U.S. Department of Defense (DoD)

Comments on the Interagency Science Consultation Draft

IRIS Assessment of Perfluorobutanoic Acid (PFBA) and Related Compound Ammonium Perfluorobutanoic Acid August 2020

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Department of Defense Comments on Toxicological Review of Perfluorobutanoic Acid and Related Compound Ammonium Perfluorobutanoic Acid

Comments submitted by: OASD(EI&E), ESOH Directorate, CMRM Program	Organization: Department of Defense	Date Submitted: 9/10/2020

*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
1	Executive Summary and General	xii, Lines 3 -10	Concerns for PFBA and other PFAS are stated to stem from their resistance to degradation and persistence in the environment but then a couple sentences later PFBA is described first as a breakdown product of other PFAS followed by commercial and manufacturing uses. This presentation is confusing even to those with experience in the field and warrants improvement for the broad audience this assessment will serve.	Suggest noting where or how breakdown of other PFAS would result in PFBA as a product and contrast that with more common degradation mechanisms that occur in the environment.	S
2	Exec Summary	xiv	There is no consistent justification for the "... use of a NOAEL roughly equivalent with a decrease of 1 standard deviation for thyroid	Please explain why the decrease in the NOAEL by 1 SD is used and referenced by applicable BMD guidance, and please also describe what would have influenced selection of	S

			effects (suggesting that this POD may not be substantially more uncertain than a BMD-based POD, although one source of uncertainty impacting confidence is the observation of responses only in the high dose group)." It is not clear why the decrease in the NOAEL by 1 standard deviation (SD) used here and referenced by applicable BMD guidance, but a 0.5 standard deviation is used on the BMDL in another recent EPA assessment, PFBS.	a different, perhaps lower standard deviation. The discussion in Table 5-8 warrants improvement as well.	
3	Executive Summary	xiv	Since there is a move to adopting the BMD/BMDL10 approach, why is it that authors have stated both BMDL and NOAEL values for POD derivation? As presented in this section, this is confusing and inconsistent with the argument of adopting the BMD/BMDL10 approach.	Please clearly define or explain use of BOTH BMD and NOAEL values here and in Section 5. A clear rationale for the dichotomy is needed, the rather brief discussion presented here and even in Table 5-8 didn't provide a complete explanation.	S
4	Table ES-1	xiii	The overall RfD is not listed in this table and the text at line 14 on page xiv does not refer to the "selected RfD" as the overall RfD. See also comment below on presentation of "osRfDs".	Suggest including the overall RfD in this table and consistently referring to it as such throughout the document for clarity purposes.	E
5	Table 1-1	1-2	Log Kow is presented as Log P: Octanol-Water, whereas the citations presented refer to it as Log Kow.	Recommend using LogKow as this is the more recognized terminology, its abbreviation may be spelled out in a footnote if EPA deems that necessary.	E
6	1.2.5.	1-12 and General	In as much as this section is very nicely described as aligned to the U.S. EPA's dose-response modeling framework, it does	Please consider BMA or simply Bayesian Benchmark Dose approaches in this and future health risk estimates, and not solely rely on traditional BMD/BMDL approaches. Increasing	S

			not seem that other alternative approaches such as Bayesian Model Averaging (BMA) were considered. Increasing evidence strongly suggests that for one to account for the uncertainty due to the choice of the dose-response model, model averaging can be successfully utilized in a number of risk assessment problems and particularly in determining an estimated benchmark dose in cancer AND non-cancer studies. Some authors have shown that "an uncomfortably high percentage of instances can occur where the true extra risk at the BMD lower confidence limit (BMDL) under miss-specified or incorrectly selected model can surpass the target BMR, exposing potential danger of traditional strategies for model selection when calculating BMDs and BMDLs" please see: R. W. West, W. W. Piegorsch, E. A. Pena, W. Wu, A A. Wickens, H. Xiong, W. and Chen, The impact of model uncertainty on benchmark dose estimation, Environmetrics, Vol.23, No.8, pp.706-716 (2012).	evidence strongly suggests that for one to account for the uncertainty due to the choice of the dose-response model, model averaging can be successfully utilized in a number of risk assessment problems and particularly in determining an estimated benchmark dose in cancer AND non-cancer studies. The following studies successfully provided a demonstration of this some time ago: 1) M. W. Wheeler, and M. J. Bailer, Properties of model averaged BMDLs: A study of model averaging in dichotomous response risk estimation, Risk Anal, Vol. 27, No.3, pp.659-670 (2007); and 2) M. W. Wheeler, and M. J. Bailer, Bayesian monotonic semiparametric benchmark dose analysis, Risk Anal, Vol.32, No.7, pp.1207-1218 (2012). Model averaging like Bayesian Model Averaging (BMA), which is increasing in popularity and may prove superior to the BMD/BMDL approach. The advantage of BMA is that the weights are determined to be proportional to the posterior probability that each model is correct given the available observations. Furthermore, others have found that there was consideration of the properties of the BMA technique in benchmark dose estimation and it was shown that the derived estimates more accurately reflected uncertainty in the understanding of the effects of exposure on the occurrence of adverse responses. M. Whitney, and L. M. Ryan, Quantifying dose-response uncertainty using Bayesian model averaging, In: Uncertainty Modeling in Dose-Response, R.M. Cooke (ed.). Wiley, N. J. Hoboken, pp.165-179 (2009).	
7	2.0 Literature Search Strategy	Table 2-1, Page 2-2	The Flow Chart structure as described in Table 2-1 does not seem to align to a typical DistillerSR business rules workflow. Does Table 2-1 summarize the workflow of the	Suggest clarification be given for Table 2-1 and better alignment be provided between Table 2-1 and Table B-7.	S

			Distiller-SR approach? Authors mentioned that Distiller-SR was followed. It is noted that Table B-7, page B-17 summarizes the key work-flow questions of the Distiller-SR literature search strategy, but it does not appear to immediately or easily align with Table 2-1 on page 2-2. There seems to be a disconnection when contrasting both tables. It would be more useful to see Table B-7 distill in logical sequence flow the selected and rejected articles as aligned to the question work-flow rules depicted in Table B-7. It is challenging to understand the literature search strategy as currently presented across two dichotomous illustrations of the procedure.		
	Figure 2-1		The structure for PFBA ammonium salt (10495-86-0) does not match those on ComTox Dashboard/PubChem/etc.	Please correct or clarify	E
	Figure 2-3	2-4	In figure 2-3, we note that a critically deficient overall rating assigned without any critically deficient scores in the individual categories (Li et al., 2017a). Song et al., (2018), Li et al. (2017b), Fu et al. (2014) have more deficient individual scores than Li et al. (2017a) but does not get a critically deficient overall score. In the textual explanation of the studies excluded as uninformative, the Li et al. (2017b) study is referenced, but this study has a deficient/low	A nuanced scoring methodology needs more description or the figure should be adjusted to make the nuanced scoring obvious. For example, may yellows add up to red, and how many yellows equal a red. Please also reconsider scoring of Li et al, 2017a and Li et al., 2017b.	S

			score in Fig. 2-3, while Li et al., (2017a) is marked as critically deficient. Additionally, for the Li et al. (2017b) study, the early statements say “these studies are not referred to in this assessment” but later sections on thyroid effects and the backing for human effects specifically reference this study. The included “low confidence” caveat is strongly included and acceptable, but this disjointed approach to inclusion vs exclusion introduces uncertainty into the stream of evidence/logic. Even if it is a simple a vs b typo in the in-line citation, the individual vs overall evaluation results in Fig 2-3 do not add up		
	3	3.2	The assumption that analogous PFAS are actually analogous may not be a sufficient assumption as evidence grows (Cheng et al. 2019). Given the uncertainty, however, it is likely the best path forward in adaptive management development. Fortunately, at the end of this section, the analogous PFAS is specifically mentioned as PFBS, which given the difference between e.g. PFOA and PFOS, seems tenuous. The text has a continued lack of clarity about the confidence, reliance, or typographical correctness of the Li et al. (2017b) study. In this case, even low confidence is supporting overall evidence. PFOA and PFOS	This is a rather critical area of uncertainty and warrants some consideration especially when describing uncertainty associated with the toxicological assessment. Importantly, for the high confidence animal studies, effects observed in hormones and related tissues is a sufficient evidential tie that is synthesized. Please see: 1) Russell, M.H., Himmelstein, M.W. and Buck, R.C., 2015. "Inhalation and oral toxicokinetics of 6: 2 FTOH and its metabolites in mammals." Chemosphere, 120, pp.328-335. 2) Crebelli, R., Caiola, S., Conti, L., Cordelli, E., De Luca, G., Dellatte, E., Eleuteri, P., Iacovella, N., Leopardi, P., Marcon, F. and Sanchez, M., 2019. "Can sustained exposure to PFAS trigger a genotoxic response? A comprehensive genotoxicity assessment in mice after subacute oral	S

			have different excretion rates; PFBA has different excretion rates between male and female rodents which influences effects observed; we question whether it makes sense to assume that effects across PFAS will be similar if functional group moiety influences excretion.	administration of PFOA and PFBA." Regulatory Toxicology and Pharmacology, 106, pp.169-177. Please also address text about exclusion or typographical error in Li et al. 2017a vs 2017b.	
	3.1.2	3-2	Regarding discussion of Das et al., 2008, it is notable this study found that serum concentrations of PFNA in non-pregnant mice exposed for the same duration were approximately twice as high as those detected in pregnant mice.	Please note the differences between serum concentration and discuss with respect to the PFBA rat results.	S
	3.1.4	3-5	Two entire paragraphs on page 3-5, lines 1-14, do not have a citation. Assumed citation is Chang et al. (2008) (Hero ID=2325359). Another clarification point is related to figure-based description of dose-response data. Most of the studies referenced used multiplicative spaced treatments, having all the figures log-scaled dose axis would seem useful.	Please provide citation for paragraphs on page 3-5. Please consider log-scaled axes for figures describing dose-response data,	S

12	Table 5-4	5-10	The types of PODs are not clearly provided, one should not be required to consult Appendix D to determine the abbreviations used here i.e. RD, ER and SD.	Suggest adding footnotes with definitions for clarity.	E
13	5.2.2	5-7	The calculation of the Clearance Level (CL) uses a volume of distribution (Vd) determined in monkeys by Chang et al. (2008). How is the Vd different from that used for PFOA or PFOS and how does the knowledge that PFBA distribution is principally extracellular affect the determination of Vd?.	Consider describing how the Vd is different from that used for PFOA or PFOS and how the principally extracellular distribution of PFBA affects the determination of Vd.	S
14	5.2.2	5-18 and 5-19	The text notes that the "..NOAEL approach for decreased total T4 is not substantially more uncertain than using the BMD approach given the relatively similar values in PODs that would be derived using either approach". However, this is not evident given the lack of information provided in the main body of the document, perhaps it is in Appendix D, but it was not evident when searched.	Please add further details or cite the tables or section where this information may be found.	S
15	5.2.2, Table 5-5	5-11	The application of a UFH of 10, applied for interindividual variability in the absence of quantitative information on the toxicokinetics and toxicodynamics of NH4+PFBA/PFBA in humans, seems overly conservative approximation given the Chang et al (2008) data.	Please consider reducing UFA or UFH to account for decreased sensitivity of humans to effects observed in rodents. Please also note that Chang et al. (2008) is not included in the list of references at the end of the document.	S

16	5.2.2	5-20	The use of developmental delayed responses as the basis for a Subchronic RfD is not well justified. None of the delayed developmental responses may be defined as a permanent given the current information.	Please reconsider or further justify use of developmental delayed responses as the basis for the subchronic RfD.	S/M
17	Table 5-8		We have seen organ/system-specific reference values developed in other IRIS assessments, but do not recall them being abbreviated to "os". We find this more confusing than useful since it is not utilized in the RfD/RfC document that EPA uses to guide development of reference values, also because it seems to unduly highlight them and without an organ designation they don't seem of direct use when assessing risk of exposure to a given chemcical.	Please reconsider use of the abbreviation osRfD.	E
18	Appendix B	Table B-1; Page B-1	It is noted that for the major search engines/databases resourced by this report, were inclusive to February 14, 2018. Recognizing that one has to stop at some convenient point to focus on report writing. However, the time clock has now elapsed by 2 and half years, and an additional literature search is warranted to bring key components up to date.	Please consider bringing the literature search strategy up to date to the extent possible and logistically permitted. Please also consider casting the net wider during their literature searches. Since the IRIS authors are using Distiller-SR, it behooves them to adopt a more thorough literature search strategy. For example, consider other databases and grey literature sources to include: 1) EMBASE https://www.elsevier.com/solutions/embase-biomedical-research 2) Defense Technical Information Center (DTIC) https://cmd.dtic.mil 3) ECHA (European Chemicals Agency) http://echa.europa.eu/ 4) IPCS's INCHEM (International Program on Chemical Safety INCHEM) http://www.inchem.org/ 5) Grey Literature: GESTIS Substance Database: Information system on hazardous	S

				substances of the German Social Accident Insurance http://www.dguv.de/ifa/gestis/gestis-stoffdatenbank/index-2.jsp Health Canada http://www.hc-sc.gc.ca/index-eng.php ITER "International Toxicity Estimates for Risk https://iter.ctc.com/publicURL/pub_search_list.cfm (original ITER) CA OEHHA (California Office of Environmental Health Hazard Assessment) http://oehha.ca.gov/ Australia's NICNAS (National Industrial Chemicals Notification and Assessment Scheme) http://www.nicnas.gov.au/ RIVM (Netherlands National Institute for Public Health and the Environment) http://www.rivm.nl/en EU Scientific Committee (European Union) http://ec.europa.eu/health/scientific_committees/index_en.htm	
19	Appendix C-1	C-4	It is not clear how studies such as this one extracted from Appendix C-1 actually made it through the Distiller-SR process to be considered and discussed as a relevant quality study: "Chang et al. (2008) only evaluated one PFBA dose in monkeys, so it is not possible to determine whether the biphasic clearance pattern is due to the classical distinction."	Please provide a better explanation of where some studies such as Chang et al., (2008) were isolated for consideration and discussion when in fact the Distiller-SR process would have rejected it for the reasons provided in their logical decision tree in Table B-1 and Table 2-1. It seems odd to "cherry pick" such studies when in fact they have no place in the discussion or report. If this is done for this study, then all rejected studies likely have some merit to be discussed further by an approach that at least has the appearance of functional or directed bias.	S
20	D.1 BMD Modeling Approaches	D-2	These sections have the same heading as the previous one when they cover different aspects of the modeling procedure.	Correct the headings.	E
21	Tables D-10 and D-11	D-20	Selection of the Exponential 3 Model here seems to go against the parameters outlined at the beginning. Exponential 2 model	Please provide an explanation of the selection of this particular model when it appears to go against EPA's selection procedures.	S

			seems to show a slightly lower BMDL while its AIC is equal to the Exponential 3 model. This makes a very minor difference in the overall calculations, but there needs to be internal consistency here or it needs to be adequately explained in a subsequent footnote. This comment also applies to Table D-11		
22	Table D-24	D-39	Again, there is a discrepancy in the EPA's model selection procedures. It would appear that the Multistage 1st model provides a better estimate of the BMDL based on the parameters that have already been put forth. We understand using the lowest BMDL here as a matter of making conservative choices on frank effects, but the BMDL for the Log-probit model is sixfold smaller than the BMD.	If judgment calls are made that are contrary to model selection procedures or guidelines, the rationale should be described or at least be pointed out in a footnote of some kind.	S