Department of Defense
Comments on the Interagency Science Consultation
Draft IRIS Toxicological Review of Inorganic Arsenic
November 2022
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Department of Defense Comments on **Draft IRIS Toxicological Review of Inorganic Arsenic** 12/20/2022				
*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.				
Section	**Pages**	**Comment**	**Suggested Action, Revision and References (if necessary)**	***Category**
General	NA	In past IRIS assessment, a short reference and discussion on prior IRIS values was made at the end of the document. It may be beneficial to the stakeholders to do the same at the end of this document and maintain a historical perspective. The prior iAs determination had the same composite UF of 3 and a RfD of 0.3 µg/kg-d (CVD and dermal effects) compared to the current document, where a Bayesian meta-analysis approach was used to develop a new RfD of 0.031 µg/kg-day for CVD incidence.	Consider referring to the prior iAs RfD in a wrap-up statement.	S
General (Charge Question 2)	NA	It is unclear whether enough evidence has been examined to be confident that the risk of diabetes attributable to arsenic exposure is separate from obesity, an independent risk factor for diabetes. Does the proposed model of health effects include iAs exposure as an independent risk for diabetes?	Consider clarifying or discussing that obesity and iAs exposure have been independently assessed for their impact on the incidence of diabetes and the modelling used for risk assessment.	S

Section ES.2 Toxicity Values for Cancer and Noncancer Effects	Page xvi, line 7-10.	The high values for cardiac disease risk could also inadvertently include exposure to other known cardiovascular environmental toxicants, especially Pb which is associated with increased blood pressure, coronary artery disease, stroke, and peripheral arterial disease and is widely present in the environment. It may be possible that the attributable risk to diabetes and CVD has not been accurately assigned to iAs and could be including other unaccounted for exposures.	Clarify that Pb exposure, which is a risk factor for CVD, has been properly adjusted for in the main studies used for modelling of risk.	S
Section ES.2 Toxicity Values for Cancer and Noncancer Effects (Charge Question 3)	page xv, line 28-32	The sentence ending “these studies …do not provide compelling evidence for a threshold arsenic dose or exposure below which no adverse effect would be predicted for a U.S. population.” This statement implies that diabetes and DCS have a linear dose-response down to zero iAs exposure. Non-cancer toxicity, especially for metals/metalloids, normally would have a threshold, given that detoxification mechanisms exist.	Please clarify the statement regarding non-thresholds for non-carcinogenic health effects.	S
1.2 Background Information on Inorganic Arsenic	1-1	Section 1.1 does not provide an overview of the physiochemical properties, human exposure and environmental fate.	Please edit as appropriate.	E
1.4 Sources, Production, and Use	1-2, Line 12-13	Mining, metal smelting or ores and burning of fossil fuels are major sources of As contamination. This statement implies that the remaining two-thirds of arsenic in the atmosphere is anthropogenic in source.	Suggest adding information on of how much anthropogenic sources add to atmospheric iAs in this section or section 1.4.3.	E
1.5.1 Potential for Human Exposure and Populations with Potentially Greater Exposure	1-5	What is said about the dermal exposure route seems to conflict with Hostynek et al., 1993, cited on page D-2 of Appendix D, which states that "systemic toxicity to high dermal occupational exposure to aqueous iAs solutions indicate that the skin may be a significant exposure route". The animal studies cited in Appendix D, also indicate relatively high percentages of dermally applied arsenic being absorbed.	Please provide more details for not including dermal absorption. Recommend reviewing the cited study below. Their results demonstrate oral route of exposure is predominant, and dietary	S

			pathway is dominant for iAs compared to drinking water pathway; inhalation and dermal pathways are very minor for the US populations that they examined, and probably the US in general. Georgopoulos PG, Wang S-W, Yang Y-C, Xue J, Zartarian VG, McCurdy T, Ozkaynak H 2008. Biologically based modeling of multimedia, multipathway, multiroute population exposures to arsenic. J. of Expo. Sci. and Environ. Epidemiol 18, 462-476.	
3.1 Pharmacokinetics	3-1 Line 23-25	A reference for the genomic tools being employed to characterize human arsenic metabolism and susceptible individuals is needed here.	Please add a reference for the tools mentioned.	E
3.1 Pharmacokinetics	3-1	The second paragraph seems to suggest that ingestion is the only pathway. While consumption of contaminated drinking water is the major source of iAs poisoning, inhalation and dermal still exist, although they are minor. Yet, this section does not mention if the metabolic transformations are the same from these other exposure pathways.	Please clarify.	S
3.1, Figure 3-2	3-3	There is something off with Figure 3-2 (measured and predicted urinary As vs. drinking water concentration) as support for the "adequacy" of the PBPK model of El Masri et al., 2018. What is assumed to be the same figure from the original paper (Fig 2B in El Masri et al., 2018) seems to show the trends better. Drinking-water dependence really starts at log10	Please re-examine Figure 2B in El Masri et al., 2018. The section on the PBPK model does not indicate that the model fit was improved by the inclusion of As in food, as well	S/M

		As concentrations great than 1.5 or so (right side on-third or so of the Fig 2B in the original paper, where the fit really isn't all that good (model over-predicts the slope and overestimates the urine concentration at higher end). The model's apparent good fit on the left side of Fig 2B (the same as Fig 3.2 in the IRIS document) is due entirely to As in food, and has nothing to do with drinking water intake. Thus, plotting urine As against drinking water concentrations seems an odd way to show the "adequacy" of the model. It really doesn't look all that good, but there can be considerable variability when normalizing urine concentrations to creatinine. It also indicates that the kinetics of iAs are quite complicated.	as drinking water into the simulated data.	