PFAS Scientific Advisory Panel

This draft paper forms part of the literature reviews for the development of the Panel's second report: An assessment of the impact on PFAS exposure on health.

PFAS in the human body

Exposure routes and pathways

The presence of organic fluorine in human blood was first detected by the dental researcher Donald Taves in the 1960s (Taves, 1968). In 2024, it is now known that virtually all humans on the planet have certain PFAS in their bodies at low microgram per litre levels.(Sunderland et al., 2019). Human blood concentrations of long-chain perfluoroalkyl acids (PFAAs) such as PFOS, PFHxS and PFOA, peaked in the late 1990s/early 2000s in the general population of most countries and have declined since the 3M industrial phase-out of long-chain PFAS chemistries (the phase-out was between the years 2000 and 2002).(Sunderland et al., 2019).

For humans, exposure to PFAS occurs by three routes, namely; ingestion, inhalation, and dermal absorption, as described below. Some special exposure routes for prenatal stages and infants are discussed further down this section.

- Ingestion exposure of PFAS for humans occurs via consumption of contaminated food, water, and other beverages. Exposure by ingestion also occurs via the intentional or inadvertent non-dietary ingestion of soil, dust, or chemical residues on surfaces or objects that are contacted via hand-to-mouth or object-to-mouth activity (especially important for young children)
- Inhalation exposure of PFAS for humans results from breathing air that is contaminated with fine particulate matter or gas-phase volatile PFAS. Individuals can be exposed via the inhalation route during a variety of activities outdoors and indoors. Individuals indoors could also be exposed to outdoor air contaminants that infiltrate the indoor environment
- Dermal exposure of PFAS by humans results from skin contact with PFAS-containing consumer products and contaminated environmental media, including: water (e.g., during bathing, washing, swimming), bottom sediments in surface waters (e.g., while wading, fishing), outdoor soil or dust (e.g., during recreational and gardening activities), and indoor dust that has settled on carpets, floors, clothing, counter tops, or other surfaces

The relative importance of the many different PFAS exposure pathways (e.g. dietary ingestion, versus dust ingestion, versus gaseous inhalation, etc.) has been estimated in multiple studies (e.g. (Gebbink et al., 2015)) and these have been reviewed in the literature.(De Silva et al., 2021; Sunderland et al., 2019). There is general agreement that for PFOS, PFHxS and PFOA, and other long-chain PFAAs, dietary intake is the dominant exposure pathway for the general population compared to air inhalation or dermal contact.(Sunderland et al., 2019). Furthermore, it is known that protein-rich foods such as eggs, meat and fish make the largest contribution to dietary exposure for the long-chain PFAAs.(Vestergren et al., 2012).

In areas such as the plume area on Jersey where drinking water levels of PFAS have been substantially elevated due to contamination with AFFF, drinking water ingestion is the dominant exposure pathway for PFOS, PFHxS and PFOA.(Li et al., 2018) (Xu et al., 2021) (AECOM, 2016). In some areas (e.g. in Oakey, Australia) where contaminated water has been used for watering

livestock or irrigating crops, substantial additional exposure can be derived from consumption of local produce.(AECOM, 2016).

A further complication to understanding exposure to PFAS is that humans can be exposed to the so-called precursors, which are substances that transform to PFAAs either in organisms (including in the human body) or in the environment.(Vestergren et al., 2008). Precursors are sometimes, but not often, measured when analysing exposure media for PFAS, which means that human exposure to certain PFAS is likely underestimated. Although these precursors certainly make an additional contribution to human exposure to PFAS, the extent of this contribution, and which precursors contribute, has been debated among scientists.(Vestergren et al., 2008).

Toxicokinetics is the study of the absorption, distribution, metabolism, and excretion of a chemical within an organism. Within the following sections we review the current knowledge of toxicokinetics of PFAS with particular focus on PFOS, PFHxS and PFOA. The chemical structure (e.g. chain length, functional groups, branching of the carbon chains) all impact the toxicokinetics. An exhaustive review of toxicokinetics for all PFAS is not possible here and we therefore aim to summarize the key points.

Absorption of PFAS into the body

The absorption behaviour of PFAS has been studied in laboratory animals (e.g., rodents and monkeys),(Gannon et al., 2011) but not typically in humans due to ethical considerations. Absorption of PFOS, PFHxS and PFOA via ingestion has been determined in animal experiments and it has been shown that 66–100% is absorbed into the body.(OECD, 2002, OCA.0029.0001.0063) (Gannon et al., 2011) (Sundström et al., 2012) (Kudo & Kawashima, 2003). Animal studies also suggest that PFOA is easily absorbed via the lungs.(Kennedy et al., 2004) Due to the high absorption of PFAS in animal studies, the absorption of PFOS, PFHxS and PFOA is typically set to 100% as a conservative assumption in human exposure modelling studies.(Trudel et al., 2008) (Vestergren et al., 2008) (Gebbink et al., 2015). These reported absorption efficiencies for PFAS are higher than for other well studied hydrophobic organic contaminants (such as polychlorinated biphenyls).(Schlummer et al., 1998).

Experimental studies on dermal absorption are scarce. *In vitro* exposure studies using rat and human skin replicates conducted by Fasano et al. in 2005 have shown that PFOA can penetrate the skin, albeit with a low absorption efficiency (1.44% and 0.048% of PFOA absorbed through the rat and human skin, respectively, after 48 h of exposure).(Fasano et al., 2005). A more recent study by Franko et al. in 2012(Franko et al., 2012) suggested that PFOA is readily absorbed by human and mouse skin, but on close examination this only occurred at unrealistically low pH (2.25) when PFOA was in its acidic neutral form. Franko et al., admitted in their study that PFOA will most likely be ionized on the skin surface. Interestingly, Franko et al. achieved similarly low absorption as in the 2005 Fasano study when PFOA was in its ionized form. These observations are consistent with the pH-partition hypothesis,(Shore et al., 1957) which suggests that the passive transport of charged chemical species across biological membranes is small, owing to their poor solubility in lipids.

Abraham and Monien (2022)(Abraham & Monien, 2022) investigated the dermal absorption of $^{13}C_4$-perfluorooctanoic acid ($^{13}C_4$-PFOA) mixed into a sunscreen that was applied on the skin of a volunteer. The blood concentrations of $^{13}C_4$-PFOA were monitoring over 115 days after application. After application, $^{13}C_4$-PFOA blood levels increased continuously with a maximum level measured 22 days after application. The fraction absorbed was estimated to be 1.6 % of the dose, which is still relatively low compared to ingestion and inhalation.

Unfortunately, there are a lack of dermal contact studies for PFOS and PFHxS, but given their similar properties to PFOA, it seems reasonable to assume that absorption of these PFAS is also low through animal or human skin. In exposure modelling studies,(Gebbink et al., 2015) it is typically assumed that dermal absorption is <1% for PFOS, PFHxS and PFOA based on animal experiments for PFOA.

Distribution of PFAS in the human body

As discuss above, PFAS are readily absorbed into the human body via ingestion and inhalation routes, and to a much lesser extent via the dermal route. Once absorbed, PFAS are distributed throughout the body both in the blood and into extravascular tissues (i.e. in tissues other than the blood vessels).(De Silva et al., 2021). In the tissues, PFAS bind to both phospholipids and proteins (e.g. in the blood serum to a protein called human serum albumin (HSA) and also to fatty acid binding-proteins (FABPs)).(De Silva et al., 2021). It has long been considered that the blood, liver, and kidneys are the main tissues of distribution for PFAAs in humans.(De Silva et al., 2021) A recent study measured the distribution of PFAAs between liver, kidneys, lungs, spleen, brain and the whole blood of 19 diseased adult humans.(Nielsen et al., 2024). The highest extravascular tissue PFAA concentrations were in the liver, lungs and kidneys with concentrations in the brain and spleen being much lower. PFOS was particularly high in the liver compared to other organs. PFHxS was the only PFAA that showed higher concentrations in the kidney than in the liver, while PFOA was higher in the lungs than in the liver. Extravascular PFAA tissue concentrations were generally well-correlated with those in the blood and in reasonable agreement with the partitioning predicted by theoretical models. The differing accumulation of PFAAs in various tissues has been associated with their relative binding affinities to phospholipids and proteins (e.g. HSA and FABPs).(De Silva et al., 2021). Higher binding affinities to HSA and FABPs have been observed for long-chain PFAAs compared with short-chain PFAAs.(Fischer et al., 2024).

Metabolism

PFAAs are not chemically modified or metabolized within the human body due to their chemical inertness.(Wang et al., 2017). However, and as mentioned above, there are precursor substances which can metabolize to form PFAAs within the human body.(Vestergren et al., 2008).

Elimination

Long-chain PFAAs are primarily eliminated slowly via urine(Cui et al., 2010) with some elimination also expected via the faeces.(Ma et al., 2020). Women have some additional elimination pathways discussed below. Previous studies have shown relatively long human elimination half-lives (the time it takes for the amount of PFAS in the body to be reduced by 50 percent) of long-chain PFAAs. For example, average serum half-lives for PFOS, PFHxS and PFOA of 2.9-8.5, and 2.9-7.3, 1.8-3.5 years, respectively, have been reported in different studies.(Xu et al.) (Li et al., 2018) (Olsen et al., 2007). Shorter human serum half-lives have been observed for short-chain PFAAs (e.g. perfluorobutane sulfonate (PFBS) of 44 d, and perfluoropentane sulfonate (PFPeS) of 230 d).(Xu et al.) However, elimination half-lives are not only dependent on the length of the perfluoroalkyl chain. The head group (sulfonate versus carboxylate) and degree of branching in the perfluoroalkyl chain also impacts elimination rates of PFAAs.(Xu et al.)

Some of the differences in elimination half-lives for individual PFAAs between studies can be due to differing exposure histories. For example, the half-lives in retired fluorochemical workers (PFOS average elimination half-life of 8.5 years)(Olsen et al., 2007) are much higher compared to residents of contaminated communities who have received historical exposure via contaminated drinking

water (PFOS half-life of 2.9 years).(Xu et al.) Elimination half-lives have also been reported to be highly variable between individuals and the reasons for this variability remain unknown.(Xu et al.)

Women between 12.5 and 50 years old have been shown to have lower blood serum levels of PFOS than men and this is thought to be primarily because women eliminate PFOS (and other long-chain PFAAs) more readily due to their additional elimination pathway of monthly menstrual blood loss.(Upson et al., 2022) Women can also eliminate PFAS from their bodies to some extent during pregnancy, child birth and breast feeding.(Wong et al., 2014).

The long elimination half-lives of long-chain PFAAs in humans is thought to be due to their ability to be reabsorbed by organic anion transporters (OATs) in the kidneys and to a lesser extent due to their uptake from enterohepatic circulation.(Niu et al., 2023). Therefore, renal elimination/reabsorption in the kidneys is the most critical process in determining the elimination of PFAAs. However, the interactions between PFAAs and the renal transporters (i.e. OATs) are not fully understood.(Niu et al., 2023). The active transport processes differ between different PFAAs and possibly also can explain differences in elimination between individuals. It is further possible that kidney disease can alter the expression of the renal transporters and further influence renal elimination of PFAS.(Niu et al., 2023). However, little is current known about how altered kidney function affects elimination rates of PFAS; this is an area of ongoing research.

Transmission

In-utero transfer
It has been shown that PFAS can pass the placental barrier from mother to child during pregnancy.(Beesoon et al., 2011; Gützkow et al., 2012; S. Kim et al., 2011; Liu et al., 2011; Monroy et al., 2008; Pan et al., 2017) These studies have measured serum concentrations of PFAS in maternal and cord, or new-born serum samples directly after birth. The transplacental transfer efficiency (TTE) can be calculated for each individual mother-child pair as the quotient of foetal and maternal blood or serum concentrations, and these data have been reviewed and summarised.(Winkens et al., 2017). TTEs vary significantly within and between the different studies. Strong positive correlations between maternal and foetal serum concentrations have generally been observed for PFOS, PFOA and other long-chain PFAAs. A comparison of TTEs for different PFAAs suggests a negative relationship with the perfluoroalkyl chain-length and a slightly lower transfer efficiency for sulfonates compared to carboxylates.

Breastfeeding

PFAS have been measured in human breast milk and they are thus excreted through lactation.(Kärrman et al., 2007; S.-K. Kim et al., 2011; Liu et al., 2010; Llorca et al., 2010; So et al., 2006; Sundström et al., 2011; Tao, Kannan, et al., 2008; Tao, Ma, et al., 2008; Thomsen et al., 2010; Völkel et al., 2008). Breastfeeding is therefore an additional elimination pathway for breastfeeding mothers. Breastfeeding gradually reduces the mothers' concentration of PFOA and PFOS in serum and breast milk.(Fei et al., 2010; Mondal et al., 2014; Thomsen et al., 2010). For PFOA and PFOS, a common 3% reduction has been observed per month of breastfeeding, whereas for PFNA and PFHxS a 2 and 1% reduction, respectively, per month of breastfeeding has been observed.(Mondal et al., 2014). This is in accordance with the finding that primiparous women have the highest loads of PFOS and PFOA in their breast milk.(Fei et al., 2010; Tao, Kannan, et al., 2008).

Breastfeeding is the dominant exposure pathway for PFAS for breastfeeding infants.(Mogensen et al., 2015; Verner et al., 2016). Early-life longitudinal studies have shown a consistent increasing trend of both PFOS and PFOA during the first six months of life and this has been attributed to intake via

breastfeeding.(Fromme et al., 2010; Gyllenhammar et al., 2016; Mogensen et al., 2015) (Koponen et al., 2018). The level of exposure to an infant depends on a number of circumstances, some of which include the level of PFAS in the mother, the amount of PFAS that transfers to her breast milk, and the duration of breastfeeding.(Winkens et al., 2017).

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