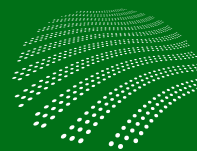


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TECHNICAL REPORT NO. 42

A human health review of PFOS and PFOA

Cooperative Research Centre for Contamination Assessment and Remediation of the Environment, Technical Report series, no. 42

August 2016

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CRC for Contamination Assessment and Remediation of the Environment

Technical Report no. 42

A human health review of PFOS and PFOA

August 2016



Executive summary

Perfluorooctanesulfonate (PFOS) and perfluorooctanoic acid (PFOA) have been identified as contaminants of emerging concern in Australia. PFOS and PFOA both comprise a perfluorinated carbon chain (or 'tail') that is both lipid and water repellent. The generic term perfluoroalkyl substances (PFAS) is used to describe the mix of straight- and branched-chain congeners that normally comprise the human exposure matrix. PFOS and PFOS-related substances have been used globally in many applications. These include aqueous film forming foams (AFFF), semiconductors, hydraulic fluids, photolithography, as a key ingredient in Scotchgard brand fabric treatment products, grease repellents for packaging, surface treatments for rugs and carpets, paper and packaging, coatings and coating additives, industrial and household cleaning products, pesticides and insecticides. Both PFOS and PFOA are known to be persistent, bioaccumulative and potentially toxic, and proven to exist at a number of sites, particularly where AFFF fire-fighting foams have been used, in concentrations of potential concern.

Large differences in the half-lives of PFOS and PFOA have been observed between animals and humans. For animals, reported half-lives range from 2 hours to 150 days. The half-lives for humans have been reported to be in the range of 2~9 years. Based on epidemiological studies, we estimate that the mean half-lives for PFOS and PFOA are 5.5 years and 3.2 years, respectively.

Numerous adverse health outcomes have been observed in animal studies following chronic low dose exposures including harm done to the liver, gastrointestinal tract, thyroid hormone levels, as well as immunological, reproductive and developmental problems. Animal studies at low levels of exposure (<1 mg/kg/day) suggest moderate acute oral toxicity of PFOS/PFOA, with effects on the liver and gastrointestinal tract. No data are available for assessing acute toxicity in humans.

Epidemiological studies conclude that there is a weak positive association between serum PFOS/PFOA and increased serum cholesterol and uric acid levels. There are also a few inconsistent positive correlations with some health outcomes such as increased serum liver enzymes, or immune system effects. Statistically significant associations have been observed between PFOA exposure and kidney and testicular cancers. Most results are from cross-sectional analysis and therefore the data are insufficient to draw unambiguous conclusions about the effects of PFOS/PFOA in the progress of any particular disease. For some effects, 'reverse causation' cannot be ruled out, where the increased incidence of the effect under consideration is associated with a potentially greater accumulation of the PFAS.

Originally, this report was developed to recommend tolerable daily intake (TDI) values for PFOS and PFOA, at a time when there were no national TDI values available (early 2016). This version of the report does not recommend TDIs, and has been published for information only. The report refers to data from animal studies to estimate effects on human health in order to derive TDI values – while this introduces interspecies uncertainties, animal models exclude human variability factors (such as diet, drugs, infections, radiation and endogenous processes). An in-depth discussion of the issues was published as a peer-reviewed paper – see Dong *et al* (2017).

This report was completed in early 2016 to complement the CRC CARE work on developing PFAS guidance at a time when there was limited Australian human health advice on PFAS. The policy, scientific and political landscape has changed substantially several times since this work was completed, and it is strongly recommended that readers refer to the most up-to-date advice published by Food Standards Australia New Zealand (FSANZ) and the Commonwealth Department of Health, as well as any jurisdictional requirements. This report provides an overview of the international studies used in considering TDI values. It also recommends background intake levels for PFOS and PFOA in Australia, which may be useful when assessing multiple exposure pathways.

A recent study shows that the mean background for Australian serum concentrations for PFOS and PFOA are 10.2 ng/mL and 4.5 ng/mL, respectively. Several reports based on national surveys indicate a decrease in serum PFOS and PFOA concentrations from 2002 to 2011 in the Australian population. The total daily intakes for PFOS and PFOA are estimated to be 0.89 ng/kg/day and 0.50 ng/kg/day, respectively. The background exposure level is far below the TDI. In particular, the ratios of intake to TDI for PFOS and PFOA are estimated to be 0.006 and 0.0003, respectively, indicating that Australians are generally at a low risk of danger to their health from typical PFOS/PFOA exposures.

Abbreviations

AFFF	Aqueous film forming foams
APFO	Ammonium perfluorooctanoate
BAF	Bioaccumulation factor
BCF	Bioconcentration factor
BMDL	Benchmark dose modelling
BMF	Biomagnification factor
CSAF	Chemical-specific adjustment factor
EFSA	European Food Standards Authority
HED	Human equivalent dose
HQ	Hazard quotients
LC50	Median lethal concentration
LD50	Median lethal dose
LOAEL	Low observed adverse effects level
NOAEL	No observed adverse effects level
PFAS	Per- and polyfluoroalkyl substances
PFOA	Perfluorooctanoic acid
PFOS	Perfluorooctanesulfonate
PoD	Point of departure
RfD	Reference dose
TDI	Tolerable daily intake
TMF	Trophic magnification factor
UF	Uncertainty factor
UK COT	United Kingdom Committee on Toxicity
US EPA	United States Environmental Protection Agency

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1. Introduction

1.1. Project background

Perfluorooctanesulfonate (PFOS) and perfluorooctanoic acid (PFOA) have been identified as contaminants of emerging concern in Australia. These contaminants belong to the large group of chemicals referred to as per- and polyfluoroalkyl substances (PFAS) or fluorosurfactants. The term PFAS describes both fully fluorinated compounds which are resistant to degradation, as denoted by the per prefix, and partially fluorinated compounds such as fluorotelomers, including 6:2FtS and 8:2FtS.

PFAS are known to be persistent, bioaccumulative and potentially toxic, and are present in concentrations of potential concern at a number of sites. This is particularly the case where aqueous film forming foams (AFFF) have been used for fire-fighting. Industry and public awareness of the presence of PFOS and to a lesser extent PFOA is growing rapidly, with regular reporting of PFOS contamination in the news media. Concerns have been raised regarding the risk that PFAS contamination poses to the health of people who may be exposed.

In general, there is limited and incomplete information surrounding the occurrence, fate and toxicity of PFAS in Australia and Australian criteria for protection of human health have not been established. This makes it difficult to determine the potential risk that PFAS contamination poses.

More information about the toxicity of PFOS and PFOA has become available in recent years, with many jurisdictions now revising or formulating health-based guidance. Several reports recently published by international authoritative bodies provide detailed discussions about human exposures, dose-response relationships, and effects on human health (ATSDR 2015; Danish EPA 2015; US EPA 2016a; US EPA 2016b). A comprehensive literature review on the potential health effects of PFOS and PFOA has been prepared by Professor Brian Priestly (2015).

A consistent, practicable approach to the risk-based assessment of PFAS contamination is required in Australia. The aim of this project is to facilitate this requirement by developing human health toxicity criteria for PFOS and PFOA. The tolerable daily intake has been selected by enHealth (2016) and is adopted in this report. This report facilitates the development of additional information on background levels (e.g. daily intakes levels and hazard quotient) which are also required for the calculation of health toxicity criteria.

1.2. Approach

Although the toxicity database for PFAS is rapidly evolving, for this current effort we have summarised what is known about the health effects of PFOS and PFOA. This report provides information on the background exposure levels in Australian populations.

2. Properties of PFOS/PFOA

PFOS and PFOA are synthetic chemicals that are chemically and biologically stable and hence are persistent in the environment, and resistant to biodegradation, atmospheric photooxidation, direct photolysis, and hydrolysis (US EPA 2014). PFOS and PFOA can also be formed as breakdown products from related substances, by microbial degradation of precursor compounds, or as an end-product of biological metabolism (e.g. rainbow trout transform precursor perfluorinated acids into PFOS and PFOA) (CRCCARE 2014). Although the ultimate net contribution to environmental loadings of PFOS from individual PFOS-related substances cannot be easily predicted, any molecule containing the PFOS moiety could be a potential precursor to PFOS (UNEP 2006). It is possible that as PFAS are gradually phased out, precursor transformation may contribute significantly to the PFOS contaminant load (CRC CARE 2014).

Both PFOS and PFOA consist of an eight-carbon chain that is completely substituted with fluorine atoms – making it both lipid repellent (oleophobic) and water repellent (hydrophobic) – and a charged hydrophilic head (CRC CARE 2014). PFOS is a perfluoroalkyl sulfonate, with a sulfonic acid moiety forming the hydrophilic head, while PFOA has a carboxylic acid moiety and is often called C8 (Seow 2013). The stability of these PFAS is due to the strength of the carbon–fluorine bonds; each fluorine atom is shielded by three electron pairs, and the carbon atoms are shielded by the fluorine atoms (CRC CARE 2014).

PFOS and PFOA are moderately soluble and have long half-lives in water (41 years and 92 years, respectively) (CRC CARE 2014). They are persistent in groundwater and surface waters, although they have been found to partition from the groundwater column into organic matter rich sediments and soil particles due to their propensity to adsorb to organic carbon (US EPA 2014).

The vapour pressure for PFOS at 20 °C is 2.48×10^{-6} mmHg and for PFOA it is 0.017 mm Hg (US EPA 2014), so vaporisation appears to be of little concern. However, PFOS and PFOA can be transported long distances in the air because of their high atmospheric half-lives (114 days and 90 days, respectively) (US EPA 2014).

3. Sources and uses of PFOS/PFOA

PFOA- and PFOS-related substances have been used globally in many applications. These include aqueous film forming foams (AFFF), chromium plating, semiconductors, hydraulic fluids, photolithography, as a key ingredient in Scotchgard brand fabric treatment products, grease repellents for packaging, surface treatments for rugs and carpets, paper and packaging, coatings and coating additives, industrial and household cleaning products, pesticides and insecticides (CRC CARE 2014; Seow 2013; UNEP 2006).

PFOA is used in the production of other fluoropolymers, which are fire resistant, and oil, stain, grease and water repellent (US EPA 2014). PFOA is contained in trace amounts in Teflon™ (polytetrafluoroethylene) used on non-stick cookware, waterproof and breathable membranes for clothing, and in the aerospace, automotive, building/construction, chemical processing, electronics, semiconductors and textile industries (CRC CARE 2014; Seow 2013). PFOA may also be produced under certain conditions from the breakdown of some fluorotelomers such as 8:2 fluorotelomer sulfonate (8:2FtS) which is also used in stain, grease and water resistant surface treatment products, paints, coatings, cleaning products, fire-fighting foams or engineering coatings (Seow 2013).

Disposing of PFAS into sewers may result in the accumulation of PFAS in the biosolids of sewage treatment plants. Furthermore landfilling of products containing PFAS may result in contamination of groundwater in the vicinity of landfills.

Although the use of PFOS and PFOA in Australia has been largely phased out, legacy contamination issues remain due to the persistent nature of the chemicals. It is expected that most of the sources of PFOS and PFOA contamination noted above have existed in Australia, with the use of AFFF at fire-fighting training grounds being probably the most significant, and one that requires particular attention.

4. Background exposure in Australia

Human exposure to PFOS/PFOA can occur via multiple pathways. Potential pathways which may lead to widespread exposure include ingestion of food and water, use of commercial products, or inhalation from long-range air transport (ATSDR 2015). A national survey in Australia showed PFOS and PFOA detected in drinking water at levels of 0–15.6 ng/L and 0–9.6 ng/L with corresponding uptake rates estimated to be 0–11 ng PFOS/day and 0–13 ng PFOA/day (Thompson, Eaglesham & Mueller 2011). However, limited information for other pathways is available in Australia. For example, in Europe, fish and fishery products appear to be one of the primary sources of human exposure to PFOS (EFSA 2008). However, few data for PFOS/PFOA content in fish are available for Australia. Taking the lack of exposure information into consideration, daily intake for Australians is estimated by using biomonitoring information.

In 2002–03, 3802 serum samples were collected and analysed for PFOS and PFOA. The samples were collected from five different age groups, both genders, and from rural and urban regions in Australia (Kärman *et al* 2006). The mean concentrations for PFOS and PFOA were 20.8 ng/mL and 7.6 ng/mL respectively, and an increase in PFOS concentration with increasing age in both regions and genders was observed (Kärman *et al* 2006).

In 2006–07, 2420 serum samples were collected in southeast Queensland, and were pooled according to age. Across all pools, PFOS and PFOA were detected with mean concentrations of 15.2 ng/mL and 6.4 ng/mL respectively (Toms *et al* 2009). More recently, serum PFAS concentrations were determined in pooled human sera from 2008–09 (n=24 pools, representing 2400 individual samples) and 2010–11 (n=24 pools, representing 2400 individual samples) obtained from de-identified surplus pathology samples (Toms *et al* 2014).

Table 1 summarises biomonitoring information from the studies referred to above for PFOS and PFOA (Toms *et al* 2014).

Table 1. Hematologic biomarkers for PFAS exposure from Australian epidemiological studies

Data collected	Chemical	Range (ng/mL)	Mean (St.d) (ng/mL)	Median (ng/mL)
2002–03	PFOS	19.1–36.1	25.9 (4.7)	25.4
2006–07		5.0–28.5	15.2 (4.9)	14.8
2008–09		5.3–19.2	11.9 (4.6)	11
2010–11		4.4–17.4	10.2 (3.7)	9.4
2002–03	PFOA	7–14.5	10.2 (1.7)	10.6
2006–07		0.8–9.1	6.4 (1.5)	6.4
2008–09		2.8–7.3	5.2 (1)	5.1
2010–11		3.1–6.5	4.5 (0.8)	4.3

Global use of PFAS has been in decline since around 2002 and hence primary exposure levels are expected to decrease (Toms *et al* 2014). Calafat *et al* (2007) compared human data on the serum concentrations of some of the PFAS available from the US National Health and Nutrition Examination Survey (NHANES) database. The study compared data available from 2003–04 with 1999–2000, and found PFOS

and PFOA concentrations had decreased. The decrease was attributed to the discontinuation in 2002 of industrial production of PFOS and related compounds.

From table Table 1, it can be seen that serum PFOS and PFOA concentrations appear to have decreased from 2002 to 2011 in the Australian population (based on available data). For the purpose of estimating daily intake figures, the most recent biomonitoring data (2010–11) for PFOS and PFOA have been selected. The mean concentrations for PFOS and PFOA in the Australian population are considered to be 10.2 ng/mL and 4.5 ng/mL respectively (mean values from table Table 1).

5. Toxicity review

This section provides a brief discussion of the available data and information. While the information provided is not comprehensive, it has been sourced from authoritative literature reviews and government publications. Firstly, the toxicokinetics of PFOS and PFOA is reviewed to identify time and species dependent processes related to these toxicants. Secondly, we have presented a brief summary of some effects of these toxicants, including acute and chronic toxicity.

5.1. Toxicokinetics of PFOS/PFOA

5.1.1. Uptake

Animal experiments demonstrate that the uptake of PFAS usually occurs via oral, inhalation or dermal exposure. Oral uptake and inhalation of these compounds results in quick assimilation (Stahl *et al* 2011).

Oral uptake has been confirmed by Gibson and Johnson (1979), who reported that 95% of a radioactively labelled PFOS dose (4.3 mg/kg) and 93% of a labelled PFOA dose (11 mg/kg) were retained by male rats within 24 hours. These estimates were based on recovery of 5% and 7% of the total radioactivity in faeces and in the digestive tract.

Uptake via inhalation was estimated by Kennedy *et al* (1986), who measured 108 mg/L of ammonium perfluorooctanoate (APFO) in the blood of male rats which were exposed ten times to 84 mg/m³ APFO.

Uptake via dermal exposure appears to be somewhat weaker (Kudo & Kawashima 2003). Kennedy (1985) also showed a dose-dependent increase in blood concentration of organofluoro compounds in rats after dermal application of APFO. Subchronic dermal treatment with 2,000 mg/kg APFO resulted in a blood concentration of 118 µg/mL.

5.1.2. Distribution

Both PFOS and PFOA are water soluble, weakly lipophilic and in the body are principally found bound to proteins. In the body, PFOS and PFOA bind primarily to serum albumin (Han *et al* 2003), but they also bind to fatty acid binding proteins in the liver (Luebker *et al* 2002). The chain length and functional group of PFAS have an impact on the preferential binding sites and binding affinity, and it was found that the PFAS have the same binding sites and similar affinity to proteins as fatty acids (Chen & Guo 2009). PFOS and PFOA are primarily extracellular and accumulate in the liver, blood serum and kidneys (Stahl, Mattern & Brunn 2011).

5.1.3. Bioaccumulation

According to the European Chemicals Regulation (*Annex XIII REACH EC No. 1907/2006*), a chemical is regarded as bioaccumulative if it has a bioconcentration factor (BCF) in aquatic species higher than 2,000 (EU 2006). This differs from the US EPA criterion (BCF 1,000–5,000) and the National Industrial Chemicals Notification and Assessment Scheme (NICNAS 2013) criterion (BCF >5,000).

Both BCF and bioaccumulation factor (BAF) are generally calculated as the ratio, at equilibrium, of internal biota concentration to exposure concentration (McGeer *et al* 2003). Although the calculation of BCF and BAF are usually the same, the interpretations are slightly different, with accumulation in an organism arising from multiple exposure conditions for BAF and from water only for BCF. Therefore, in general, BCF is measured under laboratory conditions and BAF is derived from measurements in natural environments.

Studies showed that the BAF values of PFOS are considerably greater than the bioaccumulation criteria (table Table 2), which indicates that PFOS is highly bioaccumulative in some aquatic species. The reported BCFs or BAFs of PFOA in aquatic organisms are well below the bioaccumulation criteria.

The relatively high water solubility of PFOA could explain its effective excretion by fish via gill permeation, facilitated by high water throughput (Vierke *et al* 2012). Air-breathing animals do not have this possible excretion pathway. Therefore, the defined criteria for BCF in fish may not be the most relevant endpoint to consider for humans.

Table 2. BCF and BAF values for PFOS and PFOA

PFOS	Organism	Location	BCF (L/kg)	BAF (L/kg)	Reference
	Rainbow trout (<i>Oncorhynchus mykiss</i>)	Experimental, Ontario	3,100 (blood) 2,900 (liver)	n.r.	Martin <i>et al</i> 2003
	Lake Trout (<i>Salvelinus namaycush</i>)	Lake Ontario	n.r.	16,000	Houde <i>et al</i> 2008
	Alewife (<i>Alosa pseudoharengus</i>)	Lake Ontario	n.r.	9,800	Houde <i>et al</i> 2008
	Rainbow Smelt (<i>Osmerus mordax</i>)	Lake Ontario	n.r.	19,000	Houde <i>et al</i> 2008
	Sculpin (<i>Cottus cognatus</i>)	Lake Ontario	n.r.	95,000	Houde <i>et al</i> 2008
	Wild turtles (<i>Trachemys scripta elegans</i> and <i>Chinemys reevesii</i>)	Arai River, Japan	n.r.	10,964	Morikawa <i>et al</i> 2006
	Fish	Review		4,000~> 10,000	Fujii <i>et al</i> 2007; Sinclair <i>et al</i> 2006
PFOA	Organism	Location	BCF (L/kg)	BAF (L/kg)	Reference
	Rainbow trout (<i>Oncorhynchus mykiss</i>)	Experimental, Ontario	25 (blood) 12 (liver)	n.r.	Martin <i>et al</i> 2003
	Zebra fish (<i>Danio rerio</i>)	Experimental (¹⁴ C-PFOA), Sweden	20–30	n.r.	Ulhaq <i>et al</i> 2015
	Wild turtles (<i>Trachemys scripta</i>)	Arai River, Japan	n.r.	3.2	Morikawa <i>et al</i> 2006
	Fish	Review		<200	Fujii <i>et al</i> 2007

Not reported (n.r.); median lethal dose (LD50); median lethal concentration (LC50).

In the revised Annex XIII of the REACH regulation (*Commission Regulation (EU) No. 253/2011*), the bioaccumulation criteria are expanded to include more recent findings with respect to biomagnification, bioaccumulation in terrestrial species and concentrations in human body fluids (Gobas *et al* 2009; Vierke *et al* 2012). A number of studies have reported the presence of PFOA in air-breathing animals, for example: piscivorous mammals and high trophic level avian predators (Kannan *et al* 2004); herring gull eggs where PFOA ranged from 6.5–111 ng/g (ww) (Rüdel *et al* 2011); and polar bear liver where PFOA ranged from 3–13 ng/g (Martin *et al* 2003). Furthermore,

Müller *et al* (2011) studied the biomagnification behaviour of PFAS in terrestrial food webs consisting of lichen and plants, caribou, and wolves from remote areas of northern Canada. They have reported that the calculated biomagnification factor (BMF) and trophic magnification factor (TMF) ranged from 0.3–11 and 1.1–2.4, respectively. Additionally, the detection of PFOA in human body fluids strongly indicates bioaccumulation of PFOA. It can therefore be concluded that PFOA is bioaccumulative.

5.1.4. Metabolism

It is well known from the literature that PFOS and PFOA do not undergo metabolism in mammals (ATSDR 2015). Therefore, they are not subject to defluorination or phase-II metabolism of biotransformation (Kudo & Kawashima 2003).

5.1.5. Elimination

Since PFOS and PFOA cannot be metabolised by mammals, these substances are excreted unchanged (Stahl *et al* 2011). PFAS are excreted in the urine and faeces, and the reported biological half-lives differ among species and between genders in some species (table Table 3 and table 4), due to differences in renal clearance rates (Kudo & Kawashima 2003).

Table 3. Elimination half-lives of PFOS/PFOA for various species (Lau *et al* 2007; Stahl *et al* 2011).

Species	PFOS	PFOA		References
	Males/Females	Males	Females	
Rat	100 days	4–6 h	2–4 h	Gibson & Johnson 1979; Chang <i>et al</i> 2008
Mouse	n.r.	19 days	17 days	Lau <i>et al</i> 2006
Rabbit	n.r.	5.5 h	7 h	Hundley, Sarraf & Kennedy Jr 2006
Dog	n.r.	20–30 days	8–13 days	Hanhijärvi, Ophaug & Singer 1982
Monkey	150 days	21 days	30 days	Perkins <i>et al</i> 2004

Not reported (n.r.).

Table 4. Elimination half-lives of PFOS/PFOA for humans

	Population	Mean (years)	Reference
PFOS	Retired production workers, US	5.4 (3.9–6.3)	Olsen <i>et al</i> 2007
PFOS	Primiparous women, Sweden	8.7	Gebbink, Glynn & Berger 2015
PFOS	China, adult	6.2 (0.5)	Zhang <i>et al</i> 2013
PFOS	Germany, adult	4.3–4.8	Yeung <i>et al</i> 2013
PFOS	Cross-section (age 10 to 69), US	4.3	Olsen <i>et al</i> 2012
PFOS	US infants	4.4	Spliethoff <i>et al</i> 2008
PFOS	US, general population	4.7	Wong <i>et al</i> 2014
PFOA	China, adult	2.1 (0.3)	Zhang <i>et al</i> 2013
PFOA	Retired production workers, US	3.8 (3.1–4.4)	Olsen <i>et al</i> 2007
PFOA	US infants	4.1	Spliethoff <i>et al</i> 2008
PFOA	Arnsberg residents, 2006–2008	2.93	Russell, Waterland & Wong 2015

For animals, the reported half-lives can range from 2 hours to 150 days. This is in marked contrast to the half-life documented in humans. For humans, the mean half-lives for PFOS and PFOA are 5.5 years and 3.2 years, respectively. This is because humans have an active reabsorption process using organic anion transport proteins in the kidney (ATSDR 2015). Due to the complicated toxicokinetic and toxicodynamic processes involved, comparison of dose response across different species requires derivation of a human equivalent dose (HED).

5.1.6. Total daily intakes for PFOS and PFOA

Limited information is available to estimate total daily intakes for Australians. The actual pharmacokinetics of PFOS and PFOA in humans is not likely to be consistent with a first order model distribution, but the model is able to describe the repeated dose exposure and serum concentration reasonably well (see Thompson *et al* 2010). Olsen *et al* (2007) also used a first order model to monitor the serum concentration for occupational workers, and good agreement was observed between observations and simulations.

A first order model is applied based on available human biomonitoring data to calculate total daily intakes for PFOS and PFOA. The relevant equation is:

$$dc / dt = -k \times c + u \times f / Vd \quad (1)$$

where c (ng/mL) is the serum concentration; k (/day) is the elimination rate; u (ng/kg/day) is the daily uptake; Vd is the apparent volume of distribution (230 mL/kg bw for PFOS and 170 mL/kg bw for PFOA) (Thompson *et al* 2010); and f is gastrointestinal absorption (91% as used by Thompson *et al* (2010)). The initial condition is $c(0)=0$.

Thus, the relationship between serum concentration and daily uptake can be described as:

$$c(u, t) = u \times f / k / Vd \times (1 - e^{-k \times t}); \quad (2)$$

Considering a stable stage, the equations can be converted into:

$$c(u) = u \times f / k / Vd; \quad (3)$$

where the elimination rate k is $\ln(2)/\text{half-life}$.

Combining all the equations, the final function between half-life and serum concentration is:

$$c(u) = \text{half-life} \times u \times f / Vd / 0.693; \quad (4)$$

Thus, the daily uptake can be derived:

$$u = c(u) \times 0.693 \times Vd / \text{half-life} / f; \quad (5)$$

Using the half-lives derived from table 4 (5.5 years, 2007 days) for PFOS and 3.2 years (1168 days) for PFOA and the toxicokinetic model developed, together with the background exposure information for Australian populations (10.2 and 4.5 ng/mL for PFOS and PFOA respectively), the total daily intakes for PFOS and PFOA are estimated to be 0.89 ng/kg/day and 0.50 ng/kg/day respectively. These estimates are similar to a recent study conducted in Australia (Thompson *et al* 2010).

5.2. Toxicology of PFOS/PFOA

5.2.1. Acute toxicity

The available data indicate that acute toxicity is not observed following high exposure of PFOS/PFOA by means of inhalation, ingestion, dermal or ocular contact in humans (ATSDR 2015). However, animal studies demonstrate a moderate acute oral toxicity resulting in harm to the liver and gastrointestinal tract (PHE 2009). Table 5 summarises the acute toxicity of PFOS/PFOA in terms of median lethal dose (LD50) and median lethal concentration (LC50) values. In the studies where PFOA and PFOS can be directly compared, PFOS is found to be more toxic than PFOA in fresh water organisms (Ji *et al* 2008; Li 2009).

Table 5. Acute toxicity criteria for PFOS/PFOA in animals

Toxicity criterion	PFOS	PFOA	Animal species	References
LD50	n.r.	430–680 mg/kg, oral	Rats	Dean, Jessup & Thompson 1978
LD50	n.r.	189 mg/kg, IP injection	Rats	Olson & Andersen 1983
LD50	n.r.	0.98 mg/L APFO, inhalation	Rats	Kennedy <i>et al</i> 1986
LD50	n.r.	540 mg/kg APFO, inhalation	Rats	Griffith & Long 1980
LD50	n.r.	4,300 mg/kg APFO, dermal	Rabbits	Kennedy <i>et al</i> 1986
LD50	n.r.	7,000 mg/kg 7,500 mg/kg, dermal	Male rats Female rats	Kennedy <i>et al</i> 1986
LC50	n.r.	2,000 mg/kg, dermal	Rabbits	Glaza 1995
LD50	251 mg/kg, oral	n.r.	Rats	US EPA 2000
48 h LC50 96 h LC50	27–233 mg/l 10–178 mg/l	181–732 mg/L 337–672 mg/L	Water flea, water snail, shrimp, planarian	Li 2009
LC50	18 mg/l	200 mg/L	Japanese water flea	Ji <i>et al</i> 2008

Not reported (n.r.); median lethal dose (LD50); median lethal concentration (LC50); ammonium perfluorooctanoate (APFO).

5.2.2. Health effects of chronic exposure: animal data

A number of studies over the years have investigated health outcomes in mice, rats and monkeys resulting from chronic exposure to PFOS/PFOA. The most sensitive effects are presented in table Table 6 and table 7. The following impacts were observed from chronic exposure to PFOS and PFOA at low doses and are considered critical effects for a point of departure (PoD) when deriving a TDI.

PFOS:

- increased liver weight
- liver cell hypertrophy
- histopathological changes to lungs
- decreased hormone level
- decreased reproductive outcome, and
- development delays.

PFOA:

- increased liver weight, and
- reduced Immunoglobulin M (IgM) antibody titres.

Table 6. Adverse effects observed in chronic exposure: animal studies (PFOS) (Wambaugh 2015)

Species	Dose (mg/kg/day)	Exposure	Endpoints	LOAEL (mg/kg/day)	NOAEL (mg/kg/day)	Reference
Monkey	0.03, 0.15, 0.75	26 weeks	Increased absolute and relative liver weight	0.75	0.15	Seacat <i>et al</i> 2002
Rat	0.038, 0.15, 0.38, 1.56	14 weeks	Increased relative liver weight	1.56	0.38	Seacat <i>et al</i> 2003
Rat	0.035, 0.14, 0.35, 1.4	14 weeks	Centrilobular hepatic hypertrophy	0.35	0.14	Seacat <i>et al</i> 2003
Mouse	1.5, 10, 15, 20	GD 1–18	Decreased pup survival	10	5	Lau <i>et al</i> 2003
Rat	1, 2, 3, 5, 10	GD 2–20	Decreased pup survival and development delays	2	1	Lau <i>et al</i> 2003; Thibodeaux <i>et al</i> 2003
Rat	0.1, 0.4, 1.6, 3.2	63–76 days, oral gavage	Decreased F1 reproductive outcome	1.6	0.4	Luebker <i>et al</i> 2005a
Rat	0.4, 0.8, 1.0, 1.2, 1.6, 2.0	63–76 days, oral gavage	Decreased F1 reproductive outcome	1.6	1.2	Luebker <i>et al</i> 2005a
Rat	0.1, 0.4, 1.6, 3.2	63–76 days, oral gavage	Development delays	0.4	0.1	Luebker <i>et al</i> 2005b
Rat	0.14, 1.33, 3.21, 6.34	28 days	Liver weight, decreased serum total T4	1.33	0.14	Curran <i>et al</i> 2008
Rat	0.14, 1.33, 3.21, 6.34	28 days	Decreased total T4	1.33	0.14	Curran <i>et al</i> 2008
Rat	0.15, 1.43, 3.73, 7.58	28 days	Liver weight	0.15	n.r.	Curran <i>et al</i> 2008
Rat	0.15, 1.43, 3.73, 7.58	28 days	Decreased total T4	1.43	0.15	Curran <i>et al</i> 2008
Rat	15	28 days	Thyroid	15	n.r.	Chang <i>et al</i> 2008
Mouse	0.00018, 0.0018, 0.0036, 0.019, 0.036, 0.18	28 days	Suppressed SBRC plaque-forming cell response	0.0036	0.0018	Peden-Adams <i>et al</i> 2008
Mouse	0.0083, 0.083, 0.42, 0.83, 2.08	60 days	Increased splenic natural killer cell activity	0.083	0.008	Dong <i>et al</i> 2009
Rat	0, 0.1, 0.3, 1.0	GD 0–41	Decreased habituation response	1	0.3	Chang <i>et al</i> 2009; Butenhoff <i>et al</i> 2009
Rat	0.1, 2.0	GD 1–2	Histopathological changes to lungs	2	0.1	Chen <i>et al</i> 2012

Low observed adverse effects level (LOAEL); no observed adverse effects level (NOAEL); not reported (n.r.).

Table 7. Adverse effects observed in chronic exposure: animal studies (PFOA) (Wambaugh 2015)

Species	Dose (mg/kg/day)	Exposure duration	Endpoints	LOAEL (mg/kg/day)	NOAEL (mg/kg/day)	Reference
Monkey	3,10, 30/20 ^a	26 weeks	Increased liver weight	3	n.r.	Butenhoff <i>et al</i> 2002
Rat	1, 3, 10, 30 ^b	6 weeks pre mating	Increased absolute and relative liver weight	1	n.r.	Butenhoff <i>et al</i> 2004
Rat	0, 0.06, 0.64, 1.94, 6.5	13 weeks	Higher producing adaptive and reversible liver changes	0.64	0.06	Perkins <i>et al</i> 2004
Mouse	1, 3, 5, 10, 20, 40	gestational days 1–17	Increased liver weight for G1 and development-accelerated sexual maturity in males for G2	1	n.r.	Lau <i>et al</i> 2006
Mouse	3, 5	gestational days 1–17	Increased liver weight for G1	3	n.r.	Wolf <i>et al</i> 2007; White <i>et al</i> 2009
Mouse	3.75, 7.5, 15, 30	15 days	Increased liver weight	3.75	n.r.	DeWitt <i>et al</i> 2008
Mouse	3.75, 7.5, 15, 30	15 days	Reduced IgM antibody titres	3.75	n.r.	DeWitt <i>et al</i> 2008
Mouse	0.3, 1, 3	gestational days 1–17	Increased offspring relative liver weights	0.3	n.r.	Macon <i>et al</i> 2011
Mouse	0.3, 1, 3	gestational days 1–17	Increased offspring relative liver weights	0.3	n.r.	Macon <i>et al</i> 2011

a) 30 mg/kg/day for the first 22 days and then reduced to 20 mg/kg/day; b) 30 mg/kg/day for the first 12 days and then reduced to 20 mg/kg/day; not reported (n.r.).

5.2.3. Human data: epidemiological studies

Biomonitoring of people in the community for evidence of PFAS in various countries began in 2000, although occupationally exposed populations have been monitored for much longer periods of time. In general, workers occupationally exposed have serum levels of both PFOS and PFOA approximately one order of magnitude higher than those reported in the general population (Lau *et al* 2007).

In one study of occupationally exposed workers, the serum to plasma ratio for PFOS and PFOA was 1:1, independent of the concentrations measured. The serum or plasma to whole blood ratio was approximately 2:1 (Ehresman *et al* 2007). This implies that the PFOS/PFOA remains in the serum and does not enter the blood cells.

Human studies addressing potential PFOS/PFOA toxicity are growing, with more than 50 epidemiological studies published from 2015 onwards. A number of epidemiological studies have been conducted as cross-sectional or longitudinal analyses of routine medical surveillance at PFOS/PFOA production facilities. Thus these studies focused on groups of people who were occupationally exposed to PFAS. More recently epidemiological studies have also been conducted on general populations. All the studies have attempted to assess the possible correlations between PFAS concentration in the human body and various health endpoints, and the main approach taken in these studies has been to compare the incidence of disease markers and/or other effects between the highest and lowest quartiles/tertiles of blood PFAS levels. The results from recent epidemiological studies are summarised in table Table 8 and table 9.

The following observations may be made based on the epidemiological studies.

Hematologic biomarkers:

- there is relatively consistent evidence of modest positive associations of the PFOS/PFOA in serum with elevated serum cholesterol
- higher serum levels of PFOA are associated with increased uric acid in the blood, but for PFOS, less pronounced trends are found
- no significant association was observed with blood cell counts or thyroid hormones, and
- there is some but much less consistent evidence of a modest positive correlation with increased liver enzymes in the blood.

Carcinogenicity:

- no significant correlation between PFOS exposures and increased risks of cancer has been reported
- higher PFOA serum levels were found to be associated with kidney and testicular cancer whereas null or inverse association was observed with lower exposure groups. According to the recent classification of carcinogenic agents by IARC Monographs (IARC 2015), PFOA is considered to be possibly carcinogenic to humans which leaves the previous classification unchanged. Similar to the conclusions drawn in this review, this is on the basis of:
 - limited evidence in humans that PFOA causes testicular and renal cancer
 - limited evidence in experimental animals, and
 - moderate evidence for PFOA-associated carcinogenesis mechanisms .

Reproductive and development toxicity:

- positive associations between serum PFOS/PFOA concentrations and adverse reproductive and developmental outcomes, were not observed in all epidemiology studies. Fei *et al* (2009) suggested that the plasma levels PFOS/PFOA may reduce fecundity in the general population.

Mutagenic and genotoxic effects:

- negative results in a large series of *in vitro* and/or *in vivo* short-term tests at gene and/or chromosome or DNA repair levels suggest genotoxicity does not appear to be a property of PFOS (EFSA 2008), and
- from the database on both *in vitro* and *in vivo* mutagenicity testing on the ammonium salt of PFOA, APFO, it was concluded that PFOA should not be considered a genotoxic substance (EFSA 2008).

Table 8. Epidemiological studies related to PFOS exposure

Disease/health indicator	Reference	Study details	Serum PFOS level	Observations/health effects
Lipids	Geiger <i>et al</i> 2014	Cross-sectional study, n=815 ≤18 years), National Health and Nutrition Examination Survey 1999–2008	Mean ± SE serum PFOS: 17.7 ± 0.7 ng/mL	Exposure to PFOS was positively associated with high serum lipid levels in a representative, multi-ethnic sample of US adolescents.
	Starling <i>et al</i> 2014	Cross-sectional study, n=819 pregnant women, Norwegian Mother and Child Cohort Study 2003–04.	Median plasma PFOS 13.03 ng/mL	PFOS concentration was associated with total cholesterol, which increased 4.2 mg/dL per inter-quantile shift 95%CI = 0.8, 7.7) in adjusted models.
	Château-Degat <i>et al</i> 2010	Cross-sectional study, n=723 Inuit adults from Nunavik (Quebec) who are exposed to environmental contaminants through their traditional diet), Fall 2004	Plasma mean 25.7 ng/mL	Triacylglycerol and ratio of total cholesterol to HDL-C levels were negatively associated with PFOS plasma levels. HDL-C levels were positively associated, after adjustment for circulating levels of n-3 PUFAs and for the interaction between gender and PFOS plasma levels.
	Frisbee <i>et al</i> 2010	Cross-sectional community-based study at Mid-Ohio River Valley during 2005–06. The participants were 12,476 children and adolescents aged 1.0–17.9 years included in the C8 Health Project.	Mean ± SD 22.7 ± 12.6 ng/mL	PFOS was significantly associated with increased total cholesterol, HDL-C and LDL-C.
	Steenland <i>et al</i> 2009	Cross-sectional study C8 Project (2005–06) among 46,294 community residents ≥18 years) who drank PFOA-contaminated water from a chemical plant in West Virginia	Mean 22.4 Range 0.25–759.2 ng/mL	Higher serum PFOS was associated with higher levels of total cholesterol, LDL and triglycerides.
Uric acid	Steenland <i>et al</i> 2010	Cross-sectional study under C8 project among 54,951 adult community residents in Ohio and West Virginia, who lived or worked in six water districts contaminated with PFOA from a chemical plant. Study period 2005–06	Mean ± SD 23.4 ± 16.1 ng/mL	PFOS was significantly associated with serum uric acid.
Immune function	Ashley-Martin <i>et al</i> 2015; Grandjean <i>et al</i> 2012	A trans-Canada cohort study of 2,001 pregnant women and their newborns from 10 Canadian cities during 2008–11. n=1,258 for statistical analysis		No association between cord blood levels of PFOS and immunotoxicity.
	Grandjean <i>et al</i> 2012	A longitudinal study of a birth cohort from the National Hospital in the Faroe Islands. A total of 656 consecutive singleton births were recruited during 1997–2000, and 587 participated in follow-up through 2008. The serum antibody concentrations against tetanus and diphtheria were measured in children aged 5 and 7 years.	Maternal serum PFOS geometric mean 27.3 ng/mL; serum PFOS in children at age 5 years 16.7 ng/mL	Strong negative correlation between maternal pregnancy serum PFOS concentration and antibody concentration in children of age 5 years.
Thyroid function	Olsen <i>et al</i> 2003	Cross-sectional study in two PFOA manufacturing locations (Belgium and Alabama), n=255 and 163 workers; Longitudinal study, n=174 workers	Mean serum PFOS 800 ng/mL (Belgium) and 1320 ng/mL (Alabama)	Cross-sectional: no significant association of PFOS with T3, T4, or TSH.

Cancer	Alexander & Olsen 2007	Current and former workers in PFOS production (PFOS); 1,400 questionnaires, and 144 death certificates	Serum PFOS 1.30–1.97 mg/L	Eleven cases of primary bladder cancer were identified from the surveys (n = 6) and death certificates (n=5)
	Alexander <i>et al</i> 2003	Retrospective cohort mortality study, n=2,083 workers in PFOS production (USA). Minimal time of employment was one year	Geometric mean serum PFOS ca. 100–900 ng/mL	High-exposure group: deaths resulting from bladder cancer, 3; standard mortality rate (SMR), 12.8. Two deaths from liver cancer, SMR 3.08
Reproductive and developmental outcomes	Fei <i>et al</i> 2009	General population, Danish National Birth Cohort, 1996–2002	Median plasma PFOS 33.7 ng/mL	Fertility disorders related to elevated plasma PFOS concentrations
	Monroy <i>et al</i> 2008	General population, Canada (n=101 pregnant women)	Mean \pm SD maternal serum at delivery 16.19 \pm 10.43 ng/mL	No association between serum PFAS and birth weight
	Inoue <i>et al</i> 2004	General population (n=15), Japan	PFOS <0.5 to 2.3 ng/mL to 2.3 ng/mL (maternal samples), 1.6–5.3 ng/mL (fetal samples)	No significant correlations between PFOS concentration in maternal and cord blood samples and age bracket, birth weight, or levels of thyroid-stimulating hormone or free thyroxine

Table 9. Epidemiological studies related to PFOA exposure

Disease/health indicator	Reference	Study details	Serum PFOA level	Observations/health effects
Lipids	Geiger <i>et al</i> 2014	Cross-sectional study, n=815 (\leq 18 years), National Health and Nutrition Examination Survey 1999–2008	Mean \pm SE serum PFOA: 4.2 \pm 0.2 ng/mL	Exposure to PFOA was positively associated with high serum lipid levels in a representative, multi-ethnic sample of US adolescents.
	Fu <i>et al</i> 2014	n=133 (0–88 yrs old), which were randomly selected from the people coming for health check-up in Yuanyang Red Cross Hospital of Henan, China in the year 2011	Median serum PFOA 1.43 ng/mL, range 0.32–39.46 ng/mL	Serum PFOA concentration was positively associated with total cholesterol and LDL.
	Frisbee <i>et al</i> 2010	Cross-sectional community-based study at Mid-Ohio River Valley during 2005–06. The participants were 12,476 children and adolescents aged 1.0–17.9 years included in the C8 Health Project.	Mean \pm SD 69.2 \pm 111.9 ng/mL	PFOA was significantly associated with increased total cholesterol and LDL-C.
	Steenland <i>et al</i> 2009	Cross-sectional study (C8 Project 2005–06) among 46,294 community residents (\geq 18 years), who drank PFOA-contaminated water from a chemical plant in West Virginia	Mean 80 ng/mL, range 0.25–17,556.6 ng/mL	Higher serum PFOA was associated with higher levels of total cholesterol, LDL and triglycerides.
Uric acid	Steenland <i>et al</i> 2010	Cross-sectional study under C8 project among 54,951 adult community residents in Ohio and West Virginia, who lived or worked in six water districts contaminated with PFOA from a chemical plant. Study period 2005–06	Mean \pm SD 86.4 \pm 261.3 ng/mL	Higher serum levels of PFOA were associated with a higher prevalence of hyperuricemia.
	Costa, Sartori & Consonni 2009	Longitudinal study (1978–2007) of medical surveillance of male workers engaged in PFOA production plant; n=53	Serum PFOA range in the latest survey: currently exposed workers 0.20 to 47.04 ng/mL, formerly	Evidence for a significant association between total cholesterol and uric acid and PFOA serum level.

			exposed workers 0.53 to 18.66 ng/mL	
Cardiovascular disease	Winquist & Steenland 2014	A modelled PFOA exposure study included a community cohort (n=40,145; ≥20 years old; C8 projects participants) and a worker cohort (n=6,026; worked at the chemical plant during 1948–2002). Location Mid-Ohio Valley.	Mean ± SD measured in 2005–06: community cohort 70.9 ± 151.2 ng/mL; worker cohort 324.6 ± 920.6 ng/mL; combined cohort 86.6 ± 278.9 ng/mL	Higher PFOA exposure was associated with incident hypercholesterolemia with medication, but not with hypertension or coronary artery disease.
	Sakr <i>et al</i> 2007; Sakr <i>et al</i> 2009	Cross-sectional study in 2004 (2007): n=1,025 active workers; Cohort study (2009): n=4,747. Washington works site, where ammonium perfluorooctanoate (APFO) is used, opened in 1948	Median serum PFOA 494 ng/mL in 2004 (among workers in the PFOA areas)	Cross-sectional study: exposure to ammonium perfluorooctanoate (APFO) has been associated with increased serum lipid levels. Cohort study: no convincing evidence of increased ischaemic heart disease mortality risk for APFO-exposed workers.
Immune function	Ashley-Martin <i>et al</i> 2015	A trans-Canada cohort study of 2,001 pregnant women and their newborns from 10 Canadian cities during 2008–2011. n=1,258 for statistical analysis		No association between cord blood levels of PFOA and immunotoxicity.
	Emmett <i>et al</i> 2006a	Cross-sectional community study, n=371, Ohio, USA	Median serum PFOA 354 ng/mL	No association between serum PFOA and with red cell indices, white cell or platelet counts. One small significant association was found between PFOA and absolute monocyte counts.
Liver function	Costa <i>et al</i> 2009	Longitudinal study (1978–2007) of medical surveillance of male workers engaged in PFOA production plant; n=53	Serum PFOA range in the latest survey: currently exposed workers 0.20–47.04 ng/mL, formerly exposed workers 0.53–18.66 ng/mL	No clinical evidence of any specific trouble or disease has been recorded over the 30 years, and all the biochemical parameters, including liver, kidney and hormonal functions, turned out to be within the reference ranges.
	Emmett <i>et al</i> 2006b	Cross-sectional community study, n=371, Ohio, USA	Median serum PFOA 354 ng/mL	No significant positive relationships between serum PFOA and liver or renal function tests.
Thyroid function	Emmett <i>et al</i> 2006a	Cross-sectional community study, n=371, Ohio, USA	Median serum PFOA 354 ng/mL	No significant positive relationships between serum PFOA and TSH.
	Olsen <i>et al</i> 2003	Cross-sectional study in two PFOA manufacturing locations (Belgium and Alabama), n=255 and 163 workers; longitudinal study, n=174 workers	Mean serum PFOA 840 ng/mL (Belgium) and 1780 ng/mL (Alabama)	Cross-sectional: no significant association of either compound with T3, T4, or TSH. Longitudinal: No association between PFOA and thyroid hormones.
Cancer	Vieira <i>et al</i> 2013	The study population consisted of residents in PFOA-exposed water districts and unexposed geographic areas outside of the C8 Health Project area.	The distribution of estimated annual PFOA serum levels among the exposed study population ranged from 3.7–655 ng/mL for 10-	Probable link between higher PFOA serum levels and testicular, kidney, prostate, and ovarian cancers and non-Hodgkin lymphoma.

			year residency, assuming 10-year latency	
Reproductive and developmental outcomes	Barry, Winquist & Steenland 2013	The cohort consisted of adult community residents who resided in contaminated water districts or worked at a local chemical plant in Mid-Ohio Valley.	Measured PFOA median serum levels: community 24.2 ng/mL, worker 112.7 ng/mL	Estimated cumulative serum PFOA concentrations were positively associated with kidney and testicular cancer.
	Steenland & Woskie 2012	5,791 workers exposed to PFOA at a DuPont chemical plant in West Virginia. Serum data for 1,308 workers from 1979–2004	Average serum PFOA 350 ng/mL	Significant positive exposure-response trends occurred for both malignant and non-malignant renal disease.
	Lundin <i>et al</i> 2009	3,993 workers of 3M plant (USA)	Median serum PFOA levels : definitely exposed category 2,600–5,200 ng/mL; probably exposed category 300–1,500 ng/mL	No association with liver, pancreatic, and testicular cancer or cirrhosis of the liver. However, elevated SMR for prostate cancer, cerebrovascular disease, and diabetes were evident.
	Fei <i>et al</i> 2007	General population, Danish National Cohort	Average maternal plasma PFOA 5.6 ng/mL	Inverse association between maternal plasma PFOA and birth weight.
	Bach <i>et al</i> 2015	A review of 14 studies that addressed the effects of PFAS on birth weight.		Higher PFOA concentration was associated with decreased average birth weight in most studies, but only some results were statistically significant.
	Vélez, Arbuckle & Fraser 2015	A cohort study of 2,001 Canadian women (the Maternal-Infant Research on Environmental Chemicals Study) between 2008 and 2011.	Median plasma PFOA 1.7 ng/mL	Increasing concentration of PFOA in maternal plasma was associated with reduced fecundability and infertility.
	Monroy <i>et al</i> 2008	General population, Canada (n=101 pregnant women)	Mean ± SD maternal serum at delivery 2.24 ± 1.61 ng/mL	No association between serum PFAS and birth weight.
	Nolan <i>et al</i> 2009	General population, Ohio, USA,	Median serum PFOA level 354 ng/mL	No association between elevated PFOA exposure via drinking water and increased risk of lowered birth weight or gestational age.
	Fei <i>et al</i> 2009	General population, Danish National Birth Cohort, 1996–2002	Median plasma PFOA 5.3 ng/mL	Fertility disorders related to elevated plasma PFOA concentrations.

6. Tolerable daily intake and the hazard quotient

Hazard quotients (HQ) indicate the overall risk to Australians from contaminants, and are the quotient of the total daily intake divided by tolerable daily intake (TDI). The total daily intake was derived in section 5.

6.1. Tolerable daily intake

Two types of data may be used to derive a human TDI – human data and animal data. Epidemiological studies have indicated a link between PFOS/PFOA exposure and public health. However, most studies only show the odds ratio between control and exposure groups, or the potential association between exposure and risk. Thus far, epidemiological studies have concluded there is a weak positive association between serum PFOS/PFOA and increased serum cholesterol and uric acid levels (table Table 8 and table

Table 9). Also, a few but inconsistent positive correlations occur with liver enzymes. Although recent studies associate exposure to PFAS with adverse health outcomes, most studies are cross-sectional analyses and therefore the data are insufficient to draw any unambiguous conclusions about the effects of PFOS/PFOA in the progress of any particular disease. At this stage, it is therefore difficult to establish a TDI based on human blood (or serum) data.

As laboratory-based animal studies can mimic a pure exposure scenario, excluding the impacts of extraneous factors, they may provide useful dose-response data. This is despite the fact that interspecies uncertainties remain. Due to the pharmacokinetic differences seen with PFAS in different species, administered doses are not directly comparable. Administered doses are normalised to a HED using the species-specific half-lives and volume of distribution as discussed in section 5.1.6.

US EPA and International Programme on Chemical Safety have highlighted two types of uncertainty when deriving human TDI from animal studies, the determination of the appropriate most sensitive critical effect for the PoD, and uncertainty introduced in extrapolation from the PoD to a human TDI incorporating differences between species, routes of exposure, doses and durations (Dong *et al* 2015).

Over a 10-year period, various organisations such as UK Committee on Toxicity (UK COT), European Food Standards Authority (EFSA), and US EPA have developed TDI values for PFOS and PFOA (table 10). The early approaches used included a default uncertainty factor of 100 to account for inter- and intra- species uncertainties (UK COT 2006). Later, EFSA applied another uncertainty factor of 2 to connect the relatively short duration of the key study and the internal dose kinetics (EFSA 2008). For its 2009 *Provisional Health Advisory*, the US EPA used a chemical-specific adjustment factor (CSAF) method to account for the interspecies uncertainties to estimate a TDI. These adjustment factors account for the differences in volume of distribution and half-lives of the compounds in different species. Specifically, a factor of 13 was used for PFOS, for extrapolation from monkey to human, and a factor of 81 was employed for PFOA, for extrapolation from rat to human. Together with the uncertainty factor of 10 to represent the intraspecies uncertainties and uncertainty factor of 3 to denote the toxicodynamic uncertainties, the total uncertainty factors in

US EPA's 2009 version are estimated to be 390 for PFOS T pharmacokinetic differences between species were accounted for by deriving a HED from modelled animal serum values (US EPA 2016a; US EPA 2016b).

Table 10. Comparison of TDI values from various organisations

Organisation	PFOS (ng/kg/day)			PFOA (ng/kg/day)		
	PoD	UF	TDI	PoD	UF	TDI
UK COT (UK COT 2006)	30,000 (NOAEL)	100 ^a	300	300,000 (BMDL)	100 ^a	3,000
EFSA (2008)	30,000 (NOAEL)	200 ^b	150	300,000 (BMDL)	200 ^b	1,500
US EPA 2009 (US EPA 2009)	30,000 (NOAEL)	390	80	460,000 (BMDL)	2,430	200
BfR (Germany) (Priestly 2015)	NA	NA	100	NA	NA	100
US EPA 2016 (US EPA 2016a; US EPA 2016b)	510 (HED)	30	20	5300 (HED)	300	20
Danish EPA (Danish EPA 2015)	33,000 (BMDL ₁₀)	1230	30	3,000 (HED)	30	100

a) inter- and intra- species uncertainties; b) uncertainty factor of 100 for inter- and intra- species uncertainties and uncertainty factor of 2 to compensate for uncertainties in connection to the relatively short duration of the key study and internal dose kinetics; benchmark dose modelling (BMDL).

In 2006, the UK COT established a reference dose (RfD) of 300 ng/kg/day for PFOS (table 1), based on decreased serum T3 levels in a 26-week monkey study (Seacat et al 2002; UK COT 2006). Two types of uncertainty factors (UFs) were further considered – inter-species UF of 10 and intra-species UF of 10. Subsequently, EFSA issued a RfD of 150 ng/kg/day, with an additional UF of 2 to account for the fact that this monkey study did not measure life time exposure (EFSA 2008). Similarly, considering hepatic effects in male rats (Palazzolo 1993; Perkins et al 2004), the UK COT (2006) and EFSA (2008) proposed the PFOA RfDs of 3000 ng/kg/day and 1500 ng/kg/day respectively (table 10).

6.2. Hazard quotient

The recommended enHealth interim TDI values are 150 mg/kg/d for PFOS/PFHxS and 1500 mg/kg/d for PFOA (based on EFSA 2008). Consequently HQs were estimated for PFOS and PFOA in order to indicate the overall risk to Australians from these compounds. The HQ is the quotient between the total daily intake (*E*) divided by *TDI*:

$$HQ = \frac{E}{TDI} \quad (9)$$

As the total daily intakes for PFOS and PFOA are estimated to be 0.89 ng/kg/day and 0.50 ng/kg/day respectively, the HQ were estimated to be 0.006 and 0.0003 respectively.

7. Conclusions

- 1) The elimination rate of PFOS/PFOA in humans is much lower than that in experimental animals. The half-lives in humans are estimated to be 5.5 and 3.2 years for PFOS and PFOA respectively.
- 2) A recent study of Australians' blood samples shows that the mean concentrations for PFOS and PFOA are 10.2 ng/mL and 4.5 ng/mL respectively. Several reports based on national surveys indicate a decrease in serum PFOS and PFOA concentrations from 2002 to 2011 in the Australian population.
- 3) Limited information is available to estimate total exposure for Australians, and thus it is reasonable to use human biomonitoring data to estimate daily exposure. A first order model can well describe the repeated dose exposure and steady serum concentration. Thus, the total daily intake rates for PFOS and PFOA are estimated to be 0.89 ng/kg/day and 0.50 ng/kg/day respectively.
- 4) Animal studies suggest moderate acute oral toxicity of PFOS/PFOA resulting in effects on the liver and gastrointestinal tract. Numerous health outcomes have been observed in animals following chronic exposure including changes in the liver, gastrointestinal tract, thyroid hormone levels, behaviour and reproductive and developmental activity. However, no data are available to assess the level of acute toxicity in humans.
- 5) Epidemiological studies have concluded that there is a weak positive association between serum PFOS/PFOA and blood cholesterol and uric acid levels. Also, a few but inconsistent positive correlations occur with liver enzymes. Although recent studies associate exposure to PFAS with adverse health outcomes, most studies are cross-sectional analyses and therefore the data are insufficient to draw any unambiguous conclusions about the effects of PFOS/PFOA in the progress of any particular disease.
- 6) Epidemiological studies of exposure to PFOS/PFOA and adverse health outcomes in humans are not sufficient to quantify dose-response relationships. Based on animal data, previous studies have used HED, BMDL or NOAEL approaches.
- 7) The hazard quotients are estimated to be 0.006 and 0.0003 for PFOS and PFOA respectively. These findings indicate that Australians are at a low risk of experiencing adverse health effects from typical PFOS/PFOA exposures.

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