Draft Charge to the Science Advisory Board for the
IRIS Toxicological Review of Hexahydro-1,3,5-trinitro-1,3,5-triazine (RDX)

September 2016 (Updated November 2016[1])

Introduction

The U.S. Environmental Protection Agency (EPA) is seeking a scientific peer review of a draft Toxicological Review of Hexahydro-1,3,5-trinitro-1,3,5-triazine (RDX) developed in support of the Agency's online database, the Integrated Risk Information System (IRIS). IRIS is prepared and maintained by EPA's National Center for Environmental Assessment (NCEA) within the Office of Research and Development (ORD).

IRIS is a human health assessment program that evaluates scientific information on effects that may result from exposure to specific chemicals in the environment. Through IRIS, EPA provides high quality science-based human health assessments to support the Agency's regulatory activities and decisions to protect public health. IRIS assessments contain information for chemicals that can be used to support hazard identification and dose-response assessment, two of the four steps in the human health risk assessment process. When supported by available data, IRIS provides health effects information and toxicity values for health effects (including cancer and effects other than cancer) resulting from chronic exposure. IRIS toxicity values may be combined with exposure information to characterize public health risks of chemicals; this risk characterization information can then be used to support risk management decisions.

An existing assessment for RDX includes a reference dose (RfD) posted on the IRIS database in 1988 and oral slope factor (OSF) and a cancer descriptor posted in 1990. The IRIS Program is conducting a reassessment of RDX. The draft Toxicological Review of RDX is based on a comprehensive review of the available scientific literature on the noncancer and cancer health effects in humans and experimental animals exposed to RDX. Additionally, appendices for chemical and physical properties, toxicokinetic information, summaries of toxicity studies, and other supporting materials are provided as *Supplemental Information* (see Appendices A to D) to the draft Toxicological Review.

The draft assessment was developed according to guidelines and technical reports published by EPA (see *Preamble*), and contains both qualitative and quantitative characterizations of the human health hazards for RDX, including a cancer descriptor of the chemical's human carcinogenic potential, a noncancer toxicity value for chronic oral exposure (RfD), and a cancer risk estimate for oral exposure.

---

[1] The charge questions were modified (as shown in bold font) as a result of panel discussions during the November 17, 2016 teleconference

Charge questions on the draft Toxicological Review of RDX

1. **Literature search/study selection and evaluation.** The section on *Literature Search Strategy | Study Selection and Evaluation* describes the process for identifying and selecting pertinent studies. Please comment on whether the literature search strategy, study selection considerations **including exclusion criteria**, and study evaluation considerations, are appropriate and clearly described. Please identify additional peer-reviewed studies that the assessment should consider.

2. **Toxicokinetic modeling.** In Appendix C, Section C.1.5, the draft assessment presents a summary, evaluation, and further development of published PBPK models for RDX in rats, mice, and humans (Sweeney et al., 2012a; Sweeney et al., 2012b).

   2a. Are the conclusions reached based on EPA's evaluation of the models scientifically supported? Do the revised PBPK models adequately represent RDX toxicokinetics? Are the model assumptions and parameters clearly presented and scientifically supported? Are the uncertainties in the model appropriately considered and discussed?

   2b. The average concentration of RDX in arterial blood (expressed as area under the curve) was selected over peak concentration as the dose metric for interspecies extrapolation for oral points of departure (PODs) derived from rat data. Is the choice of dose metric for each hazard sufficiently explained and appropriate? The mouse PBPK model was not used to derive PODs for noncancer or cancer endpoints because of uncertainties in the model and because of uncertainties associated with selection of a dose metric for cancer endpoints. Is this decision scientifically supported?

   2c. In Section 2.1.3 of the draft assessment, an uncertainty factor of 10 for human variation is applied in the derivation of the RfD. Does the toxicokinetic modeling support the use of a different factor instead?

3. **Hazard identification and dose–response assessment.** In Chapter 1, the draft assessment evaluates the available human, animal, and mechanistic studies to identify health outcomes that may result from exposure to RDX. In Chapter 2, the draft assessment develops organ/system- specific reference values for the health outcomes identified in Chapter 1, then selects overall reference values for each route of exposure. The draft assessment uses EPA's guidance documents (see http://www.epa.gov/iris/basic-information-about-integrated-risk-information-system#guidance) to reach the following conclusions.

   [Note: As suggested by the Chemical Assessment Advisory Committee panel that reviewed the draft IRIS assessment of benzo[a]pyrene, the charge questions in this section are organized by health outcome, with a question on each hazard identification followed by questions on the corresponding organ/system-specific toxicity values. This suggestion, however, entails some redundancy, as some questions apply equally to multiple health outcomes.]

3a. **Nervous system effects**

(i) **Nervous system hazard** (Sections 1.2.1, 1.3.1)**.** The draft assessment concludes that nervous system toxicity is a human hazard of RDX exposure. Please comment on whether the available human, animal, and mechanistic studies support this conclusion. **Are all hazards to the nervous system adequately assessed? Is there an appropriate endpoint to address the spectrum of effects?**

(ii) **Nervous system-specific toxicity values** (Section 2.1.1). Please comment on whether the selection of studies reporting nervous system effects is scientifically supported and clearly described. Considering the difference in toxicokinetics between gavage and dietary administration (described in Appendix C, Section C.1, and in the context of specific hazards in the toxicological review), is it appropriate to consider the Crouse et al. (2006) study, which used gavage administration? Is the characterization of convulsions as a severe endpoint, and the potential relationship to mortality, appropriately described?

(iii) **Points of departure for nervous system endpoints** (Section 2.1.2). **Is the selection of convulsions as the endpoint to represent this hazard scientifically supported and clearly described?** Are the calculations of PODs for these studies scientifically supported and clearly described**? Is the calculation of the HEDs for these studies scientifically supported and clearly described?** Does the severity of convulsions warrant the use of a benchmark response level of 1% extra risk? Is calculation of the lower bound on the benchmark dose (BMDL) for convulsions appropriate and consistent with the EPA's Benchmark Dose Guidance?

(iv) **Uncertainty factors for nervous system endpoints** (Section 2.1.3). Is the application of uncertainty factors to these PODs scientifically supported and clearly described? The subchronic and database uncertainty factors incorporate multiple considerations; please comment specifically on the scientific rationale for the application of a subchronic uncertainty factor of 1 and a database uncertainty factor of 3.[2]

(v) **Nervous system-specific reference dose** (Section 2.1.4). Is the organ/system-specific reference dose derived for nervous system effects scientifically supported and clearly characterized?

---

[2] Note that the database uncertainty factor applies to each of the hazards identified in the toxicological review.

3b. **Kidney and other urogenital system effects**

(i) **Kidney and other urogenital system hazard** (Sections 1.2.2, 1.3.1). The draft assessment concludes that kidney and other urogenital system toxicity is a potential human hazard of RDX exposure. Please comment on whether the available human, animal, and mechanistic studies support this conclusion. **Are all hazards to kidney and urogenital system adequately assessed?** Is the selection of suppurative prostatitis as the endpoint to represent this hazard scientifically supported and clearly described?

(ii) **Kidney and other urogenital system-specific toxicity values** (Section 2.1.1). Is the selection of the Levine et al. (1983) study that describes kidney and other urogenital system effects scientifically supported and clearly described?

(iii) **Points of departure for kidney and other urogenital system endpoints** (Section 2.1.2). Is the calculation of a POD for this study scientifically supported and clearly described**? Is the calculation of the HED for this study scientifically supported and clearly described?**

(iv) **Uncertainty factors for kidney and other urogenital system endpoints** (Section 2.1.3). Is the application of uncertainty factors to the POD scientifically supported and clearly described?

(v) **Kidney and other urogenital system-specific reference dose** (Section 2.1.4). Is the organ/system-specific reference dose derived for kidney and other urogenital system effects scientifically supported and clearly characterized?

3c. **Developmental and reproductive system effects**

(i) **Developmental and reproductive system hazard** (Sections 1.2.3, 1.3.1). The draft assessment concludes that there is suggestive evidence of male reproductive effects associated with RDX exposure, based on evidence of testicular degeneration in male mice. The draft assessment did not draw any conclusions as to whether developmental effects are a human hazard of RDX exposure. Please comment on whether the available human, animal, and mechanistic studies support these **decisions. Are other hazards to human reproductive and developmental outcome adequately addressed?**

(ii) **Reproductive system-specific toxicity values** (Section 2.1.1). Is the selection of the Lish et al. (1984) study that describes male reproductive system effects scientifically supported and clearly described?

(iii) **Points of departure for reproductive system endpoints** (Section 2.1.2). Is the calculation of a POD for this study scientifically supported and clearly described? **Is the calculation of the HED for this study scientifically supported and clearly described?**

(iv) **Uncertainty factors for reproductive system endpoints** (Section 2.1.3). Is the application of uncertainty factors to the POD scientifically supported and clearly described?

(v) **Reproductive system-specific reference dose** (Section 2.1.4). Is the organ/system-specific reference dose derived for reproductive system effects scientifically supported and clearly characterized?

3d. **Other noncancer hazards** (Sections 1.2.4, 1.2.6, 1.3.1). The draft assessment did not draw any conclusions as to whether liver, ocular, musculoskeletal, cardiovascular, immune, or gastrointestinal effects are human hazards of RDX exposure. Please comment on whether the available human, animal, and mechanistic studies support this **decision. Are other non-cancer hazard adequately described?**

3e. **Cancer**

(i) **Cancer hazard** (Sections 1.2.5, 1.3.2). There are plausible scientific arguments for more than one hazard descriptor as discussed in Section 1.3.2. The draft assessment concludes that there is *suggestive evidence of carcinogenic potential* for RDX, and that this descriptor applies to all routes of human exposure. Please comment on whether the available human, animal, and mechanistic studies support these conclusions.

(ii) **Cancer-specific toxicity values** (Section 2.3.1). As noted in EPA's 2005 *Guidelines for Carcinogen Risk Assessment*, "When there is suggestive evidence, the Agency generally would not attempt a dose-response assessment, as the nature of the data generally would not support one; however, when the evidence includes a well-conducted study, quantitative analyses may be useful for some purposes, for example, providing a sense of the magnitude and uncertainty of potential risks, ranking potential hazards, or setting research priorities." Does the draft assessment adequately explain the rationale for quantitative analysis, considering the uncertainty in the data and the suggestive nature of the weight of evidence, and is the selection of the Lish et al. (1984) study for this purpose scientifically supported and clearly described?

(iii) **Points of departure for cancer endpoints** (Section 2.3.2, 2.3.3). Are the calculations of PODs and oral slope factors scientifically supported and clearly described?

4. **Dose-response analysis.** In Chapter 2, the draft assessment uses the available human, animal, and mechanistic studies to derive candidate toxicity values for each hazard that is credibly associated with RDX exposure in Chapter 1, identify an organ/system-specific RfD, then selects an overall toxicity value for each route of exposure. The draft assessment uses EPA's guidance documents (see http://www.epa.gov/iris/basic-information-about-integrated-risk- information-system#guidance) in the following analyses.

4a. **Oral reference dose for effects other than cancer** (Sections 2.1.5–2.1.8). The draft assessment presents an overall oral reference dose of 3×10^{-3} mg/kg-day, based on

nervous system effects as described in the Crouse et al. (2006) study. Is this selection scientifically supported and clearly described, including consideration of mortality as described in Section 2.1.6, and consideration of the organ/system-specific reference dose derived from the toxicity study by Cholakis et al. (1980) that is lower (by approximately fivefold) as described in Section 2.1.4?

4b. **Inhalation reference concentration for effects other than cancer** (Section 2.2). The draft assessment does not derive an inhalation reference concentration as the available studies were insufficient to characterize inhalation hazard and conduct dose-response analysis, and no toxicokinetic studies of RDX were available to support development of a PBPK inhalation model. If you believe that the available data might support an inhalation reference concentration, please describe how one might be derived.

4c. **Oral slope factor for cancer** (Section 2.3.3–2.3.4). The draft assessment presents an overall oral slope factor of 0.038 per mg/kg-day based **on** the combination of liver and lung tumors in female mice. Is this derivation scientifically supported and clearly described?

4d. **Inhalation unit risk for cancer** (Section 2.4). The draft assessment does not derive an inhalation unit risk because inhalation carcinogenicity data were not available, nor were toxicokinetic studies of inhalation of RDX available to support development of an inhalation PBPK model. If you believe that the available data might support an inhalation unit risk, please describe how one might be derived.

5. **Executive summary**. Does the executive summary clearly and **adequately** present the major conclusions of the assessment?

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.

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.

Levine, BS; Lish, PM; Furedi, EM; Rac, VS; Sagartz, JM. (1983). Determination of the chronic mammalian toxicological effects of RDX (twenty-four month chronic toxicity/carcinogenicity study of hexahydro-1,3,5-trinitro-1,3,5-triazine (RDX) in the Fischer 344 rat): Final report--phase V. Chicago, IL: IIT Research Institute.

Lish, PM; Levine, BS; Furedi, EM; Sagartz, JM; Rac, VS. (1984). Determination of the chronic mammalian toxicological effects of RDX: Twenty-four month chronic toxicity/carcinogenicity study of hexahydro-1,3,5-trinitro-1,3,5-triazine (RDX) in the B6C3F1 hybrid mouse (Volumes1-3). (ADA181766. DAMD17-79-C-9161). Fort Detrick, Frederick, MD: U.S. Army Medical Research and Development Command. http://oai.dtic.mil/oai/oai?verb=getRecord&metadataPrefix=html&identifier=ADA181766

Sweeney, LM; Gut, CP, Jr; Gargas, ML; Reddy, G; Williams, LR; Johnson, MS. (2012a). Assessing the non-cancer risk for RDX (hexahydro-1,3,5-trinitro-1,3,5-triazine) using physiologically based pharmacokinetic (PBPK) modeling [Review]. Regul Toxicol Pharmacol 62: 107-114. http://dx.doi.org/10.1016/j.yrtph.2011.12.007

Sweeney, LM; Okolica, MR; Gut, CP, Jr; Gargas, ML. (2012b). Cancer mode of action, weight of evidence, and proposed cancer reference value for hexahydro-1,3,5-trinitro-1,3,5-triazine (RDX). Regul Toxicol Pharmacol 64: 205-224. http://dx.doi.org/10.1016/j.yrtph.2012.07.005