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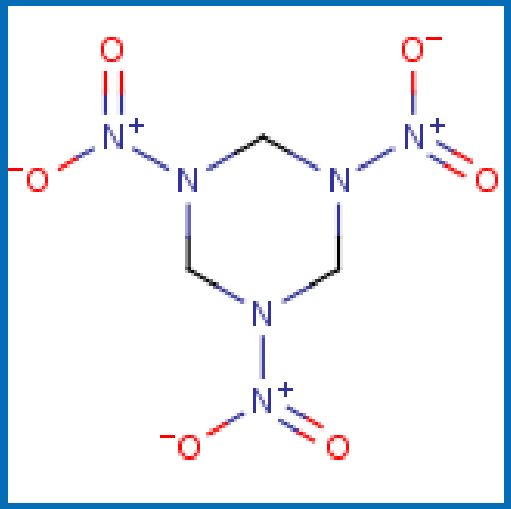
IRIS Draft Toxicological Review of Hexahydro-1,3,5-trinitro-1,3,5-triazine (RDX)

Louis D'Amico, Assessment Manager



Office of Research and Development
National Center for Environmental Assessment, Integrated Risk Information System

May 10, 2016

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Introduction

The purpose of this IRIS Public Science Meeting is to discuss the science that informs the **Public Comment** draft of the Toxicological Review of RDX.

This presentation updates stakeholders and the public on the status of the RDX assessment, and provides a framework for discussion of key science topics prior to peer review.

The draft assessment and this presentation do not represent and should not be construed to represent any Agency determination or policy.

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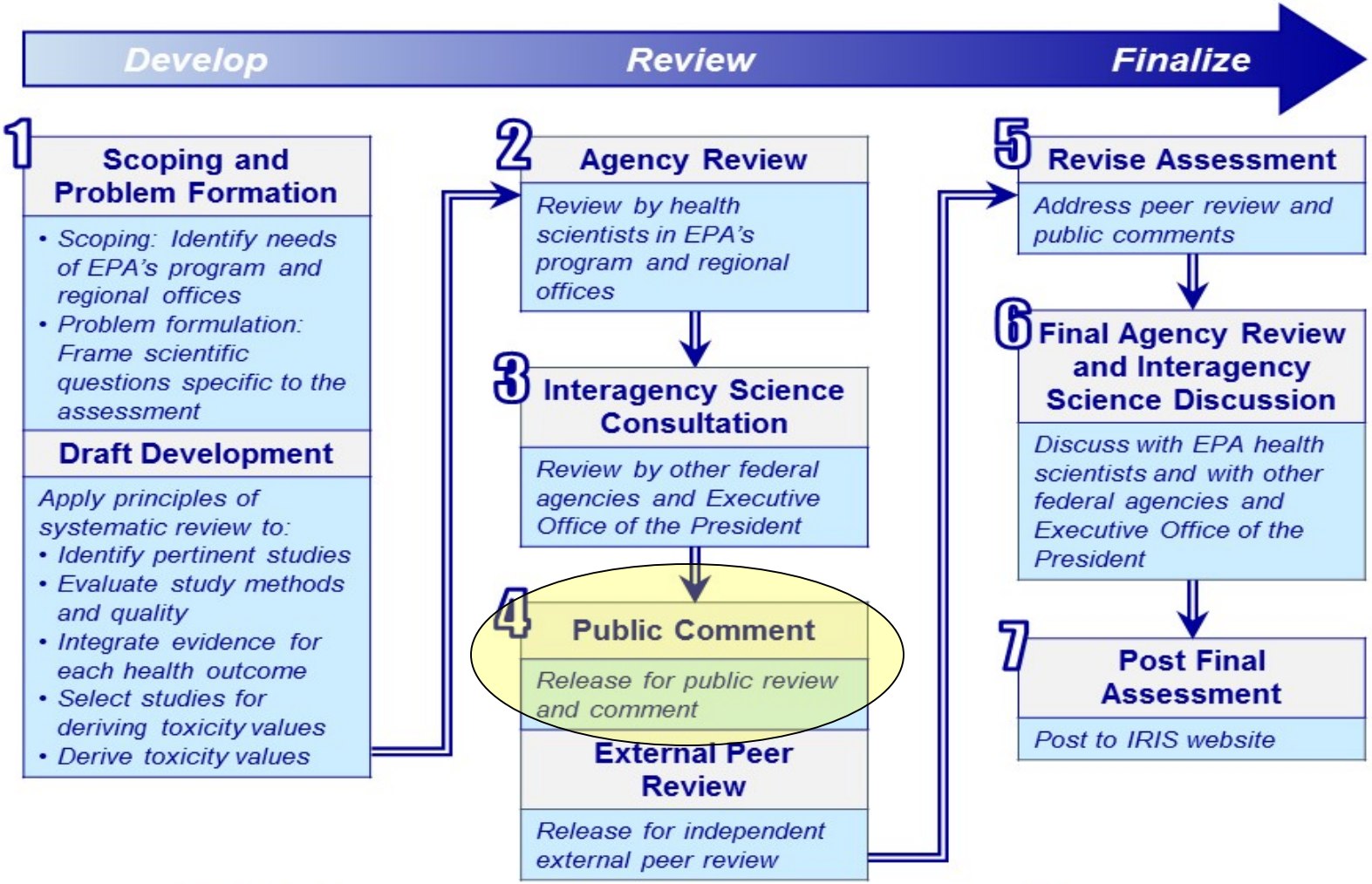

IRIS Assessment Development Process

The 7-step process has not changed. This figure refines earlier versions and includes the 2013 IRIS enhancements and the incorporation of systematic review approaches.

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General Information

- RDX is a white crystalline solid, produced at Army munition plants and used as an explosive. It is not found naturally in the environment.

- In 2011, aggregate national production volume was approximately 6.3 million pounds/year (U.S. EPA Chemical Data Reporting, http://java.epa.gov/chemview).

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.

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Agency Interest in RDX

- As of 2015, RDX was detected in surface water, groundwater, sediment, or soil at 34 current U.S. EPA National Priorities List (NPL) sites. Gadagbui et al. (2012) report contamination at 76 active military sites, 9 closed sites, and 15 sites under the Formerly Used Defense Sites (FUDS) program.

- 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).

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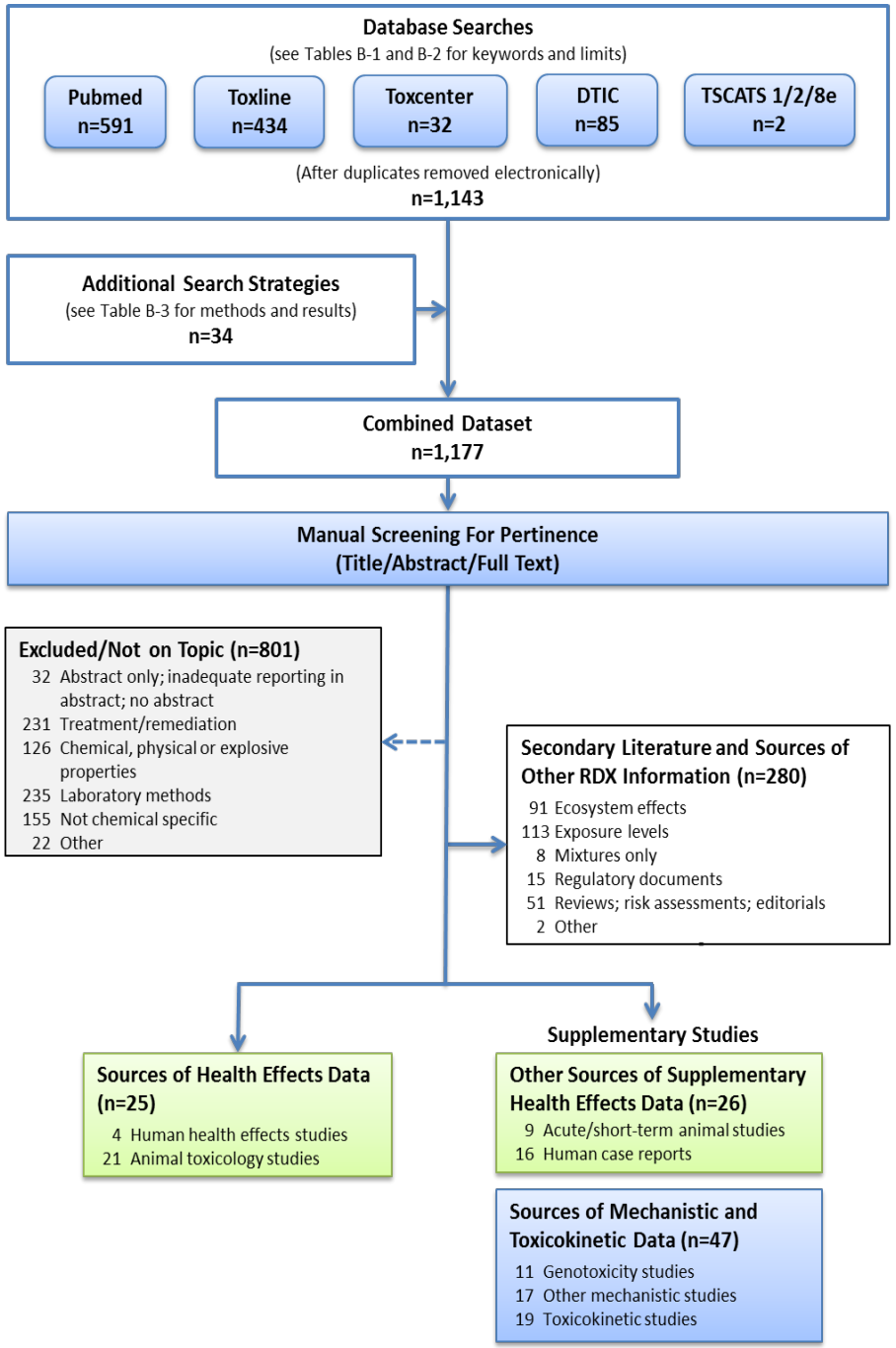
Literature Search Strategy

- The literature search identified more than 1,100 studies for RDX.
- Approximately 100 references provided primary information on the health effects and toxicokinetics of RDX.
- Initial literature search conducted in 2012, with yearly updates thereafter. Informal search of PubMed prior to this meeting identified no new studies of health effects associated with RDX exposure.



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Health Hazards Identified in the Public Comment Draft

Hazard	Level of evidence
Nervous system	Increased incidence of seizures or convulsions, tremors, hyperirritability, hyperactivity, and behavioral changes, as demonstrated in: -- multiple animal studies -- human case reports
Urogenital system, including kidney	Histopathological changes in male rats.
Male reproductive system	Testicular degeneration in male mice.
Cancer	Under EPA's cancer guidelines, there is *suggestive evidence of carcinogenic potential* for RDX, based on the identification of benign and malignant tumors in the liver and lungs of mice or rats.

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Key Science Topics Identified for Further Discussion

- Suppurative prostatitis as a marker for hazard to the urogenital system following RDX exposure.
- Evaluation and use of RDX PBPK models.
- Neurotoxicity observed with RDX – including consideration of dose and duration of exposure and the potential relationship to mortality.

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Session 1: Suppurative prostatitis as a marker for hazard to the urogenital system following RDX exposure.

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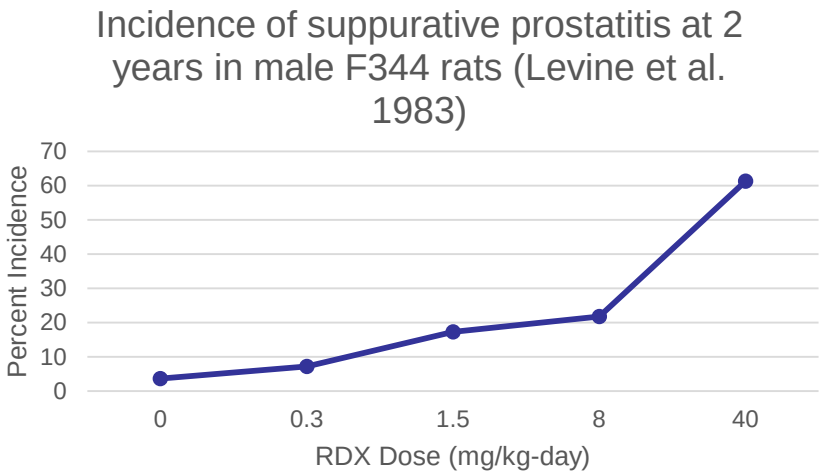
Suppurative Prostatitis

A dose-related increase in the incidence of suppurative prostatitis was observed in a 2-year feeding study in male F344 rats (Levine et al. 1983).

Dose (mg/kg-d)	0	0.3	1.5	8	40
SS	0/38	1/36	2/25*	4/29*	0/4
SDMS	2/16	3/19	7/27*	8/26	19/27*
Sum	2/54	4/55	9/52*	12/55*	19/31*

* Statistically significant ($p<0.05$) based on analysis by study authors.

SS: scheduled sacrifice
SDMS: spontaneous death/moribund sacrifice



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Suppurative Prostatitis (continued)

- Some reports identified prostatitis as an effect secondary to a bacterial infection, and unrelated to RDX toxicity.

- EPA proposes that infection may have been secondary to urogenital effects associated with RDX exposure, and that this effect is a marker for the broader array of urogenital effects observed by Levine et al. (1983).

EPA is seeking public discussion on the evaluation of suppurative prostatitis, and the interpretation of the kidney/urogenital effects.

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Session 2: Evaluation and use of RDX PBPK models.

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Evaluation of RDX PBPK Models

- Published PBPK models for RDX in rats, mice, and humans, were evaluated and further developed by EPA (detailed in Appendix C.1.5).

- Rat and human models
  - Relatively high confidence; the models were used to derive internal doses to support interspecies extrapolation.

- Mouse model
  - Low confidence in the model. Major uncertainties included:
    - The mouse PBPK model is based on a set of blood measurements from a single pharmacokinetic (PK) study (time points up to 3–4 hours post-dosing).
    - The single data set was used to fit both absorption and metabolic rate constants.
    - The RDX blood concentration in the low-dose group (35 mg/kg, at 4 hours) represents measurements from a single animal; other data points were non-detects or excluded as outliers. Confidence in model calibration reduced.
    - Type of additional data that increased confidence in the rat model (e.g., in vitro measurements of RDX metabolism, RDX elimination data) were not available for mice.
  - Given uncertainties, allometric ($BW^{3/4}$) scaling was used in preference to the mouse PBPK model for interspecies extrapolation.

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Selection of Dose Metric

- Two dose metrics were considered for internal dose calculation and interspecies extrapolation – average concentration in arterial blood (AUC) and peak blood concentration (C_{max}).

- EPA chose AUC as the dose metric for noncancer oral PODs based on some evidence of longer-term effects associated with binding to the $GABA_A$ receptor, and because of comparatively less uncertainty in model estimates based on AUC.

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RDX PBPK Models

EPA would like to encourage further discussion on:

1) *the development and application of the existing PBPK models,*
2) *the utility of the mouse model, and*
3) *selection of dose metric for modeling noncancer endpoints.*

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Session 3: Neurotoxicity observed with RDX – Including consideration of dose and duration of exposure and the potential relationship to mortality.

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Relationship between RDX Exposure, Convulsions, and Mortality

- RDX exposure is associated with convulsions in the majority of studies; mechanistic information supports this association.
- Animals studies provide some evidence that convulsion induction is more strongly correlated with dose level than exposure duration, and that gavage dosing induces convulsions at lower doses than dietary administration.
- Evidence for a relationship between mortality and convulsions is based on:
  - Observations of convulsions preceding deaths in several studies
  - Treatment-related mortality in several studies at doses as low as those associated with nervous system effects

  However, individual animal data from the most informative study on RDX neurotoxicity (Crouse et al. 2006) did not show a clear correspondence between convulsions and mortality.
- Comparison of LD_{01} values with BMD_{01} values for convulsions indicated that reference values for RDX based on mortality data would be similar to the overall RfD based on convulsions.

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Benchmark Response

- EPA considered the critical effect of convulsions to be a severe effect, and applied a benchmark response (BMR) of 1% extra risk.
- Uncertainties associated with this extrapolation are presented in the assessment.
- For comparative purposes, calculations using BMRs of 5% and 10% are provided in Appendix D.1.

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RDX Neurotoxicity

EPA is seeking public discussion on:

1) the relationship between convulsions and mortality,

2) consideration of dose and duration of exposure on incidence, and

3) the scientific rationale for the BMR for convulsions.

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Session 4: Public comment on other science topics in the RDX assessment.