EPA's Response to Interagency Comments on the Final Interagency Science Discussion Draft of the IRIS Toxicological Review of Hexahydro-1,3,5-trinitro-1,3,5-triazine (RDX)

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Purpose: The Integrated Risk Information System (IRIS) assessment development process of May 2009 includes two steps (Step 3 and 6b) where the Executive Office of the President and other federal agencies can comment on draft assessments. Comments on the Final Interagency Science Discussion draft of the IRIS Toxicological Review of Hexahydro-1,3,5-trinitro-1,3,5-triazine (RDX) were provided by the Department of Defense (DOD), none of which DoD considered to be major scientific comments. The following are EPA's responses to interagency comments. All interagency comments were taken into consideration in revising the draft assessment prior to posting on the IRIS database.

For a complete description of the IRIS process, including Interagency Science Discussion, visit the IRIS website at www.epa.gov/iris.

Interagency Science Discussion Comments and Responses:

Topic #1: Qualifiers regarding the relative potency of RDX and bicuculline – DoD observed that text comparing RDX to bicuculline, added in response to the SAB recommendation to include more material in support of subclinical effects of RDX and the potential for developmental neurotoxicity, may be somewhat misleading. DoD pointed to evidence that RDX is a significantly weaker inhibitor of $GABA_A$ than bicuculline and therefore potentially significantly less likely to cause developmental neurotoxicity.

> **EPA Response:** EPA agrees that the evidence is consistent with bicuculline as a more potent $GABA_A$ inhibitor than RDX. Section 1.3.3 (Susceptible Populations and Life Stages for Cancer and Noncancer Outcomes) was revised to note differences in potencies of RDX and bicuculline as $GABA_A$ inhibitors.

Topic #2: Calculation of point of departure (POD) values when expressed as a human equivalent dose (HED) – DoD offered the comment that the POD_{HED} values based on peak RDX concentration in arterial blood (C_{max}) as the dose metric and data from the Crouse et al. (2006) and Cholakis et al. (1980) studies were incorrectly calculated. Specifically, they noted in Table 2-2 that a factor of 0.540 should have been applied to the lower bound on the benchmark dose ($BMDL_{05}$) of 2.66 mg/kg-day from Crouse et al. (2006) to obtain a POD_{HED} of 1.4 mg/kg-day (rather than

1.7 mg/kg-day). Similarly, the POD_{HED} derived from the Cholakis et al. (1980) study using C_{max} as the dose metric should have been 0.34 mg/kg-day rather than 0.41 mg/kg-day.

> **EPA Response:** The calculations in the final Agency Review/Interagency Science Discussion draft were in fact correct, but EPA agrees that the assessment was not sufficiently clear about which factors to apply when calculating the POD using either area under the curve (AUC) or C_{max} as the dose metric. Table 2-2 [Summary of derivation of point of departures (PODs) following oral exposure to hexahydro-1,3,5-trinitro-1,3,5-triazine (RDX)] and the PBPK appendix (Section C.1.5, "Rat to Human Extrapolations" and "Mouse to Human Extrapolations") were revised to clarify which factors to apply in calculating POD_{HED} values with the different dose metrics.

Topic #3: Clarification regarding the use of organ/system-specific values – DoD commented that the SAB recommendation to develop or cite documentation for the use of organ-specific reference values for individual chemicals was not entirely addressed. DoD observed that it was not clear when organ-specific reference values would be used, but presumed from the revisions made that these values would be reserved for estimating organ-specific hazard as dictated by circumstances described in *Risk Assessment Guidance for Superfund* Part A (U.S. EPA, 1989).

> **EPA Response:** EPA revised Section 2.1.4 of the Toxicological Review to clarify that the use of organ/system-specific values could be useful not only for assessments performed using EPA's *Risk Assessment Guidance for Superfund* (U.S. EPA, 1989), but more generally for EPA program and regional offices to identify other potential health hazards above the reference dose and to inform decisions involving multiple-chemical exposures based on a common target organ.

References

Cholakis, JM; Wong, LCK; Van Goethem, DL; Minor, J; Short, R; Sprinz, H; Ellis, HV, III. (1980). Mammalian toxicological evaluation of RDX. (DAMD17-78-C-8027). Kansas City, MO: Midwest Research Institute. http://www.dtic.mil/dtic/tr/fulltext/u2/a092531.pdf

Crouse, LCB; Michie, MW; Major, M; Johnson, MS; Lee, RB; Paulus, HI. (2006). Subchronic oral toxicity of RDX in rats. (Toxicology Study No. 85-XC-5131-03). Aberdeen Proving Ground, MD: U.S. Army Center for Health Promotion and Preventive Medicine. http://www.dtic.mil/dtic/tr/fulltext/u2/1050903.pdf

U.S. EPA (U.S. Environmental Protection Agency). (1989). Risk assessment guidance for superfund [EPA Report]. (EPA/540/1-89/002). Washington, DC.