepatotoxicity in chronic and developmental studies, and the Panel therefore also used an already existing BMD approach for these studies with an effect size of 10% (COT, 2006b) and set a point-of-departure of 0.3 mg/kg bw/day, with no corresponding serum level, to establish a tolerable daily intake (TDI).

In 2008, the MDH performed a risk assessment of PFOA (MDH, 2009b). The most sensitive endpoint identified and used as POD was 10% increased relative liver weight at a BMDL of 23 µg/ml serum in a six months study in Cynomolgus monkeys orally dosed with PFOA at the doses 0, 3, 10 or 20/30 mg/kg bw/day (Butenhoff et al., 2002)

In 2009, a Chemical Safety Report (CSR) on PFOA was completed by the industry and German authorities within the REACH regulation (German UBA, 2009), largely based on the previous OECD hazard assessment of PFOA (OECD, 2007). From the hazard assessment in the CSR, PODs were selected for five key endpoints – 1) clinical/epidemiological indications of disease in humans, 2) reproductive toxicity with regard to fertility impairment or 3) developmental effects, 4) repeated-dose toxicity and 5) carcinogenicity. The most sensitive endpoint for reproductive/developmental toxicity was decreased pup body weight at PND23 in a developmental toxicity study in CD-1 mice where dams were dosed 0, 1, 3, 5, 10, 20, or 40 mg/kg bw/day PFOA via gavage during gestational days (GD) 1–17 (Lau et al., 2006). A NOAEL of 1 mg/kg bw/day and a BMDL at a 5% response of 0.86 mg/kg bw/day, respectively, was identified. At BMDL, the corresponding BMCL for PFOA in maternal serum at GD17 was 15.7 µg/ml. No hepatic concentrations were available for this BMCL. A similar and more sensitive developmental toxicity study in 129S1/Svlmj mice performed by Abbott et al. (2007) was also reviewed, where dams were orally dosed 0, 0.1, 0.3, 0.6, 1, 3, 5, 10, or 20 mg/kg bw/day PFOA. A NOAEL of 0.3 mg/kg bw/day was derived for reduced pup survival from birth to weaning at the higher dose. Serum levels of PFOA at NOAEL after weaning on postnatal day (PND) 22 in dams with pups at wean and in dams with no pups at wean were 2.8 and 10.4 µg/ml, respectively. However, the authors argued that the study by Lau et al. (2006) was more appropriate to use for the risk characterization due to standardized protocol, species and endpoints used, and that the outcome of the risk assessment are similar between the two studies. The study selected for repeated dose-toxicity in the CSR was a six months study in Cynomolgus monkeys orally dosed with PFOA at the doses 0, 3, 10 or 20/30 mg/kg bw/day (Butenhoff et al., 2002). NOAEL in the CSR report from this study was set to 10 mg/kg bw/day based on reduced body weight, with a corresponding $BMCL_{10}$ serum level of 60 µg/ml. The study NOAEL of 3 mg/kg bw/day for increased liver weight was not considered

In 2009, ATSDR completed a draft toxicological profile of 13 different PFASs where PFOA was included (ATDSR, 2009). Of the studies examined, a lowest NOAEL of 0.06 mg/kg bw/day was derived from a 13-week study in male rats dosed with PFOA via the diet at doses equivalent to 0, 0.06, 0.64, 1.94 or 6.4 mg/kg bw/day (Perkins et al. 2004). It was based on minimal to moderate hepatocellular hypertrophy at the higher dose and the corresponding serum PFOA level at NOAEL was 7.1 µg/ml. No hepatic level of PFOA at this NOAEL was available.

In 2009, the U.S. EPA performed a risk assessment of PFOA (U.S. EPA, 2009). The critical study selected was a reproductive/developmental toxicity study in CD-1 mice by Lau et al. (2006), where dams were dosed 0, 1, 3, 5, 10, 20, or 40 mg/kg bw/day PFOA via gavage during gestational days (GD) 1–17 (Lau et al., 2006), and the critical effect selected was 10% increased maternal liver weight observed at a BMDL of 0.46 mg/kg bw/day.

In 2010, a risk assessment initiated by the European Commission on the use of PFOA and its ammonium salt (APFO) in industrial and consumer applications was completed (Van der Putte et al., 2010). Also this assessment was based on the OECD hazard assessment of PFOA (OECD, 2007) as well as on the Chemical Safety Report (CSR) on PFOA (German UBA, 2010), and used the same conclusions from the hazard assessment as in the CSR.

In 2010, Health Canada performed a draft screening assessment of PFOA and its precursors (Health Canada, 2010). Among the critical studies identified for hepatotoxicity in the hazard assessment, and the study highlighted in the risk characterization based on the lowest LOAEL, was a study where mice were dosed orally for 14 days with 0, 0.3, 1, 3, 10 or 30 mg/kg bw/day linear or branched PFOA (Loveless et al., 2006). LOAEL was set to 0.3 mg/kg based on increased liver weight in male mice and with a corresponding linear PFOA serum concentration of 13 µg/ml. For reproductive toxicity studies, a lowest LOAEL of 1 mg/kg bw/day for decreased pup body weight at PND23 was highlighted from the study by Lau et al., (2006), with a corresponding concentration of PFOA in maternal serum at GD17 of 21.9 µg/ml. No hepatic concentrations were available. The similar and more sensitive by Abbott et al. (2007), with a NOAEL of 0.3 mg/kg bw/day for reduced pup survival from birth to weaning, was not used in the risk characterization based on the late time-point for serum sampling of PFOA in the dams (PND22).

Additional scientific publications of interest

Hines et al. (2009) exposed CD-1 mice to PFOA during pregnancy on GD 1–17 or as young adults to the doses 0, 0.01, 0.1, 0.3, 1, 3 or 5 mg/kg bw/day. On PND 1, the weights of offspring developmentally exposed to 5 mg/kg bw/day were significantly less than controls. At weaning, body weights were significantly decreased in the 1 and 5 mg/kg bw/day groups as compared to the control pups. Notable was that offspring exposed to the lowest doses, 0.01 and 0.1 mg/kg bw/day, showed significant increases in body weight as compared to the controls in mid-life until 40 weeks of age. This observation was correlated with increased serum leptin and insulin levels in those dose groups. Serum PFOA levels were measured at 18 months of age and the levels in the majority of samples were < LOD. LOAEL in the study was set to 0.01 mg/kg bw/day.

Macon et al. (2011) performed a developmental toxicity study in CD-1 mice, aiming to further investigate low-dose effects of PFOA on mammary gland development in the offspring, which in other studies have been shown to be a target tissue to PFOA, and to derive NOAEL, LOAEL and corresponding internal dosimetry to these effects. The dams were exposed via gavage to

0, 0.3, 1.0 or 3.0 mg/kg bw/day PFOA during GD 1–17 (full gestation exposure study) or to 0, 0.01, 0.1 or 1.0 mg/kg bw/day PFOA during GD 10–17 (late gestation exposure study). The results showed for all doses, in both exposure regimens, that the offspring exhibited significantly stunted growth of mammary glands. Liver weights at PND7 were significantly increased in all dose groups in offspring in the full gestation exposure study, and significantly increased at 1.0 mg/kg bw/day in offspring in the late gestation exposure study. For the full gestation exposure study, a LOAEL of 0.3 mg/kg bw/day was derived for increased liver weight and stunted mammary gland growth in the offspring, and no NOAEL could be established for these effects. For the late gestation exposure study, a LOAEL of 0.01 was derived for stunted mammary gland growth where no NOAEL could be established, and a LOAEL of 1.0 mg/kg bw/day for increased liver weight with a NOAEL of 0.1 mg/kg bw/day. The levels of PFOA in serum and liver of offspring at PND7 at 0.3 mg/kg bw/day groups in the full gestation exposure study were 5.0 and 5.9 µg/ml and 2.1 and 2.6 µg/g in females and males, respectively. The serum levels at PND7 in female offspring in the late gestation exposure study at 0.01 and 0.1 mg/kg bw/day were 0.15 and 1.3 µg/ml, respectively, and no hepatic concentrations were measured. These results are supported by similar findings by White et al. (2007; 2009, 2011) in CD-1 mice, in which effects on mammary gland development have been noted already at doses as low as 5 ppb in drinking water (White et al., 2011), corresponding to measured serum levels of approximately 50–60 ng/ml.

Points of Departure
Based on the data presented above, the selected points of departure for PFOA are:

- Hepatotoxicity (rat, subchronic exposure, NOAEL, hepatocellular hypertrophy): 0.06 mg/kg bw/day, 7.1 µg/ml serum. No hepatic levels were available. However, based on kinetic studies on PFOA in rats, commonly showing liver/serum ratios of 2–4:1 (Kudo et al., 2007; U.S.EPA, 2005), a conservative approach is to use a liver/serum ratio of 2:1.
- Reproductive toxicity (mouse, reduced F_1 body weight, BMDL): 0.86 mg/kg bw/day, 15.7 µg/ml serum, as also selected by the OECD (2007) and the German UBA (2009). No hepatic levels were available. However, a conservative approach is to assume a liver/serum ratio of 2:1.
- Other endpoints (mouse, mammary gland development, increased body weight, LOAEL): 0.01 mg/kg bw/day, 0.15 µg/ml serum.

PFNA
PFNA was included in the ATSDR PFASs assessment (ATSDR, 2009). The studies reviewed were limited to two subacute toxicity studies. The most sensitive of these was a study in mice that were fed PFNA for 14 days via the diet at

doses corresponding to approximately 0, 0.5, 1.5, 5, 50 or 500 mg/kg bw/day (Kennedy, 1987). At the lowest dose, 0.5 mg/kg bw/day a significant increase in liver weight occurred (50–70%). Hence no NOAEL could be established. There was no serum levels measured in this study.

Additional scientific publications of interest
Wolf et al (2010) performed a developmental toxicity study in 129S1/Svlmj mice where dams were exposed to 0, 0.83, 1.1, 1.5 or 2 mg/kg bw/day PFNA during GDs 1–18. Significantly reduced survival was noted in the offspring at 1.1 mg/kg bw/day, giving a NOAEL of 0.83 mg/kg bw/day for this effect. In addition, increased liver weight was observed in non-pregnant adult females and in the offspring on PND21 at the lowest dose, 0.83 mg/kg bw/day, hence no NOAEL could be established. Serum levels of PFNA were 8.9 and 28.5 µg/ml in adult female mice with/without live pups at 23 days post-dose, respectively.

Tatum-Gibbs et al. (2011) showed that following a single oral dose of 1, 3 or 10 mg/kg PFNA in rats and 1 or 10 mg/kg in mice, the liver/plasma concentration ratio varied from 3.7 to 9.3 after 50 days in male rats, and from approximately 2 to 20 in male and female mice from 4 hours until 50 days, with the ratio becoming lesser with increasing dose, similar as for PFOA (Kudo et al., 2007).

Points of Departure
Based on the data presented above, the selected points of departure for PFNA are:

- Hepatotoxicity (mouse, subacute exposure, LOAEL, increased liver weight): 0.83 mg/kg bw/day, 28.5 µg/ml serum. No hepatic levels were available. However, based on kinetic data on PFNA in male and female mice by Tatum-Gibbs et al. (2011), showing liver:serum ratios between approximately 2–20:1, a conservative approach is to use a liver:serum ratio of 2:1.
- Reproductive toxicity (mouse, reduced F_1 survival, NOAEL): 0.83 mg/kg bw/day, 8.9 µg/ml serum. No hepatic levels were available. However, a conservative approach is to assume a liver/serum ratio of 2:1.

PFDA
PFDA was included in the ATSDR PFASs assessment (ATSDR, 2009). The studies reviewed were limited to acute-duration oral studies, most of these studies providing information on liver effects. The lowest NOAEL was obtained in a study in rats that were exposed to PFDA via the diet at doses corresponding 0, 1.2, 2.4, 4.8, or 9.5 mg/kg bw/day for 7 days (Kawashima et al. 1995). NOAEL was set to 1.2 mg/kg/day for increased absolute liver weight at the higher dose. Data on serum or hepatic levels of PFDA were not available in any of the studies reviewed.

Additional scientific publications of interest
Harris and Birnbaum (1989) investigated the developmental toxicity of PFDA in mice that were exposed during different windows of gestation. Offspring to dams exposed during GDs 6–15 showed significantly reduced body weights at 0.1 mg/kg bw/day, resulting in a NOAEL of 0.03 mg/kg bw/day. Increased liver weight was observed in the dams at 1.0 mg/kg bw/day, resulting in a NOAEL of 0.3 mg/kg bw/day. No serum or hepatic levels of PFDA were measured.

Points of Departure
Based on the data presented above, the selected points of departure for PFDA are:

- Hepatotoxicity (rat, acute exposure, NOAEL, increased liver weight): 0.3 mg/kg bw/day.
- Reproductive toxicity (mouse, reduced F_1 body weight): 0.03 mg/kg bw/day.

Due to lack of internal dose measurements for PFDA, data on PFNA will instead be used for the risk characterization.

PFUnDA
No assessments or relevant scientific publications on the toxicity of PFUnDA were found.

Points of Departure
Due to the lack of toxicity data on PFUnDA, data from PFNA will be used

PFDoDA
PFDoDA was included in the ATSDR PFASs assessment (ATSDR, 2009). One study was reviewed, where PFDoDA were administered to male rats for 14 days at the doses 0, 1, 5, or 10 mg/kg bw/day in a study aiming to examine effects on testes (Shi et al., 2007). A lowest NOAEL of 1 mg/kg bw/day was set based on decreased body weight. No serum levels of PFDoDA were measured.

Additional scientific publications of interest
Ding et al (2009) and Shi et al. (2009) used a similar experimental setup and exposed male rats orally to PFDoDA for 110 days at the doses 0.02, 0.05, 0.2 or 0.5 mg/kg bw/day. Ding et al. (2009) reported hepatic steatosis ("fatty liver") at the lowest dose in the study, 0.02 mg/kg bw/day (LOAEL), becoming more pronounced at the higher doses. Shi et al. (2009) reported significantly decreased serum testosterone levels at 0.05 mg/kg bw/day, hence resulting in a NOAEL of 0.02 mg/kg bw/day, and significantly decreased body weights at 0.5 mg/kg bw/day giving a NOAEL of 0.2 mg/kg bw/day. No serum or hepatic levels of PFDoDA were measured in the studies.

Points of Departure
Based on the data presented above, the selected points of departure for PFNA are:

- Hepatotoxicity (rat, subchronic, LOAEL, hepatic steatosis): 0.02 mg/kg bw/day.
- Reproductive toxicity: Not available.

Due to lack of internal doses for hepatotoxicity and lack of data on reproductive toxicity for PFDoDA, data on PFNA will instead be used.

PFTrDA
No assessments or relevant scientific publications on the toxicity of PFTrDA were found.

Point of Departure
Due to the lack of toxicity data for PFTrDA, data on PFNA will instead be used.

PFTeDA
No assessments or relevant scientific publications on the toxicity of PFTeDA were found.

Point of Departure
Due to the lack of toxicity data for PFTeDA, data on PFNA will instead be used.

PFPeDA
Not considered for the hazard assessment due to lack of human exposure data

PFHxDA
Not considered for the hazard assessment due to lack of human exposure data

6:2 FTSA
No assessments of 6:2 FTSA were found. In a literature survey of PFASs, one study showing a NOAEL of 15 mg/kg bw/day for 6:2 FTSA in a 28-day oral toxicity study in rats for nephrotoxicity at the doses 50 and 150 mg/kg bw/day was reported (Norwegian Institute of Public Health, 2006).

POINT OF DEPARTURE
Due to the lack of adequate toxicity data for 6:2, data on the structurally most similar congener PFOS will instead be used

PFASs MIXTURE TOXICITY STUDIES
Mertens et al. (2010) and Stump et al. (2008) investigated the toxicity of S–111-S-EB, a technical mixture of C6–C13 perfluorinated acids, the major component being PFNA, in an oral subchronic 90-day toxicity study and an oral two-generation reproductive toxicity study in rats, both using the doses 0,

0.025, 0.125 or 0.6 mg/kg bw/day. The result of the subchronic toxicity study showed a NOAEL of 0.025 mg/kg bw/day for hepatocellular hypertrophy and increased liver weight at 0.125 mg/kg bw/day. In the two-generation reproductive toxicity study, the authors derived a NOAEL for neonatal toxicity of 0.025 mg/kg bw/day based on increased liver weights in the offspring. Litter size, offspring weight and survival were unaffected at all doses. For parental toxicity, a LOAEL of 0.025 mg/kg bw/day was set based on hepatocellular hypertrophy observed in all dose groups; hence no NOAEL could be established.

For a summary of the hazard data in for the respective congeners that will be used for the risk characterization in humans see Table 31 and Table 32.

Table 31. Summary of points of departure (PODs) for hepatotoxicity and reproductive toxicity for PFAS congeners. Doses represent NOAELs if not stated other. For congeners lacking data, read-across has been performed to the closest most conservative congener as described in the hazard assessment. Original congener-specific data is marked in bold.

Congener	Hepatotoxicity		Reproductive toxicity	
	External dose (mg/kg bw/day)	Internal dose (µg/ml serum)	External dose (mg/kg bw/day)	Internal dose (µg/ml serum)
PFBS (read-across from PFHxS)	1	89	> 10	> 60
PFHxS	**1**	**89**	**> 10**	**> 60**
PFOS	**0.025**	**4.04**	**0.1**	**4.9**
PFOSi (read-across from PFOS)	0.025	4.04	0.1	4.9
PFOSA (read-across from PFOS)	0.025	4.04	0.1	4.9
PFDS (read-across from PFOS)	0.025	4.04	0.1	4.9
PFBA	**6**	**14**	**175**	**4.4**
PFPeA (read-across from PFOA)	0.06	7.1	0.86	15.7
PFHxA (read-across from PFOA)	0.06	7.1	0.86	15.7
PFHpA (read-across from PFOA)	0.06	7.1	0.86	15.7
PFOA	**0.06**	**7.1**	**0.86**	**15.7**
PFNA	**0.83**[a]	**28.5**	**0.83**	**8.9**
PFDA (read-across from PFNA)	0.83	28.5	0.83	8.9
PFUnDA (read-across from PFNA)	0.83	28.5	0.83	8.9
PFDoDA (read-across from PFNA)	0.83	28.5	0.83	8.9
PFTrDA (read-across from PFNA)	0.83	28.5	0.83	8.9
PFTeDA (read-across from PFNA)	0.83	28.5	0.83	8.9
6:2 FTSA (read-across from PFOS)	0.025	4.04	0.1	4.9

[a] = LOAEL.

Table 32. Summary of points of departure (PODs) for endpoints observed at a lower effect level than for hepatotoxicity and reproductive toxicity. Doses represent NOAELs if not stated other.

Congener	Effect	External dose (mg/kg bw/day)	Internal dose (µg/ml serum)
PFBS	Hematology	60	No data available[a]
PFHxS	Hematology	0.3 (LOAEL)	44
PFOS	Immunotoxicity	0.000166	0.0178
PFBA	Lipid metabolism	3.0	No data available[a]
PFOA	Mammary gland development, growth	0.01 (LOAEL)	0.15

[a] – will not be used in the risk characterization based on the lack of serum concentration.

4.4 Derivation of derived-no-effect-levels (DNELs)

DNELs were derived in accordance with REACH guidelines (ECHA 2010; 2011). The PODs for the respective endpoints in Table 31 and Table 32 were divided with the following assessment factors (specified in section R.8.4 "Derive DNEL(s) for threshold endpoints" in ECHA (2010):

- Extrapolation of exposure duration, i.e. short term exposure to chronic exposure. For subchronic to chronic exposure and subacute to chronic exposure, a factor of 2 is used for hepatotoxicity. Common default factors for these extrapolation are 2 and 6, however hepatotoxicity occur rapidly after PFAS exposure and seem independent on the exposure duration and a factor of 2 is therefore also applied for subacute exposure. For other effects than hepatotoxicity the default factors of 2 and 6 are applied.
- Extrapolation from LOAELs to NOAELs in studies where no NOAEL could be established. Herein a factor of 3 is applied for these extrapolations.
- Species differences, i.e. animals to humans, with regard to toxicokinetics and toxicodynamics. Default factors of 4/7 are commonly applied for kinetic differences between rats/mice and humans according to the principle of allometric scaling. However, herein internal doses (serum levels) are compared between animals and humans which eliminate the need of this factor. For differences in dynamics, i.e. the interaction between the compound and the target tissue, the common assessment factor of 2.5 is applied.
- Differences in sensitivity among humans to protect sensitive subgroups such as children and elderly. The common factors of 10 for the average population and 5 for workers, since this subgroup represent healthy adult individuals, are applied herein.
- Quality of the database. A factor of 3 is applied when read-across is performed from a shorter to a longer congener, due to the differences in elimination half-lives where shorter congeners are being excreted more rapidly (Table 29) and thus tend to be less toxic. Read-across from longer chain congeners to shorter chain congeners is considered conservative and no assessment factor is then used.

The respective DNELs for hepatotoxicity, reproductive toxicity and other endpoints are presented in Table 33, Table 34 and Table 35, respectively.

Table 33. Derived-No-Effect-Levels (DNELs) for hepatotoxicity in individuals exposed indirectly via the environment and in occupationally exposed individuals. Original congener-specific data is marked in bold.

Congener	POD (ng/ml serum)	Assessment Factors								DNEL (ng/ml serum)	
		Exposure duration[a]	LOAEL to NOAEL	Read-across[b]	Inter-species[c]	Intra species[d]		Overall AF			
						Ind. Exp.	Workers	Ind. Exp.	Workers	Ind. Exp.	Workers
PFBS (read-across from PFHxS)	89 000	2	–	–	2.5	10	5	50	75	1 780	3 560
PFHxS	**89 000**	2	–	–	2.5	10	5	50	25	**1 780**	**3 560**
PFOS	**4 040**	–	–	–	2.5	10	5	25	12.5	162	323
PFOSA (read-across from PFOS)	4 040	–	–	–	2.5	10	5	25	12.5	162	323
PFDS (read-across from PFOS)	4 040	–	–	3	2.5	10	5	75	37.5	54	108
PFBA	**14 000**	2	–	–	2.5	N.I.	5	N.I.	25	N.I.	**560**
PFPeA (read-across from PFOA)	7 100	2	–	–	2.5	N.I.	5	N.I.	25	N.I.	284
PFHxA (read-across from PFOA)	7 100	2	–	–	2.5	10	5	50	25	142	284
PFHpA (read-across from PFOA)	7 100	2	–	–	2.5	10	5	50	25	142	284
PFOA	**7 100**	2	–	–	2.5	10	5	50	25	**142**	**284**
PFNA (LOAEL)	**28 500**	2	3	–	2.5	10	5	150	75	**190**	**380**
PFDA (read-across from PFNA)	28 500	2	3	3	2.5	10	5	450	225	64	127
PFUnDA (read-across from PFNA)	28 500	2	3	3	2.5	10	5	450	225	64	127
PFDoDA (read-across from PFNA)	28 500	2	3	3	2.5	10	5	450	225	64	127
PFTrDA (read-across from PFNA)	28 500	2	3	3	2.5	10	5	450	225	64	127
PFTeDA (read-across from PFNA)	28 500	2	3	3	2.5	10	5	450	225	64	127
6:2 FTSA (read-across from PFOS)	4 040	–	–	–	2.5	10	5	25	12.5	162	323

N.I. = Not included due to lack of exposure data.

[a] – A factor of 2 is used for extrapolation from subacute and subchronic to chronic exposure due to small differences between study durations and effects.

[b] – For read-across from a shorter to a longer chain congener. Read-across from a longer to a shorter chain congener is considered conservative and no assessment factor is then used.

[c] – For differences in toxicodynamics between species = 2.5. Due to comparisons in internal doses no assessment factor for kinetic differences is needed.

[d] – For differences in sensitivity in human populations. Commonly default factors of 10 and 5 are applied for normal populations and workers, respectively.

Table 34. Derived-No-Effect-Levels (DNELs) for reproductive toxicity in individuals exposed indirectly via the environment and in occupationally exposed individuals. Original congener-specific data is marked in bold.

Congener	POD (ng/ml serum)	Assessment Factors						DNEL (ng/ml serum)	
		Inter-species[a]	Read-across[b]	Intra species[c]		Overall AF			
				Ind. Exp.	Workers	Ind. Exp.	Workers	Ind. Exp.	Workers
PFBS (read-across from PFHxS)	> 60 000	2.5	–	10	5	25	12.5	> 2 400	> 4 800
PFHxS	**> 60 000**	2.5	–	10	5	25	12.5	**> 2 400**	**> 4 800**
PFOS	**4 900**	2.5	–	10	5	25	12.5	**196**	**392**
PFOSA (read-across from PFOS)	4 900	2.5	–	10	5	25	12.5	196	392
PFDS (read-across from PFOS)	4 900	2.5	3	10	5	75	37.5	65	131
PFBA	**4 400**	2.5	–	N.I.	5	N.I.	12.5	N.I.	**352**
PFPeA (read-across from PFOA)	15 700	2.5	–	N.I.	5	N.I.	12.5	N.I.	1 256
PFHxA (read-across from PFOA)	15 700	2.5	–	10	5	25	12.5	628	1 256
PFHpA (read-across from PFOA)	15 700	2.5	–	10	5	25	12.5	628	1 256
PFOA	**15 700**	2.5	–	10	5	25	12.5	**628**	**1 256**
PFNA	**8 900**	2.5	–	10	5	25	12.5	**356**	**712**
PFDA (read-across from PFNA)	8 900	2.5	3	10	5	75	37.5	119	237
PFUnDA (read-across from PFNA)	8 900	2.5	3	10	5	75	37.5	119	237
PFDoDA (read-across from PFNA)	8 900	2.5	3	10	5	75	37.5	119	237
PFTrDA (read-across from PFNA)	8 900	2.5	3	10	5	75	37.5	119	237
PFTeDA (read-across from PFNA)	8 900	2.5	3	10	5	75	37.5	119	237
6:2 FTSA (read-across from PFOS)	4 900	2.5	–	10	5	25	12.5	196	392

N.I. = Not included due to lack of exposure data.

[a] – For differences in toxicodynamics between species = 2.5 Due to comparisons in internal doses no assessment factor for kinetic differences is needed.

[b] – For read-across from a shorter to a longer chain congener. Read-across from a longer to a shorter chain congener is considered conservative and no assessment factor is then used.

[c] – For differences in sensitivity in human populations. Commonly a default factors of 10 and 5 are applied for normal populations and workers, respectively.

Table 35. No-Effect-Levels (DNELs) for effects at lower doses than hepatotoxicity and reproductive toxicity in indirectly exposed and occupationally exposed individuals.

Congener	Effect	POD (ng/ml serum)	Assessment Factors							DNEL (ng/ml serum)	
			Exposure Duration[a]	LOAEL to NOAEL	Inter-species[b]	Intra species[c]		Overall AF			
						Ind. Exp.	Workers	Ind. Exp.	Workers	Ind. Exp.	Workers
PFHxS	Hematology	44 000	6	3	2.5	10	5	450	225	98	196
PFOS	Immunotoxicity	17.8	6	–	2.5	10	5	150	75	0.12	0.24
PFOA	Mammary gland development, growth	150	–	3	2.5	10	5	75	37.5	2.0	4.0

[a] – For conversion from subacute to chronic exposure = 6, from subchronic to chronic exposure = 3.

[b] – For differences in toxicodynamics between species = 2.5. Due to comparisons in internal doses no assessment factor for kinetic differences is needed.

[c] – For differences in sensitivity in human populations. Commonly a default factor of 10 is used for normal populations and 5 for workers.

4.5 Epidemiological data

Epidemiological studies on PFASs are available for general and highly exposed populations. Costa et al. (2009) found in PFOA production workers an association between increased levels of PFOA and increased levels of cholesterol and uric acid in serum, a result opposite to the decreased levels of serum cholesterol often observed in animal studies following PFASs exposure. No association was found between PFOA-levels and markers of hepatotoxicity. Similarly, in a population highly exposed to PFOA via contaminated drinking water, Steenland et al. (2010a) found an association between levels of PFOA and increased serum uric acid in adults. Also, Steenland et al. (2009) and Frisbee et al. (2010) found associations between levels of PFOA and increased serum levels of cholesterol and lipids in children, adults and adolescents, though the authors in a subsequent publication considered the data insufficient to draw any firm conclusions (Steenland et al., 2010b). Emmett et al. (2006) did not find levels of PFOA to be associated with cholesterol and markers of liver function in the same population, nor did Olsen et al. (2003) observe any correlations between levels of PFOS and PFOA and cholesterol levels or markers for liver injury in serum of PFAS production workers.

For reproductive toxicity, Apelberg et al. (2007) observed a small association between increased serum levels of PFOA and PFOS in umbilical cord blood and decreased birth weight. Fei et al. (2007) reported a correlation between increased maternal plasma levels of PFOA and decreased birth weight, however not for PFOS. In contrast, Washino et al. (2009) found increased maternal serum levels to be correlated with decreased birth weight for PFOS but not for PFOA. Monroy et al. (2008) did not find any correlations between maternal serum levels of different PFASs and birth weight; neither did Grice et al. (2007) between serum levels of PFOS in production workers and pregnancy outcome. In a population highly exposed to PFOA via contaminated drinking water, no clear associations were found between serum levels of PFOA and pregnancy outcomes or birth defects (Nolan et al., 2009; 2010; Savitz et al., 2012a [5], b [5]), though weak and/or inconsistent associations with early preterm birth, fetal growth restriction and pregnancy induced hypertension were seen (Savitz et al., 2012a [5], b [5]). These conclusions were also shared by an independent scientific panel (C8 Science Panel (2011a, b, c, d).

Epidemiological studies on PFASs and immunotoxicity, obesity or mammary gland development are limited. Grandjean et al. (2012)[5] reported an association between increasing levels of PFASs and decreased antibody response following vaccination in children. In contrast, Fei et al., (2010) did not find any correlation between prenatal exposure to PFOS and PFOA and increased risk of severe infectious diseases in early childhood. Halldorsson et al. (2012)[5] found an association between increasing levels of PFOA during *in utero* exposure and overweight/obesity in females at 20 years of age. Also, the maternal

[5] Added subsequent to the last literature search in August, 2011.

levels of PFOA were positively associated with biomarkers of obesity – serum insulin and leptin and negatively associated with adiponectin in the female offspring. No correlations were found for PFOS, PFOSA or PFNA. In a population highly exposed to PFOA, no clear associations were found between prenatal serum levels of PFOA and increased risk of metabolic syndrome, childhood obesity or infections (C8 Science Panel, 2012[5]).

4.6 Hazard assessment results/discussion

The hazard assessment shows that the various PFAS congeners were relatively similar with regard to their hepatotoxic and reproductive toxic properties, with PODs ranging from 4–89 µg/ml serum for hepatotoxicity and 4–> 60 µg/ml for reproductive toxicity. The data available indicated that the potency of the congeners was related to the carbon chain length, i.e. longer chain PFASs were generally more potent than the shorter chains. This was apparent for four-carbon chains as compared to eight-carbon chains; however with less difference between different longer chain congeners, e.g. PFOA, PFNA and PFDA, showing similar effect levels. The difference in potency between congeners is likely to some extent due to kinetic differences, with the short chains congeners being more rapidly excreted than the longer chain congeners. Kudo et al. (2000; 2003; 2006) showed that the hepatotoxicity is dependent on the hepatic concentration of the congener and not on the structure of the congener itself. Whether this is similar also for reproductive toxicity has not been shown, but it is likely since most PFASs reproductive toxicity studies are carried out in mice due to rapid excretion and lack of effects in rats. In addition, differential affinity to and activation of the PPAR-α receptor may also contribute to the difference in potency between the congeners. For PFBS, PFHxS, PFOS and PFOA, a few studies were identified showing effects on other endpoints at lower levels than hepatotoxicity and reproductive toxicity. In particular, PFOS and PFOA affected the immune system, mammary gland development and growth at very low doses, similar to or even below current human exposure levels.

Toxicological data with internal dose measurements were available for five of seventeen congeners; thus data for twelve had to be extrapolated. This was done by a read-across approach where data from the closest most conservative congener was used, i.e. the congener with a longer carbon chain. For some congeners (e.g. PFDA) extrapolation to a congener with a shorter carbon chain was done, which may underestimate their potency due to differences in kinetics (i.e. slower excretion than its shorter homologue) and was therefore compensated for with an extra AF. Overall, given the structural, physicochemical and toxicological similarities between the congeners, this approach can be considered fairly robust and also represent the only method today to perform a cumulative assessment of PFASs.

DNELs for hepatotoxicity and reproductive toxicity were relatively similar. For hepatotoxicity the DNELs ranged from 54 to 1 780 ng/ml serum for individuals exposed indirectly via the environment, and from 108 to 3 560 ng/ml serum for workers (Table 31). For reproductive toxicity the corresponding DNELs were 65–2 400 ng/ml serum and 131–4 800 ng/ml serum, respectively (Table 32). For other identified endpoints, DNELs ranged from 0.12–98 ng/ml serum for individuals exposed indirectly via the environment and from 0.24–196 ng/ml serum for workers, respectively.

Epidemiological studies related to hepatotoxicity and reproductive toxicity showed inconsistent results and did not provide any firm conclusions. Epidemiological data on PFASs and other endpoints such as effects on immune function and obesity were limited.

5. Environmental Hazard Assessment

5.1 Toxicity to mammals, birds and fish

For the assessment of toxicity to mammalian species, see section 4.3.2. The same PODs are used as in the human hazard assessment, but with hepatic PFASs levels instead of serum levels to be compared to the hepatic PFASs levels in the exposure assessment. Due to lack of toxicological information or internal dose measurements for many congeners, a read-across to the closest most potent congener for the respective endpoint is performed.

As for the human/mammalian hazard assessment, most information on the toxicity of PFASs to birds and fish is available for PFOS and PFOA. For the majority of other congeners, the information in the open literature is very limited, or completely absent. Therefore, assumptions have to be made to estimate the toxicity of these congeners.

For toxicity to birds, only reproductive toxicity studies will be reviewed since PFASs levels in the exposure assessment are available for eggs only. Consequently, PFASs levels in eggs in toxicity studies will therefore be used as POD for comparison to levels in eggs in the exposure assessment. However, the toxicological information available is very limited for most congeners and assumptions and extrapolations therefore have to be made.

For toxicity to fish, tissue levels of PFAS congeners in toxicity studies will be used as POD. Also for fish, the toxicological information available is very limited and therefore assumptions and extrapolations have to be made. The acute toxicity has e.g. been shown to be dependent on the fluorinated carbon chain length and the functional group (Figure 11), which can be used.

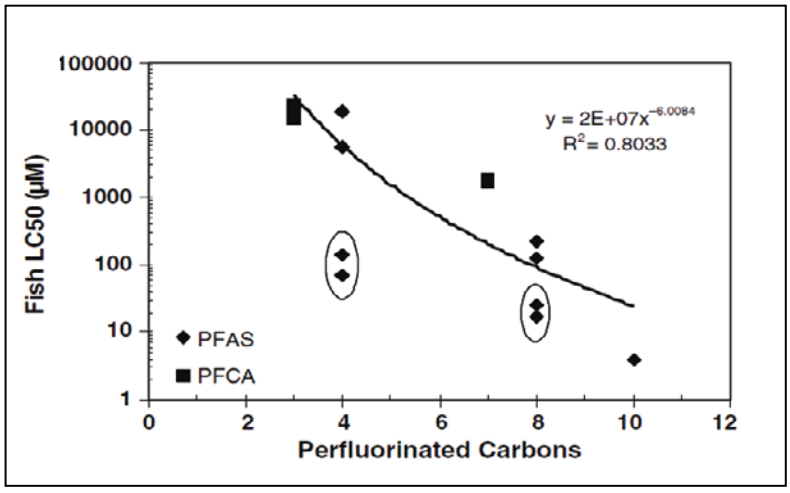


Figure 11. Acute toxicity (96h LC50) of perfluorinated sulfonates (PFAS) and carboxylates (PFCA) to bluegill sunfish, fathead minnow and rainbow trout. Circles identify alcohol and amide sulfonic acids and were not in-cluded in the regression analysis. Source: Giesy et al. (2010).

For many congeners, tissue levels in toxicity studies have not been measured, and therefore extrapolations have to be made from concentrations in water to concentrations in liver, based on correlations between carbon chain length and BCF in liver (Figure 12).

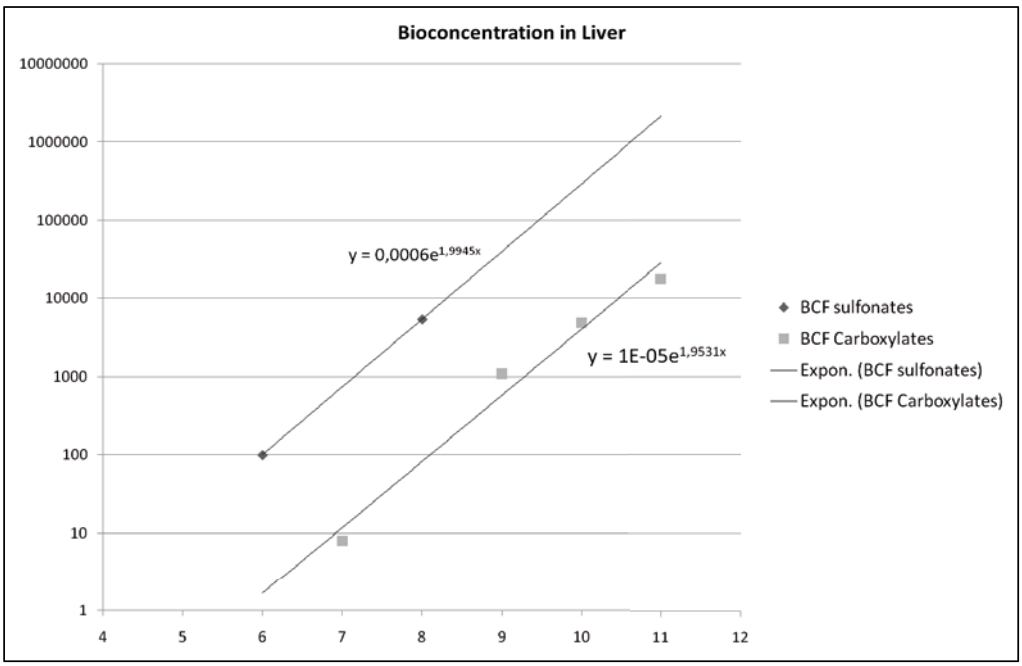


Figure 12. Bioconcentration factors (BCF) of PFAS with different carbon chain lengths in liver of Rainbow trout (Ochorhynchus mykiss) after 12 days exposure based on data presented in Martin et al. (2003a). The solid lines represent trend lines that will be used for extrapolation of BCFs.

5.2 Points of departure for individual PFAS-congeners

PFBS

In 2005, an environmental hazard assessment of PFBS was carried out by NICNAS (NICNAS, 2005) where fish and birds were included. For fish, only acute toxicity studies were reviewed. Among these, a lowest No-Observed-Effect Concentration (NOEC) of 888 mg/l was set for mortality in Fathead minnow (*Pimephales promelas*; Wildlife International, 2001). For birds, a 21 weeks reproductive toxicity study on PFBS in Northern Bobwhite quail was reviewed, showing no effects at the highest dose 900 mg/kg PFBS in the diet. Concentrations in eggs at 900 mg/kg were between 51 and 93µg/g w.w. (Wildlife international, 2005, Newsted et al., 2008).

Additional scientific publications of interest

Martin et al. (2003a), reported a BCF of < 1 in liver, blood and carcass of rainbow trout exposed to 1.4 µg/l PFBS during flow-through conditions for 12 days.

In a prolonged zebrafish early life-stage test investigating lethal, sublethal and teratogenic endpoints, Hagenaars et al. (2011) identified a NOEC of 250 mg/l PFBS in a static system; however the exact endpoint was not stated.

Point of Departure

- Fish (Zebrafish, NOEC, early life-stage test, endpoint not stated): 250 mg/l. Using a BCF of < 1 for liver based on results from Martin et al. (2003a), the corresponding liver concentrations would be < 250 µg/g.
- Birds (Northern Bobwhite quail, dietary exposure, no effects): > 51 µg/g egg.

PFPS

Not considered due to lack of exposure data in fish and birds.

PFHxS

No assessments of PFHxS on fish or birds were found.

Additional scientific publications of interest

Martin et al. (2003a), reported BCFs of 100 in liver, 76 in blood and 9.6 in carcass of rainbow trout, respectively, exposed to 1.4 µg/l PFHxS during flow-through conditions for 12 days.

Point of Departure

- Fish: No data for fish are available. Therefore data on PFOS will be used.
- Birds: No data for birds are available. Therefore data on PFOS will be used.

PFHpS

Not considered due to lack of exposure data in fish and birds.

PFOS

In 2002, an environmental hazard assessment of PFOS was carried out by OECD (OECD, 2002) in which PFOS was concluded to be a cause of concern for its persistence, presence in the environment and bioaccumulation. Of the studies reviewed for fish, a lowest (NOEC) of 300 µg/l was determined in Fathead Minnow for decreased survival and growth in a long-term (42 days) study. No avian reproductive toxicity studies were available.

In 2003, the 3M Company performed an environmental health risk assessment of PFOS (3M, 2003). From the hazard assessment, the NOEC for fish used as POD in the risk characterization was 86 µg/L, based on a long-term (62 days) study in bluegill sunfish (*Lepomis macrochirus*), where mortality occurred at the higher dose. At NOEC, tissue concentrations of PFOS was 48 µg/g in "edible tissues" (fish except head, fins, viscera) and 81 µg/g whole carcass. No avian reproductive toxicity studies were available.

In 2004, The Swedish Chemicals Agency (KemI) performed an environmental risk assessment of PFOS (KemI, 2004). From the hazard assessment, the lowest (NOEC) for fish was 300 µg/l, based on decreased survival and growth in a long-term (42 days) study on Fathead Minnow (OECD, 2002). For birds, the most sensitive effect was identified in a 21-week reproductive toxicity in Bobwhite Quail with a LOEC of 10 mg/kg feed for reduced survival in the offspring, though no levels of PFOS were measured in the eggs.

In 2006, Environment Canada published an ecological screening assessment report on PFOS and related compounds (Environment Canada, 2006), to a large extent based on the OECD hazard assessment of PFOS (OECD, 2002). For fish, the lowest NOEC in the report was 300 µg/l based on decreased survival and growth in Fathead Minnow (OECD, 2002). For birds, two long-term (21 weeks) reproductive toxicity studies in Mallard ducks and Bobwhite quail were acknowledged, in which both a LOEC of 10 mg/kg feed for reduced testes size and decreased spermatogenesis in the Mallard ducks, and for increased liver weight, increased incidence of small testes size and reduction in survivability in chicks for the quail, respectively. No levels of PFOS were measured in the eggs.

In 2010, the National Institute for Public Health and the Environment (RIVM) in the Netherlands derived national environmental limit values for PFOS (Moermond et al., 2010). For fish, a NOEC of 27 µg/l was used, based on reduced spawning in a chronic toxicity study (21 days) on Fathead Minnow in a static exposure system (Ankley et al., 2005). Another more sensitive study was also noted, showing a LOEC of 10 µg/ml, the lowest dose used, for decreased larval survival in a two-generation study on Japanese Medaka (*Oryzias latipes*) (Ji et al., 2008). However, this LOEC was only used for motivation of the application of a large assessment factor to the data from Ankley et al., 2005), and no justification was made for not using the data from Ji et al. (2008). No avian toxicity studies were reviewed.

Additional scientific publications of interest

Martin et al. (2003a), reported BCFs of 5400 in liver, 4300 in blood and 1100 in carcass of rainbow trout, respectively, exposed to 0.35 µg/l PFOS during flow-through conditions for 12 days.

Ji et al. (2008) performed one acute and one two-generation toxicity test on Japanese medaka exposed to PFOS in a static exposure system. A LOEC of 10 µg/ml, the lowest dose tested, was set for both studies based on increased female gonad size in the acute toxicity test and on decreased body weight and size in the offspring as well as a dose-dependent significantly decreased survival in the offspring at all doses in the two-generation toxicity study. In addition, Du et al. (2009) reported reduced body-weight gain and decreased female gonad size in zebrafish after 70-days exposure to 50 µg/l PFOS in a semi-static exposure system, with a NOEC of 10 µg/l. In a prolonged zebrafish early life stage test investigating lethal, sublethal and teratogenic endpoints, Hagenaars et al. (2011) identified a lowest NOEC for PFOS of 100 µg/l based on increased heart rate.

The results from the 21 weeks reproductive toxicity studies in Mallard ducks and Bobwhite quail used in the assessments by KemI (2004) and Environment Canada (2006), was subsequently published by Newsted et al. (2007). Newsted et al. (2005) also derived avian toxicity references values based on acute and reproductive toxicity studies in Mallard ducks and Bobwhite quail. Based on effects on several reproductive endpoints in the 21-weeks study in the quail, a LOAEL of 10 mg/kg in the diet was used as a point-of departure. The estimated daily intake at LOAEL, based on the average feed consumption per pen, was 0.77 mg/kg bw/day, and the level of PFOS in egg yolk was 62 µg/g.

Molina et al. (2006), O'Brien et al., (2009a) and Peden-Adams et al. (2009) investigated developmental toxicity in white leghorn chickens (*Gallus domesticus*) after *in ovo* exposure to PFOS. Molina et al. (2006) reported a lowest LOAEL of 0.1 µg PFOS/g egg, the lowest dose used in the study, for reduced hatchability. In contrast, O'Brien et al. (2009a) reported a NOAEL of 5.0 µg/g egg for reduced hatchability. Peden-Adams et al. (2009) reported effects on immunological, morphological and neurological parameters in chicks 14 days after hatching at the lowest *in ovo* exposure dose tested 1 µg/g egg. The hatching rate was not affected in this study.

POINT OF DEPARTURE

- Fish (Zebrafish, LOEC, two-generation study, decreased F_1 body weight, size and survival): 10 µg/l. This POD is conservative and slightly lower than the POD selected by RIVM (but where a large assessment factor was used), but can be motivated by that no assessment factors are used herein. Using a BCF for liver of 5400 (Martin et al., 2003a; Figure 12) the corresponding liver concentration of PFOS would be 54 000 µg/g.
- Birds (White leghorn chicken, *in ovo* exposure, LOAEL, reduced hatching): 0.1 µg/g egg.

PFOSi

Not considered due to lack of exposure data in fish and birds.

PFOSA

No environmental assessments or relevant scientific publications of PFOSA were found.

Point of Departure

- Fish: No data for fish are available. Therefore data on PFOS will be used.
- Birds: No data for birds are available. Therefore data on PFOS will be used.

EtFOSA

Not considered due to lack of exposure data in fish and birds.

PFDS

No assessments of PFDS on fish or birds was found.

Additional scientific publications of interest

Giesy et al. (2010) presented an acute (96h) LC_{50} for PFDS in fish of approximately 3.5 µM (Figure 11), equal to approximately 2100 µg/l without specifying which species that was used.

O'Brien et al. (2009) performed a study to examine pipping success and gene expression of white leghorn chicken embryos exposed *in ovo* to PFDS. The results showed no effects on pipping success at doses up to 10 µg/g egg.

Point of Departure

- Fish (LC50, species not specified): 2100 µg/l. However, due to that no reliable extrapolation to tissue levels can be performed, data on PFOS will instead be used.
- Birds (White leghorn chicken, no effects): > 10 µg/g egg.

PFBA

Only fish is considered for the hazard assessment of PFBA due to lack of exposure data in birds.

No assessments of PFBA in fish were found.

Additional scientific publications of interest

In a prolonged zebrafish early life stage test investigating lethal, sublethal and teratogenic endpoints, Hagenaars et al. (2011) identified a NOEC for PFBA of 500 mg/l, however the exact endpoint for this NOEC was not stated.

Point of Departure

- Fish (Zebrafish, NOEC, prolonged early life-stage test, endpoint not stated): 500 mg/l. Using a BCF of 0.004 (extrapolation from Figure 12), the corresponding liver concentration would be 2 µg/g.
- Birds: Not considered.

PFPeA

Not considered due to lack of exposure data in fish and birds.

PFHxA

No assessments or relevant scientific publications of PFHxA toxicity in fish or birds were found.

Point of Departure

- Fish: No data for fish are available. Therefore data on PFOA will be used.
- Birds: No data for birds are available. Therefore data on PFOA will be used.

PFHpA

No assessments or relevant scientific publications of PFHpA were found.

Point of Departure

- Fish: No data for fish are available. Therefore data on PFOA will be used.
- Birds: No data for birds are available. Therefore data on PFOA will be used.

PFOA

In 2007, OECD completed an environmental hazard assessment report of PFOA (OECD, 2007). For fish, a lowest NOEC of 40 mg/l for mortality in embryos, larvae and juveniles was identified in a long term (85 days) study in rainbow trout (*Oncorhynchus mykiss*) (CIT, 2004). In separate tests with Rainbow trout, BCFs for PFOA of 8 in liver, 27 in blood and 4 in carcass (Martin et al., 2003a) and a bioaccumulation factor of 0.038 (Martin et al., 2003b) were reported. No toxicity studies in birds were reviewed.

In 2009, a Chemical Safety Report (CSR) on PFOA was completed by the industry and German authorities within the REACH regulation (German UBA, 2009), largely based on the previous OECD hazard assessment of PFOA (OECD, 2007). The conclusions were in accordance with the OECD assessment. For fish, the lowest NOEC of 40 mg/l for mortality in embryos, larvae and juveniles was identified in a long term (85 days) study in rainbow trout (*Oncorhynchus mykiss*) (CIT, 2004). No toxicity studies in birds were reviewed.

Scientific publications of interest

Ji et al. (2008) performed one acute and one two-generation toxicity test on Japanese medaka exposed to PFOA at the concentrations 10, 100 or 1000 µg/l in a static exposure system. No effects on survival and gonad weights were noted in the acute toxicity test. In offspring in the two-generation toxicity study, dose-dependent significantly decreased survival occurred at all doses; hence the LOEC was 10 µg/l.

Colombo et al. (2008) tested PFOA in a static acute (96h) toxicity test and in an early-life-stage test (flow through conditions) in rainbow trout. The authors observed sublethal toxicity of PFOA in the acute toxicity test at 250 mg/l, giving a NOEC of 125 mg/l. In the early-life-stage test, a slight dose-dependent increase in embryo mortality was observed with 2%, 3%, 4%, 5% and 7% at the concentrations 2.2, 4.5, 11, 21 and 40 mg/l. For mortality in juvenile fish, the corresponding numbers were 3%, 5%, 20%, 12% and 13%, respectively, to be compared to 10% mortality in the control. Due to the lack of statistical significance for both embryonic as well as juvenile mortality, NOEC was set at the highest dose 40 mg/l.

Hagenars et al. (2011) identified in a prolonged zebrafish early life stage test investigating lethal, sublethal and teratogenic endpoints, a lowest NOEC for PFOA of 50 mg/l, however the exact endpoint was not stated.

O'Brien et al. (2009) examined pipping success and gene expression of white leghorn chicken embryos exposed *in ovo* to PFOA. The results showed no effects on pipping success at doses up to 10 µg/g egg.

Point of Departure
Based on the data presented above, the selected points of departure for PFOA are:

- Fish (Rainbow trout, NOEC, early life-stage test, embryonal/juvenile mortality: > 40 mg/l. This is the same POD that was selected by the German UBA (2009). Using a BCF of 8 for liver from Martin et al. (2003a), the corresponding concentration in liver would be > 320 µg/g, respectively.
- Birds (White leghorn chicken, no effects): > 10 µg/g egg.

PFNA
No assessments of PFNA on fish or birds were found.

Scientific publications of interest
Liu et al. (2011) and Zhang et al (2011) performed a long-term transgenerational study on zebrafish that were exposed for 180 days to PFNA in a static system at the doses 0, 0.05, 0.1, 0.5 or 1 mg/l and 0. 0.1, 0.5 or 1 mg/l, respectively. Liu et al (2011) reported increased plasma triiodothyronine (T_3) levels in adult fish as well as offspring at the lowest dose tested (0.05 mg/l), 5.2 ng/ml as compared to 2.3 ng/ml in the control in F_0 adults and with a maximum response of 7.4 ng/ml in the 0.1 mg/l group. A similar result was obtained in the F_1-generation. Hence the LOEC for this effect is 0.05 mg/l. Zhang et al (2011) reported hepatocellular swelling at the lowest dose tested, 0.1 mg/l, hence the LOEC for this effect.

Point of Departure
Based on the data presented above, the selected points of departure for PFNA are:

- Fish (Zebrafish, LOEC, long-term two-generation study, increased plasma T_3): 0.05 mg/l. This can be considered conservative based on uncertainties regarding the functional relevance of this effect. Using a BCF of 61 for liver based on Martin et al., 2003a (Figure 12). the corresponding liver concentration at LOEC would be 3.1 µg/g.
- Birds: No data for birds are available. Therefore data on PFUnDA will be used.

PFDA
No assessments of PFDA on fish or birds were found.

Scientific publications of interest
Martin et al. (2003a), reported a BCF of 1 100 in liver, 1 900 in blood and 350 in carcass of rainbow trout, respectively, exposed to 0.71 µg/l PFDA during flow-through conditions for 12 days.

No relevant studies on the reproductive toxicity of birds were found.

Point of Departure
- Fish: No data for fish are available. Therefore data on PFNA will be used.
- Birds: No data for birds are available. Therefore data on PFUnDA will be used.

PFUnDA
No assessments of PFUnDA on fish or birds were found.

Scientific publications of interest
Martin et al. (2003a), reported BCFs of 4 900 in liver, 11 000 in blood and 2 700 in carcass of rainbow trout, respectively, exposed to 0.48 µg/l PFUnDA during flow-through conditions for 12 days.

O'Brien et al. (2009) examined pipping success and gene expression of white leghorn chicken embryos exposed *in ovo* to PFUnDA. The results showed no effects on pipping success at doses up to 10 µg/g egg.

Point of Departure
Based on the data presented above, the selected points of departure for PFUnDA are:
- Fish: No data for fish are available. Therefore data on PFNA will be used.
- Birds (White leghorn chicken, no effects): > 10 µg/g egg.

PFDoDA
No assessments of PFDoDA on fish or birds were found.

Scientific publications of interest
Liu et al. (2009) exposed female zebrafish to a single intraperitoneal injection of 0, 20, 40 or 80 µg/g PFDoDA. Hepatic toxicity was observed, with hepatocellular hypertrophy at the lowest dose 20 µg/g, becoming more severe at the higher doses. No tissue levels of PFDoDA were measured.

Martin et al. (2003a), reported BCFs of 18 000 in liver, 40 000 in blood and 18 000 in carcass of rainbow trout, respectively, exposed to 0.20 µg/l PFDoDA during flow-through conditions for 12 days.

Point of Departure
Based on the data presented above, the selected points of departure for PFDoDA are:

- Fish: No relevant data for fish are available. Therefore data on PFNA will be used.
- Birds: No data for birds are available. Therefore data on PFUnDA will be used.

PFTrDA
No assessments or relevant scientific publications of PFTrDA were found.

Point of Departure

- Fish: No data for fish are available. Therefore data on PFNA will be used.
- Birds: No data for birds are available. Therefore data on PFUnDA will be used

PFTeDA
No assessments of PFTeDA on fish or birds were found.

Scientific publications of interest
Martin et al. (2003a), reported BCFs of 30 000 in liver, 30 000 in blood and 23 000 in carcass of rainbow trout, respectively, exposed to 0.014 µg/l for PFTeDA during flow-through conditions for 12 days.

POINT OF DEPARTURE

- Fish: No data for fish are available. Therefore data on PFNA will be used.
- Birds: No data for birds are available. Therefore data on PFUnDA will be used.

PFPeDA
No assessments or relevant scientific publications of PFPeDA were found.

Point of Departure

- Fish: No data for fish are available. Therefore data on PFNA will be used.
- Birds: No data for birds are available. Therefore data on PFUnDA will be used.

PFHxDA
Not considered due to lack of exposure data in fish and birds.

6:2 FTSA

Only fish is considered for the hazard assessment of 6:2 FTSA due to lack of exposure data in birds.

No assessments of 6:2 FTSA were found.

Scientific publications of interest

- Fish: No data for fish are available. Therefore data on PFOS will be used.

For a summary of the hazard data in for the respective congeners that will be used for the risk characterization of mammals, birds and fish see Table 36, Table 37 and Table 38, respectively. In addition, DNELs are calculated for the mammalian species, seals and otters, in order to allow a comparison of the situation for these species to humans (Table 39 and Table 40). The derivation of the DNELs was performed as for the human situation described in section 4.4.

Table 36. Summary of points of departure (PODs) for hepatotoxicity and reproductive toxicity for the respective PFAS congeners that will be used in the risk characterization for mammals (seals and otters), with external and internal doses. Doses represent NOAELs if other not stated. Original congener-specific data is marked in bold.

Congener	Hepatotoxicity		Reproductive toxicity	
	External dose (mg/kg bw/day)	Internal dose (µg/g liver)	External dose (mg/kg bw/day)	Internal dose (µg/g liver)
PFBS (read-across from PFHxS)	1	150	> 10	> 17
PFPS (read-across from PFHxS)	1	150	> 10	> 17
PFHxS	**1**	**150**	**> 10**	**> 17**
PFHpS (read across from PFOS)	0.025	19.2	0.1	9.2
PFOS	**0.025**	**19.2**	**0.1**	**9.2**
PFOSi (read across from PFOS)	0.025	19.2	0.1	9.2
PFOSA (read across from PFOS)	0.025	19.2	0.1	9.2
EtFOSA (read across from PFOS)	0.025	19.2	0.1	9.2
PFDS (read across from PFOS)	0.025	19.2	0.1	9.2
PFHpA (read across from PFOA)	0.06	14.2	0.86	31.4
PFOA	**0.06**	**14.2**	**0.86[b]**	**31.4[a]**
PFNA	**0.83[c]**	**57.0[a,c]**	**0.83**	**17.8[a]**
PFDA (read-across from PFNA)	0.83	28.5	0.83	8.9
PFUnDA (read-across from PFNA)	0.83	28.5	0.83	8.9
PFDoDA (read-across from PFNA)	0.83	28.5	0.83	8.9
PFTrDA (read-across from PFNA)	0.83	28.5	0.83	8.9
PFTeDA (read-across from PFNA)	0.83	28.5	0.83	8.9

[a] = assuming a liver/serum ratio of 2.

[b] = BMDL.

[c] = LOAEL.

Table 37. Summary of points of departure (PODs) (egg concentrations) for the respective PFAS congeners that will be used in the risk characterization for reproductive toxicity in birds. Doses represent NOAELs. If no effect has been shown or if only LOAEL exist for a congener this is stated. Original congener-specific data is marked in bold.

Congener	Internal dose (µg/g egg)
PFBS (Northern bobwhite quail, dietary exposure, no effect)	**> 51**
PFHxS (read-across from PFOS)	0.1
PFOS (White leghorn chicken, in ovo exposure, LOAEL, reduced hatchability)	**0.1**
PFOSA (read-across from PFOS)	0.1
PFDS (White leghorn chicken, in ovo exposure, no effect)	**> 10**
PFHxA (read-across from PFOA)	> 10
PFHpA (read-across from PFOA)	> 10
PFOA (White leghorn chicken, in ovo exposure, no effect)	**> 10**
PFNA (read-across from PFUnDA)	> 10
PFDA (read-across from PFUnDA)	> 10
PFUnDA (White leghorn chicken, in ovo exposure, no effect)	**> 10**
PFDoDA (read-across from PFUnDA)	> 10
PFTrDA (read-across from PFUnDA)	> 10
PFTeDA (read-across from PFUnDA)	> 10
PFPeDA (read-across from PFUnDA)	> 10

Table 38. Summary of points of departure (PODs) from toxicity studies for the respective PFAS congeners that will be used in the risk characterization for fish with external water concentration and calculated internal concentrations in liver. The point of departure (NOEC, LOEC, effect) is stated. Original congener-specific data is marked in bold.

Congener	Water concentration (µg/l)	Calculated hepatic concentration (µg/g)
PFBS (Zebrafish, NOEC, early life-stage test, endpoints not stated)	**250 000**	**< 250**[a]
PFHxS (read-across from PFOS)	10	54 000
PFOS (Zebrafish, LOEC, two-generation study, decreased F1 body weight/size/survival)	**10**	**54 000**
PFOSA (read-across from PFOS)	10	54 000
PFDS (read-across from PFOS)	10	54 000
PFBA (Zebrafish, NOEC, prolonged early life-stage test, no effects)	**500 000**	**2**[c]
PFHxA (read-across from PFOA)	> 40 000	> 320
PFHpA (read-across from PFOA)	> 40 000	> 320
PFOA (Rainbow trout, NOEC, early life-stage test, embryonal/juvenile mortality)	**> 40 000**	**> 320**[d]
PFNA (Zebrafish, LOEC, long-term two-generation study, increased plasma T3)	**50**	**3.1**[e]
PFDA (read-across from PFNA)	50	3.1
PFUnDA (read-across from PFNA)	50	3.1
PFDoDA (read-across from PFNA)	50	3.1
PFTrDA (read-across from PFNA)	50	3.1
PFTeDA (read-across from PFNA)	50	3.1
PFPeDA (read-across from PFNA)	50	3.1
6:2 FTSA (read-across from PFOS)	10	54 000

[a] = derived from a hepatic BCF of < 1 based on Martin et al. (2003a,Figure 12).
[b] = derived from a hepatic BCF of 5400 based on Martin et al. (2003a, Figure 12).
[c] = derived from an estimated hepatic BCF of 0.004 based on Martin et al. (2003a, Figure 12).
[d] = derived from a hepatic BCF of 8 based on Martin et al. (2003a, Figure 12).
[e] = derived from an estimated hepatic BCF of 61 based on Martin et al. (2003a, Figure 12).

Table 39. Derived-No-Effect-Levels (DNELs) for hepatotoxicity in mammals (seals and otters). Original congener-specific data is marked in bold. Doses represent NOAELs if other not stated.

Congener	POD (ng/g liver)	Assessment Factors						DNEL (ng/g liver)
		Exposure duration[a]	Read-across[b]	LOAEL to NOAEL	Inter-species[c]	Intra-species[d]	Overall AF	
PFBS (read-across from PFHxS)	150 000	2	1	1	2.5	10	50	3000
PFPS (read-across from PFHxS)	150 000	2	1	1	2.5	10	50	3000
PFHxS	**150 000**	2	1	1	2.5	10	50	3000
PFHpS (read-across from PFOS)	19 200	1	1	1	2.5	10	25	768
PFOS	**19 200**	1	1	1	2.5	10	25	768
PFOSi	19 200	1	1	1	2.5	10	25	768
PFOSA (read-across from PFOS)	19 200	1	1	1	2.5	10	25	768
EtFOSA (read-across from PFOS)	19 200	1	1	1	2.5	10	25	768
PFDS (read-across from PFOS)	19 200	1	3	1	2.5	10	75	256
PFHpA (read-across from PFOA)	14 200	2	1	1	2.5	10	50	284
PFOA	**14 200**	2	1	1	2.5	10	50	284
PFNA (LOAEL)	**57 000**	2	1	3	2.5	10	150	380
PFDA (read-across from PFNA)	28 500	2	3	3	2.5	10	450	63
PFUnDA (read-across from PFNA)	28 500	2	3	3	2.5	10	450	63
PFDoDA (read-across from PFNA)	28 500	2	3	3	2.5	10	450	63
PFTrDA (read-across from PFNA)	28 500	2	3	3	2.5	10	450	63
PFTeDA (read-across from PFNA)	28 500	2	3	3	2.5	10	450	63

[a] – A factor of 2 is used for extrapolation from subacute and subchronic to chronic exposure due to small differences between study durations and effects.

[b] – For read-across from a shorter-chain congener. Read-across from a longer carbon chain congener is considered conservative and no assessment factor is then needed.

[c] – For differences in toxicodynamics between species = 2.5. Due to comparisons in internal doses no assessment factor for kinetic differences is needed.

[d] – For differences in sensitivity within species. Commonly a default factor of 10 is used.

Table 40. Derived-No-Effect-Levels (DNELs) for reproductive toxicity in mammals (seals and otters). Original congener-specific data is marked in bold.

Congener	POD (ng/g liver)	Assessment Factors				DNEL (ng/g liver)
		Read-across[a]	Inter-species[b]	Intra-species[c]	Overall AF	
PFBS (read-across from PFHxS)	> 17 000	1	2.5	10	25	> 680
PFPS (read-across from PFHxS)	> 17 000	1	2.5	10	25	> 680
PFHxS	**> 17 000**	1	2.5	10	25	> 680
PFHpS (read-across from PFOS)	9 200	1	2.5	10	25	368
PFOS	**9 200**	1	2.5	10	25	368
PFOSi (read-across from PFOS)	9 200	1	2.5	10	25	368
PFOSA (read-across from PFOS)	9 200	1	2.5	10	25	368
EtFOSA (read-across from PFOS)	9 200	1	2.5	10	25	368
PFDS (read-across from PFOS)	9 200	3	2.5	10	75	123
PFHpA (read-across from PFOA)	31 400	1	2.5	10	25	1 256
PFOA	**31 400**	1	2.5	10	25	1 256
PFNA	**17 800**	1	2.5	10	25	712
PFDA (read-across from PFNA)	8 900	3	2.5	10	75	119
PFUnDA (read-across from PFNA)	8 900	3	2.5	10	75	119
PFDoDA (read-across from PFNA)	8 900	3	2.5	10	75	119
PFTrDA (read-across from PFNA)	8 900	3	2.5	10	75	119
PFTeDA (read-across from PFNA)	8 900	3	2.5	10	75	119

[a] – For read-across from a shorter-chain congener. Read-across from a longer carbon chain congener is considered conservative and no assessment factor is then needed.

[b] – For differences in toxicodynamics between species = 2.5. Due to comparisons in internal doses no assessment factor for kinetic differences is needed.

[c] – For differences in sensitivity within species. Commonly a default factor of 10 is used.

5.3 Hazard assessment results/discussion

For mammals, the result of the hazard assessment is similar to the human hazard assessment, with the same PODs used due to their shared toxicological database, but with slight differences in the specific congeners assessed based on the differences in congeners available for seals and otters in the exposure assessment. Also, hepatic concentrations were used as internal doses as opposed to serum levels, based on the comparison to hepatic concentrations from the environmental exposure assessment. Hepatic concentrations were to a large extent lacking from the toxicological studies and extrapolations therefore had to be made. Toxicological data with internal dose measurements were available for four of seventeen congeners; thus data for thirteen had to be extrapolated. This was done by a read-across approach where data from the closest most conservative congener was used, i.e. the congener with a longer carbon chain. In addition, extrapolation from serum levels to hepatic levels had to be performed for PFOA and PFNA. For some congeners (e.g. PFDA and longer-chain congeners) extrapolation to a congener with a shorter carbon chain was done, which may underestimate their potency and therefore an additional assessment factor was included. However, given the similarities between

the congeners with regard to physicochemical and toxicological properties, the read-across approach can be considered fairly robust. The PODs were in the same order of magnitude, ranging from 14–150 µg/g liver for hepatotoxicity and 9–31 µg/g liver for reproductive toxicity.

DNELs for hepatotoxicity and reproductive toxicity in mammals were relatively similar, ranging from 63–3000 ng/g liver and 119–1256 ng/g liver, respectively (Table 39 and Table 40), with the lower DNELs to being to a large extend due to large overall assessment factors.

For birds, only data from reproductive toxicity studies with internal dose measurements in eggs were considered, in order to be compared with exposure levels in eggs from the exposure assessment. Toxicological data with exposure levels in eggs or with *in ovo* exposure was available for five of fifteen congeners, thus data for 10 congeners had to be extrapolated using a similar read-across approach as for mammals. Few studies on the toxicity of PFAS in birds following *in ovo* exposure were available, with effects being shown for only one congener – PFOS. In addition, the studies available were only performed in two different species. Hence the data can be considered uncertain with regard to effects and effect levels, and consequently, the extrapolations are considered highly uncertain.

For fish, data were available for five of 17 congeners. The toxicity data can be considered uncertain, based on that different species, study durations and endpoints have been used in the different studies, some resulting in large differences in effect levels for the same congener. Extrapolations had to be performed for twelve congeners which can be considered highly uncertain based on the differences in bioconcentration (Figure 12) as well as a likely difference in the toxicity between congeners (e.g. acute toxicity, Figure 11). For e.g. the longer chain carboxylic acids, a read-across was made from a shorter congener (PFNA), which may underestimate their PODs.

6. Risk characterization

6.1 Human health

For the assessment of human health, the results of the risk characterization for individuals exposed indirectly via the environment with regard to hepatotoxicity and reproductive toxicity are presented in Table 41 and Table 42, respectively. Similarly, the results for occupationally exposed individuals are presented in Table 43 and Table 44. The RCRs are calculated for each congener individually as well as for all congeners combined as described in section 1.2.3.

Table 41. Risk characterization ratios (RCRs) for hepatotoxicity in individuals exposed indirectly via the environment. A cumulative RCR is calculated by addition of RCRs for individual congeners. Congener-specific data is marked in bold.

Congener	Exposure (ng/ml serum)	DNEL (ng/ml serum)	RCR[a]	Contribution to cumulative RCR (%)	Concern		Trend
					Yes	No	
PFBS (read-across from PFHxS)	0.108	1 780	0.000061	0.02		√	↑
PFHxS	8.50	1 780	0.0048	1.8		√	↑
PFOS	27.5	162	0.17	63.6		√	↓
PFOSA (read-across from PFOS)	< 0.040	162	< 0.00025	< 0.09		√	↓
PFDS (read-across from PFOS)	0.035	54	0.00065	0.2		√	↓
PFHxA (read-across from PFOA)	< 0.22	142	0.0015	< 0.6		√	N.A.
PFHpA (read-across from PFOA)	0.135	142	0.00095	0.4		√	↔
PFOA	5.3	190	0.04	13.8		√	↓
PFNA	2.6	64	0.014	5.1		√	↑
PFDA (read-across from PFNA)	0.70	64	0.011	4.1		√	↑
PFUnDA (read-across from PFNA)	0.83	64	0.013	4.8		√	↔
PFDoDA (read-across from PFNA)	< 0.03	64	< 0.00047	< 0.2		√	N.A.
PFTrDA (read-across from PFNA)	< 0.15	64	< 0.0023	< 0.9		√	N.A.
PFTeDA (read-across from PFNA)	< 0.04	162	< 0.00063	< 0.2		√	N.A.
6:2 FTSA (read-across from PFOS)	< 1.82		< 0.011	< 4.2		√	N.A.
		Cumulative	≤ 0.27				

N.A. = Not available/not applicable.

[a] – RCR = Exposure/DNEL, ratio < 1 = risk is considered controlled, ratio of > 1 = risk is considered not controlled.

Table 42. Risk characterization ratios (RCRs) for reproductive toxicity in individuals exposed indirectly via the environment. A cumulative RCR is calculated by addition of RCRs for individual congeners. Congeners marked in bold represent congeners with original toxicity data.

Congener	Exposure (ng/ml serum)	DNEL (ng/ml serum)	RCR[a]	Contribution to cumulative RCR (%)	Concern		Trend
					Yes	No	
PFBS (read-across from PFHxS)	0.108	> 2 400	< 0.000045	< 0.02		√	↑
PFHxS	8.50	> 2 400	< 0.0035	< 1.9		√	↑
PFOS	27.5	196	0.14	75.9		√	↓
PFOSA (read-across from PFOS)	< 0.040	196	< 0.0002	< 0.1		√	↓
PFDS (read-across from PFOS)	0.035	65	0.0005	0.3		√	↓
PFHxA (read-across from PFOA)	< 0.22	628	0.0004	< 0.2		√	N.A.
PFHpA (read-across from PFOA)	0.135	628	0.0002	0.1		√	↔
PFOA	5.24	628	0.008	4.5		√	↓
PFNA	2.6	356	0.0073	4.0		√	↑
PFDA (read-across from PFNA)	0.70	119	0.0059	3.2		√	↑
PFUnDA (read-across from PFNA)	0.83	119	0.0070	3.8		√	↔
PFDoDA (read-across from PFNA)	< 0.03	119	< 0.0003	< 0.1		√	N.A.
PFTrDA (read-across from PFNA)	< 0.15	119	< 0.001	< 0.7		√	N.A.
PFTeDA (read-across from PFNA)	< 0.04	119	< 0.0003	< 0.2		√	N.A.
6:2 FTSA (read-across from PFOS)	< 1.82	196	< 0.009	< 5.0		√	N.A.
		Cumulative	≤ 0.18				

N.A. = Not available/not applicable.

[a] – RCR = Exposure/DNEL, ratio < 1 = risk is considered controlled, ratio of > 1 = risk is considered not controlled.

Table 43. Risk characterization ratios (RCRs) for hepatotoxicity in occupationally exposed individuals. A cumulative RCR is calculated by addition of RCRs for individual congeners. Congeners marked in bold represent congeners with original toxicity data.

Congener	Exposure (ng/ml serum)	DNEL (ng/ml serum)	RCR[a]	Contribution to cumulative RCR (%)	Concern	
					Yes	No
PFBS (read-across from PFHxS)	5.6	3 560	0.002	0.03		√
PFHxS	8.6	3 560	0.002	0.04		√
PFOS	54	323	0.17	3.1		√
PFOSA (read-across from PFOS)	< 0.040	323	< 0.00012	< 0.002		√
PFDS (read-across from PFOS)	0.035	108	0.00032	0.006		√
PFBA	2.2	560	0.0039	0.07		√
PFPeA (read-across from PFOA)	0.28	284	0.00099	0.02		√
PFHxA (read-across from PFOA)	24	284	0.085	1.5		√
PFHpA (read-across from PFOA)	40	284	0.14	2.6		√
PFOA	1070	284	3.8	69.0	√	
PFNA	326	380	0.86	15.7		√
PFDA (read-across from PFNA)	48	127	0.38	6.9		√
PFUnDA (read-across from PFNA)	5.6	127	0.044	0.8		√
PFDoDA (read-across from PFNA)	< 0.03	127	< 0.00023	< 0.004		√
PFTrDA (read-across from PFNA)	< 0.15	127	< 0.0012	< 0.02		√
PFTeDA (read-across from PFNA)	< 0.04	127	< 0.00032	< 0.006		√
6:2 FTSA (read-across from PFOS)	< 1.82	323	< 0.0056	< 0.1		√
		Cumulative	≤ 5.5		√	

[a] – RCR = Exposure/DNEL, ratio < 1 = risk is considered controlled, ratio of > 1 = risk is considered not controlled.

Table 44. Risk characterization ratios (RCRs) for reproductive toxicity in occupationally exposed individuals. A cumulative RCR is calculated by addition of RCRs for individual congeners. Congeners marked in bold represent congeners with original toxicity data.

Congener	Exposure (ng/ml serum)	DNEL (ng/ml serum)	RCR[a]	Contribution to cumulative RCR (%)	Concern	
					Yes	No
PFBS (read-across from PFHxS)	5.6	> 4 800	< 0.0012	< 0.07		√
PFHxS	8.6	> 4 800	< 0.0018	< 0.1		√
PFOS	54	392	0.14	7.9		√
PFOSA (read-across from PFOS)	< 0.040	392	< 0.00010	< 0.006		√
PFDS (read-across from PFOS)	0.035	131	0.00027	0.02		√
PFBA	2.2	352	0.0063	0.4		√
PFPeA (read-across from PFOA)	0.28	1 256	0.00022	0.01		√
PFHxA (read-across from PFOA)	24	1 256	0.019	1.1		√
PFHpA (read-across from PFOA)	40	1 256	0.031	1.8		√
PFOA	1070	1 256	0.85	49.0		√
PFNA	326	712	0.46	26.3		√
PFDA (read-across from PFNA)	48	237	0.20	11.6		√
PFUnDA (read-across from PFNA)	5.6	237	0.024	1.4		√
PFDoDA (read-across from PFNA)	< 0.03	237	< 0.00013	< 0.007		√
PFTrDA (read-across from PFNA)	< 0.15	237	< 0.00063	< 0.04		√
PFTeDA (read-across from PFNA)	< 0.04	237	< 0.00017	< 0.01		√
6:2 FTSA (read-across from PFOS)	< 1.82	392	< 0.0046	< 0.3		√
		Cumulative	≤ 1.7		√	

[a] – RCR = Exposure/DNEL, ratio < 1 = risk is considered controlled, ratio of > 1 = risk is considered not controlled.

6.1.1 Risk characterization results/discussion

INDIRECT EXPOSURE VIA THE ENVIRONMENT

The result of the risk characterization indicate that at current exposure levels there is no cause for concern for hepatotoxicity or reproductive toxicity for individuals exposed indirectly via the environment (i.e. the general population).

For hepatotoxicity, RCRs were highest for PFOS and PFOA, 0.17 and 0.04, respectively, contributing in total with 77% to the cumulative RCR. However these congeners show decreasing trends in human blood/serum. PFNA, on the other hand, with a RCR of 0.014 show an increasing trend, though the levels of PFNA would need to increase approximately 75 times to reach a RCR of 1. A cumulative RCR for all congeners combined, obtained by summarizing individual RCRs, resulted in a RCR of ≤ 0.27. Hence, all congeners combined are not expected to give any cause for concern for hepatotoxicity. The subpopulation that consumed contaminated fish showed the highest RCR for hepatotoxicity, 1.3 (data not shown), indicating a cause for concern.

For reproductive toxicity, the RCR was highest for PFOS, 0.14, contributing with 76% to the cumulative RCR. PFNA and PFUnDA, both with RCRs of approximately 0.007, show increasing trends in human blood/serum, though the levels of these congeners would need to increase about 137 times to reach a RCR of 1. The cumulative RCR was ≤ 0.18; hence, all congeners combined are not expected to give any cause for concern for reproductive toxicity. The subpopulation that consumed contaminated fish showed the highest RCR for reproductive toxicity, 1.0 (data not shown i.e. close to being of concern.

RCRs of 229 were obtained for immunotoxicity by PFOS (data not shown), and 2.6 for effects on mammary gland development and growth by PFOA (data not shown), indicating a cause for concern..

OCCUPATIONAL EXPOSURE (PROFESSIONAL SKI WAXERS)

For the occupationally exposed subpopulation, a cause for concern with regard to hepatotoxicity for PFOA was identified, with a RCR of 3.8, followed by PFNA and PFOS, with RCRs of 0.86 and 0.17, respectively. The cumulative RCR was ≤ 5.5, with PFOA contributing 69% to this.

For reproductive toxicity, no cause for concern was identified for congeners individually, but for all congeners combined, based on the cumulative RCR of ≤ 1.7. PFOA and PFNA were the main contributors with 49% and 26%, respectively. This subpopulation consisted entirely of males and this cause for concern is therefore not directly applicable to those individuals since PODs for reproductive toxicity are based on effects in the offspring after *in utero* exposure of the dam as well as on maternal blood levels.

RCRs of 228 were obtained for immunotoxicity by PFOS (data not shown), and 268 for effects on mammary gland development and growth by PFOA (data not shown), indicating a cause for concern.

6.2 Environment

For the environmental risk assessment, a margin of exposure approach (MOE) is used for all species – seals, otters, birds and fish. In addition, a risk characterization ratios (RCRs) approach will be performed for seals and otters, similarly as for human health, in order to allow for a comparison to the human situation. Correspondingly, a cumulative risk characterization will also be done for all the congeners combined by addition of the respective RCR values. This is, however not performed for birds and fish, as different endpoints are being used in the evaluation of the toxicological data for these species as well as to the large uncertainties in the read-across extrapolations for these species.

The results of the risk characterization for seals, otters, birds and marine as well as freshwater fish are presented in Tables 45–51.

Table 45. Margins of exposure (MOEs) and risk characterization ratios (RCRs) for hepatotoxicity in seals. A cumulative RCR is calculated by addition of RCRs for individual congeners. Congeners marked in bold represent congeners with original toxicity data.

Congener	Exposure (ng/g liver)	MOE Approach		RCR Approach					Trend
		POD (ng/liver)	MOE	DNEL (ng/g liver)	RCR[a]	Contribution to cumulative RCR (%)	Concern		
							Yes	No	
PFBS	< 0.006	150 000	> 25 000 000	> 3 000	< 0.000002	< 0.0001		√	N.A.
PFPS	0.1	150 000	1 500 000	3 000	0.00003	0.002		√	N.A.
PFHxS	1.2	150 000	125 000	3 000	0.0004	0.02		√	↓
PFHpS	0.4	19 200	48 000	768	0.0005	0.03		√	↓
PFOS	494	19 200	39	768	0.64	31.2		√	↔
PFOSA	2.3	19 200	8 348	768	0.003	0.15		√	↔
PFOSi	0.2	19 200	96 000	768	0.0003	0.01		√	↓
EtFOSA	0.7	19 200	27 429	768	0.0009	0.04		√	N.A.
PFDS	0.2	19 200	96 000	256	0.0008	0.04		√	N.A.
PFHpA	0.04	14 200	355 000	284	0.0001	0.007		√	N.A.
PFOA	11	14 200	1 291	284	0.038	1.9		√	↔
PFNA	109	57 000[b]	523	380	0.29	13.9		√	↔
PFDA	22	28 500[b]	1 295	63	0.35	16.8		√	↑
PFUnDA	15	28 500[b]	1 900	63	0.24	11.5		√	↑
PFDoDA	1.5	28 500[b]	19 000	63	0.024	1.1		√	↑
PFTrDA	24.6	28 500[b]	1 159	63	0.39	18.8		√	↑
PFTeDA	5.8	28 500[b]	4 914	63	0.09	4.4		√	↔
				Cumulative	≤ 2.1		√		

[a] – RCR = Exposure/DNEL, ratio < 1 = risk is considered controlled, ratio of > 1 = risk is considered not controlled.

[b] – LOAEL.

Table 46. Margins of exposure (MOEs) and risk characterization ratios (RCRs) for reproductive toxicity in seals. A cumulative RCR is calculated by addition of RCRs for individual congeners. Congeners marked in bold represent congeners with original toxicity data.

Congener	Exposure (ng/g liver)	MOE Approach		RCR Approach					Trend
		POD (ng/liver)	MOE	DNEL (ng/g liver)	RCR[a]	Contribution to cumulative RCR (%)	Concern		
							Yes	No	
PFBS	< 0.006	> 17 000	> 2 833 333	> 680	< 0.000009	< 0.0004		√	N.A.
PFPS	0.1	> 17 000	> 170 000	> 680	< 0.0001	< 0.007		√	N.A.
PFHxS	1.2	> 17 000	> 14 167	> 680	< 0.002	< 0.09		√	↓
PFHpS	0.4	9 200	23 000	368	0.001	0.05		√	↓
PFOS	494	9 200	19	368	1.3	65.1	√		↔
PFOSA	2.3	9 200	4 000	368	0.006	0.3		√	↔
PFOSi	0.2	9 200	46 000	368	0.0005	0.03		√	↓
EtFOSA	0.7	9 200	13 143	368	0.002	0.09		√	N.A.
PFDS	0.2	9 200	46 000	123	0.002	0.08		√	N.A.
PFHpA	0.04	31 400	785 000	1 256	0.00003	0.002		√	N.A.
PFOA	11	31 400	2 855	1 256	0.01	0.4		√	↔
PFNA	109	17 800	163	712	0.2	7.4		√	↔
PFDA	22	8 900	405	119	0.2	9.0		√	↑
PFUnDA	15	8 900	593	119	0.1	6.1		√	↑
PFDoDA	1.5	8 900	5 933	119	0.01	0.6		√	↑
PFTrDA	24.6	8 900	362	119	0.2	10.0		√	↑
PFTeDA	5.8	8 900	1 534	119	0.05	2.4		√	↔
				Cumulative	≤ 2.1		√		

[a] – RCR = Exposure/DNEL, ratio < 1 = risk is considered controlled, ratio of > 1 = risk is considered not controlled.

Table 47. Margins of exposure (MOEs) and risk characterization ratios (RCRs) for hepatotoxicity in otters. A cumulative RCR is calculated by addition of RCRs for individual congeners. Congeners marked in bold represent congeners with original toxicity data.

Congener	Exposure (ng/g liver)	MOE Approach		RCR Approach					Trend
		POD (ng/liver)	MOE	DNEL (ng/g liver)	RCR[a]	Contribution to cumulative RCR (%)	Concern		
							Yes	No	
PFHxS	5	150 000	30 000	3 000	0.002	0.04		√	↔
PFOS	280	19 200	69	768	0.4	9.2		√	↓
PFOSA	30	19 200	640	768	0.04	1.0		√	↓
PFDS	2	19 200	9 600	256	0.008	0.2		√	↓
PFOA	15	14 200	947	284	0.05	1.3		√	↑
PFNA	125	57 000[b]	456	380	0.3	8.3		√	↑
PFDA	100	28 500[b]	285	63	1.6	40.0	√		↑
PFUnDA	75	28 500[b]	380	63	1.2	30.0	√		↓
PFDoDA	10	28 500[b]	2 850	63	0.2	4.0		√	↓
PFTrDA	13	28 500[b]	2 192	63	0.2	5.2		√	↓
PFTeDA	1.5	28 500[b]	19 000	63	0.02	0.6		√	↓
				Cumulative	3.9		√		

[a] – RCR = Exposure/DNEL, ratio < 1 = risk is considered controlled, ratio of > 1 = risk is considered not controlled.

[b] – LOAEL.

Table 48. Margins of exposure (MOEs) and risk characterization ratios (RCRs) for reproductive toxicity in otters. A cumulative RCR is calculated by addition of RCRs for individual congeners. Congeners marked in bold represent congeners with original toxicity data.

Congener	Exposure (ng/g liver)	MOE Approach		RCR Approach					Trend
		POD (ng/liver)	MOE	DNEL (ng/g liver)	RCR[a]	Contribution to cumulative RCR (%)	Concern		
							Yes	No	
PFHxS	5	> 17 000	> 3 400	> 680	< 0.007	< 0.27		√	↔
PFOS	280	9 200	33	368	0.8	27.8		√	↓
PFOSA	30	9 200	307	368	0.08	3.0		√	↓
PFDS	2	9 200	4 600	123	0.02	0.6		√	↓
PFOA	15	31 400	2 093	1 256	0.01	0.4		√	↑
PFNA	125	17 800	142	712	0.2	6.4		√	↑
PFDA	100	8 900	89	119	0.8	30.8		√	↑
PFUnDA	75	8 900	119	119	0.6	23.1		√	↓
PFDoDA	10	8 900	890	119	0.08	3.1		√	↓
PFTrDA	13	8 900	685	119	0.1	4.0		√	↓
PFTeDA	1.5	8 900	5 933	119	0.01	0.5		√	↓
				Cumulative	≤ 2.7		√		

[a] – RCR = Exposure/DNEL, ratio < 1 = risk is considered controlled, ratio of > 1 = risk is considered not controlled.

Table 49. Margins of exposure (MOEs) for reproductive toxicity in birds. Congeners marked in bold represent congeners with original toxicity data.

Congener	Exposure (ng/g egg)	POD (ng/g egg)	MOE	Trend	Concern	
					Yes	No
PFBS (Northern bobwhite quail, No effect)	< 0.08	> 51 000	> 637 500	N.A.		√
PFHxS (read-across from PFOS)	1.9	100	53	↓	√	
PFOS (White leghorn chicken, LOAEL, reduced hatchability)	220	100	0.45	↑	√	
PFOSA (read-across from PFOS)	< 0.1	100	> 1 000	N.A.		√
PFDS (White leghorn chicken, no effect)	2.3	> 10 000	> 4 348	↓		√
PFHxA (read-across from PFOA)	< 0.6	> 10 000	> 16 667	N.A.		√
PFHpA (read-across from PFOA)	< 1.4	> 10 000	> 7 143	N.A.		√
PFOA (White leghorn chicken, no effect)	< 2.2	> 10 000	> 4 545	N.A.		√
PFNA (read-across from PFUnDA)	2.3	> 10 000	> 4 348	↑		√
PFDA (read-across from PFUnDA)	9.6	> 10 000	> 1 042	↑		√
PFUnDA (White leghorn chicken, no effect)	9.7	> 10 000	> 1 031	↓		√
PFDoDA (read-across from PFUnDA)	5.6	> 10 000	> 1 786	↓		√
PFTrDA (read-across from PFUnDA)	14	> 10 000	> 714	↓		√
PFTeDA (read-across from PFUnDA)	4.9	> 10 000	> 2 041	↓		√
PFPeDA (read-across from PFUnDA)	1.1	> 10 000	> 9 091	↓		√

Table 50. Margins of exposure (MOEs) for toxicity to marine fish. The points of departure (PODs) represent different toxicological endpoints. Congeners marked in bold represent congeners with original toxicity data.

Congener	Exposure (ng/g liver)	POD (ng/g liver)	MOE	Concern	
				Yes	No
PFBS (Zebrafish, NOEC, early life-stage test, endpoints not stated)	< 0.6	250 000	> 416 667		√
PFHxS (read-across from PFOS)	1.3	54 x 10^6	41 538		√
PFOS (Zebrafish, LOEC, two-generation study, decreased F_1 body weight/size/survival)	18.7	54 x 10^6	2 888		√
PFOSA (read-across from PFOS)	7.1	54 x 10^6	7 606		√
PFDS (read-across from PFOS)	< 0.6	54 x 10^6	> 90 000		√
PFBA (Zebrafish, NOEC, prolonged early life-stage test, no effects)	< 0.6	> 2 000	> 3 333		√
PFHxA (read-across from PFOA)	< 0.6	> 320 000	> 533 333		√
PFHpA (read-across from PFOA)	< 0.6	> 320 000	> 533 333		√
PFOA (Rainbow trout, NOEC, early life-stage test, embryonal/juvenile mortality)	< 0.6	> 320 000	> 533 333		√
PFNA (Zebrafish, LOEC, long-term two-generation study, increased plasma T_3)	2.9	3 100	1 069		√
PFDA (read-across from PFNA)	2.1	3 100	1 476		√
PFUnDA (read-across from PFNA)	3.0	3 100	1 033		√
PFDoDA (read-across from PFNA)	< 0.6	3 100	> 5 167		√
PFTrDA (read-across from PFNA)	3.3	3 100	939		√
PFTeDA (read-across from PFNA)	< 0.6	3 100	> 5 167		√
PFPeDA (read-across from PFNA)	< 0.6	3 100	> 5 167		√
6:2 FTSA (read-across from PFOS)	< 0.6	54 x 10^6	> 90 000		√

Table 51. Margins of exposure (MOEs) for toxicity to freshwater fish. The points of departure (PODs) represent different toxicological endpoints. Congeners marked in bold represent congeners with original toxicity data.

Congener	Exposure (ng/g liver)	POD (ng/g liver)	MOE	Concern	
				Yes	No
PFBS (Zebrafish, NOEC, early life-stage test, endpoints not stated)	< 0.2	250 000	> 1.3 x 10^9		√
PFHxS (read-across from PFOS)	11.3	54 x 10^6	4.7 x 10^6		√
PFOS - Contaminated lake (Zebrafish, LOEC, two-generation study, decreased F_1 body weight/size/survival)	16 300	54 x 10^6	3 313		√
PFOS - Reference lake (Zebrafish, LOEC, two-generation study, decreased F_1 body weight/size/survival)	97	54 x 10^6	556 701		√
PFOSA (read-across from PFOS)	1 030	54 x 10^6	52 427		√
PFDS (read-across from PFOS)	8.7	54 x 10^6	6.2 x 10^6		√
PFBA (Zebrafish, NOEC, prolonged early life-stage test, no effects)	< 4.4	> 2 000	> 454 545		√
PFHxA (read-across from PFOA)	14.8	> 320 000	> 2.2 x 10^7		√
PFHpA (read-across from PFOA)	< 0.02	> 320 000	> 1.6 x 10^{10}		√
PFOA (Rainbow trout, NOEC, early life-stage test, embryonal/juvenile mortality)	4.3	> 320 000	> 7.4 x 10^7		√
PFNA (Zebrafish, LOEC, long-term two-generation study, increased plasma T_3)	0.1	3 100	3.1 x 10^7		√
PFDA (read-across from PFNA)	60.3	3 100	51 410		√
PFUnDA (read-across from PFNA)	25.7	3 100	120 623		√

6.2.1 Risk characterization results/discussion

The result of the environmental risk characterization indicate for the investigated mammals – seals and otters, a cause for concern with regard to hepatotoxicity and reproductive toxicity based on available toxicity and exposure data, by using either the MOE approach (i.e. MOE ≤ 100) or by the RCR approach (i.e. RCR ≥ 1).

For hepatotoxicity in seals, a cause for concern was indicated for PFOS with a MOE of 39, but not for any other congener (Table 43). In contrast, with the RCR approach no cause for concern was shown for individual congeners, but for all congeners combined with a cumulative RCR of ≤ 2.1 and with PFOS, PFTrDA, and PFDA being the dominant contributors. For reproductive toxicity in seals, a cause for concern was indicated for PFOS with a MOE of 19 (Table 44). Using the RCR-approach, a cause for concern was indicated for PFOS as well as for all congeners combined, with RCRs of 1.3 and ≤ 2.1, respectively.

For hepatotoxicity in otters, a cause for concern was indicated for PFOS with a MOE of 69, but not for any other congener (Table 45). With the RCR approach, concern was instead indicated for PFDA and PFUnDA, as well as all congeners combined, with RCRs of 1.6, 1.2 and 3.9, respectively. This is partly due to large assessment factors that were used to derive the DNELs for PFDA and PFUnDA. For reproductive toxicity in otters, a cause for concern was indicated for PFOS and PFDA with MOEs of 33and 89, respectively (Table 46). In contrast, using the RCR-approach, no cause for concern was indicated for individual congeners, but for all congeners combined with a RCR ≤ 2.7.

The MOEs and/or RCRs for seals and otters are based on the average PFAS-levels at the latest time-point in temporal studies, and it should be noted that the levels can be higher on an individual basis, which could result in lower MOEs and higher RCRs.

For reproductive toxicity in birds, a cause for concern was indicated for PFOS, with a MOE of 0.45 (Table 47), i.e. with an exposure level exceeding the identified toxic effect level. In addition, a MOE of 53 was derived for PFHxS, based on read-across data from PFOS.

For marine fish, MOEs ranged from 939–> 533 000, i.e. the data does not indicate any cause for concern. Similarly for freshwater fish, the available data does not indicate any cause for concern based on MOEs ranging from approximately 3300 (in a PFOS-contaminated lake) to > 1.6×10^{10} for PFHpA. It should be noted that the toxicity data for fish is highly uncertain.

7. Conclusion

7.1 Human health

This is the first human health risk assessment investigating a large number of PFASs, individually and in combination.

The results showed that at current blood/serum levels of the general population no cause for concern was identified for hepatotoxicity or reproductive toxicity, neither for congeners assessed individually or combined. The levels can, according to risk assessment principles, be considered well below those that would cause concern. However, it should be kept in mind that the congeners herein represent only those that have been measured in the Swedish population and that other classes of PFASs, such as perfluorinated phosphonates (PAPs) that has recently been discovered and detected in human serum (D'Eon., 2009), are not included. It should also be noted that one subpopulation that had consumed fish contaminated with PFOS showed RCRs that were, or were close to, being of concern.

For the occupationally exposed subpopulation (professional ski waxers), a cause for concern was identified for hepatotoxicity based on single and cumulative PFASs exposure, as well as for reproductive toxicity based on cumulative PFASs exposure. It should be noted, however, that this group comprises a very limited number of people in Sweden. Regarding hepatotoxicity, humans appear to be less sensitive than rodents to PFAS-induced hepatotoxicity. PFASs production workers have displayed serum levels of PFOS and PFOA of up to 10 000 and 12 700 ng/ml, approximately 200 and 10 times higher, respectively, without any changes in biomarkers of hepatotoxicity (Olsen et al., 2003). However, the hepatotoxic effects in rodents may also be viewed upon as biomarker of PFASs toxicity in general, since other effects on e.g. lipid metabolism occur at similar dose-levels. Correlations between PFASs exposure and effects on lipid metabolism have been observed in epidemiological studies, though with increased serum levels of lipids and cholesterol as opposed to decreased levels in laboratory animals. Regarding reproductive toxicity, epidemiological studies in highly exposed populations, e.g. populations exposed via contaminated drinking water and PFASs production workers, have not found any correlations between PFASs-levels and e.g. pregnancy outcomes, birth weight or birth defects.

A cause for concern was identified for other endpoints – immunotoxicity and disrupted mammary gland development and growth (obesity), for both individuals exposed via the environment and professional ski waxers. Since these effects occur at levels below current human exposure, high RCR values were derived. However, the data for these endpoints are limited and more studies are needed.

This risk assessment contains data gaps and uncertainties. The most important is the lack of toxicological data for some congeners, which required read-across extrapolations for these congeners and therefore the toxicity data

used as POD for these congeners may not be fully accurate. Also, the human relevance of the endpoints investigated herein is not clearly established; however, as the mode and mechanisms of action for PFASs remain unknown, human relevance has to be assumed.

7.2 Environmental health

The result of the environmental risk characterization indicate that for the investigated mammalian species – seals and otters, there is a cause for concern with regard to hepatotoxicity and reproductive toxicity based on the available toxicity and exposure data, for either individual congeners and/or all congeners combined. The different outcomes are due to that two different approaches were being used, the MOE approach where all MOE ≤ 100 are considered inadequate by default, and the RCR-approach where uncertainties in the data are taken into account when deriving DNELs, by the use of assessment factors. This can lead to that congeners with a solid dataset require less safety margins and congeners with less data require a greater safety margin. With the MOE-approach, a cause for concern was identified for PFOS for both endpoints in seals and otters, a result of PFOS being the dominant congener in these species. Also PFDA and PFUnDA could be considered of concern in otters. It should be noted that the MOEs and/or RCRs for seals and otters are based on the average PFASs-levels at the latest time-point in temporal studies, and it should be noted that the levels can be higher on an individual basis, which could result in lower MOEs and higher RCRs.

For reproductive toxicity in birds, a cause for concern was indicated for PFOS where the highest level in peregrine falcons eggs (220 ng/g egg) sampled in 2006 exceeds the toxic effect level identified in one study (100 ng/g egg, LOAEL, Molina et al., 2006), and where the average PFOS level (83 ng/g egg) is close to the toxic effect level. Thus, it cannot be excluded that these levels of PFOS in the eggs could give rise to adverse effects. Continued monitoring of PFASs levels in eggs is therefore warranted. In addition, an inadequate MOE was obtained for PFHxS.

For marine as well as freshwater fish the available data does not indicate any cause for concern, even in waters contaminated by PFOS from e.g. runoffs from airports. However, it should be noted that the data for fish, monitoring as well as toxicity data, is highly uncertain and that uncertain assumption and extrapolations have been performed in this assessment.

There are data gaps and uncertainties in the environmental risk assessment. The major of those is the lack of toxicological data for some congeners, where extrapolations thus have been needed to perform, such as read-across for lack of toxicity and conversion of serum levels to hepatic levels. However, the extrapolations have to most extent been performed in a conservative manner.

8. Data gaps and future research needs

The following data gaps and need for future activities that would improve risk assessment of PFASs were identified during the course of the project:

- Biomonitoring of new and "emerging" PFASs that were not included in this project, e.g. perfluoroalkylphosponates (PAPs).
- Toxicological data with internal dose measurements for PFAS congeners that were subject to read-across extrapolations.
- Further investigation on the potential toxicity of PFASs to the immune system and mammary gland development, both toxicological (with internal dose measurements) and epidemiological studies.
- Mechanistic data on PFASs, particularly their mode of action, to allow better and more confident extrapolations of animal data to humans.
- Continued monitoring of PFASs in birds eggs, e.g. Peregrine Falcon and Guillemot eggs, to monitor temporal trends.
- More studies on the reproductive toxicity of PFASs in birds, with either direct *in ovo* exposure or, if exposure via another route, measurement of the levels in eggs for comparison to environmental monitoring in eggs.
- More studies on the toxicity of PFASs in fish including measurements of PFASs in tissues (liver, muscle).

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Environmental and Health Risk Assessment of Perfluoroalkylated and Polyfluoroalkylated Substances (PFASs) in Sweden

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This report summarizes the outcome of a project with the purpose and aim to present new information and knowledge about possible environmental- and health risks of perfluoroalkylated and polyfluoroalkylated substances (PFASs) in the Swedish population and in Swedish biota.

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