Department of Defense Comments on
Toxicological Review of Hexahydro-1,3,5-trinitro-1,3,5-triazine (RDX)
Draft Final (IRIS Step 6b)

Comments submitted by: Chemical & Material Risk Management Program, Office of the Assistant Secretary of Defense (Energy, Installations, & Environment) OASD(EI&E)	Organization: Department of Defense	Date Submitted: June 27, 2018

*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	1.3.3	1-84 and others	Susceptible Populations and Life stages for Cancer and Noncancer Outcomes: While the EPA have responded as requested by the SAB to suggestions to add more material to support sub-clinical effects of RDX and the potential for developmental neurotoxicity, the additional text comparing RDX to bicuculline may be somewhat misleading. The Ki (affinity constant) for RDX is 21.1 ÂµM (Williams et al) whereas that of bicuculline could be as low as 3.5 ÂµM (Thampy and Barnes, JBC, 1983). The relative potency of bicuculline versus RDX is further demonstrated in Fig 4 of Williams et al., where the recovery currents after RDX exposure are completely blocked by bicuculline. Notwithstanding the different routes of exposure	Please consider including some qualifiers about the relative potency when comparing RDX with bicuculline when using bicuculline as a potential rationale for developmental neurotoxicity.	S

			used for bicuculline studies (IP injections) there is clear evidence that RDX is a significantly weaker inhibitor of GABAA than bicuculline and therefore potentially significantly less likely to cause developmental neurotoxicity.		
2	Table 2.2	2-8	For Crouse Study: In the columns using AUC or CMax ratios of 0.487 or 0.540 applied to BMDL5 of 2.66 gives values of 1.3 and 1.4 respectively (note that 1.7 is incorrect for Cmax). For Cholakis Study: the calculated value for the Cmax column should be 0.34 not 0.41. For Crouse study calculations, this implies that the POD-HED for using either AUC or Cmax are basically the same.	Please correct the entries for POD-HED in the Cmax Column as indicated above.	S
3	2.1.4	2-18	As suggested by the SAB and stakeholders, the Crouse study was used instead of the Cholakis study to derived POD for neurotoxicity. This shows that the EPA IRIS review process is not just a passive event but that stakeholders input was considered. There were clearly too many ambiguities surrounding the Cholakis study (as outlined in this section) and the final choice of study vindicates the philosophy of using the best science available to derive regulatory numbers.	No suggested action.	S
4	Appendix E and Section 2.1.4	E-9 and 2-24	The SAB comment to develop or cite documentation for the use of organ-specific reference values for individual chemicals was not entirely addressed. It is not clear when	Please clarify with additional details as described in the comment.	S

			organ specific reference values would be used. From the revisions made, we presume they would be reserved for estimating organ specific hazard as dictated by circumstances described in the Risk Assessment Guidance for Superfund Part A and prior to that stage in the site risk assessment process the overall RfD or RfC would exclusively be utilized to estimate hazard indices. We acknowledge that it would be not necessarily be the IRIS program's role to issue Superfund guidance for using their values in that program, but believe discussions likely occurred with users of IRIS values prior to the program's decision to develop organ specific reference values and more elaboration might be provided.		