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 Supplemental Information_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	D	General	As noted in specific comments herein, there are several errors, issues and inconsistencies within EPA's dose-response modeling.	Please ensure a careful review and quality control of the documents prior to public release.	S
2	D	D-1	Line 4: There is an error within the document's internal referencing.	Please correct.	E
3	1.1.1	D-1	EPA provides no information regarding the combined data except that they can be combined statistically. Since the individual data do not demonstrate a statistically significant increase in tumors, i.e., since all of the tumor incidences are consistent with controls, it would be expected that the combined data would also be not different than controls. However, it is not indicated if the combined data (1) had any doses that resulted in tumors that were	Please clearly demonstrate the statistical evaluation of the combined data. In the absence of any indication -- even the limited indication of a positive trend -- that the combined data show an increase in tumor incidence over controls, DoD does not feel that quantitative analyses of the data should be performed. Additionally, please discuss how (1) type 1 error (false positive associations), including the use of normal ranges (historical data) from laboratory	S/M

			statistically significantly increased over controls or (2) if there were a statistically significant trend.	animals are considered, and (2) which tests to assess statistical fit (e.g. least square error) have been applied, either to the combined or individual data sets.	
4	D.1.	D-2	In Table D-1. Noncancer endpoints selected for dose-response modeling for RDX, footnote "b" is not used.	Please indicate the study from which the highest dose was dropped before modeling.	S
5	D.1.2.	D-3	"If the BMDL estimates were not sufficiently close, the lowest BMDL was selected as the POD." As mentioned in other DoD comments, the lowest BMDL may result from the most uncertainty, i.e., the lowest quality study. One of the stated advantages for using BMD methodology was to encourage the use of better study designs; the quoted practice does the opposite of that goal.	DoD recommends that EPA examine the BMD, not the BMDL, to determine which study has the lowest BMD, and then select the corresponding BMDL. Selection of the lowest BMDL may be unnecessarily increasing the uncertainty and imprecision of the estimate.	S/M
6	D.1.3	D-19 to D-25	The increasing statistical uncertainty of the point of departure with decreasing BMR can be clearly observed by looking at the BMD/BMDL ratios for convulsions in male and female F344 rats in the Crouse study. The Multistage 2 model (which was the model selected for BMR = 1%) is selected as an example. The BMD/BMDL ratios are 1.3, 1.6, and 2.8 for BMRs of 10, 5, and 1% respectively.	The BMR 10 exhibits the lowest statistical uncertainty, demonstrated by an evaluation of the BMD/BMDL. Following EPA's BMD Guidance, EPA should evaluate statistical information when selecting the BMR. DoD recommends that EPA use a BMR of 10% for seizures in rats. (Note additional comments from DoD on this topic throughout the various RDX documents.)	S/M
7	D.1.3.	D-23	While DoD agrees with EPA's decision not to choose the Quantal-Linear model in Table D-9, DoD notes that EPA did not follow the appropriate selection rules by making this	The EPA choice of model-selection should be made based on biological consistency and plausibility as well as statistical considerations. DoD suggests that the selection of dose-	S

			choice. The BMDL of the Quantal-Linear model, 0.860, is greater than 3-fold lower than other BMDLs, specifically, the BMDL of the selected model, i.e., 3 x 0.86 = 2.58 is less than 2.66. DoD notes that this is inconsistent with decisions EPA made with similar values for other data sets, e.g., Table D-2. 1. DoD recommends that EPA use the totality of the information provided by the use of multiple models to select and provide justification for the selection of the most statistically AND biologically justifiable model.	response models is an inconsistency within EPA, especially within this particular document, but also found between IRIS documents.	
8	D.1.3. Modeling Results	D-23	In Table D-9, it is unclear why if three of the multistage models reduced to the same model, the reported BMDLs differ.	There is either an error in the footnote, EPA's software, or the reporting of the results. Please correct the error.	S
9	D.1.3.	D-25	As stated in other comments, DoD disagrees with EPA’s choice of BMDL01. Given that the BMDL10 for noncancer risks is almost 10-fold higher than the BMDL01 that EPA chose to use for RDX, the RfD would also be substantially changed. At the very least, this difference in ultimate RfD should be presented for comparison.	As not all of the procedures are linear, DoD recommends that EPA also derive an RfD from the BMDL10 so that the public and the external peer reviewers can determine the quantitative effect of EPA's decision. By presenting this information, EPA will also provide a measure of the uncertainty in the RfD as currently estimated.	S/M
10	D.1.3.	D-31	In Table D-13, the reason for the choice of the Quantal-Linear model is that it has the "lowest AIC". However, the AIC of that model is reported to be 42.077, and the LogLogistic (AIC = 41.996), LogProbit (AIC = 41.963), Weibull (AIC = 42.026), and Gamma (AIC = 42.003)	Please correct and please review all of the data in Appendix D to ensure the model selection is both accurately explained and either follows EPA decision rules as stated in this document, or explains why the decision rules were not followed.	S

			models have lower AICs. The selected model has the lowest BMDL. In Table D-9, it is unclear why if three of the multistage models reduced to the same model, the reported BMDLs differ.		