Department of Defense (DoD) **Comments on the Interagency Science Consultation (Step 3)** **Draft IRIS Toxicological Review of Perfluorononanoic Acid (PFNA) and Related Salts** **Appendix D.1 Modeling results for liver toxicity EPA/635/R-23/152** **Dated December 2023**
*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	Page (Lines)	Comment	Suggested Action	Category
General	-	For literature search of relevant studies, has the U.S. EPA also interrogated the grey literature to identify sources of data suitable for modeling exposure to PFNA from other national and international data sources, for example the Canadian, British, Australian and European data sources?	Please consider including these international sources	S
General	-	The U.S. EPA should consider using the online Bayesian BMD system. There are some concerns with the EPA's Bayesian BMD modeling function for dichotomous dose-response data that is implemented in EPA's BMDS products (including the Excel-based BMDS and BMDS online). The concerns with the "Bayesian" modeling function in BMDS are related to the fact that the U.S. EPA might have not adequately justified the plausibility and scientific rigor of the software tool. At the top-level, the concerns can be boiled down to two main questions: (1) Why is Laplace's approximation approach the best available scientific approach for Bayesian BMD analysis? (2) Why is the specific informative prior implemented in BMDS the DEFAULT and ONLY choice? As noted by others, the Laplace's approximation method implemented in BMDS cannot generate BMD estimates with adequate precision unless the prior is informative enough. The informative prior is used in BMDS to operate the BMDL and BMDU estimates (which also impact the BMD estimates). A few other critical limitations of the Laplace's approximation (e.g., requires large sample size) also make this approach problematic for Bayesian dose-response analysis. It should be noted that a comparison in BBMD and BMDS' performance of BMD analysis using dose-response datasets published/used in regulatory risk assessments reports was recently done. Please see the below, which provides two comparison reports using the data in recent U.S. EPA IRIS Toxicological Review of PFBA and ETBE. PFBA: https://benchmarkdose.com/events/files/PFBAReport/ ETBE: https://benchmarkdose.com/events/files/ETBEReport/	For reference – further analysis, here are ten recently published papers that cited or used the BBMD system. See [1]References after table.	S

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Table D-17	Footnote b	Table D-17, footnote b; states the "PODHED = POD internal dose (mg/L) x 0.090 mL/kg-day x 10-3 L/mL, using the estimated clearance for men and women above age 40." How was this clearance estimated? What is the supporting evidence justifying that clearance estimate? Why was the estimated clearance for men and women above age 40 used instead of the estimated clearance for women of reproductive age (Table D-19)? The latter is used to calculate the POD_{HEC} from the high confidence Sagiv *et al.* study. Does clearance change with the endpoint of interest? Use of the later clearance estimate increases the calculated POD_{HED}.	Please clarify.	S

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