Opinion of the Scientific Panel on Contaminants in the Food chain on perfluorooctane sulfonate (PFOS), perfluorooctanoic acid (PFOA) and their salts

Benford, D.; de Boer, J.; Carere, A.; di Domenico, A.; Johansson, N.; Schrenk, D.; Schoeters, G.; de Voogt, P.; Dellatte, E.

Publication date
2008

Published in
EFSA Journal

The EFSA Journal (2008) 653, 1-131

Perfluorooctane sulfonate (PFOS), perfluorooctanoic acid (PFOA) and their salts

Scientific Opinion of the Panel on Contaminants in the Food chain[1]

(Question N° EFSA-Q-2004-163)

Adopted on 21 February 2008

PANEL MEMBERS

Jan Alexander, Guðjón Atli Auðunsson, Diane Benford, Andrew Cockburn, Jean-Pierre Cravedi, Eugenia Dogliotti, Alessandro Di Domenico, María Luisa Fernández-Cruz, Johanna Fink-Gremmels, Peter Fürst, Corrado Galli, Philippe Grandjean, Jadwiga Gzyl, Gerhard Heinemeyer, Niklas Johansson, Antonio Mutti, Josef Schlatter, Rolaf van Leeuwen, Carlos van Peteghem, Philippe Verger.

SUMMARY

Perfluoroalkylated substances (PFAS) is the collective name for a vast group of fluorinated compounds, including oligomers and polymers, which consist of neutral and anionic surface active compounds with high thermal, chemical and biological inertness. Perfluorinated compounds are generally hydrophobic but also lipophobic and will therefore not accumulate in fatty tissues as is usually the case with other persistent halogenated compounds. An important subset is the (per)fluorinated organic surfactants, to which perfluorooctane sulfonate (PFOS) and perfluorooctanoic acid (PFOA) belong.

The analytical detection method of choice for PFOS and PFOA is currently liquid chromatography-mass spectrometry/mass spectrometry (LC-MS/MS), whereas both LC-

[1] For citation purposes: Opinion of the Scientific Panel on Contaminants in the Food chain on Perfluorooctane sulfonate (PFOS), perfluorooctanoic acid (PFOA) and their salts, *The EFSA Journal* (2008) Journal number, 653, 1-131.

MS/MS and gas chromatography-mass spectrometry (GC-MS) can be used for the determination of precursors of PFOS and PFOA. There are few reports of analysis of food items using these methods. Due to the substantial lack of suitable analytical data, many assumptions have been made in order to derive exposure estimates. Therefore, figures on levels in food and exposure provided in this opinion should be taken as indicative.

PFOS, PFOA and other perfluorinated organic compounds have been widely used in industrial and consumer applications including stain- and water-resistant coatings for fabrics and carpets, oil-resistant coatings for paper products approved for food contact, fire-fighting foams, mining and oil well surfactants, floor polishes, and insecticide formulations. A number of different perfluorinated organic compounds have been widely found in the environment.

PFOS

PFOS has been analysed in a limited number of European environmental and food samples (mainly fish). The PFOS concentrations are almost invariably higher than PFOA concentrations and the PFOS concentrations in fish liver are consistently higher than those in fillet. PFOS has been shown to bioaccumulate in fish and a kinetic bioconcentration factor has been estimated to be in the range 1000 – 4000. The time to reach 50% clearance in fish has been estimated to be around 100 days.

Fish seems to be an important source of human exposure to PFOS, although the data might be influenced by results of studies in relatively polluted areas, which is likely to over-estimate exposure from commonly consumed fish. There are very few data, especially for Europe, that can serve as reliable indicators of the relative importance of most other kinds of food. Drinking water is estimated to contribute less than 0.5% of the indicative exposure. The importance of fish is, however, not supported by all studies, indicating other important sources of human exposure might exist which have not yet been identified. It is possible that additional exposure to PFOS could result from precursors and other sources.

Such possible sources could be related to food (e.g. *via* packaging material or cookware) or be a result of more direct exposure from the technosphere (e.g. household dust). Based primarily on the available data for fish and fishery products, indicative estimates of dietary exposure to PFOS were 60 ng/kg body weight (b.w.) per day for average consumers, and 200 ng/kg b.w. per day for high consumers of fish. In contrast, recent studies have indicated much lower exposures, demonstrating the uncertainty in the assessments. The importance of possible pathways of non-food human exposure to PFOS has been estimated to decrease when moving from childhood into adulthood. The total contribution from non-food articles was estimated to be less than 2% compared to the average total PFOS exposure. In individuals with high fish consumption, the percentage contribution from non-food exposure is expected to be lower.
Following absorption, PFOS is slowly eliminated and therefore accumulates in the body. PFOS shows moderate acute toxicity. In subacute and chronic studies the liver was the major

target organ and also developmental toxicity was seen. Other sensitive effects were changes in thyroid hormones and high density lipoprotein (HDL) levels in rats and Cynomolgus monkeys. PFOS induced liver tumours in rats, which appears to be due to a non-genotoxic mode of action.

Epidemiological studies in PFOS exposed workers have not shown convincing evidence of increased cancer risk. An increase in serum T3 and triglyceride levels was observed, which is the opposite direction to the findings in rodents and monkeys. The very few epidemiological data available for the general population do not indicate a risk of reduced birth weight or gestational age.

From a subchronic study in Cynomolgus monkeys, the Scientific Panel on Contaminants in the Food Chain (CONTAM) identified 0.03 mg/kg b.w. per day as the lowest no-observed-adverse-effect level (NOAEL) and considered this a suitable basis for deriving a Tolerable Daily Intake (TDI). The CONTAM Panel established a TDI for PFOS of 150 ng/kg b.w. per day by applying an overall uncertainty factor (UF) of 200 to the NOAEL. An UF of 100 was used for inter and intra-species differences and an additional UF of 2 to compensate for uncertainties in connection to the relatively short duration of the key study and the internal dose kinetics.

The CONTAM Panel noted that the indicative dietary exposure of 60 ng/kg b.w. per day is below the TDI of 150 ng/kg b.w. but that the highest exposed people within the general population might slightly exceed this TDI.

The CONTAM Panel recognised that a significant part of the body burden could result from exposure to other sources and also from precursors that could be transformed into PFOS in the body. However, there was no reliable information on body burdens in humans, and therefore the Panel decided to compare blood levels in humans and animals recognising the uncertainties in attainment of steady-state conditions. The margin between serum levels in the monkeys at the NOAEL and the serum levels in the general population was between 200 and 3,000. Given this margin, the Panel considered it unlikely that adverse effects of PFOS are occurring in the general population.

PFOA

PFOA has been analysed in a limited number of European environmental and food samples (mainly fish) and concentrations are almost invariably lower than PFOS concentrations. PFOA has been shown to bioaccumulate in fish but probably less than PFOS. The importance of possible pathways of non-food human exposure to PFOA has been estimated to decrease when moving from childhood into adulthood. For PFOA, the total contribution from the non-food sources, mainly indoor exposure, could be as high as 50% compared to the estimated average dietary exposure to PFOA.

Fish seems to be an important source of human exposure to PFOA, although the data might be influenced by results of studies in relatively polluted areas, which is likely to over-estimate exposure from commonly consumed fish. There are very few data, especially for Europe, that can serve as reliable indicators of the relative importance of most other kinds of food. Drinking water is estimated to contribute less than 16% to the indicative exposure. Based on the limited data, the CONTAM Panel identified the indicative average and high level dietary exposures of 2 and 6 ng/kg b.w. per day, respectively. Persons with higher fish consumption do not always show higher levels of PFOA in blood compared to persons with "normal" fish consumption. It is possible that additional exposure to PFOA could result from non food sources and precursors.

PFOA is readily absorbed. Elimination is dependent on active transport mechanisms which vary between different species, and between sexes in some species. PFOA shows moderate acute toxicity. In sub acute and chronic studies, PFOA affected primarily the liver and can cause developmental and reproductive toxic effects at relatively low dose levels in experimental animals. It increased the tumour incidence in rats, mainly in the liver. Based on the weight of evidence at present, the carcinogenic effects in rats appear to be due to indirect/non-genotoxic modes of action.

Epidemiological studies in PFOA-exposed workers do not indicate an increased cancer risk. Some have shown associations with elevated cholesterol and triglycerides, or with changes in thyroid hormones, but overall there is no consistent pattern of changes. In two recent studies, PFOA exposure of pregnant women, measured by maternal and/or cord serum levels was associated with reduced birth weight. The Panel noted that these observations could be due to chance, or to factors other than PFOA.

The lowest NOAEL identified of 0.06 mg/kg per day, originated from a subchronic study in male rats, whereas results from long-term studies indicated higher NOAELs for effects on the liver. The Panel noted that the 95% lower confidence limit of the benchmark dose for a 10% increase in effects on the liver (BMDL10) values from a number of studies in mice and male rats were in the region of 0.3 - 0.7 mg/kg b.w. per day. Therefore, the CONTAM Panel concluded that the lowest BMDL10 of 0.3 mg/kg b.w. per day was an appropriate point of departure for deriving a TDI. The CONTAM Panel established a TDI for PFOA of 1.5 µg/kg b.w. per day by applying an overall UF of 200 to the BMDL10. An UF of 100 was used for inter- and intra-species differences and an additional UF of 2 to compensate for uncertainties relating to the internal dose kinetics.

The CONTAM Panel noted that the indicative human average and high level dietary exposure for PFOA of 2 and 6 ng/kg b.w. per day, respectively, are well below the TDI of 1.5 µg/kg b.w. per day.

The serum levels in rats at the BMDL10 are expected to be in the region of three orders of magnitude higher than in serum levels of PFOA from European citizens who do not have occupational exposure. Given this margin, the CONTAM Panel considered it unlikely that adverse effects of PFOA are occurring in the general population, but noted uncertainties with regards to developmental effects.

Finally the CONTAM Panel recommended that further data on PFAS levels in food and in humans would be desirable, particularly with respect to monitoring trends in exposure.

KEY WORDS

Perfluorooctane sulfonate (PFOS), perfluorooctanoic acid (PFOA), occurrence, food, exposure assessment, toxicology, risk characterisation, tolerable daily intake, BMDL10

Table of content

BACKGROUND AS PROVIDED BY REQUESTOR

Perfluorinated (fully fluorinated) organic compounds such as perfluorooctane sulfonate (PFOS)[2] represent a class of compounds showing high thermal, chemical and biological inertness. They can be widely found in the environment primarily resulting from anthropogenic sources. PFOS and other perfluorinated organic compounds are widely used in industrial and consumer applications including stain-resistant coatings for fabrics and carpets, oil-resistant coatings for paper products approved for food contact, fire-fighting foams, mining and oil well surfactants, floor polishes, and insecticide formulations (Renner, 2001). PFOS and many other perfluorinated compounds are oleophobic and will therefore not accumulate in fatty tissues as is usually the case with other persistent halogenated compounds. PFOS has been shown to bioaccumulate in fish and a kinetic bioconcentration factor has been estimated to be in the range 1000 – 4000, where the higher figure represents non-edible parts of the fish. The time to reach 50% clearance in fish has been estimated to be around 100 days.

Most of the available information on the toxic potential of the perfluorinated organic compounds is related to PFOS and its salts. In experimental animals, exposure to PFOS results in hepatotoxicity and increased mortality. In addition, a long-term study in rats has shown that exposure to PFOS can induce hepatocellular adenomas and thyroid follicular cell adenomas. In pregnant rodents PFOS led to severe birth defects and growth retardation in the offspring. Epidemiological studies have suggested an association between PFOS exposure and the incidence of bladder cancer.

So far, a few assessments have been carried out in relation to perfluorinated organic compounds. The Organisation for Economic Co-operation and Development (OECD) published a hazard assessment of PFOS and its salts in 2002 (OECD, 2002). In 2003, the United States Environmental Protection Agency (U.S. EPA) released a preliminary risk assessment of the developmental toxicity associated with exposure to perfluorooctanoic acid and its salts (U.S. EPA, 2003). The OECD concluded that PFOS is persistent, bioaccumulative and toxic to mammalian species. The OECD identified a no-observed-adverse-effect (NOAEL) of 0.1 mg/kg b.w. per day, based on the results from a two-generation study in rats.

PFOS and a number of related perfluorinated organic sulfonates have been found in the environment in fish, birds and mammals. It is however not well understood how, and *via* which routes, these substances are transported into the environment. There is some information on current levels of PFOS in the general population, revealing a rather uniform burden with respect to age, sex, etc., but there is almost no information on the most important routes of human exposure. As these substances are found in environmental biota, it is likely that food is a human exposure route. The relative contribution of the various foodstuffs to the total human exposure is, however, not known. There is limited information indicating an

[2] http://ecb.jrc.it/classlab/2405a2_S_PFOS.doc

increasing trend in levels of PFOS and related substances in the environment (~ 10% per year). However, no information about temporal trends in exposure or on body burdens in the general population is available.

In summary, PFOS and other perfluorinated organic compounds:

- are / have been broadly used in various industrial and consumer applications
- are extremely resistant towards thermal, chemical and biological degradation processes,
- have entered the environment as a result of the before mentioned applications,
- tend to accumulate in the food chain, and
- have been reported to produce a wide range of toxic effects.

Based on the above aspects and in view of preliminary information indicating increasing levels in the environment, reported levels of these substances in the food chain and in the general population, there is a clear need to improve the database to assess the potential risks associated with the human exposure to this class of substances.

TERMS OF REFERENCE AS PROVIDED BY REQUESTOR

The Scientific Panel on Contaminants in the Food Chain (CONTAM) is requested by the European Food Safety Authority:

- To prepare an opinion on the importance of food and the relative contribution of the different foodstuffs and food contact materials to human exposure to PFOS and its salts. The Panel should consider existing hazard assessments and also the information provided for the assessment of the use of a perfluorinated compound in food contact materials by the Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food (AFC).

- To advise on further steps in relation to the risk assessment of perfluorinated organic compounds such as PFOS on the basis of the available information on the toxic properties of these compounds and the additional information on the relative contribution of food and other sources to total human exposure.

Interpretation of the terms of reference by the CONTAM Panel

The term “PFOS and its salts” is interpreted as PFOS in its uncharged and anionic form.

Applying this interpretation, perfluorooctanoic acid (PFOA) is not included in the TOR although “risk assessment of perfluorinated organic compounds such as PFOS” in the second

bullet allows for a wider interpretation. Directive 2006/122/EC[3] of the European Parliament and of the Council of 12 December 2006 states that PFOA and its salts are suspected to have a similar risk profile to PFOS. The CONTAM Panel has also considered PFOA and related compounds during its task on PFOS, as information on PFOA was available from the same studies. Furthermore, PFOS and PFOA could contaminate food and feed *via* similar pathways.

ACKNOWLEDGEMENT

EFSA wishes to thank the working group members Diane Benford, Jacob de Boer, Angelo Carere, Alessandro Di Domenico, Niklas Johansson, Dieter Schrenk, Greet Schoeters, Pim de Voogt and *ad hoc* expert Elena Dellatte.

ASSESSMENT

1. Introduction

This opinion is based on literature searches performed using the web pages of international and national regulatory bodies such as the U.S. Environmental Protection Agency, Health Canada, the Organisation for Economic Co-operation and Development (OECD), the UK, Germany and Sweden as well as scientific search engines such as Pubmed from NCBI (1966 to February 2008). Also a number of Good Laboratory Practice (GLP) compliant studies carried out on behalf of major manufacturers of perfluorinated compounds referred to in this opinion are not published in the open literature, but the results have been made available to the European Food Safety Authority (EFSA) and to the public domain through U.S. Environmental Protection Agency (EPA) dockets.

Perfluoroalkylated substances (PFAS) is the collective name for a vast group of fluorinated compounds, including oligomers and polymers. The group comprises several hundreds of compounds, and can be divided into 23 categories (NCEHS, 2001). Important subsets are the (per)fluorinated organic surfactants and the fluorinated organic polymers such as perfluorooctane sulfonate (PFOS) and perfluorooctanoic acid (PFOA). In the literature many individual compounds as well as groups of compounds are described under more than one acronym and also compounds or groups are discussed under identical acronyms.

Perfluorooctane sulfonate (PFOS) is a completely fluorinated compound containing eight carbon atoms and a sulfonate group. Due to its surface-active properties it is used in a wide variety of applications. PFOS can be formed by degradation from a large group of substances, referred to as PFOS-related substances, as defined by OECD 2002, which may be simple salts of PFOS, e.g., potassium, lithium, ammonium, potassium, or polymers that contain PFOS.

[3] OJ L 372, 27.12.2006, p. 32-34.

The majority of PFOS related substances are high molecular weight polymers in which PFOS is only a fraction of the polymer and final product (OECD, 2002).

Perfluorooctanoic acid (PFOA) is a completely fluorinated organic acid that is produced synthetically as its salts. It can also appear as a result of degradation of some precursors e.g. fluorotelomer alcohols. PFOA is primarily used as an emulsifier in industrial applications, for example in the production of fluoropolymers. The typical structure has a linear chain of eight carbon atoms. The PFOA derivative that is most widely used and therefore of most concern is the ammonium salt (APFO).

The U.S. EPA, Health Canada and national agencies have issued preliminary human health risk assessments on PFOA, PFOS or PFOS- and PFOA-related substances (Health Canada, 2004; KEMI, 2004a and b; U.S. EPA, 2005; COT, 2006 a and b; BfR, 2006).

1.1 Selection of compounds

Recently both PFOS and PFOA have raised scientific interest because of their wide-spread occurrence in the environment and their ability to bioaccumulate. Also, recent studies indicate adverse effects of these compounds on organisms. There are few data on the occurrence of PFOS and PFOA in food. A study of PFOS has been undertaken by Risk & Policy Analysts Limited (Brooke *et al*., 2004) commissioned by the UK Environment Agency.

1.2 Chemical identity

Polyfluorinated alkylated substances (R-X) are compounds consisting of a hydrophobic alkyl chain, R, of varying length (typically C4 to C16) and a hydrophilic end group, X. The hydrophobic part may be fully [R=F(CF_2)$_n$-]or partially fluorinated. When fully fluorinated the molecules are also called perfluorinated substances. Their general structure is given in Figure 1.

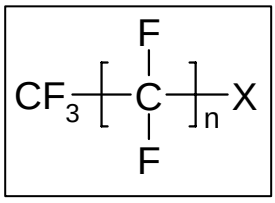

Figure 1. General structure of perfluorinated alkylated substances

The hydrophilic end group can be neutral, or positively or negatively charged. The resulting compounds are non-ionic, cationic or anionic surface active agents due to their amphiphilic character. Examples of anionic end groups are the sulfonates (-SO_3^-), which include PFOS,

the carboxylates (-COO^-) which include PFOA, and the phosphates (-OPO_3^-). In cationic PFAS, the fluorinated hydrophobic part is attached to e.g. a quaternary ammonium group. Examples of neutral end groups X are: -OH, -SO_3NH_2. Both PFOS and PFOA are perfluorinated compounds and appear to be highly persistent, because of the strong covalent C-F bond.

Many of the neutral PFAS are considered to be potential precursors of PFOS (e.g., perfluorooctane sulfonamide (PFOSA), *N*-ethyl perfluorooctane sulfonamidoethanol (*N*-EtFOSE) or PFOA (e.g., 8:2 fluorotelomer alcohol, PFOSA and *N*-EtFOSE). Because the precursors include products that are not fully fluorinated, some of the partially fluorinated alkylated substances are also discussed in this opinion. For the partially fluorinated compounds the position and number of fluorines determine the characteristics of the compound. This opinion only considers those partially fluorinated compounds that contain a -CH_2CH_2- moiety between the hydrophilic part and the fully fluorinated remaining carbon chain: $F(CF_2)_n$-CH_2CH_2-X. These partially fluorinated compounds are called telomer substances and derive their name from the telomerisation production process (see section 1.3). The telomerisation process results only in compounds consisting of a linear alkyl chain with an even number of carbon atoms.

1.2.1 PFOS

Chemical name: Perfluorooctane sulfonate (PFOS)
Molecular formula: $C_8F_{17}SO_3^-$
CAS number: 2795-39-3

Synonyms PFOS

1-Octanesulfonic acid, 1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-heptadecafluoro;
1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-heptadecafluoro-1-octanesulfonic acid;
1-Octanesulfonic acid, heptadecafluoro-;
1-Perfluorooctanesulfonic acid;
Heptadecafluoro-1-octanesulfonic acid;
Perfluoro-n-octanesulfonic acid;
Perfluoroctanesulfonic acid;
Perfluoroctylsulfonic acid.

The physical and chemical properties of the potassium salt of PFOS are listed in Table 1. The chemical structure of the potassium salt of PFOS is shown in Figure 2.

Table 1. Physical and chemical properties of PFOS potassium salt. (Data from OECD, 2002, unless otherwise noted).

Property	Value
Appearance at normal temperature and pressure	White powder
Molecular weight	538 g/mol
Vapour Pressure	3.31×10^{-4} Pa (20 ºC)
Water solubility in pure water	519 mg/L (20 ± 0,5ºC) 680 mg/L (24 - 25ºC)
Melting point	> 400 ºC
Boiling point	Not measurable
Log K_{OW}	Not measurable
Log K_{OC}[4]	2.57 (Higgins and Luthy, 2006)
Log K_D[4]	0.30-1.04 (de Voogt *et al.*, 2006a); 0.87-1.55 (Beach *et al*., 2006)
Air-water partition coefficient	$< 2 \times 10^{-6}$ (3M Company, 2003)
Henry's Law Constant (calculated)	3.05×10^{-9} atm. m^3/mol pure water
pK_a	-3.3 (calculated value for acid, Brooke *et al.*, 2004)

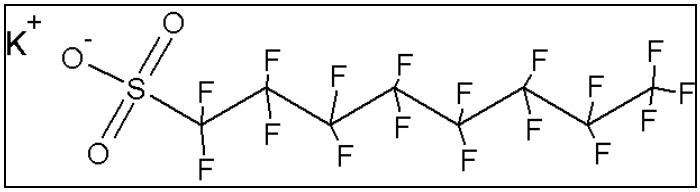

Figure 2. Structural formula of PFOS as its potassium salt

PFOS is a fully fluorinated anion, which is commonly used as a salt (potassium, sodium, ammonium) or incorporated into larger polymers. The schematic structure of perfluoroalkane sulfonate substances is given in Figure 3.

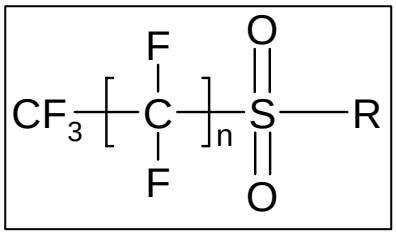

Figure 3. Schematic structure of perfluoroalkane sulfonates

R is equal to any given functional group such as OH, NH_2, etc. For PFOS-related substances, n = 7.

[4] Data refer to the anion rather than to the the salt

PFOS can be formed by environmental microbial degradation or by metabolism by higher organisms of PFOS-related substances, i.e., molecules containing the PFOS-moiety depicted in Figure 3. PFOS-related substances have been defined somewhat differently in different contexts and there are currently a number of lists of PFOS-related substances (Table 2). The lists contain varying numbers of PFOS-related substances that are thought to have the potential to break down to PFOS. The lists overlap to varying extents and it is therefore not clearly evident how many substances are believed to be precursors to PFOS.

Table 2. Number of PFOS-related substances as proposed by UK Department for Environmental, Food and Rural Affairs (DEFRA), U.S. EPA, Organisation for Economic Co-operation and Development (OECD) and the Convention for the Protection of the Marine Environment of the North-East Atlantic (OSPAR).

Source	Number of PFOS-related substances
UK DEFRA (2004)	96
U.S. EPA (2002)	88
OECD (2002)	172 (22 classes of PFAS)
OSPAR (2002)	48

Recently, the OECD has presented draft lists of PFOS, PFAS, PFOA and PFCA and their respective related compounds (OECD, 2005a and b).

1.2.2 PFOA

Chemical name: perfluorooctanoic acid
Molecular formula: C_8 H F_{15} O_2
CAS number 335-67-1

Synonyms to PFOA
2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-pentadecafluorooctanoic acid; perfluoroheptanecarboxylic acid; perfluoro-n-octanoic acid; Fluorad FC-26; perfluorocaprylic acid.

PFOA is a completely fluorinated organic acid. The free acid is expected to completely dissociate in water, leaving the anionic carboxylate in the water and the perfluoroalkyl chain on the surface. At pH 4, about 6% of the molecules will be undissociated. In aqueous solutions, individual molecules of PFOA anion loosely associate on the water surface and partition between the air/water interface (U.S. EPA, 2005). Water solubility has been reported for PFOA, but it is unclear whether these values are for a microdispersion of micelles, rather than true solubility.

The dissociated acid (PFO) has a negligible vapour pressure, high water solubility, and moderate sorption to solids. Based on these properties, accumulation in surface waters is expected (Prevedouros *et al.,* 2006).

The chemical structure of PFOA is presented in Figure 4.

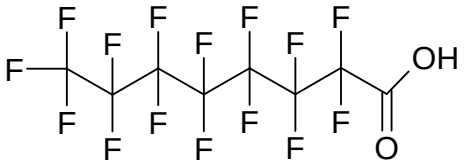

Figure 4. Chemical structure of PFOA

PFOA can enter the environment from direct and indirect sources. Direct sources include the manufacture and use of PFOA, whereas indirect sources are reaction impurities or (bio)degradation of related compounds (Prevedouros *et al.*, 2006). Indirect sources mentioned in the literature include *N*-EtFOSE, *N*-methyl perfluorooctanesulfonamidoethanol (*N*-MeFOSE), perfluorosulfonamides, and fluorotelomer raw materials (Prevedouros *et al.*, 2006). The transformation pathways include biodegradation (Wang *et al.*, 2005a and b), reaction with OH_x, ozonolysis (Ellis and Mabury, 2003; Ellis *et al.*, 2004; Vesine *et al.*, 2000).

Table 3. Physical and chemical properties of PFOA[a)] (Data from U.S. EPA, 2005 unless otherwise noted).

Property	Value
Appearance at normal temperature and pressure	White powder/waxy white solid
Molecular weight	414.1 g/mol
Vapour Pressure	0.1 kPa (20 ºC) 10 mm Hg (25 ºC) 4.2 Pa (25ºC) (APFO: 0.0081 Pa at 20ºC)
Water solubility in pure water	3.4 g/L 4.1 g/L (22 ºC) 9.5 g/L (25 ºC)
Melting point	45-50 ºC
Boiling point	189-192 ºC (736 mm Hg)
Log K_{OW}	Not measurable (APFO: 0.7; 3M Company, 1979)
Log K_{oc}	2.06 (Higgins and Luthy, 2006)
Log K_D	-0.22-0.55 (deVoogt *et al.*, 2006a]); -0.39-0.94 soils (DuPont, 2003a), 1.10-1.57 sludge (DuPont, 2003)
Air-water partition coefficient	Not available
Henry's Law constant	Cannot be estimated [b)]
pK_a	2.5, 2 to 3 (Prevedouros *et al.*, 2006)

a) As free acid unless otherwise stated

b) The vapour pressure of the pure solid is sufficient to sustain mg/kg concentrations of vapour in the atmosphere, but in practice this is unlikely as PFOA will dissociate in aqueous media thereby reducing its vapour pressure above aqueous solutions. For this reason the Henry's Law constant cannot be estimated from the vapour pressure and solubility.

From the data presented in Tables 1 and 3 it can be concluded that both PFOS and PFOA dissolve readily in water, with PFOA having the highest aqueous solubility. In water at environmentally relevant pH values (pH = 3 - 8), PFOS will occur in an entirely dissociated (ionised) form, whereas about 6% of PFOA molecules be protonated at pH 4 (at pH 7, only 3 - 6 in 100,000 molecules of PFOA are protonated, with the remaining being dissociated).

1.3 Synthesis

Information in this section is taken from the 3M assessment (3M Company, 2003), the OECD hazard assessment (OECD, 2002) *via* the report from UK Environment Agency (Brooke *et al.*, 2004) and the PERFORCE report (de Voogt *et al.*, 2006a). Two major processes exist for production of PFAS, viz. Simons Electro-Chemical Fluorination (ECF), and telomerisation (TM) (Hekster *et al.*, 2003). In the ECF process, organic feed stocks are dispersed in liquid anhydrous hydrogen fluoride, and an electric current is passed through the solution, leading to the replacement of all of the hydrogen atoms in the molecule with fluorine atoms. In the telomerisation process, tetrafluoroethylene is reacted with IF_5 to produce fluorinated alkyl iodide with linear, even numbered alkyl chain lengths, so called fluorotelomers.

1.3.1 PFOS

Perfluorooctane sulfonate is manufactured by the ECF process (see Figure 5). The starting feedstock for this process is 1-octanesulfonyl fluoride, and the initial product is perfluorooctanesulfonyl fluoride (POSF). This product is sold commercially to some extent, but is mainly used as an intermediate in the production of other substances. The simplest of these is PFOS itself, produced by hydrolysis of POSF. The various salts are then produced from this.

The majority of POSF is reacted first with either methylamine or ethylamine to give *N*-methyl- or *N*-ethyl perfluorooctane sulfonamide, respectively. These intermediates can be used to make various amides, oxazolidinones, silanes, carboxylates and alkoxylates which are available commercially.

The sulfonamide derivatives can react with ethyl carbonate to form either *N*-MeFOSE and *N*-EtFOSE. These then form the basis of adipates, phosphate esters, fatty acid esters, urethanes, copolymers and acrylates as commercialised products. The majority of the POSF-related products were from this group of products (OECD, 2002, 2005a and b).

It should be noted that the secondary reactions producing the various products are single or sequential batch reactions, and do not necessarily lead to pure products. There may be varying amounts of fluorochemical residuals (unreacted or partially reacted starting materials or intermediate products) carried forward into the final product. These residues are present at around 1% or less in the final commercial products (OECD, 2002).

Although (for the production process for PFOS-related substances) the starting material is n-octane sulfonyl fluoride, this will contain some non-linear C_8 compounds. The fluorination process is expected to lead to some fragmentation of the chain. Thus the product of the fluorination step will contain linear and non-linear chains, mostly C_8 but with other chain lengths present. Hekster *et al.,* (2002) quote 3M Company as reporting a final product (as POSF) of approximately 70% *n*-POSF and 30% branched impurities including odd and even chain lengths. An alternative description of the content is 90% of C_8 molecules, of which 25% are branched, with 5 – 10% C_6 compounds and the remainder C_7 (2 – 5%) and C_5 compounds. A similar distribution is assumed to apply to all products based on the ECF process (see Section 2.1.1), whether produced by 3M Company or by other companies. No specific information on other companies' products has been identified.

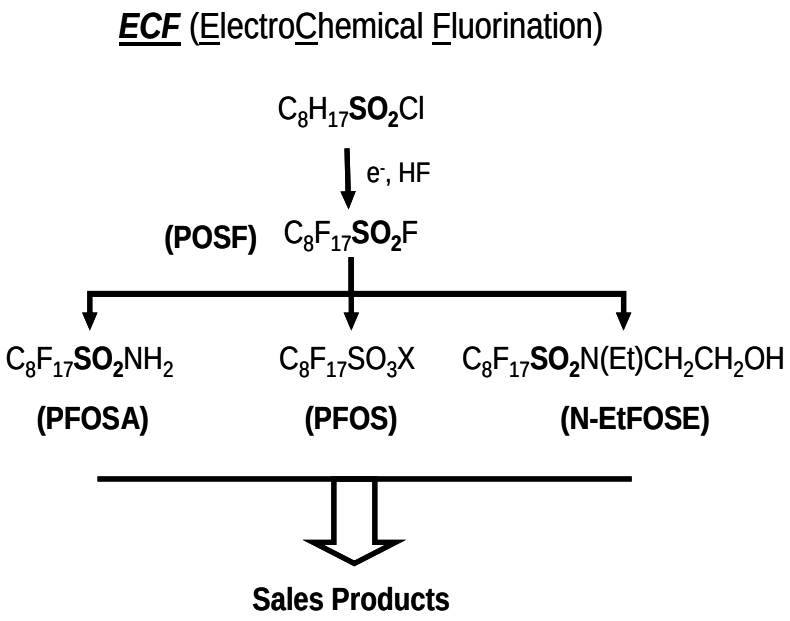

Figure 5. Electrochemical fluorination (ECF) process schematic.

The production (3M Company, 2000a and b), use, distribution and environmental releases (3M Company, 1999) of PFOS and POSF-based substances has been well documented by the major global producer, who terminated manufacture in 2002, and by global regulatory agencies (OECD, 2002; Brooke *et al*., 2004). PFOS is the major impurity in, as well as the primary degradation product of, POSF-based products. PFOS is chemically and biologically stable and not expected to degrade in the environment.

1.3.2 PFOA

Commercial Manufacturing Processes: Ammonium Perfluorooctanoate (APFO) $F(CF_2)_7COONH_4$

- Electrochemical Fluorination (ECF): $H(CH_2)_7COF$ + e- + HF (Branched & Linear Isomers)
- Perfluorooctyl Iodide Oxidation: $F(CF_2)_8I$ + [O] (Linear Isomers Only)

Perfluorooctanoate (PFO) was first manufactured in 1947 by the electrochemical fluorination process and has been used for over fifty years. The ammonium salt (APFO) is the most widely produced form used as an essential surfactant for the manufacture of fluoropolymers such as polytetrafluoroethylene (PTFE). The ECF process for the manufacture of PFO yields a complex mixture containing fluorinated carbon chains, with lengths ranging from four to nine carbons, comprised of linear ($\geq$ 70%) and branched ($\leq$ 30%) isomers. The branched isomers are numerous and arise due to the free-radical nature of the ECF process. The perfluorooctyl iodide process utilises high purity starting material yielding only linear PFOA of high chemical purity ($\geq$ 99%). A recent critical review article provided significant details on the production, use, environmental releases and physico-chemical properties of PFO as well as other potential sources of PFO (Prevedouros *et al.,* 2006).

The largest historic production sites for APFO were in the U.S. and Belgium, the next largest in Italy and small scale producers in Japan. The remaining 10-20% of APFO was manufactured from about 1975 to the present by direct oxidation of perfluorooctyl iodide (Grottenmuller *et al.,* 2002) at one site in Germany and at least one site in Japan. Solid APFO was used in making fluoropolymers (e.g. Fluorad™ FC-143) (3M Company, 1995). An aqueous solution (e.g. Fluorad™ FC-118) has been used in recent years because solid APFO readily sublimes and proved difficult to handle. Additional production, use and disposal of limited research quantities of perfluorocarboxylic acid (PFCA) has taken place in numerous academic and industrial locations worldwide over the past fifty years as indicated by patents and papers in the scientific literature. In 1999, global annual APFO production was approximately 260 tonnes (FMG, 2002). PFO emissions from the largest ECF production plant, located in the U.S., were reported to be approximately 20 tonnes (5-10% of total annual production) in 2000, roughly 5% discharged to air and 95% to water (3M Company, 2000b). During 1951-2004 the estimated industry-wide global emissions from APFO manufacture were 400 - 700 tonnes (Prevedouros *et al.,* 2006).

By 2002, the principal worldwide APFO manufacturer by the ECF process discontinued external sales and ceased production leaving only a number of relatively small producers in Europe and in Asia (OECD, 2004). New APFO production capacity based on >99% pure perfluorooctyl iodide commenced in the U.S. in late 2002 with reported annual releases of approximately 50 kilograms per year to air (DuPont, 2005). With the termination of U.S. ECF-based manufacture, current and future U.S. releases from APFO manufacture have been

dramatically reduced from many tonnes per year to kilograms per year. As a result, global APFO manufacturing emissions decreased from about 45 tonnes in 1999 to about 15 tonnes in 2004 and to an expected 7 tonnes in 2006 (FMG, 2002). Recently, a number of global companies who manufacture or use PFOA have committed to a voluntary stewardship program to reduce manufacturing emissions and product content (U.S. EPA, 2006). The 3M company, a major world producer of PFOS, using the ECF process, with manufacturing plants in North America and Europe, announced the termination of the ECF production process by May 2002. This decision was probably based partially on findings of PFAS in occupationally exposed persons and in the environment (e.g., in terrestrial, estuarine and Arctic ecosystems) (Hoff *et al*., 2003, 2004; Martin *et al*., 2004b). As a result, the telomerisation based production has increased.

1.4 Use of the compounds

PFAS have found numerous applications, including textile, carpet and leather treatment (water and dirt proofing), surfactants, fire fighting foams and paper grease proofing treatments. The PFAS products found hitherto in the environment are known to be possible end products resulting from ECF, but recently more information has become available suggesting that TM building blocks or end products may also be precursors of PFAS in the environment.

Perfluorinated substances with long carbon chains, including PFOS, are both lipid-repellent and water-repellent. Therefore, the PFOS-related substances are used as surface-active agents in different applications. The extreme persistence of these substances makes them suitable for high temperature applications and for applications in contact with strong acids or bases. It is the very strong carbon-fluorine bindings that cause the persistence of perfluorinated substances.

2. Regulations

In the European Union (EU) Directive 2006/122/EC[3] of the European Parliament and of the Council of 12 December 2006 lays down restrictions on the marketing and use of PFOS for new products in the non-food area which will apply from 27 June 2008 onwards. This Directive also states that ongoing risk assessment activities for PFOA shall be kept under review. There is currently no legislation for perfluorinated organic substances such as PFOS or PFOA in food or feed within the EU. Their use in plastics and coatings for food contact materials has been approved in The Netherlands and Germany. The EFSA Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food (AFC) issued an opinion on the safety of ammonium salt of PFOA as a food contact material (EFSA, 2005a), but this has not so far led to regulatory measures.

Currently, there is a proposal for hazard classification for PFOS in the European Inventory of Existing Commercial chemical Substances (EINECS)[5]. PFOS is currently being reviewed for inclusion in UNECE-CLRTAP protocol on persistent organic pollutants (POPs).

3. Methods of analysis

The analytical chemistry of PFAS and related compounds has recently been reviewed by de Voogt and Sáez (2006).

Analytical methods for the determination of organic fluorine were initially based on converting organic fluorine to soluble fluoride (Sweetser, 1965, Kissa, 1986).

Gas chromatography (GC) can be used for the direct determination of the neutral, volatile per- and poly-fluorinated alkylated substances including several precursors of PFOS and PFOA, e.g., the sulfonamides, fluorotelomer alcohols (Martin *et al.*, 2002), and olefins. These compounds have high vapour pressures (typically up to several hundreds of Pa).

The perfluorinated alkanoic acids cannot be determined directly, and need to be derivatised in order to be amenable to GC analysis (Ylinen *et al.*, 1985). Derivatisation reactions yields can be non-reproducible, however (Bonesteel and Kaiser, 2003). PFOS has a very low vapour pressure and its derivatives are unstable (Hekster *et al.*, 2002).

Liquid chromatography (LC) has been used with several conventional detectors for the separation of PFAS. These include a conductimetric detection (Hori *et al.*, 2004) and fluorescence detection (LC-FLU). The latter can only be employed after derivatisation (e.g. with 3-bromoacetyl-7-methoxycoumarin) because of the general absence of fluorophores in PFAS (Ohya *et al.*, 1998).

The development of LC – electrospray ionisation (ESI) mass spectrometry (MS) and LC-tandem MS has enabled substantial improvements of the analytical chemistry of the PFAS. LC-MS and in particular LC-MS/MS can be considered the current standard for analysis of anionic perfluorinated surfactants. LC with single quadrupole MS, though a sensitive technique, requires more thorough clean up of the sample in order to remove interferences, because of its inherent lower selectivity. The majority of reports in the literature employed LC-ESIMS/MS as the analytical method.

Currently quadrupole-time-of-flight (Q-TOF) MS analysers have a lower sensitivity than triple quadrupole MS/MS systems, but seem to be suitable instruments for the identification of PFAS in the environment (Hansen *et al.*, 2001; Martin *et al.*, 2004c). Berger *et al.* (2004) compared three different mass spectrometric techniques coupled to LC, viz. ion trap MS,

[5] See URL: http://ecb.jrc.it/classlab/2405a2_S_PFOS.doc

triple quadrupole MS and high resolution TOF. For all instruments ESI was the best suited interface for analysis of PFAS. Ion trap MS was best suited for qualitative purposes and identification of branched isomers. Triple quadrupole MS-MS appeared to be the method of choice for quantitative analysis of telomer alcohols, having a limit of detection (LOD) in the low picogram range, and with typical detection limits for other PFAS of 10 to 100 pg. TOF-MS appeared to be the optimum quantitative method for PFAS, combining high selectivity with high sensitivity (2 to 10 pg).

3.1 Standards

Analytical standards for per- and polyfluorinated alkylated substances are available from several manufacturers of fine chemicals. However, the purity of the non-isotopically labelled standards can vary considerably and may lead to systematic errors, as has been pointed out by Martin and co-workers (2004c). For example, standards of alkanoic acids often contain short chain analogues. Moreover, the isomeric composition of these standards may also vary as a result of the production process used (Hekster *et al.*, 2003). Electrochemical fluorination will generally produce branched isomers next to the linear one and e.g. up to nine isomers have been shown to be present in a commercial PFOS standard (Martin *et al.*, 2004c; Langlois and Oehme, 2004). An estimation of the overall composition of commercial PFOS is still not possible because of the different fragmentation patterns and their probably varying response factors (Langlois and Oehme, 2004). Different PFAS isomers have indeed been detected in biota (Hansen *et al.*, 2001), but are usually not completely separated and reported as an additional signal 'shoulder'.

3.2 Analysis in air, water, food and consumer products

Many reports have been published on the analysis of PFAS in surface waters, but only very few report on the contents of PFAS in air or drinking water. Methods for drinking water are similar to those used for surface water analysis. Until now only a few reports have been published on the analysis of PFAS in food and feed. In general the methods applied for the determination of PFAS in biological samples can be used for evaluating food items.

Background contamination of samples by PFAS, in particular by PFOA, may occur in any laboratory due to the frequent use of polyfluorinated polymers (e.g., PTFE) e.g. in tubing present in instruments and in filter devices.

3.2.1 Analysis in air

Air samples are usually collected using high-volume air samplers employing sampling modules containing glass-fibre filters (GFFs, particle phase), and glass columns with a polyurethane foam (PUF)/XAD-2/PUF sandwich (gaseous phase) (Jahnke *et al.*, 2007). Typical outdoor air volumes required for analysis range from 600-1500 m^3. GFFs and

PUF/XAD2/PUF columns can be analysed separately to obtain information on phase partitioning.

Volatile PFAS are extracted from air samples by cold-column immersion with ethyl acetate, and analysed by gas chromatography-mass spectrometry in the positive chemical ionisation mode (GC/PCI-MS) using single ion monitoring (SIM), with subsequent analysis in negative chemical ionisation (NCI) mode for confirmation (Jahnke *et al.*, 2007). Ionic PFAS are extracted from GFFs by sonication in methanol, and analysed by liquid chromatography/time-of-flight mass spectrometry (LC-TOF-MS) using electrospray ionisation in the negative ion mode (ESI-) (Berger and Haukås, 2005).

3.2.2 Analysis in water

The analytical methods applied to water samples generally employ C18-SPE, either with or without ion pairing or acidification, followed by LC-MS/MS (de Voogt and Sáez, 2006). LC with single quadrupole MS has also been used successfully for the determination of PFAS employing styrenedivinylbenzene polymethacrylate cartridges for the SPE, and a reported LOD of 0.1 ng/L (Saito *et al*., 2003; Harada *et al.*, 2003).

3.2.3 Analysis in biological samples and food

Currently three methods of analysis are used most often for the determination of anionic PFAS in biological samples, all involving detection by LC-MS/MS. The method used most often is the ion pairing extraction method introduced by Ylinen and co-workers (1985) and modified by Hansen *et al*. (2001). This method is flexible and reported recoveries are generally good (70-120%). It can be used for a wide range of matrices, including egg, liver, muscle and other biological tissues. However, the method is quite time consuming and matrix-matched calibration standards are not routinely employed, i.e. matrix-induced ionisation disturbances in the ion source of the mass spectrometer are usually not accounted for (Berger and Haukås, 2005). Instead of using a cation such as tetrabutylammonium, the sample can be acidified prior to extraction of the (then protonated) neutral acid (van den Heuvel *et al.*, 1989).

Berger and Haukås (2005) have developed a screening method for the analysis of PFAS in biological samples. Extraction is by sonication with 2mM ammonium acetate in MeOH:H_2O (50:20). The method showed excellent agreement with the method of Hansen and co-workers (2001). Although the method is matrix and internal standard dependent and does not work well for less polar PFAS (e.g., the PFOS precursor PFOSA), it has some advantages, such as time and cost efficiency, short and straightforward sample handing (reducing risk of contamination and loss of analytes, since samples are not evaporated to dryness) and it works well for lipid rich samples.

Powley *et al.,* (2005) have developed a matrix-effect free method for perfluorinated carboxylic acids (6-14 C atoms), consisting of a dispersive solid phase extraction with graphitised carbon, which does not extract the interfering matrix components. The analysis is performed by LC-MS/MS analysis. Recovery values generally were in the 70-120% range, with limits of quantitation of 1 ng/g.

The few studies on PFAS analysis in food and feed available in the literature mostly applied the method based on the Hansen paper, using ion-paired extraction and LC-MS/MS detection (Hansen *et al.,* 2001). The method developed by Powley and Buck (2005) for biota is likely to be equally applicable to food items from animal origin. Recently, the method has been found applicable to plant tissues (Powley and Buck, 2005).

The uncertainties associated with the determination of PFAS in environmental matrices including water and food items have been illustrated by the results of the first interlaboratory exercise on PFAS (van Leeuwen *et al.,* 2005). The in-between laboratory variabilities obtained for water and fish tissue analysis were unsatisfactory. The authors concluded that further improvement of the analytical methodologies and comparability was essential.

3.2.4 Analysis of consumer products

The contents of several materials known or suspected to contain PFAS have been reported in several documents. In a Danish study the contents of several consumer products were analysed (Vejrup and Lindblom, 2002), including floor polish waxes and impregnating agents for shoes and textiles. Waxes and liquids from aerosol cans were diluted with MeOH, dichloromethane or acetone, and analysed by LC-MS/MS. Limits of detection for all analytes were less than 1 mg/L of product.

A method for the analysis of extractable PFOA was developed to evaluate leaching of PFOA from treated textiles and carpet (Mawn *et al*., 2005). The method compared extraction efficiencies of water, sweat simulant and saliva simulants with that of MeOH using LC-MS/MS. Limits of detection of between 1 and 3 µg/kg of sample were reported.

Both pressurised solvent extraction (PSE) and reflux extraction in various solvents were used to select the most efficient system for the determination of PFOA in polytetrafluoroethylene polymers (Larsen *et al*., 2005). After evaporating the solvent, PFOA was determined using LC-MS/MS. Ethanol, water and methanol gave comparable results and were shown to be good solvents for this extraction. Acetonitrile was a reasonable solvent using the reflux extraction method, but not with PSE. Chloroform resulted in poor recovery for both extraction methods. PSE proved to be the more efficient extraction method.

Unbound residues of fluorotelomer alcohols in commercially available polymer and surfactants products, including carpet protector products were analysed by dissolving the products in water, purging the volatiles from the resulting suspensions, and trapping these in XAD-2 resin cartridges (Dinglasan-Panlilio and Mabury, 2006). The cartridges were extracted with ethyl acetate and analysed by GC-MS using EI or PCI.

Washburn and co-workers (2005) investigated the exposure to PFOA through consumer use of a variety of articles, including upholstery, textiles, sealants, garments, waxes, paints and cleaners. Analytical methods were similar to those reported above for textiles and carpet (Mawn *et al*., 2005) or polymers (Larsen *et al*., 2005) and involved liquid extraction followed by LC-MS/MS.

3.3 Conclusions

The group of PFAS considered in this opinion consists of neutral and anionic surface active compounds. The anionic compounds (notably PFOS and PFOA) can be extracted from environmental media by conventional methods using either acidification or ion pairing in order to obtain a neutral form of the analyte. Neutral per- and poly-fluorinated alkylated substances, which include potential precursors of PFOA, can be extracted directly into organic solvents. Published clean up methods are relatively simple and straightforward and involve normal phase adsorption chromatography with e.g. silica, or C18 materials in a SPE set up or, alternatively, use of graphitised carbon.

The analytical detection method of choice for PFAS is currently LC-MS or LC-MS/MS for the anionic compounds (including PFOS and PFOA), whereas both LC-MS(MS) and GC-MS can be used for the determination of the neutral per- and poly-fluorinated alkylated substances including several precursors of PFOS (e.g., PFOSA) and PFOA (e.g., *N*-EtFOSE, telomer alcohols). In LC-MS of anionic PFAS, usually the dissociated acid (pseudo molecular) ion [M-H]- is observed, which can be used for quantitative purposes in LC-single quad MS, or as the precursor ion for multiple ion reaction monitoring in LC-MS/MS. In GC-MS both positive and negative CI, as well as EI can be used. Detection limits of LC-MS(MS) and GC-MS methods are sufficiently low to allow in principle for the determination of environmental levels of PFAS in drinking water and in food samples. Analysis of food items has been reported rarely so far, and has been based on existing methods, i.e. either the ion-pair extraction method or the solvent extraction followed by active carbon clean up. The analytical problems associated with the determination of neutral and anionic PFAS are multiple, and include diverse aspects such as unique physicochemical properties, reliable standards, impurities, complicated mixtures of isomers and congeners, ion suppression, and contamination during all stages of the analytical procedure, including instrumental sources. Interlaboratory exercises have revealed that until now large between laboratory variabilities can be observed in the analysis of water or food samples. Hence, much work remains to be done before the analysis of this group of analytes will be fully understood and controlled.

4. Occurrence in food

Two recent surveys of PFAS in food samples, carried out in the UK and Sweden (UK FSA, 2006; Berger *et al*., 2007), provide some European country-related data, although these were mostly non-detects. Data on PFAS in food from monitoring activities in the EU countries are on the whole insufficient and the contamination of most foodstuffs cannot be characterised at present. The occurrence assessments described in 4.1.4 and 4.2.4, could be carried out for two food items only, i.e. drinking water (due to a deficit of specific data, surface freshwater was on the whole taken as a possible precursor) and fish and fishery products. Fish liver data were not included in the occurrence studies for evaluation of exposure, since fish liver is rarely eaten in the EU. The assessments were based on data gathered from published papers, presentations at scientific *fora*, and declassified technical reports. These data have a number of limitations, including:

- sampling protocols mostly not designed for exposure assessment;
- a general sparseness of data, lack of harmonisation, and presumably little inter-laboratory comparability (van Leeuwen *et al*., 2005; Fluoros Report, 2006);
- data generally do not reflect European conditions.

In order to improve the comparability of the occurrence data used in the exposure assessment and to obtain data as representative as possible of the present situation, the following selection criteria were adopted:

- only data on samples obtained since 2001 were included;
- when appropriate, data were excluded in order to eliminate inconsistencies between relatively high limits of determination (LD) and the low PFOS or PFOA concentrations detected in some of the investigations;
- concentration values were excluded when the fish and fishery products or the freshwater samples were described to come from unusually polluted water bodies;
- average concentrations from determinations on several specimens, provided by the data processing authors in some cases, were entered in statistics with frequency weighting;
- fish liver data were not included in the exposure assessment.

Due to a lack of normality or log-normality in the data distributions, the available data sets were analysed with non-parametric statistics. In general, the "medium bound" approach was adopted when dealing with LDs (WHO, 1995); however, "lower bound" and "upper bound" evaluations were also carried out in one specific case with a relatively high frequency (43.4%) of non-detects. Data sets were characterised with canonical descriptors including median (Q_{50}), arithmetic mean (‹X›) and standard deviation (SD), and various percentiles (Qs). A marked difference between medians and arithmetic means was often observed when both estimates were available: the greater arithmetic mean values being associated with distributions tailing towards high values. The PFOA values were less numerous than those for PFOS, and therefore the statistical descriptors of PFOS may be more robust than those for PFOA.

4.1 PFOS

In 2004 the UK Environment Agency presented an Environmental Risk Evaluation report on PFOS (Brooke *et al*., 2004). Environmental concentrations were predicted using the methods of the EU Technical Guidance Document on Risk Assessment. Firstly, estimations were made of emissions from each use of PFOS. Then, predictions of the environmental distribution and concentrations were generated using the European Union System for the Evaluation of Substances software (EUSES 2). Also, concentrations of PFOS in some foodstuffs were predicted, as shown in Table 4.

Table 4. Predicted PFOS concentrations in plants, meat, milk and fish in µg/g (Brooke *et al*., 2004).

Sample	Regional	Use area										
		Chromium plating	Photo-graphy formu-lation	Photo-graphy processing	Aviation	Fire-fighting foams			Photo-litho-graphy	Fabrics appli-cation	Paper treatment	Coatings
						Formu-lation	Use A[a)]	Use B[b)]				
Plant root	0.02–0.18	0.022–0.038	0.28–0.29	1.3 × 10^{-3}	0.18–0.20	328	1.3 × 10^{-4}–0.016	139	3.04	1.54	207	5.1
Plant leaf	(2.5–24) × 10^{-5}	(2.8–54) × 10^{-5}	(5.6-6) × 10^{-4}	1.8 × 10^{-6}	(2.3–2.6) × 10^{-4}	0.67	(0.26–31) × 10^{-6}	0.17	3.8 × 10^{-3}	1.9 × 10^{-3}	0.26	6.4 × 10^{-3}
Meat	(7.4–67) × 10^{-6}	(5.3–12) × 10^{-6}	(0.95–1.0) × 10^{-4}	4.1 × 10^{-6}	(4.4–5.1) × 10^{-5}	0.11	(0.62–1.3) × 10^{-5}	0.033	7.3 × 10^{-4}	3.7 × 10^{-4}	0.05	1.2 × 10^{-3}
Milk	(2.3–21) × 10^{-6}	(1.7–3.9) × 10^{-6}	(3–3.2) × 10^{-5}	1.3 × 10^{-6}	(1.4–1.6) × 10^{-5}	0.034–0.036	(2.0–4.1) × 10^{-6}	0.011	2.3 × 10^{-4}	1.2 × 10^{-4}	0.011	3.9 × 10^{-4}
Freshwater fish	0.21–0.49	0.21–0.49	0.40–0.68	< 0.42	0.35–0.64	224	0.44–0.71	0.53–0.81	< 2.9	< 1.21	< 141	—
Marine fish	0.020–0.048	0.021–0.048	0.048–0.0.75	< 0.042	0.041–0.069	31	0.043–0.070	0.065–0.092	< 0.39	< 0.15	< 19.6	—
Marine predators	0.041–0.096	0.043–0.097	0.054–0.11	< 0.083	0.050–0.11	12.5	0.052–0.11	0.061–0.11	< 0.22	< 0.13	< 7.9	—

[a)] Use A (fire-fighting foams) is scenario for release to the environment without containment of the foam and water.

[b)] Use B is a scenario for release to the environment in which the foam and water are collected and passed to a waste water treatment plant. The model assumes no degradation in the plant and that there is direct application of the sewage sludge to a field once a year for 10 years.

It should be noted that these predictions involved the use of an estimated log K_{ow} value and hence the results have a high degree of uncertainty.

The report noted that the majority of the available data on measured concentrations in cow's milk corresponded with the predictions. However, data for comparison were limited. The U.K. Environment Agency doubted the accuracy of the calculations for plant root and plant leaf because the plant-to-soil concentration ratios for the measured and predicted concentrations did not correspond. These predictions indicate that fish is likely to be a major dietary contributor to PFOS exposure, and also that some human activities could have an impact on PFOS content of foods. However, the CONTAM Panel concluded that there was too much uncertainty in the data for them to be used in the exposure assessment.

4.1.1 PFOS in fish and fishery products

Data on PFOS concentrations in fish and fishery products, grouped by broad geographical regions are summarised below. Some statistical descriptors of the data selected for exposure assessment are presented in Table 5. Apart from the North America data sets for "Crustaceans" and "Molluscs", which are very limited and therefore unlikely to be representative (N = 7 and 5, respectively), the Asian data sets generally exhibit the lowest average and $Q_{.25}$–$Q_{.75}$ contamination levels. For the "Fish" data sets, the average and $Q_{.25}$–$Q_{.75}$ PFOS contents are lowest for Asia and highest for North America.

Europe

Studies carried out in the Western Scheldt and the Belgian part of the North Sea showed the occurrence of PFOS in marine and estuarine organisms (Hoff *et al*., 2003; van de Vijver *et al*., 2003). Concentrations in shrimps (*Crangon crangon*) ranged from 19–520 ng/g w.w., the highest mean concentration (319 ± 70 ng/g w.w.) being in shrimp from the Western Scheldt, close to Antwerp. The mean PFOS concentrations in crab (*Carcinus maenas*) tissue ranged from 93 ± 36 to 292 ± 45 ng/g w.w. (van de Vijver *et al*., 2003). In bib (*Trisopterus luscus*) and plaice (*Pleuronectes platessa*), PFOS was between <10 and 39 ng/g w.w., with peak values up to 111 ng/g w.w. for bib specimens caught in the Western Scheldt (Hoff *et al*., 2003). The PFOS concentrations in samples from the coastal region were higher than in those from open water. Fillet of flounder (*Platichthys flesus*) from the Western Scheldt appeared to be the most contaminated, with PFOS levels in the range of 93–230 ng/g w.w. (van Leeuwen *et al*., 2006). Pikeperch (*Sander lucioperca*) fillets from two water bodies in The Netherlands contained PFOS in the range 40–150 ng/g w.w. It should be noted that the Western Scheldt, a recreational and commercial fishing area, is known to be particularly contaminated with PFAS due to industrial activities in the area. In order to not underestimate the occurrence of PFOS in food, data from the Western Scheldt were not excluded from the evaluation. In doing so, the occurrence of PFOS in food might be overestimated in the present general occurrence assessment.

In North Sea herring (*Clupea harengus*) and mackerel (*Scomber scombrus*), PFOS levels were 7.8–51 and 7–22 ng/g w.w., respectively. Examples of low PFOS concentrations (<1.2–<1.7 ng/g w.w.) were also available, for example, for North Sea cod (*Gadus morhua*), English Channel herring (*Clupea harengus*), farmed eel (*Anguilla anguilla*) from Italy, and Mediterranean tuna. Cunha *et al*. (2005) detected PFOS in mussels (*Mytilus galloprovincialis*) from Portugal estuaries in the range of 38.81–125.9 ng/g w.w. A few fish specimens from UK fresh water had PFOS concentrations of 5–150 ng/g w.w. (CSL, 2006). Berger *et al*. (2007) reported upon PFOS findings in several fish specimens from Lake Vättern (Sweden) and the Baltic Sea, the respective values falling in the ranges of 0.97–23.1 and 0.47–3.34 ng/g w.w.

Kannan *et al*. (2002a), Kallenborn *et al*. (2004), van de Vijver *et al*. (2005) and van Leeuwen *et al*. (2006) reported PFOS in liver samples of several fish species from different European areas. High PFOS levels, up to 3800 ng/g w.w. in sea bass (*Dicentrarchus labrax*), were detected in livers of specimens from the Western Scheldt, near Antwerp: plaice and flounder livers from the Western Scheldt contained 730 and 540 ng/g w.w. of PFOS, respectively; sole (*Sola sola*) liver from the North Sea contained 130 ng/g w.w. of PFOS (van de Vijver *et al*., 2005; van Leeuwen *et al*., 2006). In livers of several marine and fresh water fish species from the Nordic environment, PFOS was detected in the range of 0.85–551 ng/g w.w. (Kallenborn *et al*., 2004): perch (*Perca fluviatilis*) and pike (*Esox lucius*) liver samples, from fish specimens respectively caught in Swedish and Finnish waters, showed the highest PFOS levels (>100 ng/g w.w.). According to Kannan *et al*. (2002a), Mediterranean fish livers had PFOS concentrations of <1–87 ng/g w.w. PFOS was found at concentrations of 250 ng/g w.w. in the liver of a few fish specimens from UK fresh water (CSL, 2006).

Asia

Several studies were conducted in Asia (China, Japan, and Taiwan) to determine the PFOS concentrations in different aquatic species. According to Nakata *et al*. (2006) and So *et al*. (2006a), the PFOS levels detected in 25 samples of crustaceans and molluscs were 0.114–0.586 ng/g w.w. Concentrations in fish, crustaceans, and molluscs were reported by Gulkowska *et al*. (2006) in the ranges of 0.38–2.93, 0.58–13.9, and 0.33–1.32 ng/g w.w., respectively. The highest levels (35.8–47.2 ng/g w.w., converted from dry weight to whole weight for this Opinion) were found in tilapia fish (*Oreochromis sp.*) and oysters (*Crassostrea gigas*) from Taiwan (Tseng *et al*., 2006). According to Taniyasu *et al*. (2003), PFOS was detected in liver of 13 fish species from Japanese marine and fresh water in the range of 3–558 ng/g w.w.: three species (conger eel (*Conger conger*), bluegill (*Lepomis macrochirus*), and largemouth bass (*Micropterus salmoides*)) exhibited PFOS concentrations above 200 ng/g w.w.

North America

Tomy *et al*. (2004) found PFOS concentrations of 0.08–4.7 ng/g w.w. in Arctic cod (*Boreogadus saida*), clams (*Mya truncate* and *Serripes groenlandica*), and shrimps (*Pandalus borealis* and *Hymenodora glacialis*) caught in 2000–2002 in the Arctic region. Other studies on biota of the Great Lakes and Michigan surface waters reported PFOS levels in a variety of species — such as carp (*Cyprinus carpio*), Chinook salmon (*Oncorhynchus tshawytscha*), crayfish (*Orconectes rusticus*), lake whitefish (*Coregonus clupeaformis*), round gobies (*Neogobius melanostomus*), smallmouth bass (*Micropterus dolomieu*), smelt (*Osmerus mordax*), and trout (*Salvelinus namaycush*, *Salmo trutta*) — in the range of <2–410 ng/g w.w. (Giesy and Kannan, 2001; Martin *et al*., 2004a; Furdui *et al*., 2005a; Kannan *et al*., 2005): PFOS levels >100 ng/g w.w. were detected in carp, salmon, whitefish, smelt, and trout,

whereas lower PFOS levels (2.4–4.3 ng/g w.w.) were reported for crayfish. Oysters (*Crassostrea virginia*) sampled in 1996–1998 in the Chesapeake Bay and the Gulf of Mexico had a PFOS content of <9.9–99.5 ng/g w.w. (the original data were converted from dry weight for this Opinion) (Kannan *et al*., 2002b). Several studies were carried out on fish liver (Martin *et al*., 2004b; Tomy *et al*., 2004; Tittlemier *et al*., 2005): PFOS levels detected in nine species of the Canadian Arctic region (arctic char (*Salvelinus alpinus*), arctic sculpin (*Myoxocephalus scorpioides*), brook trout (*Salvelinus fontinalis*), burbot (*Lota lota*), lake trout (*Salvelinus namaycush*), northern pike (*Esox lucius*), redfish (*Sebastes marinus*), whitefish (*Coregonus clupeaformis*), white sucker (*Catostomus commersonii*)) were <0.06 – 39 ng/g w.w. A previous investigation by Giesy and Kannan (2001) on fish from different world regions showed concentrations spanning <7–170 ng/g w.w. All the samples investigated by Giesy and Kannan (2001) and Kannan *et al*. (2002a and b; 2005) were obtained before 2001.

Table 5. Summary of statistics for the PFOS concentrations (ng/g w.w.) in fish and fishery products selected for exposure assessment. Data refer to samples obtained from 2001 onward and are expressed with two to three figures regardless of significance.

Region	N	N_{ND} [a]	$Q_{.50}$	‹X›	$Q_{.25}$–$Q_{.75}$	$Q_{.10}$–$Q_{.90}$	X_{MIN}–X_{MAX}	Refs
				Fish, muscle or whole body				
Europe	107	22.4	5.00	15.3	2.13–12.0	0.992–37.8	*0.60* [b]–230	(c)
Asia	19	0.0	0.920	7.01	0.860–2.56	0.612–37.3	0.380–37.3	(d)
North America	12	0.0	110	129	110–119	54.3–167	15.1–410	(e)
				Crustaceans, edible part				
Europe	48	0.0	120	184	93.0–294	40.0–319	8.30–319	(f)
Asia	20	10.0	1.82	2.99	0.940–2.80	0.537–5.52	*0.15*–13.9	(g)
North America	7	n.a.	—	0.350	—	—	*0.030*–0.900	(h)
				Molluscs, edible part				
Europe	97	2.1	71.7	69.1	66.0–77.2	63.0–79.6	*0.80*–79.8	(i)
Asia	49	32.7	0.420	5.44	*0.15*–0.870	*0.15*–35.8	0.114–47.2	(j)
North America	5	0.0	—	0.280	—	—	0.080–0.600	(h)

(a) Fraction (%) of non-detects (n.a., not available).
(b) In italics, the medium bound values ("0.5 × LD") derived from limits of determination.
(c) Hoff *et al*., 2003; van Leeuwen *et al*., 2006; CSL, 2006.; Berger *et al*., 2007.
(d) Gulkowska *et al*., 2006; Tseng *et al*., 2006.
(e) Martin *et al*., 2004a; Furdui *et al*., 2005a.
(f) van de Vijver *et al*., 2003; van Leeuwen *et al*., 2006
(g) Gulkowska *et al*., 2006; Nakata *et al*., 2006.
(h) Tomy *et al*., 2004.
(i) Cunha *et al*., 2005; van Leeuwen *et al*., 2006
(j) Gulkowska *et al*., 2006; Nakata *et al*., 2006; So *et al*., 2006a; Tseng *et al*., 2006.

4.1.2 PFOS in drinking and surface fresh water

A description of fresh water findings, grouped by broad geographical sampling regions, is reported in the following paragraphs. Some relevant statistical descriptors of the data selected for exposure assessment are summarised in Table 6. The North America "Drinking water" data set is not representative (N = 2, both non-detects). Regardless of the high frequency (56.0%) of non-detects in Europe data set, Europe and Asia "Drinking water" data sets exhibit similar average ($Q_{.50}$ and ‹X›) contamination levels. For "Surface fresh water", apart from sporadic contamination peaks present in the Asia data set, the average and $Q_{.25}$–$Q_{.75}$ PFOS contents are similar for North America and Asia, and somewhat higher for Europe.

Europe

According to Skutlarek *et al*. (2006), Tanaka *et al*. (2006), and Loos *et al*. (2007), PFOS concentrations in European drinking water samples were in the range 0.4–9.7 ng/L. However, for the Ruhr area in North Rhine-Westphalia (Germany), Skutlarek *et al*. (2006) also determined PFOS in drinking water at levels in the range <2–22 ng/L, on the whole above average background and likely reflecting contamination from the area. According to the same authors, PFOS was measured at concentrations between <2–193 ng/L in surface water of the rivers Ruhr and Moehne (river Rhine hydrological system); in selected tributaries of the river Moehne, concentrations up to 5900 ng/L were detected. Water contamination most likely stemmed from inorganic and organic waste materials applied to agricultural areas on the upper reach of the river Moehne. Additional environmental data from Norway, The Netherlands, and other European locations provided PFOS concentrations in surface fresh water of <0.02–0.48, <10–56, and <2–26 ng/L, respectively (Kallenborn *et al*., 2004; de Voogt *et al*., 2006a and b; Skutlarek *et al*., 2006; Weremiuk *et al*., 2006). In Lake Maggiore (Italy) surface waters, PFOS was detected in the range 7.2–8.6 ng/L, whereas in nearby Alpine rivers the level of the chemical was close to non-detect (0.1 ng/L) (Loos *et al*., 2007).

Asia

Harada *et al*. (2003), Saito *et al*. (2004), and Tanaka *et al*. (2006) reported PFOS in drinking water at levels of <0.05–12.0 ng/L in Japan and other Asian areas. In the Tokyo area of Kinuta, the PFOS concentrations were higher (43.7 and 50.9 ng/L) probably due to contamination of the Tama river from which the Kinuta Waterworks took the fresh water supply to treat into drinking water (Harada *et al*., 2003). PFOS levels in surface fresh waters from several locations — mostly in Japan but also including China, Malaysia, Thailand, and Vietnam — were reported in the range <0.01–12 ng/L (Harada *et al*., 2003; Taniyasu *et al*., 2003; Tanaka *et al*., 2006; So *et al*., 2007). Higher concentrations, up to 135 ng/L, were sporadically reported for a few Japanese rivers by Saito *et al*. (2003). A concentration as high as 157 ng/L and some other high values were not included in the database since according to

the authors these values were for samples taken from the vicinity of sewer or industrial waste water discharges.

North America

PFOS was measured in drinking water samples collected over the 1999–2000 period during a Multi-City Study that was conducted by the 3M Company in the U.S. In four cities (Decatur, Mobile, Colombus, and Pensacola), perfluorinated compounds were either manufactured or industrially used; two other cities (Cleveland and Port St. Lucie) were studied as controls. Only in Columbus and Pensacola was PFOS detected in drinking water-related samples (raw water, treated water, and/or tap water) with levels of 59 ng/L (average of 10 data) and from non-detect to 45 ng/L, respectively. The treatment process seemed to have little influence on the concentrations of PFOS. In the other cities PFOS was not found above the LOD of 2.5 ng/L (3M Environmental Laboratory, 2001). The Tennessee river water was sampled (N = 40) in 2000: average PFOS concentrations were 32 ± 11 and 114 ± 19 ng/L, respectively upstream and downstream of the discharge of a fluorochemical plant (Hansen *et al*., 2002). According to Tanaka *et al*. (2006), PFOS was analysed in drinking and surface fresh water samples from the cities of Calgary and Vancouver (Canada): concentrations were <0.05–0.1 ng/L. According to a number of other studies carried out on surface water of the Great Lakes region (Sinclair *et al*., 2004, 2006; Furdui *et al*., 2005b; Kannan *et al*., 2005), the PFOS concentrations were <0.8–13 ng/L.

Table 6. Summary of statistics for the PFOS concentrations (ng/L) in drinking and surface fresh water selected for exposure assessment. Data refer to samples obtained from 2001 onward and are expressed with two to three figures regardless of significance.

Region	N	N_{ND} [a]	$Q_{.50}$	‹X›	$Q_{.25}$–$Q_{.75}$	$Q_{.10}$–$Q_{.90}$	X_{MIN}–X_{MAX}	Refs
				Surface fresh water				
Europe	76	10.5	5.00	8.45	1.30–8.00	*1.0* [b]–21.0	*0.010*–56.0	(c)
Asia	298	≈0.7	1.10	4.01	0.500–3.65	0.400–7.86	*0.0050*–135	(d)
North America	104	1.0	2.85	3.33	1.70–4.90	1.60–5.47	0.100–13.0	(e)
				Drinking water				
Europe	25	56.0	*1.0*	2.99	*1.0*–6.00	0.640–8.10	0.400–8.10	(f)
Asia	74	18.9	1.25	3.38	0.100–2.83	*0.015*–6.30	*0.015*–50.9	(g)
North America	2	100	—	—	—	—	*0.025–0.025*	(h)

(a) Fraction (%) of non-detects.
(b) In italics, the medium bound values ("0.5 × LD") derived from limits of determination.
(c) Kallenborn *et al*., 2004; de Voogt *et al*., 2006; Skutlarek *et al*., 2006; Tanaka *et al*., 2006; Weremiuk *et al*., 2006; Loos *et al*., 2007.
(d) Harada *et al*., 2003; Saito *et al*., 2003, 2004; Taniyasu *et al*., 2003; Tanaka *et al*., 2006; So *et al*., 2007.
(e) Sinclair *et al*., 2004, 2006; Furdui *et al*., 2005b; Kannan *et al*., 2005; Tanaka *et al*., 2006.
(f) Skutlarek *et al*., 2006; Tanaka *et al*., 2006; Loos *et al*., 2007.
(g) Harada *et al*., 2003; Saito *et al*., 2004; Tanaka *et al*., 2006.
(h) Tanaka *et al*., 2006.

4.1.3 PFOS in other food items

During a Multi City Study, PFOS was determined in over 200 samples of a variety of foodstuffs collected in 2000. Green beans, apples, pork muscle, cow's milk, chicken muscle, chicken eggs, bread, hot dogs, catfish, and ground beef were bought at the market and analysed. With a LD of 0.5 ng/g, PFOS was found only in four whole milk samples and one ground beef sample, with a maximal value of 0.852 ng/g (3M Company, 2001).

Tittlemier *et al*. (2005) analysed PFOS in several samples of traditional food from the Arctic. The highest PFOS levels (74.3–291.7 ng/g w.w.) were in the ringed seal liver. Walrus and caribou liver samples contained PFOS concentrations of 8.1–38.6 and 3.8–24.2 ng/g w.w., respectively. Following papers by Tittlemier and co-workers (2006, 2007) provided additional data on PFAS occurrence in some composite food samples collected between 1992 and 2004 as part of a Canadian "total diet study" (TDS). PFAS were detected in only nine out of the 54 composites analyzed and at a level of a few ng/g w.w. In particular, PFOS findings in meat, fish, and microwave popcorn were 0.5–2.7, 1.3–2.6, and 0.98 ng/g w.w., respectively.

A UK Food Standards Agency report (UK FSA, 2006) contains PFOS data, mostly non-detects, for composite food samples. PFOS concentrations were quantifiable only for the eggs, sugars and preserves, potatoes, and canned vegetables food groups: among these, the potatoes group — a mix of fresh, prepared, and processed products — had the highest PFOS level (10 ng/g w.w.). However, because these were composite samples it is not possible to draw conclusions on the origin(s) of the PFOS in these foods.

PFOS and related compounds were included in a monitoring study focused on the dietary exposure to a number of persistent environmental pollutants of the general population in Bavaria, Germany (Fromme *et al*., 2007a). In 2005, daily food and beverage duplicates were collected by 15 female and 16 male adult volunteers over a seven-day period. The daily samples of each volunteer were pooled, homogenised, and frozen for later analysis: PFOS was measurable in only 70 of the 214 pools available (LOD, 0.05 ng/g w.w.). According to the medium bound approach, concentrations covered the range of 0.025–1.03 ng/g w.w., with median and mean values respectively of 0.025 and 0.06 ng/g w.w.

Lastly, according to Berger *et al*. (2007) PFOS could not be quantified with a LD of 2.2 ng/g w.w. in four market basket samples of meat and meat products, dairy products, eggs, and seafood and seafood products collected in Uppsala (Sweden).

4.1.4 Occurrence assessment

PFOS in fish and fishery products

The statistical descriptors for the selected PFOS occurrence data that were used for exposure evaluation are summarised in Table 7. As described in chapter 4.1.1, data were selected to represent a variety of marine and freshwater organisms of direct or potential dietary interest. It should however be noted that samples collected from areas with uncertain relevance for the exposure assessment have not been excluded. Based on general dietary habits and the greater relevance of fish muscle, PFOS data in liver and muscle (or whole body) samples were treated separately: only the latter data were used for exposure evaluation. In the selected data set on concentrations in fish muscle or whole body, 69.2, 24.2, and 6.6% of the data were from Europe, Asia, and North America regions, respectively.

In Table 7, the "All items" PFOS concentration distribution covers three to four orders of magnitude; however, the magnitude of the spread diminishes considerably when extreme values are excluded: for instance, the $Q_{.10}$–$Q_{.90}$ range is 0.35–120 ng/g w.w. The distribution is skewed towards high values because of the variety of organisms taken into account, including marine and freshwater species (primarily wild, some farmed), fish from various regions of the world, fish belonging to different trophic levels, molluscs, and crustaceans.

Table 7 shows the outcomes of two correlated statistical analyses: on the entire data set and on a subgroup of PFOS values in samples of European origin ("European items"). The two data sets are statistically different; however, they present a few analogies relevant for exposure assessment. There is a fair amount of data overlap, as seen for example by the $Q_{.10}$–$Q_{.90}$ ranges (respectively, 0.35–120 and 2.1–150 ng/g w.w.). Other parallel descriptor estimates — such as the mean and high percentiles — are approximately within 50% of each other (e.g., for the two data sets the mean values are 53 ("All items") and 68 ("European items") ng/g w.w., respectively), indicating a reasonable degree of comparability in view of the overall underlying uncertainties. Therefore, the European mean value of 68 ng/g w.w. has conservatively been chosen for the exposure scenario as the indicative concentration of PFOS in fish and fishery products.

PFOS in drinking water

From chapter 4.1.2, it is clear that surface fresh water has been the target of analytical investigations in different parts of the world. However, there is a lack of representative data for drinking water. Therefore fresh water was assumed to be a possible precursor of drinking water for the purposes of occurrence assessment to be used in exposure evaluation in this Opinion. This approach is broadly supported, for instance, by the outcome of the 3M Company's investigation of 1999–2000, which indicated that the treatment process to produce tap water from raw water had little influence on the concentrations of PFOS (see chapter 4.1.2 "North America"); similar observations were also reported by other authors (Skutlarek *et al.*,

2006; Loos *et al*., 2007). Many determinations were produced from investigations in Japan, in general investigating fresh waters in a number of territorial districts. In the final data set ("All items"), 17.4, 64.2, and 18.3% of the data were from Europe, Asia, and North America regions, respectively.

Table 7 shows that the PFOS data distributions are wide, covering four orders of magnitude, with much overlap. The $Q_{.10}$–$Q_{.90}$ ranges for PFOS in drinking and surface fresh water in the "All items" and "European items" data sets range from 0.35 to 18 ng/L. Other parallel descriptor estimates (e.g., mean, $Q_{.75}$) are approximately within 50% of each other: as for PFOS in fish and fishery products, this indicates a reasonable degree of comparability. Therefore, the European mean value of 7.1 ng/L (0.0071 ng/g) has conservatively been taken as the indicative concentration of PFOS in drinking water for use in the exposure evaluation.

Table 7. Statistical descriptors of PFOS occurrence in fish and fishery products and in drinking and surface fresh water based on samples obtained from 2001 onward. Concentration units shown in parentheses; values rounded off to two or three figures regardless of significance.

N	N_{ND} [a]	X_{MIN}	$Q_{.10}$	$Q_{.25}$	$Q_{.50}$	‹X›	SD	$Q_{.75}$	$Q_{.90}$	$Q_{.95}$	X_{MAX}
Fish and fishery products, muscle or whole body (ng/g w.w.) — All items											
364	12.1	0.114	0.351	1.31	14.6	52.7	75.6	77.0	120	237	410
Fish and fishery products, muscle or whole body (ng/g w.w.) — European items											
252	10.3	*0.60* [b]	2.13	5.73	65.1	68.1	79.8	79.5	147	292	319
Drinking and surface fresh water (ng/L) — All items											
579	7.1	*0.0050*	0.350	0.680	1.70	4.33	9.01	4.90	8.10	15.8	135
Drinking and surface fresh water (ng/L) — European items											
101	21.8	*0.010*	*1.0*	*1.0*	5.00	7.10	9.46	8.00	18.0	26.0	56.0

(a) Fraction (%) of non-detects.
(b) In italics the medium bound values ("0.5 × LD") derived from limits of determination.

4.2 PFOA

Compared to PFOS, fewer data are available for PFOA, as described below. PFOA occurrence data for only two food items were available and used in the exposure assessment.

4.2.1 PFOA in fish and fishery products

Generally PFOA concentrations in fish and fishery products are lower than those of PFOS. As for PFOS the preferred accumulation of PFOA is in liver and blood, with less in the edible tissue (Martin *et al*., 2003). Some statistical descriptors of the data selected for exposure assessment are shown in Table 8. The data sets for Europe and North America "Crustaceans" and "Molluscs" are limited and unlikely to be representative (N = 7 or less, mostly non-detects). The Asia data sets exhibit approximately similar descriptors for the three food macro

components examined. For "Fish", the average and $Q_{.25}$–$Q_{.75}$ PFOA contents are low for the three geographical regions. Both Europe and Asia "Fish" data sets are mostly comprised of non-detects (respectively, 57.0 and 84.2%).

Europe

The PFOA concentrations detected in 39 edible tissue samples of several fish, crustacean, and mollusc species from various European waters were 1.1–3.2 ng/g w.w. (non-detect rate, 82.1%) (van Leeuwen *et al*., 2006). Berger *et al*. (2007) reported upon PFOA findings in several fish specimens from Lake Vättern (Sweden) and the Baltic Sea, the respective values falling in the ranges of <0.10–0.25 and <0.10–0.39 ng/g w.w. PFOA was not quantifiable in a few fish specimens from UK fresh water with a LD of 10 ng/g w.w.; an assay of fish liver also yielded a non-detect (<20 ng/g w.w.) (van Leeuwen *et al*., 2006. Various authors investigated PFAS levels in fish liver: for instance, in 51 European fish specimens (Kallenborn *et al*., 2004; van Leeuwen *et al*., 2006), PFOA levels in liver were detected in the range of 0.89–53.0 ng/g w.w. (non-detect rate, 86.3%). As for PFOS, the Western Scheldt appeared to show the highest levels of PFOA in The Netherlands, including coastal waters. It should be noted that the Western Scheldt, a recreational and commercial fishing area, is known to be particularly contaminated with PFAS due to industrial activities in the area. In order to not underestimate the occurrence of PFOA in food, data from the Western Scheldt were not excluded from the evaluation. In doing so, the occurrence of PFOA in food might be overestimated in the present general occurrence assessment.

Asia

Several studies were conducted in Asia (China, Japan, and Taiwan) to determine the PFOA levels in different aquatic species of dietary interest. Gulkowska *et al*. (2006) and So *et al*. (2006a), detected PFOA in 61 samples of several species, including a large fraction of molluscs, at concentrations of <0.204–1.67 ng/g w.w. Higher concentrations, in the range of 6.0–22.9 ng/g w.w., were reported by Nakata *et al*. (2006) and Tseng *et al*. (2006). The highest levels (18.6–22.9 ng/g w.w.) were found in tilapia fish (*Oreochromis sp*.) and oysters (*Crassostrea gigas*) from Taiwan (Tseng *et al*., 2006). The values reported by Tseng *et al*. (2006) were originally expressed on a dry weight basis and were converted to wet weight in this opinion.

North America

In several muscle samples of a few species collected in surface fresh waters in Michigan and Indiana over the 1998–1999 period, Kannan *et al*. (2005) could not detect PFOA with a LD of 0.2 ng/g w.w. PFOA concentrations in muscle of smelt (*Osmerus mordax*) and trout (*Salvelinus namaycush*) caught in 2001 in the Great Lakes were in the range 0.76–3.1 ng/g w.w. (N = 12) (Martin *et al*., 2004a; Furdui *et al*., 2005a). In the meat of 18 samples of Arctic

cod (*Boreogadus saida*), shrimps (*Pandalus borealis*, *Hymenodora glacialis*), and clams (*Mya truncate*, *Serripes groenlandica*), PFOA concentrations were in the order of the LD (0.2 ng/g w.w.) (Tomy *et al*., 2004). Several assessments have been carried out on fish liver samples. For instance, Martin *et al*. (2004b), Tomy *et al*. (2004), and Tittlemier *et al*. (2005) reported PFOA in the livers of several fish species from the Canadian Arctic region at levels in the range of 0.16–5.3 ng/g w.w. (N = 17) and one value as high as 26.5 ng/g w.w.

Table 8. Summary of statistics for the PFOA concentrations (ng/g w.w.) in fish and fishery products selected for exposure assessment. Data refer to samples obtained from 2001 onward and are expressed with two to three figures regardless of significance.

Region	N	N_{ND} [a]	$Q_{.50}$	‹X›	$Q_{.25}$–$Q_{.75}$	$Q_{.10}$–$Q_{.90}$	X_{MIN}–X_{MAX}	Refs
Fish, muscle or whole body								
Europe	86	57.0	0.200	*0.73* [b]	0.100–*0.85*	*0.050*–1.95	*0.050–5.0*	(c)
Asia	19	84.2	*0.13*	3.05	*0.13–0.13*	*0.13*–18.7	*0.13*–18.7	(d)
North America	12	0.0	2.00	1.56	0.900–2.00	0.810–2.00	0.700–2.40	(e)
Crustaceans, edible part								
Europe	3	100	—	—	—	—	*0.80–0.90*	(f)
Asia	20	30.0	0.420	1.40	*0.13*–0.870	*0.13*–2.45	*0.13*–9.50	(g)
North America	7	n.a.	—	0.170	—	—	*0.10*–0.500	(h)
Molluscs, edible part								
Europe	4	100	—	—	—	—	*0.95–1.2*	(f)
Asia	49	12.2	0.480	5.20	0.290–7.50	*0.13*–18.6	*0.10*–22.9	(i)
North America	5	100	—	—	—	—	*0.10–0.10*	(h)

(a) Fraction (%) of non-detects (n.a., not available).
(b) In italics, the medium bound values ("0.5 × LD") derived from limits of determination.
(c) van Leeuwen *et al*., 2006, CSL, 2006; Berger *et al*., 2007.
(d) Gulkowska *et al*., 2006; Tseng *et al*., 2006.
(e) Martin *et al*., 2004a; Furdui *et al*., 2005a.
(f) van Leeuwen *et al*., 2006.
(g) Gulkowska *et al*., 2006; Nakata *et al*., 2006.
(h) Tomy *et al*., 2004.
(i) Gulkowska *et al*., 2006; Nakata *et al*., 2006; So *et al*., 2006a; Tseng *et al*., 2006.

4.2.2 PFOA in drinking and surface fresh water

Fresh water findings for broad geographical sampling regions are described in the following paragraphs. Some relevant statistical descriptors of the data selected for exposure assessment are summarised in Table 9. The North America "Drinking water" data set is not representative (N = 2). The Europe data set has a high frequency (52.0%) of non-detects, and relatively low average and $Q_{.25}$–$Q_{.75}$ contamination levels of "Drinking water", whereas the Asia data set contains some high values that influence the mean and $Q_{.25}$–$Q_{.75}$ estimates. For the "Surface fresh water", there are sporadic high concentrations in the Asia data set, but the mean and $Q_{.10}$–$Q_{.90}$ PFOA contents are similar for the three geographical regions.

Europe

Tanaka *et al*. (2006) and Loos *et al*. (2007) reported PFOA presence in drinking water at 1.0–2.9 ng/L, in samples respectively from Örebro (Sweden) and the Lake Maggiore area (Northern Italy). Skutlarek *et al*. (2006) described the presence of PFOA in drinking water from various European locations (primarily German) at values of <2–4 ng/L, although drinking water samples from the German Ruhr area were found to have higher PFOA contents (up to 519 ng/L) (see also chapter 4.1.2). In general, the PFOA values above background were explained by the presence of a possible contamination source in the river Rhine hydrological system (see chapter 4.2.2): in the surface fresh water of the Ruhr area and of the river Moehne and selected contaminated tributaries, PFOA was measured at concentrations up to 3640 and 33,900 ng/L, respectively. PFOA concentrations in several fresh water bodies of the European region were found to fall in the range of <0.65–57 ng/L (Kallenborn *et al*., 2004; de Voogt *et al*., 2006a, 2006b; Skutlarek *et al*., 2006; Tanaka *et al*., 2006; Weremiuk *et al*., 2006; Loos *et al*., 2007): approximately 75% of the data appear to be comprised between non-detect and 8 ng/L and refer to samples from several countries including Germany, Italy, Norway, and Sweden. The highest PFOA concentrations were found in surface waters from Germany and the Netherlands, whereas the lowest values were reported for Italian Alpine river and spring waters and Swedish rivers.

Asia

Saito *et al*. (2004) and Tanaka *et al*. (2006) reported PFOA to be present in drinking water respectively at levels of 0.12–40.0 and <0.1–3 ng/L in Japan and other Asian areas. The higher concentrations (5.4–40.0 ng/L) were found in the Osaka area. The previous mentioned authors and So *et al*. (2007) reported that several surface fresh water bodies in China, Japan, and other Asian areas had PFOA concentrations mostly in the range of 0.10–41.60 ng/L, with sporadic peaks up to 456 ng/L. Several data for Japanese water bodies described as more exposed were not dealt with here.

North America

Concentrations of PFOA in drinking water (influent, treated, and tap) were measured in the Multi-City Study conducted by the 3M Company in the U.S. (see 4.1.2). PFOA was quantifiable only in Columbus drinking water, with levels up to approximately 27 ng/L, which was close to the limit of quantification (25 ng/L). PFOA was not found above the LOD (7.5 ng/L) in the other five cities (3M Environmental Laboratory, 2001). Tanaka *et al*. (2006) analysed PFOA in drinking and surface fresh water samples from the cities of Calgary and Vancouver (Canada): concentrations were 0.2–0.8 ng/L. A number of studies of surface water of the Great Lakes region reported PFOA concentrations of <2–59 ng/L (Sinclair *et al*., 2004, 2006; Furdui *et al*., 2005b; Kannan *et al*., 2005).

Table 9. Summary of statistics for the PFOA concentrations (ng/L) in drinking and surface fresh water selected for exposure assessment. Data refer to samplings from 2001 onward and are expressed with two to three figures regardless of significance

Region	N	N_{ND} [a]	$Q_{.50}$	‹X›	$Q_{.25}$–$Q_{.75}$	$Q_{.10}$–$Q_{.90}$	X_{MIN}–X_{MAX}	Refs
				Surface fresh water				
Europe	94	24.5	2.40	7.48	*1.0* [b]–8.00	0.900–22.7	*0.33*–57.0	(c)
Asia	167	0.0	2.78	9.93	1.00–11.7	0.600–18.0	0.100–456	(d)
North America	104	9.6	13.0	13.6	5.63–21.0	2.23–24.7	0.800–59.0	(e)
				Drinking water				
Europe	25	52.0	*1.0*	1.54	*1.0*–2.40	*1.0*–2.40	1.00–4.00	(f)
Asia	48	8.3	0.700	6.41	0.120–5.40	0.100–20.8	*0.050*–40.0	(g)
North America	2	0.0	—	—	—	—	0.200–0.200	(h)

(a) Fraction (%) of non-detects.
(b) In italics, the medium bound values ("0.5 × LD") derived from limits of determination.
(c) Kallenborn *et al*., 2004; de Voogt *et al*., 2006a, 2006b; Skutlarek *et al*., 2006; Tanaka *et al*., 2006; Weremiuk *et al*., 2006; Loos *et al*., 2007.
(d) Saito *et al*., 2004; Tanaka *et al*., 2006; So *et al*., 2007.
(e) Sinclair *et al*., 2004, 2006; Furdui *et al*., 2005b; Kannan *et al*., 2005; Tanaka *et al*., 2006.
(f) Skutlarek *et al*., 2006; Tanaka *et al*., 2006; Loos *et al*., 2007.
(g) Saito *et al*., 2004; Tanaka *et al*., 2006.
(h) Tanaka *et al*., 2006.

4.2.3 PFOA in other food items

PFOA was determined in a large variety of foodstuffs in a Multi City Study (see chapter 4.1.3). Measurable levels (above 0.5 ng/g) were found only in two ground beef samples, two bread samples, two apple samples, and one green bean sample, with a maximal concentration of 2.35 ng/g (3M Company, 2001).

Tittlemier *et al*. (2005) analysed PFOA and other PFAS in traditional food from the Arctic (15 liver samples). PFOA concentrations (<0.3–12.2 ng/kg w.w.) were 2–100-fold lower than PFOS concentrations in ringed seal, walrus, and caribou liver samples (see chapter 4.1.3). Further work by Tittlemier and co-workers (2006, 2007) provided PFAS occurrence data in a few composite food samples collected between 1992 and 2004 as part of a Canadian TDS. PFAS were detected in approximately 17% of the 54 composites analyzed and at a level of a few ng/g w.w. PFOA was measured only in roast beef, pizza, and microwave popcorn at the levels of 2.6, 0.74, and 3.6 ng/g w.w.

In addition to PFOS, the UK Food Standards Agency (UK FSA, 2006) reported PFOA data for composite food samples, all but one of which were non-detects. A concentration of 1 ng/g w.w. was found for the potato food group (a mix of fresh, prepared, and processed products), for which according to the authors "… further investigations will be considered for individual foods …".

As reported in chapter 4.1.3, duplicate diet samples were collected in 2005 in Bavaria, Germany, by 31 subjects of both sexes within the framework of a dietary intake study concerning various persistent environmental pollutants, including PFOA (Fromme *et al*., 2007a). The compound was detected in 97 of the 214 pools available (LOD, 0.05 ng/g w.w.). Based on the medium bound approach, the overall concentration range was 0.025–118.29 ng/g w.w., with median and mean of 0.05 and 0.69 ng/g w.w., respectively.

Berger *et al*. (2007) reported that PFOA could not be quantified (detection limit 3.2 ng/g w.w.) in four market basket samples of meat and meat products, dairy products, eggs, and seafood and seafood products collected in Uppsala, Sweden.

4.2.4 Occurrence assessment

PFOA in fish and fishery products

The PFOA data summarized in Table 10 were selected from the studies of PFAS in a variety of marine and freshwater organisms of direct or potential dietary interest. As for PFOS (chapter 4.1.4), PFOA data in liver and muscle (or whole body) samples were treated separately. In the selected data set on concentrations in fish muscle or whole body, 45.4, 42.9, and 11.7% of the data were from Europe, Asia, and North America regions, respectively.

In Table 10, the ranges of PFOA concentrations in the "All items" and "European items" data sets are narrower than those of PFOS. This may be due to the effect of PFOA values being lower than PFOS without a concurrent increase in analytical sensitivity to lower the minimal concentrations detected.

Due to the large number of non-detects in both data sets, PFOA occurrence requires further characterisation. This particularly applies to the "European items" set, where the frequency of non-detects is well above 50%: for this reason, the mean estimate has not been reported. In the absence of a mean European estimate, the indicative PFOA level for the exposure scenario was selected as the conservative mean value of 2.1 ng/g w.w. from the "All items" data set. This data set contained 43.4% of non-detects, with "lower" and "upper bound" means calculated as 1.8 and 2.4 ng/g w.w., respectively: these values are within <20% of 2.1 ng/g w.w., demonstrating that this value could be used as the indicative PFOA level in the exposure assessment.

PFOA in drinking water

As noted for PFOS (see chapter 4.1.4), surface fresh water was the target of analytical investigations. In the final PFOA data set ("All items"), 27.0, 48.9, and 24.1% of the data were from Europe, Asia, and North America regions, respectively. A summary of descriptor

estimates is reported in Table 10 for the "All items" data set and the "European items" selection.

The "All items" PFOA distribution is wide, covering four orders of magnitude; whereas the spread of the "Europeans items" distribution covers only two orders of magnitude. However, the $Q_{.10}$–$Q_{.90}$ ranges of both distributions are in practice indistinguishable (respectively, 0.60–21 and 0.90–21 ng/L) and are similar to those reported for PFOS. Some of the other statistical estimates (e.g., $Q_{.25}$, $Q_{.50}$, mean) are also comparable as they are within approximately 50% of each other or less. For the exposure assessment the mean "All items" value of 9.4 ng/L (0.0094 ng/g) has conservatively been taken as the indicative concentration of PFOA in drinking water.

Table 10. Statistical descriptors of PFOA occurrence in fish and fishery products and in drinking and surface fresh water based on samples obtained from 2001 onward. Concentration units shown in parentheses; values rounded to two or three figures regardless of significance.

N	N_{ND} [a]	X_{MIN}	$Q_{.10}$	$Q_{.25}$	$Q_{.50}$	‹X›	SD	$Q_{.75}$	$Q_{.90}$	$Q_{.95}$	X_{MAX}
Fish and fishery products, muscle or whole body (ng/g w.w.) [b] *— All items*											
205	43.4	*0.050* [c]	0.100	*0.13*	0.340	2.10	4.49	*1.1*	7.50	9.50	22.9
Fish and fishery products, muscle or whole body (ng/g w.w.) — European items											
93	60.2	*0.050*	*0.050*	0.100	0.250	— [d]	— [d]	*0.90*	1.59	2.90	*5.0*
Drinking and surface fresh water (ng/L) — All items											
440	11.4	*0.050*	0.600	1.00	3.00	9.37	24.5	14.0	21.0	33.1	456
Drinking and surface fresh water (ng/L) — European items											
119	30.3	*0.33*	0.900	1.00	2.00	6.23	10.0	5.51	21.2	25.4	57.0

(a) Fraction (%) of non-detects.
(b) w.w., wet weight.
(c) In italics the medium bound values ("0.5 × LD") derived from limits of determination.
(d) Omitted due to the high frequency of non-detects.

4.2.5 PFOA from food contact materials

Two main applications are known for the use of perfluorochemicals in food contact materials: as starting substances to make polytetrafluoroethylene (PTFE) for non-stick coatings on cookware and as additives in paper coatings to provide oil and moisture resistance to paper food packaging.

Up to now, there has been little investigation of the migration levels and the potential for exposure from food contact materials. This is mainly due to the difficulty in measuring of perfluorochemicals by the conventional analytical techniques used such as GC/MS or LC-UV. Many perfluorochemicals are not detectable by these conventional methods and only the development of LC/MS methods made possible the measurement of these compounds at low levels.

Non-stick coatings

Begley *et al*. (2005) reported that PTFE-coated cookware contained residual amounts of PFOA in the low ng/g range. These low levels were rationalised in terms of the high temperature conditions used to apply the non-stick coating to the metal cookware, which leads to volatilisation and a diminution of any residual amounts of PFOA present during the manufacturing process. Bearing in mind the very thin nature of the coatings and their repeated-use character, the migration potential into foods was concluded to be in the very low ng/g range. The U.S. Food and Drug Administration (FDA) found frying pans to be a negligible source. This conclusion was based on a worst-case calculation for the migration of PFOA from PTFE-coated cookware into food (Raloff, 2005). Measurement in food simulators was not considered to be feasible as the residual amount of extractable PFOA found in PTFE-coated cookware is not high enough to determine whether mass transfer of PFOA occurs from PTFE-coated cookware into water or oil at cooking temperatures. The authors did not give a limit of detection for the analytical method.

In its opinion related to a 9th list of substances for food contact materials, the EFSA AFC Panel recommended restricting the use of the ammonium salt of PFOA to repeated use articles, sintered at high temperatures only (EFSA, 2005a). Analytical data provided with the petition showed that the substance when being used as a production aid for the PTFE manufacture was not detectable in the final article with detection limits of 20 ng/g. The worst case migration calculated by the AFC Panel was 17 ng/g food.

Paper coatings

Begley *et al*. (2005) determined the amounts of PFOA and other fluorochemicals in different commercial paper-making formulations. The PFOA concentration in microwave popcorn paper bags was as high as 300 ng/g. During microwaving, the grease-resistant paper used in popcorn bags releases traces of PFOA to the oil that coats the kernels. Paper temperatures that can exceed 200 °C significantly increased the potential for PFOA migration. The U.S. FDA considered treated paper as the greatest potential source of fluorochemicals (Raloff, 2005).

Migration tests showed a relatively small (in the low µg/g range) transfer of fluorotelomers to food simulators — such as water or oil (Miglyol) — and to actual food (popcorn oil) (Begley *et al*., 2005). However, Begley's ongoing work, using various emulsions as food simulators, provides indications that fluorotelomer migration to foods may be greater that previously assessed (Renner, 2007).

4.3 *N*-EtFOSA as a precursor of PFOS and PFOA

Tittlemier *et al*. (2003) investigated fast food composites for *N*-ethyl perfluorooctane sulfonamide (*N*-EtFOSA), which is a possible precursor of PFOS and PFOA. Seven fast food

composites were analysed from a total diet study undertaken from 1999 to 2002 in which all foods that comprise more that 1% of the average Canadian diet were sampled (Tittlemier *et al*. (2003). The results are shown in Table 11.

Table 11. *N*-EtFOSA in seven fast food composites.

Composite food	Concentration of *N*-EtFOSA (ng/g wet weight)							
	1992	1993	1994	1998	1999	2000	2001	2002
Chicken burger	—	—	—	0.212	0.098	<0.01 [a]	<0.01	<0.01
Fish burger	<0.01	<0.01	<0.01	<0.01	1.24	—	—	—
Hot dog	—	—	—	3.45	<0.01	<0.01	<0.01	<0.01
Chicken nuggets	—	—	—	1.66	6.73	0.294	0.709	<0.01
Hamburger	<0.01	0.0999	0.583	<0.01	<0.01	<0.01	<0.01	<0.01
Pizza	<0.01	3.19	0.576	23.5	0.466	0.0498	0.0658	<0.01
French fries	12.4	6.73	8.33	1.47	1.49	0.213	0.932	0.0151

(a) Estimated method detection limit = 0.01 ng/g wet weight (Tittlemier *et al*., 2003)

N-EtFOSA concentrations ranged from non-detectable to 23.5 ng/g in pizza composites sampled during 1992 to 2002. After 1999, a decrease in concentrations was observed. The authors concluded that the decrease in *N*-EtFOSA would most likely be due to the cessation in production of perfluorooctyl compounds, and would contribute to a decrease in human dietary exposure to *N*-EtFOSA. However, the food items analysed were only from one fast food company, and may, therefore, not be representative for the entire fast food sector or of other PFAS. From Table 11, it may also be observed the PFAS contents in at least certain foods could change very rapidly. If this is also true for the European scenario, then only recently obtained PFAS data are likely to be suitable for an up-to-date exposure assessment.

5. Human exposure to PFOS and PFOA

5.1 Introduction

Human exposure to PFAS, including PFOA and PFOS, is likely to occur *via* a number of vectors and routes e.g. ingestion of non-food materials, dermal contact and inhalation. Circumstantial factors such as place of residence, age, nature of PFAS vector etc., may also influence exposure. For example, according to Tittlemier *et al*. (2007), food seems to represent the major intake pathway of PFAS in adult Canadians; however, house dust, solution-treated carpeting and treated apparel might contribute a non-negligible 40% to the overall exposure.

In Europe, the first studies of per- and polyfluorinated compounds in air samples were recently reported in the framework of the Perforce project (de Voogt *et al*, 2006a). The anionic compounds were in general only found in the particulate phase, with PFOA often the

predominant analyte. Therefore, it is possible that non-volatile ionic compounds might directly undergo atmospheric transport on particles from source regions. The levels of ionic PFAS at a rural Norwegian site were significantly lower than those found in the UK. Generally, levels of PFAS are reported to be slightly higher in urban areas than rural sites.

Food might become contaminated during production processes and/or cooking due to contact with treated cookware that can release PFAS. However, as outlined in chapter 4 (4.2.5 and 4.4), for the rapid changes in food-production technology at industrial level, direct food contamination from processing, packaging, or cooking may be expected to have been of less importance to total human exposure to certain PFAS in later years (Begley *et al*., 2005; Powley *et al*., 2005; Tittlemier *et al*., 2003, 2006). It must be stressed that the data in general are insufficient to allow for a general evaluation of the contribution of food contact materials to total dietary exposure to PFAS.

5.2 PFOS

5.2.1 Dietary intake studies from EU countries

5.2.1.1 National dietary intake studies

Germany

As also mentioned in chapter 4.1.3, PFOS was included in a monitoring study on dietary exposure to persistent environmental pollutants of the general population in Bavaria, Germany (Fromme *et al*., 2007a). Daily food and beverage duplicates were in 2005 collected from 31 volunteers, aged 16–45 years during seven consecutive days. The daily samples from each volunteer were pooled and homogenised. Based on the medians of seven sampling days and the food consumption figures collected during the study, the authors estimated PFOS daily intake for the general population in the range of 0.6–4.4 ng/kg b.w, with median, mean, and $Q_{.90}$ values of 1.4, 1.8, and 3.8 ng/kg b.w.

United Kingdom

Within the framework of a UK total diet study, several composite food group samples were analysed for PFOS, PFOA, and other fluorinated compounds (UK FSA, 2006; Mortimer *et al*., 2006). Due to the high numbers of non-detects, PFOS dietary exposures were estimated in adults as ranges of lower bound to upper bound values, and were approximately 10–100 and 30–200 ng/kg b.w. per day, respectively for average and high level adult consumers. Estimates for average and high level consumers aged 1.5–4.5 years were 50–300 and 100–500 ng/kg b.w. per day, respectively.

5.2.1.2 Estimate of national dietary intake of PFOS based on occurrence data

As no data on PFAS in food from systematic monitoring activities in the EU countries were available, an intake assessment was carried out based on occurrence data from published papers, presentations in scientific fora, and declassified technical reports, as described in chapter 4. The obvious lack of appropriate occurrence data for most foodstuffs is described more in detail in chapter 4.1. As a consequence of this shortcoming, the following evaluation must be regarded as highly provisional. Despite the obvious uncertainties, the Panel decided to perform an estimation of the possible dietary intake of PFOS in Europe. The reason for this estimation was to achieve an approximate level of the dietary intake of PFOS that could be used in a rough comparison with possible effect levels.

For the purpose of this tentative estimation, the EFSA "Concise European Food Consumption Database" was used. This database comprises consumption data for 15 broad food categories and 21 subcategories from different national food consumption surveys. At the time of preparing the exposure chapter of the opinion this database was under construction and contained only data from four countries, i.e. Italy (Turrini, 2001), the Netherlands (DNFCS, 1998), Sweden (Becker and Pearson, 2002), and the UK (NDNS, 2002). A draft template for the format of the database can be found in the appendix of the opinion on exposure assessment of the EFSA´s Scientific Committee (EFSA, 2005b). It includes consumption by adults from the entire population and by consumers only, expressed in grams per person and day. A consumer of a certain food category is defined as an individual consuming this food at least once during the duration of the survey. In the meantime however, the EFSA "Concise European Food Consumption Database" with consumption data provided by Member States is available on the Authorities webpage[6].

To include intake *via* drinking water, a default consumption of 2 L/day *per capita* was conservatively used. In both cases, the indicative mean contamination levels estimated in chapter 4.1.4 were used. The estimated average PFOS intake of the general adult populations of Italy, the Netherlands, Sweden, and UK is in the range 45–58 ng/kg b.w. per day based on the mean consumption rate for fish and fishery products (Table 12). For the high (97.5th percentile) consumers of fish and fishery products, daily intakes were estimated to be in the range 140–230 ng/kg b.w. Intake of PFOS with drinking water was estimated to be 0.24 ng/kg b.w. per day. Although conservatively estimated, this amount is only 0.5% or less of the average consumer intake from fish and fishery products, and is thus negligible in high consumers of fish and fishery products.

[6] http://www.efsa.europa.eu/EFSA/ScientificPanels/DATEX/efsa_locale-1178620753812_ConciseEuropeanConsumptionDatabase.htm

Table 12. Estimates of PFOS intake in four European adult populations (consumers only) based on consumption of fish and fishery products using the draft EFSA European Concise Food Consumption Database and the indicative occurrence values estimated in this opinion. Drinking water consumption is a conservative default figure. Concentration, consumption, and intake values are rounded to three figures regardless of significance.

Item	Italy	The Netherlands	Sweden	UK
		Drinking water		
Indicative PFOS level [a]	0.00710	0.00710	0.00710	0.00710
Mean consumption in adults [b]	2000	2000	2000	2000
Intake *via* drinking water [c]	14.2	14.2	14.2	14.2
		Fish and fishery products [d]		
Indicative PFOS level [e]	68.1	68.1	68.1	68.1
Mean consumption in adults [b]	50.9 *152*	50.0 [f] *206*	39.5 *121*	43.2 *132*
Intake *via* fish and fishery products [c]	3470 *10400*	3410 *14000*	2690 *8210*	2940 *8990*
		Total intake [g]		
ng/person per day	3480 *10400*	3420 *14000*	2700 *8230*	2960 *9000*
ng/kg b.w. per day [h]	58.0 *173*	57.0 *234*	45.1 *137*	49.3 *150*

(a) In ng/g (see Table 7 in chapter 4.1.4). The estimate used come mainly from surface fresh water data.
(b) In g/person per day.
(c) In ng/person per day.
(d) In italics consumption and intake estimates for high consumers (97.5th percentile).
(e) In ng/g (see Table 7 in chapter 4.1.4). Concentration given on a wet or whole weight (w.w.) basis.
(f) Median (mean not available).
(g) In italics the total intake estimates related to high consumers of fish and fishery products.
(h) Based on an average body weight of 60 kg.

With a statistical approach differing from that described above, PFOS (and PFOA) intakes through the combined consumption of drinking water and fish and fishery products were preliminarily evaluated by Dellatte *et al*. (2006) for "consumers only" of the Italian general population. The assessment was limited to these food groups as no other suitable data seemed to be available at the time for an overall assessment of dietary intake. The following estimates come from a re-assessment by the same authors. The occurrence data were obtained as described in chapter 4.1.4. Food consumption and other relevant data were available from a 1994–1996 national survey of 1940 Italian people: from the database, 1613 "consumers only" were selected. For each subject, the estimated combined intake of PFOS from drinking water (and congruent beverages) and fish and fishery products was divided by the paired individual body weight available from the survey database. The mean intake values estimated for toddlers (N = 63), children (N = 92), and adults (N = 1458) were respectively 120, 66, and 53 ng/kg b.w. per day. For high level (95th percentile) consumers, the corresponding daily estimates were 310, 160, and 140 ng/kg b.w. Intake in toddlers and children is higher than in adults due to the greater amount of food per body weight unit consumed. Drinking water appeared to contribute to PFOS intake negligibly (<0.2%).

5.2.1.3 Pre- and postnatal exposure

PFOS has been shown to be present in cord blood in studies from Northern Canada, Germany, Japan and the US (Inoue *et al.,* 2004; Tittlemier *et al.,* 2006; Apelberg *el al.* 2007b; Midasch 2007). The mean concentration in the study performed in Northern Canada was around 17 ng/mL, whereas in the other studies the level ranged from around 3 to 7 ng/mL. It should be noted that the samples in the study from Northern Canada were collected in 1994 to 2001 whereas the samples in the other studies were collected during 2003 to 2005. Midash *et al.* (2007) also demonstrated that the PFOS levels in cord plasma were lower than in maternal plasma by a factor of 0.6 indicating that prenatal exposure could be lower than the maternal.

Few data are available for PFAS in human milk. The results of local measurements in Sweden and China (Zhoushan area) were recently reported by Kärrman *et al*. (2006; 2007b) and So *et al*. (2006b), respectively. In both cases, milk was collected in 2004 from several primiparous donors. PFOS was present at similar concentrations in the milk from either country: 0.060–0.470 (mean, 0.201) ng/mL in Sweden and 0.045–0.360 (mean, 0.121) ng/mL in China. In the Swedish study, PFOS concentration in milk samples was on average two orders of magnitude lower than its concentration in the sera of the same donors. In a pilot study Völkel *et al.* (2007) analysed 57 breast milk samples from Germany and 13 samples from Gyor/Hungary. The PFOS concentrations ranged between 0.028 and 0.309 (median 0.119) ng/mL in the German samples and between 0.096 and 0.639 (median 0.330) ng/mL in the Hungarian samples. No PFOS could be quantified at an analytical LOD of 0.1–0.4 ng/mL in pooled milk samples collected between 2000–2004 in Germany from a total of 103 mothers (Suchenwirth *et al.,* 2006).

No temporal trend was clearly detected by Kärrman *et al*. (2007b) for PFOS from the analysis of composite samples of milk collected yearly in Sweden between 1996 and 2004.

For instance, for a 5-kg Swedish child consuming breast milk at a rate of 800 mL/day, PFOS intake can be estimated at 48–380 (mean, 160) ng/day, or approximately 9.6–75 (mean, 32) ng/kg b.w. per day. As the Swedish human milk samples all came from the area of Uppsala, this intake estimate may not be representative of breastfed infant exposure to PFOS throughout Sweden. Likewise, the Swedish milk-based intake values may not in principle be extendable to the other European breastfed infants despite the concentrations detected in the Swedish human milk seem to be corroborated by the Chinese findings.

5.2.2 Exposure to PFOS from sources other than food

In spite of the great number of possible non-food PFOS sources for human exposure, there are only sparse data of PFOS occurrence in non-food products. For these exposure pathways, exposure assessment may tentatively be carried out by modelling. An example of extensive modelling applied to exposure assessment and risk characterisation for PFOA in selected

consumer articles is the work by Washburn *et al*. (2005) (see chapter 5.3.2.1). A model approach was also chosen here for PFOS, as described below.

On the whole, due to a substantial lack of data and the many assumptions used in modelling, the following paragraphs give only broad indications and the relative importance of each exposure route or vector require further study. The estimates obtained in this chapter were carried out according to the "lifetime average daily dose" (LADD) approach (U.S. EPA, 2000), which includes the distinct contributions to exposure of childhood up to six years of age and adulthood. The critical exposure parameter (CEP) values shown in Table 13 were derived from U.S. EPA (1996, 2000). In all cases, the bioavailability of the chemical from the air particulate carrier was conservatively set at 100%; similarly, for inhalatory exposure assessment the air particulate was assumed to be 100% inhalable fraction. A summary of the basic available information is presented below together with the exposure values obtained.

Table 13. Critical exposure parameters (CEPs) to evaluate exposure to PFAS *via* routes other than food. Parameters for lifetime average daily dose (LADD) estimates were adapted from U.S. EPA (1996, 2000). Transfer rate and bioavailability magnitudes were conservatively set to 100%.

Critical exposure parameter	Acro-nym	Inhalation (outdoor) [a]	Inhalation (indoor) [b]	Ingestion (outdoor dust) [c]	Ingestion (indoor dust) [d]	Dermal exposure [e]
CEPs for subjects of all ages, with the exceptions shown for children						
Exposed body area	BS	—	—	—	—	4300 cm^2
Body weight	b.w.	60 kg	60 kg	60 kg	60 kg	60 kg
Contact rate [f]	CR	—	—	—	—	0.005 mg cm^{-2}
Dust ingestion rate [g]	DIR	—	—	—	0.05 g day^{-1}	—
Dust ingestion rate [h]	DIR	—	—	0.00075 g day^{-1}	—	—
Event frequency	EF	—	—	—	—	1 event day^{-1}
Exposure duration	ED	64 years	64 years	64 years	64 years	64 years
Inhalation rate	IR	15 m^3 day^{-1}	15 m^3 day^{-1}	—	—	—
Lifetime	LT	70 years	70 years	70 years	70 years	70 years
CEPs specific for children up to six years						
Exposed body area	BS	—	—	—	—	1800 cm^2
Body weight	b.w.	16 kg	16 kg	16 kg	16 kg	16 kg
Dust ingestion rate [g]	DIR	—	—	—	0.1 g day^{-1}	—
Dust ingestion rate [h]	DIR	—	—	0.00044 g day^{-1}	—	—
Event frequency	EF	—	—	—	—	10 event day^{-1}
Exposure duration	ED	6 years	6 years	6 years	6 years	6 years
Inhalation rate	IR	8.7 m^3 day^{-1}	8.7 m^3 day^{-1}	—	—	—

(a) LADD = $(C \times IR \times ED) \times (b.w. \times LT)^{-1}$. Indicative values for the high exposure scenario (ng m^{-3}): C_{PFOS}, 0.01; C_{PFOA}, 0.3. Indicative values for the low exposure scenario (ng m^{-3}): C_{PFOS}, 0.001; C_{PFOA}, 0.003.

(b) LADD = $(C \times IR \times ED) \times (b.w. \times LT)^{-1}$. Indicative values based on a presumed average indoor air-borne dust level of 50 µg m^{-3} (ng m^{-3}): C_{PFOS}, 0.022; C_{PFOA}, 0.019.

(c) LADD = $(C \times DIR \times ED) \times (b.w. \times LT)^{-1}$. Indicative values based on a presumed average outdoor air-borne dust level of 100 µg m^{-3} and a 50%-fraction of the inhaled amount being swallowed. High exposure scenario (ng g^{-1}): C_{PFOS}, 100; C_{PFOA}, 4000. Low exposure scenario (ng g^{-1}): C_{PFOS}, 30; C_{PFOA}, 400.

(d) LADD = $(C \times DIR \times ED) \times (b.w. \times LT)^{-1}$. Based on PFAS concentrations on vacuum-cleaning house dust (ng g^{-1}):

C_{PFOS}, 440; C_{PFOA}, 380.
(e) LADD = (C × CR × ED × BS × EF) × (b.w. × LT)$^{-1}$. Based on PFAS concentrations on vacuum-cleaning house dust (ng g^{-1}): C_{PFOS}, 440; C_{PFOA}, 380.
(f) For each event. This CEP is the adherence factor of soil to skin as defined by U.S. EPA, 2000, arbitrarily applied to contact with indoor dust collectable by vacuum-cleaning.
(g) Indoor.
(h) Outdoor.

5.2.2.1 House dust and indoor air

PFOS in indoor dust collected by vacuum cleaning in 16 Japanese houses was detected at concentrations of 11–2500 (mean, 200) ng/g (Moriwaki *et al*., 2003). In a similar study, PFOS was present at concentrations in the range <4.6–5065 (mean, 443.68) ng/g in 67 samples of dust (size, <150 μm) obtained from as many Canadian houses in Ottawa (Kubwabo *et al*., 2005).

These investigations were carried out by different teams and in locations far apart. However, considering that one data set fell fully within the other, the higher mean concentration of 440 ng/g was conservatively used in this Opinion to estimate indoor exposure to PFOS by ingestion of, and dermal contact with, contaminated house dust (Table 13). The same PFOS concentration in house dust and a default dust level in indoor air of 50 μg/m^3 were utilized to evaluate inhalation exposure to indoor PFOS at a level in air of 0.022 ng/m^3 (Table 13): this value is compatible with indoor air contamination due to outdoor air (see chapter 5.2.2.2). Based on the above assumptions, the combined indoor LADD value for PFOS from the three pathways was estimated to be 0.93 ng/kg b.w. per day. This total is comprised of (ng/kg b.w. per day): dust ingestion, 0.57; dermal contact, 0.36; inhalation, 0.0061.

In Norway, PFOS levels were determined in May 2005 in the particulate phase of one indoor air location. The concentrations were below the LD of 0.0474 ng/m^3 (de Voogt *et al*., 2006a). This is in substantial agreement with the above modelled estimate.

5.2.2.2 Atmospheric levels

Concentrations of PFOS in the particulate phase of European air were recently reported (de Voogt *et al*., 2006a). Air samples were collected in 2005 at two locations in the UK and two locations in Norway. PFOS levels in an urban area ranged from 0.041 to 0.051 ng/m^3 in the UK in March and from 0.0009 to 0.0071 ng/m^3 in the UK in November. In southern Norway PFOS levels ranged from 0.0009 to 0.0011 ng/m^3 in November. The levels of PFOS in the particulate phase of air in the UK were the highest data reported anywhere to date

Recently, atmospheric levels of PFOS in Japan have been recorded (Sasaki *et al*., 2003; Harada *et al*., 2005, 2006; Nakayama *et al*., 2005). Sasaki *et al*. (2003) investigated the outdoor presence of PFOS by monthly sampling the suspended air dust (geometric mean (GM) concentrations, 30.9 and 54.0 μg/m^3) in two Japanese urban settings for a year. Air dust in the cities of Fukuchiyama and Oyamazaki carried PFOS at GM concentrations of 19.2 and 97.4 ng/g, respectively; individual monitored values from non-detectable up to 427.4 ng/g

were also reported. The GM levels of PFOS in air were 0.0006 and 0.0053 ng/m^3, respectively. Harada *et al*. (2005; 2006) also investigated PFOS concentrations at different sites in an urban setting (Kyoto area), obtaining results in agreement with those of Sasaki *et al*. PFOS on air dust was not determined at the site with lower contamination (Morioka); at the site with higher contamination (Oyamazaki), PFOS GM concentration on dust was estimated 72.2 (range, from non-detect to 168.0) ng/g. The GM levels in air were, respectively, 0.0007 and 0.0052 (overall range, 0.00046–0.0098) ng/m^3. At a third location, Route 171, the PFOS concentrations on dust and in air were measured in a single trial at 103.9 ng/g and 0.0068 ng/m^3, respectively.

Boulanger *et al*. (2005) reported the results of an investigation to estimate the atmospheric contribution to the mass supply of PFOS and PFOS-related substances in lake Ontario (North America). PFOS was measured in the range 0.0025–0.0081 ng/m^3 in four of the eight particulate-phase air samples available; it was not detected in the remaining four samples of the same type or in any gaseous-phase air samples.

With reference to the above results, and taking into account the marked variability of the outdoor air concentrations of PFOS, the following four indicative values were used to define two scenarios for ingestion and inhalation, respectively characterizing exposures "low" and "high": PFOS on dust, 30 and 100 ng/g; PFOS in air, 0.001 and 0.01 ng/m^3. As specific data for PFOS in soil were not located, ingestion concerned exclusively the swallowed dust available at a presumed 50% rate from inhalation (correction for a predictable extra-exposure to PFOS was conservatively not performed). Due to the small amount of dust in air, dermal contact was considered to be negligible relative to the parallel contribution of indoor dust (treated as "soil"). Based on the aforesaid assumptions, the combined outdoor LADD values for PFOS from the two mentioned pathways were estimated as 0.00069 and 0.0041 ng/kg b.w. per day, respectively. It is notable that even the high outdoor exposure scenario predicts a contribution <0.5% of the indoor contribution. A relevant outcome of the study was that the air levels of PFOS — and consequently its inhalation exposure values — were confirmed to be strongly dependent on geographical location and sampling period.

5.2.3 Summary

PFOS daily intake was estimated in the range of 0.6–4.4 ng/kg b.w. for the adult general population in Bavaria, Germany, with median and mean values respectively of 1.4 and 1.8 ng/kg b.w. For high (90th percentile) consumers, the intake estimate was 3.8 ng/kg b.w. Due to the high number of non-detects, PFOS dietary daily exposures in UK adults were evaluated as ranges of lower bound to upper bound values, as follows: 10–100 and 30–200 ng/kg b.w. for average and high consumers, respectively.

According to PFOS intake evaluations performed for this opinion based on international occurrence data for fish and fishery products and fresh (drinking) water, the average PFOS

intakes of the adult general populations ("consumers only") of Italy, the Netherlands, Sweden, and UK were estimated to be 45–58 ng/kg b.w. per day. For the high (97.5th percentile) consumers of fish and fishery products, daily intakes were estimated to be 140–230 ng/kg b.w. An additional exposure evaluation carried out for Italy with the same international PFOS occurrence data and based on the distributions of intake in a group of 1613 "consumers only" subjects subdivided into toddlers, children, and adults, yielded mean intake values of 120, 66, and 53 ng/kg b.w. per day, respectively. For high consumers (95th percentile), the parallel daily estimates were 310, 160, and 140 ng/kg b.w. From these data, the Panel concluded that indicative dietary exposure could be in the region of 60 and 200 ng/kg b.w. per day; for average consumers and high consumers of fish, respectively. In the above studies, humans seemed to ingest PFOS with drinking water at the low rate of 0.24 ng/kg b.w. per day or less, which was at most some 0.5% of cumulative intakes in the average or high consumers (97.5th percentile) of fish and fishery products. Intake normalised on body weight show that toddlers and children had some two–three times higher intakes compared to adults.

Based on determinations of PFOS on house dust collected by vacuum-cleaning in Japan and Canada, the combined indoor LADD of PFOS by ingestion, inhalation and dermal contact with the contaminated dust was estimated to be 0.93 ng/kg b.w. per day, with predominant contributions from dust ingestion and dermal contact (0.57 and 0.36 ng/kg b.w. per day, respectively).

Data for PFOS in outdoor air were available mainly from a few locations in Europe (UK and Norway) and in Japan (Kyoto area). A marked variability was observed in the outdoor air concentrations of PFOS: therefore, two scenarios were defined for ingestion and inhalation, characterizing exposures "low" and "high". The combined outdoor LADD values for PFOS from these two pathways were estimated as 0.00069 ("low") and 0.0041 ("high") ng/kg b.w. per day. As data for PFOS in soil were not located, estimates of ingestion were exclusively for the swallowed dust available at a presumed 50% rate from inhalation. Due to the small amount of dust in air, dermal contact was considered to be negligible. Both contributions to exposure appeared to be negligible relative to estimated PFOS dietary intakes; the high outdoor exposure scenario predicted a contribution <0.5% of indoor contribution.

The data available do not allow for an identification of representative values of dietary exposures of average or high European consumers. However, such values may be expected to fall respectively within 2–100 and 4–200 ng/kg b.w. per day; the intake of high consumers should be two–three times higher than the average. Consequently, while outdoor exposure seems to be unimportant, the relevance of indoor exposure cannot be assessed. For instance, if dietary exposures were in the order of the lower ends of the aforesaid ranges — values in fair agreement with the results of a Canadian study by Tittlemier *et al*. (2007) — indoor contributions could be some 50 or 25%, respectively, of intake. Under such conditions, even PFOS intake *via* drinking water (≤0.24 ng/kg b.w. per day) might no longer be irrelevant.

It should be pointed out that the outcome of the indicative dietary exposure evaluation based on consumption of fish and fishery products and drinking water (e.g., approximately 60 ng/kg b.w. per day) and the results from dietary studies in Canada and Germany (e.g., <2 ng/kg b.w. per day) are in visible disagreement: the latter can only partly be explained by taking into account analytical problems, and further investigations are necessary to clarify the issue.

Lastly, due to the limited availability of suitable analytical data and the many assumptions generally used in modelling to derive exposure estimates, the relative importance of exposure routes (and individual vectors) requires further investigation.

5.2.4 Biomonitoring

PFOS is found in serum of occupationally exposed populations and in the serum of the general population (see Tables 14-16). The presence of organic fluoride in humans was actually first reported by Taves (1968) and Shen and Taves (1974) over 30 years ago, but until the 1990s not much attention was paid to the occurrence of these compounds. Since 1993 several studies have been conducted to determine the serum concentration of production workers with an occupational exposure. Data on serum concentrations of the general population were not reported until 1998.

PFOS accumulates in liver and serum. Reported mean serum concentrations of PFOS in occupationally exposed workers are in the order of 1000-2000 ng/mL (see Table 16), serum levels of the general population are about 100 times lower (Olsen*., et al*., 1999 and 2003a). Recent reports (Kärrman *et al.*, 2006; So *et al.*, 2006b; Suchenwirth *et al.*, 2006) suggest that human milk is not a suitable marker for serum levels.

In a study by Kannan *et al.* (2004) (see Table 14-15) PFOS was measured in 473 human blood/serum/plasma samples collected from the United States, Colombia, Brazil, Belgium, Italy, Poland, India, Malaysia, and Korea. Among the four perfluorochemicals measured, PFOS was the predominant compound in blood, as confirmed in other studies (Calafat *et al.*, 2005; Olsen *et al.*, 2005a). Concentrations of PFOS were highest in the samples collected from the United States and Poland (>30 ng/mL); moderate in Korea, Belgium, Malaysia, Brazil, Italy and Colombia (3 to 29 ng/mL); and lowest in India (<3 ng/mL). Serum or plasma to whole blood ratios for PFHS, PFOS, and PFOA, regardless of the anticoagulant used, approximate 2 to 1. The difference between plasma and serum and whole blood corresponds to volume displacement by red blood cells, suggesting that the fluorochemicals are not found intracellularly or attached to the red blood cells (Ehresman *et al*., 2007).

Olsen *et al*. (2003c) reported liver concentrations and serum concentrations from 31 donors from the general population. Liver PFOS concentrations ranged from below 4.5 to 57 µg/kg. Serum PFOS concentrations ranged from below 6.1 to 58.3 µg/L. Among 23 paired samples the mean liver to serum ratio was 1.3 to 1. This liver to serum ratio is comparable to the liver

to serum ratio in PFOS-treated Cynomolgus monkeys with PFOS levels 2-3 orders of magnitude higher than in the human donors.

Calafat *et al.* (2007) reported serum levels of PFOS from 1562 US citizens above 12 years of age. The study was made with material from the NHANES collection during 1999-2000. The 50th percentile was 30.2 ng/mL (range 27.8 to 33.8). The corresponding findings for the 10th and 95th percentile were 15.1 ng/mL (range 13.0 to 17.4) and 75.6 ng/mL (58,1 to 97.5) respectively. In a study within the Danish National Birth Cohort, the average level of PFOA in maternal plasma was 35.3 ng/mL (Fei *et al*., 2007). In another study on PFOS in plasma in samples from Australia, Sweden and the UK the following mean levels were reported: 23.4, 33.4 and 14.2 ng/mL respectively (Kärrman *et al*., 2007a). In a pilot study on PFOS in residents in Catalonia, Ericson *et al.* (2007) found the mean level in blood to be 7.64 ng/mL.

Gender and age effect

Most studies did not find clear gender or age related differences in the concentrations of PFOS e.g. analysis of 645 individual blood samples from adult Red Cross blood donors of six U.S. cities (332 males, 313 females, aged 20-69 years) (Olsen *et al*., 2003b), U.S. study with children (599 samples, Olsen *et al.*, (2002c) and elderly (238 samples, Olsen *et al*., 2002b) and the study of Kannan and co-workers (2004) in which 473 human blood/serum/plasma samples were analysed. Recent data from U.S. in which 50 pooled samples were analysed from 1836 persons (National Health and Nutrition Examination Survey) showed significantly higher levels of PFOS in males than in females but no significant differences among age groups (Calafat *et al.*, 2005). This was confirmed in U.S. samples collected in 1974 and 1989, which were analysed recently (Olsen *et al*., 2005 a). A recent Japanese study (48 participants) also revealed higher serum concentrations in men than in women, but in women the serum concentrations increased with age, while not in men. As a result the concentrations in the older women (> 60 yrs) were similar to those measured in men (Harada *et al.*, 2004).

Also the foetus and neonate may be exposed. A study in Japan, of 15 pairs of maternal and cord blood samples, showed PFOS concentrations in maternal samples ranged from 4.9 to 17.6 µg/L, whereas those in foetal samples ranged from 1.6 to 5.3 µg/L (Inoue et *al.,* 2004).

Demographic and ethnic differences

The study of Kannan and co-workers (2004) in which samples were obtained from 9 different countries showed differences in levels of PFOS in relation to the country of the donors. The U.S. study (Calafat *et al.*, 2005) showed that non-Hispanic whites had statistically significantly higher concentrations of PFOS than both non-Hispanic blacks and Mexican Americans; Mexican Americans had statistically significantly lower concentrations than non-Hispanic blacks. Genetic variability, diet, lifestyle, or a combination of all these factors may

contribute to the different patterns of human exposure to PFOS observed among the population groups.

Time trend

An increase in serum levels of PFOS was observed in a study in which 178 U.S. serum samples were collected in 1974 and 1989. Comparison with U.S. serum samples collected in 2001 (Olsen *et al.*, 2003b), indicated no further increase (Olsen *et al.*, 2005a). Based on analysis of historical samples, a Japanese study showed that PFOS serum concentrations increased over the last 25 years by a factor of 3 (Harada *et al.*, 2004).

Serum levels of PFOS in relation to diet

A recent study in Sweden, which included 108 women, showed a weak association of serum PFOS concentration with increasing consumption of predatory fish species such as pike, perch and pikeperch but not with total fish consumption. PFOS was also correlated to consumption of shellfish. Concentrations of PFOS were not correlated to consumption of fatty fish, such as salmon and herring. No correlation was found with other types of food in the survey (Holmström *et al.*, 2005). Concentrations of 10 perfluorochemicals accumulating in the human body have been quantified in human blood and in some marine food resources from the region of the Gulf of Gdansk at the Baltic Sea south coast in Poland. Food was found to be an important route of exposure for all 10 perfluoroalkyl compounds detected in non-occupationally exposed humans. Individuals who claimed to have a high fish consumption in their diet (mainly Baltic fish) on average contained the highest load of all 10 fluorochemicals including PFOS when compared with the other human subpopulations (Falandysz *et al.*, 2006).

Table 14. PFOS and PFOA serum concentration in the European non-occupationally exposed population.

Origin	Reference	Year	N	PFOS Mean (ng/mL)	PFOS Range (ng/mL)	PFOA Mean (ng/mL)	PFOA Range (ng/mL)
Belgium (Flanders, Wallonia)	Kannan *et al*., 2004	1998 and 2000	4 (F[a])	11.1	-	4.1	-
		1998 and 2000	16 (M[b])	16.8	-	5	-
Belgium (blood banks, 6 pooled samples)	3M Company, 2003	1999	6	17	4.9 – 22.2	-	-
Denmark (mother at delivery <25 years of age)	Fei *et al*., 2007	1996-2002	118	38.6	12.0[g]	6.2	2.1[g]
Denmark (mother at delivery 25-29 years of age)	Fei *et al*., 2007	1996-2002	547	36.8	12.8[g]	6.0	2.8[g]
Denmark (mother at delivery 30-34 years of age)	Fei *et al*., 2007	1996-2002	504	33.9	13.2[g]	5.2	2.2[g]
Denmark (mother at delivery <25 years of age)	Fei *et al*., 2007	1996-2002	230	33.0	12.7[g]	5.1	2.4[g]
Germany (blood banks, 6 pooled samples)	3M Company, 2003	1999	6	37	32 – 45.6	-	-
Germany (general adult population)	Fromme *et al*., 2007b	2005	168 (F)	10.9[ce]	2.5-30.7	4.8	1.5-16.2
			188 (M)	13.7[ce]	2.1- 55.0	5.7	0.5-19.1
Germany Non-smokers	Midash *et al*., 2006	2003-2004	54 (F)	19.9[ce]	6.2-130.7	5.8[ce]	1.7-39.3
			51 (M)	27.1[ce]		8.3[ce]	
The Netherlands (blood banks, 5 pooled samples)	3M Company, 2003	1999	5	53	39 - 61	-	-
Sweden (Swedish population)	Kärrman *et al*., 2004	1997-2000	17	33.4	10.1– 90.9	4.0	1.1-8.4
Sweden (primipara women)	Kärrman *et al*., 2006	2004	12 (F)	20.7[d,e]	8.2-48.0	3.8[d,e]	2.4-5.3
Sweden (Swedish women with high fish consumption	Holmström *et al*., 2005a	2001	108	36	6.0 - 130	4.0	0.8 - 10
Sweden (Swedish women with high fish consumption	Kärrman *et al*., 2007b	1997-2000	10 (M)	33.4	19.6[g]		
			7 (F)				
UK (Swedish women with high fish consumption	Kärrman *et al*., 2007b	2003	6 (M)	14.2	6.0[g]		
			7 (F)				
Spain (Catalonia) Men 20-60 years	Ericson *et al*., 2007	2006	24	8.47	3.9[g]	2.02	0.71[g]
Spain (Catalonia) Women 20-59 years	Ericson *et al*., 2007	2006	24	6.81	2.98[g]	1.57	0.52[g]
Italy (Siena)	Kannan *et al*., 2004	2001	8 (F[a])	4.4	-	<3	-
		2001	42 (M[b])	4.3	-	<3	-
Poland (Gdansk)	Kannan *et al*. 2004	2003	15 (F[a])	33.3	-	21.9	-
		2003	10 (M[b])	55.4	-	20.5	-
Poland	Falandysz *et al*., 2006	2003	45 ("Normal" fish consumption)	13.7	5.2 – 46	3.0	1.2 – 6.2
			15 High fish consumption	41	14 – 84	4.1	1.7 – 8.7

(a) Female (b) Male (c) median (d) mean (e) serum or plasma (f) whole blood (g) standard deviation

Table 15. PFOS and PFOA serum concentration in the non-European non-occupationally exposed population.

Origin	Reference	Year	N	PFOS		PFOA	
				Mean (ng/mL)	Range (ng/mL)	Mean (ng/mL)	Range (ng/mL)
USA (mother at delivery <18 years of age)	Apelberg *et al.*, 2007a	2004-2005	24	5.0	(3.3-7.5)	1.4	(1.1-2.3)
USA (mother at delivery 18-35 years of age))	Apelberg *et al.*, 2007a	2004-2005	246	5.0	(3.5-7.9)	1.6	(1.2-2.1)
USA (mother at delivery > 35 years of age)	Apelberg *et al.*, 2007a	2004-2005	23	4.1	(3.3-8.7)	1.6	(0.9-2.0)
USA (Adults 30-60 yrs)	Olsen *et al.*, 2005 a	1974	178	30.1	27.8 - 32.6	2.1	1.9-2.2
USA (Adults 39-65 yrs)	Olsen *et al.*, 2005 a	1989	178	33.3	31.1-35.6	5.5	5.2-6.9
USA (Elderly)	Olsen *et al.*, , 2004	-	238	31	3.4-17 5	-	-
USA (3M corporate managers)	3M Company, 2003	1998	31	47	26-96	12.5[(d)]	5.2-6.9
USA (Com. sources, Intergen)	OECD, 2002	1998	500	44	43-44	-	-
USA (Commercial sources, Sigma)	OECD, 2002	1998	200	33	26-45	-	-
USA (U.S. blood banks)	OECD, 2002	1998	18	29.7	9-56	17[(e)]	12-22
USA Children (2-12y)	Olsen *et al.*, 2002c	1999	599	37.5	6.7-515	5.6	4.27-56.1
USA (Other commercial sources)	OECD, 2002	1999	35	35	5-85		
USA (Am. Red Cross bl.bank)	Olsen *et al.*, 2002a,	2000	652	34.9	4.3-1656	5.6	
USA (Central Michigan)	Kannan *et al.*, 2004	2000 2000	46 (F^a) 29 (M^b)	32.5 32.9	- -	4.7 5.7	
India (Coimbatore)	Kannan *et al.*, 2004	2000 2000	11 (F^a) 34 (M^b)	2.3 1.7	- -	<3 3.5	- -
USA (Murray, Kentucky)	Kannan *et al.*, 2004	2002 2002	11 (F^a) 19 (M^b)	66 73.2	- -	23 41.6	
USA (New York City)	Kannan *et al.*, 2004	2002	70	42.8	-	27.5	
Japan (Plant management, Tokyo)	Burris, 1999	1999	30	52.3	33-96.7		
Japan (Sagamihara)	OECD, 2002	1999	32	40.3	31.9-56.6		
Japan [(c)] (Yokohama & Tsukuba)	Kannan *et al.*, 2004	2002 2002	11 (F^a) 19 (M^b)	66 73.2	- -	23 41.6	
Japan	Harada *et al.*, 2004	2004	20 (F^f) 8 (F^g) 12 (M^f) 8 (M^g)	13.18 24.00 28.28 29.44	5.03[h] 7.55[h] 10.19[h] 16.44	7.89 12.63 12.69 12.41	3.61[h] 2.4[h] 3.43[h] 4.09[h]
USA (Autopsies, 5-74 y)	Olsen *et al.*, 2003c	2003	24	17.7	6.1-58.3		
Columbia (Cartagena)	Kannan *et al.*, 2004	2003 2003	25 (F^a) 31 (M^b)	8 8.5	- -	6.1 6.2	- -
Brazil (Rio Grande)	Kannan *et al.*, 2004	2003 2003	17 (F^a) 10 (M^b)	10.7 13.5.8	- -	<20 <20	- -
Korea (Daegu)	Kannan *et al.*, 2004	2003 2003	25 (F^a) 25 (M^b)	15.1 27.1	- -	88.1 35.5	- -
Malaysia (Kuala Lumpur)	Kannan *et al.*, 2004	2004 2004	7 (F^a) 16 (M^b)	11.7 13.2	- -	<10 <10	- -
USA Bio. supplies companies	Hansen, 2001	_	65	28.4	6.7- 81.5	6.4	

(a) Female
(b) Male
(c) Values from Masunaga *et al.*, 2002 and Taniyasu *et al.*, 2003
(d) Only 4 employees were above LOD of 10 µg/L. (Hekster *et al.*, 2002)
(e) PFOA detected in about 1/3 of the pooled samples but quantifiable in only two
(f) 20 – 50 years old
(g) < 50 years old
(h) Standard deviation

Table 16. PFOS and PFOA serum concentration in production workers

Origin	Reference	Year	N	PFOS		PFOA	
				Mean (ng/mL)	Range (ng/mL)	Mean (ng/mL)	Range (ng/mL)
Belgium (Antwerp plant)	cited in Hekster *et al*., 2002	1995	93	1,930	100 - 9,930	1,130	0 - 13,200
		1997	65	1,480	100 - 4,800	-	-
		2000	258	800	40 - 6,240	830	10 - 7,040
Japan (Sagamihara)	cited in Hekster *et al*., 2002	1999	32	135	47.5-628	-	-
USA (Cottage Grove Plant)	cited in Hekster *et al*., 2002	1993	111	-	-	5,000	0 - 80,000
		1995	80	2,190	0 - 12,830	6,800	0 - 114,100
		1997	74	1,750	100 - 9,930	6,400	100 - 81,300
USA (Decatur plant)	cited in Hekster *et al*., 2002	1995	90	2,440	250 - 12,830	1,460	-
		1997	84	1,960	100 - 9,930	1,570	-
		1998	126	1,510	90 - 10,600	1,540	20 - 6,760
		2000	263	1,320	60 - 10,060	1,780	40 - 12,700
USA (Building 236)	cited in Hekster *et al*., 2002	2000	45	182	<370 - 1,036	106	8 - 668

In summary PFOS is the predominant perfluorochemical which has been measured worldwide in human serum samples. Mean serum levels in studies of EU inhabitants vary between 4 (Italy) and 55 (Poland) ng/mL. Geographical differences have been observed. PFOS is also detectable in human milk samples, the first indications are that the concentrations are about 100 times lower than serum levels. No clear age trends in relation to serum concentrations have been observed. There is evidence that serum levels have increased over the past decades, however it is not clear whether this trend is still continuing. In some studies a relation with high levels of fish consumption has been described.

5.3 PFOA

5.3.1 Dietary intake studies from EU countries

5.3.1.1 National dietary intake studies

Germany

As described in chapter 4.2.3, duplicate diet samples were collected in 2005 in Bavaria, Germany by 31 adult subjects of both sexes, aged 16–45 years, within the framework of a dietary intake study including PFOA (Fromme *et al*., 2007a). The daily food and beverage samples of each volunteer were pooled and homogenised. Based on the medians of seven sampling days and the recorded food consumption figures, PFOA daily intake was estimated in the range of 1.1–11.6 ng/kg b.w. (lower to upper bound), with median, mean, and Q_{90} values of 2.9, 3.9, and 8.4 ng/kg b.w., respectively.

United Kingdom

As noted in chapter 5.2.1.1, PFOA was analyzed in composite food group samples from the 2004 UK total diet study (UK FSA, 2006; Mortimer *et al*., 2006). PFOA was not detected in any of the food groups except the potatoes group. Due to the high number of non-detects, PFOA dietary intakes in adults were estimated as a range from lower bound to upper bound values, and were approximately 1–70 and 3–100 ng/kg b.w. per day, in the average and high consumers respectively. The highest estimated daily intakes were for the 1.5–4.5 year age group, being in the order of 4–200 and 10–300 ng/kg b.w. for average and high consumers respectively.

5.3.1.2 Examples of national dietary intake estimates based on international PFOA occurrence data

Italy, The Netherlands, Sweden, and UK

As there were no data on PFOA in food from systematic monitoring activities in the EU countries, an intake assessment for adults was carried out based on the occurrence data derived as described in chapter 4 as well as on food consumption patterns of Italy, the Netherlands, Sweden and the UK as described in chapter 5.2.1.2. In spite of the relatively limited descriptive power of the PFOA data sets, the overall picture is consistent with an average PFOA intake of 1.7–2.1 ng/kg b.w. per day (Table 17. For high (97.5th percentile) consumers of fish and fishery products, PFOA daily intake appears to be in the range 4.5–7.5 ng/kg b.w. Ingestion of PFOA with drinking water was estimated to be at the relative low rate of 0.31 ng/kg b.w. per day: this amount is a minor (≈19%) to small (≈6%) proportion of intakes from fish and fishery products in average or high consumers, respectively.

As described in chapter 5.2.1.2, a study of PFOA dietary intake for "consumers only" subjects of the Italian general population was carried out by Dellatte *et al*. in 2006. An update of the study has recently been performed. The mean intake estimates for "consumers only" toddlers, children, and adults were respectively 3.8, 2.2, and 1.7 ng/kg b.w. per day. For high (95th percentile) consumers, the corresponding daily intakes were estimated at 10, 4.9, and 4.3 ng/kg b.w. Intake in toddlers and children is higher than in adults due to the greater amount of food per body weight unit consumed by young humans. The contribution of drinking water to intake was found to be small (<7%).

Table 17. Estimates of PFOA intakes in four European adult populations (consumers only) based on consumption of fish and fishery products using the draft EFSA European Concise Food Consumption Database and the indicative occurrence values estimated in this Opinion. Drinking water consumption is a conservative default figure. Concentration, consumption, and intake values are rounded to three figures regardless of significance.

Food group	Italy	The Netherlands	Sweden	UK
		Drinking water		
Indicative PFOA level [a]	0.00937	0.00937	0.00937	0.00937
Mean consumption in adults [b]	2000	2000	2000	2000
Intake *via* drinking water [c]	18.7	18.7	18.7	18.7
		Fish and fishery products [d]		
Indicative PFOA level [e]	2.10	2.10	2.10	2.10
Average consumption in adults [b]	50.9 *152*	50.0 [f] *206*	39.5 *121*	43.2 *132*
Intake *via* fish and fishery products [c]	107 *320*	105 *433*	83.0 *253*	90.7 *277*
		Total intake [g]		
ng/person per day	126 *339*	124 *451*	102 *272*	110 *296*
ng/kg b.w. per day [h]	2.09 *5.65*	2.06 *7.52*	1.69 *4.53*	1.82 *4.93*

(a) In ng/g (see Table 7 in chapter 4.1.4). The estimate used come mainly from surface fresh water data.
(b) In g/person per day.
(c) In ng/person per day.
(d) In italics consumption and intake estimates for high consumers (97.5th percentile).
(e) In ng/g (see Table 7 in chapter 4.1.4). Concentration given on a wet or whole weight (w.w.) basis.
(f) Median (mean not available).
(g) In italics the total intake estimates related to high consumers of fish and fishery products.
(h) Based on an average body weight of 60 kg.

5.3.1.3 Pre- and postnatal exposure

PFOA has been shown to be present in cord blood in studies from Northern Canada, Germany and the U.S. (Tittlemier et al. 2007, Midasch 2007 and Apelberg *el al.* 2007a). The mean concentration in the study performed in Northern Canada was around 3.4 ng/mL, whereas in the other studies the mean level ranged from around 1.6 to 3.4 ng/mL. It should be noted that the samples in the study from Northern Canada were collected in 1994 to 2001 whereas the samples in the other studies were collected during 2003 to 2005. Midash et al. (2007) found that the levels cord plasma were higher than in maternal plasma by a factor 1.26 indicating that prenatal exposure could be higher than the maternal. This finding is opposite to the result for PFOS.

As noted in chapter 5.2.1.3, very sparse data are available for PFAS in human milk. In samples collected in 2004 from primiparous donors, PFOA was found to be present at concentrations of <0.209–0.492 ng/mL in Sweden (Kärrman *et al*., 2006; 2007b) and 0.047–0.210 (mean, 0.106) ng/mL in China, Zhoushan area (So *et al*., 2006b). In the Swedish assessment (N = 12), the results were below the blank level (0.209 ng/mL) in all samples but

one. It is therefore impossible to perform a more reliable estimation of the ratio of PFOA concentration in milk and sera samples of the same donors. Although based on limited data, it appears that the levels of PFOA in human milk could be at least one order of magnitude below those in serum and similar to those of PFOS. In the study by Völkel *et al*. (2007) only 11 out of the total of 70 samples analysed from German and Hungarian mothers reached the limit of quantification (LOQ) of 0.2 ng/mL. The levels in the positive samples ranged from 0.201 – 0.460 ng/mL. PFOA was quantified in pooled milk samples collected over the period 2000–2004 from a total of 103 mothers living in Germany: concentrations were found to be between one and two orders of magnitude greater than those reported for the human milk samples from other investigations (Suchenwirth *et al*., 2006). The Panel noted the high concentrations and the unusual distribution of the PFAS determined in this study and concluded that these data have to be considered with care.

Based on the aforesaid data, a 5-kg Swedish child consuming breast milk at a rate of 800 mL/day would have a PFOA intake of <170–390 ng/day, or approximately <33–79 ng/kg b.w. per day. The Swedish human milk samples were collected in the area of Uppsala and these intake estimates may not be representative of exposure in other regions. However, as for PFOS, the concentrations detected in the Swedish human milk are reasonably comparable to the Chinese findings. However, if the human milk PFOA concentrations in Germany reported by Suchenwirth *et al*. (2006) were taken as a reference, breastfeeding would result in higher exposure rates.

5.3.2 Exposure to PFOA from sources other than food

A summary of the available information is presented here together with the exposure values obtained. Introductory comments are in chapter 5.2.2. The CEP values for LADD are summarized in the Table 12.

5.3.2.1 Exposure assessment for PFOA in selected consumer articles

Washburn *et al.* (2005) provided an example of a model for evaluating pathways of non-food human exposure to PFAS that focused on PFO (the PFOA anion) in selected consumer articles, primarily mill- and solution-treated carpeting and treated clothing. The results, obtained by extensive and complex modelling, were presented as “hypothetical” and are categorised as “more typical exposure” (MTE) or “reasonable maximum exposure” (RME) scenarios. The authors noted that exposure may be expected to decrease by one to two orders of magnitude when moving from childhood through adolescence into adulthood. The total MTE and RME contributions to daily exposures in adults from the non-food articles taken into account would be approximately 0.09 and 3.1 ng/kg b.w., respectively

There are considerable uncertainties in the results presented by Washburn *et al.* (2005), due to the many assumptions and extensive modelling and a substantial lack of experimental evidence. The Supporting Information of the paper provides indications of how ingestion, dermal contact, and inhalation exposure pathways were dealt with in the modelling process.

5.3.2.2 House dust and indoor air

Moriwaki *et al.* (2003) reported detection of PFOA in the indoor dust of Japanese houses at levels of 69–3700 (mean, 380) ng/g. Kubwabo *et al*. (2005) reported PFOA at concentrations of <2.3–1234 (mean, 106.00) ng/g in fine dust of Canadian houses.

As noted in chapter 5.2.2.1, these investigations were independent and geographically far apart. However, the ranges of the two groups of findings seemed to overlap. Therefore, the indicative mean concentration of 380 ng/g was conservatively taken in this Opinion to estimate indoor exposure to PFOA by ingestion of, and dermal contact with contaminated house dust. Inhalation exposure was calculated at a PFOA concentration in air of 0.019 ng/m^3, obtained as described in chapter 5.2.2.1. The combined indoor LADD value for PFOA from these three pathways was estimated at 0.81 ng/kg b.w. per day, comprising (ng/kg b.w. per day): dust ingestion, 0.49; dermal contact, 0.31; inhalation, 0.0052.

PFOA levels in the particulate phase of Norwegian indoor air were reported to be between 0.0034 and 0.0069 ng/m^3 (de Voogt *et al*., 2006). These values are lower than the modelled concentration in Table 13.

5.3.2.3 Atmospheric levels

Levels of PFOA in the particulate phase of air in Europe were recently reported (de Voogt *et al*., 2006a). In the UK, levels varied from 0.226–0.828 ng/m^3 in March 2005, and from 0.006–0.222 ng/m^3 in November. Differences in PFOA levels between the rural and the urban site in the UK were less clear than for PFOS. The levels of PFOA at the rural Norwegian site were significantly lower than those found in the UK. In southern Norway (data from November) levels varied between 0.0014 and 0.0017 ng/m^3.

Atmospheric PFOA levels, measured at different locations in an urban setting (Kyoto environment), were reported by Harada and co-workers (2005, 2006) and Nakayama *et al*. (2005). According to Harada *et al*. (2005; 2006), PFOA on air particulate was not quantified at a site with lower contamination (Morioka); whereas at a site with higher contamination (Oyamazaki), the GM PFOA concentration on particulate was 3412.8 (range, from non-detect to 9049) ng/g. The GM levels in air at these two sites were, respectively, 0.0020 and 0.2627 (overall range, 0.00159–0.919) ng/m^3. At a third location, Route 171, the PFOA

concentrations on particulate and in air were measured in a single trial at 4916 ng/g and 0.3197 ng/m^3, respectively.

Barton *et al*. (2006) reported high PFOA concentrations (up to 900 ng/m^3; non-detects, 78.6%) in air at some of the sampling sites by the fence of a fluoropolymer manufacturing facility in the U.S. Sampling was carried out over a 10-week period. While no vapour-phase PFOA was detected above a LD of approximately 70 ng/m^3, more than 94% of the air-borne particles were below a 4-µm size and a large fraction below a 0.3-µm size and hence a substantial proportion of the PFOA fraction was inhalable.

Compared to data published from Japan and North America, the concentrations of PFOA in the UK were similar to one location in Japan, and the concentrations in Norway were similar to other much lower reported values.

Due to the variability in the outdoor air concentrations of PFOA, similarly to PFOS (see chapter 5.2.2.2) four indicative values were used to define two scenarios for ingestion and inhalation, respectively characterising "low" and "high" exposures: PFOA on dust, 400 and 4000 ng/g; PFOA in air, 0.003 and 0.3 ng/m^3. As for PFOS, data for PFOA in soil were not available and therefore estimates for ingestion were restricted to the swallowed dust from inhalation. Based on the above conditions, the combined outdoor LADD values for PFOA from the two mentioned pathways were estimated to be 0.0063 and 0.14 ng/kg b.w. per day, respectively: the contribution to exposure of the low outdoor exposure scenario is negligible to indoor exposure (see chapter 5.3.2.2). However, a contribution to exposure in the order of 17% of indoor LADD may approximately be estimated from the high outdoor exposure scenario. The air levels of PFOA appear to be dependent on geographical location and sampling period even more than PFOS.

5.3.3 Summary

PFOA daily intake was estimated in the range of 1.1–11.6 ng/kg b.w. (lower and upper bound) for the German adult general population in Bavaria, with median and mean values respectively of 2.9 and 3.9 ng/kg b.w. For high (90th percentile) consumers, the intake estimate was 8.4 ng/kg b.w. Due to the high number of non-detects, PFOA dietary exposures in UK adults were estimated as ranges of lower bound to upper bound values, as follows: 1–70 and 3–100 ng/kg b.w. per day for average and high consumers, respectively.

According to PFOA intake evaluations performed for this opinion based on international PFOA occurrence data for fish and fishery products and fresh (drinking) water, the average PFOA intake estimates for the adult general populations ("consumers only") of Italy, the Netherlands, Sweden, and UK are in the range of 1.7–2.1 ng/kg b.w. per day. For the high (97.5th percentile) consumers of fish and fishery products, PFOA daily intakes were estimated to be in the range 4.5–7.5 ng/kg b.w. A preliminary parallel exposure evaluation

carried out for "consumers only" Italian subjects (toddlers, children, and adults) yielded mean daily intake values of 3.8, 2.2, and 1.7 ng/kg b.w., respectively. For high consumers (95th percentile), the corresponding daily intakes were estimated at 10, 4.9, and 4.3 ng/kg b.w. Humans appeared to ingest PFOA with drinking water at the relatively low rate of 0.31 ng/kg b.w. per day or less, which was at most some 16% or 5% of cumulative intakes in the average or high consumers (97.5th percentile) of fish and fishery products. As already observed for PFOS, the intake normalized on body weight is higher in children.

In the light of the above, there is some evidence that the average dietary exposure to PFOA of the general European population would not exceed 4 ng/kg b.w. per day, an observation also in reasonable agreement with the results of a Canadian study by Tittlemier *et al*. (2007). Based on the information in Table 17, the Panel decided that an indicative estimate of PFOA exposure from food and water would be in the region of 2 ng/kg b.w. per day. The high consumers' intake could be expected to be two–three times higher and is indicatively taken as 6 ng/kg b.w. per day.

With reference to PFOA in selected consumer articles (e.g., treated clothing and mill- and solution-treated carpeting), modelling indicates that exposure decreases by one to two orders of magnitude when moving from childhood into adulthood. The total contribution to daily exposures in adults from the non-food articles taken into account would be approximately 0.09 ng/kg b.w., a very minor fraction of the average PFOA intake from food and negligible relative to PFOA intake of high consumers. Higher contributions to PFOA exposure from consumer articles were also more conservatively estimated (≈3.1 ng/kg b.w. per day), a value in the order of the average dietary intake.

Based on determinations of PFOA on vacuum-cleaning house dust collected in Japan and Canada, the combined indoor exposure (LADD) to PFOA by ingestion and inhalation of, and dermal contact with, contaminated house dust was estimated for this Opinion as 0.81 ng/kg b.w. per day, with predominant contributions from dust ingestion and dermal contact (respectively, 0.49 and 0.31 ng/kg b.w. per day).

Data for PFOA in outdoor air were available mainly from a few locations in Europe (UK and Norway) and in Japan (Kyoto area). Some particularly high concentrations were detected near a fluoropolymer manufacturing facility in the U.S. and were therefore not taken into account in considering exposure of the general population in the EU. Due to the variability in PFOA concentrations in outdoor air, two scenarios were defined in this Opinion for ingestion and inhalation, respectively characterizing exposures "low" and "high". The combined outdoor LADD values for PFOA from these two pathways were estimated as 0.0063 ("low") and 0.14 ("high") ng/kg b.w. per day, respectively. As data for PFOA in soil were not available, ingestion focussed exclusively on the swallowed dust available at a presumed 50% rate from

inhalation. Dermal contact was considered to be negligible. The contribution to exposure of the low outdoor exposure scenario is negligible relative to PFOA dietary intakes and relative to indoor exposure. However, the high outdoor exposure scenario predicts a contribution to exposure in the order of a few percents of PFOA average dietary intake and approximately 17% of the indoor contribution.

In conclusion, the PFOA contributions to human exposure from the non-food sources examined — such as indoor house dust and atmospheric dust — are approximately in the order of 1 ng/kg b.w. per day, i.e. some 25% or possibly more, of average dietary exposure, with a clear predominance of indoor exposure. Drinking water appears to contribute to a modest extent (<16%). Therefore, taking into account the non-food sources examined, the total average daily exposure to PFOA of the adult general European population may be estimated not exceeding 5 ng/kg b.w. and at 10 ng/kg b.w. for high consumers.

However, due to a substantial lack of suitable analytical data and the many assumptions used in modelling to derive exposure estimates, the figures provided above should be taken as indicative. The relative importance of exposure routes (and individual vectors) is an issue requiring further investigation.

5.3.4 Biomonitoring

Tables 14-16 above give an overview of the PFOA serum concentration of production workers and of the general population at various locations.
Kannan *et al.* (2004) (see Tables 14 and 15) reported PFOA concentrations in 473 human blood/serum/plasma samples collected from the United States, Colombia, Brazil, Belgium, Italy, Poland, India, Malaysia, and Korea. Concentrations of PFOA were lower than those of PFOS in most countries except for India and Korea. This may indicate that pollutant sources and exposure patterns for the perfluorocompounds may differ between countries.

Calafat *et al.* (2007) reported serum levels of PFOA from 1562 US citizens above 12 years of age. The study was made with material from the NHANES collection during 1999-2000. The 50^{th} percentile was 5.1 ng/mL (range 4.7 to 5.7). The corresponding findings for the 10^{th} and 95^{th} percentile were 2.8 ng/mL (range 2.5 to 3.0) and 11.9 ng/mL (10.9 to 13.5) respectively.
In a study within the Danish National Birth Cohort the average level of PFOA in maternal plasma was 5.6. In a pilot study on PFOA in residents in Catalonia, Ericson *et al.* (2007) found the mean level in blood to be 1.8 ng/mL.

Gender and age effect

No clear gender or age related differences in the concentrations of PFOA have been demonstrated. Recent data from the U.S.A., in which 50 pooled samples from 1836 persons

were analysed (National Health and Nutrition Examination Survey), showed significantly higher levels of PFOA in males than in females but no significant differences among age groups (Calafat *et al.*, 2005). Results from samples collected in U.S.A. in 1974 and 1989 did not indicate differences by age or sex (Olsen *et al.*, 2005a). A Japanese study showed higher serum concentrations in men compared to women. A subsequent small study with 48 participants (Kyoto city dwellers) showed a clear age associated increase in serum concentrations in female study participants but not in men (Harada *et al.*, 2004).

Demographic and ethnic differences

The study of Kannan and co-workers (2004), in which samples were obtained from 9 different countries, showed differences in serum levels of PFOA in relation to the country of the donors. The U.S.A. study (Calafat *et al.*, 2005) showed that non-Hispanic whites had statistically significantly higher concentrations of PFOA than both non-Hispanic blacks and Mexican Americans; Mexican Americans had statistically significant lower PFOA concentrations than non-Hispanic blacks. Genetic variability, diet, lifestyle, or a combination of all these factors may contribute to the different patterns of human PFOA exposure observed among the population groups. In Japan, clear differences in serum PFOA concentrations were observed according to the area of residence (Harada *et al*., 2004).

Time trend

An increase in serum PFOA levels was observed in a study in which 178 U.S. serum samples were collected in 1974 and 1989. Serum samples collected in 2001 in the US (Olsen *et al.*, 2003b) showed no further increase (Olsen *et al*, 2005a). Based on analysis of historical samples, a Japanese study showed that serum PFOA concentrations increased over the last 25 years by a factor of 14 (Harada *et al*., 2004).

Serum PFOA levels in relation to diet

Concentrations of 10 perfluorochemicals accumulating in the human body have been quantified in human blood and in some marine food resources from the region of the Gulf of Gdansk at the Baltic Sea south coast in Poland. Food was found to be an important route of exposure for all 10 perfluoroalkyl compounds detected in non-occupationally exposed humans. Individuals who claimed to have high fish consumption in their diet (mainly Baltic fish) on average had the highest serum concentrations of all 10 fluorochemicals including PFOA, when compared with the other human subpopulations (Falandysz *et al.*, 2006).

In summary PFOA is found worldwide in serum of the non-occupationally exposed populations. Mean PFOA levels in studies of EU inhabitants vary between 4 and 20 µg/L. These levels are about 100 times lower than serum levels found in occupationally exposed persons. In general PFOA concentrations in humans are lower than those of PFOS (Olsen,

1999 and 2003a). There are no clear age trends. There is evidence that serum PFOA levels have increased over the last decades, however it is not clear whether this trend is still continuing.

6. Hazard identification and characterisation

6.1 PFOS

6.1.1 Toxicokinetics

6.1.1.1 Animal studies

In a study by Johnson and co-workers (1979a), ^{14}C-labeled PFOS was administered orally to male rats at a mean dose of 4.3 mg/kg b.w. Within 48 h the authors found about 5% of the total radioactivity remaining in the faeces and the digestive tract including the tissue and the luminal contents. From these findings the authors concluded that about 95% of the radioactivity was absorbed.

In addition 86% of the administered radioactivity was recovered in the carcasses at 24 to 48 h after dosage. Traces of radioactivity were found in urine (1 - 2% per day). No selective retention of radioactivity was found in the spleen or in erythrocytes.

Eighty nine days after a single *i.v.* administration of 4.2 mg PFOS/kg b.w. to male rats the tissue concentration of radioactivity (expressed as µg PFOS/g) were: liver 20.6; plasma 2.2; kidney 1.1; lung 1.1 (Johnson *et al.*, 1979b). In other tissues concentrations were at, or below 0.6 µg/g. No radioactivity was found in the brain. Thus the liver contained the largest proportion of the radioactivity recovered after 89 days. Excretion *via* the kidney was found to be the major route of elimination. A mean of 30.2% of the total radioactivity administered was found in urine by 89 days. Mean faecal elimination was 12.6% within the same period. The redistribution half-life from plasma was calculated as 7.5 days. (Johnson *et al.*, 1979a). The elimination half-life in rats has been estimated at >90 days for male rats (Johnson *et al.*, 1979b).

Austin *et al.* (2003) analysed four to five female rats injected *i.p.* daily with PFOS at dose evels of 0, 1 and 10 mg/kg b.w. for 2 weeks. At the end of the treatment PFOS was found in various tissues as summarised in Table 18. At both doses, the highest concentrations of the compound was found in liver, kidneys and serum whilst other organs, including the brain, also contained relatively high concentrations at the higher dose level. The Panel noted that the authors did not provide information on whether the variability parameters represented SDs or SEMs, but nevertheless considered the data to be a useful indication of tissue distribution.

Table 18. PFOS concentrations in serum (ng/mL) and in various other tissues (ng/g w.w.) of female rats resulting from exposure to 1 and 10 mg/kg b.w. per day (quoted from Austin *et al*., 2003).

Site	PFOS concentration following exposure to	
	1 mg/kg b.w. per day	10 mg/kg b.w. per day
Serum (ng/mL)	10,480 ± 1,428 [a]	45,446 ± 4,120*
Tissue (ng/g w.w.)		
Liver	26,617 ± 4,044	97,358 ± 25,668*
Heart	1,280 ± 697	23,490 ± 10,036*
Kidneys	9,581 ± 4,836	47,799 ± 29,512*
Spleen	76 [b]	15,873
Ovary	3,028	15,489
Adrenal	1,539	30,087
Brain (ng/g w.w.)		
Hypothalamus	<50	15,706
Cortex	294	4,487
Hippocampus	115	8,966
Brain stem	363	5,346
Cerebellum	289	5,540
Rest of the brain	396	4,256

* $p \leq 0.05$ significantly different, relative to the other groups

[a] Mean of 4-5 female rats

[b] Tissues from animals in each group were pooled for the measurement of PFOS in spleen, ovaries, adrenals and in specific parts of the brain.

Seacat *et al*. (2003) administered PFOS to rats at dietary concentrations of 0, 0.5, 2.0, 5.0 and 20 mg/kg for 4 or 14 weeks. Daily intake, cumulative dose and the concentration of PFOS in the liver and sera indicated that the levels of PFOS increased proportionally with cumulative dose in both males and females. On average, female rats had approximately 31 - 42% higher serum PFOS levels than male rats. Liver concentrations were roughly comparable between males and females. The male rats had higher liver-to-serum PFOS ratios than female rats, due to the fact that female serum PFOS concentrations were higher. Individual liver-to-serum PFOS concentration ratios ranged from 2.4. to 10. The amount of PFOS in the sera as a percentage of the cumulative dose remained relatively constant amongst all dose groups and between sexes with a range of 4.3 - 6.8%. In contrast, the percentage of the cumulative dose in the liver varied widely with a range of 15 - 57% showing no clear dose-dependence.

Lau and co-workers (2003) administered PFOS by gavage at a daily dose of 1, 2, 3, 5 or 10 mg/kg b.w. to pregnant rats from gestation day (GD) 2 to 21. Serum concentrations of PFOS in newborn rats mirrored the maternal administered dose and were similar to those in the maternal circulation at GD 21. Thibodeaux and co-workers (2003) reported that foetal rat liver also accumulated PFOS proportional to the maternal dose. Fetal livers appeared to contain approximately half as much PFOS as the maternal liver.

In pregnant mice treated by oral gavage with 1, 5, 10, 15 or 20 mg/kg b.w. per day from GD 1 to 17, serum PFOS concentrations were comparable to those in rats under similar treatment conditions (Thibodeaux *et al*., 2003). In mouse serum and liver, a level of saturation was achieved at the two highest doses.

Cynomolgus monkeys were administered orally with 0, 0.03, 0.15, or 0.75 mg PFOS/kg b.w. per day by oral intubation for 183 days (Seacat *et al*., 2002). Serum PFOS levels showed a linear increase in the low- and mid-dose groups and a non-linear response in the high-dose group which appeared to plateau. The average liver-to-serum PFOS concentration ratios ranged from 0.9:1 to 2.7:1 without a dose-response relationship. The average percent of the cumulative dose of PFOS found in the liver ranged from 4.4 ± 1.6% to 8.7 ± 1.0% without any apparent correlation to the dose group or gender. After the end of treatment (recovery phase) the PFOS concentrations declined. The PFOS elimination curves appeared to be multiphasic for the 0.75 mg/kg b.w. dose group and linear for the 0.15 mg/kg b.w. dose group recovery monkeys. Toward the end of the one-year recovery period, the slopes of the two recovery group elimination curves were similar, suggesting that the elimination half-lives were approximately 200 days for both dose groups.

After absorption, PFOS binds to rat liver fatty acid-binding protein (L-FABP) which may contribute to its high retention in rat liver (Luebker *et al*., 2002).

6.1.1.2 Human studies

From a study in maternal and cord blood samples in pregnant Japanese women with no known history of specific exposure, Inoue *et al.* (2004) concluded that PFOS partially passes from the maternal into the foetal circulation. In a recent study by Midash *et al.* (2007) the ratio between concentration in neonates' and mothers' plasma was reported to be significantly below 1 (0.60, p=0.003) indicating that PFOS can cross the blood-placenta border but that the transfer is slow. Fei *et al*. (2007) compared the maternal blood PFOS levels during weeks 4-14, and then later in pregnancy with the cord blood levels. The ratios decreased from 3.40 to 2.96.

An investigation in three former workers of the 3M Company revealed an elimination half-life of PFOS from blood of almost four years (3M Company, 2000a).

From a larger cohort of former workers preliminary (interim) reports were submitted (Burris *et al.*, 2000; 2002). In a subgroup of nine individuals a mean serum half-life of 8.67 years with a considerable variability (range 2.29 - 21.3 years; S.D. 6.12 years) was found. Major uncertainties in these calculations of elimination half-lives in blood comprise unknown changes in background exposure over time, rate of conversion of other fluorinated compounds into PFOS, and the effects of other fluorochemicals present in the blood of the test persons on the elimination of PFOS. From more recent data, Olsen *et al*. (2005 b) estimated a half-life for

PFOS elimination from serum in humans of 5.4 years (95% CI 3.9 - 6.9). The Panel noted the variability in half-life, but concluded the study by Olsen *et al*., (2005b) to be more reliable and therefore, for its further evaluation the Panel used 5.4 years as an estimate for the half-life in humans.

Harada *et al.* (2004) studied the influence of age and gender on PFOS blood levels and urinary excretion in a cohort in Kyoto (Japan). In the sub-cohort of 20-50 years old individuals blood levels were higher in males than in females, while in the group of an age > 50 years the mean levels in males and females were not different. The interpretation of the data is limited by the small size of the cohort. Renal clearance calculated from blood and urine levels was negligible.

Summary

After oral exposure PFOS is readily absorbed. In primates metabolic elimination seems to play no relevant role as can be derived from the long elimination half-lives. In rats, PFOS also shows a tendency to accumulate when repeatedly administered (Seacat *et al.*, 2003). There are no reports on PFOS metabolites formed *in vivo*. In rats, PFOS is mainly found in the liver, kidneys and blood with lower levels in most other organs including the central nervous system. It can cross the placenta and enter the foetus where it is mainly found in the liver. Elimination in rats occurs mainly *via* the kidneys and to a lesser extent *via* faecal excretion, whilst renal elimination seems to be negligible in humans. The elimination half-life has been estimated as > 90 days in rats, about 200 days in Cynomolgus monkeys, and about 5.4 years in humans.

6.1.2 Toxicity data

6.1.2.1 Acute toxicity

Exposure of Sprague-Dawley rats, 5/sex/group, to PFOS dust in air for one hour yielded an inhalation LC_{50} of 5.2 mg/L with 95% confidence limits of 4.4 and 6.4 mg/L. A Wright dust-feed mechanism with dry air at a flow rate of 12 to 16 litres per minute was used to administer the PFOS dust (Rusch *et al.*, 1979).

A mean oral LD_{50} value of 251 (199-318) mg/kg b.w. was calculated based on a single administration of PFOS by gavage to CD rats, 5/sex/group (Dean *et al*., 1978).

Skin and eye irritation were not observed in albino New Zealand White rabbits (Biesemeier and Harris, 1974).

6.1.2.2 Subacute and subchronic toxicity

Goldenthal *et al*. (1978a,b) reported mortality of both rats and rhesus monkeys treated with PFOS orally at doses of a few mg/kg per day.

In a 90 day subchronic study groups of CD rats (5/sex/group) received PFOS at 0, 30, 100, 300, 1000 or 3000 mg/kg in the diet, equivalent to 0, 2, 6, 18, 60 and 200 mg/kg b.w. per day (Goldenthal *et al*., 1978a). At the 100 mg/kg level and above, body weight means and food consumption were lower than in controls and all rats died before the termination of the study. Slight increases in creatinine phosphokinase and alkaline phosphatase, slight to moderate increases in blood glucose and blood urea nitrogen, and slight to marked increases in plasma glutamic oxalacetic transaminase (PGOT) and glutamic pyruvic transaminase (PGPT) activities were seen after one month of the study. At the end of the study, slight to moderate decreases in haemoglobin, haematocrit and erythrocyte counts were seen in male and female rats, and slight to moderate increases in PGOT and PGPT in two out of three surviving female rats. All treated rats showed centrilobular to midzonal hypertrophy of hepatocytes and focal necrosis of the liver at the 300 mg/kg level and above, multiple changes in various organs were observed microscopically.

Seacat *et al*. (2003), administered PFOS in the diet of Sprague Dawley rats at doses of 0, 0.5, 2.0, 5.0, and 20 mg/kg equivalent to 0, 0.05, 0.2, 0.4 and 1.5 mg/kg b.w. per day for 4 or 14 weeks. After 4 weeks, increases in relative liver weight and blood glucose were found in males at the highest level in the diet. In females no consistent and significant changes were found after 4 weeks. After 14 weeks increases in absolute and relative liver weight, increased numbers of segmented neutrophils in peripheral blood, decreased blood cholesterol, and increased serum alanine aminotransferase and urea nitrogen were observed in males at the highest dose level. In females, relative liver weight and blood urea nitrogen were increased at the highest dose level. Hepatic hypertrophy and cytoplasmic vacuolisation were observed after 14 weeks in the 5 and 20 mg/kg groups in males and in the 20 mg/kg group in females. The highest mean dose level of 1.5 mg/kg b.w. per day was considered as the lowest-observed-adverse-effect-level (LOAEL). The average hepatocyte proliferation index was not significantly increased and there was no effect on palmitoyl CoA oxidase, a marker of peroxisome proliferation. Serum and liver PFOS concentrations were proportional to dose and cumulative dose. Serum concentrations were generally higher in females than in males. The mean dose of 0.4 mg/kg b.w. per day was considered as the no-observed-adverse-effect (NOAEL) in this study. After 14 weeks of PFOS administration at this dose the PFOS serum concentration was 44 µg/mL in male rats and 64 µg/mL in female rats (Thomford, 2002; Seacat *et al*., 2003).

In a gavage study with rhesus monkeys, 2/sex/group, doses of 0, 10, 30, 100 or 300 mg/kg/day PFOS, all animals died within 20 days (Goldenthal *et al.*, 1979).

In a subsequent study, rhesus monkeys (2/sex/group) were administered 0, 0.5, 1.5 or 4.5 mg/kg/day by gavage for 90 days (Goldenthal *et al*., 1978b). The animals survived in the 0.5 and 1.5 mg/kg/day group, whereas those in the top dose group died or were sacrificed in extremis between weeks 5 and 7. At 1.5 mg/kg/day, the animals occasionally exhibited signs of gastrointestinal tract toxicity such as black stools, diarrhoea, mucous in the stools and bloody stool and exhibited dehydration or general body trembling at the end of study. Furthermore, serum alkaline phosphatase activity and the concentration of inorganic phosphate in the serum were decreased. At 0.5 mg/kg/day the animals occasionally exhibited soft stools, diarrhoea, anorexia and emesis. A slight decrease in the serum alkaline phosphatase activity was noted at the end of the study.

In a study in which male and female Cynomolgus monkeys (4 to 6 animals per group) received 0, 0.03, 0.15, or 0.75 mg/kg b.w. per day potassium PFOS by oral intubation for 183 days, compound-related mortality occurred in 2 of 6 male monkeys in the 0.75 mg/kg b.w. per day dose group. The remaining animals showed decreased body weights, increased liver weights, lowered serum total cholesterol and high-density lipoproteins (HDL), increased TSH levels, lowered triiodothyronine (T3) concentrations, and lowered estradiol levels (male animals). At various time points following treatment at the lowest dose level of 0.03 mg/kg, cholesterol levels were statistically significantly decreased compared to controls in male and female monkeys, and HDL levels were decreased in male monkeys, with no clear dose or time relationship. At 0.15 mg/kg b.w. per day the following changes were observed: lowered levels of HDL (female animals), increased levels of TSH (male animals) and lowered triiodothyronine concentrations (male and female animals). The thyroid hormone levels of some of the serum samples taken at the end of the study were subsequently reanalysed in an independent laboratory, and were not statistically significantly different from control. Serum PFOS concentrations (mean $\pm$ SD) measured at termination of the treatment, were 82.6 $\pm$ 25.2 mg/L for males and 66.8 $\pm$ 10.8 mg/L for females, at the dose level of 0.15 mg/kg b.w. per day and 15.8 $\pm$ 1.4 and 13.2 $\pm$ 1.4 mg/L at 0.03 mg/kg b.w. per day, respectively (Seacat *et al*., 2002). Complete reversal of clinical and hepatic effects and significant decreases in serum and liver PFOS occurred within 211 days post treatment. Seacat *et al*. (2002) concluded that the NOAEL in this study was 0.15 mg/kg b.w. per day. However, the Panel considered that the changes in thyroid hormones and in HDL observed at this dose level were treatment-related and therefore concluded that it was justified to consider 0.03 mg/kg b.w. per day as a NOAEL.

In summary these studies showed PFOS affected primarily the liver and biochemical parameters associated with lipid metabolism. Increased liver weight and vacuolisation and hypertrophy of hepatic cells were observed in the animal species tested (rat and monkey). PFOS also reduced body weight, serum cholesterol, serum triglycerides, and triiodothyronine levels. Changes in thyroid hormones have been observed, although the underlying mechanisms are not understood. A steep dose response curve was observed in the Cynomolgus monkey since the dose range between no observed adverse effects and treatment

related death was narrow. Monkeys died at doses of a few mg/kg per day. Rats were less sensitive than monkeys. Male rats appear to be more sensitive than female rats.

6.1.2.3 Chronic toxicity and carcinogenicity

The chronic toxicity and carcinogenicity of PFOS were evaluated by OECD (2002), Health Canada (2004) and U.S. EPA (2006).

A chronic toxicity and carcinogenicity study of PFOS potassium salt was carried out in rats in compliance with Good Laboratory Practice (GLP) (Thomford., 2002). Groups of 40-70 male and female Crl:CD(SD)IGS BR rats were given PFOS at doses of 0.5, 2, 5 or 20 mg/kg in the diet, corresponding to mean achieved doses of 0.04, 0.14, 0.36 and 1.42 mg/kg b.w. per day in males and 0.035, 0.14, 0.37 and 1.49 mg/kg b.w. per day in females. An additional (recovery) group received the top dose of PFOS for 52 weeks followed by control diet for 52 weeks. There was a significant trend for increased survival in males, due to significant increases in the 5 mg/kg and high dose group (20 mg/kg), compared to the controls. No significant trend was noted in survival for females, although there was a statistically significant decrease at 2 mg/kg. Hepatotoxicity, characterized by significant increases in centrilobular hypertrophy, centrilobular eosinophilic hepatocytic granules, centrilobular hepatocytic pigment, or centrilobular hepatocytic vacuolation was noted in male or female rats given 5 or 20 mg/kg. A significant increase in hepatocellular centrilobular hypertrophy was also observed in the male rats receiving 2 mg/kg PFOS. Electron microscopy was conducted on livers from a subset of animals administered 0 and 20 mg/kg PFOS in the diet. PFOS treatment resulted in mild to moderate smooth endoplasmic reticulum hyperplasia and minimal to mild hepatocellular hypertrophy, but not in peroxisomal proliferation.

For neoplastic effects, a significant increase in the incidence of hepatocellular adenomas was noted in male rats in the high-dose group (7/60) compared to the control (0/60). A significantly increased incidence was observed for thyroid follicular cell adenomas in the recovery group (9/39) compared to the controls (3/60) and high dose group (4/59). No other neoplastic effects were seen in the males. In the females, significant increase in the incidences of hepatocellular adenomas (5/60) and combined hepatocellular adenomas and carcinomas (6/60) was observed in the high-dose group (20 mg/kg). A significant increase in combined thyroid follicular cell adenomas and carcinomas was observed in the 5 mg/kg group (3/50) compared to the controls (0/60). Increased incidences of mammary fibroadenomas/adenomas were observed in all treated female groups, apart from the high-dose group which showed a significant decrease. The incidences of combined mammary fibroadenomas/adenomas/carcinomas were significantly increased in the low-dose (0.5 mg/kg) and 2 mg/kg dose groups, (36/50 and 31/48, respectively), but not in the 5 mg/kg or 20 mg/kg dose groups (29/50 and 24/60, respectively), compared to the controls (29/60).

In conclusion, the results of this study showed that PFOS is hepatotoxic and carcinogenic, inducing tumours of the liver. The CONTAM Panel considered the evidence for induction of thyroid and mammary tumours was limited.

For non-neoplastic effects, based on histopathological findings in the liver, the no-observed-adverse-effect level (NOAEL) for PFOS is considered to be 2 mg/kg in the diet (0.14 mg/kg b.w. per day) in male and female rats.

6.1.2.4 Genotoxicity

The genotoxicity of PFOS and its salts was reviewed by OECD (2002), Health Canada (2004), the U.S. EPA (2006) and the UK Committee on toxicity of chemicals in food, consumer products and the environment (COT, 2006a and b).

Potassium PFOS was found negative in the *Salmonella typhimurium* reversion gene mutation assay at concentrations of 0.01–500 µg/plate (-S9) and 0.1<500 µg/plate (+S9). The strains used were TA100, TA1535, TA1537, TA1538 and TA09 (Litton Bionetics, Inc., 1978). It was negative in the mitotic recombination test in *Saccharomyces cerevisiae* (D4) (Litton Bionetics, Inc., 1978). It was negative in the Salmonella-Escherichia coli/reverse mutation assay with and without metabolic activation (S9) up to the concentration of 5000 µg/plate. The strains used were *S. typhimurium* TA1535, TA100, TA98, TA1537 and *E. coli* WP2uvrA (Mecchi, 1999). It did not induce chromosomal aberrations in cultured human lymphocytes up to the concentrations of 599 µg/mL without activation (S9) and of 449 µg/mL with activation (S9) (Cifone., 1999). It did not induce unscheduled DNA synthesis (UDS) in primary cultured rat liver cells up to the concentration of 4000 µg/mL (Cifone, 1999). Finally, it was negative in the *in vivo* bone marrow mouse micronucleus assay at single oral doses of 237.5, 450 and 950 mg/kg b.w., with sampling at 24, 48 and 72 hours (Corning Hazleton, Inc., 1993). The PCE:NCE ratio was reduced in both males and females at certain doses/intervals.

Also precursors such as *N*-ethyl perfluorooctane sulfonamidoethanol (*N*-EtFOSE), *N*-ethyl perfluorooctane sulfonamide *N*-EtFOSA), *N*-ethylperfluorooctane sulfonamidoethanol (*N*-MeFOSE), *N*-methyl perfluorooctane sulfonamide (*N*-MeFOSA) and potassium-*N*-ethyl-*N* ((hepatodecafluorooctyl)-sulfonyl)-glycinate (PFOSAA) were tested and found negative in different *in vitro* and *in vivo* tests (e.g. NOTOX, 1994a and b and c; Murli., 1996; SRI International, 1982, 1985; Covance Laboratories, Inc., 2000).

Based on the negativity in a large series of *in vitro* and/or *in vivo* short-term tests at gene and/or chromosome or DNA repair levels genotoxicity does not appear to be a property of PFOS, its salts.

6.1.2.5 Developmental and reproductive toxicity

Data on developmental toxicity have been reviewed by Lau and co-workers (2004) and in the OECD report (2002). Prenatal developmental toxicity studies of PFOS have been conducted in rats, mice and rabbits. One two-generation study has been performed in rats.

Administration of PFOS by gavage to groups of 22 pregnant rats during GD 6-15 at doses of 0, 1, 5 and 10 mg/kg b.w. per day (Gortner, 1980) resulted in maternal toxicity (decreased body weight) with a NOAEL of 5 mg/kg b.w. per day and a LOAEL of 10 mg/kg b.w. per day while in all dose groups the most notable signs of developmental toxicity were abnormalities of the lens of the eye, the incidence of which was significantly greater than control only in the top dose group (10 mg/kg b.w. per day. In a similar study, gavage administration of PFOS to pregnant rats between GD 6 and 15 resulted in maternal weight loss and developmental toxicity in the 5 and 10 mg/kg b.w. per day dose groups. Reduced birth weight as well as visceral anomalies, delayed ossification and skeletal variations were observed. A NOAEL of 1 mg/kg b.w. per day and a LOAEL of 5 mg/kg b.w. per day for maternal and developmental toxicity were indicated. (Wetzel, 1983).

Studies with Sprague-Dawley rats and CD-1 mice in which PFOS was administered by gavage during pregnancy indicated that in utero exposure to PFOS severely compromised postnatal survival of neonatal rats and mice, and caused delays in growth and development that were accompanied by hypothyroxinemia in the surviving rat pups. The rats received by gavage PFOS doses of 1, 2, 3, 5 and 10 mg/kg b.w. per day during GD2 to 21. Maternal weight gain was reduced in a dose-dependent manner, which was statistically significant compared to control at 2 mg/kg b.w. per day and above. There was a marked reduction in maternal serum T_4 and T_3 in all dose groups from GD7. At 10 mg/kg b.w. per day, there was a reduction in foetal body weight and an increase in cleft palate and anasarca and all pups died within 4-6 hours after birth. In the 5 mg/kg b.w. per day group 95% of the pups died within 24 hours, approximately 50% of the offspring died after 3 mg/kg b.w. per day in rats. The maternal dose corresponding to the $BMDL_5$ (lower limit of the 95% confidence interval on the benchmark dose for a 5% increase in response above background incidence) for survival of rat pups at postnatal day 8 was estimated at 0.58 mg/kg (Lau *et al.*, 2003). Post-natal growth rate and the average age at eye opening were significantly delayed at 2 mg/kg b.w. per day and above. PFOS-exposed neonates showed reductions of T_4 at all dose groups, but not T_3 or TSH. Cross-fostering the PFOS-exposed rat neonates (5 mg/kg) to control nursing dams failed to improve survival (Thibodeaux *et al.*, 2003; Lau *et al.*, 2003). Changes in thyroid hormones, observed after exposure of pregnant rats to PFOS may influence brain development and hence affect behaviour in the offspring. The ontogeny of neurochemical and neurobehavioral markers was evaluated after prenatal PFOS exposure (Lau *et al.*, 2003). Prenatal exposure to PFOS did not affect learning and memory behaviours determined by T-maze delayed alternation. However marginal but statistically significant deficits in the developmental patterns of choline acetyltransferase activity (an enzyme marker sensitive to thyroid hormone status) were observed in rats with a LOAEL of 1 mg/kg b.w. per day.

The mice received doses of 1, 5, 10, 15 and 20 mg/kg b.w. per day during GD1 to GD18. The survival of the lower dose groups (1 and 5 mg/kg) was not different from that of controls. A statistically significant trend in growth lags was detected in surviving mouse pups exposed to PFOS prenatally. Slight delays in eye opening were statistically significant at all doses and liver weight was significantly increased at 5 mg/kg b.w. per day and above. (Lau *et al.*, 2003; Thibodeaux *et al.*, 2003).

Grasty *et al*., (2003) investigated the critical window for prenatal exposure to PFOS, by administering PFOS potassium salt to pregnant rats by gavage at 25 mg/kg b.w. on GD 2-5, 6-9, 10-13, 14-17 or 17-20, or at 25 or 50 mg/kg b.w. on GD 19-20. Neonatal rat mortality occurred after dosing in all time periods, but the incidence of neonatal death increased as the exposure period occurred later during gestation, reaching 100% in the treatment group of GD 17–20). Considering that PFOS-induced organ toxicity is incompatible with postnatal survival, the authors suggested that maturation of the lung and pulmonary function is a plausible target for PFOS. In a subsequent study, Grasty *et al*. (2005) found that the alveolar walls were thicker in PFOS-exposed newborn mice compared to controls, but the failure of rescue agents and the normal pulmonary surfactant profile indicated that this was not likely to be due to lung immaturity.

Luebker *et al*. (2005b) administered PFOS by gavage to female rats for 6 weeks prior to mating and through gestation to day 4 of lactation at doses of 0, 0.4, 0.8, 1.0, 1.2, 1.6 and 2.0 mg/kg b.w. per day. Statistically significant decreases in gestation length and pup viability were observed at 0.8 mg/kg b.w. per day and above. A range of BMDL5 values of 0.27 to 0.89 mg/kg b.w. per day was calculated for these effects.

A two generation study in rats (Christian *et al*., 1999), showed high sensitivity for PFOS. PFOS was administered by gavage at doses of 0, 0.1, 0.4, 1.6 and 3.2 mg/kg b.w. per day for 42 days before mating and in females also during pregnancy and lactation. Gestation length was significantly reduced in the high-dose group and there also was a significant reduction in the number of implantation sites followed by a concomitant reduction in litter size. Reduced survival was observed in F1 offspring at the highest doses of 1.6 and 3.2 mg/ kg per day (26% of the offspring died within 4 days after birth in the 1.6 mg/kg b.w. per day dose group). In the 3.2 mg/kg b.w. per day dose group 45% of the pups died within one day after birth and 100% died thereafter). Pup body weights were significantly reduced at the two highest dose groups. Transient delays in reflex and physical development were observed in the F1 generation offspring which raises concerns about possible neurotoxicity of PFOS. At post weaning days 1-8 animals showed significant reductions in absolute food consumption at the 0.1 and 0.4 mg/kg b.w. per day dose levels.

In the F2 generation of the group treated with 0.4 mg/kg b.w. per day birth weight was reduced (LOAEL). No other toxicological signs were reported in the F2 mice. Serum concentration in the group treated with 0.4 mg/kg b.w. per day (F0) at gestation day 21 was

26.2 mg/kg, in the foetuses it was 34.3 mg/kg (pooled liver and serum). The NOAEL was 0.1 mg/kg b.w. per day (Christian *et al*., 1999). A study in which neonates of treated mothers were suckled by untreated mothers showed that *in utero* exposure was responsible for some of the effects in the offspring (Luebker *et al*., 2005a).

Case *et al*. (2001) administered PFOS to pregnant New Zealand white rabbits by gavage at 0, 0.1, 1.0, 2.5 and 3.75 mg/kg b.w. per day from GD 6-20. Reduced birth weight and delayed ossification of the offspring were reported at the two higher doses. The LOAELs and NOAELs were respectively 1 and 0.1 mg/kg b.w. per day for maternal toxicity (decreased weight gain); 2.5 and 1.0 mg/kg b.w. per day for foetal toxicity.

In summary: the database on developmental studies is elaborate. Foetal toxicity and neonatal effects have been observed at doses similar to or below those resulting in maternal toxicity. Observed developmental effects include reduction of foetal weight, cleft palate, anasarca (oedema), delayed ossification of bones (sternebrae and phalanges) and cardiac abnormalities (ventricular septal defects and enlargement of the right atrium). Dose response curves are generally steep, with high mortality observed early after birth. Late gestational age seems to be a very vulnerable period. Two-generation reproduction studies have revealed effects in the F1 and F2 generation, with a LOAEL of 0.4 mg/kg b.w. per day and NOAEL of 0.1 mg/kg b.w. per day.

6.1.3 Neurotoxicity

Administration of PFOS to 10-day old mice by gastric tube at 0.75 or 11.3 mg/kg b.w. has been reported to result in impaired performance in behavioural tests conducted when the mice were 2 and 4 months old. There were no overt signs of clinical toxicity. Based on the response to nicotine, these effects were considered to be mediated via the cholinergic system (Johansson *et al*., 2008).

6.1.4 Human data

Several occupational studies on the health effects associated with PFOS exposure have been conducted at the 3M Decatur, Alabama plant where PFOS has been manufactured since 1991, and PFOA since 1998. The studies conducted in 2000 also included the Antwerp, Belgium plant. Mean serum PFOS and PFOA concentrations for 263 Decatur employees were 1.32 (range 0.06–10.06) mg/kg and 1.78 (range 0.04–12.7) mg/kg respectively, mean concentrations were approximately 50% lower in 255 Antwerp employees (Olsen *et al*., 2003a).

Several endpoints have been examined in medical surveillance programs including haematology, clinical chemistry, urine analysis, thyroid hormones and reproductive

hormones. Also parameters related to health outcome such as retrospective mortality studies, cancer incidence and need for medical care episodes have been looked at. However the data set is limited and many confounders, including exposure to different compounds, make the interpretation of the data difficult. The use of "episodes of care" analysis in occupational epidemiological studies is not common and findings can only be used for hypothesis generation (Olsen *et al*., 2003 a).

Carcinogenicity

Follow up of 2083 Decatur workers (Alabama) showed that workers in jobs involving high exposure to PFOS based materials had 13 times increased risk for bladder cancer mortality compared with the general population of Alabama (SMR= 12.77, 95% confidence limit 2.63–37.35). However this observation was based on only 3 cases of bladder cancer and the workers were exposed to several compounds, hence it is difficult to draw definite conclusions (Alexander *et al.*, 2003). In a follow-up study, eleven cases of bladder cancer were identified from 1400 of the workers who responded to a questionnaire, and from 185 death certificates. There were no statistically significante associations between PFOS exposure and an increased risk of bladder cancer (Alexander and Olsen, 2007).

Episodes of medical care, identified in employees' health claims records of the Decatur plant, were used as an estimate of morbidity of workers. Comparison of the risk ratio for episodes of medical care for overall cancers was greatest in the group of employees with the highest and longest exposures to fluorochemicals (RREpC = 1.6, 95% CI = 1.2 – 2.1). Increased risk of episodes of medical care was also reported for male reproductive cancers in long-time, high-exposure employees (RREpC = 9.7, 95% CI = 1.1–458) (Olsen *et al.*, 2001).

Health endpoints other than cancer

Data on liver function, serum cholesterol and thyroid hormone levels have been collected and associated with levels of PFOS in serum of occupationally exposed workers. In a cross sectional analysis, male employees at the Decatur plant with the highest PFOS levels showed lower mean HDL values. Taking data from workers at the Decatur and Antwerp plant together showed that mean values for triglycerides, alkaline phosphatase, total bilirubin, and ALT were significantly ($p < 0.05$) higher in male workers ($n = 421$) with PFOS levels in the highest quartile (upper quartile Q4 with mean PFOS level 2.69 versus mean PFOS level of 0.27 mg/kg in Q1). Thyroid results for male production employees indicated that T3 was significantly higher ($p< 0.05$) and THBR (T3 uptake) was significantly lower ($p < 0.05$) in Q4 than in Q1. After multiple regressions with adjustment for potential confounders, PFOS exposure remained positively associated with serum T3 levels, and with triglycerides but not with cholesterol. A longitudinal analysis over a six year time period of 174 male employees using multiple regressions could no longer find any statistical significant association with

PFOS levels, but the number of workers available for this longitudinal follow up was limited. Firm conclusions are difficult to draw due to a lot of short comings with regard to low numbers of participants, representativeness and lack of information on confounders such as exposure to other compounds and a lack of follow up. It should be also noted that the observed changes are in the opposite direction to those observed in animal studies (Olsen *et al*., 2003d).

Apelberg *et al*. (2007b) investigated the association between PFOS concentrations in cord serum and gestational age, birth weight and size of 293 singleton births delivered in November 2004 to March 2005 in Baltimore, USA. PFOS was detected in >99% of the cord blood samples, with a median concentration of 5 ng/mL (range <0.2-34.8 ng/mL). PFOS was significantly associated with small decreases in birth weight and size, but not newborn length or gestational age. The concentrations of PFOS in cord serum were highly correlated with those of PFOA. A study conducted in the Danish National Birth Cohort suggests that the association might be related to PFOA rather than PFOS. In this cohort of 1400 women delivering a single child between March 1996 and November 2002, the average maternal plasma level of PFOS was 35.3 ng/mL (range 6.4-106.7 ng/mL) and the cord plasma levels in a subset of 50 subjects were 11 $\pm$ 4.7 ng/mL (mean $\pm$. S.D.). Maternal plasma levels of PFOS did not show a consistent association with birth weight or gestational age (Fei *et al*., 2007).

6.1.5 Mode of action

Liver Toxicity

Several studies show that PFOS interferes with fatty acid metabolism and metabolism of lipids and lipoproteins. The link to the liver toxicity that is observed in rodents and monkeys is not well understood.

PFOS has been shown to activate the PPARα in *in vitro* experiments. (Sohlenius and Eriksson, 1993; van den Heuvel *et al.,* 2006). Studies in COS-1 cells confirmed this finding for the mouse and human PPARα (Shipley *et al.*, 2004).Takacs and Abbott (2007) reported that PFOS was less active than PFOA for both mouse and human PPARα and PPARβ, but neither substance showed significant activation of mouse or human PPARγ.

Peroxisome proliferation has been reported in some rodent studies but not in others (Ikeda *et al.,* 1985; Sohlenius *et al.,* 1992a; Seacat *et al.*, 2003).

This mechanism is unlikely to be responsible for the observed liver toxicity in primates after PFOS exposure, given current knowledge of relative susceptibility of primates compared with rodents to peroxisome proliferation. In primates lipid accumulation has been observed in the liver without peroxisome proliferation (Seacat *et al*., 2002).

There are other pathways by which PFOS can interfere with lipid metabolism in the liver. One of these is competition of PFOS with fatty acids and other endogenous ligands for binding to the important intracellular liver fatty acid transporter proteins (as shown *in vitro*, Luebkner *et al*., 2002 which may contribute to hepatotoxicity and lower serum cholesterol levels.

In addition the induction of a spectrum of liver enzymes such as carboxylesterase (Hosokawa and Satoh., 1993), cytochrome P450 (CYP) 4A1, acyl-CoA oxidases and dehydrogenases, carnitine acetyltransferase was shown (Ikeda *et al*., 1986; Kozuka *et al.*,1991).

Reduction in the activity of 3-hydroxy-3-methylglutaryl coenzyme A reductase has been observed which may be linked to reduced levels of cholesterol and triglycerides (Haughom and Spydovold, 1992).

Recent gene expression studies in rat hepatoma cells and in liver cells from orally dosed Sprague-Dawley rats have shown that PFOS induced alterations in genes that were primarily involved in peroxisomal but not mitochondrial fatty acid metabolism, hormone regulation and genes coding for different cytochrome P450s, including CYP 2B and CYP 3A, which are also phenobarbital inducible, P450 4A1 was not up-regulated in these gene expression array experiments (Martin *et al*., 2007).

Finally, PFOS has been shown to inhibit *in vitro* gap junction intercellular communication in rat liver cell lines and in the liver of PFOS-treated rats. This mechanism may also be involved in liver carcinogenesis (Hu *et al*., 2002; Lau *et al*., 2007).

Carcinogenicity

Based on the complete lack of genotoxicity in a wide range of in vitro and in vivo assays at gene and/or chromosome level, the weight of evidence indicates an indirect (non-genotoxic) mechanism for the carcinogenicity of PFOS. The induction of hepatocellular tumours does not appear directly related to peroxisome proliferation; however, the increased incidences of tumours were observed at doses above those associated with non-neoplastic toxic effects. Thyroid tumours are likely to be secondary to hormonal imbalance. The thyroid and mammary gland tumours are difficult to evaluate because of the lack of dose-response relationship.

Other endpoints

In rats, oral administration of PFOS resulted in increased tissue availability of thyroid hormones and turnover of T4, but the pattern of changes seen was not typical of a hypothyroid state (Chang *et al*., 2007). Although reproductive and developmental toxicity

have been described, the underlying mechanism remains unclear. Part of the toxicity may be related to changes in thyroid hormone levels which may affect early development. The extent to which changes in lipid metabolism, changes in transport of fatty acids or induction of metabolising liver enzymes contribute to the changes in hormone levels is currently unknown. It is noteworthy that opposite effects have been observed in experimental studies (lower levels of cholesterol and estradiol after PFOS exposure in rodents and monkeys, increased levels of estradiol in humans (increased levels of cholesterol and estradiol in male workers reported in OECD (2002). There is also evidence that PFOS has effects on membrane permeability (Jernbro *et al*., 2007).

A study in adult female rats that were injected intraperitoneally with 0, 1, or 10 mg PFOS/kg b.w. for 2 weeks showed that PFOS can cross the blood brain barrier and accumulated in the hypothalamus at the higher dose level (Austin *et al.*, 2003). It increased norepinephrine concentrations in the para ventricular nucleus of the hypothalamus. Treatment with PFOS affected oestrous cyclicity and increased serum corticosterone levels while decreasing serum leptin concentrations (Austin *et al.*, 2003). PFOS was shown to activate the stress axis while inhibiting the reproductive axis. Hypothalamic nor-epinephrine levels could play a role.

6.1.6 Derivation of TDI

Several toxicological studies discussed in the previous sections are summarised with respect to type of study, endpoint and associated LOAEL and/or NOAEL in Table 19.

Table 19. Summary of selected studies on PFOS toxicity.

Subchronic toxicity			
Type of study	**Most sensitive endpoint**	**LOAEL mg/kg per day**	**NOAEL mg/kg per day**
Oral diet 98 days rats 5/sex/group	Increased liver weight, decreased serum cholesterol, increased ALT (Seacat *et al.*, 2003)	1.5	0.4 corresponding to 44 (m) and 64 (f) µg/mL serum
Oral (capsule) 183 days Cynomolgus monkeys (m/f); 4-6/group	Increased TSH (m) Reduced T_3 (m,f) Reduced HDL (f) (Seacat *et al*., 2002)	0.15 (0.75 according to Seacat *et al*., 2002)	0.03 corresponding to 16 (m) and 13 (f) µg/mL serum ; (0.15 according to Seacat *et al*., 2002 [corresponding to 80 (m) and 65 (f) µg/mL serum])
Chronic toxicity/carcinogenicity			
Oral diet 104 weeks rats (m/f); 60-70 rats/group	- Liver pathology: hepatocellular hypertrophy - Neoplastic effects: hepatocellular adenomas (m/f); thyroid follicular cell adenomas/carcinomas (f; 0.15 – 0.57 mg/kg b.w. / day.); (Thomford., 2002)	0.06-0.2 (m) 0.14 * 0.2-0.6 (f) 0.37 *	0.02-0.06 (m) 0.04 * 0.07-0.2 (f) 0.14 *
Developmental toxicity			
Oral gavage Rabbits	GD7-20 Maternal: reduced body weight and food consumption Foetal: reduced birth weight and delayed ossification (Case *et al.*, 2001)	Maternal: 1 Foetal: 2.5	Maternal: 0.1 Foetal: 1
Oral gavage Rats (f)	GD2-21 Maternal: reduced body weight Reduced serum T4 Newborns: Post natal death Reduced weight gain Delayed eye opening Sternal defects Reduced serum T4 (Lau *et al.* 2003, Thibodeaux *et al.*, 2003)	Maternal: 1 Foetus: 1	Maternal: - Foetus: -
Oral gavage Mice	GD1-18 Maternal: increased liver weight and reduced serum triglycerides Foetus: Postnatal death Reduced foetal weight Delayed eye opening (Lau *et al.*, 2003, Thibodeaux *et al.*, 2003)	Maternal: 5 Foetal: 1	Maternal: 1 Foetal: -
Oral gavage Two generation study Rats (m/f) 35 rats /dose group	F0 (m): from 42 days prior to mating, to the end of mating,(f):from 42 days prior to mating to LD21 F1(m):from 22 days after birth to the end of mating F1(f):from 22 days after birth to LD21 of F2 F0 (m/f) reduced body weight gain F1 reduced weight gain F2 reductions in mean pup body weight(Christian *et al.*, 1999)	 0.4 0.1 (m) (lowest dose tested) 0.4	 0.1

*) The mean daily exposure values as calculated as the average of the range of calculated exposure cited in the report (Thomford, 2002). LD: Lactation day

The lowest NOAEL identified, 0.03 mg/kg b.w. per day, originates from a subchronic study with Cynomolgus monkeys showing changes in lipids and thyroid hormones at the next higher dose of 0.15 mg/kg b.w. per day (see Table 19). The Panel considered these biochemical changes observed at this dose level to be treatment-related and therefore

concluded that 0.03 mg/kg b.w. per day should be used as the NOAEL in the assessment. The NOAEL was in females associated with a plasma concentration of 13.2 µg/mL PFOS at the end of the exposure period (day 183). However, as the estimated half-life of PFOS in monkeys is about 200 days, this internal dose does not represent steady state.

From the observations in Cynomolgus monkeys, the CONTAM Panel identified 0.03 mg/kg b.w. per day as the lowest NOAEL and considered this a suitable basis for deriving a Tolerable Daily Intake (TDI). The CONTAM Panel established a TDI for PFOS of 150 ng/kg b.w. per day by applying an overall uncertainty factor (UF) of 200 to the NOAEL of 0.03 mg/kg b.w. per day. An UF of 100 was used for inter and intra-species differences and an additional UF of 2 to compensate for uncertainties in connection to the relatively short duration of the key study and the internal dose kinetics. The CONTAM Panel used this figure together with a margin of exposure consideration (chapter 7.2) to assess the potential significance of the total human exposure to PFOS.

6.2 PFOA

6.2.1 Toxicokinetics

6.2.1.1 Animal studies

^{14}C-labelled PFOA, applied as a single oral dose, was rapidly absorbed. After 24 h absorption of radioactivity was almost complete (93%). Peak levels in blood were attained 1-2 hours after treatment. Analysis of PFOA derived ^{14}C in tissues showed that the liver and plasma of male rats and the liver, plasma and kidney of female rats were the primary tissues of distribution (van den Heuvel *et al*., 1991). Protein-binding is an important factor in determining the distribution (Han *et al*., 2005), including binding to rat liver fatty acid-binding protein (L-FABP) (Luebker *et al*., 2002).

Following i.v. administration of PFOA to male rats at 0.041 and 16.56 mg/kg b.w. a greater proportion of the low dose was distributed to the liver, whereas at the higher dose the larger proportion was distributed to serum, other tissues and the carcass. There were also dose-related differences in distribution between membrane fractions and cytosol (Kudo *et al*., 2007). Han *et al*. (2003) estimated that greater than 90% of PFOA would be bound to serum albumin in rat blood.

Hinderliter and co-workers (2005) showed that after oral application to rats PFOA is transferred from the dam to the foetus *via* the placenta and to the pup by lactation. Concentrations in foetal plasma were half the steady-state concentrations in maternal plasma, while steady state concentrations in milk were approximately one tenth less than those in maternal plasma.

The available data indicate that PFOA is not metabolised (Kemper and Nabb, 2005).

Female rats eliminated PFOA derived radioactivity rapidly in the urine with 91% of the dose being excreted in the first 24 hours. In the same period male rats eliminated only 6% of the administered ^{14}C in urine (van den Heuvel *et al*., 1991). This sex-related difference in elimination is attributed to an active secretory mechanism in the female rat (Hanhijarvi *et al*., 1982), whereas testosterone has been found to suppress renal elimination in the male rat (van den Heuvel *et al*., 1992). These observations are considered to be related to the involvement of the organic anion transporters, OAT2 and OAT3 (Kudo *et al*., 2002). There are also age-related differences in elimination of PFOA in rats, with less marked differences between males and females at ages less than about 30 days, which also could be related to expression of OAT2 (Hinderliter *et al*., 2006). After a single ***i.p.*** injection of PFOA (20 mg/kg b.w.), in male rats 55% of the dose was eliminated *via* the urine, and less than 5% *via* the faeces within 120 h (Kudo and Kawashima, 2001). In females, 80% was excreted *via* urine, whilst no sex-difference was found for faecal elimination. After castration of male rats, urinary elimination was similar to that in females whilst application of testosterone reduced urinary elimination in castrated male rats and female rats. Elimination half-lives were estimated at 1.9–24 h for females and 4.4–9 days for males (Hanhijarvi *et al*., 1982; Kemper and Jepson, 2003a and b; Kudo *et al*., 2002; Ophaug and Singer, 1980; van den Heuvel *et al*., 1991; Ylinen *et al*., 1990).

There were no important gender differences in PFOA elimination in primates and humans (Burris *et al*., 2002; Noker and Gorman, 2003) and appear to be unlikely in the mouse (Sohlenius *et al*., 1992b; Uy-Yu *et al*., 1990; U.S. EPA, 2003).

Butenhoff *et al*. (2002) treated male Cynomolgus monkeys with PFOA by oral capsule at daily doses of 0, 3, 10 or 30 (reduced to 20) mg/kg b.w. over 26 weeks. The concentrations of PFOA in liver at the end of treatment showed a high degree of variability, particularly at the highest dose. The elimination half-life for PFOA in Cynomolgus monkeys was approximately 21 and 30 days in male and female animals, respectively.

6.2.1.2 Human studies

Preliminary (interim) reports from a large cohort of former workers were submitted to EFSA (Burris *et al.*, 2000; 2002). A mean serum half-life of 4.37 years with a considerable variability (range 1.5 – 13.49 years; S.D. 3.53 years) was estimated in a subgroup of nine individuals. Major uncertainties in these calculations of elimination half-lives in blood comprise unknown changes in non-occupational background exposure over time, rate of conversion of other fluorinated compounds into PFOA, and the effects of other fluorochemicals present in the blood of the test persons on the elimination of PFOA. In a recent follow up, Olsen *et al*. (2005b) estimated half-lives for elimination from serum in humans of 3.8 years (95% CI 3.1–4.4) for PFOA.

Greater than 90% of PFOA would be bound to serum albumin in human blood (Han *et al*. 2003). Harada *et al.* (2004) studied the influence of age and gender on PFOA blood levels and urinary excretion in a cohort in Kyoto (Japan). In the sub-cohort of 20-50 years old individuals blood levels were higher in males than in females, whilst in the age group > 50 years the mean levels in males and females were not different. The interpretation of these data is limited by the small size of the cohort. Renal clearance calculated from blood and urine levels was negligible in both sexes, i.e., much lower than in rats or monkeys.

The information on transfer of PFOA through the human placenta is limited, in contrast to PFOS. PFOA was detected only in 3 out of 15 maternal samples and not in cord blood samples in a Japanese study in which 15 paired samples were analysed (Inoue *et al.,* 2004). In a recent study by Midash *et al.* (2007) the ratio between concentration in neonates' and mothers' plasma was reported to be slightly but significantly above 1 (1.26, p=0.009) indicating that PFOA can not only cross the blood-placenta border but also be bioaccumulated in the foetus. Fei *et al*. (2007) compared maternal blood PFOA levels during weeks 4-14, and then later in pregnancy with the cord blood levels. The ratios decreased from 1.83 to 1.46.

6.2.1.3 Formation of PFOA from precursors

PFOA has been detected in tissues and excreta of rats and mice administered 8-2 fluorotelomer alcohol (FTOH). PFOA was detected in serum, urine and faeces of rats administered FTOH by gavage at 5 and 125 mg/kg b.w. (Fasano *et al*., 2006). Similarly, PFOA was detected in serum and liver of mice following administration of FTOH by gavage at 30 mg/kg b.w. on gestational day 8 of pregnancy. The highest concentrations detected were 789 $\pm$ 41 ng/mL and 668 $\pm$ 23 ng/mL in maternal serum and liver, respectively. PFOA was also detected in the foetuses from 24h after treatment and increased to 140 $\pm$ 32 ng/mL on gestational day 18. Cross-fostering studies indicated that neonates were also exposed to PFOA via lactation of FTOH-treated dams (Henderson and Smith, 2007). Studies of Kudo *et al*. (2005) suggest that PFOA is responsible for the peroxisome proliferation resulting from administration of FTOH. These studies demonstrate that systemic PFOA exposure can result from oral exposure to precursor substances.

An *in vitro* metabolism study using hepatocytes and microsomal fractions prepared from livers of different species indicated that the FTOH clearance rates were in the order of rat > mouse > human $\geq$ trout (Nabb *et al*., 2007).

Summary

After oral exposure PFOA is readily absorbed. Metabolic elimination seems to play no relevant role. In rats PFOA is mainly found in the liver, kidneys and blood with lower levels in many other organs including the central nervous system. It can cross the blood-placenta

border in a facilitated way and enter the foetus were it is mainly found in the liver. Elimination in rats occurs *via* the kidneys and to a lesser extent *via* faecal excretion. Urinary excretion is the major route of elimination in female rats, both urinary and faecal excretion the major route in male rats. Renal elimination seems to be negligible in humans. Protein-binding and expression of transporters have an important role in determining distribution and elimination. Elimination half-lives of < 24 h in female and < 9 days in male rats, of 21 – 30 days in Cynomolgus monkeys, and of about 3.8 years in humans have been estimated.

6.2.2 Toxicity data

6.2.2.1 Acute toxicity

In male CD rats the LC_{50} upon inhalation of APFO for 4 hrs was 980 mg/m³. This concentration produced an increase in liver size and corneal opacity. Repeated treatment for 10 days suppressed body weight gain (84 mg/m³) and increased liver weight. The no-observed effect level was 1 mg/m³ (Kennedy *et al.,* 1986). Oral LD_{50} values in rats were about 500 mg/kg b.w.: 680 and 430 mg/kg b.w. in male and female CD rats respectively (average (540 mg/kg b.w.) (Dean and Jessup, 1978, reviewed in Griffith and Long, 1980). More recently Glaza (1997) reported an oral LD_{50} for PFOA greater than 500 mg/kg and between 250 and 500 mg/kg in female rats.

The dermal LC_{50} was reported to be greater than 2000 mg/kg b.w. in New Zealand White rabbits (Glaza, 1995).

It can be concluded that PFOA has moderate acute toxicity after inhalation or oral administration.

PFOA is a weak skin irritant as determined in rabbit experiments. Rats were less sensitive than rabbits (Kennedy, 1985).

6.2.2.2 Subacute and subchronic toxicity

Studies have been conducted in rodents and in non-human primates.

Twenty-eight day oral toxicity studies in rats and mice showed mortality and dose-related reduced weight gain and increased liver weight at PFOA dietary concentrations of 30 mg/kg and higher (Christopher and Martin, 1977; Metrick and Marias, 1977) or drinking water concentrations of 50 mg/L and above (So *et al*., 2007).

In a 90 day study Crl: CDBR rats (5/sex/group) received dietary concentrations of 0, 10, 30, 100, 300 and 1000 mg/kg PFOA equivalent to doses of 0.6, 1.7, 5.6, 18 and 64 mg/kg b.w. per day in males and 0.7, 2.3, 7.7, 22.4 and 76 mg/kg b.w. per day in females. Absolute and relative liver weights were increased at the two highest doses in males and at the highest dose

in females, with an increased absolute liver weight at the 1.7 mg/kg b.w. per day. in males. Hepatocellular hypertrophy was observed in males at doses of 5.6 mg/kg b.w. per day and higher with hepatocellular necrosis from doses of 1.7 mg/kg b.w. per day and above. Based on these liver effects the NOAEL was 0.6 mg/kg b.w. per day for males and 22 mg/kg b.w. per day for females (Goldenthal, 1978b).

A 90 day dietary toxicity study in male Crl: CDBR rats (dietary levels equivalent to 0, 0.06, 0.64, 1.94 and 6.4 mg/kg b.w. per day) showed reduced body weight gain in the highest dose group. Doses of 0.64 mg/kg b.w. per day and higher showed increased hepatic palmitoyl CoA oxidase activity, which is a marker for peroxisome proliferation, and increased relative liver weights. Histopathological changes included hepatocellular hypertrophy and necrosis of liver cells (Perkins *et al.*, 2004).

A 90 day oral toxicity study performed in rhesus monkeys (2/sex/group) with doses of 0, 3, 10, 30 and 100 mg/kg b.w. per day PFOA resulted in mortality of all monkeys at week 5 at 100 mg/kg b.w. per day, and three monkeys from the 30 mg/kg b.w. per day group at week 13. In the females dosed with PFOA at 10 mg/kg b.w. per day, the heart and brain weights were decreased. No histopathological changes were observed. No treatment related lesions were seen in the organs of animals from the 3 and 10 mg/kg b.w. per day dose groups. Occasionally marked or moderate diarrhoea was observed in the 3 mg/kg b.w. per day dose group (Goldenthal, 1978a).

Studies in which male Cynomolgus monkeys were given daily oral PFOA doses of 0, 3, 10 or 30 mg/kg b.w. for 6 months, showed dose dependent increases in liver weight associated with mitochondrial proliferation in all treatment groups. No histopathological evidence of liver injury was observed at either the 3 or 10 mg/kg b.w. per day group. No changes in clinical chemistry, hormones, urine composition or haematological effects were noticed. Two male animals died before termination of the study, one in the 3 mg/kg b.w. group and one in the 30 mg/kg b.w. (Butenhoff *et al.*, 2002).

Loveless *et al*. (2006) compared the toxicity of linear PFOA, which is now in use, with that of the 80% linear 20% branched chain PFOA formerly used in commercial products, and a 100% branched form synthesised for the purposes of this study. Groups of rats and mice were given the different preparations by intubation at PFOA doses of 0, 0.3, 1, 3, 10 or 30 mg/kg b.w. per day for 14 days. In rats the LOAEL was 1 mg/kg b.w. per day for linear/branched PFOA and 0.3 mg/kg b.w. per day for linear PFOA, based on reductions in total cholesterol and triglycerides. In mice, the LOAEL was 0.3 mg/kg b.w. per day for all of the PFOA materials, based on liver weight, peroxisomal β-oxidation (and increased triglycerides for the linear/branched material). These LOAEL doses corresponded to serum PFOA levels of 20-51 µg/mL in rats and 10-14 µg/mL in mice. The authors concluded that the toxicity profiles were similar but the branched form of PFOA appears to be less potent.

6.2.2.3 Chronic toxicity/carcinogenicity

The chronic toxicity and carcinogenicity of PFOA has been recently evaluated by U.S. EPA (2006).

Two dietary studies have been carried out in rats. The first was a 104-week chronic toxicity/carcinogenicity study (Sibinski, 1987) in which groups of 50 male and 50 female Sprague-Dawley (Crl: CDBR) rats were fed diets containing 0, 30 or 300 mg/kg APFO for two years, equal to mean doses of 0, 1.3 and 14.2 mg/kg b.w. per day for males and 0, 1.6 and 16.1 mg/kg b.w. per day for females, respectively. There was a dose-related decrease in body weight-gains in the male rats and to a lesser extent in the female rats compared to the controls; the decreases were statistically significant in the high-dose group of both sexes. The only clinical sign observed was a dose-related increase in ataxia in the female rats, most commonly associated with moribund animals. No significant differences were noted in survival, urinalysis or ophthalmoscopic findings. Significant non-neoplastic findings included, slightly decreased RBC, haemoglobin and haematocrit values in males (300 mg/kg), increased WBC in males (30 mg/kg), elevated serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (AP) and creatinine phosphokinase in males (30 mg/kg), liver masses and nodules (300 mg/kg), Leydig cell masses in males (300 mg/kg), mammary tissue masses in females (30 mg/kg), increased kidney weight in females (300 mg/kg), diffuse hepatomegalocytosis, hepatocellular necrosis, portal mononuclear cell infiltration and hepatic cystoid degeneration (300 mg/kg), tubular hyperplasia of ovarian stroma (30 mg/kg). The biological significance of the ovarian lesions was questioned by the authors on the basis of the lack of evidence of progression to tumours. Moreover, based on a re-evaluation of the slides by Mann and Frame (2004), the ovarian lesions were diagnosed and graded as gonadal stromal hyperplasia and/or adenomas, with particular emphasis placed on the proliferative effects. A NOAEL of 1.3 mg/kg b.w. per day was established for males on the basis of increases in liver weight and hepatic changes. In females, on the basis of reduced body weight gain and haematological changes, a NOAEL of 1.6 mg/kg b.w. per day was established.

Concerning carcinogenicity, there was a significant increase in the incidence of testicular Leydig cell adenomas (0/50, 2/50 and 7/50 at 0, 30 and 300 mg/kg, respectively). There was also a significant increase in the incidence of mammary fibroadenomas in both groups of females (10/46, 19/45 and 21/44 at 0, 30 and 300 mg/kg, respectively). The tumour incidences were comparable to historical controls, and therefore not considered to be biologically significant.

In a follow-up 2-year mechanistic study, male CD rats (153 treated animals and 80 animals in the control group) were administered APFO at a dietary level of 300 mg/kg, equal to 14 mg/kg b.w. per day (Cook *et al.*, 1994; Biegel *et al.*, 2001). Interim sacrifices were performed at 1 or 3 months intervals. Ten rats from each group were randomly selected at each sampling point for hormonal analysis (estradiol, testosterone, LH, FSH and prolactin), 6 for cell

proliferation and 6 for peroxisome proliferation (β-oxidation activity) analysis. In the treated group, relative liver weights and hepatic β-oxidation activity were statistically significantly increased at all the sampling time points, while absolute testis weights were increased only at 24 months. There were no significant differences in serum testosterone, FSH, LH, or prolactin in the treated rats compared to the controls. There was a significant increase in the incidence of Leydig cell adenomas in the treated rats (8/76; 11%) compared to the controls (0/80, 0%). In addition, the treated group had a significant increase in the incidence of liver adenomas (10/76, 13% vs. 2/80, 3%) and pancreatic acinar cell tumours (7/76, 9% vs. 0/80, 0%). This observation prompted a re-examination of the pancreas sections from the Sibinski and Biegel studies: it was then reported that APFO increased the incidences of proliferative pancreatic acinar cell lesions in both studies at 14.2 mg/kg b.w. per day, but not adenomas/carcinomas (Frame and McConnell, 2003). There was a greater tendency of progression to adenomas in the study by Biegel *et al*. (2001) than in the Sibinski study.

In conclusion, the two carcinogenicity dietary studies of PFOA (APFO) have shown that this compound induced hepatocellular adenomas, Leydig cell adenomas and pancreatic acinar cell hyperplasia in male rats.

PFOA has also been shown to promote liver carcinogenesis in male Wistar rats initiated with 200 mg/kg b.w. per day diethylnitrosamine by i.p., followed by treatment with APFO at 0.02% in the diet for 12 months (Abdellatif *et al.*, 1991; Nilsson *et al.*, 1991).

6.2.2.4 Genotoxicity

The genotoxicity of the ammonium salt of PFOA (APFO) was recently reviewed by U.S. EPA (2006).

APFO did not induce bacterial gene mutations in *Salmonella typhimurium-Escherichia coli*/reverse mutation assay with and without mammalian microsomal metabolic activation (Lawlor, 1995; 1996). APFO did not induce gene mutations in the Chinese Hamster Ovary (CHO) HGPRT forward mutation assay with and without mammalian microsomal metabolic activation (Sadhu, 2002). APFO did not induce chromosomal aberrations in cultured human lymphocytes when tested with and without metabolic activation up to cytotoxic concentrations (Murli, 1996d, e; NOTOX, 2000). APFO was tested twice for its ability to induce chromosomal aberrations in CHO cells (Murli, 1996c). In the first assay, APFO induced chromosomal aberrations and polyploidy in the presence and absence of metabolic activation, while in the second assay it induced chromosomal aberrations and polyploidy only when tested in the absence of metabolic activation. These effects were observed only at toxic concentrations. Recently, Yao and Zhong (2005) have reported that PFOA was able to induce DNA strand breaks as assessed by the single cell gel electrophoresis (SCGE) assay and micronuclei in cultured human hepatoma HepG2 cells. Significant increases in the levels of reactive oxygen species (ROS) and 8-hydroxydeoxyguanosine (8-dG) were also observed.

These findings indicate that the genotoxic effects observed in these cells are likely to be induced indirectly by oxidative DNA damage caused by intracellular ROS. Significant increases of 8-dG were observed in the liver of Fisher 344 rats treated with PFOA by *i.p.* at 100 mg/kg b.w. and sacrificed 1, 3, 5 and 8 days after treatment and in rats receiving PFOA at a dietary concentration of 200 mg/kg for two weeks (Takagi *et al*., 1991). The interpretation of these results is unclear, because increased oxidative DNA damage is most likely to be secondary to peroxisomal proliferation.

APFO did not induce a significant increase in micronuclei when tested twice in an *in vivo* bone marrow micronucleus assay in mice at the single oral dose of 950 mg/kg b.w. (Murli, 1996b). APFO did not induce cell transformation in $C_3H10T½$ mouse embryo fibroblasts (Garry and Nelson, 1981).

In conclusion, notwithstanding the positive results in an *in vitro* chromosomal assay in CHO cells at a toxic concentration, the negative outcome in a comprehensive series of *in vitro* and *in vivo* short-term tests at gene and/or chromosome level indicates that APFO is devoid of significant genotoxic activity

6.2.2.5 Developmental and reproductive toxicity

Teratological studies of PFOA have been conducted with rats and rabbits. Doses up to 100–150 mg/kg b.w. per day for rats and 50 mg/kg b.w. per day for rabbits showed no significant effects (Gortner, 1981; 1982 and review Lau *et al.*, 2004). No teratogenicity has been found in rats after administration of PFOA by inhalation (0, 0.1, 1, 10, and 25 mg/m³) or in the diet (100 mg/kg b.w. per day) between day 6 and 15 of pregnancy (Staples and Burgess, 1984). In rats, the NOAEL for maternal toxicity and developmental toxicity were 5 and 150 mg/kg b.w. per day respectively.

A recent study by Lau *et al.* (2006) revealed dose dependent growth deficits in the litters of CD-1 mice treated daily during pregnancy from day 1 until birth by oral gavage (1, 3, 5, 10, 20, 40 mg/kg b.w. per day). PFOA induced enlarged liver in treated dams at all dosages, but did not alter the number of implantations or malformations. The 40 mg/kg b.w. per day group resorbed their litters, the 20 mg/kg b.w. per day group had a reduced percentage of live foetuses and their weight was significantly lower. Post natal survival was significantly reduced in the 5, 10 and 20 mg/kg b.w. per day group. Dose dependent growth deficits were noted in all dose groups except in the 1 mg/kg b.w. per day dose group. Significant delays in eye opening were noted at 5 mg/kg b.w. per day and at higher dosages but not in the 1 mg/kg b.w. per day dose group. Accelerated sexual maturation was observed in male offspring but not in females.

Wolf *et al*. (2007) investigated the critical windows of PFOA exposure in mice together with the relationship between lactational exposure and neonatal viability. Administration of PFOA

at oral doses of 3 to 20 mg/kg b.w. per day resulted in increased maternal liver weight and deficits in postnatal weight gain of the pups. Pups of dams dosed on GD 7-17, and 10-17 also showed developmental delay in eye opening and hair growth. Cross-fostering studies showed that the effects were due to *in utero* rather than lactational exposure. A NOAEL was not identified.

Another recent study was carried out in pregnant mice to determine whether PFOA effects were linked to gestational time of exposure or to subsequent lactational changes. The study used an oral dose of 5 mg/kg b.w. per day PFOA at GD 1–17, 8–17, 12–17, or a vehicle on GD 1–17, Overall, mean pup bodyweights on postnatal day (PND) 1 in all PFOA-exposed groups were significantly reduced and these effects persisted until weaning. Mammary gland differentiation was also affected among dams exposed GD 1–17 or 8–17 on PND 10 and normal epithelial involution and alterations in milk protein gene expression were observed on PND 20. Overall, these findings suggest that in addition to gestational exposure, abnormal lactational development of dams may play a role in the early growth retardation of developmentally exposed offspring (White *et al*., 2007).

Abbott *et al*, (2007) investigated the involvement of PPARα in PFOA-induced developmental toxicity using wild type (WT) and PPARα knock out (KO) pregnant mice dosed orally with PFOA at 0.1, 0.3, 0.6, 1, 3, 5, 10 or 20 mg/kg b.w. per day on GD 1-17. PFOA did not affect maternal weight, embryonic implantation, or number or weight of pups at birth. At 5 mg/kg b.w., the incidence of full litter resorptions increased in both WT and KO mic. At 1 mg/kg b.w. per day, pup weights were significantly lower than control at some time points in WT, but not in KO mice. In WT, but not KO, a reduction in neonatal survival was observed at 0.6 mg/kg b.w. per day giving a NOAEL of 0.3 mg/kg b.w. per day. Eye opening was delayed at 1 mg/kg b.w. per day in WT mice. The authors concluded that early pregnancy loss was independent of PPARα expression whereas PPARα appeared to have a role in delayed eye opening and deficits in postnatal weight gain, although other mechanisms may also contribute.

In a two generation reproduction study, rats were given PFOA 1, 3, 10 or 30 mg/kg b.w. per day by oral gavage (Butenhoff *et al.*, 2004). Male rats in the parental and F1 generations administered 3, 10 and 30 mg/kg b.w. per day showed decreased body weight. Liver and kidney weight increased in all treatment groups. The F1 generation at 30 mg/kg b.w. per day showed reduced birth weight, increased post weaning mortality and delayed pubertal onset. No effects were observed on mating or fertility parameters. From this study the NOAELs were 30 mg/kg b.w. for reproductive function, 10 mg/kg b.w. for sexual maturation, and < 1 mg/kg b.w. for body weight and increased liver weight.

6.2.3 Neurotoxicity

Administration of PFOA to 10-day old mice by gastric tube at 0.58 or 10.8 mg/kg b.w. has been reported to result in impaired performance in behavioural tests conducted when the mice were 2 and 4 months old. Based on the response to nicotine, these effects were considered to be mediated via the cholinergic system (Johansson *et al*., 2008).

6.2.4 Human data

Most studies on PFOA have been carried out by 3M in the Cottage Grove plant (Minnesota, USA), where PFOA has been produced since 1947. PFOA has been manufactured since 1998 at the 3M Decatur, Alabama plant.

A cross sectional study among 191 workers engaged in PFOA production revealed an increase in mean estradiol levels among employees that had the highest levels of serum PFOA (>30 ng/mL) although this association was confounded by body mass index (Olsen *et al.*, 1998).

A number of studies have investigated associations between concentrations of PFOA and various biochemical parameters in the serum of occupationally exposed workers, Some of these have found a positive association between PFOA and cholesterol and triglycerides (Olsen *et al*., 2003d; Sakr *et al*., 2007a and b) whereas other studies found no such association (Ubel et al., 1980; Gilliland and Mandel, 1996; Olsen *et al*., 1998; Olsen *et al*., 2000). The most recent report of Olsen and Zobel (2007) included workers from three separate 3M PFOA production sites in Antwerp (n=306), Minnesota (n=131) and Alabama (n=215). PFOA was not statistically significantly associated with total cholesterol or low-density lipoproteins (LDL). High-density lipoproteins (HDL) were negatively associated with PFOA for the three facilities combined, but not for the individual sites. Serum triglycerides were positively associated with PFOA for the three facilities combined, and individually for Antwerp but not for the other two sites. No consistent associations were found with PFOA and thyroid hormones. Overall T4 was negatively associated with PFOA and T3 was positively associated but the trends were within normal reference ranges. The authors considered that the HDL association was likely to be explained by residual confounding, but could not rule out a biological explanation for the triglyceride observation.

A retrospective cohort study investigated causes of mortality in 6,027 men and women who had worked in a Dupont polymer manufacturing plant between 1948 and 2002. Mortality associated with diabetes was significantly increased compared to a regional worker population (SMR = 1.97; 95% CI = 1.23–2.98) but not compared with two general populations (U.S. and West Virginia state). There was no significant increased risk of ischaemic heart disease or cancer (Leonard *et al*., 2008).

Apelberg *et al*. (2007b) investigated the association between PFOA concentrations in cord serum and gestational age, birth weight and size of 293 singleton births delivered in November 2004 to March 2005 in Baltimore, USA. PFOA was detected in all of the cord blood samples, with a median concentration of 1.6 ng/mL (range 0.3-7.1 ng/mL). PFOA was inversely associated with birth weight and head circumference, but not length or gestational duration. The concentrations of PFOA in cord serum were highly correlated with those of PFOS. In the Danish National Birth Cohort of 1400 women delivering a single child between March 1996 and November 2002, the average maternal plasma level of PFOA was 5.6 ng/mL (range < 1.0 – 41.5 ng/mL) and the cord plasma levels in a subset of 50 subjects were 3.7 $\pm$ 3.4 ng/mL (mean + S.D.) Maternal plasma levels of PFOA were inversely associated with birth weight but not with risk of low birth weight (< 2500g) or small for gestational age (Fei *et al*., 2007).

Carcinogenicity

The epidemiological data on PFOA, as for PFOS, are limited to occupationally exposed worker studies, mostly involving male workers. Two limited retrospective cohort studies (Gilliland and Mandel, 1993; Alexander, 2001a and b) were carried out on employees at a 3M plant.
A weak association with PFOA exposure and prostate cancer (SMR=1.3, 95% Cl=0.03–7.2) was reported in one study; however this result was not observed in an update to the study in which the exposure categories were modified.

A retrospective cohort mortality study was performed on workers at the 3M Cottage Grove MN plant (Gilliland and Mandel, 1993). The cohort consisted of workers who had been employed at the plant for at least 6 months between January 1947 and December 1983. The number of months provided the cumulative exposure measurements. Of the 3537 (2788 men and 749 women) employees, 398 (348 men and 50 women) were deceased. Eleven of the 50 women and 148 of the 348 men were considered exposed to APFO. The Standardised Mortality Ratios (SMRs), adjusted for age, sex and race, and stratified for 3 latency periods (10, 15 and 20 years) and 3 periods of duration of employment (5, 10 and 20 years), were compared to U.S. and Minnesota white death rates for men. For women, only state rates were available. When exposure status was considered, SMRs for all causes of death and all cancers were lower than expected. When compared to Minnesota death rates, the SMR for prostate cancer was 2.03 (95% CI 0.55–4.59), based on 4 deaths (1.97 expected). There was a statistically significant (p=0.03) association with length of employment. The relative risk for a 1-year increase in employment was 1.13 (95% CI 1.01–1.27). It rose to 3.3 (95% CI 1.02–10.6) for workers employed for 10 years (Gilliland and Mandel, 1993).

An update of this study was conducted to include mortality through to 1997 (Alexander, 2001a). The cohort consisted of 3992 workers, placed into 3 exposure groups based on job history information; definite exposure (n=492); probable exposure (1685) and not exposed

(1815). In this new cohort, 607 deaths were identified: 46 in the exposure group, 267 in the probable exposure group, and 294 in the non-exposed group. The highest SMR reported was for bladder cancer (SMR=1.31, 95% CI=0.42–3.05). A few SMRs were elevated for employees in the definite exposure group: 2 deaths from cancer at the large intestine (SMR=1.67, 95% CI=0.02–6.02), 1 from pancreatic cancer (SMR=1.34, 95% CI=0.03–7.42), and 1 from prostate cancer (SMR=1.30, CI=0.03–7.20). In the probable exposure group, 3 SMRs were elevated: cancer of the testis and other male genital organs (SMR=2.75, 95% CI=0.07–15.3); pancreatic cancer (SMR=1.24, 95% CI=0.45–2.70); malignant melanoma of the skin (SMR=1.42, CI=0.17–5.11). These SMRs were not statistically significant at $p \leq 0.05$. There were no notable excesses in SMRs in the non-exposed group, except for cancer of the bladder and other urinary organs (4 cases against 1.89 expected).

It is difficult to interpret the results of the prostate cancer deaths between the first study and the update because the exposure categories were modified in the update. This issue has become more apparent, given the results of a biomonitoring study that took place at the Cottage Grove plant in 2000 in which PFOA concentrations were not correlated with years worked but instead were associated with the specific area of the plant where APFO was produced.

Limited data are available on mortality and cancer incidence in studies conducted at DuPont's Washington Works Plant (DuPont, 2003b). These studies provide little information about the relationship of PFOA to mortality or cancer incidence since no exposure information, use of other compounds, or lifestyle information was collected on the employees.

In summary, a retrospective cohort mortality study showed a statistically significant association between prostate cancer mortality and employment duration in the chemical facility of a plant that manufactures APFO. However, in an update of this study, in which more specific exposure measures were used, a significant association for prostate cancer was not observed. Other mortality studies lacked adequate exposure data which could be linked to health outcomes. A number of studies have investigated possible associations between PFOA serum levels and biochemical parameters associated with lipid metabolism. Some have shown associations with elevated cholesterol and triglycerides, or with changes in thyroid hormones, but overall there is no consistent pattern of changes. In two recent ecological studies PFOA exposure of pregnant women, measured by maternal and/or cord serum levels was associated with reduced birth weight. The Panel noted that these observations could be due to chance, or to factors other than PFOA, but indicate a need for further research into possible developmental effects in humans.

6.2.5 Mode of action

Liver toxicity

The critical effects of PFOA in rodents and monkeys are on the liver (moderate grade hypertrophy, changes in liver enzyme activity, absolute or relative liver weight increases, hypolipidemia, proliferation of smooth endoplasmic reticulum and peroxisomes).

In rodents these effects may be related to the peroxisome proliferating activity of PFOA (Ikeda *et al.*, 1985; Pastoor *et al.*, 1987; Sohlenius *et al.*, 1992b). Rats showed PPAR activity at exposure levels of 0.64 mg/kg b.w. per day and more (Perkins *et al*., 2004) showing that PFOA acts as a PPARα-agonist. Maloney and Waxman (1999) showed that PFOA activates PPARα using COS1 cells transfected with a luciferase reporter gene. Like many other peroxisome proliferators, PFOA has also been shown to cause hepatomegaly in rats (Takagi *et al*., 1992; Cook *et al.,* 1994) and mice (Kennedy, 1986), oxidative DNA damage in liver of rats (Takagi *et al*., 1991) and apoptosis in HepG2 liver cells (Shabalina *et al*., 1999). Takacs and Abbott (2007) reported that PFOA was more active than PFOS for both mouse and human PPARα and PPARβ, but neither substance showed significant activation of mouse or human PPARγ. By activating PPARα PFOA also interferes with lipid and lipoprotein metabolism. This was also seen in studies including gene expression analysis of livers from PFOA fed rats, which showed alterations in the genes associated with lipid and fatty acid metabolism in rats treated with PFOA. The induced enzymes for fatty acid oxidation might increase the normal oxidation of fatty acids and might disrupt the normal balance of fatty acid metabolism in mammals (Yin Yeung *et al.*, 2005). Moreover, genomic studies in rat liver showed that the largest cluster of induced genes treated with PFOA were those involved in the metabolism and transport of lipids, particularly fatty acids (Guruge *et al*., 2006; Martin *et al*., 2007; Rosen *et al*., 2007). Another recent study showed that PFOA exhibits the properties of a mixed type enzyme inducer since CYP2B2, CYP3A4 and CYP4A1 were induced in liver microsomes. Such an induction profile also suggests the interaction between PFOA and members of the nuclear hormone super family particularly PPARα, (mentioned above), constitutive androstane receptor and pregnane X receptor (PXR) (Elcombe *et al*., 2007). In a study in which PFOA was administered to wild-type and PPARα-null mice in the diet for 7 days (dose approximately 3 mg/kg b.w. per day), similar increases in liver weight were seen in both strains, whereas hepatic peroxisomal acyl-coA oxidase activity was increased in the livers of the wild-type mice only (Yang *et al., 2002)*.

In Cynomolgus monkeys dose dependent increases in liver weight associated with mitochondrial proliferation have been observed from the lowest dose tested (3 mg/kg per day during 26 weeks), the mechanism of action remains to be resolved since peroxisomal markers were not altered (Butenhoff *et al.*, 2002).

The Panel therefore concluded that not all of the liver toxicity could be ascribed to PPARα activity and other possible mechanisms such as induction of genes involved in lipid

metabolism and transport of lipids and drug-metabolising enzymes could be of relevance to human health.

Carcinogenicity

As for PFOS, the negative outcome in a comprehensive series of genotoxicity tests at gene and/or chromosome level indicates an indirect (non-genotoxic) mechanism for the carcinogenicity of PFOA (APFO). The mechanisms underlying its carcinogenic activity in rats have been recently reviewed by U.S. EPA (2006), which attributed it to a non-genotoxic mechanism, involving activation of receptors and perturbations of the endocrine system. APFO is a PPARα-agonist which suggests that liver carcinogenicity/toxicity could be mediated by binding to PPARα in the liver. However, taking into account that PFOA also caused liver effects in monkeys the Panel could not discount the relevance of liver toxicity due to other mechanisms. The data presently available suggest that the induction of Leydig cell tumours and mammary gland neoplasms may be due to hormonal imbalance resulting from activation of the PPARα and induction of the cytochrome P450 enzyme, aromatase. A mechanistic role for sustained increase of serum estradiol in the mechanism of induction of Leydig cell adenomas was hypothesised by Biegel *et al.* (2001).

Other end points

The study of Abbott *et al*. (2007) reported in section 6.2.2.5, investigated the role of PPARα in the developmental toxicity of PFOA using wild-type and PPARα-null mice. The authors concluded that early pregnancy loss was independent of PPARα expression but delayed eye opening and deficits in postnatal weight gain appeared to depend on PPARα expression, although other mechanisms may contribute.

Oral administration of PFOA for 10 days to C57 Bl mice induced severe atrophy of thymus and spleen (Yang *et al.*, 2000) and suppressed humoral and cellular immunity (Yang *et al.*, 2002). This effect may be associated with the peroxisomal proliferation mode of action of PFOA since both PPAR alpha and PPAR gamma have been reported to be involved in the regulation of inflammatory responses.

Inhibition of testosterone biosynthesis by PFOA has been observed in a mixture of *in vivo*, *ex vivo* and *in vitro* studies (Biegel *et al.*, 1995). Increased serum estradiol levels may be related to induction of hepatic aromatase activity. Estradiol also stimulates the production of growth factors such as the transforming growth factor α which induces Leydig cell proliferation.

6.2.6. Derivation of TDI

Several toxicological studies discussed in the previous chapter are summarised with respect to type of study, endpoint and associated LOAEL and/or NOAEL in Table 20.

Table 20. Summary of selected studies on PFOA toxicity.

Subchronic toxicity			
Type of study	**Most sensitive endpoint (Reference)**	**LOAEL mg/kg per day**	**NOAEL mg/kg per day**
Oral gavage 14 days Mice (m) 10 per group (linear and linear/branched chain PFOA)	Liver weight (Loveless *et al*., 2006)	0.3 corresponding to serum levels of 10-14 µg/mL	-
Oral gavage 14 days Rats (m) 10 per group (linear/branched chain PFOA)	Reductions in total cholesterol and triglycerides (Loveless *et al*., 2006)	1.0 corresponding to serum levels of 51±10 µg/mL	0.3
Oral gavage 14 days Rats (m) 10 per group (linear PFOA)	Reductions in total cholesterol and triglycerides (Loveless *et al*., 2006)	0.3 corresponding to serum levels of 20±3.2 µg/mL	-
Oral diet 90 days Rats; 5/sex/group	Hepatocyte necrosis (m) Increased liver weight (f) (Goldentha *et al.*, 1978c)	1.7 (m) [a] 76 (f)	0.6 (m) 22(f) [b]
Oral diet 90 days rats(m); 45-55 /group	Hepatocellular hypertrophy and increased liver weight (Perkins *et al.* 2004)	0.6 corresponding to serum levels of 41.2±13.0 µg/mL	0.06 corresponding to serum levels of 7.1±1.15 µg/mL
Oral (capsule) 180 days Cynomolgus monkeys 4-6 (m) /group	Increased liver weight and mortality (Butenhoff *et al.*, 2002)	3 lowest dose tested steady state serum levels corresponded with 77+/-39 µg/mL	
Developmental and reproductive toxicology			
Oral gavage Rats (f)	GD 6-15 Reduced maternal body weight No foetal effects (Gortner, 1981)	Maternal: 150	Maternal: 5 Foetal: >150
Oral, gavage Rabbits (f)	GD6-18 No maternal effects No foetal effects (Gortner *et al.*, 1982)		>50 (highest dose tested) >50 (highest dose tested)
Oral , gavage CD-1 mice	GD1-18 Enlarged liver in dams Growth deficits of the litters (Lau *et al*., 2006)	Maternal: 1 Foetal: 3	Maternal: - Foetal: 1
Oral gavage Two generation study Rats (m/f) 30 rats /dose group	F0: from 42 days prior to mating, to the end of mating (m), and to LD21 (f) F1:from 22 days after birth to the end of mating (m) and to LD 21 (f) F0 (m) increased liver weight F1(m)reduced body weight F1(f)mortality, reduced body weight gain and delayed sexual maturation F2: no significant effects (Butenhoff *et al.*, 2004)	 Paternal: 1 Foetal: 1 Foetal: >30	 Maternal:>30 (highest dose tested) Foetal:10 Foetal: >30
Oral, gavage CD-1 mice WT pregnant mice KO pregnant mice PPAR α	GD1-17 No maternal effects Neonatal survival Neonatal survival (Abbott *et al*., 2007)	 0.6 5	 0.3 3

Table 20. Summary of selected studies on PFOA toxicity – continued.

Subchronic toxicity			
Type of study	**Most sensitive endpoint**	**LOAEL mg/kg per day**	**NOAEL mg/kg per day**
Chronic toxicity/carcinogenicity			
Oral diet Rats 50/sex/group	Increase in liver weight and hepatic changes (m) Reduced body weight gain and haematological changes (f) (Sibinski, 1987)	14.2 (m) 16.1 (f)	1.3 (m) 1.6 (f)

[a)] male
[b] female
[c)] dietary concentration converted to daily intake level : assuming a daily food consumption for mice of 4.5 g/ mouse and a mean body weight of 23.5 g (Bachmanov *et al.*, 2002).

The lowest NOAEL identified was 0.06 mg/kg per day in a subchronic study in male rats. At the next higher dose (0.64 mg/kg b.w.), hepatocellular hypertrophy and increased liver weight was seen. These changes are often classified as adaptive and reversible. However, as these represent biological changes possibly related to effects such as tumour promotion and/or changes in drug-metabolizing enzyme activities, and that reversibility is of limited importance when assessing compounds with high persistence and long biological half-life, the findings should be critically evaluated. On the other hand, Sibinski (1987) reported a NOAEL at 1.3 mg/kg b.w. per day for increased liver weight in the two-year study in rats. In the two-generation reproductive study by Butenhoff *et al.* (2004) at the lowest dose studied (1 mg/kg b.w. per day) increased liver weight and focal to multifocal hepatic necrosis in the F_0- and F_1-generational male rats was seen. When these dose-response data on increased liver weight were modelled the lower confidence limits of the benchmark dose for a 10% effect size ($BMDL_{10}$) was 0.31 mg/kg b.w. per day in the males of both generations. From a developmental study in mice, Lau *et al*. (2006) estimated a $BMDL_5$ for increased maternal absolute liver weight to 0.17 mg/kg b.w. per day. The COT estimated $BMDL_{10}$ values for effects on liver (Table 21). The Panel decided also to adopt a BMDL approach.

Table 21. $BMDL_{10}$ values from animal data (taken from COT, 2006b).

Effect	Study duration, weeks	BMD_{10}, mg/kg b.w. per day	$BMDL_{10}$, mg/kg b.w. per day
Maternal liver weight at term in pregnant mice [a]	GD 1-17	0.52	0.46
Increased absolute liver weight in male rats [b]	4	0.6	0.4
Increased absolute liver weight in male rats [b]	7	0.69	0.29
Increased absolute liver weight in male rats [b]	13	0.89	0.44
Hepatocytic megalocytosis in male rats [c]	104	1.1	0.74
Increased liver weight and focal to multifocal hepatic necrosis in male offspring [d]	GD 15 - 17	0.78	0.31

[a] Lau *et al*. (2006)
[b] Palazzolo (1993) and Perkins *et al.* (2004)
[c] Sibinski (1987)
[d] Butenhoff *et al.* (2004)

It should be noted that the kinetic properties of PFOA in rats as well as humans are not well understood. The striking difference between male and female rats, as given by the much shorter half-lives for females indicates that studies on female rats on reproduction and offspring development should be interpreted with care. As Table 21 shows similar $BMDL_{10}$ values for effects in mice and male rats the Panel concluded that the lowest $BMDL_{10}$ of 0.3 mg/kg b.w. per day was an appropriate point of departure for deriving a TDI.

The CONTAM Panel established a TDI for PFOA of 1.5 µg/kg b.w. per day by applying an overall UF of 200 to the lowest BMDL10 of 0.3 mg/kg b.w. per day. An UF of 100 was used for inter- and intra-species differences and an additional UF of 2 to compensate for uncertainties relating to the internal dose kinetics. The CONTAM Panel used this figure together with a margin of exposure consideration (chapter 7.3) to assess the potential significance of the total human exposure to PFOA.

7. Risk characterisation

7.1 Exposure to PFAS

For the general population, the common routes of exposure to environmental compounds are ingestion, dermal contact, and inhalation. Many PFAS are environmentally persistent but not lipophilic; rather they have mixed lipophobic and hydrophobic properties. The exposure scenario is complex as PFAS have a large variety of applications. Oral exposure from materials other than food, inhalation and dermal contact may be important exposure routes for certain segments of the population. Dust inhalation could also be a possible source of exposure. However, the information on concentrations of PFAS in indoor dust is very limited and the bioavailability of the current compounds from dust is unknown.

There are some data on PFOS and PFOA in fish and water from European countries. However, there is a general lack of occurrence data for most foodstuffs. This evaluation, based on food consumption patterns of the EU countries Italy, The Netherlands, Sweden, and the UK, must be regarded as provisional while waiting for the necessary food monitoring results to be gathered.

7.2 Risk characterisation of PFOS

The currently available information is inadequate to characterise dietary exposure in the different regions in the European Union. Data presented in a German total diet study estimate the PFOS exposure in the region of 1 to 4 ng/kg b.w. (Fromme *et al*., 2007 b) whereas data from the UK indicated lower bound to upper bound ranges of 10 to 100 and 30 to 200 ng/kg b.w for average and high level consumers, respectively.

From the few food items investigated so far, the data do not allow a complete assessment of different food sources of PFOS, but fish may be an important contributor. Based on the occurrence of PFOS in fish and fishery products and drinking water together with consumption data from four Member States (Table 12) the Panel selected an indicative figure of 60 ng/kg b.w. per day for further consideration.

In most studies, no direct correlation has been demonstrated between PFOS levels in human plasma and total fish consumption, although Falandysz *et al*. (2006) reported three times higher PFOS levels in high level consumers of fish in Poland compared to individuals with "normal" fish consumption. The commonly observed lack of correlation could be a result of "dilution" by different fish species as PFOS also has found to be correlated to intake of certain lean fish at high trophic level such as pike and pikeperch. Another possibility is contribution to exposure *via* air, house dust and other kinds of food such as potatoes and microwaved popcorn or *via* yet unidentified sources. Mean human serum concentrations reported in Table 14 ranged roughly within one order of magnitude. In the duplicate diet study by Fromme *et al.* (2007b) the total range was between 6 and 28 ng/mL plasma with no direct correlation with dietary exposure.

Humans may be exposed to small quantities of PFOS from drinking water; on average, 0.24 ng/kg b.w. per day. Thus drinking water appears to contribute <0.5% of the indicative dietary exposure. The contributions to human exposure from the non-food sources examined were in the order of 3% or less. These contributions are expected to be even smaller when related to the high level consumers of fish and fishery products. It should however be noted that, probably, levels measured in human plasma do not only reflect human exposure to PFOS from food and non-food sources as there are other potentially important sources to human exposure which influence the body burden. Such possible sources could include precursors of PFOS with the potential to be transformed into PFOS in the body, although the extent to

which this occurs is still unknown. There is currently almost no information on human exposure to such precursors or their occurrence in food and feed.

The CONTAM Panel noted that the indicative dietary exposure of 60 ng/kg b.w. per day is below the TDI of 150 ng/kg b.w. but that the highest exposed people within the general population might exceed this TDI.

It might be that a significant part of the body burden could be a result of exposure to precursors that could be transformed into PFOS in the body. However, there is no reliable information on body burdens in humans, and therefore the Panel decided to compare blood levels in humans and animals recognising the uncertainties in attainment of steady-state conditions.

The margin between serum levels in the monkeys at the NOAEL and the current European average serum levels of PFOS in the general population, as given in Table 14, was in the range of 200 – 3,000. Given this margin, the CONTAM Panel considered it unlikely that adverse effects of PFOS are occurring in the general population. Further data on PFOS levels in humans would be desirable, particularly with respect to monitoring trends in exposure

7.3 Risk characterisation of PFOA

The currently available information is inadequate to characterise dietary exposure in the different regions in the European Union. Data presented in a German total diet study estimate a PFOA mean intake of 3.9 ng/kg b.w. with a range of 1.1 to 11.6 ng/kg b.w. (Fromme *et al*., 2007b) whereas data from the UK indicated lower bound to upper bound ranges of 1 to 70 and 3 to 100 ng/kg b.w. for average and high level consumers, respectively. The upper bounds of these ranges are likely to be considerable overestimates because they are based on a very large number of samples in which PFOA could not be detected.

From the few food items investigated so far, the data do not allow a complete assessment of different food sources of PFOA, but fish may be an important contributor. The Panel noted that the average dietary exposure to PFOA is unlikely to exceed 4 ng/kg b.w. per day. The data on the occurrence of PFOA in fish and fishery products and drinking water together with consumption data from four Member States (Table 17) provided an indicative average exposure of 2 ng/kg b.w. per day.

Studies of blood levels in relation to fish consumption do not show a strong correlation. In a Swedish study reported in Berglund *et al.* (2004) and Holmström *et al.* (2005) of 108 women with high consumption of fish the mean level of PFOA in whole blood was 2 ng/mL and the maximum level was 4.8 ng/mL. Assuming a factor 2 between whole blood and serum or plasma (Ehresman *et al.,* 2007), this maximum level corresponds to about 10 ng/mL plasma which is below the highest European levels given in Table 14. Mean human serum

concentrations reported in Table 14 ranged roughly within one order of magnitude. The total range in the group studied by Fromme *et al.* (2007b) was between 3 and 13 ng/mL plasma showing no direct correlation with dietary exposure as measured by the duplicate diet study.

Humans may be exposed to small quantities of PFOA from drinking water on average, 0.31 ng/kg b.w. per day, which appears to be a modest contribution to the dietary exposure. The contribution to human PFOA exposure from the non-food sources examined may reach approximately 50% of average indicative dietary exposure, with a clear predominance of exposure to house dust.

The CONTAM Panel noted that the indicative dietary exposure of 2 ng/kg b.w. per day is well below the TDI of 1.5 µg/kg b.w.

It should be noted that the levels recorded in human plasma do not only reflect human exposure to PFOA from food and non-food sources as there exist other potentially important sources to human exposure which influence the body burden. Such possible sources could be contribution from PFOA precursors which could be transformed into PFOA in the body, although the extent to which this occurs is still unknown. There is currently almost no information on human exposure to such precursors or their occurrence in food and feed.

The Panel noted that it would be possible to, at least partially, take into account possible contributions from precursors by comparing the observed body burden at the NOAEL or LOAEL in animals with human body burden. As there is no reliable information on body burdens in humans, the estimated or measured levels in human blood, plasma or serum could be compared with the corresponding levels found in laboratory animals at the NOAEL or LOAEL. This could then be expressed as the margin of blood (or plasma/serum) level by dividing the estimated animal level with the estimated median human blood (or plasma/serum) level. The lowest reported LOAEL of 0.3 mg/kg b.w. per day, for increased liver weight was associated with a PFOA level in serum of approximately 20 µg/mL (Loveless *et al*., 2006) and this would therefore also be expected to be the serum level at the $BMDL_{10}$ of 0.3 mg. The CONTAM Panel noted that this level was in the region of three orders of magnitude higher than the reported mean levels of PFOA in serum from the European population (Table 14). Given this margin, the Panel considered it unlikely that adverse effects of PFOA are occurring in the general population, but noted uncertainties with regards to developmental effects. Further data on PFOA levels in humans would be desirable, particularly with respect to monitoring trends in exposure.

.

CONCLUSIONS

General to PFOS and PFOA

- Perfluorooctane sulfonate (PFOS) and perfluorooctanoic acid (PFOA) are two members of the group of perfluorinated alkylated substances (PFAS) and are highly persistent, able to bio-accumulate and slowly cleared from humans. As many PFOS- and PFOA-related compounds are commercially produced and used in a vast number of applications in relatively large amounts, these compounds are today widely distributed in the environment and PFOS is generally the dominating member of the PFAS family.
- PFAS in polymers can break down to PFOS and PFOA. The relative importance of such precursors to the current environmental load of PFOS and PFOA is, as yet, unknown.
- Analytical methods are available for PFOS and PFOA and related substances in different matrices. However, a comprehensive international inter-laboratory study dealing with several matrices showed large variability between laboratory results.
- There are no systematic investigations of the occurrence of PFAS in in European food available that could form a basis for a comprehensive dietary exposure assessment.

PFOS

Exposure

- Due to the lack of data, it has not been possible to perform an assessment of the relative contribution from different foodstuffs to human exposure to PFOS.
- Based on the limited information available, fish and fishery products seem to be one important source of human exposure to PFOS.
- Based on the occurrence of PFOS in fish and fishery products and drinking water together with consumption data from four Member States the Panel selected an indicative figure of 60 ng/kg b.w. per day for human exposure. The estimated indicative exposure of high consumers of fish and fishery products is approximately three times as high (200 ng/g b.w. per day). However these estimates are substantially influenced by data that might be more representative for fish from polluted areas rather than for the exposure of the general European population. Much lower dietary exposure estimate were recently found in Germany (Bavaria) and Canada, highlighting the uncertainty in these exposure assessments.
- Non-food sources of PFOS were estimated to contribute in the order of 2% or less of average dietary exposure. Drinking water appears to contribute less than 0.5%.
- PFOS blood and tissue levels measured in humans do not necessarily reflect exposure to PFOS from food and non-food sources as there is a number of potentially important precursors which could be transformed into PFOS in the body. There is currently no information on human exposure to such precursors, on their rate of transformation in the body, or on their occurrence in food and feed.

Hazard characterisation

- PFOS is readily absorbed after oral exposure. Biotransformation does not seem to play a relevant role for its elimination. Half-lives in rats, Cynomolgus monkeys and humans are in the region of > 90 days, 200 days and 5.4 years, respectively.
- PFOS can cross the blood brain barrier. It can also cross the placenta and thus be transferred to the foetus. PFOS can also be transferred to the offspring *via* lactation, although the levels recorded in milk are lower than those in the maternal plasma.
- In animal experiments, steep dose response curves were often observed with a narrow dose range between no observed adverse effects and treatment related death. The critical effects of PFOS are effects on the liver including hypertrophy, changes in enzyme activities, and increases in absolute or relative liver weight, but also developmental effects have been observed in experimental animals.
- Several studies have shown that PFOS can interfere with fatty acid metabolism and may deregulate metabolism of lipids and lipoproteins. The links to the liver toxicity that is observed in rodents and monkeys is not well understood.
- PFOS induces liver tumours in rats but there are no indications of a genotoxic potential.
- Epidemiological studies in PFOS exposed workers have not shown convincing evidence of increased cancer risk. An increase in serum T3 and triglyceride levels has been observed. These findings are opposite to the findings in rodents and monkeys.
- The lowest no-observed-adverse-effect (NOAEL) of 0.03 mg/kg b.w. per day was identified from a subchronic study with Cynomolgus monkeys showing changes in lipids and thyroid hormones at the next higher dose level. The CONTAM Panel established a Tolerable Daily Intake (TDI) for PFOS of 150 ng/kg b.w. per day by applying an overall uncertainty factor (UF) of 200 to the NOAEL of 0.03 mg/kg b.w. per day. An UF of 100 was used for inter and intra-species differences and an additional UF of 2 to compensate for uncertainties related to the duration of the key study and the elimination kinetics of PFOS.

Risk characterisation

- The CONTAM Panel noted that the indicative dietary exposure of 60 ng/kg b.w. per day is below the TDI of 150 ng/kg b.w. but that the highest exposed people within the general population might slightly exceed this TDI.
- The margin between serum levels in the monkeys at the NOAEL and the serum levels in the general population are between 200 and 3,000. Given this margin, the CONTAM Panel considered it unlikely that adverse effects of PFOS are occurring in the general population.

PFOA

Exposure

- Due to the lack of data, it has not been possible to perform an assessment of the relative contribution from different foodstuffs to human exposure to PFOA.
- Based on the limited information available, fish and fishery products seem to be one important source of human exposure to PFOA.
- Based on the occurrence of PFOA in fish and fishery products and drinking water together with consumption data from four Member States the Panel selected an indicative figure of 2 ng/kg b.w. per day for average human exposure. The estimated exposure of high consumers of fish and fishery products is approximately three times as high (indicative figure of 6 ng/g b.w. per day). However, these estimates are substantially influenced by data that might be more representative for fish from polluted areas rather than for the exposure of the general European population. Consequently, these estimates of the exposure to PFOA within the EU general population are likely to be overestimations.
- At these estimated intakes, non-food sources could contribute up to 50% of average dietary exposure, whereas drinking water would contribute less than 16%.
- PFOA has been identified in non-stick coatings and in food contact material such as microwave popcorn bags, but no substantial transfer to food has been demonstrated.
- PFOA blood and tissue levels measured in humans do not necessarily reflect exposure to PFOA from food and non-food sources as there are a number of potentially important precursors which could be transformed into PFOA in the body. There is currently little information on human exposure to such precursors and on their rate of transformation in the body, or on their occurrence in food and feed.

Hazard identification and characterisation

- PFOA is readily absorbed after oral exposure. Biotransformation does not seem to play a relevant role for its elimination. Distribution and elimination is dependent on protein binding and the expression of transporter proteins. In treated animals the highest concentrations of PFOA are found in liver, kidney and blood.
- Estimated elimination half-lives are < 24 h in female rats, < 9 days in male rats, 21 and 30 days for male and female Cynomolgus monkeys, respectively, and about 3.8 years in humans.
- PFOA can cross the blood brain barrier. It can also cross the placenta and thus be transferred to the foetus. PFOA can also be transferred to the offspring via lactation, although the levels in breast milk are approximately one tenth than those in the maternal plasma.
- In animal experiments, the critical effects of PFOA are on the liver, including hypertrophy, changes in enzyme activities, and absolute or relative liver weight increases and developmental effects.

- PFOA interferes with fatty acid metabolism and may deregulate metabolism of lipids and lipoproteins. It activates the PPARα and is a peroxisome proliferator, however this property is unlikely to be responsible for the observed liver toxicity in primates where lipid accumulation has been observed in the liver without the activation of the PPARα receptor. Mechanistic studies demonstrated that some, but not all, of the developmental effects are mediated via the PPARα.
- PFOA induces liver tumours in rats but there are no indications of a genotoxic potential.
- Epidemiological studies in PFOA-exposed workers do not indicate increased cancer risk. Some have shown associations with elevated cholesterol and triglycerides, or with changes in thyroid hormones, but overall there is no consistent pattern of changes.
- In two recent studies, PFOA exposure of pregnant women, measured by maternal and/or cord serum levels was associated with reduced birth weight. The CONTAMPanel noted that these observations could be due to chance, or to factors other than PFOA.
- The CONTAM Panel used modelling of the dose-response data of effects on liver from mice and male rats to calculate the lower confidence limits of the benchmark dose for a 10% effect size (BMDL10). The CONTAM Panel concluded that the lowest BMDL10 of 0.3 mg/kg b.w. per day was an appropriate point of departure for deriving a TDI. The CONTAM Panel established a TDI for PFOA of 1.5 µg/kg b.w. per day by applying an overall UF of 200 to the BMDL10 of 0.3 mg/kg b.w. per day. An UF of 100 was used for inter and intra-species differences and an additional UF of 2 to compensate for uncertainties relating to the internal dose kinetics.

Risk characterisation

- The CONTAM Panel noted that the indicative average human dietary exposure of 2 ng/kg b.w. is well below the TDI of 1.5 µg/kg b.w.
- The serum levels in rats at the BMDL10 are expected to be in the region of three orders of magnitude higher than in serum levels of PFOA from European citicens. Given this margin, the CONTAM Panel considered it unlikely that adverse effects of PFOA are occurring in the general population, but noted uncertainties with regards to developmental effects.

RECOMMENDATIONS

- The nomenclature for per- and polyfluoroalkylated substances should be harmonised as currently in the literature many individual compounds, and groups of compounds, are described under more than one acronym.

- Validated analytical methods and in particular pure reference standards and eventually certified reference materials should be developed for PFOS and PFOA and their precursors.
- Data on the occurrence of PFOS and PFOA and possibly other PFAS in different foods and feedingstuffs should be collected in order to assess the relative contribution of these to the human dietary exposure.
- Studies on toxicokinetics and metabolism of PFOS and PFOA in humans are needed.
- Studies on PFAS are needed to further understand their mode of action and potential interactions.
- Further data on PFAS levels in humans would be desirable, particularly with respect to monitoring trends in exposure.

REFERENCES

3M Company, 1979. Technical report summary - final comprehensive report: FC-143. (U.S. EPA AR-226 528).

3M Company, 1999. Perfluorooctane sulfonate: Current summary of human sera, health and toxicity data. 3M Company, 21 January 1999.

3M Company, 2000a. Determination of serum half-lives of several fluorochemicals, June 8, 2000, 3M Company. FYI-07000-1378, 8(e) Supplemental Submission, 8EHQ-0373/0374.

3M Company, 2000b. US EPA Administrative Record AR226-0595, Publicly available at www.regulations.gov

3M Company, 2001. Analysis of PFOS, FOSA and PFOA From Various Food Matrices Using HPLC Electrospray Mass Spectrometry. Analytical Report, June 21, 2001.

3M Company, 2003. Environmental and Health Assessment of Perfuorooctane Sulfonic Acid and its Salts. Prepared by 3M in consultation with Moore, J., DABT, Hollyhouse, Inc. Rodricks, J., DABT, and Turnbull, D. DABT, Environ Corp. Warren-Hicks, W. and colleagues, The Cadmus Group, Inc. August 20, 2003.

3M Environmental Laboratory 2001. Environmental Monitoring — Multi-City Study — Water, Sludge, Sediment, POTW Effluent and Landfill Leachate Samples – Executive Summary, June 25, 2001.

Abbott,B.D., Wolf,C.J., Schmid,J.E., Das,K.P., Zehr,R.D., Helfant,L., Nakayama,S., Lindstrom,A.B., Strynar,M.J., and Lau,C. 2007. Perfluorooctanoic Acid Induced Developmental Toxicity in the Mouse is Dependent on Expression of Peroxisome Proliferator Activated Receptor-alpha. Toxicol.Sci. 98, 571-581.

Abdellatif, A.G., Preat, V., Taper, H.S. and Roberfroid, M. 1991. The modulation of rat liver carcinogenesis by perfluorooctanoic acid, a peroxisome proliferator. Toxicol Appl Pharmacol 111, 530-537.

Alexander, B.H. 2001a. Mortality study of workers employed at the 3M Cottage Grove facility. Final Report. Division of Environmental and Occupational Health, School of Public Health, University of Minnesota. April 26, 2001. US EPA AR226-1030a018.

Alexander, B.H. 2001b. Mortality study of workers employed at the 3M Decatur facility. Final Report. Division of Envvironmental and Occupational Health, School of Public Health, University of Minnesota. April 26, 2001. US EPA AR226-1030a019.

Alexander, B.H., Olsen, G.W., Burris, J.M., Mandel, J.H. and Mandel, J.S. 2003. Mortality of employees of a perfluorooctanesulphonyl fluoride manufacturing facility. Occupational and Environmental Medicine 60, 722-729.

Alexander,B.H. and Olsen,G.W. 2007. Bladder cancer in perfluorooctanesulfonyl fluoride manufacturing workers. Ann.Epidemiol. 17, 471-478.

Apelberg,B.J., Goldman,L.R., Calafat,A.M., Herbstman,J.B., Kuklenyik,Z., Heidler,J., Needham,L.L., Halden,R.U., and Witter,F.R. 2007a. Determinants of fetal exposure to polyfluoroalkyl compounds in Baltimore, Maryland. Environ.Sci.Technol. 41, 3891-3897.

Apelberg,B.J., Witter,F.R., Herbstman,J.B., Calafat,A.M., Halden,R.U., Needham,L.L., and Goldman,L.R. 2007b. Cord serum concentrations of perfluorooctane sulfonate (PFOS) and perfluorooctanoate (PFOA) in relation to weight and size at birth. Environ.Health Perspect. 115, 1670-1676.

Austin, M.E., Kasturi, B.S., Barber, M., Kannan, K., MohanKumar, P.S. and MohanKumar, S.M.J. 2003. Neuroendocrine effects of perfluorooctane sulfonate in rats. Environ Health Perspect 111, 1485-1489.

Barton C.A., Butler L.E., Zarzecki C.J., Flaherty J., and Kaiser M. 2006. Characterizing perfluorooctanoate in ambient air near the fence line of a manufacturing facility: comparing modeled and monitored values. Journal of Air Waste Management Association 56, 48–55.

Bachmanov, A.A., Reed, D.R., Beauchamp, G.K., Tordoff, M.G.2002. Food intake, water intake, and drinking spout side preference of 28 mouse strains. Behav Genet. 32, 435-443.

Beach,S.A., Newsted,J.L., Coady,K., and Giesy,J.P. 2006. Ecotoxicological evaluation of perfluorooctanesulfonate (PFOS). Rev.Environ.Contam Toxicol. 186, 133-174.

Becker, W. and Pearson, M. 2002. Riksmaten 1997-98. Dietary habits and nutrient intake in Sweden 1997-98, in Swedish. National Food Administration, Uppsala, Sweden. Available under URL www.slv.se.

Begley, T.H., White, K., Honigfort, P., Twaroski, M.L., Neches, R. and Walker R.A. 2005. Perfluorochemicals: Potential sources of and migration from food packaging. Food Additives and Contaminants 22(10): 1023–1031.

Berger, U., Langlois, I., Oehme, M. and Kallenborn, R. 2004. Comparison of three types of mass spectrometers for HPLC/MS analysis of perfluoroalkylated substances and fluorotelomer alcohols. Eur J Mass Spectrom 10: 579-588

Berger, U. and Haukås, M. 2005. Validation of a screening method based on liquid 2chromatography coupled to high-resolution mass spectrometry for analysis of perfluoroalkylated substances in biota. J Chromatogr A1081(2): 210-7.

Berger U., Holmström K., Glynn A., Berglund M., Ankarberg E., Törnkvist A. 2007. Perfluorinated alkyl substances in market basket food samples and fish from Lake Vättern and the Baltic Sea. Rapport till Naturvårdsverket Programområde Miljögiftssamordning Överenskommelse nr 219 0641 Dnr: 721-5953-06Mm. Stockholm/Uppsala 2007-04-03.

Berglund M., Holmström K., Ask K,. Petersson-Grawé K., Pickowa J. and Järnberg U. 2004. Resultatrapport, (kontrakt 215 0307, 215 0309, 215 0310). Report to the Swedish EPA, in Swedish only.

BfR (Bundesinstitut für Risikobewertung). 2006. Hohe Gehalte an perfluorierten organischen Tensiden (PFT) in Fischen sind gesundheitlich nicht unbedenklich Stellungnahme Nr. 035/2006 des BfR vom 27. Juli 2006. In German only. Available at URL: http://www.bfr.bund.de/cm/208/hohe_gehalte_an_perfluorierten_organischen_tensiden_in_fischen_sind_gesundheitlich_nicht_unbedenklich.pdf

Biegel, L.B., Liu, R.C.M., Hurtt, M.E. and Cook, J.C. 1995. Effects of ammonium perfluoroctanoate on Leydig cell function. Toxicol Appl Pharmacol 134, 18-25.

Biegel, L.B., Hurtt, M.E., Frame, S.R., O'Conner, J.C. and Cook J.C. 2001. Mechanisms of extrahepatic tumour induction by peroxisome proliferators in male CD rats. Toxicol Sci 60, 44-55.

Biesemeier, J.A. and Harris, D.L. 1974. Eye and Skin Irritation Report on Sample T-1117. Report. Project No. 4102871, WARF Institute Inc.

Bonesteel, J.A.K. and Kaiser, M.A. 2003. Workshop analytical methods for PFOA, Hamburg, Germany. PIM to you have more details for this reference e.g. date

Boulanger, B., Peck, A.M., Schnoor, J.L. and Hornbuckle, Boulanger, B., Peck, A.M., Schnoor, J.L. and Hornbuckle, K.C. 2005. Mass budget of perfluorooctane surfactants in Lake Ontario. Environ Sci Technol 39, 74-79.

Brooke D., Footitt A., and Nwaogu T.A. 2004. Environmental risk evaluation report: Perfluorooctanesulphonate (PFOS). Reseach Contrctor: Building Research Establishment Ltd, Risk and Policy Analysts Ltd. This report was produced by the Environment Agency´s Science Group. Available at URL: http://www.environment-agency.gov.uk/commondata/105385/pfos_rer_sept04_864557.pdf

Burris, J.M., Olsen, G., Simpson, C. and Mandel, J. 2000. Determination of serum half-lives of several fluorochemicals. 3M Company. Interim Report 2. January 11, 2002. U.S. EPA AR- 226-1086.

Burris, J.M., Lundberg, J.K., Olsen, G., Simpson, C. and Mandel, J. 2002. Interim report No. 2, Determination of serum half-lives of several fluorochemicals. St. Paul (MN), 3M Company. U.S.A EPA Docket AR-226-1086.

Butenhoff, J., Costa, G., Elcombe, C., Farrar, D., Hansen, K., Iwai, H., Jung, R., Kennedy, G., Lieder, P., Olsen, G. and Thomford, P. 2002. Toxicity of amonium perfluorooctanoate in male cynomolgus monkeys after oral dosing for 6 months, Toxicological Sciences 69: 244-257.

Butenhoff, John L; Kennedy, Gerald L, Jr; Frame, Steven R; O'Connor, John C; York, Raymond G. 2004. The reproductive toxicology of ammonium perfluorooctanoate (APFO) in the rat. Toxicology 196: 95-116.

Calafat, A., Kuklenyik, Z., Reidy, J.A., Tully, J.S. and Needham, L.L. 2005. Perfluorochemicals in residents of the United States in 2001 through 2002. ANA019 Calafat. "Fluoros" 9th International Symposium on Fluorinated Alkyl Organics in the Environment, Toronto, August 2005.

Calafat,A.M., Kuklenyik,Z., Reidy,J.A., Caudill,S.P., Tully,J.S., and Needham,L.L. 2007. Serum concentrations of 11 polyfluoroalkyl compounds in the u.s. population: data from the national health and nutrition examination survey (NHANES). Environ.Sci.Technol. 41, 2237-2242.

Case, M.T., York, R.G., Christian, M.S. 2001. Rat and rabbit oral developmental toxicology studies with two perfluorinated compounds. Int J Toxicol. 20, 101-109.

Chang,S.C., Thibodeaux,J.R., Eastvold,M.L., Ehresman,D.J., Bjork,J.A., Froehlich,J.W., Lau,C.S., Singh,R.J., Wallace,K.B., and Butenhoff,J.L. 2007. Negative bias from analog methods used in the analysis of free thyroxine in rat serum containing perfluorooctanesulfonate (PFOS). Toxicology 234, 21-33.

Christian, M.S., Hoberman, A.M. and York, R.G. 1999. Combined Oral (gavage) Fertility, Developmental and Perinatal/Postnatal Reproduction Toxicity Study of PFOS in Rats. Argus Research Laboratories, Inc., Horsham, PA U.S EPA. Docket 8EHQ-0200-00374.

Christopher, B. and Martin, J. W. 1977. 28-Day oral toxicity study with FC-143 in albinomice. 8532-10655, T-1742CoC. Industrial Bio-Test Laboratories, Inc.

Cifone, M.A., 1999. Unscheduled DNA synthesis in rat liver primary cell cultures with PFOS. 20780-0-447. Covance Laboratories Inc.

Cook, J.C., Hurtt, M.E., Frame, S.R. and Biegel, L.B. 1994. Mechanisms of extrahepatic tumour induction by peroxisome proliferators in Crl: CD BR(CD) rats. Toxicologist 14: 301.

Corning Hazleton, Inc. 1993. Mutagenicity test on T-5710 in an in vivo rat micronucleus assay. No 15516-0-454.

COT (Committee on toxicity of chemicals in food, consumer products and the environment). 2006 a Statement on the tolerable daily intake for Perfluorooctane sulphonate. Expressed on 8 November 2006. Available at URL: http://www.food.gov.uk/multimedia/pdfs/cotstatementpfos200609.pdf

COT (Committee on toxicity of chemicals in food, consumer products and the environment). 2006 b Statement on the tolerable daily intake for Perfluorooctanoic acid. Expressed on 8 November 2006. Available at URL: http://www.food.gov.uk/multimedia/pdfs/cotstatementpfoa200610.pdf

Covance Laboratories, Inc. 2000. Rapport final. L5178Y TK+ mouse lymphoma forward mutation assay with a confirmatory assay with N-EtFOSE, T-6316. No 20785-0-431 ICH.

CSL (Central Science Laboratory). 2006. Perfluoroctane sulphonic acid (PFOS), perfluorooctanoic acid (PFOA) and related compounds in food, development and validation of a method and analysis of Total Diet Study samples. CSL report, FD 05/23. Central Science Laboratory.

Cunha I., Hoff P., van de Vijver K., Guilhermino L., Esmans E., and de Coen W. 2005. Baseline study of perfluorooctane sulfonate occurrence in mussels, Mytilus galloprovincialis, from north-central Portuguese estuaries. Marine Pollution Bulletin 50, 1128–1132

de Voogt, P. and Sáez, M. 2006. Analytical chemistry of perfluoroalkylated substances. Trends Anal Chem. 25, 326-342.

de Voogt P, Berger U, de Coen W, de Wolf W, Heimstad E, McLachlan M, van Leeuwen S, van Roon A 2006a. Perfluorinated organic compounds in the European environment (Perforce). Report to the EU, University of Amsterdam, Amsterdam, NL. pp1-126.

de Voogt P., Sàez M., Serné P., Fahner W., van Roon A., and Mons M.N. 2006b. Perfluorinated alkilated substances in surface waters of the Netherlands. Poster presented at the: Institute for Biodiversity and Ecosystem Dynamics, University of Amsterdam.SETAC Europe Annual Metting-The Hague.

Dean, W.P. and Jessup, A.C. 1978, Acute oral toxicity (LD50) study in rats International research and development corporation, Study 137-091, 1978, USEPA AR226-0419.

Dean, W.P., Jessup, D.C., Thompson G., Romig, G. and Powell, D. 1978. Fluorad Fluorochemical Surfactant FC-95 Acute Oral Toxicity (LD50) Study in Rats. Study No. 137-083, International Research and Development Corporation.

Dellatte, E., Fattore E., Turrini A., and Di Domenico A. 2006. Assessment of the PFOS and PFOA intake through drinking water and fish consumption in the Italian general population. Organohalogen Compounds 68, 1692–1695.

Dinglasan-Panlilio, M.J. and Mabury,S.A. 2006. Significant Residual Fluorinated Alcohols Present in Various Fluorinated Materials. Environ. Sci.Technol. 40, 1447 -1453.

DNFCS (Dutch National Food Consumption Survey), 1998.: Zo eet Nederland: resultaten van de Voedselconsumptiepeiling, 1997-1998. Den Haag: Voedingscentrum. 1998. (The Hague: Nutrition Centre, 1998).

DuPont Company, 2003a. Adsorption/desorption of ammonium perfluoroctanoate to soil (OECD 106). Dupont EMSE report No 17-03.

DuPont Company, 2003b. Epidemiology surveillance report: Cancer incidence for Washington works site 1959-2001. U.S. EPA AR226-1307.

DuPont Company, 2005. U.S. EPA Administrative record AR 226-1914. Available at URL:www.regulations.gov. U.S.

EFSA (European Food Safety Authority) 2005 a: Opinion of the Scientific Panel on food additives, flavourings, processing aids and materials in contact with food (AFC) on a request related to a 9th list of substances for food contact materials. Question N° EFSA-Q-2004-071, EFSA-Q-2004-094, EFSA-Q-2003-214, EFSA-Q-2003-222. Adopted on 29 June 2005. Available at URL http://www.efsa.eu.int/science/afc/afc_opinions/1056/afc_op_ej248_9thlist_en2.pdf

EFSA (European Food Safety Authority), 2005b. Opinion of the Scientific Committee on a request from EFSA related to Exposure Assessments. Adopted on 22 June 2005. http://www.efsa.eu.int/science/sc_commitee/sc_opinions/1028_en.html.

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

Elcombe, CR, BM Elcombe, JR Foster, DG Farrar. 2007. Characterization of the hepatomegaly induced by ammonium perfluorooctanoic acid (APFO) in rats. The Toxicologist, Abstract # 867.

Ellis, D.A. and Mabury,S.A. 2003. Chemical ionization pathways of polyfluorinated chemicals--a connection to environmental atmospheric processes. J.Am.Soc.Mass Spectrom. 14, 1177-1191.

Ellis,D.A., Martin,J.W., De Silva,A.O., Mabury,S.A., Hurley,M.D., Sulbaek Andersen,M.P., and Wallington,T.J. 2004. Degradation of fluorotelomer alcohols: a likely atmospheric source of perfluorinated carboxylic acids. Environ.Sci.Technol. 38, 3316-3321.

Ericson, I., Gomez,M., Nadal,M., Van,B.B., Lindstrom,G., and Domingo,J.L. 2007. Perfluorinated chemicals in blood of residents in Catalonia (Spain) in relation to age and gender: a pilot study. Environ.Int. 33, 616-623.

Falandysz,J., Taniyasu,S., Yamashita,N., Jecek,L., Rostkowski,P., Gulkowska,A., Mostrag,A., Walczykiewicz,B., Zegarowski,L., Falandysz,J., and Zalewski,K. 2006. Perfluorinated chemicals in the environment, food and human body. Rocz.Panstw.Zakl.Hig. 57, 113-124.

Fasano, W.J., Carpenter, S.C., Gannon, S.A., Snow, T.A., Stadler, J.C., Kennedy, G.L., Buck, R.C., Korzeniowski, S.H., Hinderliter, P.M., Kemper, R.A.2006 Absorption, distribution, metabolism, and elimination of 8-2 fluorotelomer alcohol in the rt. Toxicol Sci. 91,341-355.

Fei, C., McLaughlin, J.K., Tarone, R.E., Olsen, J. 2007. Perfluorinated Chemicals and Fetal Growth: A Study within the Danish National Birth Cohort. Environ. Health Perspect. 115, 11, 1677-1682.

FMG (Fluoropolymer Manufacturing Group), 2002. U.S. EPA Administrative Record AR226-1094 Publicly available at www.regulations.gov.

Fluoros Report 2006. 2nd Worldwide Interlaboratory Study on PCFs. December 2006.

Frame, S.R. and McConnell, E.E. 2003. Review of the proliferative lesions of the exocrine pancreas in two chronic studies in rats with ammonium perfluorooctanoate. DuPont-13788. Oct. 16, 2003.

Fromme, H., Midasch, O., Twardella, D., Angerer, J., Boehmer, S., Liebl, B. 2007a. Occurrence of perfluorinated substances in an adult German population in southern Bavaria. Int. Arch. Occup. Environ. Health, 80, 313-319.

Fromme, H.; Schlummer, M., Möller, A., Gruber, L., Wolz, G.; Ungewiß, J., Böhmer, S., Dekant, W. 2007b. Exposure of an adult population to perfluorinated substances using duplicate diet portions and biomonitoring data. Environ. Sci. Techn., 41, 7928-7933.

Furdui, V.I., Stock, N., Whittle, D.M., Crozier, P., Reiner, E., Muir, D.C.G. and Mabury, S.A. 2005a. Perfluoroalkyl contaminants in lake trout from the Great Lakes. ENV024 Furdui. "Fluoros" 9th International Symposium on Fluorinated Alkyl Organics in the Environment, August 2005, Toronto, Canada.

Furdui V.I., Crozier P., Reiner E., and Mabury S.A. 2005b. Direct measurement of perfluoroalkylated surfactants in Great Lakes water samples. Presented at the 9th International Symposium on Fluorinated Alkyl Organics in the Environment, August 18–20 (Toronto, Canada). ANA031 Furdui.

Garry, V.F. and R.L. Nelson. 1981. An assay of cell transformation and cytotoxicity in C3H10T½ clonal cell line for the test on chemical T-2942 CoC. Stone Research Laboratories, Minneapolis, MN, March 4, 1981. US EPA AR226-0428.

Giesy, J.P. and Kannan, K. 2001. Global distribution of perfluorooctane sulfonate in wildlife. Environ Sci Technol 35: 1339-1342.

Gilliland, F.D. and Mandel, J.S. 1993. Mortality among employes of a perfluorooctanoic acid production plant. J Occup Med 35(9):, 950-954.

Gilliland,F.D. and Mandel,J.S. 1996. Serum perfluorooctanoic acid and hepatic enzymes, lipoproteins, and cholesterol: a study of occupationally exposed men. Am.J.Ind.Med. 29, 560-568.

Glaza, S. 1995. Acute dermal toxicity study of T-6342 in rabbits. Coming Hazelton Inc., Madison, WI., 3M Company, St Paul. USEPA AR226-0427.

Glaza, S.M., 1997. Acute oral toxicity study of T-6669 in rats. Corning Hazalton Inc. CHW 61001760. Sponsored by 3M Company, St. Paul, Minnesota. January 10. USEPA AR226-0420.

Goldenthal, E.I. 1978a. Final report, ninety day subacute Rhesus monkey toxicity study. 137-090. International Research and Development Corporation.

Goldenthal, E.I., 1978b. Final Report, Ninety Day Subacute Rat Toxicity Study on Fluorad Fluorochemical FC-143, International Research and Development Corporation, Study No. 137-089, November 6, 1978. U.S. EPA Public Docket AR-226-441

Goldenthal, E.I., Jessup, D.C., Geil, R.G., Mehring, J.S. 1978a Ninety-day subacute rat toxicity study. 137-085. International Research and Development Corporation.

Goldenthal, E.I., Jessup, D.C., Geil, R.G., Mehring, J.S. 1978b. Ninety-day subacute rhesus monkey toxicity study. 137-092. Internation Research and Development Corporation.

Goldenthal, E.I., Jessup, D.C., Geil, R.G., Mehring, J.S. 1979. Ninety-day subacute rhesus monkey toxicity study. 137-087. International Research and Development Corporation (aborted study!).

Gortner, E.G. 1980. Oral Teratology Study of FC-95 in Rats. Riker Laboratories, Inc. Experiment Number: 0680TR0008, December, 1980. AR-226 226-0016. U.S. Environmental Protection Agency, Washington, DC, U.S.A.

Gortner, E.G. 1981. Oral Teratology Study of T-2998CoC in Rats. Report prepared by Safety Evaluation Laboratory and Riker Laboratories, Inc. Experiment No. 0681TR0110. AR226-1136. U.S. Environmental Protection Agency, Washington, DC, U.S.A.

Gortner, E.G., 1982. Oral teratology study of T-3141CoC in rabbits. Experiment Number 0681TB0398. Safety Evaluation Laboratory and Riker Laboratories, Inc., St. Paul, MN. USEPA Public Docket AR-226-0465.

Grasty, R.C., Grey, B.E., Lau, C. and Rogers, J.M. 2003. Prenatal window of susceptibility to perfluorooctane sulfonate-induced neonatal mortality in the Sprague Dawley rat. Birth Defects Res 68 Part B: 465–471.

Grasty,R.C., Bjork,J.A., Wallace,K.B., Wolf,D.C., Lau,C.S., and Rogers,J.M. 2005. Effects of prenatal perfluorooctane sulfonate (PFOS) exposure on lung maturation in the perinatal rat. Birth Defects Res.B Dev.Reprod.Toxicol. 74, 405-416.

Griffith, F.D. and Long, J.E. 1980. Animal toxicity studies with ammonium perfluorooctanoate. American Industrial Hygiene Association 41:576-583.

Grottenmuller R, Knaup, W, Probst A, Dullinger K (2002) European Patent 1172350 Clariant, GmbH.

Gulkowska A., Jiang Q., So M.K., Taniyasu S., Lam P.K.S., Yamashita N. 2006. Persistent perfluorinated acids in seafood collected from two cities of China. Environmental Science and Technology 40, 3736–3741.

Guruge,K.S., Yeung,L.W., Yamanaka,N., Miyazaki,S., Lam,P.K., Giesy,J.P., Jones,P.D., and Yamashita,N. 2006. Gene expression profiles in rat liver treated with perfluorooctanoic acid (PFOA). Toxicol.Sci. 89, 93-107.

Han,X., Snow,T.A., Kemper,R.A., and Jepson,G.W. 2003. Binding of perfluorooctanoic acid to rat and human plasma proteins. Chem.Res.Toxicol. 16, 775-781.

Han,X., Kemper,R.A., and Jepson,G.W. 2005. Subcellular distribution and protein binding of perfluorooctanoic acid in rat liver and kidney. Drug Chem.Toxicol. 28, 197-209.

Hanhijarvi, H., Ophaug, R.H. and Singer, L. 1982. The sex-related difference in perfluorooctanoate excretion in the rat. Proc Soc Exp Biol Med 171, 50-55.

Hansen, K.J., Clemen, L.A., Ellefson, M.E. and Johnson, H.O. 2001. Compound-specific, quantitative characterisation of organic fluorochemicals in biological matrices. Environ Sci Technol 35, 766-770

Hansen K.J., Johnson H.O., Eldridge J.S., Butenhoff J.L., and Dick L.A. 2002. Quantitative characterisation of trace levels of PFOS and PFOA in the Tennessee river. Environmental Science and Technology 36, 1681–1685.

Harada, K., Saito, N., Sasaki, K., Inoue, K. and Koizumi, A. 2003. Perfluorooctane sulfonate contamination of drinking water in the Tama River, Japan: estimated effects on resident serum levels. Bull Environ Contam Toxicol 71, 31-36.

Harada, K., Saito,N., Inoue,K., Yoshinaga,T., Watanabe,T., Sasaki,S., Kamiyama,S., and Koizumi,A. 2004. The influence of time, sex and geographic factors on levels of perfluorooctane sulfonate and perfluorooctanoate in human serum over the last 25 years. J.Occup.Health 46, 141-147.

Harada K., Nakanishi S., Saito N., Tsutsui T., Koizumi A. 2005. Airborne perfluorooctanoate may be a substantial source contamination in Kyoto area, Japan. Bulletin of Environmental Contamination and Toxicology 74, 64–69.

Harada K., Nakanishi S., Sasaki K., Furuyama K., Nakayama S., Saito N., Yamakawa K., and Koizumi A. 2006. Particle size distribution and respiratory deposition estimates of airborne perfluorooctanoate and perfluorooctanesulfonate in Kyoto area, Japan. Bull Environ Contam Toxicol 76, 306–310.

Haughom, B. and Spydevold, O. 1992. The mechanism underlying the hypolipemic effect of perfluorooctanoic acid (PFOA), perfluorooctane sulphonic acid (PFOSA) and clofibric acid. Biochimica Biophysica Acta 1128, 65-72.

Health Canada, 2004. Perfluoroocate sulfonate, its Salts, and its precursors that contain the C8F17SO2 or C8F17SO3 moiety. Screening Assessment Report, Health Canada (Ottawa). Available at URL: http://www.ec.gc.ca/CEPARegistry/documents/subs_list/pfos.pdf

Hekster, F.M., P. de Voogt, A.M.,. Pijinenburg C.M and Laane R.W.P.M., 2002. Perfluoroalkylated substances — aquatic environmental assessment. Report RIKZ/2002.043. Prepared at the University of Amsterdam and RIKZ (The State Institute for Coast and Sea), July 1, 2002. 99 pp.

Hekster, F.M., Laane, R.W.P.M. and de Voogt, P. 2003. Environmental and toxicity effects of perfluoroalkylated substances. Rev Environ Contam Toxicol 179, 99-121.

Henderson,W.M. and Smith,M.A. 2007. Perfluorooctanoic acid and perfluorononanoic acid in fetal and neonatal mice following in utero exposure to 8-2 fluorotelomer alcohol. Toxicol.Sci. 95, 452-461.

Higgins, C.P. and Luthy,R.G. 2006. Sorption of perfluorinated surfactants on sediments. Environ.Sci.Technol. 40, 7251-7256.

Hinderliter, P.M., Mylchreest, E., Gannon, S.A., Butenhoff, J.L. and Kennedy, Jr. G.L. 2005. Perfluorooctane: Placental and lactational transport pharmacokinetics in rats. Toxicology 211, 139-148.

Hinderliter,P.M., Han,X., Kennedy,G.L., and Butenhoff,J.L. 2006. Age effect on perfluorooctanoate (PFOA) plasma concentration in post-weaning rats following oral gavage with ammonium perfluorooctanoate (APFO). Toxicology 225, 195-203.

Hoff, P.T., van de Vijver, K., van Dongen, W., Esmans, E.L., Blust, R. and de Coen, W.M. 2003. Perfluorooctane sulfonic acid in bib (Trisopterus luscus) and plaice (Pleuronectes platessa) from the Western Scheldt and the Belgian North Sea: Distribution and biochemical effects. Environ Toxicol Chem. 22, 608–614.

Hoff, P.T., Scheirs, J., van de Vijver, K., van Dongen, W., Esmans, E.L., Blust, R. and de Coen, W. 2004. Biochemical effect evaluation of perfluorooctane sulfonic acid contaminated Wood Mice (*Apodemicus sylvaticus*). Environ Health Perspect 112, 681-686.

Holmström, K.E., Berglund, M. and Järnberg, U. 2005a. Exposure to perfluorinated acids in 108 Swedish women in relation to methylmercury and fish consumption. Poster ANA003.. Fluoros" 9th International Symposium on Fluorinated Alkyl Organics in the Environment, August 2005, Toronto, Canada.

Hori, H., Hayakawa, E., Yamashita, N., Taniyasu, S., Nakata, F., Kobayashi, Y. 2004. High-performance liquid chromatography with conductimetric detection of perfluorocarboxylic acids and perfluorosulfonates. Chemosphere. 57, 273-282.

Hosokawa, M. and Satoh, R. 1993. Differences in the induction of carboxylesterase isozymes in rat liver microsomes by perfluorinated fatty acids. Xenobiotica 23,1125-1133.

Hu, W., Jones, P. D., Upham, B. L., Trosko, J. E., Lau, C,. and Giesy, J. P. (2002). Inhibition of gap junctional intercellular communication by perfluorinated compounds in rat liver and dolphin kidney epithelial cell lines in vitro and Sprague-Dawley rats in vivo. Toxicol. Sci. 68, 429-436.

Ikeda, T., Aiba, K. and Fukuda, K. 1985. The induction of peroxisome proliferation in rat liver by perfluorinated fatty acids, metabolically inert derivatives of fatty acids J Biochem. 98, 475-482.

Ikeda, T., Fukuda, K. and Mori, I. 1986. Induction of cytochrome-P-450 and peroxisome proliferation in rat-liver by perfluorinated octane sulfonic acid (PFOS) Eur J Cell Biol. 41, 20. cant find it is this the one below then change in text. ?

Inoue, K., Okada, F., Ito, R., Kato, S., Sasaki, S., Nakajima, S., Uno, A., Saijo, Y., Sata, F., Yoshimura, Y. and Kishi, R. 2004. Nakazawa H. Perfluorooctane sulfonate (PFOS) and related perfluorinated compounds in human maternal and cord blood samples: assessment of PFOS exposure in a susceptible population during pregnancy. Environ Health Perspect 112, 1204-1207.

Jahnke, A., Ahrens, L., Ebinghaus, R., Berger, U., Barber, J.L., Temme, C. 2007. An improved method for the analysis of volatile polyfluorinated alkyl substances in environmental air samples. Anal Bioanal Chem. 387, 965-975.

Jernbro,S., Rocha,P.S., Keiter,S., Skutlarek,D., Farber,H., Jones,P.D., Giesy,J.P., Hollert,H., and Engwall,M. 2007. Perfluorooctane sulfonate increases the genotoxicity of cyclophosphamide in the micronucleus assay with V79 cells. Further proof of alterations in cell membrane properties caused by PFOS. Environ.Sci.Pollut.Res.Int. 14, 85-87.

Johansson, N., Fredriksson,A., and Eriksson,P. 2008. Neonatal exposure to perfluorooctane sulfonate (PFOS) and perfluorooctanoic acid (PFOA) causes neurobehavioural defects in adult mice. Neurotoxicology 29, 160-169.

Johnson, J.D., Gibson, S.J. and Ober, R.F. 1979a. Absorption of FC-95-14C in rats after a single oral dose. Project No. 890310200.Riker Laboratories, Inc., Subsidiary of 3M, St. Paul, MN. (U.S. EPA Docket No. 8(e)HQ-1180–00374).

Johnson, J.D., Gibson, S.J. and Ober, R.E. 1979b. Extent and Route of Excretion and Tissue Distribution of Total Carbon-14 in Rats after a Single Intravenous Dose of FC-95-14C. Project No. 8900310200, Riker Laboratories, Inc., Subsidiary of 3M, St. Paul, MN. (U.S. EPA Docket No. 8(e)HQ-1180–00374).

Kallenborn R., Berger U., and Järnberg U. 2004. Perfluorinated alkylated substances (PFAs) in the nordic environment. A TemaNord report of the Norwegian Institute for Air Research (NILU) (Kjeller, Norway) and the Institute for Applied Environmental Research (ITM), Stockholm University (Stockholm, Sweden).

Kannan, K., Corsolini, S., Falandysz, J., Oheme, G., Focardi, S. and Giesy, J.P. 2002a. Perfluorooctanesulfonate and related fluorinated hydrocarbons in marine mammals, fishes, and birds from coasts of the Baltic and the Mediterranean seas. Environmental Science and Technology 36, 3210–3216.

Kannan, K., Hansen, K.J., Wade, T.L. and Giesy, J.P. 2002b. Perfluorooctane sulfonate in oysters, Crassostrea virginica, from the Gulf of Mexico and the Chesapeake Bay, USA. Archives of Environmental Contamination and Toxicology 42,: 313–318.

Kannan, K., Corsolini, S., Falandysz, J., Fillmann, G., Kumar, K.S., Loganathan, B.G., Mohd, M.A., Olivero, J., van Wouwe, N., Yang, J.H. and Aldous, K.M. 2004. Perfluorooctanesulfonate and related fluorochemicals in human blood from several countries. Environmental Science and Technology 38,: 4489–4495.

Kannan K., Tao L., Sinclair E., Pastva S.D., Jude D.J., and Giesy J.P. 2005. Perfluorinated compounds in aquatic organisms at various trophic levels in a Great Lakes food chain. Archives of Environmental Contamination and Toxicology 48, 559–566.

Kärrman, A., van Bavel, B., Järnberg, U., Hardell, L. and Lindström, G. 2004. Levels of perfluoroalkylated compounds in whole blood from Sweden. Organohalogen Compounds 66,: 4058-4062.

Kärrman A, Ericson I, van Bavel B, Lindström G. 2006. Levels of Perfluorinated chemicals in matched samples of human breast milk and serum. Organohalogen Compounds 68, 544–547.

Kärrman, A., I. Ericson, B. van Bavel, P.O. Darnerud, M. Aune, A. Glynn, S. Lignell, G. Lindström. 2007b. Exposure of perfluorinated chemicals through lactation: levels of matched human milk and serum and temporal trend, 1996-2004, in Sweden. Environ. Health Perspect. 115, 226-230.

Kärrman, A., Langlois, I., van Bavel, B., Lindström, G., Oehme, M. 2007a. Identification and pattern of perfluorooctane sulfonate (PFOS) isomers in human serum and plasma. Environ. Internat. 33, 782–788.

KEMI (Kemikalieninspektionen), 2004a. PFOS-relaterade ämnen. Strategi för utfasning. Avaialble at URL: http://www.kemi.se/upload/Trycksaker/Pdf/Rapporter/Rapport3_04.pdf. In Swedish. Summary in English

KEMI (Kemikalieninspektionen), 2004b. Riskbedömning för PFOS Bilaga 3. Avaialble at URL: http://www.kemi.se/upload/Trycksaker/Pdf/Rapporter/Bilaga3_Rapport3_04.pdf In Swedish.

Kemper, R.A., Jepson, G.W., 2003a. Perfluorooctanoic Acid: Toxicokinetics in the Rat. Unpublished Report, DuPont-7473.

Kemper, R.A. and Jepson, G.W. 2003b. Pharmacokinetics of perfluorooctanoic acid in male and female rats. Toxicologist 72:, 148.

Kemper, R.A. and Nabb,D.L. 2005. In vitro studies in microsomes from rat and human liver, kidney, and intestine suggest that perfluorooctanoic acid is not a substrate for microsomal UDP-glucuronosyltransferases. Drug Chem.Toxicol. 28, 281-287.

Kennedy, G.L., Jr. 1985. Dermal toxicity of ammonium perfluorooctanoate. Toxicol.Appl.Pharmacol. 81, 348-355.

Kennedy, G.L., Hall, G.T., Brittelli, M.R., Barnes, J.R. and Chen, H.C. 1986. Inhalation toxicity of ammonium perfluorooctanoate. Food Chem Toxicol. 24, 1325-1329.

Kissa, E. 1986. Determination of organofluorine in air. Environ Sci Technol. 20, 1254-1257.

Kozuka, H., Yamada, J., Horie, S., Watanabe, T., Suga, T. and Ikeda, T. 1991. Characteristics of induction of peroxisomal fatty acid oxidation-related enzymes in rat liver by drugs. Biochem Pharmacol 41, 617-623.

Kubwabo C., Stewart B., Zhu J., and Marro L. 2005. Occurrence of perfluorosulfonates and other perfluorochemicals in dust from selected homes in the city of Ottawa, Canada. Journal of Environmental Monitoring 7, 1074–1078.

Kudo, N. and Kawashima, Y. 2001. Effects of Perfluorooctanoic Acid on the Synthesis of Phosphorlipids in the Liver of Mice Fed a Dietary Soybean Oil, Perilla Oil or Fish Oil. Jof Health Sci. 47, 168-174.

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

Kudo, N., Iwase, Y., Okayachi, H., Yamakawa, Y., Kawashima, Y. 2005. Induction of hepatic peroxisome proliferation by 8-2 telomer alcohol feeding in mice: formation of perfluorooctanoic acid in the liver. Toxicol Sci. 86, 231-238.

Kudo, N., Sakai,A., Mitsumoto,A., Hibino,Y., Tsuda,T., and Kawashima,Y. 2007. Tissue distribution and hepatic subcellular distribution of perfluorooctanoic acid at low dose are different from those at high dose in rats. Biol.Pharm.Bull. 30, 1535-1540.

Langlois, I. and Oehme, M. 2004. Identification of the isomer composition in technical perfluorooctane sulfonate solution by LC-ESI(-)-IT-MS2. Organohalogen Compounds 66, 4023-4028.

Larsen, B.S., Kaiser, M.A., Botelho, M., Wooler, G.R. and Buxton, L.W. 2005. Comparison of pressurised solvent and reflux extraction methods for the determination of perfluorooctanoic acid in polytetrafluoroethylene polymers using LC-MS-MS. Analyst 130, 59-62.

Lau, C., Thibodeaux, J.R., Hanson, R.G., Rogers, J.M., Grey, B.E., Stanton, M.E., Butenhoff, J.L. and Stevenson, L.A. 2003. Exposure to perfluorooctane sulfonate during pregnancy in rat and mouse: II. Postnatal evaluation. Toxicol Sci. 74, 382–392.

Lau, C., Butenhoff, J.L. and Rogers, J.M. 2004, The developmental toxicity of perfluoroalkyl acids and their derivatives. Toxicol Appl Pharmacol. 198, 231-241.

Lau, C., Thibodeaux, J.R., Hanson,R.G., Narotsky,M.G., Rogers,J.M., Lindstrom,A.B., and Strynar,M.J. 2006. Effects of perfluorooctanoic acid exposure during pregnancy in the mouse. Toxicol.Sci. 90, 510-518.

Lau,C., Anitole,K., Hodes,C., Lai,D., Pfahles-Hutchens,A., and Seed,J. 2007. Perfluoroalkyl acids: a review of monitoring and toxicological findings. Toxicol.Sci. 99, 366-394.

Lawlor, T.E. 1995. Mutagenicity test with T-6342 in the Salmonella-Escherichia coli/mammalian microsome reverse mutation assay. Laboratory Number: 17073-0-409. Corning Hazleton, Inc., Vienna, VA. 3M Company St. Paul, MN. US E.PA. AR226-0436.

Lawlor, T.E. 1996. Mutagenicity test with T-6564 in the Salmonella-Escherichia coli/mammalian-microsome reverse mutation assay. with a confirmatory assay. Corning Hazleton Inc., Final Report. CHV Study Number: 17750-0-409R. September 13, 1996.U.S. EPA AR226-0432.

Leonard, R.C., Kreckmann,K.H., Lineker,G.A., Marsh,G., Buchanich,J., and Youk,A. 2007. Comparison of standardized mortality ratios (SMRs) obtained from use of reference populations based on a company-wide registry cohort to SMRs calculated against local and national rates. Chem.Biol.Interact. 166, 317-322.

Leonard, R.C., Kreckmann, K.H., Sakr, C.J., Symons, J.M. 2008. Retrospective cohort mortality study of workers in a polymer production plant including a reference population of regional workers.Ann Epidemiol. 18, 15-22.

Litton Bionetics, Inc. 1978. Mutagenicity evaluation of T-2014 CoC in the Ames Salmonella/microsome plate test. No 20838.

Loos, R., Wollgast,J., Huber,T., and Hanke,G. 2007. Polar herbicides, pharmaceutical products, perfluorooctanesulfonate (PFOS), perfluorooctanoate (PFOA), and nonylphenol and its carboxylates and ethoxylates in surface and tap waters around Lake Maggiore in Northern Italy. Anal.Bioanal.Chem. 387, 1469-1478.

Loveless, S.E., Finlay,C., Everds,N.E., Frame,S.R., Gillies,P.J., O'Connor,J.C., Powley,C.R., and Kennedy,G.L. 2006. Comparative responses of rats and mice exposed to linear/branched, linear, or branched ammonium perfluorooctanoate (APFO). Toxicology 220, 203-217.

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

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

Luebker, D.J., York, R.G., Hansen, K.J., Moore,J.A., and Butenhoff,J.L. 2005b. Neonatal mortality from in utero exposure to perfluorooctanesulfonate (PFOS) in Sprague-Dawley rats: dose-response, and biochemical and pharamacokinetic parameters. Toxicology 215, 149-169.

Maloney, E.K. and Waxman, D.J. 1999. Trans-Activation of PPAR-alfa and PPAR-gamma by structurally diverse environmental chemicals. Toxicol Appl Pharmacol. 161, 209-218.

Mann, P.C. and Frame, S.R. 2004 FC-143: Two-year oral toxicity-oncogenicity study in rats: Peer review of ovaries. DuPont Project ID 15621, June 25, 2004. U.S. EPA AR226.

Martin, J.W., Muir, D.C.G., Kwan, W.C., Moody, C.A., Solomon, K.R. and Mabury, S.A. 2002. Collection of Airborne Fluorinated Organics and Analysis by Gas Chromatography-Chemical Ionisation-Mass Spectrometry. Anal Chem 74: 584-590.

Martin, J.W., Mabury, S.A., Solomon,K.R., and Muir,D.C. 2003. Bioconcentration and tissue distribution of perfluorinated acids in rainbow trout (Oncorhynchus mykiss). Environ.Toxicol.Chem. 22, 196-204.

Martin, J.W., Whittle, D.M., Muir, D.C.G. and Mabury, S.A. 2004a. Perfluoroalkyl contaminants in a food web from lake Ontario. Environ Sci Technol. 38, 5379–5385.

Martin, J.W., Smithwick, M.M., Braune, B.M., Hoekstra, P.F., Muir, D.C.G. and Mabury, S.A. 2004b. Identification of long-chain perfluorinated acids in biota from the Canadian Arctic. Environ Sci Technol 38, 373–380.

Martin, J.W., Kannan, K., Berger, U., de Voogt, P., Field, J., Giesy, J.P., Harner, T., Muir, D.C.G., Scott, B.F., Kaiser, M., Järnberg, U., Jones, K.C., Mabury, S.A., Schroeder, H., Simcik, M., Sottani, C., vanBavel, B., Kärrman, A., Lindström, G. and van Leeuwen, S. 2004c. Analytical challenges hamper perfluoroalkyl research. Feature Article. Environ Sci Technol. 38: 248A-255A.

Martin,M.T., Brennan,R.J., Hu,W., Ayanoglu,E., Lau,C., Ren,H., Wood,C.R., Corton,J.C., Kavlock,R.J., and Dix,D.J. 2007. Toxicogenomic study of triazole fungicides and perfluoroalkyl acids in rat livers predicts toxicity and categorizes chemicals based on mechanisms of toxicity. Toxicol.Sci. 97, 595-613.

Masunaga, S., Kannan, K., Doi, R., Nakanishi, J., Giesy, J.P. 2002. Levels of perfluorooctanesulfonate (PFOS) and other related compounds in the blood of Japanese people. Paper presented at Dioxin 2002, August 11-16, Barcelona, Spain. Organohalogen Compd. 59, 319-322.

Mawn, M.P., McKay, R.G., Ryan, T.W., Szostek, B., Powley, C.R. and Buck, R.C. 2005. Determination of extractable perfluorooctanoic acid (PFOA) in water, sweat simulant, saliva simulant, and methanol from textile and carpet samples by LC/MS/MS. Analyst 130, 670-678.

Mecchi, M. S. 1999. Salmonella - Eschericia coli/mammalian-microsome reverse mutation assay with PFOS. 20784-0-409. Covance Laboratories Inc.

Metrick, M. and Marias, A.J. 1977. 28-Day oral toxicity study with FC-143 in Albino rats. 8532-10654, T-1742CoC. Industrial Bio-Test Laboratories, Inc.

Midasch, O., Schettgen, T., and Angerer,J. 2006. Pilot study on the perfluorooctanesulfonate and perfluorooctanoate exposure of the German general population. Int.J.Hyg.Environ.Health 209, 489-496.

Midasch, O., Drexler, H., Hart, N., Beckmann, M.W., Angerer, J. 2007. Transplacental exposure of neonates to perfluorooctanesulfonate and perfluorooctanoate: a pilot study. Int Arch Occup Environ Health. 80, 643-648.

Moriwaki, H., Takata, Y. and Arakawa. R. 2003. Concentrations of perfluorooctane sulfonate (PFOS) and perfluorooctanoic acid (PFOA) in vacuum cleaner dust collected in Japanese homes. Journal of Environmental Monitoring 5, 753–757.

Mortimer D.N., Clarke D.B., Gem M., Rose M. 2006. Perfluorinated compounds in the UK 2004 Total Diet. Organohalogen Compounds 68, 371–374.

Murli, H.1996a. Mutagenicity test on T-6295 in an in vivo mouse micronucleus assay. 17403-0-455. Corning Hazleton Inc.

Murli, H. 1996b. Mutagenicity test on T-6564 in an in vivo mouse micronucleus assay. Corning Hazleton Inc., Vienna, VA. Study Number: 17750-0-455, November 1, 1996. U.S. EPA AR226-0430.

Murli, H. 1996c. Mutagenicity test on T-6564 measuring chromosomal aberrations in Chinese Hamster Ovary (CHO) cells with a confirmatory assay with multiple harvests. Corning Hazleton Inc., Vienna, VA. Study Number: 17750-0-437CO, September 16, 1996. U.S EPA. AR226-0433.

Murli, H. 1996d. Mutagenicity test on T-6342 measuring chromosomal aberrations in human whole blood lymphocytes with a confirmatory assay with multiple harvests. Corning Hazleton, Inc., Vienna, VA. Study Number: 17073-0-449CO, November 1, 1996. U.S. EPA AR226-0433.

Murli, H. 1996e. Mutagenicity test on T-6342 measuring chromosomal aberrations in Chinese Hamster Ovary (CHO) cells with a confirmatory assay with multiple harvests. Corning Hazleton Inc., Vienna VA. Study Number: 17073-0-437CO, September 16, 1996. U.S. EPA AR226-0434.

Nabb, D.L., Szostek,B., Himmelstein,M.W., Mawn,M.P., Gargas,M.L., Sweeney,L.M., Stadler, J.C., Buck,R.C., and Fasano,W.J. 2007. In vitro metabolism of 8-2 fluorotelomer alcohol: interspecies comparisons and metabolic pathway refinement. Toxicol.Sci. 100, 333-344.

Nakata H., Kannan K., Nasu T., Cho H., Sinclair E., and Takemura A. 2006. Perfluorinated Contaminants in Sediments and Aquatic Organisms Collected from Shallow Water and Tidal Flat Areas of the Ariake Sea, Japan: Environmental Fate of Perfluorooctane Sulfonate in Aquatic Ecosystems. Environ Sci Technol. 40, 4916–4921.

Nakayama S., Harada K., Inoue K., Sasaki K., Seery B., Saito N., and Koizumi A. 2005. Distributions of perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS) in Japan and their toxicities. Environ Sci. 12, 293–313.

NCEHS (United Kingdom National Centre for Ecotoxicology and Hazardous Substances), 2001, Review of occurrence and hazards of perfluoroalkylated substances in the UK: A non-confidential overview. Unpublished report. United Kingdom.

NDNS (U.K. National Diet and Nutrition Survey), 20012. Adults aged 19 to 64, Volume 1. Initial findings on food intake from a survey of the diet and nutrition of adults aged 19 to 64 years living in private households in Great Britain, carried out between July 2000 and June 2001. Available at URL: http://www.food.gov.uk/multimedia/pdfs/ndnsprintedreport.pdf

Nilsson, R., Beije, B., Preat, V., Erixon, K. and Ramel, C. 1991. On the mechanism of the hepatocarcinogenicity of peroxisome proliferators. Chem.-Biol. Interact. 78:235-250.

Noker, P.E. and Gorman, G.S. 2003. A pharmacokinetic study of potassium perfluorooctanoate in the cynomolgus monkey. Southern Research Institute. Unpublished report. Available on U.S. EPA Administrative Record 226.

NOTOX, 1994a. Evaluation of the mutagenic activity of T-5874 in the Ames Salmonella/microsome test (with independent repeat). No 115932.

NOTOX, 1994b. Evaluation of the mutagenic activity of T-5874 in an in vitro mammalian cell gene mutation test with L5178Y mouse lymphoma cells (with independent repeat). No 115921.

NOTOX, 1994c. Evaluation of the ability of T-5874 to induce chromosome aberrations in cultured peripheral human lymphocytes (with independent repeat). No 115919.

NOTOX, 2000. Evaluation of the ability of T-7524 to induce chromosome aberrations in cultured peripheral human lymphocytes. NOTOX Project Number 292062. Hertogenbosch, The Netherlands.

OECD (Organisation for Economic Co-operation and Development), 2002. Hazard assessment of perfluorooctane sulfonate (PFOS) and its salts. ENV/JM/RD(2002)17/FINAL. Joint Meeting of the Chemicals Committee and the Working Party on Chemicals, Pesticides, and Biotechnology, Environment Directorate, Organisation for Economic Co-operation and Development (Paris). Available at URL http://www.oecd.org/dataoecd/23/18/2382880.pdf

OECD (Organisation for Economic Co-operation and Development), 2004. Results of survey on production and use of PFOS, PFAS AND PFOA, related substances and products/mixtures containing these substances. Joint meeting of the chemicals committee and the working party on chemicals committee and the working party on chemicals, pesticides and Biotechnology. Available at the URL: http://www.olis.oecd.org/olis/2005doc.nsf/LinkTo/NT0000097A/$FILE/JT00176885.PDF

OECD (Organisation for Economic Co-operation and Development), 2005a. Perfluorooctane sulfonate (PFOS), perfluoroalkyl sulfonates (PFAS), and perfluorooctanoic acid (PFOA) draft lists. ENV/JM(2005)6. Joint Meeting of the Chemicals Committee and the Working Party on Chemicals, Pesticides, and Biotechnology, Environment Directorate, Organisation for Economic Co-operation and Development (Paris).

OECD (Organisation for Economic Co-operation and Development), 2005b. Draft lists of PFOS, PFAS, PFOA, and PFCA, and their respective related compounds. ENV/JM/RD(2005)7. Joint Meeting of the Chemicals Committee and the Working Party on Chemicals, Pesticides, and Biotechnology, Environment Directorate, Organisation for Economic Co-operation and Development (Paris).

Ohya, T., Kudo, N., Suzuki, E. and Kawashima, Y. 1998. Determination of perfluorinated carboxylic acids in biological samples by high-performance liquid chromatography. J Chromatogr B Biomed Sci Appl 710, 1-7.

Olsen, G.W., Gilliland, F.D., Burlew, M.M., Burris, J.M., Mandel, J.S. and Mandel, J.H. 1998. An epidemiological investigation of reproductive hormones in men with occupational exposure to perfluorooctanoic acid. J Occ Env Med 40, 614-622.

Olsen, G.W., Burris, J.M., Mandel, J.H. and Zobel, L.R. 1999. Serum perfluorooctane sulfonate and hepatic and lipid clinical chemistry tests in fluorochemical production employees. J Occup Environ Med 41, 799-806.

Olsen, G.W., Burris, J.M., Burlew, M.M., Mandel, J.H. 2000. Plasma cholecystokinin and hepatic enzymes, cholesterol and lipoproteins in ammonium perfluorooctanoate production workers.Drug Chem Toxicol. 23, 603-620.

Olsen, G.W., Burlew, M.M., Hocking, B.B., Skratt, J.C., Burris, J.M. and Mandel, J.H. 2001. An epidemiologic analysis of episodes of care of 3M Decatur chemical and film plant employees, 1993-1998. Final Report May 18, 2001.

Olsen, G.W., Burris, J.M., Lundberg, J.K., Hansen, K.J., Mandel, J.H., and Zobel, L.R. 2002a. Identification of fluorochemicals in human sera. I American Red Cross adult. 3M company. Final report. February 25, 2002. U.S. EPA AR226-1083.

Olsen, G.W., Burris, J.M., Lundberg, J.K., Hansen, K.J., Mandel, J.H., and Zobel, L.R. 2002b. Identification of fluorochemicals in human sera. II Elderly participants of the Adult changes in thought study, Seattle, Wahsington. 3M company. Final report. February 25, 2002. U.S. EPA AR226-1084.

Olsen, G.W., Burris, J.M., Lundberg, J.K., Hansen, K.J., Mandel, J.H., and Zobel, L.R. 2002c. Identification of fluorochemicals in human sera. III Pediatric participants in a group A streptococci clinical trial investigation. 3M company. Final report. February 25, 2002. U.S. EPA AR226-1085.

Olsen, G.W., Burris, J.M., Burlew, M.M. and Mandel, J.H. 2003a. Epidemiologic assessment of worker serum perfluoroctanesulfonate (PFOS) and perfluorooctanoate (PFOA) concentrations and medical surveillance examinations. J Occup Environ Med 45, 260-270.

Olsen, G.W., Church, T.R., Miller, J.P., Burris, J.M., Hansen, K.J. Lundberg, J.K., Armitage, J.B., Herron, R.M., Medhdisadehkashi, Z., Nobiletti, J.B., O'Niell, E.M., Mandel, J.H. and Zobel, L.R. 2003b. Perfluorocatanesulfonate and other fluorochemicals in the serum of American Red Cross adult blood donors. Environ Health Perspect 111: 1892-1901.

Olsen, G.W., Hansen, K.J., Stevenson, L.A., Burris, J.M. and Mandel, J.H. 2003c. Human donor liver and serum concentrations of perfluorooctanesulfonate and other perfluorochemicals. Environ Sci Technol 37: 888-891.

Olsen, G.W., Buttenhoff, J.L. and Mandel, J.N. 2003d. Assessment of lipid, hepatic and thyroid function in relation to an occupational biologic limit value for perfluorooctanoate. 3M Company. Final Report. June 9, 2003. U.S. EPA AR226-1351.

Olsen, G.W., Church, T.R., Larson, E.B., van Belle, G., Lundberg, J.K., Hansen, K.J., Burris, J.M., Mandel, J.H. and Zobel, L.R. 2004. Serum concentrations of perfluorooctanesulfonate and other fluorochemicals in an elderly population from Seattle, Washington. Chemosphere 54, 1599-611.

Olsen, G.W., Huang, H.-Y., Helzlsouer, K.J., Hansen, K.J., Butenhoff, J.L. and Mandel, J.H. 2005a. Historical Comparison of Perfluorooctanesulfonate, Perfluorooctanoate, and Other Fluorochemicals in Human Blood. Environmental Health perspectives 113, 539-545.

Olsen, G., Ehresman, D., Froehlich, J., Burris, J. and Butenhoff, J. 2005b. Evaluation of the half-life (t1/2) of elimination of perfluorooctanesulfonate (PFOS), perfluorohexanesulfonate (PFHS) and perfluorooctanoate (PFOA) from human serum. TOX017 Olsen. "Fluoros" 9th International Symposium on Fluorinated Alkyl Organics in the Environment, August 2005, Toronto, Canada.

Olsen,G.W. and Zobel,L.R. 2007. Assessment of lipid, hepatic, and thyroid parameters with serum perfluorooctanoate (PFOA) concentrations in fluorochemical production workers. Int.Arch.Occup.Environ.Health 81, 231-246.

Ophaug, R.H. and Singer, L. 1980. Metabolic handling of perfluorooctanoic acid in rats. Proc Soc Exp Biol Med 163, 19-23.

OSPAR, 2002. Convention for the protection of the marine environment of the north east atlantic. List of substances of possible concern. Revised September 2005. URL: http://www.ospar.org/eng/html/welcome.html.

Palazzolo, M.J. 1993. 13-Week toxicity study with T-5180, ammonium perfluorooctanoate (CAS No. 3825-25-1) in male rats. Report No. HWI 6329- 100, Hazleton Wisconsin, Madison, WI. USEPA Public Docket AR-226-0449 and AR-226-0450.

Pastoor, T.P., Lee, K.P., Perri, M.A. and Gillies, P.J. 1987. Biochemical and morphological studies of ammonium perfluoroctanate-induced hepatomegaly and peroxisome proliferation. Exp Mol Pathol 47, 98-109.

Perkins, R.G., Butenhoff, J.L., Kennedy, G.L. and Palazzolo, M. 2004. 13-week dietary toxicity study of ammonium perfluorooctanoate (APFO) in male rats. Drug Chem Toxicol. 27, 361-378.

Powley, C.R. and Buck, R.C. 2005. Matrix-effect free analytical methods for determination of perfluorinated carboxylic acids in biological samples, 15th Annual Meeting of SETAC Europe, May 2005, Lille, France.

Powley C.R., George, S.W., Ryan, T.W., Buck, R.C., 2005. Matrix-effect free analytical methods for determination of perfluorinated carboxylic acids in environmental matrixes Anal. Chem. 77, 6353-6358.

Prevedouros, K., Cousins, I.T., Buck, R.C., Korzeniowski, S.H.2006 Sources, fate and transport of perfluorocarboxylates. Environ Sci Technol.40, 32-44.

Raloff, J. 2005. Nonstick Taints: Fluorochemicals are in us all. Science News 168, 341.

Renner, R. 2001. Growing concern over perfluorinated chemicals. Environ Sci Technol 35, 154A-160A.

Renner R., 2007. PFOA in People. Food wrappers may be an important, overlooked source of perfluorochemicals in humans. Environmental Science& Technology Online News, May 23, 2007.

Rosen, M.B., Thibodeaux, J.R., Wood,C.R., Zehr, R.D., Schmid, J.E., Lau, C.2007 Gene expression profiling in the lung and liver of PFOA-exposed mouse fetuses. Toxicology. 239, 15-33.

Rusch, G.M., Rinehart, W.E. and Bozak, C.A. 1979. An Acute Inhalation Toxicity Study of T-2306 CoC in the Rat. Project No. 78-7185, Bio/dynamics Inc.

Sadhu, D. 2002. CHO/HGPRT forward mutation assay. Corning Hazleton Inc., Vienna, VA. Study Number: 17750-0-437CO, September 16, 1996. U.S. EPA AR226-0433.

Saito, N., Sasaki, K., Nakatome, K., Harada, K., Yoshinaga, T. and Koizumi, A. 2003. Perfluorooctane sulfonate concentrations in surface water in Japan. Arch Environ Contam Toxicol. 45, 149–158.

Saito, N., Harada, K., Inoue, K., Sasaki, K., Yoshinaga, T. and Koizumi, A. 2004. Perfluorooctanoate and perfluorooctane sulfonate concentrations in surface water in Japan. J Occup Health 46, 49-59.

Sakr, C.J., Kreckmann,K.H., Green,J.W., Gillies,P.J., Reynolds,J.L., and Leonard,R.C. 2007a. Cross-sectional study of lipids and liver enzymes related to a serum biomarker of exposure (ammonium perfluorooctanoate or APFO) as part of a general health survey in a cohort of occupationally exposed workers. J.Occup.Environ.Med. 49, 1086-1096.

Sakr, C.J., Leonard,R.C., Kreckmann,K.H., Slade,M.D., and Cullen,M.R. 2007b. Longitudinal study of serum lipids and liver enzymes in workers with occupational exposure to ammonium perfluorooctanoate. J.Occup.Environ.Med. 49, 872-879.

Sasaki, K., Harada, K., Saito, N., Tsutsui, T., Nakanishi, S., Tsuzuki, H. and Koizumi, A. 2003. Impact of airborne perfluorooctane sulfonate on the human body burden and the ecological system. Bull Environ Contam Toxicol.71, 408–413.

Schlummer, M., Gruber, L., Ungewiss, J. and Fromme, H. 2005. Human exposure to perfluorinated compounds via food. ANA036 Schlumme. 9th Fluoros International symposium on fluorinated alkyl organics in the environment. August 2005, Toronto, Canada.

Seacat, A.M., Thomford, P.J., Hansen, K.J., Olsen, G.W., Case, M.T. and Butenhoff, J.L. 2002. Subchronic toxicity studies on perfluoroctanesulfonate potassium salt in cynomolgus monkeys. Toxicol Sci. 68, 249-264.

Seacat, A.M., Thomford, P.J., Hansen, K.J., Clemen, L.A., Eldridge, S.R., Elcombe, C.R. and Butenhoff, J.L. 2003. Sub-chronic dietary toxicity of potassium perfluorooctanesulfonate in rats. Toxicology 183, 117-131.

Shabalina, I.G., Panaretakis, T. and Bergstrand, A. 1999. Effects of the rodent peroxisome proliferator and hepatocarcinogen, perfluorooctanoic acid, on apoptosis in human hepatoma HepG2 cells. Carcinogenesis 20, 2237-2246.

Shen, Y.W. and Taves, D.R. 1974. Fluoride concentrations in the human placenta and maternal and cord blood. Am J Obstet Gynecol 119, 205-207.

Shipley, J.M., Hurst, C.H., Tanaka, S.S., DeRoos, F.L., Butenhoff, J.L., Seacat, A.M. and Waxman, D.J. 2004. Trans-activation of PPARalpha and induction of PPARalpha target genes by perfluorooctane-based chemicals. Toxicol Sci. 80, 151-160.

Sibinski, L.J. 1987. Final report of a two-year oral (diet) toxicity and carcinogenicity study of fluorochemical FC-143 (perfluorooctanane ammonium carboxylate) in rats.. Vol. 1-4, 3M Company/RIKER, Exp. No. 0281CR0012; 8 EHQ-1087-0394, October 16, 1987.

Sinclair E., Taniyasu S., Yamashita N., and Kannan K. 2004. Perfluorooctanoic Acid and Perfluorooctane Sulfonate in Michigan and New York Waters. Organohalogen Compounds 66, 4019–4023

Sinclair E., Mayack D.T., Roblee K., Yamashita N., and Kannan K. 2006. Occurrence of Perfluoroalkyl Surfactants in Water, Fish, and Birds from New York State. Archives of Arch Environ Contam Toxicol. 50, 398–410.

Skutlarek D., Exner M., Farber H. 2006. Perfluorinated surfactants in surface and drinking waters. Environ. Sci. Pollut. Res. 13, 299-307.

So M.K., Taniyasu S., Lam P.K.S., Zheng G.J., Giesy J.P., and Yamashita N. 2006a. Alkaline digestion and solid phase extraction method for perfluorinated compounds in mussels and oysters from south China and Japan. Arch Environ Contam Toxicol. 50, 240–248.

So M.K., Yamashita N., Taniyasu S., Jiang Q., Giesy J.P., Chen K., Lam P.K.S., and Lam, P.K.S. 2006b. Health risks in infants associated with exposure to perfluorinated compounds in human breast milk from Zhoushan, China. Environ Sci Technol. 40, 2924–2929.

So,M.K., Miyake,Y., Yeung,W.Y., Ho,Y.M., Taniyasu,S., Rostkowski,P., Yamashita,N., Zhou,B.S., Shi,X.J., Wang,J.X., Giesy,J.P., Yu,H., and Lam,P.K. 2007. Perfluorinated compounds in the Pearl River and Yangtze River of China. Chemosphere 68, 2085-2095.

Sohlenius, A.K., Andersson, K. and DePierre, J.W. 1992b. The effects of perfluoro-octanoic acid on hepatic peroxisome proliferation and related parameters show no sex-related differences in ice. Biochem J 285, 779-783.

Sohlenius, A.K., Lundgren, B. and DePierre, J.W. 1992a. Perfluorooctanoic acid has persistent effects on peroxisome proliferation and related parameters in mouse liver. J Biochem Toxicol. 7, 205-212.

Sohlenius, A.K. and Eriksson, A.M. 1993. Perfluorooctane sulfonic acid is a potent inducer of peroxisomal fatty acid b-oxidation and other activities known to be affected by peroxisome proliferators in mouse liver. Pharmacol Toxicol. 72, 90-93.

SRI International, 1982. *In vitro* microbiological mutagenicity assays of 3M Company's compound T-3209CoC. No LSC-3145.

SRI International, 1985. *In vitro* microbiological mutagenicity assays of 3M Company's compound T-3727 and T-3752. No LSC-3145.

Staples, R.E. and Burgess, B.A. 1984. The embryo-fetal toxicity and teratogenic potential of ammonium perflurooctanoate in the rat. Fundam Appl Toxicol. 4, 429-440.

Suchenwirth, R.H., Jürling, H., Huppmann, R., Bücking, M. 2006: Perfluorierte Alkylsubstanzen (PFAS) in Muttermilch. Ergebnisse und vorläufige Bewertungen einer Pilotstudie des Niedersächsischen Landesgesundheitsamtes. Report in German. Available at URL: http://www.nlga.niedersachsen.de/servlets/download?C=23217451&L=20

Sweetser, P.B. 1965. Decomposition of organic fluorine compounds by Wickbold oxyhydrogen flame combustion method. Anal Chem 28, 1766-1768.

Takacs,M.L. and Abbott,B.D. 2007. Activation of mouse and human peroxisome proliferator-activated receptors (alpha, beta/delta, gamma) by perfluorooctanoic acid and perfluorooctane sulfonate. Toxicol.Sci. 95, 108-117.

Takagi, A., Umemura, T., Hasegawa, R. and Kurokawa, Y. 1991. Short-term exposure to the peroxisome proliferators perfluorooctanoic acid and perfluorodecanoic acid causes significant increase of 8-hydroxydeoxyguanosine in liver DNA of rats. Cancer Letters 57, 55-60.

Takagi, A., Sai, K., Ummemura, T., Hasegawa, R. and Kurogawa, Y. 1992. epatomegaly is an early biomarker for hepatocarcinogenesis induced by peroxisome proliferators. J Environ Toxicol Pathol 11, 45-149.

Tanaka S., Fujii S., Lien N.P.H., Nozoe M., Fukagawa H., Wirojanagud W., Anton A. and Lindstrom G. 2006. A simple pre-treatment procedure in PFOS and PFOA water analysis and its' application in several countries. Organohalogen Compounds 68, 527–530.

Taniyasu S., Kannan K., Horii Y., Hanari N., and Yamashita N. 2003. A survey of perfluorooctane sulfonate and related perfluorinated organic compounds in water, fish, birds, and humans from Japan. Environmental Science and Technology 37, 2634–2639.

Taves, D.R. 1968. Electrophoretic mobility of serum fluoride. Nature 217: 1050-1051.

Thibodeaux, J.R., Hanson, R.G., Rogers, J.M., Grey, B.E., Barbee, B.D., Richards, J.H., Butenhoff, J.L., Stevenson, L.A. and Lau, C. 2003. Exposure to perfluorooctane sulfonate during pregnancy in rat and mouse: I. Maternal and prenatal evaluations. Toxicol Sci 74, 369–381.

Thomford, P. J. 2002. 104-week dietary chronic toxicity and carcinogenicity study with perfluorooctane sulfonic acid potassium salt (PFOS; T-6295) in rats. 6329-183. Covance Laboratories Inc.

Tittlemier, S.A., Edwards, L. and Pepper, K. 2003. Concentrations and temporal trends of two perfluorooctyl sulfonamides in fast food composites collected during the Canadian total diet study Food. Organohalogen Compounds 62, 315-318.

Tittlemier, S.A., Pepper, K., Tomy, G. and Chan, L. 2005. Examination of dietary exposure to polyfluorinated compounds via consumption of traditional foods. Organohalogen Compounds 67, 1794–1796.

Tittlemier S.A., Moisey J., Seymour C., Pepper K. 2006. Concentrations of perfluorinated carboxylates and related compounds in Canadian Total Diet Study food composites and food packaging. Organohalogen Compounds 68, 539–542.

Tittlemier,S.A., Pepper,K., Seymour,C., Moisey,J., Bronson,R., Cao,X.L., and Dabeka,R.W. 2007. Dietary exposure of Canadians to perfluorinated carboxylates and perfluorooctane sulfonate via consumption of meat, fish, fast foods, and food items prepared in their packaging. J.Agric.Food Chem. 55, 3203-3210.

Tomy, G.T., Budakowski, W., Halldorson, T., Helm, P.A., Stern, G.A., Friesen, K., Pepper, K., Tittlemier, S.A. and Fisk, A.T. 2004. Fluorinated organic compounds in an eastern Arctic marine food web. Environmental Science and Technology 38, 6475–6481.

Tseng C., Liu L., Chen C., and Ding W. 2006. Analysis of perfluorooctanesulfonate and related fluorochemicals in water and biological tissue samples by liquid chromatography–ion trap mass spectrometry. Journal of Chromatography A 1105, 119–126.

Turrini A, Saba A, Perrone D, Cialfa E, D'Amicis A. 2001: Food consumption patterns in Italy: the INN-CA Study 1994-1996. Eur. J. Clin. Nutr. 55, 571-88.

Ubel, F.A., Sorenson, S.D., Roach, D.E., 1980) Health status of plant workers exposed to fluorochemicals - a preliminary report. *Am Ind Hyg Assoc J* 41: 584-589.

UK DEFRA (United Kingdom Department for Environment, Food and Rural Affairs), 2004. Proposal for Regulations on PFOS-Related Substances Partial Regulatory Impact Assessment. Prepared by Risk & Policy Analysts Limited and BRE Environment for Department for Environment, Food and Rural Affairs, Chemicals and GM Policy Division, United Kingdom.Project J454/PFOS RRS. Available at URL: http://www.fluoridealert.org/pesticides/pfos.uk.impact.statement.pdf

UK FSA (United Kingdom Food Standards Agency), 2006. Fluorinated chemicals: UK dietary intakes 11/06 June 2006. Available at : http://food.gov.uk/science/surveillance/fsisbranch2006/fsis1106

U.S. EPA (United States Environmental Protection Agency), 1996. Exposure Factors Handbook Volume I: General Factors. Review Draft EPA/600/P-95/002Ba. August 1996. Office of Research and Development. Washington, DC:20460.

U.S. EPA (United States Environmental Protection Agency), 2000. Draft Exposure and Human Health Reassessment of 2,3,7,8-Tetrachlorodibenzo-p-Dioxin (TCDD) and Related Compounds. Part I: Estimating Exposure to Dioxin-Like Compounds. Volume IV: Site-Specific Assessment Procedures – chapter 2. EPA/600/P-00/001Bd. September 2000. Office of Research and Development. Washington, DC:20460.

U.S. EPA (United States Environmental Protection Agency), 2002. Draft hazard assessment of perfluorooctanoic acid and its salts, February 20, 2002. Washington DC, USA.

U.S. EPA (United States Environmental Protection Agency), 2003. Preliminary risk assessment of the developmental toxicity associated with exposure to perfluorooctanoic acid and its salts. U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics, Risk Assessment Division, April 10, 2003. Washington DC, USA.

U.S. EPA (United States Environmental Protection Agency), 2005. Draft risk assessment on the potential human health effects associated with exposure to perfluorooctanoic acid and its salts. US EPA. Office of Pollution Prevention and Toxics Risk Assessment Division. Washington DC, USA.

U.S. EPA (United States Environmental Protection Agency), 2006. PFAS-Proposed Significant New Use Rule, 40CFR721. U.S. Federal Register: Vol 71 (No 47), March 10, 2006.

Uy-Yu N, Kawashima Y, and Kozuka H 1990 Comparative studies on sex-related difference in biochemical response s of livers to perfluorooctanoic acid between rats and mice. Biochem Pharmacol 39, 1492-1495.

van de Vijver K.I, Hoff P.T., van Dongen W., Esmans E.L., Blust R., and de Coen W.M. 2003. Exposure patterns of perfluorooctane sulfonate in aquatic invertebrates from the Western Scheldt estuary and the southern North sea. Environ Toxicol Chem 22, 2037–2041.

van de Vijver K.I., Blust R., de Coen W. 2005. Toxicity identification of perfluorinated compounds in the Western Scheldt estuary. FLUOROS Ninth International Symposium on Fluorinated Alkyl Organics in the Environment, Toronto, Canada, August 2005. Poster TOX007.

van den Heuvel, J.P., van Rafelghem, M.J., Manahan, L.A. and Peterson, R.E. 1989. Isolation and purification of perfluorodecanoic and perfluorooctanoic acids from rat tissues. Lipids 24, 526-531.

van den Heuvel, J.P., Kuslikis, B.I., van Rafelghem, M.J. and Peterson, R.E. 1991. Tissue distribution, metabolism, and elimination of perfluorooctanoic acid in male and female rats. J Biochem Toxicol 6: 83-92.

van den Heuvel, J.P., Davis,J.W., Sommers,R., and Peterson,R.E. 1992. Renal excretion of perfluorooctanoic acid in male rats: inhibitory effect of testosterone. J.Biochem.Toxicol. 7, 31-36.

van den Heuvel J.; Thompson J.; Frame S.; Gillies P.; J 2006. Differential activation of nuclear receptors by perfluorinated fatty acid analogs and natural fatty acids: a comparison of human, mouse, and rat peroxisome proliferator-activated receptor-alpha, -beta, and -gamma, liver X receptor-beta, and retinoid X receptor-alpha, Toxicol Sci. 92, 476-489

van Leeuwen, S., Kärrman, A., Zammit, A., van Bavel, B., van der Veen, I., Kwadijk, C., de Boer, J. and Lindström G. 2005. First worldwide interlaboratory study on perfluorinated compounds in human and environmental matrices. Joint report of the Netherlands Institute for Fisheries Research (ASG-RIVO) (The Netherlands), Man-Technology-Environment (MTM) Research Centre, Sweden, and Institute of Water Technology Laboratory, Malta.

van Leeuwen, S.P.J, van der Veen, I., Leonards, P.E.G., de Boer, J. 2006. Perfluorinated compounds in edible dutch fish. Organohalogen Compounds 68, 535-538.

Vejrup, K.V. and Lindblom, B. 2002. Survey of chemical substances in consumer products — Analysis of perfluorooctanesulfonate compounds in impregnating agents, wax, and floor polish products. Survey No. 17. Department of Environmental Chemistry, National Environmental Research Institute, Danish Environmental Protection Agency, Danish Ministry of the Environment (Denmark).

Vésine,E Bossoutrot,V, Mellouki,A , Le Bras,G., Wenger,J and Sidebottom, H.(2000). Kinetic and Mechanistic Study of OH- and Cl-Initiated Oxidation of Two Unsaturated HFCs: C4F9CH=CH2 and C6F13CH=CH2. J. Phys.Chem. A, 104, 8512 -8520, 2000.

Völkel, W., Genzel-Boroviczeny, O., Demmelmair, H., Gebauer, C., Koletzko, B., Twardella, D., Raab, U., Fromme, H. (2007). Perfluoroctane sulfonate (PFOS) and perfluoroctanoic acid (PFOA) in human breast milk: results of a pilot study. Int. J. Hyg. Environ. Health. 211, 440-446.

Wang, N., Szostek,B., Buck,R.C., Folsom,P.W., Sulecki,L.M., Capka,V., Berti,W.R., and Gannon,J.T. 2005a. Fluorotelomer alcohol biodegradation-direct evidence that perfluorinated carbon chains breakdown. Environ.Sci.Technol. 39, 7516-7528.

Wang, N., Szostek,B., Folsom,P.W., Sulecki,L.M., Capka,V., Buck,R.C., Berti,W.R., and Gannon,J.T. 2005b. Aerobic biotransformation of 14C-labeled 8-2 telomer B alcohol by activated sludge from a domestic sewage treatment plant. Environ.Sci.Technol. 39, 531-538.

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

Weremiuk A.M., Gerstmann S., Hartmut F. (2006). Quantitative determination of perfluorinated surfactants in water by LC-ESI-MS/MS. J Sep Sci.29, 2251 – 2255.

Wetzel, L.T., 1983. Rat teratology study, T-3351, final report. Hazelton Laboratories America, Inc. Project Number: 154–160, December 19, 1983. US EPA AR-226 226-0014.

White,S.S., Calafat,A.M., Kuklenyik,Z., Villanueva,L., Zehr,R.D., Helfant,L., Strynar,M.J., Lindstrom,A.B., Thibodeaux,J.R., Wood,C., and Fenton,S.E. 2007. Gestational PFOA exposure of mice is associated with altered mammary gland development in dams and female offspring. Toxicol.Sci. 96, 133-144.

WHO/GEMS/Food-EURO (World Health Organization), 1995. Second workshop on reliable evaluation of low level contamination of food. Kulmbach (Germany), May 26–27. URL: http://www.who.int/foodsafety/publications/chem/lowlevel_may1995/en/index.html.

Wolf,C.J., Fenton,S.E., Schmid,J.E., Calafat,A.M., Kuklenyik,Z., Bryant,X.A., Thibodeaux,J., Das,K.P., White,S.S., Lau,C.S., and Abbott,B.D. 2007. Developmental toxicity of perfluorooctanoic acid in the CD-1 mouse after cross-foster and restricted gestational exposures. Toxicol.Sci. 95, 462-473.

Xie,W., Kania-Korwel,I., Bummer,P.M., and Lehmler,H.J. 2007. Effect of potassium perfluorooctanesulfonate, perfluorooctanoate and octanesulfonate on the phase transition of dipalmitoylphosphatidylcholine (DPPC) bilayers. Biochim.Biophys.Acta 1768, 1299-1308.

Yang, Q., Xie, Y; Depierre, J W. 2000. Effects of peroxisome proliferators on the thymus and spleen of mice, Clinical And Experimental Immunology, 122, 219-226.

Yang,Q., Xie,Y., Alexson,S.E., Nelson,B.D., and DePierre,J.W. 2002. Involvement of the peroxisome proliferator-activated receptor alpha in the immunomodulation caused by peroxisome proliferators in mice. Biochem.Pharmacol. 63, 1893-1900.

Yao,X. and Zhong,L. 2005. Genotoxic risk and oxidative DNA damage in HepG2 cells exposed to perfluorooctanoic acid. Mutat.Res. 587, 38-44.

Yin Yeung, W., Guruge, K.S. Yamanaka, N., Miyazaki, S., Lam, P.K.S., Yamashita, N. and Geisy. 2005. Gene expression profiles in rat liver treated with pentadecafluorooctanic acid (PFOA). TOX003 Yin Yuen. 9th "Fluoros" International Symposium on Fluorinated Alkyl Organics in the Environment, Toronto, Canada.

Ylinen, M., Hanhijarvi, H., Peura, P., Ramo, O. 1985 Arch. Environ. Contam. Toxicol. 14, 713-716.

Ylinen M, Kojo A, Hanhijarvi H, and peura P 1990 Disposition of perfluorooctanoic acid in the rat after single and subchronic administration. Bull Environ Contam Toxicol 44, 46-53.

LIST OF ABBREVIATIONS

8-dG	8-hydroxydeoxyguanosine
AFC	Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food
ALT	alanine aminotransferase
AP	alkaline phosphatase
APFO	ammonium salt of PFOA
AST	aspartate aminotransferase
$BMDL_x$	lower limit of the 95% confidence interval on the benchmark dose that would predict a x% increase in response above background incidence
b.w.	body weight
CAS	Chemical abstracts service
CEP	critical exposure parameter
CHO	Chinese hamster ovary
CI	chemical ionisation, or confidence interval
CONTAM	Scientific Panel on Contaminants in the Food Chain
CYP	cytochrome P450
DCM	dichloromethane
DL-PCB	dioxin-like polychlorinated biphenyls
ECF	Simons Electro-Chemical Fluorination
ED_{50}	Effective dose, dose required to elicit effect in 50% of the test population exposed to the chemical, or cause a 50% response in a biological system that is exposed to the chemical
EI	electron impact ionisation
EINECS	European Inventory of Existing Commercial Chemical Substances Information System
ESI	electrospray ionisation
EUSES	European Union System for the Evaluation of Substances
FSH	follicle stimulating hormone
FTOH	fluorotelomer alcohol
GLP	Good laboratory practice
GC-MS	Gas chromatography coupled to mass spectrometry
GD	gestation day
GFF	glass fibre filter
GM	geometric mean
HDL	high-density lipoproteins
HGPRT	hypoxanthine-guanine phosphoribosyl transferase
K_D	sediment / water (sorption) partition coefficient
K_{oc}	sediment / water (sorption) partition coefficient normalised to organic carbon content of sediment
K_{ow}	n-octanol / water partition coefficient
LADD	lifetime average daily dose
LC	liquid chromatography
LC_{50}	Lethal concentration, concentration required to kill 50% of the test animals
LC-FLU	LC with fluorescence detection
LC-MS	LC coupled to single quadrupole mass spectrometry

LC-MS/MS	LC coupled to triple quadrupole mass spectrometry
LCT	Leydig cell adenomas
LC-UV	LC with ultraviolet detection
LD	limit of determination
LD_{50}	lethal dose, dose required to kill 50% of the test animals
LH	luteinizing hormone
LOAEL	lowest-observed-adverse-effect-level
LOD	limit of detection
MeOH	methanol
MOA	mode of action
MoBB	margin of body burden
MoBL	margin of blood level
MOE	margin of exposure
MS	mass spectrometry
MTE	more typical exposure
NCE	normochromatic erythrocytes
NCI	negative chemical ionisation
N-EtFOSA	*N*-ethyl perfluorooctane sulfonamide
N-EtFOSE	*N*-ethyl perfluorooctane sulfonamidoethanol
ng	nanogram (10^{-9} g)
N-MeFOSE	*N*-methyl perfluorooctane sulfonamidethanol
NOAEL	no-observed-adverse-effect-level
OECD	Organisation for Economic Co-operation and Development
OSPAR	Oslo Paris Commission for the protection of the marine environment of the North-East Atlantic
PCB	polychlorinated biphenyls
PCDD	polychlorinated dibenzo-p-dioxins
PCDF	polychlorinated dibenzofurans
PCE	polychromatic erythrocytes
PFCA	Perfluorocarboxylic acid
PCI	positive chemical ionisation
PFAS[7]	perfluorinated alkylated substances
PFO	perfluorooctanoate
PFOA	perfluorooctanoic acid
PFOS	perfluorooctane sulfonate
PFOSA	perfluorooctane sulfonamide
pg	picogram, 10^{-12} g
PGOT	plasma glutamic oxalacetic transaminase
PGPT	plasma glutamic pyruvic transaminase
pK_a	negative logarithm of acid dissociation constant
POP	persistent organic pollutant
POSF	perfluorooctanesulfonyl fluoride
PPAR	peroxisome proliferator activated receptors
ppb	parts per billion (10^{-9})
PSE	pressurised solvent extraction
PTFE	polytetrafluoroethylene
PUF	polyurethane foam

[7]The abbreviation PFAS is also being used for perfluorinated alkyl sulfonates by some organisations

Q	percentile of distribution
RBC	red blood cell (count)
RME	reasonable maximum exposure
ROS	reactive oxygen species
RREPC	relative risk ratio for each episode of care
SCGE	single cell gel electrophoresis
S.D.	standard deviation
SPE	solid phase extraction
SIM	selected ion monitoring
SMR	standardised mortality ratio
$T_{1/2}$	half-life, time needed to reduce level of chemical in a certain medium to 50% of initial level
T3	triiodothyronine, one of the thyroid hormones
TDI	tolerable daily intake
TM	telomerisation
TOF	quadrupole-time-of-flight
TSH	thyroid-stimulating hormone, thyrotropin
UK-DEFRA	United Kingdom Department for Environment, Food and Rural Affairs
UNECE-CLRTAP	United Nations Economic Commission for Europe - Convention on Long-Range Transboundary Air Pollution
U.S. EPA	United States Environmental Protection Agency
U.S. FDA	United States Food and Drug Administration
WBC	white blood cell (count)
w.w.	wet weight
XAD	ion exchange resin used for sample clean up