Draft IRIS Assessment of Hexahydro-1,3,5-trinitro-1,3,5-triazine (RDX)

Presentation for the
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Louis D'Amico, Ph.D.
National Center for Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency

Outline of Presentation

This presentation will cover:

- Summary of draft IRIS assessment for RDX
- Address major questions raised during the November 17, 2016 teleconference.
  - Structure of the Toxicological Review
  - Use of data from multiple tumor sites to derive cancer risk values
  - Points of departure (PODs) and human equivalent doses (HEDs)

Authors and Contributors

Assessment Team

Louis D'Amico, Ph.D. (Assessment Manager)
Todd Blessinger, Ph.D.
Christopher Brinkerhoff, Ph.D.
Ravi Subramaniam, Ph.D.

Contributors

Rob DeWoskin, Ph.D.
Belinda Hawkins, Ph.D.
Karen Hogan, MS
Anne Loccisano, Ph.D. (ORISE Postdoctoral Fellow)
Tammy Stoker, Ph.D.
Jordan Trecki, Ph.D.
Scott Wesselkamper, Ph.D.
Charles Wood, DVM, Ph.D., DACVP

Executive Direction

Michael Slimak, Ph.D.
Kenneth Olden, Ph.D., Sc.D., L.H.D. (retired)
John Vandenberg, Ph.D.
Lynn Flowers, Ph.D., DABT
Vincent Cogliano, Ph.D.
Gina Perovich, M.S.
Samantha Jones, Ph.D.
Susan Rieth, MPH

Summary of Draft RDX Assessment

- Hexahydro-1,3,5-trinitro-1,3,5-triazine (aka **R**oyal **D**emolition E**X**plosive, cyclonite, hexogen)
  - Widely used military explosive, limited civilian uses
  - Limited general population exposures; releases described in air, water, or soil as result of manufacture, use, and disposal of RDX-containing munitions.
  - Agency interest stems from detection at EPA National Priorities List (NPL) sites, and inclusion on the Office of Water's Contaminant Candidate Lists
- Hazard Identification – Noncancer
  - Nervous system effects (convulsions)
  - Kidney/urogenital effects (suppurative prostatitis)
  - Male reproductive system (testicular degeneration)
- Hazard Identification – Cancer
  - *Suggestive evidence of carcinogenic potential* for RDX. This is based on induction of benign and malignant tumors in the liver and lungs of mice or rats following chronic administration in diet.

RfD Derivation

Effect	Point of Departure (mg/kg-d)	UF	Chronic RfD (mg/kg-d)	Confidence
Nervous System: Convulsions in male and female rats Crouse et al. (2006) 90-day gavage study in F344 rats	$BMDL_{01\text{-}HED}$: 0.28	Total UF = 100 $UF_A = 3$ $UF_H = 10$ $UF_{DB} = 3$	3×10^{-3}	Medium
Kidney/Urogenital: Prostate; suppurative inflammation Levine et al. (1983) 2-year feeding study in F344 rats	$BMDL_{10\text{-}HED}$: 0.23	Total UF = 100 $UF_A = 3$ $UF_H = 10$ $UF_{DB} = 3$	2×10^{-3}	Low
Male Reproductive: Testicular degeneration Lish et al. (1984) 2-year feeding study in $B6C3F_1$ mice	$BMDL_{10\text{-}HED}$: 2.4	Total UF = 100 $UF_A = 3$ $UF_H = 10$ $UF_{DB} = 3$	2×10^{-2}	Low
Overall Reference Dose (RfD) – Nervous System			**3×10^{-3}**	**Medium**

- POD_{HED} values based on data from the rat were derived using PBPK modeling; the POD_{HED} based on data from the mouse was derived using $BW^{3/4}$ adjustment.

[see Tables 2-2, 2-3, and 2-4 of Toxicological Review]

Comparison with Existing IRIS Entry for RDX - Noncancer

Principal Study / Critical Effect	Point of Departure (mg/kg-day)	UF	Chronic RfD (mg/kg-day)
RfD currently on IRIS (1988): Prostate; suppurative inflammation Levine et al. (1983) 2-year feeding study in F344 rats	NOAEL: 0.3	Total UF = 100 $UF_A = 10$ $UF_H = 10$	3×10^{-3}
Draft RfD (2016): Convulsions in male and female rats Crouse et al. (2006) 90-day gavage study in F344 rats	$BMDL_{01\text{-}HED}$: 0.28	Total UF = 100 $UF_A = 3$ $UF_H = 10$ $UF_{DB} = 3$	3×10^{-3}

2016 draft assessment:

- Reflects consideration of severity of nervous system effects.
- Applies benchmark dose modeling to take into account entirety of data.
- Utilizes available PBPK modeling to better account for toxicokinetic information.
- Consistent with EPA risk assessment practice, applies an uncertainty factor to account for database uncertainty.

Summary of the Dose Response Analysis for Oral Cancer Data

Principal Study	Elevated Tumor Types	Extrapolation Method	Oral Slope Factor$_{HED}$ (mg/kg-d)$^{-1}$
Lish et al. (1984) 2-year feeding study in B6C3F$_1$ mice	Incidences of combined hepatocellular adenomas or carcinomas and alveolar/bronchiolar adenomas or carcinomas in female mice	Linear extrapolation from the POD (BMDL$_{10\text{-}HED}$) derived from multistage modeling of data	3.8×10^{-2}

Incidence Data Used for Quantitation of the Cancer Risk Estimate:

Tumor Type	Dose Group (mg/kg-day)				
	0	1.5	7	35	107
Hepatocellular adenomas or carcinomas	1/67	4/62	5/63	10/64	4/31
Alveolar/bronchiolar adenomas or carcinomas	7/65	3/62	8/64	12/64	7/31

Oral Slope Factor = 4×10^{-2} per mg/kg-day

[see Table 2-7 of Toxicological Review]

Comparison with Existing IRIS Entry for RDX - Cancer

Principal Study / Critical Effect	Cancer Descriptor	Extrapolation Method	Oral Slope Factor $(mg/kg\text{-}day)^{-1}$
OSF currently on IRIS (1990): Incidence of combined hepatocellular adenomas and carcinomas in female mice Lish et al. (1984) 2-year feeding study in $B6C3F_1$ mice	Classification – C; possible human carcinogen	Linearized multistage procedure, extra risk	1.1×10^{-1}
Draft OSF (2016): Incidences of combined hepatocellular adenomas or carcinomas and alveolar/bronchiolar adenomas or carcinomas in female mice Lish et al. (1984) 2-year feeding study in $B6C3F_1$ mice	Suggestive evidence of carcinogenic potential	Linear extrapolation from the POD ($BMDL_{10\text{-}HED}$) derived from multistage modeling of data	4×10^{-2}

Teleconference Questions

IRIS Toxicological Review Structure

- The Toxicological Review is structured to move from
  - Synthesis/evaluation of evidence and hazard determination (Section 1.2) to
  - Identification of endpoints representing each organ/system-specific hazard (Section 1.3.1) to
  - Selection of studies and data sets for dose-response analysis (Section 2.1.1) to
  - Derivation of organ/system-specific reference values (Section 2.1.2 to 2.1.5)

IRIS Toxicological Review Structure

- Section 1.2. Presentation and Synthesis of Health Hazard Evidence by Organ/System
  - Goal of this section
    - Provide a synthesis of the available human, animal, and mechanistic evidence related to an organ/system-specific hazard, and
    - Conclude with a determination on the hazard based on integration of the 3 evidence streams.
  - Organization
    - Brief database overview
    - Human Evidence
    - Animal Evidence
    - Mechanistic Evidence
    - Integration of Evidence
- This organization applies across IRIS assessments, and is intended to promote consistency in the presentation of health hazard evidence while still providing flexibility to the assessment team to determine the clearest way to synthesize the evidence for a given hazard.
  - When advantageous (e.g., assessments with larger databases), this document structure may be expanded to include hazard-specific literature search or study quality considerations.
  - The format may evolve further as the IRIS Program refines its implementation of systematic review methods in the assessment development process.

IRIS Toxicological Review Structure

- Section 1.3. Integration and Evaluation
  - For effects other than cancer:
    - Serves as transition from Hazard Identification (Section 1.2) to the dose-response section yet to come.
    - Briefly restates the hazard determinations for all organs/systems; focus is on outcomes/endpoints, less on studies.
    - Identifies the endpoint(s) most representative of the hazard and best for carrying forward into Chapter 2 for dose-response analysis.
  - For cancer:
    - Focuses on cancer types and consideration of the overall risk.
    - Identifies the cancer descriptor and rationale for selection.
  - Susceptible populations and lifestages
    - Summarizes susceptibility to any health effect, cancer or noncancer.
    - When applicable, considers options for data use related to susceptible populations, or the development of separate risk estimates.

IRIS Toxicological Review Structure

- Section 2.1.1. Identification of Studies for Dose-Response Analysis of Selected Effects
  - Goal of the section
    - Identify the studies that measured endpoint(s) representative of a given hazard,
    - Further describes study quality considerations, as they relate to studies being considered for dose-response analysis, and
    - Select the specific studies and data sets to be used for dose-response analysis.
  - Example: Nervous system effects
    - Of the 7 RDX studies that reported convulsions, convulsion data sets from 3 studies were brought forward for dose-response analysis (Crouse et al., 2006; Cholakis et al., 1980; Levine et al. 1983).
      - Selection based on study quality, reporting (incidence vs qualitative results), and method of administration (gavage vs diet) considerations.

IRIS Toxicological Review Structure

- Section 2.1.2 to 2.1.5
  - Goal of these sections
    - Using data sets identified in Section 2.1.1, describe the steps taken to derive reference values, including application and justification of methods and assumptions.
  - Example: Nervous system effects
    - 3 nervous system (convulsion) data sets → derivation of PODs (using BMD modeling or NOAEL/LOAEL approach) → estimation of POD_{HED} values using PBPK modeling → application of uncertainty factors → derivation of candidate reference values.
      - Summarized in Tables 2-2 and 2-3.

Analyzing Composite Tumor Incidence

- NRC (Science and Judgement in Risk Assessment, 1994) recommended analyzing composite tumor incidence across multiple types.
  - Basing unit risk estimates on incidence of only one tumor type may underestimate carcinogenic potential.
- When appropriate, such analysis has been conducted in IRIS toxicological reviews (e.g., nitrobenzene, 2009; pentachlorophenol, 2010; 1,4-dioxane, 2013).
- More recently, MS-COMBO module was developed in BMDS to apply the method recommended in NRC (1994, Appendix I) to the multistage models.
- For RDX, MS-COMBO was used for dose-response analysis of composite liver and lung tumor incidence in female mice (Lish et al., 1984).

POD vs HED

- Point of departure (POD)
  - The point on a dose-response curve that marks the beginning of low-dose extrapolation. Can be estimated as the NOAEL, LOAEL, or BMDL.
  - RDX PODs provided in Table 2-2.
- Human equivalent dose (HED)
  - Derived from the POD (i.e., BMDL or NOAEL for RDX) by application of either:
    - PBPK models
      - Applied to RDX rat data to calculate the HED
    - $(\text{Body weight})^{3/4}$ scaling
      - Applied to RDX mouse data to calculate the HED
  - Identified in Tables 2-2 and 2-3 as the POD_{HED}.

Thank You!