National Toxicology Program (NTP) Comments on the Interagency Science Consultation Draft IRIS Assessment of RDX (dated September 2014)

Date: October 28, 2014

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MEMORANDUM

Date: October 27, 2014

To: Sandra Howard

From: Michael DeVito, Ph.D.
Acting Chief, National Toxicology Program Laboratory

Subject:**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.

The NTP are not aware of any additional peer-reviewed studies.

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?
The conclusions reached by EPA's evaluation of the model are 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?
The USEPA reviewed the RDX models of Sweeney and made some modifications of these models.

The EPA has adequately justified reducing the model to a single compartment GI tract submodel compared to the 2-compartment GI tract submodel from Sweeney.

The EPA modifies some of the individual parameters in the Sweeney model without justification. The EPA should provide a rationale for these changes.

The EPA correctly points out that RDX blood concentration are sensitive to bioavailability and GI absorption rate. Due to the relationship between the parameters and the data availability, these two parameters have issues related it identifiability. Thus EPA chose to set bioavailability to 100% and fit GI absorption rate. This seems like a reasonable approach and one that is scientifically based.

At times the EPA makes comparisons between its RDX model and that of Sweeney by using terms like "worse fit" or "similar fit". It would be helpful to provide a better comparison by plotting the Sweeney fit vs the EPA fit in some of the graphs.

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?

The average concentration of RDX in arterial blood (as expressed as AUC) is a reasonable dose metric for interspecies extrapolation for the noncancer oral POD from rats and the RDX model provides reasonably accurate measurements of RDX blood concentrations. The EPA does point out that the model has some limiations at the higher dose levels and is best suited for estimating exposures below 5 mg/kg day. This should not be a limitation of the use of the model since the exposures of concern are below this value.

The limited data available for the mouse increases the uncertainty of the mouse model compared to the rat. The EPA is justified in not using the mouse model because of these limitations.

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?

The data cited by EPA supports the conclusions of the assessment.

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?

The data cited by EPA supports the conclusions of the assessment.

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?

The data cited by EPA supports the conclusions of the assessment.

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?
The data cited by EPA supports the conclusions of the assessment. There are no other toxicities of concern.

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?
The data cited by EPA supports the conclusions of the assessment.

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?
The data and models used by the EPA scientifically support the dose response analysis and the calculation of the POD and application of 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?
The data cited by EPA supports the conclusions of the assessment.

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?
The data cited by EPA supports the conclusions of the assessment.

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?
The data cited by EPA supports the conclusions of the assessment.

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

The executive summary clearly and appropriately presents the major conclusions.

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.