Department of Defense (DOD) Comments on the Interagency Science Consultation Draft IRIS Assessment of RDX (dated September 2014)

Date: October 28, 2014

Department of Defense Comments on RDX_Interagency Consultation draft Charge to External Reviewers_9-30-14.pdf		
Comments submitted by: Chemical Material Risk Management Program	Organization: Department of Defense	Date Submitted: 10/27/2014

*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	2c		DoD appreciates that EPA provided the question asking whether the choice of dose metric is appropriate. However, DoD feels that this is a critical aspect of the dose-response assessment and requests that a more thorough question be developed and perhaps separated as a subquestion to 2c.	Consider asking: “Do the animal and human data support using the AUC rather than peak plasma RDX concentrations in the PBPK model? Are the impacts of using AUC rather than peak plasma RDX concentrations on the final RfD adequately described and scientifically supported?”	S/M
2	3a		DoD appreciates that EPA asks external reviewers whether the available studies support the conclusion that nervous system toxicity is a human health hazard of RDX exposure. Given that this is the critical endpoint for RfD development, DoD feels that additional questions related to whether scientifically accurate and appropriate descriptions and considerations of mode of action and	Please consider additional questions on the interpretation of nervous system toxicity, including explicitly asking whether the reviewers believe that the differences between the toxicokinetics of gavage versus feeding studies, and whether interpretation of the mode of action for RDX neurological effects, are appropriately and accurately considered and incorporated	S/M

			toxicokinetic differences between gavage and feeding studies are warranted (either here or in question 4a).	into the hazard identification subsequent dose-response modeling.	
3	3e		DoD appreciates that EPA provided the question “Do the available…studies support this conclusion?” for the “suggestive evidence of carcinogenic potential” designation. However, we feel the opposing questions should also be provided for unbiased questioning of the external reviewers.	Please consider adding the additional question to 3e: “Conversely, could the carcinogenic weight of evidence, including no statistically significant dose-dependent increases in tumors from animal studies, and negative genotox data, support a finding that RDX is unlikely to be carcinogenic?”	S/M
4	4a		Please consider asking an explicit question on the use of the Crouse et al. gavage study.	DoD recommends asking: “Is the use of the Crouse et al. study, which uses a bolus (gavage) dosing regimen, appropriate and scientifically accurate for derivation of the RfD?” □	S/M
5	4a		Please consider asking an explicit question regarding the assumption/interpretation that seizure incidence is “severe” due to equivalence to mortality.	DoD recommends asking: “Does the weight of evidence including the overt evaluation of mortality/lethality from RDX exposure to humans, and the quantitative evaluation of mortality following convulsions in rodent studies, support the determination that seizures are a sever endpoint equivalent to mortality?”	S/M
6	4a		DoD feels that the calculation of a BMDL (95% CI) at the 1% level is a critical decision within the RfD derivation for RDX. As such, more thorough and explicit questions are warranted.	If the BMDL at the 1% BMR is retained, DoD requests that external reviewers are asked the following question: “Is calculation of a BMDL (95% CI) at the 1% level scientifically accurate per EPA BMD Guidance and technically supported, considering both statistical requirements (i.e. precision of the data) and	S/M

				biological plausibility (i.e. EPA's determination that the severity of seizures warrants additional protection via a more conservative BMR)?"	
7	4a		DoD feels specific questions of the UFD and UFH are warranted.	Please consider adding explicit charge questions on the technical accuracy and appropriateness of the UFD and UFH determinations. Including: "EPA chose to use a default UFH rather than chemical-specific information derived from analysis of toxicokinetic data via the available PBPK models. Is this decision scientifically defensible and appropriate? Would the use of PBPK models to derive a data-derived uncertainty factor for human variability improve the RfD derivation?" □ and " UFD=3. Is this decision scientifically defensible and appropriate?"	S/M
8	4c		DoD requests additional, more specific, questions should be provided to the external reviewers related to EPA's oral slope factor derivation.	Please consider asking the following questions: "Are the RDX cancer data (considering the entire weight of evidence) sufficient to support a quantitative oral slope factor derivation and is it appropriate to do so?" "Has EPA chosen an appropriate study (Lish et al. 1984) from which to calculate the oral slope factor, per established EPA guidance and guidelines?" "Has EPA accurately and appropriately evaluated and interpreted results from Lish et al., considering statistical tests and biological plausibility?"	S/M

9	6		DoD commends EPA for specifically requesting that the experts review EPA's response to public comments. DoD asks if the interagency comments supplied at this time will be included in this response.	DoD strongly suggests that these interagency comments be included in this section of the report.	S/M
10	General		The charge questions ask whether the various parts of the assessment are "appropriate". DoD suggests that this term is vague and open to multiple interpretations. DoD suggests that the experts be also asked to opine as to whether the parts of the assessment are "accurate" or "sufficiently accurate".	DoD suggests that in addition to “appropriate,” “accuracy” is a major issue on which the experts should be asked to consider.	S