Department of Defense
Comments on the Interagency Science Discussion (Step 6)
Draft IRIS Toxicological Review of Perfluorodecanoic Acid (PFDA) and Related Salts
April 2024

*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.

Section	Pages	Comment	Suggested Action, Revision and References (if necessary)	*Category
3.2.2	3-71	Throughout this section and the studies that it cites and describes, an antibody concentration of 0.1 IU/mL is used as the threshold below which a person may be considered adversely effected and susceptible to diphtheria and tetanus. This is not given proper justification or explanation, and it does not appear that this section was adequately adjusted to account for reviewer comments regarding the appropriateness of using this endpoint. One reviewer in particular pointed out that immunoprotective titers are assay-specific. The ToBI test used in the Grandjean papers in particular has a tetanus toxin protective level of 0.01 IU/mL, a ten-fold difference compared to the level cited above, according to the WHO. The WHO also describes 0.01 IU/mL as the minimum protective level for diphtheria antibodies. Ultimately, at a certain point, decreases in antibody serum concentrations are going to be indicative of an adverse, immunosuppressive effect. The uncertainty around the particular level in question	Suggest the Agency consider adding language to further justify the use of the 0.1 IU/mL titer as the threshold for adverse immunosuppression. References are provided below for consideration. WHO (2017) Tetanus Vaccines: WHO position paper. February 2017. Weekly epidemiological record. 10 Feb 2017. No 6,2017,92, 53-7. WHO (2017) Diphtheria Vaccines: WHO position paper. August 2017. Weekly epidemiological record. 4 Aug 2017. No 31 ,2017, 92, 417-436.	S

		(0.1 IU/mL as the de facto seroprotective titer) warrants more discussion in this section, especially in light of the WHO positions on protective antibody titers.		
C.1.1 Selection of the Benchmark Response	C-3, lines 14-26	The discussion here adds important context around the seroprotective antibody titer question. In particular, the quote from Galazka et al gives a clear view of the uncertainty surrounding the issue, namely that it's difficult to define an antibody titer that is truly protective.	Consider adding some summary language in the main document (Section 3.2.2.) similar to the short discussion here.	S
3.2.2.	General	US EPA does not appear to have addressed a prior comment identifying the critical effect; the reduction in antibody response to diphtheria and tetanus toxin in children (Grandjean et al. 2012, and Budtz-Jorgensen and Grandjean 2018a) as inappropriate. The National Academies of Sciences, Engineering, and Medicine. 1992. Biologic Markers in Immunotoxicology. Washington, DC: The National Academies Press. https://doi.org/10.17226/1591. states that "The concentration of immunoglobulins cannot be used as the sole criterion for the diagnosis of immunodeficiency." Guidance in immunological textbooks and published reports suggests that a	Recommend that the Agency address this comment more specifically, especially as it relates to the NASEM reference provided in the comment.	S

		change in antibody levels should not, by itself, be used to identify immunosuppression/immunodeficiency. Most texts on immunotoxicity indicate that any change in an immune system measure like antibody level should be supported by an increase in related disease incidence and/or severity. The CDC does not report any change in the incidence or severity of diphtheria or tetanus (https://www.cdc.gov/vaccines/pubs/surv-manual/chpt01-dip.html and https://www.cdc.gov/tetanus/surveillance.html).		