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

September 2014

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 chemical substances 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 chemical substances 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 chemical substances; 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 IRIS in 1988 and oral slope factor (OSF) and a cancer descriptor posted on IRIS in 1990. The IRIS Program is conducting a reassessment of RDX. The draft Toxicological Review of Hexahydro-1,3,5-trinitro-1,3,5-triazine (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.

Charge questions on the draft RDX Toxicological Review

1. **Literature search/study selection**. Is the literature search strategy well documented? Please identify additional peer-reviewed studies that might have been missed.

2. **Physiologically-based pharmacokinetic (PBPK) modeling.** In Appendix C, 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, b).

   2a. Are the conclusions reached based on EPA's evaluation of the models scientifically supported?

   2b. 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?

   2c. The average concentration of RDX in arterial blood (expressed as area under the curve) was selected as the dose metric for interspecies extrapolation for noncancer oral points of departure (PODs) derived from rat data. Is the choice of dose metric appropriate? Does this PBPK model adequately estimate internal doses of RDX? 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?

3. **Hazard identification.** In section 1, the draft assessment evaluates the available human, animal, and mechanistic studies to identify the types of toxicity that can be credibly associated with RDX exposure. The draft assessment uses EPA's guidance documents (see http://www.epa.gov/iris/backgrd.html/) to reach the following conclusions.

   3a. **Nervous system toxicity** (sections 1.1.1, 1.2.1). The draft assessment concludes that nervous system toxicity is a human hazard of RDX exposure. Do the available human, animal, and mechanistic studies support this conclusion?

   3b. **Kidney and other urogenital system toxicity** (sections 1.1.2, 1.2.1). The draft assessment concludes that kidney and other urogenital system toxicity is a potential human hazard of RDX exposure. Do the available human, animal, and mechanistic studies support this conclusion?

   3c. **Reproductive toxicity** (sections 1.1.3, 1.2.1). The draft assessment concludes that there is suggestive evidence of male reproductive toxicity as a potential human hazard of RDX exposure. Do the available human and animal studies support these conclusions?

   3d. **Other types of toxicity** (sections 1.1.3, 1.1.4, 1.1.6, 1.2.1). The draft assessment concludes that the evidence does not support other types of noncancer toxicity, including developmental and liver toxicity, as potential human hazards of RDX exposure. Do the available human and animal studies support these conclusions? Are there other types of noncancer toxicity that can be credibly associated with RDX exposure?

3e. **Cancer** (sections 1.1.5, 1.2.2). The draft assessment concludes that the database for RDX provides "suggestive evidence of carcinogenic potential" by all routes of exposure. Do the available human, animal, and mechanistic studies support this conclusion?

4. **Dose-response analysis.** In section 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 section 1, then proposes an overall toxicity value for each route of exposure. The draft assessment uses EPA's guidance documents (see http://www.epa.gov/iris/backgrd.html/) in the following analyses.

   4a. **Oral reference dose for effects other than cancer** (section 2.1). The draft assessment proposes an overall reference dose of 9×10^{-4} mg/kg-day based on nervous system effects, specifically convulsions, using a PBPK model to extrapolate the rat data to humans. Is this value scientifically supported, giving due consideration to the intermediate steps of selecting studies appropriate for dose-response analysis, calculating PODs, and applying uncertainty factors?

   4b. **Inhalation reference concentration for effects other than cancer** (section 2.2). The draft assessment concludes that the available data do not support derivation of an inhalation reference concentration (RfC) for RDX. Is this conclusion scientifically supported?

   4c. **Oral slope factor for cancer** (section 2.3). The draft assessment proposes an oral slope factor of 4×10^{-2} per mg/kg-day based on liver and lung tumors in female mice. Is this value scientifically supported, giving due consideration to the intermediate steps of selecting studies appropriate for dose-response analysis and calculating PODs?

   4d. **Inhalation unit risk for cancer** (section 2.4). The draft assessment concludes that the available data do not support derivation of an inhalation unit risk for RDX. Is this conclusion scientifically supported?

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

Charge question on the public comments

6. In [DATE TBD], EPA asked for public comments on an earlier draft of this assessment. Appendix [TBD] summarizes the public comments and this assessment's responses to them. Please comment on EPA's responses to the scientific issues raised in the public comments.