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# Interspecies differences in perfluoroalkyl substances (PFAS) toxicokinetics and application to health-based criteria

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ABSTRACT

Toxicokinetics are important for extrapolating health effects and effect levels observed in laboratory animals to humans for purposes of establishing health-based criteria. We conducted a comprehensive review of key absorption, distribution, metabolism, and excretion (ADME) parameters across different mammalian species for five perfluoroalkyl substances (PFAS) and discussed how these data can be used to inform human health risk assessment of these substances. Our analysis revealed several notable differences among the different PFAS regarding species- and substance-specific tissue partitioning, half-life, and transfer to developing offspring via the placenta or lactation, as well as highlighted data gaps for certain substances. We incorporated these observations in an analysis of whether health-based values for specific PFAS can be applied to other PFAS of differing chain length or toxicological mode of action. Overall, our analysis provides one of the first syntheses of available empirical PFAS toxicokinetic data to facilitate interpreting human relevance of animal study findings and developing health-based criteria for PFAS from such studies.

## 1. Background and introduction

Perfluoroalkyl substances (PFAS) generally refer to a class of man-made, fully fluorinated compounds with varying carbon chain lengths and unique surfactant properties that have bolstered their use in various surface coating applications (ATSDR, 2015). Although the production of certain PFAS was discontinued in the United States (US) almost 20 years ago, some of the discontinued compounds are still produced internationally and can be imported into the US in consumer goods (e.g., carpet, paper and packaging, coatings) (US EPA, 2018a). The eight-carbon substances, perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS), for example, were phased out of production in the US starting in 2000 (US EPA, 2016a,b). The production of perfluorobutanoic acid (PFBA), a four-carbon PFAS, was discontinued in 1998 due to decreased demand (3M, 2007). Other four-carbon alternatives to the eight-carbon PFAS are still in production, including perfluorobutane sulfonate (PFBS)-based products (ATSDR, 2015; ATSDR and MDH, 2012). The six-carbon PFAS, perfluorohexane sulfonate (PFHxS), is an emerging contaminant with limited toxicological data that, like the other PFAS included here, has been identified in the environment and human biological samples (ATSDR, 2015). The structures of PFOA, PFOS, PFBA, PFBS, and PFHxS are depicted in Fig. 1. We focus on these five PFAS because they are representative of both short- and long-chain entities and include a broad range of half-lives. In addition, these PFAS are commonly found in the environment, have been more extensively studied than many other PFAS, and have been the subjects of recent regulatory action (US EPA, 2016c; d; 2018b; ITRC, 2018).

Evidence of widespread human and environmental exposure has prompted regulators to evaluate the potential health effects from exposure to these substances in order to establish health-based criteria. To this end, federal and state agencies have recently developed health-based criteria for these substances (e.g., MassDEP, 2018; MDH, 2017a; b; US EPA, 2016a; b). Regulatory efforts are ongoing within the US and abroad to derive health-based criteria for these substances (e.g., US EPA, 2018c).

For risk assessment purposes, scientists and regulators are often tasked with determining how to adequately extrapolate health effects data from laboratory animals to humans. This is especially important for PFAS because existing toxicokinetic data for PFAS, in particular PFOA and PFOS, indicate significant interspecies differences in certain toxicokinetic parameters (e.g., half-life) among different PFAS. The overall body burden and target site concentration of a chemical and its metabolites is governed by its toxicokinetics (i.e., processes of absorption, distribution, metabolism, and excretion [ADME]). Thus, understanding how these processes differ between laboratory animals, in

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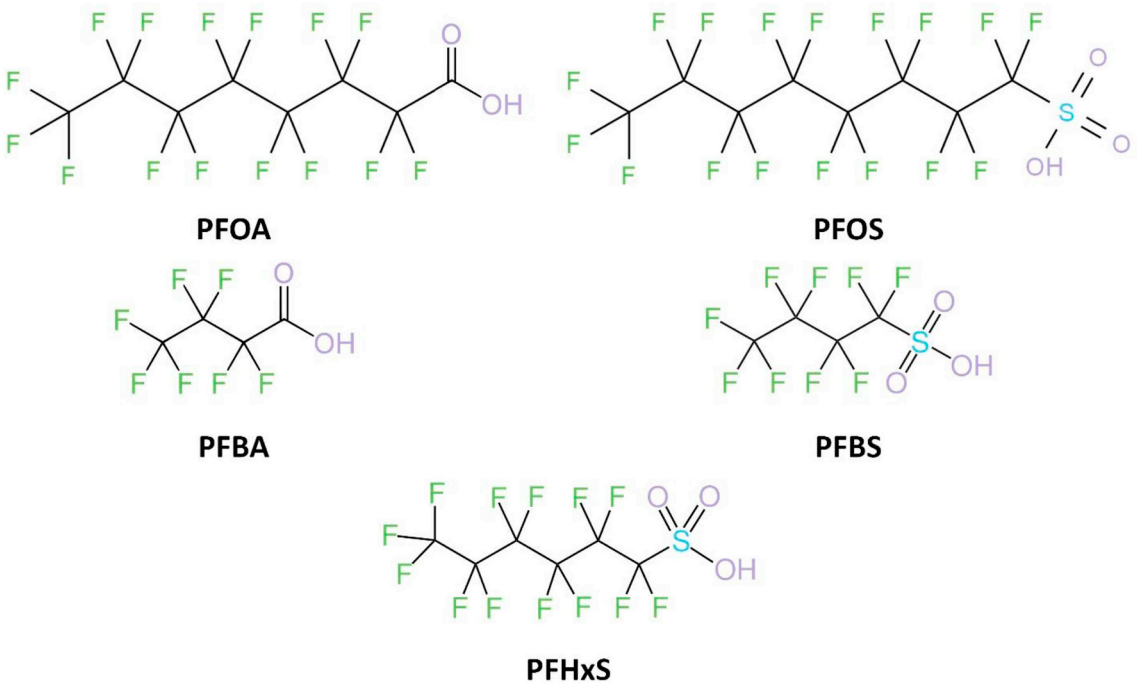


**Fig. 1. Chemical structures of PFOA, PFOS, PFBA, PFBS, and PFHxS.** PFBA = Perfluorobutanoic Acid; PFBS = Perfluorobutane Sulfonate; PFHxS = Perfluorohexane Sulfonate; PFOA = Perfluorooctanoic Acid; PFOS = Perfluorooctane Sulfonate.

which health effects of chemicals are frequently evaluated, and humans is essential to adequately characterize potential health effects and effect levels associated with these substances.

Extrapolating PFAS exposure across species is most reliably predicted by internal serum concentration rather than exposure dose (Butenhoff and Rodricks, 2015). Understanding ADME allows for appropriate interpretation of studies showing associations between serum concentrations and biological effects. For example, incorporating infant and maternal serum PFAS levels, along with age-specific toxicokinetics, aids in deriving health-protective drinking water criteria. In addition, toxicokinetic considerations can help to evaluate whether observed associations are caused by a chemical exposure or can be explained by reverse causation (i.e., a situation in which an association between a health effect and a chemical occurs because the health condition causes an increased body burden of the chemical, rather than the chemical causing the health effect [e.g., Wong et al., 2014; Wu et al., 2015]).

In this analysis, we conducted a comprehensive summary and evaluation of key ADME parameters across different animal species for PFBA, PFBS, PFHxS, PFOA, and PFOS. In particular, for each of the five substances, we evaluated patterns of target organ distribution and relative levels, biological half-lives, and patterns of placental and lactational transfer across humans and laboratory animal species. Traditional physico-chemical parameters (e.g., Log P or vapor pressure) available for these PFAS are typically estimated with software tools and do not accurately inform the toxicokinetics of these substances that tend to be governed by (often species-specific) physiological processes that alter their distribution and elimination. Thus, we expect that, by compiling this information from its disparate sources and offering context to its applications in regulatory toxicology, this review will aid inter- and intraspecies extrapolation of health effects and effect levels observed in laboratory animals to humans for purposes of establishing health-based criteria. In addition, these comparisons also highlight toxicokinetic similarities and differences among these PFAS, which will contribute to the rapidly evolving discussions regarding PFAS regulations and determining whether or not data for one substance can be applied to other PFAS.

## 2. Methods

We identified studies from comprehensive agency reviews, including the Agency for Toxic Substances and Disease Registry ((ATSDR 2015)) and the United States Environmental Protection Agency (US EPA, 2016a; b), supplemented with a search of the scientific literature through PubMed. We included studies in mammalian species relevant to human health risk assessment efforts of PFAS, including mice, rats, monkeys, and humans, but excluded aquatic organisms. Search terms included PFOA, PFOS, PFBA, PFBS, PFHxS, and their full chemical names, in combination with the following terms: mouse/mice, rat(s), monkey(s), humans, liver, absorption, distribution, metabolism, excretion, ADME, penetration, and transport. Search dates were from January 1, 2009, through May 31, 2018; we relied on the ATSDR Draft Toxicological Profile of PFAS (ATSDR, 2015) for identifying literature published before those dates.

The majority of identified studies, especially earlier studies, do not separately evaluate linear vs. branched PFAS content. If specified, we evaluated toxicokinetic parameters for linear PFAS; if not, parameters were assumed to represent mixtures of linear and branched PFAS. In studies in which these differences were differentiated and analytically defined, we incorporated results for total (i.e., linear and branched) PFAS content.

## 3. Results

From our literature evaluation, we identified a total of 70 studies that included quantitative toxicokinetic information for at least one of the five evaluated PFAS in at least one relevant mammalian species for at least one parameter summarized in this analysis (Table 1). Overall, there are more robust data regarding the ADME of PFAS in humans and rats than other species, and of PFOA and PFOS than the other PFAS included in this analysis. Parameter-specific data are summarized in the subsequent sections below; primary study details are provided in Supplemental materials.

**Table 1**
Number of studies with toxicokinetic information by species and PFAS.

| PFAS | Humans | Monkeys | Rats | Mice |
|---|---|---|---|---|
| PFOA | 33 | 1 | 12 | 3 |
| PFOS | 33 | 2 | 10 | 2 |
| PFHxS | 24 | 1 | 5 | 2 |
| PFBA | 2 | 1 | 1 | 1 |
| PFBS | 2 | 2 | 2 | 1 |

Notes: PFAS = Perfluoroalkyl Substance; PFBA = Perfluorobutanoic Acid; PFBS = Perfluorobutane Sulfonate; PFHxS = Perfluorohexane Sulfonate; PFOA = Perfluorooctanoic Acid; PFOS = Perfluorooctane Sulfonate.

### 3.1. Absorption

Quantitative absorption data are limited for PFBA, PFBS, and PFHxS. PFOA and PFOS are well absorbed following oral exposure, with estimated absorption fractions in rats of > 90% (ATSDR, 2015; US EPA, 2016a; b). Findings from a PFOA study by Hinderliter et al. (2006a) suggest that absorption is greater for fasted rats than for non-fasted rats. There is also qualitative evidence that PFOA is absorbed by rats following both inhalation and dermal exposure (Kennedy, 1985; Kennedy et al., 1986), though the evidence suggests that PFOA may be less well absorbed with inhalation (Kennedy et al., 2004) or dermal (Kennedy, 1985; Kennedy et al., 2004) exposure than with oral exposure.

PFBA oral absorption appears to be nearly complete in rats, based on comparable values for peak serum concentration following either oral or intravenous (i.v.) exposure to the same dose (Chang et al., 2008). According to Chang et al. (2008), PFBA is also well absorbed by mice, although to a lesser extent than rats. Data from a study by Olsen et al. (2009) indicate that PFBS oral absorption is also nearly complete in rats, based on comparable values for peak serum concentration and the amount excreted in the urine following either oral or i.v. exposure to the same dose. PFHxS is well absorbed orally in rats with approximately 88–96% bioavailability and more rapid absorption in females than in males (Kim et al., 2016, 2018).

Butenhoff et al. (2004) hypothesize that, in contrast to rats, absorption in monkeys may not be complete. This proposal is based, in part, on the observation of a lower steady-state serum PFOA concentration following oral exposure than that which would be predicted following i.v. exposure. As discussed by ATSDR (2015), evidence of oral PFOA absorption in humans is provided by observations that PFOA concentrations in serum or plasma are related to exposure via drinking water (e.g., Bartell et al., 2010; Hoffman et al., 2011; Holzer et al., 2008; Seals et al., 2011; Wilhelm et al., 2008). We did not identify quantitative data regarding absorption of any of the other PFAS in monkeys or humans.

Data regarding absorption after dermal or inhalation exposure to PFAS are very limited. Fasano et al. (2005) calculated a human in vitro dermal permeability coefficient for PFOA of $9.49 \times 10^{-7}$ cm/h, with approximately 0.05% of administered PFOA penetrating through the skin over a 48-h exposure period, which is on the same order of magnitude as sucrose (US EPA, 2004).

### 3.2. Distribution

#### 3.2.1. Volume of distribution

Substance distribution can be characterized by its apparent volume of distribution ($V_d$), the theoretical volume necessary to contain the total amount of a substance at the same concentration observed in the blood. Chemicals that are found primarily in physiological fluid spaces (e.g., the blood or extracellular fluid) have low $V_d$, of less than 1 L/kg, while those that are highly fat soluble or extensively bound to proteins in cells, such that the bulk of the chemical in the body is not found in blood plasma, have $V_d$s much greater than 1 L/kg (Shen, 2013).

Table 2 presents $V_d$ values for the five PFAS for humans, monkeys, rats, and mice. These values indicate that the PFAS at issue distribute primarily to the blood/extracellular fluid and not to other body compartments, such as fat or intracellular proteins (Butenhoff et al., 2004; Chang et al., 2008, 2012; Olsen et al., 2009). These observations agree with what is known about PFAS distribution and plasma protein binding. Once absorbed, PFOA, PFOS, and PFHxS bind with proteins in the blood, primarily albumin, and do not appear to either bind to or be taken up into red blood cells (Ehresman et al., 2007; Kerstner-Wood et al., 2003). In vitro, > 90% of PFOA binds to albumin, with comparable binding in rats and humans, and in male and female rats (Han et al., 2003). Ohmori et al. (2003) found that more than 98% of PFOA was bound to plasma proteins in rats. Similarly, an in vitro binding study showed that 99–100% of PFOS or PFHxS is bound to plasma proteins, such as albumin and low-density lipoproteins, in rats, monkeys, and humans (Kerstner-Wood et al., 2003).

**Table 2**
PFC volume of distribution values in humans, monkeys, rats, and mice (L/kg).

| Species | Sex | Exposure Route | PFBA | PFBS | PFHxS | PFOA | PFOS |
|---|---|---|---|---|---|---|---|
| Humans | N/A | N/A | N/A | N/A | N/A | 0.17 | 0.23 |
| Monkeys | Females | iv | 0.443 | 0.255 | 0.213 | 0.198 | 0.274 |
| | Males | | 0.526 | 0.254 | 0.287 | 0.181 | 0.202 |
| Rats | Females | iv | 0.187 | 0.351 | 0.193 | 0.191 | 0.469 |
| | Males | | 0.253 | 0.330 | 0.286 | 0.226 | 0.516 |
| Rats | Females | Oral | 0.173 | 0.391 | 0.214 | 0.154 | 0.405 |
| | Males | | 0.209 | 0.676 | 0.303 | 0.106 | 0.523 |
| Mice | Females | Oral | 0.134 | N/A | 0.147 | N/A | 0.261 |
| | Males | | 0.296 | N/A | 0.195 | N/A | 0.263 |

Notes: iv = Intravenous; N/A = Not Available; PFBA = Perfluorobutanoic Acid; PFBS = Perfluorobutane Sulfonate; PFHxS = Perfluorohexane Sulfonate; PFOA = Perfluorooctanoic Acid; PFOS = Perfluorooctane Sulfonate.
Volume of distribution ($V_d$) values for animals are all based on a single dose. Values presented as a mean of $V_d$ values from multiple studies, where applicable (Supplemental Table S1).
Individual study data provided in Supplemental Table S1 (ATSDR, 2015; Butenhoff et al., 2004; Chang et al., 2008, 2012; Kim et al., 2016, 2018; Ohmori et al., 2003; Olsen et al., 2009; Sundstrom et al., 2012; Thompson et al., 2010).

#### 3.2.2. Tissue distribution

In addition to understanding the apparent $V_d$, evaluating specific tissue distribution is important for understanding the amount of a substance reaching specific tissues (i.e., tissue dose) and, subsequently, potential target organ toxicity. As with other pharmacokinetic parameters, a better understanding of distribution patterns may help elucidate observed differences in toxicity, either among or within species, and may also help predict whether such differences might exist in the absence of information to that effect.

Table 3 presents the predominant tissues in which the PFAS distribute. While there are similarities in overall PFAS tissue distribution, there are also notable differences that appear to vary by species, to some extent by dose and, to a lesser extent, by sex. Overall, the evidence suggests that PFOA, PFOS, and PFBS preferentially distribute to the liver in most species; PFBA and PFHxS appear to preferentially distribute to the serum and, to a lesser extent, to the liver in animals. Comparing distribution across doses both within and among studies provides some evidence of dose-dependent distribution, with lower partitioning to tissues (in particular the liver) at higher vs. lower doses. This suggests that distribution may be, at least in part, saturated at higher doses and, thus, transporter mediated. Evidence that PFOA distribution may be partly governed by transporter-mediated processes is provided by a physiological-based pharmacokinetic (PBPK) model developed by Cheng and Ng (2017) in which distribution occurs via both transporter-mediated processes and passive diffusion, and which shows good agreement with measured tissue concentrations.

PFAS do not readily cross the mature blood-brain barrier. This is supported by findings from Harada et al. (2007) in which PFOA and

**Table 3**
Tissue distribution of PFAS by species and sex.

| Species | Sex | PFBA | PFBS | PFHxS | PFOA | PFOS |
|---|---|---|---|---|---|---|
| Rats | Male | Serum > > Liver[a] | N/A | Serum > > Liver > Kidney > > Spleen | ≤5 mg/kg<br>Liver > > Serum > Kidney > > Spleen > > Brain<br>≥10 mg/kg<br>Serum > > Liver > > Kidney > > Spleen > > Brain[b] | ≤0.3 mg/kg<br>Liver > > ><br>Serum ≈ Kidney > > Spleen > > Brain<br>2 mg/kg<br>Liver > > Serum > > Kidney > > > Spleen |
| | Female | N/A | N/A | Serum > > Liver > Kidney > > Spleen | ≤5 mg/kg<br>Serum ≈ Liver ≥ Kidney > > Spleen<br>≥10 mg/kg<br>Serum > Kidney > Liver > > Spleen > > > Brain | 2 mg/kg<br>Liver > > Serum > > Kidney > > Spleen |
| Mice | Male | Serum > > Liver | Liver > Kidney > > Spleen > > Brain | Serum > > Liver > > Kidney | Liver > Serum | Liver > > Kidney > > Spleen > > Brain |
| | Female | N/A | N/A | Serum > > Liver > > Kidney | Liver > > Serum | N/A |
| Monkeys | Male | N/A | N/A | N/A | Serum > > Liver | Liver > Serum |
| Humans | N/A | Kidney > > > Liver > > Brain | Kidney > > Liver (ND in brain) | Kidney > > Liver ≥ Brain | Liver > > Kidney (ND in brain) | Kidney ≥ Liver > > > Brain |

Notes:N/A = Not Available; ND = Not Detected; PFBA = Perfluorobutanoic Acid; PFBS = Perfluorobutane Sulfonate; PFHxS = Perfluorohexane Sulfonate; PFOA = Perfluorooctanoic Acid; PFOS = Perfluorooctane Sulfonate.
≥ indicates tissue concentration is comparable or slightly greater than tissue concentration in comparison tissue.
> indicates there is less than a 2-fold difference in relative tissue concentration.
> > indicates there is approximately a 2- to 10-fold difference in relative tissue concentration.
> > > indicates there is approximately a greater than 10-fold difference in relative tissue concentration.Individual study data provided in Supplemental Tables S2a-h (Benskin et al., 2009; Bogdanska et al., 2011, 2014; Hundley et al., 2006; Iwabuchi et al., 2017; Kemper, 2003; Kim et al., 2016; Kudo et al., 2007; Perez et al., 2013; Sundstrom et al., 2012; Vanden Heuvel et al., 1991; Ylinen et al., 1990) and S.3a-d (Butenhoff et al., 2004, 2009; Chang et al., 2008, 2012; 2018; Curran et al., 2008; Hundley et al., 2006; Iwabuchi et al., 2017; Kim et al., 2016, 2018; Kudo et al., 2007; Olsen et al., 2001, 2003; Seacat et al., 2002, 2003; Sundstrom et al., 2012; Vanden Heuvel et al., 1991; Ylinen et al., 1990).

PFOS cerebral spinal fluid concentrations in adult humans were more than 500-fold lower than serum concentrations. There may be potential for some PFAS to cross the immature blood-brain barrier, however. In rats, PFOS levels in fetal and pup brains are greater than in maternal brains, and levels in pup brains decreased after birth (Chang et al., 2009; Ishida et al., 2017). Zeng et al. (2011) also observed that PFOS concentrations in the rat pup hippocampus and cortex decreased between post-natal day (PND) 0 and PND 21, consistent with the fetal blood-brain barrier not being fully developed. Similarly, PFOS levels in fetal and pup mouse brains are greater than in maternal mouse brains (Borg et al., 2010). Similar evidence is not available for the other PFAS included in this analysis. Thus, the relationships shown in Table 3 apply to animals studied post-natally, but may not apply to the developing fetus.

The limited data in humans (from 20 human cadavers) indicate that, while PFOA preferentially distributes to the liver, PFOS, PFHxS, PFBS, and PFBA concentrations are higher in the kidney than in the liver (Perez et al., 2013). It is important to note that data for all species aside from rats, and for PFBA and PFBS in general, are limited; thus, it is not possible to draw strong conclusions regarding the observed differences in specific tissue distribution for species other than rats or for PFBA and PFBS for any species, based on these data.

Table 4 presents the ratios of different PFAS in the liver, a predominant tissue for PFAS distribution, to serum or plasma in various species. Liver concentrations (relative to serum or plasma) decrease in the order of PFOS > PFOA > PFHxS > PFBA; no information regarding liver-to-serum ratios was identified for PFBS. The results of these studies also indicate sex differences in the distribution of certain PFAS, particularly for PFHxS, PFOA, and PFOS in rats, in which males consistently had a higher liver-to-serum ratio than females. As discussed further in Section 3.4, the sex differences in PFHxS and PFOA (but not PFOS) distribution for rats are consistent with differences in excretion rates. The reasons for such sex differences in liver tissue distribution is unclear, but could be related to longer half-lives of PFHxS and PFOA in male vs. female rats, thus allowing for greater time for distribution to the liver. Table 4 also indicates that PFOS distributes to the liver to a lesser extent in monkeys and humans than in rats. This suggests that, given the same serum or plasma concentration, monkeys and humans may be less susceptible to liver effects of PFOS than rats. As with Table 3, the relationships shown in Table 4 apply to animals studied post-natally, and may not apply to the developing fetus.

**Table 4**
Liver to serum ratios.

| Species | Sex | PFBA | PFHxS | PFOA | PFOS |
|---|---|---|---|---|---|
| Rat | Male | 0.24[a] | 0.44 (0.13–2.1) | 1.5 (0.8–3.0) | 10.9 (2.6–43) |
| | Female | N/A | 0.16 (0.07–0.25) | 0.64 (0.50–0.81) | 3.4 (2.0–30) |
| Mouse | Male | 0.24[a] | 0.59 (0.50–0.67)[b] | 1.6[c] | N/A |
| | Female | 0.16[a] | 0.42 (0.37–0.47)[b] | 2.2[c] | N/A |
| Monkey | Male | N/A | N/A | 0.22 | 1.7 |
| | Female | N/A | N/A | N/A | 1.6 |
| Human | N/A | N/A | 0.34, 1.5[d] | 1.2, 3.2[d] | 1.3[e] |

Notes:N/A = Not Available; PFBA = Perfluorobutanoic Acid; PFBS = Perfluorobutane Sulfonate; PFHxS = Perfluorohexane Sulfonate; PFOA = Perfluorooctanoic Acid; PFOS = Perfluorooctane Sulfonate.
Unless otherwise specified, values represent median and range (in parentheses); studies report concentrations in either serum or plasma, with values in either serum or plasma considered equivalent (summarized in Supplemental Tables S3a-d [Butenhoff et al., 2004, 2009; Chang et al., 2008, 2012, 2018; Curran et al., 2008; Hundley et al., 2006; Iwabuchi et al., 2017; Kim et al., 2016, 2018; Kudo et al., 2007; Olsen et al., 2003; Seacat et al., 2002, 2003; Sundstrom et al., 2012; Vanden Heuvel et al., 1991; Ylinen et al., 1990]). No data available for PFBS.
[a] Value is the average from one study.
[b] Represents average, minimum, and maximum for data from two studies.
[c] Represents value for one dose, from one study.
[d] Individual data for two cadavers (Olsen et al., 2001).
[e] Mean of data reported by Olsen et al. (2003).

**Table 5**
Placental and lactational transfer.

| PFAS | Placental Transfer[a] | | | Lactational Transfer[b] | | Offspring/Maternal Ratio[c] | | |
|---|---|---|---|---|---|---|---|---|
| | Humans | Rats | Mice | Humans | Rats | Humans | Rats | Mice |
| PFOA | 0.79 (0.60–1.5) | 0.42 | N/A | 0.04 (0.03–0.12) | 0.10 | 3.6 (2.7–4.6) | 0.26 | 0.52 |
| PFOS | 0.37 (0.29–0.56) | 2.3 | N/A | 0.01 (0.01–0.03) | 0.31 | 0.88 (0.72–1.0) | 0.68 | N/A |
| PFHxS | 0.58 (0.35–1.28) | N/A | 1.24 | 0.01 (0.01–0.08) | N/A | 1.6 (1.1–2.0) | N/A | 0.57 |

Notes:N/A = Not Available; PFAS = Perfluoroalkyl Substance; PFHxS = Perfluorohexane Sulfonate; PFOA = Perfluorooctanoic Acid; PFOS = Perfluorooctane Sulfonate.
Values for humans represent central tendency estimate, using the median across studies, based on median (where available) or mean values from individual studies. Values represent the median and range (in parentheses).
Underlying data included in Supplemental Tables S4a-c (Cariou et al., 2015; Chang et al., 2009; Chen et al., 2017a,b; Fei et al., 2007; Fromme et al., 2010; Gutzkow et al., 2012; Gyllenhammar et al., 2018; Hanssen et al., 2010, 2013; Haug et al., 2011; Hinderliter et al., 2005; Inoue et al., 2004; Karrman et al., 2007; Kato et al., 2014; Kim et al., 2011a,b; Kuklenyik et al., 2004; Lee et al., 2013; Liu et al., 2011; Manzano-Salgado et al., 2015; Midasch et al., 2007; Monroy et al., 2008; Needham et al., 2011; Ode et al., 2013; Porpora et al., 2013; Tittlemier et al., 2004; Yang et al., 2016).
Data were not available for PFBA or PFBS.
[a] Presented as fetal (cord blood)/maternal (serum or plasma) ratio. Values for rats were selected at the lowest dose (as being most comparable to exposure and sample collection in humans).
[b] Presented as breast milk/maternal serum (or plasma) ratio. Values for rats were selected at the lowest dose and at the earliest time-point (as being most comparable to exposure and sample collection in humans). No data for mice for any PFAS.
[c] Values for rats were selected at the lowest dose, at the earliest post-natal time-point; based on PFAS concentrations quantified in either serum or plasma.

### 3.2.3. Placental and lactational transfer

Studies of humans and laboratory animals demonstrate that both PFOA and PFOS in maternal plasma can cross the placenta (placental transfer) and can also enter breast milk (lactational transfer). Thus, developing fetuses can be exposed to these substances in utero, and newborns can be exposed via lactation. Data for these parameters are limited for PFHxS in experimental animals and for PFBS in humans; the lack of information for PFBS in humans is largely due to PFBS concentrations below the limit of detection in human infants or mothers (e.g., Gyllenhammar et al., 2018; Kim et al., 2011a; Manzano-Salgado et al., 2015). There are no data regarding these parameters for PFBS in experimental animals or for PFBA in either humans or experimental animals. Results for PFOA, PFOS, and PFHxS in humans are limited to two studies that collected data from infants ≤6 months of age (Fromme et al., 2010; Gyllenhammar et al., 2018) in order to represent mainly placental and lactational transfer. Available information for PFOA, PFOS, and PFHxS is summarized in Table 5.

As shown in Table 5, although placental and lactational transfer of PFOA are comparable in rats and humans, the ratios of offspring/maternal PFOA blood concentrations are greater in humans than in rats. For PFOS, the ratios of offspring/maternal blood concentrations are similar or slightly greater in humans compared to rats, despite the fact that placental and lactational transfer of PFOS is considerably greater in rats than in humans. The basis for higher post-natal offspring/maternal blood ratio in humans compared to rats is not clear but could be related to differences in biological half-lives for PFOA and PFOS (which are considerably longer in humans than in rats) and/or differences in

physiology between the two species. The higher post-natal offspring/maternal blood ratio in humans could also be related to the longer period of lactation in humans, who typically wean (when breast feeding) by about 6 months of age, vs. rats, which typically wean by post-natal day 21 (BU, 2014; Sharma et al., 2013).

The available information for PFHxS is inconsistent, indicating that newborn humans have either similar or two-fold higher serum PFHxS levels than their mothers. There are limited data regarding transfer of PFHxS to offspring in experimental animals. Toxicokinetic information from a recent study by Chang et al. (2018) suggests that, similar to PFOA, offspring/maternal blood levels are greater in humans than in mice, although mice may be exposed to higher levels of PFHxS in utero than humans.

### 3.3. Metabolism

PFAS do not appear to undergo metabolism in the liver or other tissues (ATSDR, 2009, 2018; US EPA, 2016a; b). This precludes any concern about species differences in metabolic pathways and facilitates the comparison of exposures across species.

### 3.4. Excretion

In humans, biliary clearance of PFOA and PFOS exceeds urinary clearance (Harada et al., 2007), although results from a study by Zhang et al. (2015) indicate that urine is also an important elimination pathway for PFOA and PFOS in humans. In contrast, urinary elimination of PFOA exceeds fecal elimination in monkeys and rats (Butenhoff et al., 2004; Kemper, 2003). Urine is also a primary elimination pathway for PFOS in rats (Chang et al., 2012) and for PFBA and PFBS in monkeys and rats (Chang et al., 2008; Chengelis et al., 2009; Olsen et al., 2009).

As shown in Table 6, half-lives are longer for the eight-carbon vs. the four-carbon PFAS and are also longer for the sulfonates vs. the carboxylates. There are substantial differences in PFAS elimination rates between humans, monkeys, and rodents, with longer half-lives found in humans for all PFAS evaluated here. As discussed by Harada et al. (2007), the long half-lives for PFOA and PFOS in humans may be due to low levels of urinary excretion coupled with a high rate of biliary reabsorption (fractional rates 0.89 and 0.97 for PFOA and PFOS, respectively). Reabsorption from kidney tubules by organic anion transporter (OAT) 4 and urate transporter 1 may also contribute to the long biological half-life of PFOA in humans (Nakagawa et al., 2009; Yang et al., 2010). Although the half-lives of PFOA and PFOS are comparable to each other in humans and mice, the half-life of PFOA is considerably shorter than that of PFOS in monkeys and rats.

For PFHxS, the half-life in monkeys, mice, and male rats is comparable to that of PFOS, whereas in female rats the half-life of PFHxS is comparable to that of PFOA. In contrast, the half-life estimates for PFHxS in humans are longer than those for PFOA and PFOS (Li et al., 2018; Olsen et al., 2007; Worley et al., 2017). The contrast between animals and humans with respect to the relative difference in half-lives among the PFAS could reflect actual biological differences or uncertainty with respect to PFAS exposure in humans. As hypothesized by Sundstrom et al. (2012), the longer half-life for PFHxS could be a consequence of a slower elimination rate, ongoing exposure to low levels of PFHxS (for example related to treatment of carpets and upholstery with PFHxS for purposes of stain resistance), or both. Olsen et al. (2007) and Li et al. (2018) estimated human half-lives for PFHxS of 7.3 and 5.3 years, respectively, based on multiple serum measurements over time. In contrast, Worley et al. (2017) estimated a half-life of 15.5 years for PFHxS in humans using a one-compartment pharmacokinetic model based on PFHxS concentrations in serum and drinking water, the $V_d$ estimated for female monkeys by Sundstrom et al. (2012), and assumptions regarding drinking water intake. The longer half-life estimate for PFHxS from Worley et al. (2017) may be related to uncertainty in the assumptions used to derive the half-life estimate, and therefore, this value may be too imprecise for use in risk assessment.

#### 3.4.1. Sex differences in excretion

Urinary excretion of PFOA is greater for female rats than male rats, with > 70% eliminated in urine within 24 h in females vs. < 10% in males (Hanhijarvi et al., 1982; Kemper, 2003; Kudo et al., 2001; Lau et al., 2006; Ohmori et al., 2003; Vanden Heuvel et al., 1991). Evidence for different dose-dependent elimination patterns was also observed across sexes: in male rats, Kemper (2003) found that PFOA plasma

**Table 6**
PFAS elimination half-lives.

| Species | Sex | PFBA | PFBS | PFHxS | PFOA | PFOS |
|---|---|---|---|---|---|---|
| Human | Female/Male | 3.1 days | 25.8 days | 5.3–15.5 years | 2.3–8.5 years[a] | 3.3–5.4 years |
| Monkey | Female | 1.7 days | 3.5 days | 87 days | 32.6 days | 110–~200 days |
| | Male | 1.7 days | 4.0 days | 141 days | ~20 days | 132–~200 days |
| Rat | Female | 1.0 h (iv)<br>1.8 h (oral) | 0.64–7.4 h | 0.9–2.0 days | 1.9–4.6 h (< 25 mg/kg)<br>16.2 h (25 mg/kg)<br>24 h (50 mg/kg) | 24–83 days |
| | Male | 6.4 h (iv)<br>9.2 h (oral) | 2.1–4.7 h | 16–34 days | 1.6–15 days (< 25 mg/kg)<br>6.5 days (25 mg/kg)<br>4.4 days (50 mg/kg) | 26–82 days |
| Mouse | Female | 2.9 h (10 mg/kg)<br>3.1 h (30 mg/kg)<br>2.8 h (100 mg/kg) | N/A | 25–27 days | 1.2 days (20 mg/kg-day, 17 days)<br>15.6 days (1 or 10 mg/kg, single dose) | 38 days (1 mg/kg-day)<br>30 days (20 mg/kg-day) |
| | Male | 13.3 h (10 mg/kg)<br>16.3 h (30 mg/kg)<br>5.2 h (100 mg/kg) | N/A | 28–30 days | 21.7 days (1 or 10 mg/kg, single dose) | 43 days (1 mg/kg-day)<br>36 days (20 mg/kg-day) |

Notes:iv = Intravenous; N/A = Not Available; PFAS = Perfluoroalkyl Substance; PFBA = Perfluorobutanoic Acid; PFBS = Perfluorobutane Sulfonate; PFHxS = Perfluorohexane Sulfonate; PFOA = Perfluorooctanoic Acid; PFOS = Perfluorooctane Sulfonate.
Data for individual studies is included in Supplemental Tables S5a-f (ATSDR, 2015; Bartell et al., 2010; Benskin et al., 2009; Brede et al., 2010; Butenhoff et al., 2004; Chang et al., 2008, 2012; Chengelis et al., 2009; Costa et al., 2009; De Silva et al., 2009; Gebbink et al., 2015; Glynn et al., 2012; Johnson and Ober, 1979, 1980; Kemper, 2003; Kim et al., 2016, 2018; Kudo et al., 2002; Li et al., 2018; Lou et al., 2009; Ohmori et al., 2003; Olsen et al., 2007, 2009; 2012; Seacat et al., 2002; Seals et al., 2011; Shirai and Kissel, 1996; Spliethoff et al., 2008; Sundstrom et al., 2012; Vanden Heuvel et al., 1991; Wong et al., 2014; Worley et al., 2017; Ylinen et al., 1990; Zhang et al., 2013).
Unless otherwise specified, data represent both oral and iv exposures, both acute and chronic exposures, and a range of doses.
[a] Most community studies report half-lives of 2–3 years (see Table S5a). The 8.5-year value was derived from a study of retired workers who had been occupationally exposed to PFOA (Seals et al., 2011) and may not accurately reflect half-life values in exposed communities.

elimination half-life was independent of dose; whereas in female rats, elimination rates increased with increasing dose. The increased urinary excretion by female rats results in shorter elimination half-lives, as shown in Table 6. Sex differences with respect to elimination are also observed following inhalation exposure (Hinderliter et al., 2006b), which supports the use of plasma PFOA as a suitable dose metric for route-to-route extrapolation for rats.

Increased excretion of PFOA by female rats relative to males is likely due to differential activity of kidney OATs and organic anion transporting polypeptides (OATPs), which are kidney proteins involved in both the excretion of chemicals into the urine, and reabsorption of chemicals back into the blood (Hanhijarvi et al., 1982; Weaver et al., 2010). Although the specific OATs and OATPs involved in the sex-specific excretion of PFOA have not been definitively identified, OATP1/OATP1a1, which may be involved in reabsorption of organic anions, is expressed at higher levels in male vs. female rat kidneys (Kato et al., 2002; Kudo et al., 2002; Weaver et al., 2010; Yang et al., 2009). On the other hand, OAT2 is expressed at higher levels in female vs. male rat kidneys and may be involved in the secretion of PFOA and related organic anions (Kudo et al., 2002; Ljubojevic et al., 2007). The saturation of kidney transporters may contribute to the longer elimination rates observed in female rats exposed to higher PFOA doses (ATSDR, 2015).

In contrast to PFOA, for which the elimination half-life is shorter in female than in male rats, studies in rats demonstrated longer PFOS elimination half-lives and 3-fold higher PFOS serum concentrations for females than for males given equivalent doses (Butenhoff et al., 2012; Chang et al., 2012). Sex differences with respect to PFOS elimination have not been observed for mice (Chang et al., 2012; Hundley et al., 2006; Lau et al., 2006), rabbits (Hundley et al., 2006), monkeys (Chang et al., 2012), or humans (Harada et al., 2005; Zhang et al., 2015).

As with PFOA, urinary excretion of both PFBA and PFHxS is greater for female than for male rats. Urinary excretion of PFBA is also greater for female than for male mice. For PFBA, approximately 100% vs. 60% is excreted in the urine 24 h post-dosing in female vs. male rats, respectively; and approximately 70% vs. 35% in female vs. male mice, respectively (Chang et al., 2008). For PFHxS, > 25% is eliminated via the urine in female rats vs. < 20% in male rats at doses ≤10 mg/kg; 41% vs. 30% is eliminated in female vs. male rats at a dose of 100 mg/kg (Kim et al., 2018; Sundstrom et al., 2012). As shown in Table 6, the increased urinary excretion of PFBA and PFHxS by female rats and of PFBA by female mice, compared to males, results in shorter half-lives for females in these rodent species. Although the bases for the sex differences in elimination of PFBA and PFHxS have not been fully investigated, they may be due to the same type of sex-specific reabsorption kinetics in kidney tubules related to differential expression of OATs that govern the differences in PFOA elimination discussed above, and may involve a saturable reabsorption process in kidney tubules (Chang et al., 2008; Sundstrom et al., 2012). Further evidence of this was provided by Sundstrom et al. (2012), who observed that urinary excretion of PFHxS was substantially greater (30% vs. 6–7%) for males treated with 100 mg/kg vs. ≤ 10 mg/kg, indicating involvement of a saturable renal tubular reabsorption process.

#### 3.4.2. Excretion via menstruation and lactation

In addition to urine and feces, menstruation and lactation can be important elimination routes in women. Using a PBPK model, Wong et al.'s (2014) estimation of the PFOS serum elimination half-life for women increased from 3.7 to 4.0 years by including loss of PFOS via menstruation in their model. Compared to an estimated PFOS serum elimination half-life in men of 4.7 years, the increase of 0.3 years represents 30% of the difference between half-lives in men and women when loss of blood to menstruation is not accounted for. Kang et al. (2016) observed an inverse correlation between PFOA breastmilk concentration and length of lactation, and suggested that lactation may be an important excretion route for women. Other studies show that serum concentrations of PFOA and PFOS are lower in women who breastfeed compared to women who do not breastfeed, with maternal serum decreasing approximately 2–3% per month of breastfeeding (Brantsaeter et al., 2013; Mondal et al., 2014). The limited data available for PFHxS do not indicate a comparable effect (Kingsley et al., 2018; Mondal et al., 2014), and information on the effects of breastfeeding is not available for PFBS or PFBA.

## 4. Discussion

### 4.1. Trends across species and PFAS type

Overall, there are robust qualitative and quantitative data regarding the ADME of PFOA and PFOS in humans and animals, and limited information for PFHxS, PFBS, and PFBA. However, available data indicate some notable trends in toxicokinetic parameters for these substances. All five PFAS evaluated in this analysis are relatively well absorbed in humans and animals, systemically distributed after ingestion, and do not undergo significant metabolism. The overall evidence suggests that PFOA, PFOS, and PFBS preferentially distribute to the liver in most species and do not readily cross the mature blood-brain barrier. PFBA and PFHxS appear to preferentially distribute to the serum and, to a lesser extent, to the liver in animals. The limited data in humans (from a small number of human cadavers) indicate that, while PFOA preferentially distributes to the liver, PFOS, PFHxS, PFBS, and PFBA may preferentially distribute to the kidney. However, it is important to emphasize that data for all species aside from rats, and for PFBA and PFBS in general, are limited, and it is not possible to draw strong conclusions regarding the observed differences in specific tissue distribution for species other than rats, or for PFBA and PFBS for any species, based on available data.

The differences in placental and lactational transfer between rats and humans highlight the importance of considering toxicokinetic differences between species for risk assessment purposes. Given the same exposure level to the mother or to dams, the differences shown in Table 5 suggest that the developing human fetus would be exposed to lower serum PFOA, PFOS, or PFHxS concentrations than the developing rat fetus. However, the newborn breastfed human infant would be exposed to higher serum PFOA concentrations than the newborn rat. Median infant-to-maternal serum concentrations of PFOS, however, are similar, indicating that PFOS is retained similarly between mothers and breastfed infants. Results for PFHxS are inconsistent, indicating either similar or two-fold higher retention in the infants compared to mothers (see Supplemental Tables S4a-c for individual study details). Gyllenhammar et al. (2018) observed decreased transfer to infants with increasing PFAS chain length. As we did not identify similar data for PFBA and PFBS, it is not possible to make similar conclusions for the particular subset of PFAS included in this analysis.

Regarding elimination half-lives, there are substantial differences in PFAS elimination rates between humans, monkeys, and rats, with much longer half-lives found in humans for all PFAS evaluated here. For the PFAS included in this analysis, half-lives decrease in the order of PFHxS > PFOS > PFOA > PFBS > PFBA, and in the order of humans > monkeys > rodents. In monkeys, mice, and male rats, the half-life of PFHxS is comparable to that of PFOS, whereas in female rats the half-life of PFHxS is comparable to that of PFOA. Urinary excretion of PFOA, PFHxS, and PFBA is greater for female than for male rats. Urinary excretion of PFBA is also greater for female than for male mice.

### 4.2. Implications for risk assessment and heath-based value derivation

Recent risk assessments of PFAS chemicals, including PFOA and PFOS, primarily relied on key toxicology studies in rodents from which a point of departure (POD) was derived for health-based value derivation. Because the observed half-lives of PFOA and PFOS are significantly longer in humans than in rodents, toxicity criteria for these

compounds are based on effect levels that are, in turn, based on serum concentrations. Using the PBPK model developed by Wambaugh et al. (2013), US EPA determined serum concentrations in laboratory animals to extrapolate effect levels across species. The model-derived serum concentrations in laboratory animals were converted to human equivalent doses based on estimated half-life and volume of distribution in humans to calculate oral reference doses (RfD) for PFOA and PFOS (US EPA, 2016a; b). Incorporating chemical-specific pharmacokinetic data to account for interspecies differences enhances the risk assessment process by more fully utilizing the entirety of the data set available for a particular substance and reducing the uncertainty surrounding the ultimate health-based criterion (IPCS, 2005, 2009; US EPA, 2014).

Over the last decade or so, studies have demonstrated placental and lactational transfer of PFAS to nursing infants (e.g., Fromme et al., 2010; Mondal et al., 2014) and some toxicology studies in experimental animals observed potential developmental effects after exposure to PFOA and PFOS (e.g., Lau et al., 2006; Luebker et al., 2005). Based on these observations, more recent assessments of these substances have utilized toxicokinetic models to investigate maternal-fetal/offspring transfer of these substances and to determine health-protective levels for maternal exposure to PFAS that will also protect the developing fetus or nursing infant. Minnesota's Department of Health (MDH), for example, incorporated such toxicokinetic concepts in the development of their health-based drinking water values for PFOA and PFOS, using a toxicokinetic model for PFOA and PFOS in humans that incorporated placental and lactational transfer to infants, who were considered to be the sensitive subpopulation (MDH, 2017c). MDH included a UF of 10 for intraspecies variability within the human population in its derivation of the RfDs for PFOA and PFOS. Because intraspecies toxicokinetic variability is already built into the exposure model for the drinking water criteria, the intraspecies UF could be reduced to 3 to account for toxicodynamic variability.

The results of our analysis confirm the utility of published PBPK models that evaluated the elimination of PFOA and PFOS through lactation in humans to predict infant serum levels. These models were developed to explore the ways in which physiological changes associated with development affect the pharmacokinetics of PFOA and PFOS in the mother, fetus, and infant (Loccisano et al., 2013; Verner et al., 2016), and incorporate elements of placental and lactational transfer of these compounds to the developing fetus and infant. Loccisano et al. (2013) predicted PFOA and PFOS concentrations in maternal plasma throughout pregnancy and lactation (up to six months), fetal plasma throughout gestation, and infants during lactation up to six months of age. Verner et al. (2016) developed a PBPK model of prenatal and post-natal PFOA and PFOS exposure to predict concentrations of these substances in children from birth to three years of age. While the models differed somewhat in their construction and data sources, they both predicted approximately three to four times higher PFOA plasma concentrations in breastfeeding infants as compared to the mothers at six months post-birth. In contrast, mean or median PFOS plasma concentrations in breastfeeding infants at six months (Loccisano et al., 2013; Verner et al., 2016) or children at three years (Verner et al., 2016) were predicted to be similar or only slightly increased as compared to concentrations in lactating mothers at the same time-point. These estimates are in agreement with our synthesis of the empirical data in rats, mice, and humans for PFOA and PFOS (Table 5).

### 4.3. Considerations in setting health-based criteria for other PFAS

Regulators in the US and abroad are tasked with deriving health-based criteria for PFAS, including the data-poor substances. The available toxicokinetic data and results of our analysis can be used to guide these efforts as they highlight toxicokinetic similarities and differences among these substances that will affect parameters such as tissue dose and overall body burden to specific PFAS. For example, our analysis indicates that PFHxS is similar to PFOA and PFOS in that its half-life in humans is significantly longer than in rats or mice; in humans, PFHxS excretion may be slower than that of PFOA and PFOS, but available half-life estimates vary widely. Incorporating these data into the toxicokinetic components of interspecies UFs is essential to establishing reliable health-protective criteria for PFAS based on animal toxicity data that better reflect the available scientific data for these substances than does the use of default UF values.

The shorter-chain PFBA and PFBS are excreted much more rapidly in all species than the six- and eight-carbon PFAS. Although toxicological potency is outside the scope of this review, the shorter-chain PFAS are generally less potent than the longer-chain chemicals, in part due to their more rapid excretion. Based on this rapid excretion, and its relevance to overall body burden and internal concentration profile, grouping the longer- and shorter-chain PFAS together for the purpose of establishing health-based criteria may not result in well-founded criteria in accordance with US EPA (2000) methodology for conducting health risk assessments for mixtures of chemicals.

The additivity approach is used for those substances for which there is reliable evidence for similar modes of action or, as a proxy, the same target organ or health endpoint (Meek et al., 2011; US EPA, 1989, 2000). Because the US EPA toxicity criteria of PFOA and PFOS are based on developmental endpoints (e.g., US EPA, 2016a; b), an additive approach is appropriate when these two compounds occur together in the environment. While PFHxS has a similar biological half-life to those of PFOA and PFOS, and it may make sense to group them together from a toxicokinetic standpont, a common toxicologic endpoint (i.e., similar toxicodynamics) would first need to be established for such a grouping. The question of grouping perfluorinated substances together for regulatory purposes was recently considered by a group of over 50 scientists and regulators in the “Zürich Statement on Future Actions on Per- and Polyfluoroalkyl Substances” (Ritscher et al., 2018), which noted that, " … such a grouping approach needs to be scientifically sound. Many participants shared the view that a grouping approach requires a better mechanistic understanding of the physicochemical and toxicological properties of PFASs as well as additional data that can be used to support grouping approaches for PFASs."

## 5. Conclusions

Overall, our analysis provides one of the first syntheses of available empirical PFAS toxicokinetic data to facilitate interpreting human relevance of findings observed in animal studies and developing health-based criteria for PFAS from such studies. Our analysis highlighted several notable differences among the different PFAS regarding species- and substance-specific tissue partitioning, half-life, and transfer to developing offspring via the placenta or lactation, as well as highlighted data gaps for certain substances. These differences should be incorporated into risk assessments of these substances, especially with respect to extrapolating PFAS exposure between species and across different life stages (e.g., breastfed infants versus adults). This analysis also supports the use of serum concentration, as opposed to administered dose or external exposure (e.g., drinking water) concentration, as the key parameter to use for risk assessments; this internal measurement will allow for the most meaningful tissue-dose comparison and aid in interspecies extrapolation. Lastly, the results of this analysis indicate that there are toxicokinetic differences among the different PFAS based on chain length, and these substances should not be regulated as a group without careful consideration of how the substance-specific toxicokinetics may impact potential toxicity, including differing specific target organ toxicity and overall body burden.

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## Conflict of interest

Dr. Barbara Beck has served as an expert in several litigation matters involving perfluorinated compounds. Some of the underlying research and analysis for this paper was performed during the context of those engagements and was sponsored by the defendant. Neither the law firms nor the defendant in those matters, however, asked that this paper be written or published. The preparation of this manuscript was supported only by the authors' employer (Gradient), and its conclusions are exclusively those of the authors. Aside from the authors and internal Gradient reviewers, no one has commented on or revised this manuscript prior to its submission.

## Declaration of interests

Gradient has been involved in several litigation and non-litigation matters involving perfluorinated compounds. Dr. Barbara Beck has served as an expert in several litigation matters involving perfluorinated compounds. Some of the underlying research and analysis for this paper was performed during the context of those engagements and was sponsored by the defendant. Neither the law firms nor the defendant in those matters, however, asked that this paper be written or published. The preparation of this manuscript was supported only by the authors' employer (Gradient), and its conclusions are exclusively those of the authors. Aside from the authors and internal Gradient reviewers, no one has commented on or revised this manuscript prior to its submission.

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## Appendix A. Supplementary data

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