Considering the role of precursor compounds in consumer exposure to PFOS and PFOA

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Abstract

The exposure of humans to perfluorooctane sulfonate (PFOS) and perfluorooctanoic acid (PFOA) was quantified with emphasis on assessing the relative importance of metabolic transformation of precursor compounds. A scenario based assessment approach (SceBRA) was used to model the exposure to these compounds from a variety of different pathways, the uptake into the human body and resulting daily doses. To capture the physiological and behavioral differences of age and gender, the exposure and resulting doses for seven consumer groups were calculated. The estimated chronic doses of a general population of an industrialized country range from 3.9 to 520 ng/(kg·day) and 0.3 to 140 ng/(kg·day) for PFOS and PFOA, respectively. The uptake and subsequent biotransformation of precursors was estimated to account for 2-6% of the daily dose for PFOS and 2-8% for PFOA. Similar to a preceding study, uptake of perfluorinated acids from contaminated food and drinking water was identified as the most

important pathway of exposure for the general population. The biotransformation yields of telomer-based precursors and to a lesser extent perfluorooctanesulfonylfluoride-based precursors were identified as influential parameters in the uncertainty analysis. Fast food consumption and fraction of food packaging paper treated with PFCs were influential parameters for determining the doses of PFOA.

Keywords: perfluorinated, precursors, telomer alcohols, perfluorooctanesulfonamidoalcohols, human exposure

Introduction

Polyfluorinated compounds (PFCs) comprise a large group of specialty chemicals that have been produced since the 1950s for numerous applications in industrial processes as well as consumer products (Prevedouros et al., 2006). Recent advances in analytical techniques have enabled the detection of perfluorinated sulfonates (PFSAs) and perfluorinated carboxylates (PFCAs) in wildlife and humans identifying them as an emerging class of environmental pollutants. These compounds have been shown to be very persistent in the environment (Kissa, 2001), with PFSAs and to a lesser extent PFCAs having the potential to bioaccumulate in biota (Houde et al., 2006). Perfluorooctane sulfonate (PFOS) and perfluorooctanoic acid (PFOA) have been the most widely studied compounds. Animal studies have shown that long term exposure to high concentrations of PFOA and PFOS affect the lipid metabolism resulting in liver weight increase and adverse developmental effects in the second generation (Seacat et al., 2002; Lau, Butenhoff and Rogersa 2004; Fuentes et al., 2007; Kennedy et al., 2007). Apelberg et al., (2007) further reported effects in neonates associated to PFOA and PFOS cord blood concentrations including a decrease in

birth weight and size. In contrast, no statistically significant association has been found between adverse health effects and the levels of PFOA and PFOS found in human blood of occupationally exposed adult subpopulations displaying serum concentrations exceeding those of the general population by several orders of magnitude (Grice et al., 2007). Despite the controversy regarding relevant effect doses to humans, the long half-life of these chemicals in the environment (Kissa, 2001) and human body (Olsen et al., 2007a) has been considered to be of concern. To mitigate any future risks associated with PFOA and PFOS, there is thus an urgent need for improved understanding of the sources and routes of human exposure (U.S. EPA, 1999).

Previous studies have shown that human exposure to residual amounts of PFOA and PFOS in various consumer products is small (Washburn et al., 2005). Another assessment of exposure to PFOA and PFOS from consumer products and environmental media revealed that intake of contaminated food tends to dominate exposure of a general population (Trudel et al., 2008). Several authors have emphasized that there may be additional sources of human exposure to these chemicals from precursor compounds including fluorotelomer alcohols (FTOHs), perfluoroalkyl sulfonamides (PFOSAs) and amidoalcohols (PFOSEs) that are metabolized to form PFOA and PFOS in the human body, respectively (Hagen et al., 1981; Seacat et al., 2003; Tomy et al., 2004; Xu et al., 2004; Martin, Mabury and O'Brian, 2005; Fasano et al., 2006; Xu et al., 2006; Nabb et al., 2007).

This study builds upon the recent paper that estimated consumer exposure to PFOA and PFOS (Trudel et al., 2008). The objective was to quantify the exposure to known precursor compounds

(see Table S1 in the supplementary material) and determine if it substantially contributes to the total daily doses of PFOA and PFOS for a general population.

Methodology

The approach to estimate consumer exposure to PFOA and PFOS has previously been described within the framework of Scenario-Based Risk Assessment (SceBRA) (Trudel et al., 2008). The methodology defines typical low exposure, intermediate and high exposure scenarios to represent the full range of exposure of a general population to multiuse chemicals. To identify the most influential parameters of the exposure model an uncertainty analysis has been conducted (described in Section 6 in the supplementary material).

Concerning the sources of perfluorinated acids, a distinction was made between doses coming from *in vivo* transformation of precursor compounds and doses resulting from the direct exposure to PFOA and PFOS, denoted “precursor-based doses” and “direct-exposure-based doses”.

Routes of exposure

Estimates of exposure for the different pathways were transformed into estimated body-internal dose rates by applying empirical uptake efficiencies for the gastrointestinal tract, lung and skin. The doses were expressed on a per day basis normalized to body weight, referring to the amount of chemical that has been absorbed into the body via oral, dermal and inhalation routes. The time-integrated average doses coming from occasional contact events with consumer products and the daily doses resulting from the intake of environmental media were thus expressed with the common unit of ng/(kg·day) (see also Section 3 in the supplementary material).

To derive precursor based doses, the load of FTOHs, PFOSAs and PFOSEs absorbed into the human body was multiplied by a biotransformation factor to describe their metabolic conversion to PFOA or PFOS equivalents. Formation of PFOA as a metabolite of 8-2 FTOH has been reported from numerous in vivo and in vitro studies (Hagen et al., 1981; Martin, Mabury and O'Brian, 2005; Fasano et al., 2006; Nabb et al., 2007). Due to the interspecies differences and different experimental designs, the metabolic conversion ratio shows large variability between the different studies. To capture the uncertainty in metabolic rates, biotransformation factors of 0.0002, 0.005 and 0.017 were used in the low exposure, intermediate and high exposure scenarios. It has been hypothesized that long chain (more than eight carbons) FTOHs may undergo similar metabolic reactions as 8:2FTOH to form PFOA (Martin, Mabury and O'Brian, 2005). The conversion factor of long chain FTOHs to PFOA has however not been investigated and it was therefore assumed that the biotransformation factor of the long chain FTOHs is the same as that of 8:2 FTOH.

N-substituted PFOSAs and PFOSEs have been identified to form PFOS as a terminal metabolite (Seacat et al., 2003; Tomy et al., 2004; Xu et al., 2004; Xu et al., 2006). The yield of PFOS after oral dosing of N-EtPFOSE has been found to be 20% *in vivo* in rats (Seacat et al., 2003). As no other mammalian studies report quantitative conversion factors for PFOSAs and PFOSEs, this input value is deemed highly uncertain. We therefore assumed a wide range in the conversion factor for PFOSAs and PFOSEs for the three exposure scenarios of 0.01, 0.2 and 1, i.e. 1 to 100%. The sensitivity of the dose estimates to this assumption was investigated in the uncertainty analysis.

Pathways of exposure

A total of 17 different pathways were modeled to estimate the exposure to perfluorinated acids and their respective precursor compounds. The potential exposure to PFOA and PFOS from consumer products and environmental pathways was quantified in accordance with preceding studies (Washburn et al., 2005; Trudel et al., 2008). A more detailed description of the pathways included in this study is provided in the supplementary material (Sections 4 and 5).

Results

Exposure to PFOS

The total estimated body-internal doses of PFOS of a general western population divided into different consumer groups are summarized in Table 1. The dose range is about a factor of 20 for all consumer groups, except for infants who display a range of almost two orders of magnitude. Infants, toddlers and children receive substantially higher doses compared to adults and teens in the low, intermediate and high exposure scenarios. The highest potential dose is observed for infants, receiving up to 530 ng/(kg·day). Adult females receive the lowest estimated dose with 3.9 ng/(kg·day).

Figure 1 shows the relative importance of direct-exposure and precursor-based doses of PFOS. The low exposure and intermediate scenarios are dominated by direct exposure to PFOS with 95-99% of the daily dose coming from direct exposure to PFOS. In the high exposure scenario, 60-80% of the exposure to PFOS is accounted for by the biotransformation of precursors.

The relative importance of individual pathways contributing to exposure to PFOS is displayed in Figure S1 of the supplementary material. Consumption of contaminated food is found to be the dominant pathway of exposure in the low exposure scenario, accounting for 99% of total body internal doses for all consumer groups. Ingestion of food is also the major pathway (94-98%) for all consumer groups in the intermediate scenario. The second most important pathway of exposure in the intermediate scenario is inhalation of POSF-based precursors from indoor air (1.6-3.5% of total doses). For toddlers, infants and children other minor pathways of exposure include ingestion of dust contaminated with PFOS (0.5-1.4%) and precursor compounds (0.6-1.7%). For adults and teens the uptake of PFOSAs via food consumption is found to be a minor pathway of exposure (0.7-1.9%). The high exposure scenarios are influenced by a number of pathways. Ingestion of precursor-contaminated house dust is the major pathway of exposure (41-68%), with the highest relative importance being observed for infants and toddlers. Exposure to PFOS from contaminated food is less pronounced even though it is an important pathway of exposure (14-38%) for all consumer groups. The inhalation of precursors (10-19%) and ingestion of PFOS-contaminated house dust (4-8%) contribute as well to total daily doses in the high exposure scenario.

A contribution-to-variance analysis shows that (Figure 2) the most influential parameter affecting the total doses of PFOS of all consumer groups is the concentration in fish and shellfish. Body weight, gastrointestinal uptake fraction, biotransformation factor of precursors and concentrations in vegetables and potatoes are also found to be important. The concentration in human milk is an influential parameter for doses of infants.

Exposure to PFOA

Table 1 shows total daily body-internal doses of PFOA of all seven consumer groups. The total daily doses clearly decrease with age, indicating that the exposure of infants and toddlers is by a factor 1.5-5 higher than that of adults and teens in the same scenario. Infants (140 ng/(kg·day)) and toddlers (150 ng/(kg·day)) receive the highest potential doses, whereas the lowest doses are observed for female adults (0.3 ng/(kg·day)). Infants and toddlers face a greater dose range with a factor of 200, whereas doses of adults, teens and children vary by less than a factor of 100.

Direct exposure to PFOA accounts for the major fraction of doses (92-100% of total daily doses) in the low exposure and intermediate scenarios. The relative importance of direct-exposure and precursor-based doses for the intermediate and high exposure scenarios is displayed in Figure 3. In the high exposure scenarios the precursor-based doses are substantial, accounting for 48-55% of the total daily doses of adults and teens and 28-36% of the doses of infants, toddlers and children.

The relative importance of individual pathways contributing to exposure of PFOA is displayed in Figure S2 in the supplementary material. Ingestion of contaminated food is the dominant pathway in all scenarios accounting for 88-100% of the total daily doses in the low exposure and intermediate scenarios. The doses of PFOA in the high exposure scenario result from several different pathways. Adults and teens have a similar pattern of exposure and all younger consumer groups also have a similar pattern of exposure. Consumption of contaminated food is an important pathway for adults and teens in the high exposure scenario (26-32%), but is of less importance to exposure of children, toddlers and infants (7-20%). Migration of FTOHs from

food packaging materials, inhalation of carpet care solution and clothing impregnation sprays are all important pathways of precursors for adults and teenagers. Furthermore, house dust ingestion and transfer from food packaging materials are pathways that lead to direct exposure to PFOA of adults and teens. Infants, toddlers and children, on the other hand, receive the highest doses of PFOA from hand to mouth contact with carpets, mouthing of clothes and ingestion of dust.

The contribution to variance analysis (Figure 4) shows that all age groups, except infants, exhibit the same ranking of parameters. For infants, the most influential parameters are concentrations in human milk, fish, potatoes, and in water and the gastrointestinal uptake fraction. For the other groups the concentration in potatoes is the most influential parameter. Body weight, biotransformation factor of FTOHs, frequency of consuming fast foods, fraction of PFC treated paper, concentration in water and concentration in fish (adults only) are also of importance.

Discussion

The overall conclusion of this study is that precursor compounds cause a minor contribution to the daily doses of PFOA and PFOS. To put this conclusion into perspective, three aspects need to be considered: (i) given the wide range of human behavior and physiological characteristics influencing dose ranges of perfluorinated chemicals, there might be particular sub-groups in the population receiving considerably higher doses than the rest as displayed in the high exposure scenarios. For these sub-groups, the consideration of precursors in the assessment may be necessary. (ii) The low contribution of precursors may be due to the limited knowledge of the occurrence of especially PFOA precursors in exposure media such as indoor air and food (see Table S2 and S3 in the supplementary material), which is reflected by the few data points above

the detection limit. (iii) Exposure to identified (e.g. fluorotelomer olefins and polyfluoroalkyl phosphate surfactants) (Dimitrov et al., 2004; D'Eon and Mabury 2007) and unidentified precursor compounds not considered in this study may also add to the relative importance of precursor-based doses. However, because the precursor compounds included in this study (FTOHs, PFOSAs and PFOSEs) represent the building block of intermediates used to synthesize fluorinated polymers (Kissa, 2001; Dinglasan-Panlilio and Mabury, 2006) we believe that they make up the major part of precursor-based doses to PFOA and PFOS.

For the precursor-based doses of PFOS our biotransformation factors for PFOSEs and PFOSAs are derived from transformation factors in rats (Seacat et al., 2003) and trout (Tomy et al., 2004), which represents a source of large uncertainty. Further studies of degradation of these precursors of PFOS in mammals are therefore desirable. The degradation of N-alkylated PFOSEs and PFOSAs to PFOS is believed to occur via a common PFOSA intermediate (Xu et al., 2004; Xu et al., 2006). We assumed a similar degradation process for all other PFOS precursors. To what extent a similar biotransformation factor can be expected for all N-alkylated PFOSEs and PFOSAs is a matter of further scrutiny. Our finding of the low contribution of precursor-based doses of PFOA in humans is based on a range of biotransformation factors reported in literature indicating a low conversion ratio of FTOHs (Fasano et al., 2006; Nabb et al., 2007). To further establish this finding, additional mammalian metabolism studies are necessary.

Similarly to Trudel et al. (2008), this study suggests that the intake of contaminated food and drinking water is the dominant pathway leading to exposure to PFOA and PFOS. It has been reported that human blood levels of PFOS are significantly correlated to daily intake of fish

(Falandysz et al., 2006; Holmström, Berglund and Järnberg 2005), which coincides well with our calculations where intake of fish accounts for half of the doses caused by intake of contaminated food. Estimated doses of PFOA, however, originate from various food types such as fish, meat, snacks, fruit, potatoes and vegetables, which is in accordance with the weak correlation found between PFOA blood levels and fish intake alone (Falandysz et al., 2006; Holmström, Berglund and Järnberg 2005). This study also concluded that food packaging materials may lead to exposure to precursors of PFOA. However, the relative importance of the precursor-based dose of PFOA from food packaging materials was small compared to the direct dose of PFOA from food ingestion.

The contribution-to-variance analysis shows that the most influential factors with regard to the variance in PFOA doses all belong to the food intake pathway. This illustrates that the accuracy of data sets on concentrations of PFOA, PFOS and precursors in food is crucial to correctly estimate doses of perfluorinated acids related to food intake. As the majority of food concentration data lies below the limit of detection of PFOA and PFOS (see Table S3 in the supplementary material), large uncertainties are attached to our food datasets. A recent study quantifying exposure to PFOA and PFOS from food with duplicate servings (Fromme et al., 2007) provides a good reference point for evaluation of our estimated oral exposure to PFOA and PFOS. The median daily intake of PFOA (i.e., before crossing an absorption barrier) derived from concentrations measured in the duplicate serving samples for adults was 2.65 ng/(kg·day), which is in good agreement with our calculated intake of 2.5 ng/(kg·day). For PFOS, on the other hand, our calculated intake is a factor of 10 higher than in Fromme et al., (2007). This discrepancy may indicate (i) temporal or regional variability in PFOS concentrations in food or

(ii) regional dietary habits affecting PFOS. Concentrations of PFOS in fish and shellfish are highly influential parameters significantly affecting the variance in PFOS doses. Thus, diverging PFOS levels in fish or diverging intake of fish between the study of Fromme et al., (2007) and the present work may explain the diverging estimates of PFOS intake resulting from food intake.

The majority of monitoring data on the occurrence of perfluorinated compounds in the various exposure media is from 2002-2007. Thus, dose estimates represent recent conditions of exposure. Previous exposure assessments used a one-compartment pharmacokinetic model to evaluate the importance of individual exposure pathways for the total exposure (Harada et al., 2003; Washburn et al., 2005; Fromme et al., 2007) or to balance the total uptake doses (Trudel et al., 2008) to measured blood concentrations. This procedure relies on the assumption that blood levels of PFOA and PFOS have reached a steady state. However, recent biomonitoring studies found that blood levels of PFOA and PFOS decreased by almost 50 % between 2000 and 2005 (Olsen et al., 2007b; Calafat et al., 2007; Olsen et al., 2008). Considering the half-lives of these compounds in human blood serum of about five years (Olsen et al., 2007a), this may indicate a dramatic decline in human exposure to PFOA and PFOS or to their respective precursors. This may be a result of the phased-out manufacture of PFOA, PFOS and PFOS precursors by the major producer (3M, 2000). Additionally, measures have been taken by the telomer producing industry to reduce emissions to the environment and residuals of FTOHs and PFOA in consumer products (U.S. EPA, 2002; U.S. EPA, 2005). It is therefore possible that the sources and pathways of recent exposure may be quite different from those before the phase out and production changes took place in 2002. For example, there are some indications of additional sources and higher concentrations in exposure media from archived samples. Archived food

samples displayed dramatically higher concentrations of PFOSAs before 1998 (Tittlemier et al., 2006). PFOS levels of archived dust samples from 2000/2001 (Strynar and Lindstrom, 2008) exceeded those measured in more recent studies (Moriwaki, Takatah and Arakawa, 2003; Costner, Thorpe and McPherson, 2005; Kubwabo et al., 2005; Katsumata et al., 2006) by a factor of 3. The levels of POFSEs (Dinglasan-Panlilio and Mabury, 2006) and of PFOS (Boulanger et al., 2005) residuals in polymeric products have also been reported representing a possible source of additional historical exposure.

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Figures

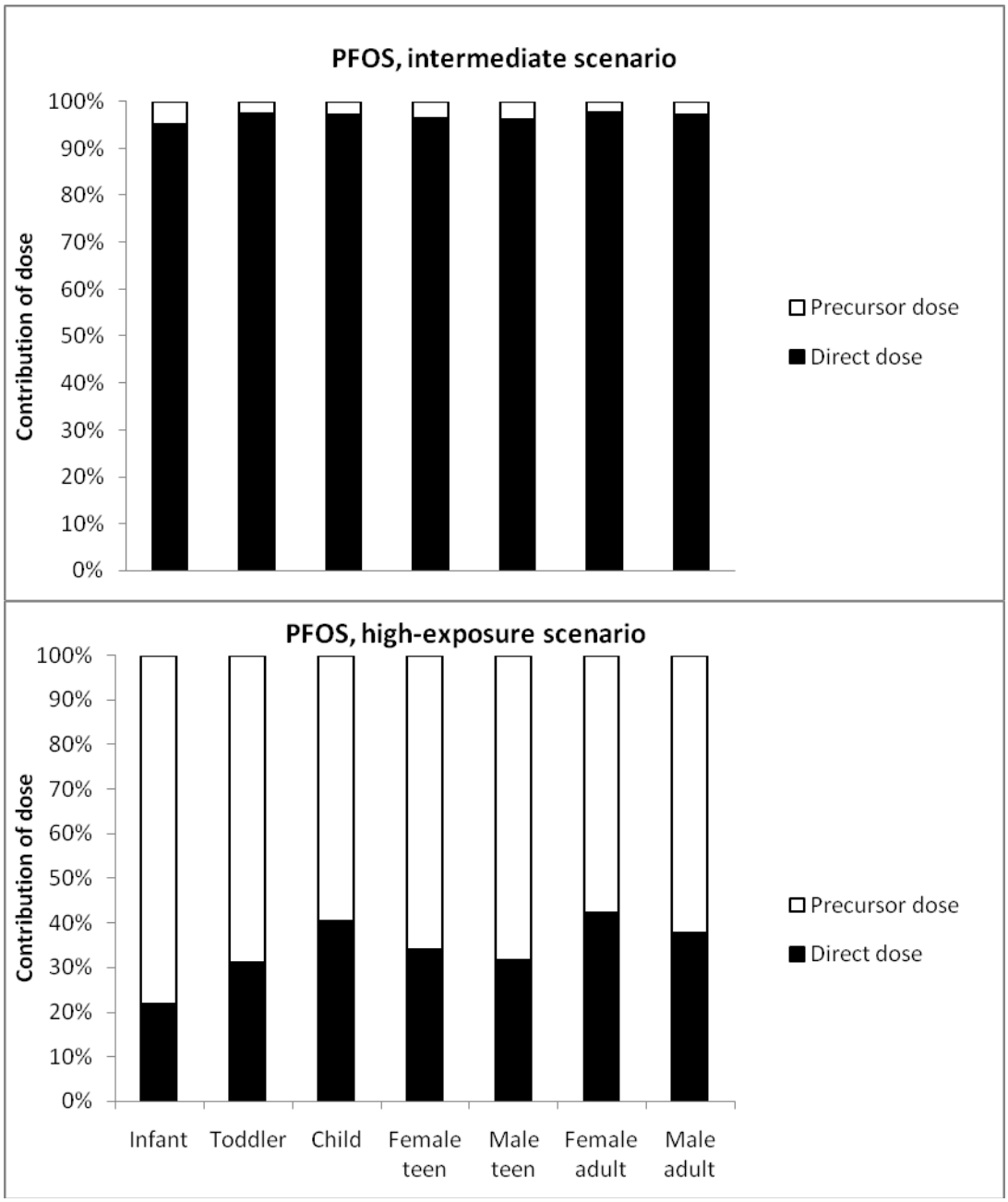

Figure 1: Relative contribution of precursor and direct-exposure based doses to total doses of PFOS in the intermediate and high exposure scenarios.

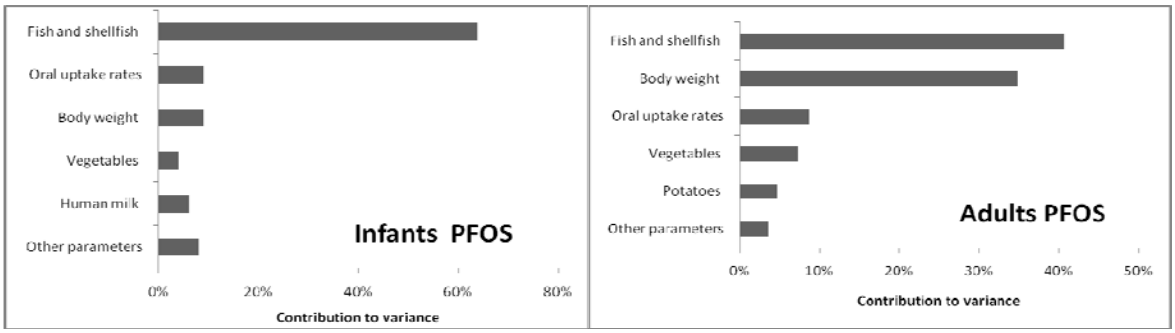

Figure 2: Contribution to variance of doses of PFOS for infants and adults

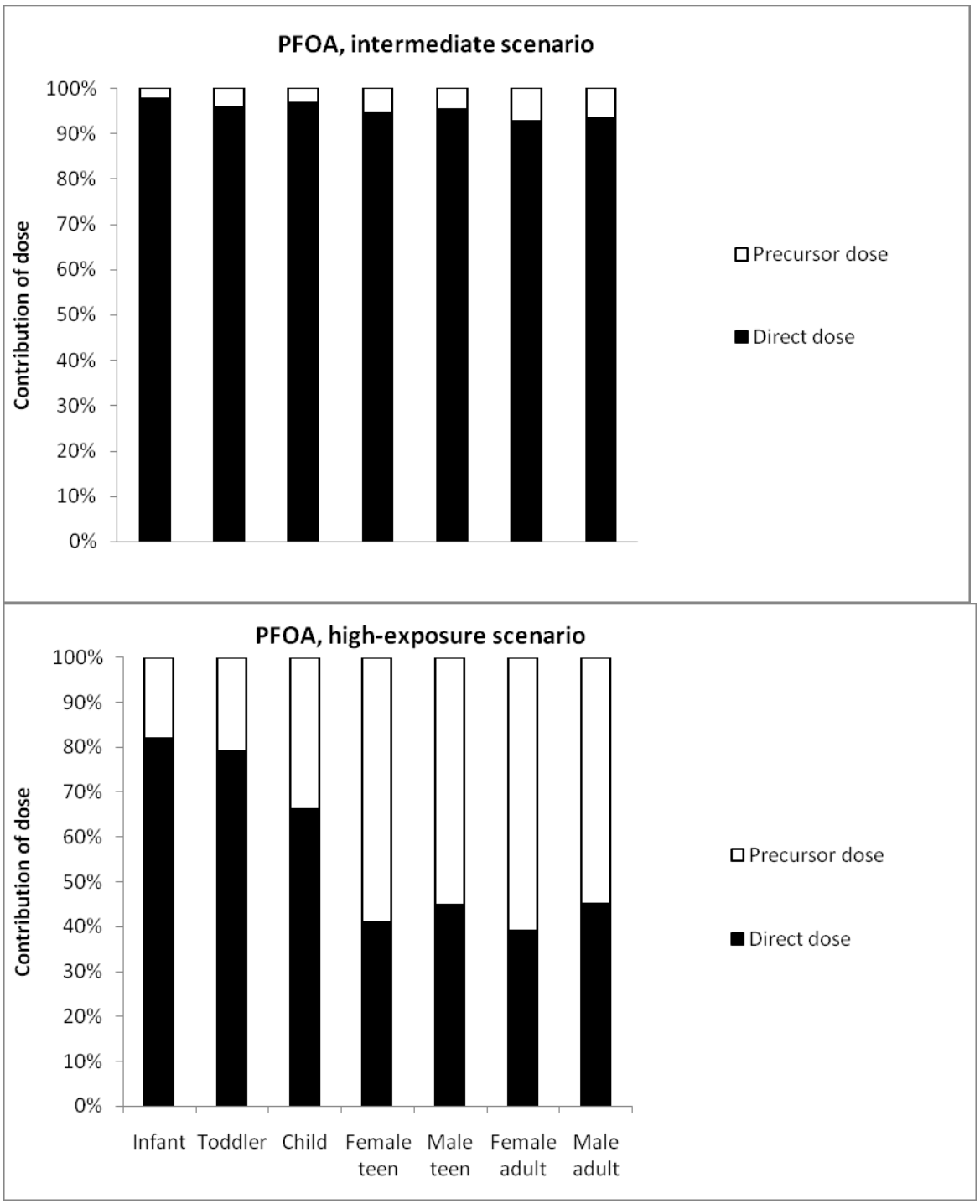

Figure 3: Relative contribution of precursor and direct-exposure based doses to total doses of PFOA in the intermediate and high exposure scenarios.

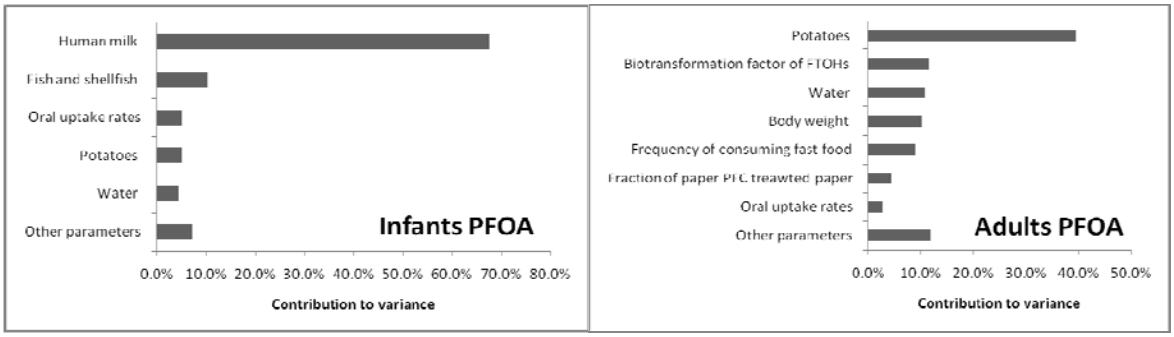

Figure 4: Contribution to variance of doses of PFOA for infants and adults

1 **Tables**

2 **Table 1:** Total daily doses of PFOS and PFOA of all consumer groups estimated with low-

3 exposure, intermediate and high-exposure scenarios.

	Scenario	Infant	Toddlers	Children	Female teens	Male teens	Female adults	Male adults
PFOS	Low	7.3	12	7.7	4.7	4.7	3.9	4.2
	Intermediate	25	33	25	15	17	16	15
	High	520	330	180	130	170	130	130
PFOA	Low	0.7	1.2	0.9	0.6	0.6	0.3	0.4
	Intermediate	3.4	5.9	4.8	3.0	3.4	2.1	2.3
	High	140	150	72	40	43	37	32

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