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

Presentation for the
RDX Augmented Chemical Assessment Advisory Committee of
the Science Advisory Board
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Outline of Presentation

This presentation will cover:

- Implementation of 2011 and 2014 NRC recommendations in the RDX assessment
- General information on RDX
- Overview of the Toxicological Review
- Major public comments and EPA's responses to those comments

Implementation of 2011 and 2014 NRC Recommendations

All IRIS assessments use a revised document structure to enhance clarity, reduce volume, and address redundancies and inconsistencies. This structure includes:

- Separate sections for hazard identification and dose-response
- An executive summary that concisely summarizes major conclusions
- A preamble that describes IRIS assessment methods
- Detailed strategies for literature searching and screening
- Separate and clearer discussion about study quality considerations
- Use of the HERO database
- Standardized presentation of evidence in tables and arrays

Assessments will continue to be updated based on feedback.

General Information

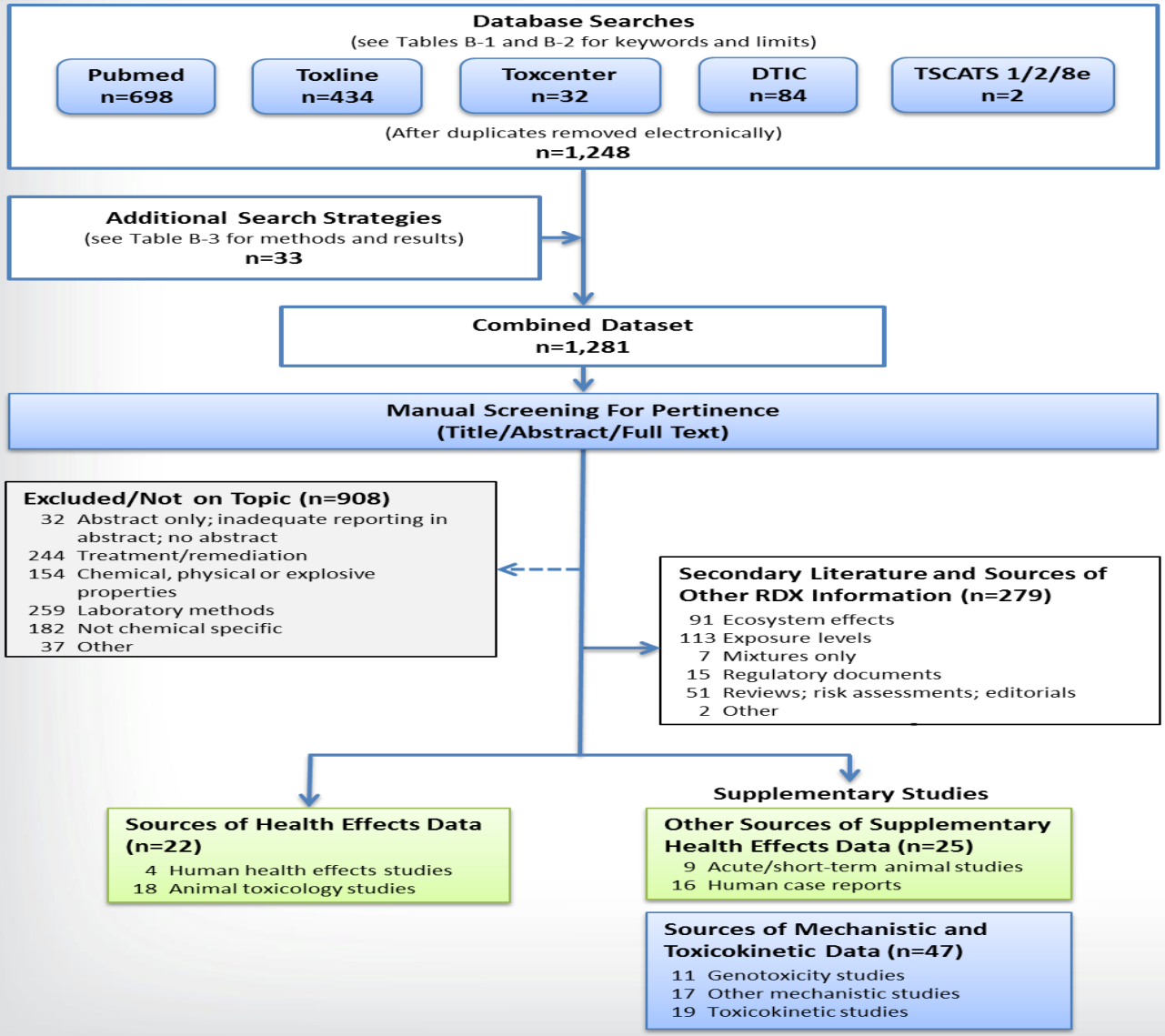
- Hexahydro-1,3,5-trinitro-1,3,5-triazine
  - Widely used military explosive, limited civilian uses
  - **R**oyal **D**emolition E**X**plosive, cyclonite, hexogen
  - 2011 aggregate national production of ~6.3 million pounds/year (U.S. EPA Chemical Data Reporting)

- Exposure:
  - Individuals working at military or other facilities where RDX is produced or used may be exposed.
  - General population exposures may occur if individuals are in or around facilities where RDX is produced or used, or in drinking water that is contaminated with RDX.
  - RDX can be released into environmental media (air, water, soil) as a result of waste generated during manufacture, packing, or disposal of the pure product or use and disposal of RDX-containing munitions.

General Information

- Agency Interest
  - As of 2015, RDX was detected in surface water, groundwater, sediment, or soil at 34 current U.S. EPA National Priorities List (NPL) sites. Additionally, contamination reported at 76 active military sites, 9 closed sites, and 15 sites under the Formerly Used Defense Sites (FUDS) program (Gadagbui et al. 2012).
  - RDX has been included in the Office of Water's Drinking Water Contaminant Candidate Lists (CCL) since the initial listing was published in 1998. The presence of a chemical on the list suggests that it is known or anticipated to occur in public water systems. RDX is not currently regulated under the Safe Drinking Water Act (SDWA).

Literature Search Strategy



Literature search output and references available on HERO (https://hero.epa.gov)

RDX Database

Human data

- Three studies on populations occupationally exposed to RDX of limited utility (small sample sizes, limited information on study design).
- Sixteen case reports describing effects after acute exposure to RDX.

Animal data

- Three chronic/carcinogenicity oral studies in rats (2) and mice (1.)
- Eight subchronic oral studies in rats, mice, dogs, and monkeys.
- Two short-term oral studies in dogs and rats.
- Four reproductive/developmental oral toxicity studies in rats and rabbits (including a two-generation reproductive study).
- Only inhalation study of RDX was excluded from consideration due to significant study design issues (lack of control group, incomplete information on exposure levels, inadequate reporting).

Other information

- Toxicokinetic information and PBPK models for humans, rats, and mice.
- Mechanistic studies.

Hazard Identification - Noncancer

- Noncancer effects
  - Nervous system effects (convulsions)
  - Kidney/urogenital effects (suppurative prostatitis)
  - Male reproductive system (testicular degeneration)

- Human case reports and animal studies provide consistent evidence of an association between RDX exposure and effects on the nervous system, including seizures or convulsions, tremors, hyperirritability, hyperreactivity, and behavioral changes.
- The available mechanistic data are consistent with nervous system effects resulting from interactions of RDX with the $GABA_A$ receptor.
- Evidence for effects on other organs/systems, including the liver and developmental effects, was more limited than for the endpoints summarized above.

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.

Cancer Characterization

Human Evidence

Animal Evidence

Mechanistic Evidence

Overall evaluation

- ☐ *Carcinogenic to humans*
- ☐ *Likely to be carcinogenic to humans*
- ☐ *Suggestive evidence of carcinogenic potential*
- ☐ *Inadequate information to assess carcinogenic potential*
- ☐ *Not likely to be carcinogenic to humans*

[See p. 2-54 of 2005 Cancer Guidelines]

Evidence for Human Carcinogenicity

- Mice:
  - Dose-related increases in the incidence of hepatocellular adenomas or carcinomas in male and female B6C3F$_1$ mice administered RDX in the diet (Lish et al. 1984, PWG reevaluation reported in Parker et al. 2006).
  - In the same study (Lish et al. 1984), dose-related increases in the incidence of alveolar/bronchiolar adenomas or carcinomas in both sexes.
  - Some of the trends for liver and lung tumors were statistically significant.
- Rats:
  - Statistically significant trend in the incidence of hepatocellular carcinomas in male, but not female, F344 rats in 2-year dietary study (Levine et al. 1983).
  - A 2-year dietary study in Sprague-Dawley rats (Hart 1976) was negative in both sexes, although at doses somewhat lower than Levine et al. (1983).

Identification of the Cancer Descriptor:

- Under EPA's Cancer Guidelines (USEPA, 2005), there is *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.

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}

Major Public Comments and EPA's Response

Mechanisms by which RDX induces seizures

Comment: Summary slides submitted to the docket detail research by USAPHC into the mechanism by which RDX induces seizures. The materials present the conclusion that binding of RDX to the $GABA_A$ receptor is the primary mechanism of seizure induction by RDX.

EPA's Response:

- The submitted materials describe findings of Williams et al. (2011), a reference cited extensively in the draft assessment. In fact, this reference was considered an important primary source of information on the mechanism of RDX neurotoxicity.
- Discussion of the mechanism of neurotoxicity in the draft assessment is consistent with Williams et al. (2011).
- Mechanism of RDX neurotoxicity is discussed in Sec 1.2.1 (pp 1-17 to 1-20).

Major Public Comments and EPA's Response

Selection of the cancer descriptor

Comment: One individual commented that selection of the cancer descriptor *suggestive evidence of carcinogenic potential* was not supported, and that RDX clearly met the criteria for *likely to be carcinogenic to humans* because RDX induced dose-related increases in tumors in two species, in both sexes, and at two sites.

EPA's Response:

- The assertion that EPA assigns cancer descriptors based on a set of criteria does not accurately describe the 2005 Cancer Guidelines – bulleted examples in the guidelines under each descriptor should not be considered a limitation in the application of a descriptor. Descriptors may be applicable to a wide variety of potential data sets and weights of evidence.
- The draft assessment presents the arguments for consideration of both the suggestive and likely descriptors. The scientific support for the selection of the cancer descriptor for RDX is an explicit charge question to the SAB CAAC.
- Discussion of the selection of the cancer descriptor is found in Sec 1.3.2 (pp 1-73 to 1-75).

Major Public Comments and EPA's Response

Application of systematic review methods in the assessment

Comment: One group commented that planning and scoping for this assessment was not adequately explained and that the assessment should include additional information on exposure to RDX.

EPA's Response:

- Formal planning and scoping was implemented by the IRIS Program in the development of assessments as part of the July 2013 enhancements to the IRIS process. This occurred well after development of the RDX assessment had been initiated; therefore formal planning and scoping was not conducted for this assessment. Instead, brief discussion of environmental occurrence, exposure potential, as well as regulatory interest is provided in the Preface to the Toxicological Review.
- A greater focus on exposure information was not added to the assessment. EPA notes that the scope of an IRIS assessment covers the first two steps of the risk assessment process: hazard identification and dose-response assessment. The preface summarizes some exposure information; however, exposure analyses falls outside the scope of an IRIS assessment.

Public Comment and the Draft Charge

- A detailed summary of public comments and EPA's response is available in the Supplemental Information for the draft toxicological review (Appendix E).

- Consideration of public comment was incorporated into development of the draft charge. Specific charge questions address comments raised during the public comment period as well as at the IRIS Public Science Meeting on the draft assessment (May 2016):
  - **2b** Selection of dose metric for interspecies extrapolation (and use of available PBPK models)
  - **3a.i** Mechanistic considerations supporting the conclusions on nervous system hazard
  - **3a.iii** Application of a benchmark response level of 1% extra risk given the severity of nervous system effects.
  - **3b.i** Use of suppurative prostatitis to represent the hazard to the kidney/urogenital system
  - **3.e.i** Conclusions on the selection of *suggestive evidence of carcinogenic potential* as the cancer descriptor

- EPA looks forward to receiving the SAB CAAC's advice on these and the other charge questions to ensure that the assessment is a rigorous, transparent evaluation of RDX toxicity that meets Agency needs.

Summary

The RDX assessment:

- Provides an updated reference dose for RDX.
- Derives multiple organ/system-specific reference values (to facilitate subsequent risk assessments of multiple chemicals).
- Provides an updated cancer descriptor and oral slope factor for RDX.
- Utilizes recent studies that inform the mechanism of RDX. neurotoxicity as well as evaluates recently published PBPK models for RDX.
- Addresses public comments.
- Reflects the IRIS Program's ongoing efforts to implement the 2011 and 2014 NRC recommendations.