**Department of Defense**
**Comments on the Interagency Science Consultation**
**Draft IRIS Toxicological Review of Perfluorodecanoic Acid (PFDA)**
**March 2022**
(Date Received April 14, 2022)

| **Comments on the Interagency Science Consultation**<br>**Draft IRIS Toxicological Review of Perfluorodecanoic Acid [CASRN 335-76-2] and Related Salts.** | | |
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| Comments submitted by: Department of Defense | Organization: Department of Defense | Date Submitted: 4/14/2022 |
| *Comment categories: Science or methods (S); Editorial, grammar/spelling, clarifications needed (E); or Other (O). Also please indicate if Major i.e. affects the outcome, conclusions or implementation of the assessment. | | |

| Comment No. | Section | Pages | Comment | Suggested Action, Revision and References (if necessary) | *Category |
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| 1 | Summary of Occurrence and Health Effects | xiii, line 6 | PFHxA here should probably be PFDA. | Correct the likely typo. | E |
| 2 | Summary of Occurrence and Health Effects | xiii, line 15-17 | While this is true for PFAS broadly speaking, it is unclear if this is the case for PFDA specifically. | Please be more specific regarding environmental sources of PFDA or clarify that these general PFAS sources also apply to PFDA. | S |
| 3 | Table ES-1 | xiv | First row: It is not clear how a transient measure of antibody levels to serum tetanus toxin, two years after measuring PFDA in serum, is relevant to a lifetime RfD or even a subchronic RfD.<br>Measuring antibody levels in serum to a specific toxin does not measure immune system competence to respond to toxin challenge. There has been no change (increase) in tetanus mortality in children | Suggest either describing how transient antibody levels relate to chronic health effects OR eliminate this health effect as that determining the Overall Lifetime and subchronic RfD.<br>There is no evidence that the ability of a toxicant to reduce serum antibody levels has any long-term (lifetime) effect on organism health. A reduction in antibody levels to an antigenic determinate(s) cannot | S |

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| | | | since 1990 (averaging 2 individuals annually). Consequently, expected/estimated child mortality is not a reasonable measure of immune system competence to respond to tetanus toxin. The Integration Judgement column reports that Evidence indicates (likely). The support for this determination is not clear. | be used alone to determine the immune system's ability to respond to challenge. | |
| 4 | 3.1.2. Distribution | 3-2 | Binding to plasma proteins, measured by Kim et al. (2019) and Ylinen and Auriola (1990), was extensive (>99 of PFDA) but if only free fraction is assumed to be available for elimination, half-lives are over predicted. Uptake into tissues and renal elimination are not determined by the free fraction alone, but by kinetics of protein binding (presumably to multiple plasma proteins, with specific on/off rates – which can be measured in vitro).<br>May explain the observation that since the fetus has a much lower level of these proteins than an adult, there is a greater proportion of PFDA in fetal tissue versus fetal serum. | Recommend detailed analyses of these binding studies or conducting in vitro assays to measure specific on/off kinetics of PFDA to different plasma proteins. | S |
| 5 | 3.1.4. Excretion – Animals (rats and mice) | 3-9 | No data on absorption of PFDA through the respiratory tract or skin have been found. Although data are lacking, these represent potentially major exposure routes for systemic distribution. | Recommend recognizing this as a limitation of the data and suggesting further study into the issue, rather than just noting that such data are not available. | S |
| 6 | 3.1.4. Excretion – Animals (rats and mice) | 3-9 to 3-12 | The half-lives in rats and mice are adjusted to reflect an apparent concentration loss resulting from dilution in the growing animal (determination of an adjusted | Please add additional clarification to the text regarding the constancy of the volume of distribution to justify such an assumption. | S |

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| | | | elimination half-life). Given the predisposition of PFAS in general, and of PFDA in particular, to bind blood proteins, why was body weight used and not estimated blood volumes. Do blood volumes change at the same rate as body weight? Asked another way, how does the volume of distribution change with age? These questions should be answered in the text if one is going to assume that the volume of distribution remains constant during dosing (equation 3-10). | | |
| 7 | 3.1.4. Excretion – Humans | 3-16 to 3-17 | Fecal excretion of PFDA is significantly greater than observed for PFOA (ECHA 2016). The potential for significant fecal elimination does not seem to be addressed in the paragraph on estimated urinary, biliary, fecal and total clearances. The fact that the Fujii et al (2015) paper only looks at fecal elimination over 24 hours, suggests that it may not be a good source of fecal elimination for PFDA. | Please consider adding text to this section regarding the possibility of significant fecal elimination of PFDA. | S |
| 8 | 3.1.4. Excretion – Humans | 3-18 | It is unclear whether the volume of distribution is species specific. | Recommend clarifying here whether or not the volume of distribution for rats and humans is the same in this case. | S |
| 9 | 5.2.1. Immune Effects | 5-5 | The two medium confidence epidemiological studies of antibody response were conducted in birth cohorts in the Faroe Islands. This same population is known to be impacted by mercury and polychlorinated biphenyls (PCBs), a result of their whale and fish diet.<br>It is hard to imagine how PFDA levels in | Recommend reevaluating the confidence ratings in the studies conducted on the populations from the Faroe Islands. These populations are confounded and warrant no greater than “low” confidence that they can be relied upon to provide any information on PFDA-related health effects (i.e., a known source of PFDA to humans is | S |

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| | | | serum (age 5) can be realistically linked to antibody effects at ages 5 and 7 in this population. It is unclear whether the author's evaluation of child serum levels resorted to any modification of serum concentrations ($POD_{HEC}$) to reflect the apparent loss of PFDA concentration resulting from increasing body mass.<br><br>The stated reason for choosing a BMR of 5% instead of 10% is to protect against tetanus acknowledges the disease rarity, but then fails to report just how rare (The CDC reports average of 30 cases a year: cdc.gov/tetanius/about/) Given the EPA reported 13% case fatality rate (2001-2008) results in fewer than 4 fatalities a year, hardly warranting its selection as the critical adverse health outcome deserving of a 5% BMR or even RfD derivation. To be protective, the BMR could be much higher to limit an extra death from PFDA-related tetanus. | consumption of fish tissue).<br><br>Recommend reporting additional clarification of the serum levels in these studies.<br><br>Please provide additional clarification of the reported BMD methods and modeling details. Request that EPA justify accepting the author's use of these methods and details in their report.<br><br>Additionally, request that EPA further justify their selection of a BMDL at a 5% BMR. | |
| 10 | 5.2.1. Approach for pharmacokinetic modeling of PFDA in rats and humans | 5-14 to 5-19 | Pharmacokinetic (PK) approaches from simple classical (one compartment) models (p. 3-13) to mechanism-based approaches (renal elimination) to Physiologically-Based Pharmacokinetic (PBPK) were evaluated for soundness and applicability.<br><br>Although a PBPK model might be considered ideal for predicting dosimetry, it appears that the only PBPK model for PFDA (Kim et al., 2019) was examined in detail (p. 5-14 to 5-16) and it was found that "the model was inconsistent with key | Recommend potentially revisiting and improving the Kim et al model, using other PFAS models as consistency checks, to enable proper extrapolation across species. | S |

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| | | | pharmacokinetic data, which was not presented with the published model, and hence it was not considered adequate for application (p. 3-12). However, the model does simulate the trend of the time course data but overpredicts by a factor of 3-4. The primary problem seems to be an unrealistically low oral bioavailability and an inability to simultaneously describe oral and iv kinetic data (in rats), even with (reasonable) parameter adjustments (see their Fig. 5.1).<br><br>Thus, a (simpler) one-compartment model using chemical-specific data was suggested for dosimetric extrapolation to estimate serum, which overpredicts serum concentrations by approximately 1.5 times, an end-of-study timepoint of PFDA in male rats (NTP, 2018) as a function of dose. How well the simpler model simulates the time course data is not shown.<br><br>Using a one compartmental model appears to be an interim solution at best and dismissing the use of the PBPK model by Kim et al. may be premature. Modeling is an iterative process and the model structure will change as additional data becomes available. Ultimately a classical one compartmental model will not be able to extrapolate across species and doses, primarily due to differences in plasma protein binding. A consistent PBPK model will be required and this may only require the addition of one or more tissues. Comparison of PBPK models for other | | |

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| | | | PFAS compounds is a useful consistency check for the data and approach. | | |