Critical Review

Tracking the Pathways of Human Exposure to Perfluorocarboxylates

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Recent analyses of perfluorooctanoate (PFOA) in human blood sera show that the background-exposed population in industrialized countries worldwide exhibits a narrow concentration range; arithmetic means of published studies range between 2 and 8 μg/L PFOA, with the exception of a few outlier studies. The globally comparable human serum concentrations of PFOA and characteristic dominance of PFOA with respect to other perfluorocarboxylate (PFCA) homologues indicate that exposure pathways of humans differ from those of wildlife, where perfluorononanoate (PFNA) is often the dominant homologue. The observed correlations between perfluorooctane sulfonate (PFOS) and PFOA in human serum together with a simultaneous downward time trend of these compounds in human blood sera and blood spots from the year 2000 onward indicate a connection between historical perfluorooctanesulfonyl (POSF) production (phased out by the major manufacturer in 2000−2002) and exposure to both PFOS and PFOA. A comparison of estimated daily intakes to humans based on samples from exposure media (collected post 2000) indicates that food intake is the major contemporary exposure pathway for the background population, whereas drinking water exposure is dominant for populations near sources of contaminated drinking water. A one-compartment pharmacokinetic model used to back-calculate daily intakes from serum levels is shown to provide agreement within a factor of 1.5−5.5 of the daily intakes derived from exposure media, which provides further supporting evidence that dietary exposure is a major ongoing exposure pathway of PFOA to the background population.

Introduction

Perfluorocarboxylates (PFCAs) have been manufactured since 1947 initially by electrochemical fluorination (ECF) and, since the 1970s, also by telomerization (*1*). Manufacture of PFCAs using the ECF process was phased out between 2000 and 2002, but manufacture by telomerization is ongoing. The main use of PFCAs is as processing aids in fluoropolymer manufacture, but historically they have had a wide range of other minor uses (*1*). Direct industrial emissions are estimated to be the major source of PFCAs to the environment (*1*), although PFCAs are also breakdown products of "precursor" compounds such as fluorotelomer alcohols (FTOHs) and perfluoroalkyl sulfonamido alcohols (FOSE−OHs) (*2*−*10*) and processing impurities in commercial products (*1*). PFCAs are of scientific and regulatory interest as they are a class of extremely persistent chemicals (*11*) that have been found globally in wildlife and in humans (*12*). Toxicology studies of PFOA in rodents have shown increased incidence of liver, pancreas, and testicular tumors in rodents although epidemiological studies indicate a lack of carcinogenic activity in humans (*13*). An observed negative association between PFOA serum concentration and birth weight has recently generated interest for the developmental toxicology of PFOA (*14*). However, further research is needed to determine if noncausal physiological associations could explain the alterations in fetal growth indicators (*15*).

Although the presence of PFCAs in human serum has generated a great deal of attention and environmental research, many questions remain about the pathways of human contamination (*16*). Source elucidation of PFCAs in humans has proven to be complicated because concentrations of PFCAs present in humans represent the integration of PFCA exposure from a vast number of pathways over an extended period of time. Here we critically evaluate the current published literature on human exposure to PFCAs with the aim of providing new insights into the pathways of human exposure. The review is divided into three sections which focus on (i) concentrations and trends in human sera, (ii) exposure estimates from concentrations of PFCAs in exposure media and, (iii) pharmacokinetics and pharmacokinetic modeling. Due to the prevalence of data, emphasis is placed on PFOA.

Concentrations, Homologue Patterns and Temporal Trends in Human Sera

PFCAs are distributed in extracellular space and are slowly eliminated in humans (*17*−*20*) with an estimated elimination half-life of 3.5 years (*20*). PFOA and occasionally longer chain homologues (C9 − C11) have been measured in human sera (*17, 21*−*49*), plasma (*50*−*54*), and whole blood (*55*−*63*). Concentrations of PFOA in serum or plasma and whole blood display an approximate 2:1 ratio (*17*) making measurements in these matrices comparable after correction. Some studies have also reported the presence of PFOA in liver, muscle, and adipose tissue (*24, 58*).

Analyzed concentrations of PFOA in sera from various populations can be divided into three categories based on the type of exposure (Figure 1). The highest serum concentrations of PFOA (median concentrations 1100−1300 μg/L) have been measured in ammonium perfluorooctanoate (APFO) production workers (*22, 26*). Elevated serum concentrations of PFOA (mean 27.4−423 μg/L) in nonoccupationally exposed populations have been reported from Little Hocking, U.S. (*48*) and Arnsberg, Germany (*52*) where the

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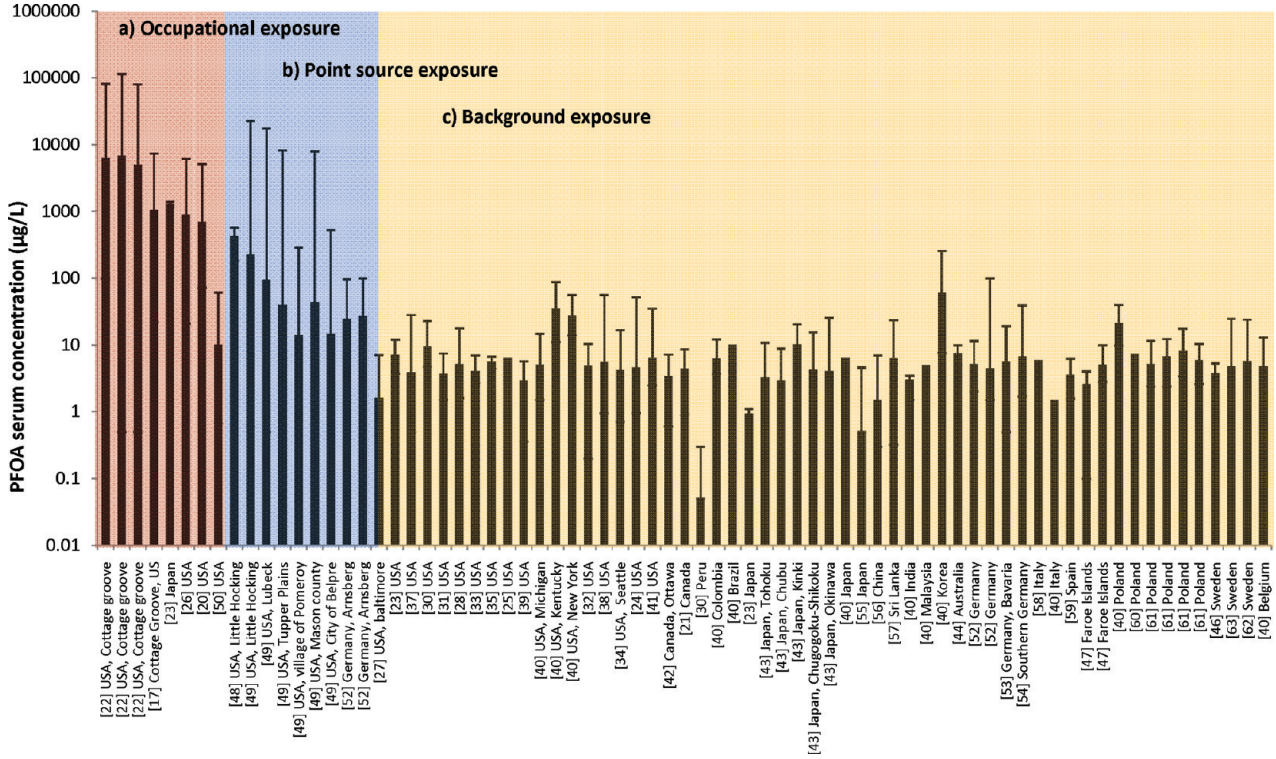

FIGURE 1. Human serum concentrations of PFOA (µg/L) in populations of (a) occupational exposure, (b) point source exposure, and (c) background exposure. Solid bars depict arithmetic mean concentrations and the min−max range is given by the error bars. Whole blood concentrations have been adjusted to serum concentration by multiplying with a factor of 2. References of the individual studies are given in square brackets on the *x*-axis.

use of contaminated soil conditioner and a fluoropolymer production site, respectively, were identified as sources of contamination. Systematic analysis showed that drinking water was the primary predictor of PFOA serum concentrations in Arnsberg and Little Hocking. However, in the majority of serum samples from the general population in different parts of the world, the concentrations of PFOA are reasonably consistent with only small interregional differences (Figure 1). For example, cross-continental biomonitoring studies of children, teenagers, adults, and elderly populations in the U.S. showed that PFOA concentrations in sera are log normally distributed with geometric mean values of 4−5 µg/L (*24, 25, 28, 34*), with most other studies from industrialized countries in the rest of the world reporting mean concentrations between 2 and 8 µg/L (Figure 1). Notable exceptions from this trend include high median concentrations of PFOA in populations from Korea (male 36.8; female 30.9 µg/L), Poland (male 20.5, female 23.2 µg/L), New York (25.2 µg/L), and Kentucky (male 38.1, female 20 µg/L) (*40*) as well as low concentrations in Peruvian citizens (75% of the samples <0.1 µg/L) (*30*). The comparable concentrations of PFOA in Brazil (10 µg/L), Colombia (6.2 µg/L) (*40*), and Australia (7.6 µg/L) (*44*) with those of Europe and North America are interesting because the Southern Hemisphere has no known manufacturing sources of PFOA (*1*) and background concentrations in the environment are much lower (*45*). Although, there are concerns about the accuracy and reproducibility in analytical methods for PFCAs, whole blood and serum measurements have been shown to be relatively reliable in an interlaboratory comparison (*65*).

The homologue pattern in human sera is typically PFOA > PFNA > PFDA (perfluorodecanoate), with PFCAs of 10 carbons or more being detected infrequently (Figure 2) (*21, 23, 28−33, 44, 56, 59−62*). A qualitative comparison of the homologue pattern in blood and other tissues of wildlife (*12, 64−69*) reveals that the dominance of PFOA is with a few exceptions (e.g., in sea turtles (*72*), sea otters (*73*), eel and flounder (*74*)) distinctive to humans (*12*). The homologue pattern in terrestrial and marine mammals, various fish, and bird species displays a characteristic dominance of odd-carbon chain lengths (e.g., C9, C11), which are at higher concentrations than the next shortest even-carbon homologues (e.g., C8, C10) (*12, 64−69*). Although wildlife samples comprise liver, egg, and whole body homogenates in addition to whole blood and serum samples, the PFCA profile is fairly consistent regardless of sampled tissue (*70*). The PFNA > PFOA pattern in biota has been attributed to increasing bioconcentration and biomagnification with PFCA chain length (*70, 71*). The dominance of PFOA in human serum leads to two different hypotheses: (i) the pathways of human exposure to PFOA are different from those of wildlife, i.e., not related to food chain bioaccumulation/biomagnification, and/or (ii) humans display different pharmacokinetics (e.g., different relative retention pattern of PFCAs with increasing chain lengths in humans relative to wildlife).

Although it is common to observe a positive correlation between serum concentrations and age for persistent compounds with relatively long elimination half-lives, no clear trend with age has been observed for PFOA (*24, 25, 28*). The lack of a trend may be due to (i) efficient *in utero* transfer of PFOA (*27, 54, 55, 76*), (ii) a higher body-weight-normalized exposure to infants, toddlers and children (*78*), (iii) increasing exposure levels over time in proportion to increasing production (*35*), or a combination of these factors. In contrast to age, a significant difference in PFOA serum concentrations has been determined with respect to sex and ethnicity (*31, 53, 54, 56, 79*), which implies that genetic variability or life-style factors affect either the exposure or pharmacokinetics of PFOA.

A number of studies analyzing PFCAs in human sera have reported a significant correlation between PFOS and PFOA in North America and Europe ($0.05 > p$-values > 0.0001, Table S2) (*27−29, 32, 34−37, 40, 42, 53, 54, 59*). The observed correlation between PFOS and PFOA is interesting because these com-

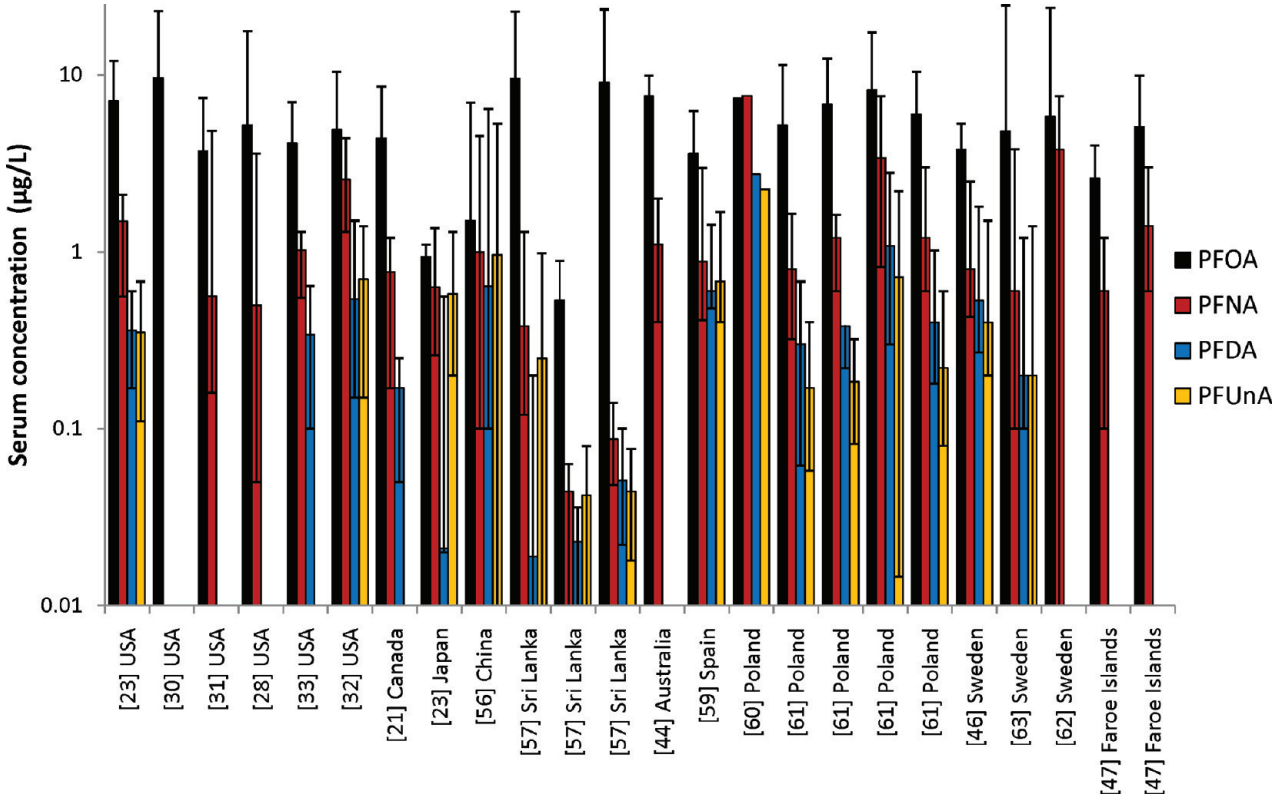

FIGURE 2. Human serum concentrations (μg/L) of PFOA, PFNA, PFDA, and PFUnA in background exposed populations. Solid bars represent arithmetic mean concentrations and the min−max range is given by the error bars. Whole blood concentrations have been adjusted to serum concentration by multiplying with a factor of 2. References of the individual studies are given in square brackets on the *x*-axis.

pounds cannot convert directly to each other, nor do they have a major source to the environment in common according to global emission inventories (*1, 80*). PFOS and other products based on POSF-based chemistry have been produced exclusively by the ECF process and furthermore PFOS is not a breakdown product of fluorochemicals produced by any other process. Releases of PFOA, however, result from both the ECF and telomerization production processes. PFOA is an intended end product and a residual impurity in products from both the main production processes, and both telomer- and POSF-based precursors that degrade to form PFOA in the environment. Pathways that could give rise to a human co-exposure of PFOA and PFOS in North America, Europe, and Australia include (i) microbial or atmospheric degradation (*8, 9*) of POSF-based precursors and subsequent coexposure to both PFOA/PFOS via environmental pathways, (ii) exposure to POSF-based precursor compounds that are metabolized to both PFOA and PFOS, or (iii) exposure to residual amounts of PFOA and PFOS from POSF-based consumer products (*1*). Regarding the second suggested pathway it should be noted that biotransformation studies have not identified PFCA metabolites from *N*-ethylsulfonamidoethanol (*N*-EtFOSE) in rats (*5, 6*) and *N*-ethylperfluorooctanesulfanoamide (*N*-EtPFOSA) in trout (*7*). However, degradation products of POSF-based polyfluoroalkyl phosphate surfactants (PAPS) and polymeric materials remain to be identified.

De Silva and Mabury (*21*) proposed quantitative analysis of linear and branched carbon chain isomers in serum as a direct tool for source elucidation. ECF-produced PFCAs have been found to contain 20−30% of branched chain isomers, whereas telomerization produces >99% linear chain PFCAs (*21*). Thus, an observed dominance of linear PFOA in Canadian human sera was suggested to be evidence for a dominance of fluorotelomer-based sources. However, studies showing a preferential elimination of branched compared to linear PFOA isomers in human (*17*), and animal studies (*18*) indicate that branched:linear ratios of PFOA isomers need to be corrected for the differences in pharmacokinetic behavior before being used for exposure interpretation.

Temporal trends of serum in the U.S. population have shown an increase of PFOA concentrations between 1974 and 1989 (from 2.2 to 5.5 μg/L) after which concentrations leveled off between 1989 and 2001 (5.5−4.2 μg/L) (*27*). A decrease in serum concentrations of PFOA has been observed in the U.S. and Norway starting at around year 2000 with estimated disappearance half-lives of approximately 4.4 years (*29, 35−37, 76, 77*) (Figure 3a), which are slightly longer than the elimination half-life reported in retired workers (*20*). Given the continued production of APFO (Figure 3b), the environmental persistence of PFOA and absence of declining concentration trends in wildlife (*67−69*), the rapid response in human serum likely reflects a decrease in consumer product exposure. As ECF was the sole manufacturing process used for PFOS, the simultaneous decrease of PFOA and PFOS (Figure S1) (*29, 35−37, 76*) indicates that exposure pathways of these compounds were historically linked. Only POSF production has reduced since 2000 (*81*) (Figure 3b) (fluorotelomer and APFO production has remained constant) indicating a link between the 2000−2002 POSF phase-out and the decline of PFOS/PFOA in human serum. In comparison to PFOA and PFOS, it is interesting to note that PFNA and PFDA serum concentrations have been constant or slightly increasing (*29, 76, 77*) after year 2000 (Figures S2 and S3), indicating an ongoing exposure for these compounds and/or that serum half-lives are much longer. Contrary to the clear downward trends in the Northern Hemisphere, preliminary data from Australian serum samples indicate no decrease in PFOA concentrations between 2002/2003 (*44*) and 2006/2007 (*82*).

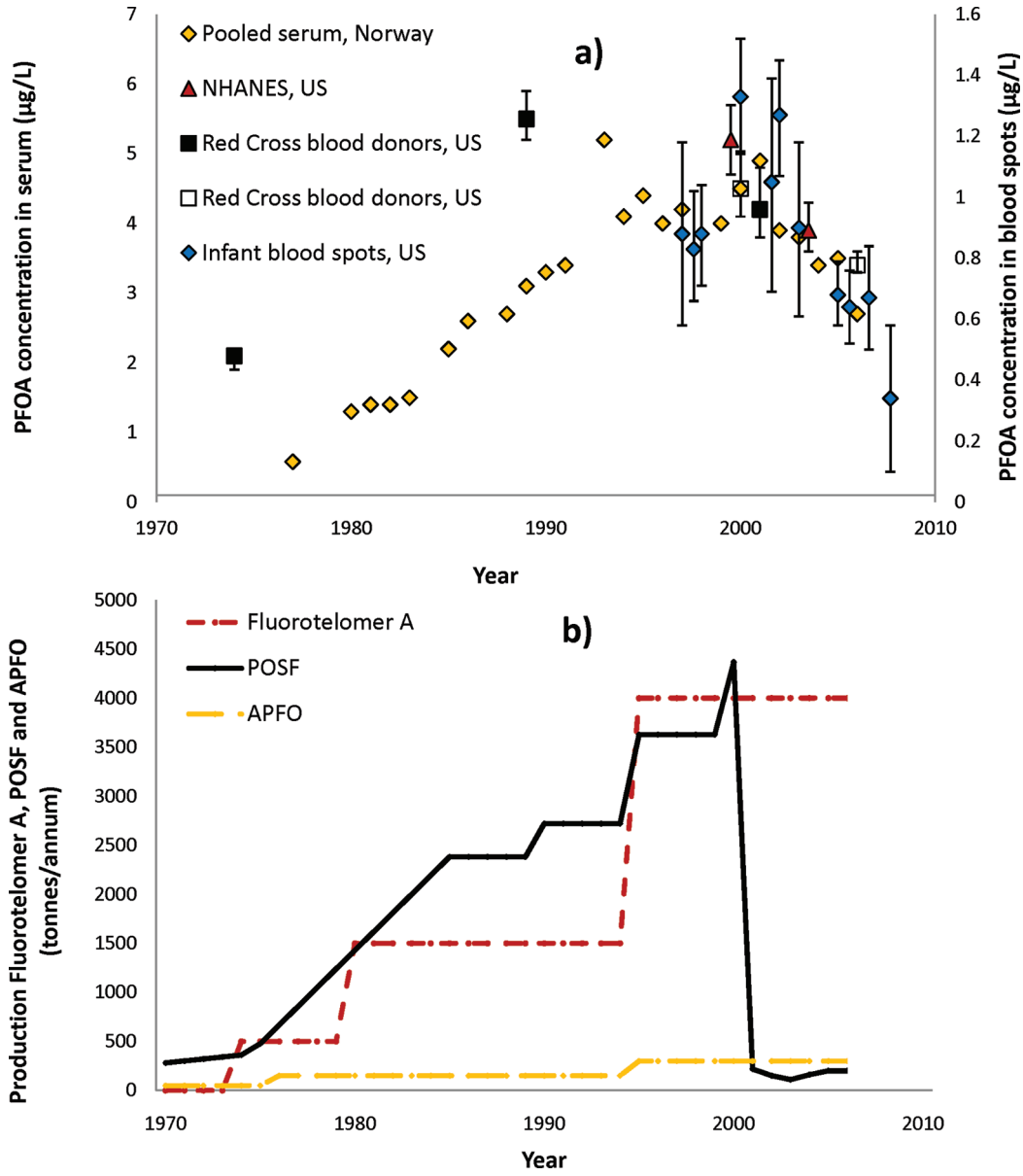

FIGURE 3. (a) Temporal trends of PFOA in human serum (µg/L) from pooled serum, Norway (*77*), NHANES, U.S. (*29*), and Red cross blood donors (*35, 37*). The temporal trend in infant blood spots (µg/L) (*76*) is plotted on the second *y*-axis. This was done to facilitate comparison of time trends. The blood spot concentrations were about a factor of 5 lower than serum concentrations presumably because (i) they were blood and not serum samples (approximately a factor of 2 lower), and (ii) they were from infants rather than adults. (b) Estimated production of POSF, APFO and Fluorotelomer A, (tonnes/annum) (*1, 81*).

Taken as a whole, the inter-regionally consistent serum concentrations of PFOA, characteristic homologue pattern (PFOA > PFNA), and rapid response to production changes indicate that exposure pathways of PFOA to humans are different from those to wildlife. Furthermore, the PFOS:PFOA correlation and similar time trend for these compounds indicate that human serum levels are influenced by a historical POSF-based exposure pathway.

Exposure Estimates, Homologue Patterns and Temporal Trends in Exposure Media

Measured concentrations in exposure media combined with estimated exposure factors provide a comparison of the relative importance of different exposure pathways. To date, measurements of multiple exposure media for a single population are not available. However, a compilation of estimated daily intakes (*83, 85*−*91*) for populations of typical background exposure, elevated water concentrations, and occupational exposure illustrate the relative importance of different exposure pathways (Figure 4). In line with previous assessments (*78*), dietary intake as determined by a duplicate serving study in Germany (*87*) is estimated to be the dominant pathway of exposure for the background exposed population (Figure 4a). House dust (*86*) and "background" drinking water (*88*) are estimated to be minor exposure pathways. Drinking water concentrations of PFOA display large interregional variability (*48, 89, 91, 93*−*95*) from below 0.32 (*88*) up to 7200 ng/L (*48*). The relative importance of drinking water as an exposure medium becomes significant at concentrations of 40 ng/L (*90*), and dominates exposure at 519 ng/L (*91*) (Figure 3b and c). Although limited data are available for occupational exposure, ambient air concentrations of PFOA (1 $\mu g/m^3$) in the vicinity of a fluoropolymer manufacture facility (*92*) suggest that inhalation is a major route of exposure for fluorochemical workers, although dermal contact and incidental ingestion (not quantified here) may also contribute (*26*) (Figure 4d).

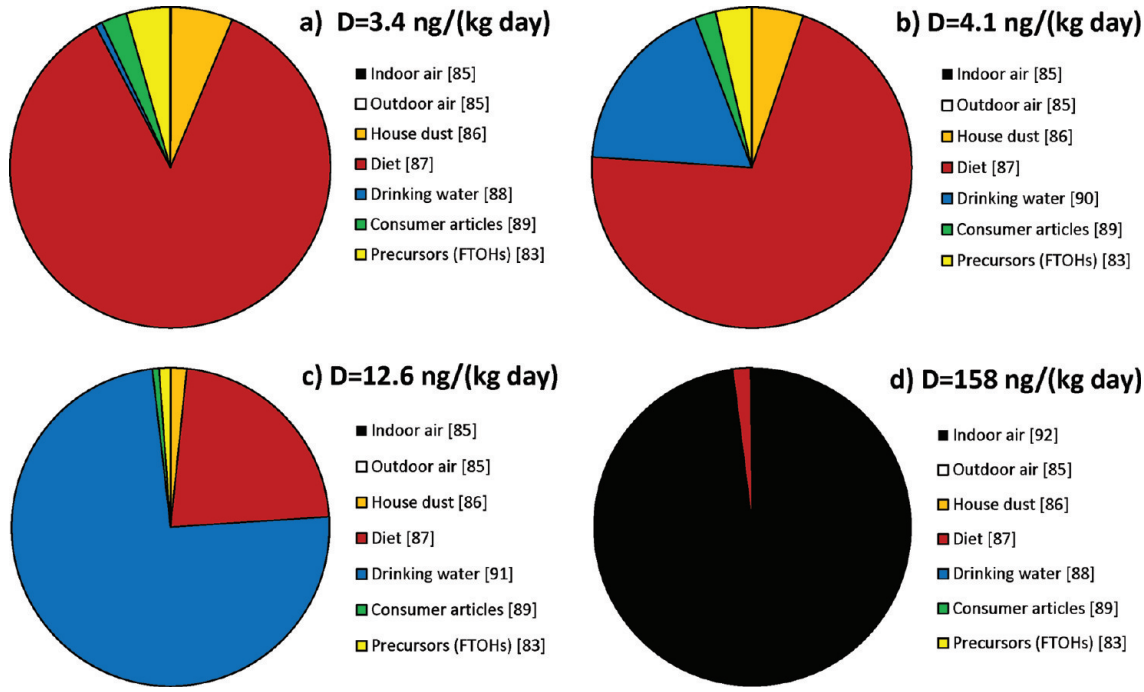

FIGURE 4. Pie charts displaying a compilation of the estimated daily intakes of male adults (D) and relative importance of exposure pathways from separate studies. Each pie chart represents an exposure scenario representative of (a) background concentrations in drinking water (1.3 ng/L); (b) elevated concentrations in drinking water (40 ng/L); (c) point sources of drinking water contamination (519 ng/L); (d) occupationally exposed individuals (indoor air concentrations 1 μg/m^3). References of the individual studies are given in square brackets in the legends of each chart.

Previous studies have identified PFOA as a metabolite of precursor compounds such as fluorotelomer alcohols (FTOHs) and telomer-based (PAPS) (*21, 84*). Exposure to FTOHs has been estimated to occur primarily via food packaging materials (*96, 97*), indoor air (*85, 98*), and house dust (*86*). As displayed in Figure 4, the biotransformation of FTOHs was estimated to be of minor significance for the daily intakes of PFOA (*83*) due to the small fraction of 8:2 FTOH forming PFOA in laboratory *in vivo* and *in vitro* experiments (*2*−*4*). A recent study showing substantial amounts of PAPS in pooled human serum from the U.S. highlights the need for inclusion of these compounds in exposure assessments (*99*). An improved pharmacokinetic understanding of FTOHs and PAPS metabolism and measured concentrations in exposure media (e.g., food) would help to evaluate the relative importance of precursor compounds.

Estimated exposures extrapolated from exposure media (*78, 83*) in Figure 4 may be limited by the variability in environmental concentrations, consumer behavior, product formulations, or as discussed later, unknown exposure pathways. Trudel et al. (*78*) illustrated that uncertainty in measured concentrations of food items had the highest influence on variability in estimated intakes. Due to the challenges of overcoming matrix effects in the analysis of foodstuffs, most current reported concentrations of PFOA in food are below the current limit of quantification of 0.1−1 ng/g. Infrequent detections of PFOA have been reported in a variety of food items including fish (*100*−*103*), meat (*100*), potatoes (*105*), fast food (*100*), milk, apples, green beans, bread, and eggs (see Table S8). Clearly, improved analytical data are needed for food items as well as an improved understanding of the sources of PFCA contamination in food.

The relationships between PFCA homologues in food items and human serum will provide valuable insights into the sources of food contamination, but unfortunately there is currently a paucity of measurements of PFCA profiles in food. It might be expected that if meat and fish contaminated via bioaccumulation in food webs were the major source of PFCAs in food then a PFNA ≥ PFOA homologue pattern would be expected in total diet intake (*100*−*102*). Interestingly, a Japanese duplicate diet study (*104*) measured PFOA at concentrations similar to those of Fromme et al. (*87*), whereas PFNA was not detected in any of the samples. The different homologue pattern of individual wild food items (*100*−*102*) compared to duplicate food samples (*104*) provides a preliminary indication that bioaccumulative pathways related to environmental contamination are not the major source of PFOA in food. Studies investigating the importance of food chain pathways found positive correlations between the consumption of seafood (*61*) and whale meat (*47*) and serum concentrations of PFNA, PFDA, PFUnA, and perfluorododecanoate (PFDoA). However, for PFOA only weak correlations were observed between serum concentrations and consumption of fish (*61*) and red meat (*75*) (other homologues were not reported for red meat). These studies indicate that exposure pathways to longer chain homologues (>C8) are distinct from those for PFOA. Potential pathways that could result in a dominance of PFOA in the total diet include the uptake in high water content crops (*88, 91, 93*−*95, 106*) or migration from food packaging paper (*96, 97*). A recent study by Stahl et al. (*106*) demonstrated that soil-to-plant uptake of PFOA occurs in maize, oats, wheat, and potatoes with concentrations in the ears, grain, and tuber reaching 0.1−3% of the concentration in soil. Recently, it has been shown that agricultural soils have been contaminated with PFOA via application of sewage sludge, providing a transfer mechanism of commercially produced food that may be different from that of wild food (*107*).

A significant drawback in understanding exposure is the lack of comprehensive time trends for PFCA concentration data in exposure media. There are, nevertheless, some indications of a decline in consumer product-related exposure pathways. House dust samples collected in 2000−2003 from American (*86*) and Canadian (*108*) homes contain higher PFOA concentrations compared to more recently collected samples from Japan (*109*), Sweden (*110*), and Germany (*111*).

Although the difference among the studies could be due to regional and methodological differences, higher concentrations of PFOA in archived carpet protectors (*112*) compared with currently used alternatives (*89*) and/or a larger historical market share of POSF-based products could explain the higher concentrations in archived samples. A positive correlation ($r > 0.82$, $p < 0.0001$) between PFOA and PFOS in house dust (*86*) indicates that POSF-based products may be a common exposure pathway of these chemicals to the indoor environment. A sharp decrease in concentrations of (8.3 − <0.1 ng/g) of *N*-ethyl perfluorooctanesulfonamide (*N*-EtPFOSA) in Canadian fast food composites has been reported between 1994 and 2002 (*113*), as a hypothesized consequence of changes in food paper formulations. Although *N*-EtPFOSA is not believed to metabolize to PFOA (*5*−*8*), POSF-based food packaging materials contained a suite of residual perfluoroalkyl compounds that were not measured in the study (*113*). Interestingly, the initiation year of the decrease (1994) indicates that certain consumer-based pathways of PFCAs disappeared before completion of the ECF phase-out in 2000−2002. To address the paucity of temporally resolved exposure data, analysis of archived exposure media (e.g., food, house dust, and consumer products) for PFCAs and related compounds is needed.

Pharmacokinetics and Pharmacokinetic Modeling of PFCAs

The pharmacokinetic behavior of PFOA, and to a lesser extent other PFCAs, have been studied in laboratory animals and humans. Oral bioavailability of APFO has been determined to be between 66 and ~100% (*20, 114*). Efficient uptake via inhalation of APFO which is rapidly converted to PFOA *in vivo* has been observed, although no quantitative uptake efficiencies have been reported (*115, 116*). Dermal exposure studies have shown that PFOA can penetrate the skin, albeit with a low absorption efficiency (*117*). The elimination half-lives of PFOA reported in rats (*114, 118*−*122*), dogs (*118*), mice (*123*), and cynomolgus monkeys (*124*) display a large interspecies variation (<1 day for female rats to approximately 1 month for monkeys) and gender specificity. In comparison, estimated serum half-lives for PFOA in human serum are much longer with a geometric mean value of 3.5 years (range 1.5−9.1 years) reported for retired workers (*20*). The half-life of serum elimination was not associated with initial concentrations, gender, age, or time elapsed between the retirement and first blood collection (*20*). Scaling of animal derived half-lives (*114, 118*−*122*) with hepatic blood flow rates (*125, 126*) cannot replicate empirically determined elimination half-lives of PFOA in humans (*20*). Recently, renal resorption mediated by organic anion transporters (OATs) was proposed as a mechanism that could explain the observed species and gender based differences in elimination half-lives (*127*). As previously mentioned, the relative retention of PFCAs with varying chain lengths has an important implication for the interpretation of the PFCA homologue patterns in human serum (PFOA >PFNA). In pharmacokinetic studies, renal clearance rates have generally been observed in the order PFOA > PFNA > PFDA (*121, 123*), which is also consistent with the current understanding of elimination behavior in wildlife (*71*). However, measured tissue distributions and elimination half-lives of PFCAs other than PFOA are still missing in humans.

A common approach to characterizing the chemical concentration in a specific physiological compartment such as blood involves the use of physiologically based pharmacokinetic (PBPK) modeling with a detailed description of the major groups of tissues or organs together with the simulation of the arterial and venous circulatory system (*128*). Under steady-state conditions when intakes are fairly constant with time, the rate of chemical intake matches the rate of chemical elimination and the concentrations in the various tissues or physiological compartments do not change significantly with time, creating constant concentration ratios among the various sites of chemical deposition in the body. In these cases, relatively simple models can be developed based on noncompartmental, one-compartment, or two-compartment concepts. A one-compartment steady-state pharmacokinetic model (eq 1) has recently been applied to relate internal concentrations of PFOA in humans to estimated daily intakes (*129*). It is thought to be particularly applicable for persistent compounds such as PFOA and for the low concentrations typical of environmental exposure.

$$C_{ss} = \frac{T_{1/2}D}{0.693 \cdot V_D} \quad (1)$$

Where the steady-state serum concentration (C_{ss}) is a function of the total elimination half-life ($T_{1/2}$) (discussed above), body weight normalized daily internal intake or dose (D), and fractional volume of distribution (V_D) (discussed below). By rearrangement, the model can also be used to back-calculate D if C_{ss} is available (aka "reverse dosimetry").

Estimates of V_D have been obtained from single-dose studies as well as multiple dosing studies; primarily in rodents and primates (see Table S3). The estimated values depend on experimental design (type of dosing) and the model used for analysis. Single-dose studies have reported values of V_D of 210−340 mL/kg (*114, 121*) in rats and 181−198 mL/kg in monkeys (*124*), indicating that single doses of PFOA are distributed primarily in the blood (*121*). Based on repeated dose studies in monkeys, V_D values of 1260−6340 mL/kg have been estimated for subchronic dosing (*124*). Thus, V_D values calculated from steady-state dosing of PFOA are approximately an order of magnitude higher than those derived from a single dose. The increase in V_D following continuous dosing indicates that PFOA distributes to extracellular fluids and highly perfused organs such as liver and kidney in addition to blood.

In the following model evaluation a V_D derived from subchronic dose studies (i.e., 3.6 L/kg) was used as it represents long-term exposure of humans more realistically. As previously shown in this review, drinking water concentrations exceeding 500 ng/L constitute the major exposure pathway for nonoccupationally exposed populations (Figure 3c). Hence, measured serum concentrations from subpopulations exposed to elevated drinking water concentrations can be used to evaluate model accuracy. To represent the variability and uncertainty in V_D, $T_{1/2}$, and C_{ss} a probabilistic approach was used to simulate the expected daily intakes associated with measured serum concentrations (parameterization in SI). Figure 5a shows the back-calculated internal daily intake from serum concentrations compared to estimated internal daily intakes derived from drinking water concentrations. The pharmacokinetic model estimates the intakes within a factor 1.5−5.5 for populations in the Arnsberg (*52, 91*), Little Hocking (*48, 49*), and Lubeck (*49, 51*) regions. Noteworthy is the large uncertainty in predicted daily intakes for Little Hocking (2005−2006) and Lubeck (2005−2006). A sensitivity analysis showed that serum concentrations had the highest influence on back-calculated daily intakes from Little Hocking and Lubeck (Figures S7−S8), indicating that duration and frequency of drinking water exposure displayed large variability. The model overprediction in Arnsberg and Little Hocking (2002−2005) suggests that the value of V_D is too high (Figures S5 and S6).

We can also use the same model parameterization to back-calculate internal daily intakes of PFOA from serum concentrations for a background exposed population in Bavaria, Germany in 2005 (*53*) for which daily dietary intakes of PFOA

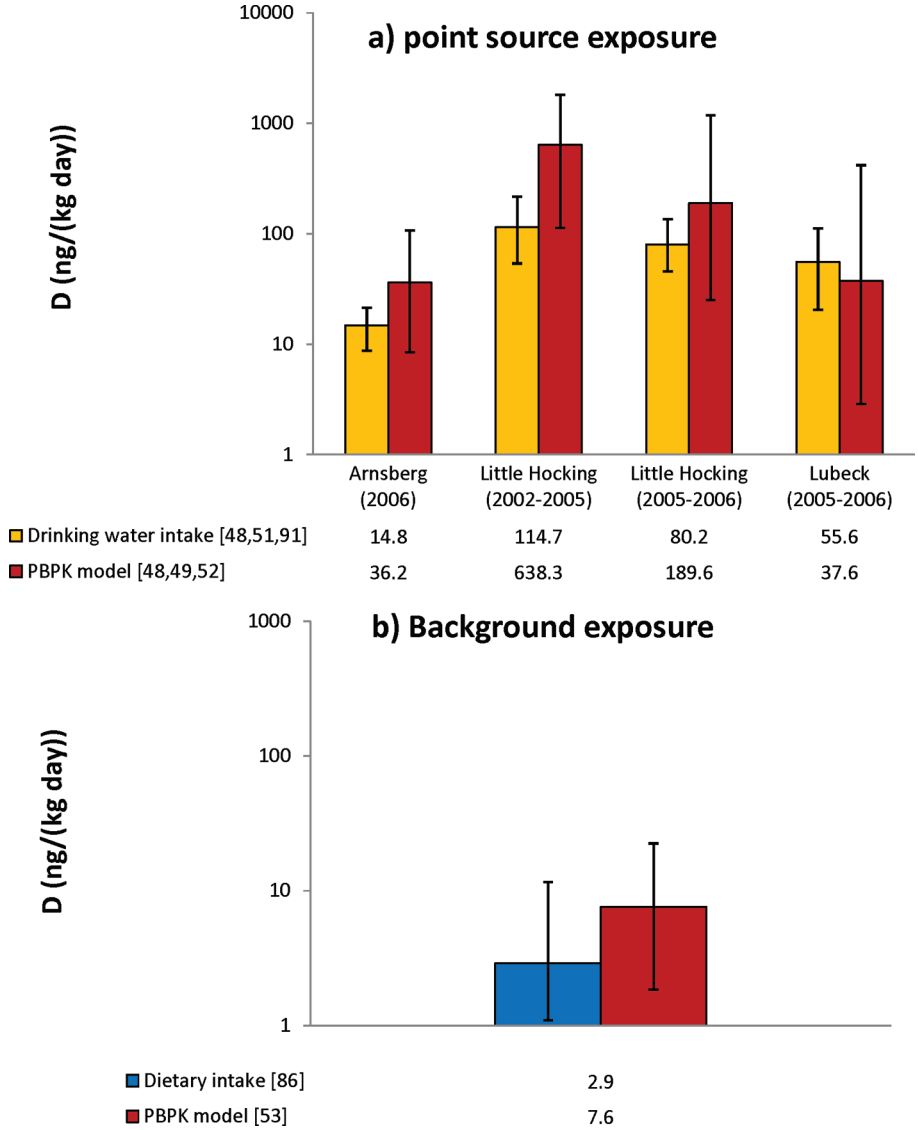

FIGURE 5. Comparison of estimated daily intakes (*D*) of PFOA using measurements of exposure media and the one-compartment pharmacokinetic relationship for (a) exposure to point source contaminated drinking water and (b) background exposure to food. Solid bars represent median values and the error bars represent the 10th and 90th percentile, respectively. References of the individual studies used for making the estimates of daily intake are given in square brackets in the chart legends. Calculations are explained in more detail in the Supporting Information.

are also available (*87*). The measured median daily internal intake of PFOA from food (*87*) was determined to be a factor of 2.6 lower than back-calculated internal daily intakes from matched serum measurements (Figure 5b) (*53*). It should be noted that similar calculations have recently been made. Trudel et al. (*78*) concluded that estimated internal daily intake from multiple pathways (3 ng/(kg day) median) were within the range of back-calculated daily internal intakes from serum concentrations for the background population. However, Fromme et al. (*87*) concluded that the daily internal intake of PFOA (derived only from dietary intake) was a factor of 6 higher than the back-calculated internal daily intake from serum concentrations despite the similar estimated intake (2.9 ng/(kg day). The discrepancy of these two earlier studies is primarily explained by the chosen value of V_D (0.2 L/kg in ref *87* and median of 3.6 L/kg in ref *78*) illustrating the importance of correct parametrization of eq 1.

Despite the incomplete understanding of the pharmacokinetic behavior of PFCAs, the one-compartment model, if correctly parameterized, provides an estimation within a factor of 1.5−5.5 of the internal daily intakes. The disagreement between the two estimates could be a result of uncertainty in model input parameters, primarily V_D. As serum concentrations of PFOA from 2005 reflect both ongoing and historical pathways the overprediction of daily intakes from the pharmacokinetic model may be due to the inappropriateness of the steady-state assumption. The model evaluations (Figure 5) provide further supporting evidence that dietary exposure is a major ongoing exposure pathway of PFCAs, except near contaminated drinking water sources, where drinking water exposure dominates.

Concluding Remarks

Research presented in this review taken as a whole supports the hypothesis that contemporary serum concentrations of PFOA in humans are influenced by an unknown historical exposure source derived from production of POSF-based consumer products prior to the 2000−2002 phase-out by the major manufacturer. The estimates made here and elsewhere that food dominates the current estimated daily intakes of PFOA are primarily supported by two separate duplicate diet studies performed in Germany (*87*) and Japan (*104*), respectively. Nevertheless, improved analytical methods and

larger analyzed sample sets within the European research collaboration, PERFOOD (*130*), will soon provide more accurate estimates of the daily intake via food as well as investigate how the food is being contaminated (i.e., the relative importance of environmental contamination versus contamination from food processing/packaging).

As the fluorine industry has announced a commitment to the phase-out of eight carbon perfluoroalkyl chemistry by 2015 (*131*), future human exposure to PFOA will depend progressively more on legacy sources of contamination in the environment and less on consumer product-derived exposure pathways. Therefore the currently observed rate of decline of PFOA in human serum since the phase-out of POSF-based products by the major manufacturer will probably not be sustained much longer as environmentally derived exposure pathways become relatively more important. There will, however, probably still be a continued albeit slower decline as the concentrations of environmentally contaminated food will also decline in proportion to the estimated future declines in environmental concentrations in temperate/source regions (*132*) where much of the global food is produced. It has been hypothesized (*132*) that (i) the worlds oceans will contain the majority of the legacy releases of PFOA, (ii) once releases cease the levels in the surface oceans will gradually become approximately the same as ocean water becomes well-mixed with respect to PFOA, and (iii) PFOA will only slowly be removed from the surface oceans by vertical transport to the deep oceans. Therefore, into the far future humans will continue to receive a fairly constant, low-level exposure to PFOA from the consumption of marine fish and other seafood.

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Supporting Information Available

Summary of PFOS:PFOA correlations in human serum; temporal trends of PFOS, PFNA, and PFDA in human serum; tables of concentrations of PFCAs and precursors in exposure media; an explanation of the derivation of the one-compartment pharmacokinetic model; and further details of the uncertainty analysis including contribution to variance plots. This material is available free of charge via the Internet at http://pubs.acs.org.

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