Human Risks of Perfluorinated Chemicals (PFCs): a Review of the Literature

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# Abstract

Perfluorinated compounds (PFCs) are a family of chemicals used widely as surfactants, anti-staining products, impregnation agents and fire fighting foams. The wide possible uses for these compounds are due to their unique water- and oil repellent properties. Notable PFCs, like perfluorooctane sulfonate (PFOS) and perfluorooctanoic acid (PFOA) and others have been found in the (mainly aquatic) environment as well as animals and humans. Several studies have investigated the effects of these chemicals, mainly PFOS and PFOA, since the first observation in human serum. The literature available on PFC exposure and potential harmful effects in humans will be discussed.

PFC exposure occurs through different routes. Indoor and outdoor air has been found to be contaminated with some degree of PFCs, from which inhalation is a form of exposure. Inhalation of contaminated house dust has been mentioned as a source of exposure as well. Most abundant route of exposure was found to be dietary, mainly through directly contaminated fish or food contaminated by PFCs through migration from the packaging. Ingestion of house dust by toddlers contributes to total exposure as well. Furthermore, occupational exposure may occur in PFC factories as well as occupations using PFC products, like ski-wax. Occupational levels of PFC exposure have been found to be several orders of magnitude higher than general population levels.

Many effects have been found to be associated with PFC exposure, mainly PFOS and PFOA, for the most part investigated in rodents. Only few effects have been observed at exposure levels comparable to the general population. Immunotoxic effects were found in relevant concentrations in rodents, causing a reduction in immune response. Epidemiological effects in the general population include reprotoxic effects, like reduced sperm count, and a recent study observed a positive correlation between PFC levels in serum and Attention Deficit Hyperactive Disorder (ADHD) in children. Higher perceived adverse effects, like carcinogenicity and neurotoxicity, have been observed in rodents, but in higher concentrations and these have not been found in the general population or the occupationally exposed.

In conclusion, epidemiological data provides the most convincing evidence of adverse effects due to PFC exposure. More toxic effects found in rodents increase the potential risk of these compounds in humans as well. Further investigation of PFOS and PFOA, but also other PFCs less abundant in humans, is needed to completely assess the risks of PFCs for humans. It is evident that the unrest caused by these compounds is substantiated, and deserves more attention.

# Introduction

Since the first observation of polyfluoroalkyl chemicals in human blood samples[[1]](#endnote-1), many studies have been conducted to investigate the potential toxicity of these compounds. As evidence emerged showing several toxic properties, the perceived risk of these chemicals increased. Recently, the unrest heightened, when in 2010 a positive correlation between Attention Deficit Hyperactive Disorder (ADHD) and the level of polyfluoroalkyl chemicals in serum was found among children aged 12-15 in the USA[[2]](#endnote-2). ADHD is a neurobehavioral developmental disorder, affecting 3 to 5 per cent of children globally, and the most commonly diagnosed psychiatric disorder in children[[3]](#endnote-3). Symptoms of this chronic disorder include inattention, hyperactivity and impulsivity, and in 30-50% of these cases the symptoms continue into adulthood[[4]](#endnote-4). This study increased the already present unrest about this family of fluorine-containing carbon chains, widely used in diverse industries because of their unique water-, oil- and stain resistant properties.

This family of fluorine-containing carbon chains is also known as polyfluorinated compounds, but mainly abbreviated to PFCs. They all consist of a hydrophobic fluorinated carbon chain of varying length (typically C4 to C16) and a hydrophilic end group, i.e. sulfonate or carboxylate. If the hydrophobic carbon chain is fully fluorinated, it is called a perfluorinated compound[[5]](#endnote-5). PFCs have specific properties due to the fluorine atoms. A carbon-fluorine bond (C-F) is extremely strong, which causes PFCs to be very stable. This stability makes them hydro- and oleophobic, and therefore water­, oil­ and stain resistant. [[6]](#endnote-6)

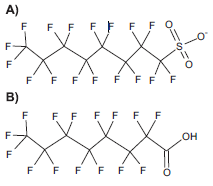
The unique properties were discovered in the 1950s; the water- and oil resistance made them suitable as surfactants as well as many other uses[[7]](#endnote-7). From that moment on, production of PFCs started, and many different PFC containing products were manufactured. Following, PFCs were emitted into the environment; but what was not known when production first started, was that the stability of PFCs makes them insensitive to environmental and biological degradation, causing them to be bioaccumulative in environment as well as organisms.

Fig. 1 Chemical structure of (A) Perfluorooctane sulfonate (PFOS) and (B) perfluorooctaonic acid (PFOA). Modified from Fromme et al. (2009)

Among the earliest PFCs to be produced were perfluorooctane sulfonate (PFOS) and perfluorooctanoic acid (PFOA). These compounds in particular have been the centre of attention of most PFC related studies, causing most concern. PFOS was the main ingredient for Scotchgard, a fabric protector made by the 3M production company. It was used on fabric, furniture and carpets, to prevent staining. Other uses for PFOS and its precursors are as impregnation agents, waxes, and cleaning products. Together with other PFCs, like PFOA, it also has a large application in fire fighting foam. PFOA shares some of these uses, but is mainly used as an antistatic additive, as well as a processing aid in producing fluoropolymers. PFOA is found in fabrics for outdoor clothing, Teflon and other products. 7,[[8]](#endnote-8),[[9]](#endnote-9),

In 1968, perfluorinated compounds were found in human serum samples1. This started the general concern, and a string of studies on the exposure and effects of PFCs. The major subject of the PFC research is their potential effects in humans. Next to the increased risk for ADHD in children, several studies suggest an array of possible toxic effects caused human PFC exposure. These effects include developmental toxicity, immunotoxicity, hepatotoxicity[[10]](#endnote-10), neurotoxicity[[11]](#endnote-11), endocrine disruption[[12]](#endnote-12) and even genotoxicity[[13]](#endnote-13).

Another major part of the PFC studies focus on environmental and human exposure. PFCs have been found to be very persistent[[14]](#endnote-14) as well as bioaccumulative[[15]](#endnote-15), especially ionic PFCs like PFOS and PFOA. The persistency of PFOS in particular caused alarm, even leading to the addition of PFOS to the list of Persistent Organic Pollutants (POPs) under the Stockholm Convention[[16]](#endnote-16). These properties cause increasing levels of PFCs in the environment, in particular the aquatic. A major source of human exposure to PFCs is via seafood[[17]](#endnote-17). Human exposure to PFOS, PFOA and other PFCs has also been related to drinking water[[18]](#endnote-18) and (indirectly) related to food packaging[[19]](#endnote-19).

The effects of PFCs, including ADHD and genotoxicity, combined with the human diet as a major exposure route, causes the perceived risks of PFCs among the public to be very high. The question remains, however, whether this unrest is substantiated. The internal human dose caused by PFC exposure has to be high enough, at the target organs, for the suggested effects to occur. Therefore, in this review of the current literature on perfluorinated compounds, the main question will be: What are the relative risks of perfluorinated compounds like PFOS and PFOA?

# Exposure

In understanding how humans are exposed to PFCs, it is important to know how these compounds reach the environment. Following, it may be assessed how this causes the potential exposure routes, like our diet.

## PFCs in the environment

Since the first production of PFC-containing products in the 1950s, the environment has been exposed to PFCs, eventually leading to the levels it has reached today.[[20]](#endnote-20) Direct sources of environmental PFC exposure include the manufacturing and use of PFCs; however, indirectly the environment is polluted through the so-called precursor PFCs. This less accumulative group of PFCs can cause an increase of accumulative PFCs through abiotic and biotic transformation. Examples of precursor PFCs include perfluorooctane sulphonamides (POSF), which can be metabolised to PFOS, and fluorotelomer alcohols (FTOH), which can be degraded in the environment to PFOA7.

Because of the relatively high water solubility and moderate sorption to solids, ionic PFCs like PFOS and PFOA accumulate mainly in the aquatic environment. Starting from the production and use of PFC products, PFCs reach the environment through wastewater treatment plants as well as surface runoff from landfill, from which they end up in the aquatic environment (Fig. 2).



**Fig. 2 Fate of PFCs in the aquatic environment**[[21]](#endnote-21)

Precursor PFCs however, are more volatile than PFOS and PFOA and can be transported through the atmosphere before they are transformed into the more persistent chemicals. These compounds, like POSF and FTOH, are not directly emitted to the atmosphere during production, but reach the air indirectly as components or through the final products, mostly in areas with dense population or industry.

Transport through the aquatic environment, has led to the detection of PFCs in the whole ecosystem, even in the arctic environment[[22]](#endnote-22). As seen in Fig. 2, PFCs do not only end up in wildlife because of their environmental fate, but also in groundwater, which leads to the occurrence of PFCs in drinking water.

PFOS levels are found to be decreasing in the aquatic environment, mainly because the production of ‘new’ classes of PFCs like perfluoroalkyl phosphonates (PAPs), which are still produced today. PFOS and PFOA have also been slowly phased out from 3Ms production process since 2000, which slowed down environmental exposure. However, the persistency of these compounds are still high enough to remain in the environment; the average half-life of PFOS and PFOA in retirees from PFC production plants have been estimated at 5.4 and 3.8 years respectively[[23]](#endnote-23). Consecutively, the transformation into these PFCs from other compounds remain sources of exposure, not to mention the PFCs still produced today. Since this report will focus on human exposure, there will be no further investigation of the environmental exposure.

## Sources of human PFC exposure

PFCs are shown to bind to the protein albumin, found in the liver and blood serum. This causes them not to accumulate in lipid layers, but mainly in blood and liver[[24]](#endnote-24). This makes PFCs easily detectable in human and animal serum. Consequently, as early as the 1960s, there have been several reports of PFC levels in humans, leading to studies describing the possible exposure routes that lead to these levels. Combined, these studies led to the conclusion that the major exposure routes are through inhalation of house dust and in- and outdoor air, but mainly as oral exposure through ingestion of contaminated food, drinking water and house dust21. Furthermore, occupational exposure, which is mainly through inhalation or ingestion, will be discussed separately.

In 2008, the European Food and Safety Authorisation (EFSA) had its Panel on Contaminants in the Food Chain establish Tolerable Daily Intakes (TDI) for PFOS and PFOA, based on the toxicological evidence at the time. For PFOS, a TDI of 150 ng/kg bw/day was established, for PFOA a TDI of 1.5 µg/kg bw/day. Reason for the difference is that the effect levels for PFOS were found to be occurring at 10 times lower concentrations than PFOA at the time. The reported average dietary exposure in Europe reported at the time, was 6 – 200 ng/kg bw/day for PFOS, and 2 – 6 ng/kg bw/day for PFOA[[25]](#endnote-25). Although most reported daily intake levels for PFOA are below these values, several studies report higher intakes for PFOS. Moreover, it has to be taken into account that more adverse toxicological data has become available since the establishment of these TDIs, and other sources of exposure (inhalation, packaged food) have not been used here. Therefore, the established TDIs might have to be altered to account for these facts.

Inhalation  
As mentioned earlier, most ionic, non-volatile PFCs like PFOS and PFOA are transported through the aquatic environment, and do not accumulate in air or dust. The volatile precursor PFCs however, can be present in air before transformation, and end up in dust as well. In a recent study, highest precursor PFC levels were found in the indoor air of shops selling outdoor equipment (products relatively high in volatile PFCs; waterproof shoes, tents etc.) in Hamburg, Germany, with FTOH among the highest concentrations. PFCs in indoor air at residential homes in the same city were found to be up to 5-fold lower than the shops, but still 1 order of magnitude higher than the air outside; a possible explanation might be the use of impregnating sprays.[[26]](#endnote-26)

Although the previous study reported higher concentrations of PFCs in indoor air than reported in earlier studies, the contribution from inhalation of precursor PFCs to the total PFC concentrations in humans remains relatively low. Total systemic absorption of FTOH by inhalation in rats was estimated between 49% and 57% for lower doses, and 27% for higher doses[[27]](#endnote-27). Moreover, only 1.4% of FTOH was metabolised to PFOA in isolated rat hepatocytes[[28]](#endnote-28). Combined with the estimation that human hepatocytes produce a 9.5-fold less PFOA compared to rat hepatocytes[[29]](#endnote-29), it can be concluded that exposure to precursor PFCs in the atmosphere does not contribute significantly to the total exposure2. However, more data is needed to rule out any exceptions.

Inhalation of dust has a more important contribution to human PFC exposure, especially considering children, who spend their time closer to the ground. A recent study on PFC concentrations in dust covered measurements of dust in homes worldwide, and classrooms, cars and offices in the UK. Homes were found to be the major source of this exposure route, since people spend most of their time there, but offices and classrooms make significant contributions as well. Differences were found in house-dust PFC concentrations between countries; Thailand and Kazakhstan showed significantly (p<0.05) lower concentrations than the European, Australian and American homes. This, and other international differences can be explained by the difference in use of PFC products, the major source of PFCs in house dust.

While most measured PFCs were significantly higher in homes among the different locations in the UK, the average concentrations of PFOS appeared to be twice as high in classrooms, while PFOA showed similar concentrations compared to homes. Contribution to the total PFC exposure in humans was shown to be important using this data, especially in the worst-case scenario for children aged 1-6. [[30]](#endnote-30) More data has to be gained in this case as well; a different study on PFC in house-dust in the USA reported up to 6- and 15-fold higher concentrations of PFOA and PFOS respectively, compared to the average[[31]](#endnote-31). While part of this difference may be methodological, it still suggests that there can be major differences in certain cases, increasing the importance of the contribution of PFC dust exposure.

For inhalation of PFCs, it is often assumed that 100% of the total inhaled concentration is taken up in the lungs7.

Ingestion  
While dietary intake is considered the major source of human PFC exposure, only few studies have been conducted on the subject. The average dietary intake (the intake responsible for the contribution to internal doses) of PFCs in these studies range from 18 to 700 ng/kg bw/day[[32]](#endnote-32), but they all agree that fish is the major source of PFC exposure in the human diet. Considering the accumulation of most PFCs in the aquatic environment, it is imaginable that fish are highly exposed to these compounds. PFOS and PFOA in particular have been reported to bioaccumulate in fish[[33]](#endnote-33). Other dietary sources for PFCs include several meat products, with an imaginable peak in liver products, dairy products, lettuce, cereal and drinking water.

Although most drinking water that has been measured showed low concentrations of PFCs, there have been some drinking water plants showing alarmingly high concentrations, up to a 1000-fold more than the average values given above18. Most of these cases can be contributed to a source of PFC pollution nearby the plant; for example, a drinking water plant in the Saurland region in Germany, drew drinking water from creeks and surface waters, which were polluted by industrial waste from a recycling company nearby[[34]](#endnote-34).

House dust, as mentioned in the inhalation subchapter, can also be an oral ingestion exposure. However, this is mainly relevant for toddlers who spent their time crawling on the ground; much less so for adults. Since effects were found associated with PFCs, like ADHD, this is an important factor of exposure for children to investigate.

As mentioned earlier, food packaging has also been put forward as a source for PFCs in food, mostly through precursor PFCs in grease- and water repellent coatings. The most prominent precursor PFCs here are polyfluoroalkyl phosphoric acid diesters, or diPAPs. Since the first evidence of these PFCs in commercial food packaging products in 2009[[35]](#endnote-35), it has been considered a potentially important, but overlooked source of human exposure to PFCs. Migration can cause diPAPs to travel through the food wrapper into the food, after which it is metabolised to PFOA and other PFCs in the human body. The few studies available that include food packaging as a potential source, indeed found higher levels of PFCs in these products[[36]](#endnote-36).

Since the observation of lowered thyroid hormone levels due to PFC exposure, which may affect foetal and neonatal development[[37]](#endnote-37),[[38]](#endnote-38),[[39]](#endnote-39) (discussed later in the Effects chapter), some researchers have conducted studies on the exposure of the foetus as well as breast milk exposure. Evidence suggests that up to 60% of the maternal serum PFOS levels end up in the umbilical cord serum[[40]](#endnote-40). Other studies even report higher levels of PFOA in cord serum compared to maternal serum[[41]](#endnote-41),[[42]](#endnote-42). These studies confirm that the foetus is indeed exposed to PFCs from the mother.

Exposure to PFC in children through breast milk and baby food has been researched as well, most recently in 2010[[43]](#endnote-43). This study found higher concentrations in breast milk from samples in Spain, than found in a previous study[[44]](#endnote-44). Highest concentrations were found PFOA and PFOS, though especially PFOA was found to have a broad concentration spectrum in the different samples. Baby food samples (milk formulas and cereals) contained relatively high concentrations in the µg/kg range of several PFCs, also including PFOS and PFOA among the highest. The corresponding dietary intake levels for breast milk and baby food did not exceed EFSAs TDIs, except for one breast milk sample. Although most dietary intake levels were a 10-fold below the established TDIs, the one outlier justifies further research, as well as the fact that dietary intake is not the only source of exposure.

Fromme et al. (2009) summarized the estimated adult daily intake based on mean or median concentrations found in literature until that time, in table 17. High intake is based on upper percentile or maximum concentrations.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Intake (ng/day)** | | **Intake ratea** | **Daily intake (pg/kg bw)b** | |
| **Mean** | **High** | **Mean** | **High** |
| *PFOA* |  | | | | |
| Indoor air | 0.053 | 0.053 | 12m3/day | 0.9 | 0.9 |
| Outdoor air | 0.076 | 0.718 | 1.3m3/day | 1.3 | 12.0 |
| House dust | 0.986 | 61.7 | 50 mg/day | 16.4 | 1028.3 |
| Diet | 169c | 689c |  | 2816.7 | 11483.3 |
| Drinking water | 1.3 | 5.2 | 1.3 l/day | 21.7 | 86.7 |
| **Overall intake** |  | | | 2857.0 | 12611.2 |
| *PFOS* |  | | | | |
| Indoor air | 0.284 | 0.284 | 12m3/day | 4.7 | 4.7 |
| Outdoor air | 0.006 | 0.060 | 1.3m3/day | 0.1 | 1.0 |
| House dust | 1.9 | 253 | 50 mg/day | 31.7 | 4216.7 |
| Diet | 90c | 269c |  | 1500.0 | 4483.3 |
| Drinking water | 1.4 | 7.8 | 1.3 l/day | 23.3 | 130.0 |
| **Overall intake** |  | | | 1559.8 | 8835.7 |

Table 1. Estimated adult daily intake of PFOS and PFOA for the general population. Daily intake given as picogram per kilogram body weight (bw) per day. aUS EPA, 2007. bAdult 60 kg. cMedian and 95th percentile. Modified from Fromme et al., 2009.

From this table, it may be cautiously concluded that dietary intake is the dominant exposure pathway, contributing for 91% of the total daily PFOS intake, and 99% of the total daily PFOA intake; these values correspond well with the plasma levels of the same population. While this data is based on more accurate exposure data, the daily intake levels are still comparable to EFSA’s estimation mentioned above, and fall well below the established TDI.

Occupational exposure

Occupational exposure to PFCs have led to the detection of very high serum PFC levels in exposed workers, data mainly from the major producers 3M and DuPont. While mostly through inhalation, these levels exceed the levels of the general population by more than 10-fold, well into the mg/l serum range, for both PFOS and PFOA. Most occupational exposure studies have followed workers from PFC-producing factories, it has to be taken into account that occupational exposure does not stop there; impregnating products or for example ski waxing include a significantly higher exposure to PFCs as well.7,[[45]](#endnote-45)

Although a 25-year medical surveillance of 3Ms occupationally exposed PFOS and PFOA workers did not observe any adverse effects[[46]](#endnote-46), this has yet to be determined by an independent source. Since the phasing out of PFOS especially, the total PFC body burden in occupationally exposed workers has a downward trend in the data available today. Occupational safety and lower emissions from processes may be involved in this observed trend as well.

## PFC internal distribution

While the exposure levels in humans are generally given as concentrations in serum, it is important to know whether the PFCs end up in target organs as well, to be able to assess whether it can cause an effect at that organ. In rats, PFC concentrations in target organs have been assessed in 2009[[47]](#endnote-47). Different concentrations of PFOS and PFOA were administered via gavage daily, with 10 rats in each group, and after 28 days of exposure the concentrations in various tissues were measured; results combined in Table 2.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Tissues** | **PFOA/PFOS** | **Concentration of PFOA** | | **Concentration of PFOS** | |
| **Daily exposure dose by gavage** | | | | |
| **0 (Control)** | **5 mg/kgbw/day PFOA** | **20 mg/kgbw/day PFOA** | **5 mg/kgbw/day PFOS** | **20 mg/kgbw/day PFOS** |
| *Blood* | ND | 39.2 ± 14.4 | 58.8 ± 17.6 | 72.0 ± 25.7 | NS |
| *Liver* | ND | 218 ± 21 | 196 ± 10 | 345 ± 40 | 648 ± 17 |
| *Kidney* | ND | 228 ± 37 | 209 ± 74 | 93.9 ± 13.6 | 248 ± 26 |
| *Lung* | ND | 63.0 ± 11.3 | 64.3 ± 15.9 | 46.6 ± 17.8 | 228 ± 122 |
| *Heart* | ND | 35.5 ± 17.6 | 34.6 ± 18.0 | 168 ± 17 | 497 ± 64 |
| *Spleen* | ND | 13.6 ± 2.4 | 6.92 ± 9.31 | 38.5 ± 11.8 | 167 ± 64 |
| *Testicle* | ND | 16.7 ± 16.9 | 16.8 ± 19.2 | 39.5 ± 10.0 | 127 ± 11 |
| *Brain* | ND | 10.5 ± 9.8 | 7.20 ± 6.03 | 13.6 ± 1.0 | 146 ± 34 |

From these results, it is clear that most accumulation of PFOA is in the liver and kidney, and for PFOS in the liver, kidney and heart. Where PFOS concentrations in the various tissues clearly follow a dose-dependent accumulation, for PFOA this is not the case, sometimes the opposite. In the study it has been suggested that this is because PFOA binds to proteins such as albumin; after saturation of binding sites, excretion of PFOA increases, and therefore the concentrations do not increase. In this fact, a significant difference between rodents and humans is observed. Investigating excretion values in humans showed absence of active excretion in human kidneys; the renal clearance that did occur was approximately one-fifth of the total clearance based on their serum half-lives[[48]](#endnote-48). Half-life of PFCs where studied in 2007, where rodent PFC half-life was found to be 5.68 days for PFOA and 7.5 days for PFOS. Reported human half-lives where much slower, 4.4 ± 3.6 years for PFOA and 8–9 years for PFOS.[[49]](#endnote-49)

Table 2. Concentrations of PFOS and PFOA in various tissues after 28 days of daily exposure in rats. Values are expressed as mean ± SD (*n* ≥ 5), as µg/mL for blood and µg/g for tissues. ND = not detected, NS = no sample because all 10 rats died before blood samples could be taken. Modified from Lin Ciu *et al.,* 2009.

PFOS, PFOA, but also perfluorohexane sulfonic acid (PFHxS), the PFCs found in highest concentrations in humans, do not metabolise in the body[[50]](#endnote-50). In a process called enterohepatic circulation, PFCs are secreted into the bile, but are re-absorbed in the intestines and reach the liver again, and the process starts anew. The existence of this process for PFCs was substantiated by Harada et al. (2007), where biliary excretion was found to be comparable in rats and humans, but high biliary reabsorption rates were found in humans[[51]](#endnote-51). The difference in PFC half-lives might therefore be attributable to low renal excretion levels in combination with high biliary reabsorption.

In humans, mostly liver tissue concentrations were measured. Fromme et al. (2009) summarized the available human data samples, and found a mean concentration of around 18 ng/g in liver of both PFOS and PFOA, but PFOA was found in fewer cases7. A mean ratio of liver to blood was found to be 1.4 for PFOS; which shows that the tissue values in rats in table 1 might not be very comparable to human situations. From the few data available on other human tissue samples, mean lung concentrations of PFOA and PFOS were 3.8 ng/g and 7.9 ng/g respectively; lowest tissue concentrations were observed in nerve tissue, 0.5 ng/g PFOA and 1.3 ng/g PFOS. The nerve tissue values suggest that there is poor transfer of PFCs through the blood-brain barrier.

# **Effects**

As seen in the Exposure chapter, the daily intake of PFOS and PFOA of the general population, even taking into account all possible exposure pathways, does not exceed the TDIs established by EFSA. However, since EFSA’s research in 2008, more data on the effects have been collected; if effects are found at lower exposure concentrations, the TDIs may need to be adjusted. In this chapter, the different effects that were found caused by PFC exposure will be discussed, especially taking into account post-2008 findings.

Immunotoxicity  
Although not among the most often studied toxic effects, PFCs have been found to be potentially immunotoxic. Experimental animal data as early as 1987 suggested PFOA as a peroxisome proliferator[[52]](#endnote-52), confirmed in later studies[[53]](#endnote-53). Peroxisome proliferators can bind to peroxisome proliferator-activated receptors (PPARs), nuclear receptor proteins involved in regulating gene expression as a transcription factor[[54]](#endnote-54). Essential roles of these PPARs include regulation of development, metabolism and tumorgenesis[[55]](#endnote-55). The immunotoxic effects due to peroxisome proliferation were investigated in mice in 2002, *in vivo* and *ex vivo*[[56]](#endnote-56). Mice were orally exposed to PFOA, after which immunization was induced. Compared to the control mice, a significant decrease in antibodies was observed, suggesting that PFOA treatment decreased the humoral immune response of mice. However, after removing PFOA exposure, a significant recovery in antibodies was observed, suggesting only continued presence of PFOA induced this effect. Examining lymphocyte proliferation *ex vivo* and *in vivo*, PFOA did not show any effect. In combination with earlier findings by the same authors[[57]](#endnote-57),[[58]](#endnote-58), their hypothesis remains that any immunosuppressing effects caused by PFOA is due to its peroxisome proliferation.

These immunotoxic effects of PFOA were confirmed in another study from 2008[[59]](#endnote-59), showing reduced immunoglobulin antibody (IgM) levels in mice after oral PFOA exposure. Again, a higher concentration than found in human exposure was needed for the observation of reduced IgM, leading to a Lowest Observed Adverse Effect Level (LOAEL) for mice of 3.75 mg PFOA/kg/day.

While PFOA is the most studied PFC in immunotoxic effects, PFOS was found to suppress IgM in mice as well[[60]](#endnote-60), reporting a LOAEL in mice of 1.66 µg/kg/day and 16.6 µg/kg/day for males and females respectively. This much lower LOAEL, especially for male rats, falls in the upper range of reported human concentrations in the general population, and even 14-fold lower than the mean blood levels of reported occupationally exposed humans. The immunotoxicity of PFOS was further emphasized in 2009, where human-relevant exposure levels (5 and 25 µg/kg/day) applied to mice resulted in a significantly increased emaciation (loss of substantial amounts of fat) and mortality to the Influenza A virus[[61]](#endnote-61).

Since PFOS has also been shown to be a peroxisome proliferator[[62]](#endnote-62), the effects of both PFOS and PFOA may be caused by this property. While still speculation, peroxisome-proliferator activated receptors-alpha, PPARα, in particular seem to be a possible target for this effect; the combined studies up to 2009 suggest that for PFOS, the immunological functional deficit may lie with B-cells, which express more PPARα than T-cells59. This hypothesis has become more credible since the immunomodulation effects of PFOA in particular were not found in mice with knocked-out PPARα[[63]](#endnote-63).

However, the effects for PFOS, a less potent PPARα agonist61 (already evident from the lower LOAEL), were only partially reduced in these mice, suggesting a more complex mechanism. Considering the human risk of PFOA in this case, it has to be taken into account that PPARα is 10 times more expressed in mice compared to humans2.

Furthermore, mouse PPARα is found to be more sensitive to PFCs than human PPARα61.  
The last study to be conducted in the immunological effects of PFCs, to my knowledge, further investigated the possible mechanisms involved, using human *in vitro* assays[[64]](#endnote-64). PFOS and PFOA were demonstrated to directly affect immune cell activation and reduce cytokine production in cultured human leukocytes, both pro- and anti-inflammatory, both through different mechanisms. As hypothesised in earlier studies, PFOA acted through PPARα to induce the immunological effects, while PFOS produced similar effects, but more potent than PFOA and independent from PPARα. The reduced cytokine release following PFOS exposure may be explained by inhibited I-κB degradation that was observed, an enzyme complex involved in propagating the cellular response to inflammation[[65]](#endnote-65). The concentrations to produce the effects were relevant for humans for PFOS, but the concentrations for PFOA are unlikely to be found in humans.

Overall, the studies reporting immunotoxic effects for PFCs must be taken seriously. While the LOAEL for PFOA are found at concentrations irrelevant to humans, PFOS effects are found at concentrations already found in human plasma; this suggests that different PFCs can have similar or even more potent effects. More research toward the potential mechanisms, including PPARα, is needed to further assess the human risks for immunotoxic effects due to PFC exposure.

Developmental/reproductive/endocrine toxicity

One of the more researched toxic effects of PFCs, is that for developmental toxicity. In 2002, the Organisation for Economic Co-operation and Development (OECD) performed a hazard assessment of PFOS, covering the literature on the toxicity of PFOS at the time[[66]](#endnote-66). The literature on developmental toxicity were mostly performed in rodents, and mainly reported a loss in foetal weights. The lowest determined LOAEL in these studies for maternal toxicity was 1.0 mg/kg/day PFOS.

Another review of the literature was performed in 2004, and reported more effects next to weight loss, like cleft palates, delayed ossification of bones, cardiac abnormalities and even pup mortality, but these effects were only observed in the highest PFOS dose groups of 10 mg/kg10. The developmental toxicity of PFOA have been reported lacking in most studies, but one study found a decrease in lactation index, as well as increased mortality in male and female pups in the highest, least relevant dose group of 30 mg/kg[[67]](#endnote-67).These reported effects for PFOA were found in lower concentrations in a study from 2010, where decreased foetal body weight and increased mortality among pups was found at concentrations of 5 mg/kg[[68]](#endnote-68). Other PFCs were not reported to show developmental toxicity.

The mechanisms discussed for these developmental effects are found to be potentially similar to that of the immunotoxic effects. While comparison to PPARα-null mice showed that the developmental effects of PFOA are predominantly mediated via PPARα, PFOS is found to have different, as of yet undetermined mechanisms. Constitutive androstane receptor (CAR) and other nuclear receptors are thought to be involved in the developmental toxicity mechanism of PFOA as well[[69]](#endnote-69). Since the mechanism of developmental toxicity seems to be similar to that of the immunotoxic effects, this increases the need for further investigation in that potential pathway.

Reproductive toxicity has been evaluated in several animal studies as well. PFCs have been reported to affect the endocrine system by decreasing testosterone[[70]](#endnote-70) and increasing oestradiol[[71]](#endnote-71) in rats. Human reproductive data on the toxicity of PFCs are still very limited, but some studies imply that this is an important subject to assess in more depth. In a study from 2009, PFC levels in serum from 105 Danish men was compared to their semen quality[[72]](#endnote-72). Most abundant PFCs found in the serum were found to be PFOS, PFHxS and PFOA, 24.5, 6.6 and 4.9 ng/mL respectively. Men with high PFOS and PFOA levels were found to have a median of 6.2 million normal spermatozoa in their ejaculate, compared to 15.5 million in men with low PFOS-PFOA levels. Combined with other yet non-significant findings, it was concluded that high levels of PFC may contribute to low semen quality seen in young men. Reprotoxicity in woman has also been evaluated, where for 1240 Danish woman were tested on time to pregnancy compared to PFOS and PFOA levels in their serum[[73]](#endnote-73). As a result, longer time to pregnancy was associated with higher maternal levels of PFOA and PFOS significantly.

The potency for human reprotoxic effects are further emphasized in a study from 2010. Several PFCs were measured for their inhibition of two hydroxysteroid dehydrogenases, 3β-HSD and 17β-HSD3, catalysts in the production of progesterone and testosterone respectively. While all PFCs inhibited these enzymes to some extent, PFOS and potassium perfluorooctane sulfonate (PFOSK) were found to be potent inhibitors for both rat 3β-HSD and human 17β-HSD3.[[74]](#endnote-74)   
The suggested mode of action underlying the male reprotoxic effects mostly include Leydig cells. A compromised Leydig cell function can be seen in reduced cholesterol transport gene expression and steroidgenesis, effects also reported after PFC exposure in some studies70. Other studies even report Leydig cell hyperplasia and the development of Leydig cell adenomas71. This suggests that PFCs can act as endocrine disruptors. According to the testicular dysgenesis syndrome (TDS) hypothesis[[75]](#endnote-75), in utero endocrine disruptor exposure can lead to reduced testis function in the adult, including reduced semen count. This, in turn, adds to the risks of PFCs in developmental toxicity.   
The mechanism for the endocrine-disrupting activities of PFCs has been discussed in 2007, evaluating PFOS, PFOA and FTOHs using vitellogenin (VTG), a precursor protein used as a biomarker to human endocrine disruption, to assess estrogenic endocrine disruptive chemicals in a dose-dependent manner. The results suggested that the estrogenic effect of PFCs may be mediated by the estrogen receptor pathway.[[76]](#endnote-76)

Among the earliest toxic effects associated with PFCs was the inhibiting effect of perfluoro-n-decanoic acid (PFDA), significantly reducing thyroxine (T4) and triiodothyronine (T3) thyroid hormone levels[[77]](#endnote-77). Since then, multiple studies have inspected the risks of PFCs on the thyroid gland. The thyroid gland is one of the largest endocrine glands in the body, and the hormones it produces are responsible for the regulation of metabolism, protein synthesis and oxygen consumption in all cells[[78]](#endnote-78). In 2010, an epidemiological study in the U.S. found evidence of enhanced potential risks of PFCs and the thyroid function, where higher concentrations of PFOS and PFOA in serum were associated with thyroid disease[[79]](#endnote-79).

The mechanism for this effect of PFCs is still not studied thoroughly enough for a decent hypothesis; however, evidence suggests that the human thyroid hormone transport protein transthyretin (TTR) is involved. A study from 2009 suggested that competitive binding of PFCs to TTR may occur, a binding which may lead to decreased thyroid hormone levels, as previously reported in animals[[80]](#endnote-80).

While the concentrations that showed developmental effects in rats are not relevant concentrations found in humans, the epidemiological studies discussed above, indicate that developmental or reproductive toxicity of PFCs pose an important potential risk for the human population.

Hepatotoxicity  
As mentioned in the Exposure section, many PFCs may accumulate in the liver of humans and rats. It is therefore not unthinkable that some effects of PFCs must occur there as well. Increased liver weight was among the first observed adverse effects in 1978[[81]](#endnote-81), and later confirmed by several other studies and other PFCs37. Following the increased liver weight, more research was conducted on the effects on the liver. An increase in hepatocellular adenomas at a high dose of PFOS was found in a 2-year bioassay in rats performed by the 3M-company, which was also observed for PFOA[[82]](#endnote-82),66. Perhaps not surprisingly, PPARα was suggested to be involved in the mode of action for rodent liver toxicity in 2003[[83]](#endnote-83), causing more investigation of the role of PPARα in PFC-induced toxicity mentioned in the developmental effects.

While these hepatotoxic effect studies have led to the evidence that serum and liver PFOS concentrations on repeated dosing are proportional to dose and cumulative dose, most adverse effects have been observed at high, human irrelevant concentrations of PFOS and PFOA. However, other PFCs have also shown hepatomegaly in rats, leading to the observation that the carbon chain length of PFCs accumulate differently in the liver, leading to different hepatic responses. This suggests that different PFCs may differ in their effects and the severity of these effects.66

Neurotoxicity  
Some anionic PFCs, like PFOS and PFOA, can cross the blood-brain barrier, which led to the detection of PFCs in the brain of rodents. While the levels were generally low (+/- 5% of liver concentrations) it was noted that at higher concentrations of PFOS (20 mg/kg/day), the permeability through the blood-brain barrier increases significantly, inducing a relatively high accumulation of PFOS in the brain. This increases the likelihood of adverse effects of PFCs in the brain at higher concentrations47.   
In 2004, developmental neurotoxic effects of PFOS were found in rats, where pups became pale, inactive and moribund, and all died soon afterwards, at a maternal exposure of 10mg/kg PFOS. Survival rate only increased to 50% at 3mg/kg; however, this is still high compared to human values[[84]](#endnote-84). Single oral exposure of PFCs did not show any neurobehavioral effects, as observed in a study of PFOS and PFOA in rats; not even up to the sublethal, largely irrelevant doses of 500 mg/kg PFOS and 1000 mg/kg PFOA11.

In a later study however, neurotoxic effects were indeed found at lower concentrations; in this case, a daily exposure to the neonates themselves was used. Exposure to 1.4 or 21 µmol/kg bw/day, showed persistent, irreversible disturbances in spontaneous behaviour, like locomotion, rearing and other activity variables of the adult mice; both hyperactivity and hypo activity were observed. The same study attempted to assess the mechanism behind these effects, and found that the susceptibility of the adult cholinergic system was affected by PFOS and PFOA, through altered responses to nicotine. This system and its neurotransmitter, acetylcholine (ACh), is one of the major transmitter systems in the brain, and involved in the motor division of the nervous system. Nicotinic ACh receptors are mainly found on muscle end plates, and this may be the pathway through which PFCs may cause these effects.[[85]](#endnote-85)

Further assessment of the involved mechanism of these effects were done by the same authors. In a study assessing neuronal protein levels in neonatal mice, 21µmol PFOS and PFOA /kg body weight (equal to 11.3 and 8.70 mg), were found to cause a significant increase of the proteins CaMKII, GAP-43 and synaptophysin in the hippocampus. The latter protein was also found to be increased in the cerebral cortex, and PFOA increased the tau protein in the hippocampus as well. All named proteins, altered by these PFCs, are important in normal brain development. In rodents, the development of the brain occurs after birth; exposure to PFOS and PFOA in the neonatal stage altering these proteins can therefore be involved in the mechanisms behind the observed behavioural effects.[[86]](#endnote-86)  
This proposed mechanism was further substantiated in 2010, where rats prenatally exposed to PFOS were found to have altered mRNA levels of synaptic vesicle associated proteins, including synaptophysin.[[87]](#endnote-87)  
However, other sources suggest that thyroid hormones are involved in these neurological developmental effects. Since thyroid hormones have a crucial role in human neurodevelopment[[88]](#endnote-88), and as mentioned above are potentially affected by PFCs, this is a valid hypothesis. However, a recent study did not find statistically significant associations between several PFCs with thyroid hormones in human serum[[89]](#endnote-89). While this does not reject the hypothesis that thyroid hormones are involved in neurological effects of PFCs, currently, the involvement of synaptophysin and other proteins remains more probable.

Finally, an epidemiological study was performed in the US in 2010, evaluating the relationship between exposure to PFCs and ADHD in children aged 12-15 years. Of the 571 children involved in the study, 48 were reported to have been diagnosed with ADHD by a doctor or healthcare professional. In all children, levels of several PFCs were measured in serum samples. Adjusted odds ratios (OR) of this study revealed significant associations between an 1µg/L PFOS, PFOA and PFHxS and ADHD.2

Carcinogenicity, DNA damage

As can be concluded from the toxic effects already named, PFCs are potential carcinogens; PFOS has been shown to induce tumours of the liver and thyroid and mammary glands[[90]](#endnote-90). In this study, the NOAEL was considered to be 0.5 ppm in male rats, and 2 ppm in female rats; the LOAEL 2 and 5 mg/kg bw for males and females respectively65. Next to PPARα, the potential carcinogenicity of PFCs are also observed through other mechanisms.

A study from 2009 assessed the potential cytotoxicity of PFOS and PFOA in Hep G2 cells. Both PFOS and PFOA were observed to induce production of Reactive Oxygen Species (ROS), dissipate the mitochondrial membrane potential and induce apoptosis of these cells. While this does not give a potential mechanism for carcinogenicity, a proposed mechanism for this cytotoxicity was given; PFCs could overwhelm the homeostasis of antioxidative systems.[[91]](#endnote-91)

In a study from 2010, the genotoxicity of PFOS and PFOA were assessed *in vivo* for DNA damage, using a comet assay, in *Paramecum Caudatum*. In accordance to the previous study, both PFOS and PFOA were found to induce ROS production. PFOA, but not PFOS, was observed to potentially cause DNA damage at a alkali labile site in the DNA, since it was only observed at pH 13. However, inhibition of ROS did not abolish the PFOA-induced DNA damage, suggesting that a different mechanism may cause this effect.[[92]](#endnote-92)

In contrast to this study, PFOS and PFOA did not show any DNA damage in Hep G2 cells in a different study from 2010, not even at alkali labile sites; while ROS production was observed. Only perfluorononanoic acid (PFNA) was observed to induce a modest increase in DNA damage, at a cytotoxic concentration level; however, this was not related to ROS generation.13  
In conclusion, ROS-formation has been observed in several studies, even in cell lines representing the human liver. While some studies report DNA damage, this has not been observed yet in relevant human situations. ROS production may still be a potential mode of action through which PFC carcinogenicity is caused, but more research is needed to further investigate this.

# Discussion

Before attempting to assess the relative risks of the current PFC exposure to humans, it is important to realise that, although several of the studies discussed in this paper report many effects of PFCs in animals, most have not been observed in humans, not even in the occupationally exposed group. While this does not by far suggest that these effects are absent in humans, it is an important factor when converting the effects found in animals to a relative risk for humans. Some effects however, like the immunotoxic effects, have not yet been studied in humans as far as I am aware. Furthermore, it may not be assumed that the occupational concentrations found as of yet are the highest concentrations to be found for these compounds.

Since most of the studies covering PFC effects in animals report those effects as grams per kilogram body weight per day, it would be convenient to have clear exposure data in those terms for humans as well. However, EFSA’s latest human exposure data did not take other sources than dietary sources into account, and as discussed earlier, other sources contribute significantly to the total human PFC exposure as well. Therefore, the exposure levels reported by Fromme et al. (2009) for the general Western population will be used7. This study included other sources of exposure and found a median of 1.6 ng/kg bw/day for PFOS and 2.9 ng/kg bw/day for PFOA in adults, with high exposure 8.8 ng/kg bw/day and 12.6 ng/kg bw/day for PFOS and PFOA respectively. These PFCs are most discussed in the effect and exposure studies, and have also been reported repeatedly as the highest found concentrations of human PFC exposure. Other PFCs can therefore be considered to have a lower daily intake, unless otherwise stated.

For the occupationally exposed, only serum levels were found to give an indication of the exposure levels to PFCs. To give an approximation of the daily occupational exposure, Western serum levels and their daily exposure levels may be compared to the occupational serum levels. PFC serum levels for the general western population were also summarized in Fromme et al., giving an average of 15.3 µg/L for PFOS and 5.5 µg/L for PFOA, and mean western occupational exposure levels 950 µg/L PFOS and 2630 µg/L PFOA (based on the latest measurements). Comparison with the serum levels and daily exposure of the general population gives an estimated mean occupational daily exposure levels, 99.3 ng/kg bw/day for PFOS and 1386.7 ng/kg bw/day for PFOA. These estimations will be used as occupational exposure reference.

For ‘converting’ rodent NOAEL to human NOAEL, the general rule of thumb gives a 10-fold increase in risk for interspecies differences, and another 10-fold increase for the most sensitive humans. In this case, however, another increase factor is used in converting rodent to human levels because, as mentioned earlier in this report, rodent PFC half-life (5.68 days for PFOA, 7.5 days for PFOS) was comparatively much faster than reported in humans (4.4 ± 3.6 years for PFOA vs. 8–9 years for PFOS, Olsen et al. 2007). Excretion of PFOA has also been reported to be high in rodents (Lin Cui et al., 2010), where 24.7–29.6% of the oral dose was excreted through urine and faeces, while for PFOS, the excretion amounts were only 2.6–2.8%. This supports the fact that the accumulation for PFOA is generally lower than for PFOS. In humans, no significant excretion of PFCs were found. Therefore, a 120-fold increase in risk will be used to convert the PFOA animal NOAEL to human NOAEL, and a 105-fold increase for PFOS, where not otherwise specified. These values are estimations by the author, to cover these extra risk factors.

## Relative toxic effects of PFOS

As the only PFC to be incorporated in the POP list under the Stockholm Convention, PFOS is often reported as the most potentially toxic compound within the PFCs16. In the immunotoxic subchapter, a 50% increased mortality rate due to the Influenza A virus was found at 5 µg PFOS/kg bw/day in rats, and even 75% increased mortality for 25 µg/kg bw/day61. Conversion to human values with the determined factor of 105, the lowest value equals 47.6 ng/kg bw/day, well within the occupationally exposed. While decreased immune response is not a life-threatening effect in normal cases, it may increase the effect of for instance influenza in humans as well as rodents. With the decrease of the immune response dose-dependent of the PFOS concentration, this suggests that the higher levels among the occupationally exposed, may have even bigger immunotoxic effects in those cases. Since immune response is not an effect studied in the occupational or general human population, this may be a prominent effect of PFOS exposure. However, since this study does not provide a potential mechanism of action, it has to be determined whether this is a mode of action relevant to humans as well.

A potential mechanism lies in the observation that reduced IgM levels were found in mice due to PFOS exposure, at levels relevant at the previous concentrations as well: 1.66 µg/kg/day and 16.6 µg/kg/day for males and females respectively60. B-cells were proposed as a potential target in this study.

Human immunological data after PFOS exposure needs to be obtained to provide a clear view on the risk of PFOS on immune response, but the levels at which it occurs in mice suggest that this may be a prominent effect.

In rodents, several developmental and reproductive toxicities have been found in combination with PFOS exposure, though not at such alarmingly high levels as the immunotoxic effects. Developmental toxicity was primarily studied as effects on offspring after maternal exposure, or neonatal exposure to the pups themselves. Lowest developmental NOAEL reported to our knowledge was found to be 0.1 mg/kg bw/day, with reduced pup body weight as endpoint66. Visceral and external anomalies, delayed ossification and skeletal variations where observed at higher concentrations, with a NOAEL of 1 mg/kg bw/day. Conversion into human NOAELS gives 0.95 µg/kg bw/day for reduced weight, and other developmental effects at 9.5 µg/kg bw/day. Both these values are outside the general population exposure, but inside some levels found in occupational exposure, marking them as a potential risk for humans. However, this potential risk is reduced with the outcomes of epidemiological human studies performed on developmental toxicity. Both occupational and general population subjects did not show significant associations between PFOS and developmental toxicity. The interspecies differences may be the reason for this difference in effects. However, the evidence from the rodent studies still suggest possible effects in this area; therefore, more research is needed to determine whether developmental effects are among the potential toxic effects in humans after PFOS exposure.

Evidence for potential reproductive toxicity was most prominent in the epidemiological studies, and provides the most convincing argument, with reduced sperm count and reduced reproductive hormone levels reported levels within the exposure for general population. While the measures of effect were not significant enough to have a high priority within all found effects, it still remains to be studied whether this effect is more prominent, and perhaps more dangerous, in the occupationally exposed. Thyroid hormones were given as a potential mechanism of action through which PFCs might cause these effects, and further investigation is needed in this area to provide a clear view of the reproductive risks involved.

Hepatotoxic effects found after PFOS exposure mostly included hepatocellular tumours, which is therefore a carcinogenic effect as well, and among the effects with the highest perceived priority in risk assessment. Lowest reported NOAEL in this case was 0.5 mg/kg bw.

Single oral exposure of 0.75 mg PFOS/kg bw caused neurobehavioral effects in mice, including hyperactivity. Converted, 7.5 µg/kg bw falls well into the occupational exposure to PFOS, and therefore increases the potential risk for neurotoxic effects in humans. The potential risk is increased with the positive correlation found between PFC serum levels and ADHD in children; combined with the previous study, this may be a prominent effect that can be associated to PFOS exposure. The proposed involvement of synaptic proteins needs to be assessed to give further clarification on this effect, but since the effect involves children at levels found in the occupational population, this is an important effect of PFCs, especially since other effects associated with differences in synaptic proteins may be found.

Another potential effect of PFOS in humans may be effects caused by ROS production; however, no specific levels have been found to estimate the human exposure at which this may happen, and no associated DNA damage has been found. Further information is needed to assess if the ROS production caused by PFOS may have a potential effect in animals, and eventually humans.

Relative toxic effects of PFOA

The effects for PFOA, as well as other PFCs, are, as suspected, largely comparable to the effects found for PFOS, only occurring at different exposure levels. The immunotoxic effects are among those comparable, but as mentioned in the Effects chapter, potentially caused by a different mechanism: PPARα. Reduced IgM levels occurred for this PFC at 3.75 mg PFOA/kg bw/day (LOAEL), which equals a human exposure level of 31.3 µg/kg bw/day60. This does not occur even at the highest general population levels, but are just within some levels found among the occupationally exposed. However, as mentioned in Effects, PPARα (which is assessed to be the prominent mechanism for this effect in rats) is ten times less expressed in humans. If this reducing factor is taken into account with the conversion, only the most extreme occupational exposure levels fall within the effect range. Including the increased sensitivity of PPARα reduces the human risk further; however, it may still be the case that the part of the mechanism least responsible for the effect in rodents, may be much larger in humans, since this has not yet been evaluated. Therefore, like PFOS, the mechanism for this effect has to be further investigated, and human epidemiological data is needed to assess the human risk appropriately.

Developmental effects for PFOA are found to occur at higher levels than for PFOS. Highest concentration showing developmental effects (mainly reduced foetal body weight) was found to be 5 mg/kg bw/day. Since the same mechanism (PPARα) has been proposed for these effects, the same conclusion can be drawn as for the immunotoxic effects66.

Reproductive, hepatological and neurological toxicity was fully comparable for PFOS in the epidemiological studies, since the epidemiological studies reported PFOS and PFOA as the most abundant PFCs in serum associated with the effects. However, it may be that PFOS or PFOA are individually most important in these effects; further investigation of the potential mechanisms is needed here as well. Neurotoxicity was also found to be comparable to the PFOS effects in animals, only occurring at higher levels.

The DNA damage found for PFOA at 100µM in *Paramecum Caudatum* is reason for further investigation of this fact; but the contradicting evidence in human Hep G2 cells lessens the potential risk from this effect92. Since the effect can have drastic effects however, further investigation is needed, especially since the proposed mechanism of ROS might not be valid.

## Other PFCs & mixtures

While the large majority of the studies focussed on PFOS or PFOA, the chemical similarity some PFCs have with these compounds suggest that they may have similar effects as well, perhaps even more intense effects. The studies reporting some toxic effects for other PFCs support this fact, but since the levels for these PFCs are not in the ranges of PFOS or PFOA, their investigation is less urgent. Precursor PFCs like FTOH and POSF have been investigated mainly because of their metabolism into PFOA and PFOS, but these are found in much lower levels in humans, and did not show effects in any degree as big as either PFOS or PFOA.

Since multiple PFCs have been found in humans, it is important to know whether the combination of multiple PFCs have a different effect, or perhaps a synergistic effect. As seen in the Effects chapter, PFCs sometimes have similar, sometimes totally different mechanisms of action for the same effect. Especially the latter may have synergistic effects, since the PFCs are not competing against each other in the same mode of action. However, this has not been investigated properly as of today. Especially PFOS and PFOA, the PFCs found in highest concentrations, should be investigated for effects due to a combined exposure. In perspective, the epidemiological human effects that have been found follow the total human exposure to PFCs, and no tumorgenesis or other more extreme effects have been reported due to exposure to PFC mixtures.

## Risks of PFCs

With the results of the many studies conducted to assess the effects of PFCs, it is clear that there is indeed reason for concern for these compounds. Epidemiologic evidence provide the most convincing argument for this, but the animal studies suggest that there may be a lot more, less outwardly visible, effects associated with this exposure, even at the levels found among the general population. The epidemiological and immunotoxic effects have not been taken into account when EFSA determined its TDI for PFOS and PFOA. With the new data available on their effects on humans, these TDI should be re-established.

Measures of decreasing exposure

While PFOA and especially PFOS production has been abandoned by most large production companies, precursors of these compounds are still being produced today. Exposure to PFOS and PFOA from precursors is relatively small, but the effects found for these PFCs are important enough to reconsider producing these precursor PFCs as well. When EFSAs TDIs for PFOS and PFOA are re-established with the new data available, general population exposure data may be already exceeding the new TDI values. Whether exceeding or close to, this is another stimulating factor in trying to decrease PFC exposure levels.

Furthermore, before producing other PFCs as alternative, it is wise to assess them for effects now found for PFOS and PFOA as well, to prevent that the same will be found for these compounds in the following years. Tracking PFOS and PFOA, but especially other PFC serum levels in humans may be productive as well, to see if the PFOS and PFOA levels indeed decrease with time, or if there is an alarming increase of a certain different PFC. Some studies have provided suggestions to decrease PFC levels in humans actively. A decline in serum levels of all PFCs was found after cholestyramine (CSM) therapy51. CSM is a bile acid sequestrant, which can bind bile to prevent reabsorption. Since enterohepatic circulation has been suggested to be applicable to PFCs, this therapy is a good method in theory; however, further investigation of this method is required to fully investigate its potential.

## Further investigation

Subjects for further investigation have been suggested throughout this report, but not yet clearly prioritized. In the writers opinion, potential effects from epidemiological studies, like reduced fertility and neurotoxicity (ADHD) are evidence enough that these effects deserve a thorough investigation, so steps may be taken among the high exposed to attempt to prevent the effects from taking place. Immunotoxic effects that were found at relevant exposure levels after conversion are an important subject of investigation as well, especially since these effects may already be evident among the occupationally exposed. Epidemiological data is needed to take steps toward reducing these effects as well, or steps preventing the effects of causing disability. Evidently, the other potential effects deserve equal attention, but are found at levels low enough, or have *not*been found in any human case, that this does not have priority.

The CSM therapy is one of the first suggested methods to lower PFC levels in humans actively. This method will be useful, but only relevant for the extreme occupationally exposed that show significant effects due to PFC exposure. If a more practicable method can be found, it can be applied to the general population as well.

Furthermore, since multiple PFCs have been found in human serum, it is important to characterize the dangers (or lack thereof) in being exposed to multiple PFCs; do they enhance the effect?

In conclusion, the large perceived risk for human PFC exposure is indeed substantiated. While no direct adverse effects have been found in humans so far, the degree of effects that have been found, are reason enough for concern.

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# List of abbreviations

|  |  |
| --- | --- |
| ACh | Acetylcholine |
| ADHD | Attention Deficit Hyperactive Disorder |
| CAR | Constitutive androstane receptor |
| CSM | cholestyramine |
| EFSA | European Food Safety Authorisation |
| FTOH | Fluorotelomer Alcohols |
| IgM | Immunoglobulin antibody |
| LOAEL | Lowest Observed Adverse Effect Level |
| NOAEL | No-Observed Adverse Effect Level |
| OECD | Organisation for Economic Co-operation and Development |
| PAP | Perfluoroalkyl phosphonates |
| PFC | Perfluoroalkyl Chemicals |
| PFDA | Perfluoro-n-decanoic acid |
| PFHxS | Perfluorohexane sulfonic acid |
| PFNA | Perfluorononanoic acid |
| PFOA | Perfluorooctanoic acid |
| PFOS | Perfluorooctane sulfonate |
| PFOSK | Potassium perfluorooctane sulfonate |
| POSF | Perfluorooctane sulphonamides |
| PPARα | Peroxisome Proliferator-Activated Receptor Alfa |
| ROS | Reactive Oxygen Species |
| TDI | Tolerable Daily Intake |
| TDS | Testicular Dysgenesis Syndrome |
| TTR | Transthyretin |
| VTG | Vitellogenin |

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