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Issues raised by the reference doses for perfluorooctane sulfonate and perfluorooctanoic acid

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ABSTRACT

On 25th May 2016, the U.S. EPA released reference doses (RfDs) for Perfluorooctane Sulfonate (PFOS) and Perfluorooctanoic Acid (PFOA) of 20 ng/kg/day, which were much more conservative than previous values. These RfDs rely on the choices of animal point of departure (PoD) and the toxicokinetics (TK) model. At this stage, considering that the human evidence is not strong enough for RfD determination, using animal data may be appropriate but with more uncertainties. In this article, the uncertainties concerning RfDs from the choices of PoD and TK models are addressed. Firstly, the candidate PoDs should include more critical endpoints (such as immunotoxicity), which may lead to lower RfDs. Secondly, the reliability of the adopted three-compartment TK model is compromised: the parameters are not non-biologically plausible; and this TK model was applied to simulate gestation and lactation exposures, while the two exposure scenarios were not actually included in the model structure.

1. Introduction

The regulations for Perfluorooctane Sulfonate (PFOS) and Perfluorooctanoic Acid (PFOA) have changed rapidly over the last decade and released reference doses (RfDs) have become increasingly conservative.(U.S. EPA, 2016a; U.S. EPA, 2016b; Danish EPA, 2015) In 2006, the UK Committee on Toxicity (COT) established a tolerable daily intake (TDI; equivalent to the U.S. RfD) of 300 ng/kg/day for PFOS (Table 1), (UK COT, 2006a) based on decreased serum T3 levels in a 26-week monkey study.(Seacat et al., 2002) Subsequently in 2008, the European Food Safety Authority (EFSA) issued a TDI of 150 ng/kg/day with an additional factor of two to take into account that the monkey study(Seacat et al., 2002) was not a life-time exposure.(EFSA, 2008) Similarly, considering the hepatic effects of PFOA in male rats, (Palazzolo, 1993; Perkins et al., 2004) the UK COT(UK COT, 2006b) and EFSA(EFSA, 2008) proposed TDIs for PFOA at 3000 ng/kg/day and 1500 ng/kg/day (Table 1), respectively. These TDIs did not compare interspecies uncertainties based on internal doses, although it is generally accepted that risk assessment of PFOA and PFOS should compare species differences based on internal dose as employed later by other agencies. For example, in 2009, the U.S. EPA drafted the RfDs for PFOS and PFOA at 77 and 189 ng/kg/day, respectively.(U.S. EPA, 2009) It should be noted that the relevant period of exposure for the two RfDs is a short-term exposure, while these values are still comparable to the longer term advisories if desired. Later in 2015, the RfDs for PFOS and PFOA were issued by the Danish EPA, these being 30 and 100 ng/kg/day, respectively.

It is important to understand why the RfDs are becoming increasingly conservative. As illustrated in Table 1, two factors are crucial: firstly, the point of departure (PoD) (includes the procedure on estimating human equivalent dose from animal PoD); and secondly, the quantifications of uncertainty factors (UFs). Currently, the derivations of most RfDs are based on animal studies rather than human evidence. As listed in Table 1, the animal PoD was adopted with a range of 0.00051–0.033 mg/kg/day and 0.003–0.46 mg/kg/day for PFOS and PFOA, respectively, since various agencies selected different toxicity studies. Specifically, for PFOS, the monkey studies were chosen by the U.S. EPA in 2009 given that monkeys are non-human primates.(UK

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Table 1
Developments of proposed reference doses for PFOS and PFOA.

Chemical	Organisation	Species, duration	Endpoint	Tolerable Daily Intake or Reference Doses (ng/kg/day)	PoD (mg/kg/day)	UFs			
						UF_1[a]	UF_2[b]	UF_3[c]	UF_4[d]
PFOS	UK COT(UK COT, 2006a)	Cynomolgus monkeys, 26 weeks	decreased serum T3 levels	300	NOAEL, 0.03	10	10	NA	NA
PFOS	EFSA(EFSA, 2008)	Cynomolgus monkeys, 26 weeks	decreased serum T3 levels	150	NOAEL, 0.03	10	10	2	NA
PFOS	U.S. EPA(U.S. EPA, 2009)	Cynomolgus monkeys, 26 weeks	decreased serum T3 levels	77[e]	NOAEL, 0.03	39[f]	10	NA	NA
PFOS	Danish EPA(Danish EPA, 2015)	Rats, 104 weeks	liver hypertrophy	30[e]	$BMDL_{10}$, 0.033	123[g]	10	NA	NA
PFOS	U.S. EPA(U.S. EPA, 2016a)	Rats, 12 weeks	pup body weight	20[e]	HED, 0.00051	3	10	NA	NA
PFOA	UK COT(UK COT, 2006b)	Male rats, 13 weeks	hepatic effects	3000	$BMDL_{10}$, 0.3	10	10	NA	NA
PFOA	EFSA(EFSA, 2008)	Male rats, 13 weeks	hepatic effects	1500	$BMDL_{10}$, 0.3	10	10	2	NA
PFOA	U.S. EPA(U.S. EPA, 2009)	Mice, 17 days	hepatic effects	189[e]	$BMDL_{10}$, 0.46	243[h]	10	NA	NA
PFOA	Danish EPA(Danish EPA, 2015)	Male rats, 13 weeks	hepatic effects	100	HED, 0.003	3	10	NA	NA
PFOA	U.S. EPA(U.S. EPA, 2016b)	Mice, 17 days	decreased pup ossification, accelerated male puberty	20	HED, 0.0053	3	10	NA	10[i]

Note: a, UF_1, interspecies uncertainty factor; b, UF_2, intraspecies uncertainty factor; c, UF_3, uncertainty factor to account for studies with less than lifetime exposure; d, other uncertainty factor; e, calculated as PoDs/UF_1/UF_2/UF_3/UF_4; f, 3(toxicodynamics differences) × 13(toxicokinetics differences); g, 3(toxicodynamics differences) × 41(toxicokinetics differences); h, 3(toxicodynamics differences) × 81(toxicokinetics differences); i, LOAEL to NOAEL uncertainty factor.
Abbreviations: Perfluorooctane Sulfonate: PFOS; Perfluorooctanoic Acid: PFOA; PoD, point of departure; UF: uncertainty factor; NOAEL: no observed adverse effect level; $BMDL_{10}$: 95% lower confidence limit of benchmark dose at benchmark response of10%; HED: human equivalent dose.

COT, 2006a; EFSA, 2008; U.S. EPA, 2009) With respect to PFOA, the hepatic effects were endorsed by the UK and EFSA.(EFSA, 2008; UK COT, 2006b; U.S. EPA, 2009) Referring to the Danish EPA, (Danish EPA, 2015) toxicity studies involving the longest exposure duration were preferred. A solid PoD should seek a balance between critical effect, experiment parameters, species and other factors.

Meanwhile, although there has been a consensus on applying default UFs of 10 for intra-species and three for inter-toxicodynamics, the quantifications of inter-toxicokinetics difference and exposure duration difference have been more variable, based on evolving toxicokinetics (TK) models. For example, using the first-order model as the TK model, the U.S. EPA has determined the inter-toxicokinetics (from monkey to human) difference of 13.(U.S. EPA, 2009) This methodology was also employed by the Danish EPA to designate a PFOS inter-toxicokinetics difference of 41 from rats to humans (Table 1).(Danish EPA, 2015) Recently, with the development of compartment models, (Andersen et al., 2006) an approach termed human equivalent dose (HED) was used to integrate the inter-toxicokinetics difference and exposure duration difference. By applying the HED approach, the total of inter-toxicokinetics difference and exposure duration difference were apparently estimated by the Danish EPA to be 133 for PFOA.(Danish EPA, 2015)

The influence on RfD determination according to the choices of PoDs and UFs quantified by the TK models has been well demonstrated by recently released RfDs. On 25 May 2016, the U.S. EPA released the new RfDs 20 ng/kg/day for both PFOS and PFOA, which were determined by employing the HED approach.(U.S. EPA, 2016a; U.S. EPA, 2016b) In detail, the animal lowest observed adverse effect (LOAEL) of 0.4 mg/kg per day for PFOS(Luebker et al., 2005a) and 1 mg/kg per day for PFOA(Lau et al., 2006) were considered.(U.S. EPA, 2016a; U.S. EPA, 2016b) Subsequently, by choosing a three-compartment model (TCM) as the TK model, the total differences of inter-toxicokinetic and exposure duration were estimated to be 250 and 188 for PFOS and PFOA, respectively. Finally, the remaining UFs were quantified as 100 for PFOS and 300 for PFOA to determine the final RfDs.(U.S. EPA, 2016a; U.S. EPA, 2016b) Compared to the draft values (77 ng/kg/day for PFOS and 189 ng/kg/day for PFOA) suggested in 2009, the new RfDs were sharply reduced by a factor of four for PFOS and nine for PFOA.

Referring to general population, daily intakes were reported to be 10.4–14.7 ng PFOS/kg bw per day and 1.7–9.68 ng PFOA/kg bw per day for infants, which were 1–2 orders of magnitude higher than the daily intakes for adults.(Zhang et al., 2010; Tao et al., 2008a; Tao et al., 2008b) Although the new established RfDs are still higher than these reported daily intakes, there is no doubt that the new RfDs will lead to more stringent environmental guidelines. For example, by adopting these values, (U.S. EPA, 2016a; U.S. EPA, 2016b) the new drinking water lifetime health advisories for PFOS/A were both recommended to be 70 ng/L. Consequently, PFOS/A concentrations in drinking water for approximately six million U.S. citizens are exceeding the new health advisories.(Hu et al., 2016) Thus, the rationale and science of the new RfDs should be examined, which requires an evaluation of which toxicological studies have been the most suitable for the RfD development, along with the most appropriate toxicokinetic models which have been used to quantify related UFs. In response to such requirements, we examined toxicological evidence from animal and epidemiological studies, and analysed the TK models to justify the newly released RfDs.

2. RfD determination

The flowchart for RfD determinations by the U.S. EPA is shown in Fig. 1. Firstly, five and six candidate animal toxicity studies were selected for PFOS and PFOA, respectively; secondly, the TCM was employed to calculate human HEDs from animal PoDs, and subsequently the candidate RfDs were derived from human HEDs; and thirdly and finally, the most sensitive values of the candidate RfDs were chosen as the final RfDs for both PFOS and PFOA. Therefore, the RfD determination can be summarised as:

$$RfDPFOS \Big/ A = \min\left(\frac{HEDi = g^{-1}(f(PoDi, t))}{UFs}\right) \quad (1)$$

where f represents the utilised animal TK model (TCM in this case) to calculate the average serum concentration (ASC) when dosing animal PoDs with an exposure duration of t; and the g represents the first-order model used to re-construct the daily dose which can reach the ASC in humans. Descriptions of the candidate studies, PoD, HED and UFs are