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Preliminary Materials
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Preliminary Materials for the Integrated Risk Information System (IRIS) Toxicological Review of Hexahydro-1,3,5-trinitro-1,3,5-triazine (RDX)

[CASRN 121-82-4]

July 2013

NOTICE

This document is comprised of **preliminary materials,** consisting of a literature search strategy, evidence tables, and exposure-response arrays. This information is distributed solely for the purpose of pre-dissemination review under applicable information quality guidelines. It has not been formally disseminated by EPA. It does not represent and should not be construed to represent any Agency determination or policy. It is being circulated for review of its technical accuracy and science policy implications.

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Washington, DC

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PREFACE

This document presents the draft literature search strategy, preliminary evidence tables, and preliminary exposure-response arrays for hexahydro-1,3,5-trinitro-1,3,5-triazine (henceforth referred to as RDX) prepared under the auspices of EPA's Integrated Risk Information System (IRIS) Program. This material is being released for public viewing and comment prior to a public meeting, providing an opportunity for the IRIS Program to engage in early discussions with stakeholders and the public on data that may be used to identify adverse health effects and characterize exposure-response relationships.

The draft literature search strategy, preliminary evidence tables, and preliminary exposure-response arrays are responsive to the National Research Council (NRC) 2011 report *Review of the Environmental Protection Agency's Draft IRIS Assessment of Formaldehyde*. The literature search strategy, which describes the processes for identifying scientific literature, screening studies for consideration, and selecting studies for inclusion in evidence tables, is responsive to NRC recommendations regarding systematic review of the scientific literature. In addition, NRC recommendations for standardized presentation of key study data are addressed in the preliminary evidence tables and preliminary exposure-response arrays.

EPA welcomes all comments on the draft literature search strategy, preliminary evidence tables, and preliminary exposure-response arrays, such as remarks on the following:

- the clarity and transparency of the materials;
- the approach for identifying pertinent studies;
- the selection of studies for data extraction to preliminary evidence tables and exposure-response arrays;
- any methodological considerations that could affect the interpretation of or confidence in study results; and
- any additional studies published or nearing publication that may provide data for the evaluation of human health hazard or dose-response relationships.

The preliminary evidence tables and exposure-response arrays should be regarded solely as representing the data on each endpoint that have been identified as a result of the draft literature search strategy. They do not reflect any conclusions as to hazard identification or dose-response assessment. After obtaining public input and conducting additional study evaluation and data integration, EPA will revise these materials to support the hazard identification and dose-response assessment in a draft Toxicological Review.

1. DRAFT LITERATURE SEARCH STRATEGY

1.1. Literature Search and Screening Strategy for RDX

The overall literature search approach is shown in Table 1-1 and the results are summarized graphically in Figure 1-1. The literature search for RDX was conducted in five online scientific databases in February 2013. For four of these databases (Pubmed, Toxline, Toxcenter, and TSCATS) the detailed search strategy is provided in Table 1-2. Given the military applications of RDX, the Defense Technical Information Center (DTIC) database was searched. Because of limitations in the classification and distribution of materials in DTIC, a separate search strategy was applied, which is described in Table 1-3. The computerized database searches were augmented by review of online regulatory sources as well as "forward" and "backward" Web of Science searches of 2 recent reviews (Table 1-4).

A special strategy was applied to searches of the DTIC online database. A total of 858 citations were identified, including 504 where the full-text document had unlimited distribution, 304 classified as "distribution limited to U.S. Government agencies only," and 50 classified as "distribution limited to Department of Defense only." Of the 858 citations, 8 citations with unlimited distribution and 10 citations with limited distribution were selected for further review. Those 8 citations with unlimited distribution (that were not duplicated in other databases) were uploaded to the Health and Environmental Research Online (HERO) website[1] (http://hero.epa.gov). The 10 limited-distribution citations were evaluated for relevance to the assessment (i.e., with a focus on whether they provided additional primary health effects data) to determine whether EPA should seek authorization for public distribution and upload to HERO. A review of the abstract or full-text of the documents associated with the citation resulted in the following determinations:

- 4 of the 10 citations could be excluded from further consideration because the reports were not specific to RDX, or addressed environmental properties (e.g., leaching);
- 3 of the citations were determined not to provide additional primary health effects data because they either described a study plan for, or reported data from, experiments that were subsequently published (Williams et al., 2011; Hathaway and Buck, 1977) and had already been identified by the literature search strategy;
- 1 citation was identified as actually having unlimited distribution (duplicate record in DTIC database), and was added to the HERO database (Lish et al., 1984);

[1] HERO is a database of scientific studies and other references used to develop EPA's risk assessments aimed at understanding the health and environmental effects of pollutants and chemicals. It is developed and managed in EPA's Office of Research and Development (ORD) by the National Center for Environmental Assessment (NCEA). The database includes more than 300,000 scientific articles from the peer-reviewed literature. New studies are added continuously to HERO.

- 1 citation was identified as relevant and provided animal inhalation data, but was not brought forward for further review because of study quality considerations. These study quality considerations included lack of a control group, small numbers of animals, incomplete information on dosage or exposure levels, and inadequate reporting;
- 1 citation did not have an abstract or full text available outside of the Department of Defense. Based on the title, this report appeared to deal specifically with the manufacture and chemical/explosive properties of RDX. Given the available information, it was determined that it was unlikely the report would provide primary health effects data that warranted further review.

The rationales for exclusion of the other 841 references that were not selected for further consideration are summarized in Table 1-5.

After electronically eliminating duplicates from the citations retrieved through these databases, 906 citations were identified. Additionally, 18 citations were obtained using additional search strategies described in Table 1-4. The resulting 924 citations were screened using the title, abstract, and in limited instances, full text for pertinence to examining the health effects of RDX exposure. A total of 652 references were identified as not being pertinent and were excluded from further consideration (see Figure 1-1 for the exclusion categories). A total of 47 references were identified as potential primary sources of health effects data and were considered for data extraction to evidence tables and exposure-response arrays (see Section 1.2.1). A total of 210 references were considered pertinent, but not as primary sources of health effects data (e.g., adsorption/distribution/metabolism/excretion [ADME] studies), and were kept as additional resources for development of the Toxicological Review (see Section 1.2.2). If a reference did not provide enough material to evaluate pertinence (e.g., no abstract), it was reserved for further possible review; 15 such studies were identified for RDX (see Section 1.2.3). EPA welcomes comments on studies identified for possible further review that may inform their utility to the development of the Toxicological Review.

As illustrated in Figure 1-1, studies were identified and "tagged" in HERO based on information provided in the title and/or abstract; in some cases this information was supplemented by further review of the full text of the corresponding document. Based on this review, studies were distributed in different groups that reflect the primary content of the citation. It should be noted that studies were not given multiple tags, and the inclusion of a citation in a given category (or tag) does not preclude its use in one or more other categories. For example, Woody et al. (1986) is a case report that describes accidental ingestion of RDX by a child. In Figure 1-1 it is included in the human studies category of primary health effects data. This case report also provides pharmacokinetic data and could be a pertinent source of information on the toxicokinetics of RDX. In this instance, however, Woody et al. (1986) is not assigned a second tag for toxicokinetics. For the purposes of this preliminary description of the literature search process, the

strategy of only using one tag per reference is utilized to allow the public and stakeholders to more easily distinguish between citations that would be excluded from further review and those that may be utilized in the development of the assessment.

Table 1-1. Overview of database search strategy for RDX

Database	Keywords
Pubmed Toxline TSCATS1 WOS Toxcenter DTIC	Chemical CASRN: 121-82-4 Synonyms: Cyclonite OR RDX OR Cyclotrimethylenetrinitramine OR "cyclotrimethylene trinitramine" OR "Hexahydro-1,3,5-trinitro-1,3,5-triazine" OR "Hexahydro-1,3,5-trinitro-s-triazine" OR Hexogen OR "1,3,5-trinitro-1,3,5-triazine" OR "1,3,5-Triaza-1,3,5-trinitrocyclohexane" OR "1,3,5-Trinitro-1,3,5-triazacyclohexane" OR "1,3,5-Trinitrohexahydro-1,3,5-triazine" OR "1,3,5-Trinitrohexahydro-s-triazine" OR "1,3,5-Trinitroperhydro-1,3,5-triazine" OR "Esaidro-1,3,5-trinitro-1,3,5-triazina" OR "Hexahydro-1,3,5-trinitro-1,3,5-triazin" OR "Perhydro-1,3,5-trinitro-1,3,5-triazine" OR Cyclotrimethylenenitramine OR Trimethylenetrinitramine OR "Trimethylene trinitramine" OR Trimethyleentrinitramine OR "Trinitrocyclotrimethylene triamine" OR Trinitrotrimethylenetriamine OR "CX 84A" OR Cyklonit OR Geksogen OR Heksogen OR Hexogeen OR Hexolite OR "KHP 281" OR "PBX (af) 108" OR "PBXW 108(E)" OR "Pbx(AF) 108" Synonym and CASRN search for all databases; Toxcenter, Pubmed, and WOS limited using toxicity-related keywords <u>Toxicity-related terms (see Table 1-2 for specific keywords)</u> Toxicity (including duration, effects to children and occupational exposure); development; reproduction; teratogenicity; exposure routes; pharmacokinetics; toxicokinetics; metabolism; body fluids; endocrinology; carcinogenicity; genotoxicity; antagonists; inhibitors
ChemID	Searched by CASRN
TSCATS 2 & 8e submissions	

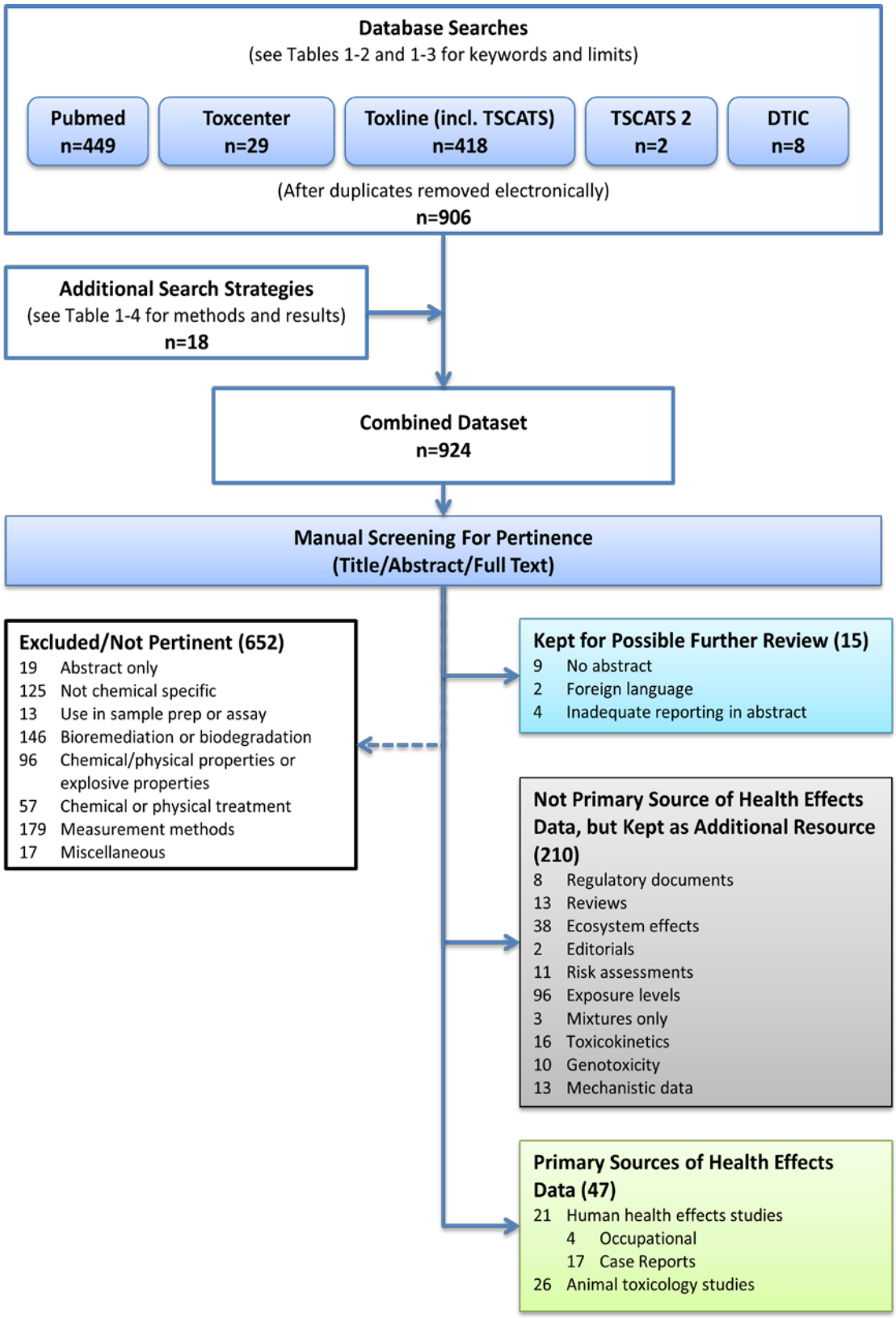

Figure 1-1. Literature search approach for RDX.

Table 1-2. Summary of detailed search strategies for RDX (Pubmed, Toxline, Toxcenter, TSCATS)

Database	Set #	Terms	Hits
PubMed **Date limit: 1/1/2012 – 2/2013**	1A1	(Cyclonite[tw] OR RDX[tw] OR Cyclotrimethylenetrinitramine[tw] OR "cyclotrimethylene trinitramine"[tw] OR "Hexahydro-1,3,5-trinitro-1,3,5-triazine"[tw] OR "Hexahydro-1,3,5-trinitro-s-triazine"[tw] OR Hexogen[tw] OR "1,3,5-trinitro-1,3,5-triazine"[tw] OR "1,3,5-Triaza-1,3,5-trinitrocyclohexane"[tw] OR "1,3,5-Trinitro-1,3,5-triazacyclohexane"[tw] OR "1,3,5-Trinitrohexahydro-1,3,5-triazine"[tw] OR "1,3,5-Trinitrohexahydro-s-triazine"[tw] OR "1,3,5-Trinitroperhydro-1,3,5-triazine"[tw] OR "Esaidro-1,3,5-trinitro-1,3,5-triazina"[tw] OR "Hexahydro-1,3,5-trinitro-1,3,5-triazin"[tw] OR "Perhydro-1,3,5-trinitro-1,3,5-triazine"[tw] OR Cyclotrimethylenenitramine[tw] OR Trimethylenetrinitramine[tw] OR "Trimethylene trinitramine"[tw] OR Trimethyleentrinitramine[tw] OR "Trinitrocyclotrimethylene triamine"[tw] OR Trinitrotrimethylenetriamine[tw] OR "CX 84A"[tw] OR Cyklonit[tw] OR Geksogen[tw] OR Heksogen[tw] OR Hexogeen[tw] OR Hexolite[tw] OR "KHP 281"[tw] OR "PBX (af) 108"[tw] OR "PBXW 108(E)"[tw] OR "Pbx(AF) 108"[tw]) AND (("2012/01/01"[Date - MeSH] : "3000"[Date - MeSH]) OR ("2012/01/01"[Date - Entrez] : "3000"[Date - Entrez]) OR ("2012/01/01"[Date - Create] : "3000"[Date - Create]))	112
PubMed **Date limit: 1950's-4/2012**	1A2	((((121-82-4) OR (Cyclonite[tw] OR Cyclotrimethylenetrinitramine[tw] OR "cyclotrimethylene trinitramine"[tw] OR "Hexahydro-1,3,5-trinitro-1,3,5-triazine"[tw] OR "Hexahydro-1,3,5-trinitro-s-triazine"[tw] OR Hexogen[tw] OR "1,3,5-trinitro-1,3,5-triazine"[tw] OR "1,3,5-Triaza-1,3,5-trinitrocyclohexane"[tw] OR "1,3,5-Trinitro-1,3,5-triazacyclohexane"[tw] OR "1,3,5-Trinitrohexahydro-1,3,5-triazine"[tw] OR "1,3,5-Trinitrohexahydro-s-triazine"[tw] OR "1,3,5-Trinitroperhydro-1,3,5-triazine"[tw] OR "Esaidro-1,3,5-trinitro-1,3,5-triazina"[tw] OR "Hexahydro-1,3,5-trinitro-1,3,5-triazin"[tw] OR "Perhydro-1,3,5-trinitro-1,3,5-triazine"[tw] OR Cyclotrimethylenenitramine[tw] OR Trimethylenetrinitramine[tw] OR "Trimethylene trinitramine"[tw] OR Trimethyleentrinitramine[tw] OR "Trinitrocyclotrimethylene triamine"[tw] OR Trinitrotrimethylenetriamine[tw] OR "CX 84A"[tw] OR Cyklonit[tw] OR Geksogen[tw] OR Heksogen[tw] OR Hexogeen[tw] OR Hexolite[tw] OR "KHP 281"[tw] OR "PBX (af) 108"[tw] OR "PBXW 108(E)"[tw] OR "Pbx(AF) 108"[tw]) OR (rdx[tw])) NOT medline[sb]) OR (((121-82-4) OR (Cyclonite[tw] OR Cyclotrimethylenetrinitramine[tw] OR "cyclotrimethylene trinitramine"[tw] OR "Hexahydro-1,3,5-trinitro-1,3,5-triazine"[tw] OR "Hexahydro-1,3,5-trinitro-s-triazine"[tw] OR Hexogen[tw] OR "1,3,5-trinitro-1,3,5-triazine"[tw] OR "1,3,5-Triaza-1,3,5-trinitrocyclohexane"[tw] OR "1,3,5-Trinitro-1,3,5-triazacyclohexane"[tw] OR "1,3,5-Trinitrohexahydro-1,3,5-triazine"[tw] OR "1,3,5-Trinitrohexahydro-s-triazine"[tw] OR "1,3,5-Trinitroperhydro-1,3,5-triazine"[tw] OR "Esaidro-1,3,5-trinitro-1,3,5-triazina"[tw] OR "Hexahydro-1,3,5-trinitro-1,3,5-triazin"[tw] OR "Perhydro-1,3,5-trinitro-1,3,5-triazine"[tw] OR Cyclotrimethylenenitramine[tw] OR Trimethylenetrinitramine[tw] OR "Trimethylene trinitramine"[tw] OR Trimethyleentrinitramine[tw] OR "Trinitrocyclotrimethylene triamine"[tw] OR Trinitrotrimethylenetriamine[tw] OR "CX 84A"[tw] OR Cyklonit[tw] OR	337

Database	Set #	Terms	Hits
		Geksogen[tw] OR Heksogen[tw] OR Hexogeen[tw] OR Hexolite[tw] OR "KHP 281"[tw] OR "PBX (af) 108"[tw] OR "PBXW 108(E)"[tw] OR "Pbx(AF) 108"[tw]) OR (rdx[tw])) AND (to[sh] OR po[sh] OR ae[sh] OR pk[sh] OR (me[sh] AND (humans[mh] OR animals[mh])) OR ci[sh] OR bl[sh] OR cf[sh] OR ur[sh] OR ((pharmacokinetics[mh] OR metabolism[mh]) AND (humans[mh] OR mammals[mh])) OR "dose-response relationship, drug"[mh] OR risk[mh] OR "toxicity tests"[mh] OR noxae[mh] OR cancer[sb] OR "endocrine system"[mh] OR "endocrine disruptors"[mh] OR "Hormones, Hormone Substitutes, and Hormone Antagonists"[mh] OR triazines/ai OR ("Inhalation Exposure"[Mesh] OR "Maternal Exposure"[Mesh] OR "Maximum Allowable Concentration"[Mesh] OR "Occupational Exposure"[Mesh] OR "Paternal Exposure"[Mesh] OR "Environmental Exposure"[Mesh:noexp]))))) NOT (((((121-82-4) OR (Cyclonite[tw] OR Cyclotrimethylenetrinitramine[tw] OR "cyclotrimethylene trinitramine"[tw] OR "Hexahydro-1,3,5-trinitro-1,3,5-triazine"[tw] OR "Hexahydro-1,3,5-trinitro-s-triazine"[tw] OR Hexogen[tw] OR "1,3,5-trinitro-1,3,5-triazine"[tw] OR "1,3,5-Triaza-1,3,5-trinitrocyclohexane"[tw] OR "1,3,5-Trinitro-1,3,5-triazacyclohexane"[tw] OR "1,3,5-Trinitrohexahydro-1,3,5-triazine"[tw] OR "1,3,5-Trinitrohexahydro-s-triazine"[tw] OR "1,3,5-Trinitroperhydro-1,3,5-triazine"[tw] OR "Esaidro-1,3,5-trinitro-1,3,5-triazina"[tw] OR "Hexahydro-1,3,5-trinitro-1,3,5-triazin"[tw] OR "Perhydro-1,3,5-trinitro-1,3,5-triazine"[tw] OR Cyclotrimethylenenitramine[tw] OR Trimethylenetrinitramine[tw] OR "Trimethylene trinitramine"[tw] OR Trimethyleentrinitramine[tw] OR "Trinitrocyclotrimethylene triamine"[tw] OR Trinitrotrimethylenetriamine[tw] OR "CX 84A"[tw] OR Cyklonit[tw] OR Geksogen[tw] OR Heksogen[tw] OR Hexogeen[tw] OR Hexolite[tw] OR "KHP 281"[tw] OR "PBX (af) 108"[tw] OR "PBXW 108(E)"[tw] OR "Pbx(AF) 108"[tw]) OR (rdx[tw])) NOT medline[sb]) OR (((121-82-4) OR (Cyclonite[tw] OR Cyclotrimethylenetrinitramine[tw] OR "cyclotrimethylene trinitramine"[tw] OR "Hexahydro-1,3,5-trinitro-1,3,5-triazine"[tw] OR "Hexahydro-1,3,5-trinitro-s-triazine"[tw] OR Hexogen[tw] OR "1,3,5-trinitro-1,3,5-triazine"[tw] OR "1,3,5-Triaza-1,3,5-trinitrocyclohexane"[tw] OR "1,3,5-Trinitro-1,3,5-triazacyclohexane"[tw] OR "1,3,5-Trinitrohexahydro-1,3,5-triazine"[tw] OR "1,3,5-Trinitrohexahydro-s-triazine"[tw] OR "1,3,5-Trinitroperhydro-1,3,5-triazine"[tw] OR "Esaidro-1,3,5-trinitro-1,3,5-triazina"[tw] OR "Hexahydro-1,3,5-trinitro-1,3,5-triazin"[tw] OR "Perhydro-1,3,5-trinitro-1,3,5-triazine"[tw] OR Cyclotrimethylenenitramine[tw] OR Trimethylenetrinitramine[tw] OR "Trimethylene trinitramine"[tw] OR Trimethyleentrinitramine[tw] OR "Trinitrocyclotrimethylene triamine"[tw] OR Trinitrotrimethylenetriamine[tw] OR "CX 84A"[tw] OR Cyklonit[tw] OR Geksogen[tw] OR Heksogen[tw] OR Hexogeen[tw] OR Hexolite[tw] OR "KHP 281"[tw] OR "PBX (af) 108"[tw] OR "PBXW 108(E)"[tw] OR "Pbx(AF) 108"[tw]) OR (rdx[tw])) AND (to[sh] OR po[sh] OR ae[sh] OR pk[sh] OR (me[sh] AND (humans[mh] OR animals[mh])) OR ci[sh] OR bl[sh] OR cf[sh] OR ur[sh] OR ((pharmacokinetics[mh] OR metabolism[mh]) AND (humans[mh] OR mammals[mh])) OR "dose-response relationship, drug"[mh] OR risk[mh] OR "toxicity tests"[mh] OR noxae[mh] OR cancer[sb] OR "endocrine system"[mh] OR "endocrine disruptors"[mh] OR "Hormones, Hormone Substitutes, and Hormone Antagonists"[mh] OR	

Database	Set #	Terms	Hits
		triazines/ai OR ("Inhalation Exposure"[Mesh] OR "Maternal Exposure"[Mesh] OR "Maximum Allowable Concentration"[Mesh] OR "Occupational Exposure"[Mesh] OR "Paternal Exposure"[Mesh] OR "Environmental Exposure"[Mesh:noexp]))))) AND (invertebrates OR aquatic organisms OR fish OR fishes OR amphibians OR earthworm*))	
Toxline **Date limit 2011-2013**	1B1	@OR+("Cyclonite"+"RDX"+"Cyclotrimethylenetrinitramine"+"cyclotrimethylene trinitramine"+"Hexahydro-1,3,5-trinitro-1,3,5-triazine"+"Hexahydro-1,3,5-trinitro-s-triazine"+"Hexogen"+"1,3,5-trinitro-1,3,5-triazine"+"1,3,5-Triaza-1,3,5-trinitrocyclohexane"+"1,3,5-Trinitro-1,3,5-triazacyclohexane"+"1,3,5-Trinitrohexahydro-1,3,5-triazine"+"1,3,5-Trinitrohexahydro-s-triazine"+@term+@rn+121-82-4)+@AND+@range+yr+2011+2013+@NOT+@org+pubmed+pubdart+crisp+tscats	5
	1B2	@OR+("1,3,5-Trinitroperhydro-1,3,5-triazine"+"Esaidro-1,3,5-trinitro-1,3,5-triazina"+"Hexahydro-1,3,5-trinitro-1,3,5-triazin"+"Perhydro-1,3,5-trinitro-1,3,5-triazine"+"Cyclotrimethylenenitramine"+"Trimethylenetrinitramine"+"Trimethylene trinitramine"+"Trimethyleentrinitramine"+"Trinitrocyclotrimethylene triamine"+"Trinitrotrimethylenetriamine"+"CX 84A"+"Cyklonit"+"Geksogen"+"Heksogen"+"Hexogeen"+"Hexolite"+"KHP 281")+@AND+@range+yr+2011+2013+@NOT+@org+pubmed+pubdart+crisp+tscats	0
Toxline **Date limit: 1907 – 4/2012**	1B3	casrn or synonyms -removed invertebrates, aquatic organisms, amphibians, earthworms	507
TSCATS	1C1	@term+@rn+121-82-4+@AND+@org+tscats	4
Toxcenter **Date limit: 1/1/2012 – 2/2013**	1D1	((121-82-4 NOT (patent/dt OR tscats/fs)) OR (Cyclonite OR RDX OR Cyclotrimethylenetrinitramine OR "cyclotrimethylene trinitramine" OR "Hexahydro-1,3,5-trinitro-1,3,5-triazine" OR "Hexahydro-1,3,5-trinitro-s-triazine" OR Hexogen OR "1,3,5-trinitro-1,3,5-triazine" OR "1,3,5-Triaza-1,3,5-trinitrocyclohexane" OR "1,3,5-Trinitro-1,3,5-triazacyclohexane" OR "1,3,5-Trinitrohexahydro-1,3,5-triazine" OR "1,3,5-Trinitrohexahydro-s-triazine" OR "1,3,5-Trinitroperhydro-1,3,5-triazine" OR "Esaidro-1,3,5-trinitro-1,3,5-triazina" OR "Hexahydro-1,3,5-trinitro-1,3,5-triazin" OR "Perhydro-1,3,5-trinitro-1,3,5-triazine" OR Cyclotrimethylenenitramine OR Trimethylenetrinitramine OR "Trimethylene trinitramine" OR Trimethyleentrinitramine OR "Trinitrocyclotrimethylene triamine" OR Trinitrotrimethylenetriamine OR "CX 84A" OR Cyklonit OR Geksogen OR Heksogen OR Hexogeen OR Hexolite OR "KHP 281" OR "PBX (af) 108" OR "PBXW 108(E)" OR "Pbx(AF) 108") AND (py>2012 OR ed>20120101) AND (chronic OR immunotox? OR neurotox? OR toxicokin? OR biomarker? OR neurolog? OR pharmacokin? OR subchronic OR pbpk OR epidemiology/st,ct, it) OR acute OR subacute OR ld50# OR lc50# OR (toxicity OR adverse OR poisoning)/st,ct,it OR inhal? OR pulmon? OR nasal? OR lung? OR respir? OR occupation? OR workplace? OR worker? OR oral OR orally OR ingest? OR gavage? OR diet OR diets OR dietary OR	26

Database	Set #	Terms	Hits
		drinking(w)water OR (maximum and concentration? and (allowable OR permissible)) OR (abort? OR abnormalit? OR embryo? OR cleft? OR fetus? OR foetus? OR fetal? OR foetal? OR fertil? OR malform? OR ovum OR ova OR ovary OR placenta? OR pregnan? OR prenatal OR perinatal? OR postnatal? OR reproduc? OR steril? OR teratogen? OR sperm OR spermac? OR spermag? OR spermati? OR spermas? OR spermatob? OR spermatoc? OR spermatog? OR spermatoi? OR spermatol? OR spermator? OR spermatox? OR spermatoz? OR spermatu? OR spermi? OR spermo? OR neonat? OR newborn OR development OR developmental? OR zygote? OR child OR children OR adolescen? OR infant OR wean? OR offspring OR age(w)factor? OR dermal? OR dermis OR skin OR epiderm? OR cutaneous? OR carcinog? OR cocarcinog? OR cancer? OR precancer? OR neoplas? OR tumor? OR tumour? OR oncogen? OR lymphoma? OR carcinom? OR genetox? OR genotox? OR mutagen? OR genetic(w)toxic? OR nephrotox? OR hepatotox? OR endocrin? OR estrogen? OR androgen? OR hormon? OR rat OR rats OR mouse OR mice OR muridae OR dog OR dogs OR rabbit? OR hamster? OR pig OR pigs OR swine OR porcine OR goat OR goats OR sheep OR monkey? OR macaque? OR marmoset? OR primate? OR mammal? OR ferret? OR gerbil? OR rodent? OR lagomorpha OR baboon? OR bovine OR canine OR cat OR cats OR feline OR pigeon? OR occupation? OR worker? OR epidem?) AND (biosis/fs AND py>1999 AND (caplus/fs AND 4-?/cc) Duplicates were removed; Biosis subfile results were date limited to avoid extensive overlap with Toxline	
Toxcenter **Date limit: 1907 – 4/2012**	1D2	((121-82-4 NOT (patent/dt OR tscats/fs)) OR (Cyclonite OR RDX OR Cyclotrimethylenetrinitramine OR "cyclotrimethylene trinitramine" OR "Hexahydro-1,3,5-trinitro-1,3,5-triazine" OR "Hexahydro-1,3,5-trinitro-s-triazine" OR Hexogen OR "1,3,5-trinitro-1,3,5-triazine" OR "1,3,5-Triaza-1,3,5-trinitrocyclohexane" OR "1,3,5-Trinitro-1,3,5-triazacyclohexane" OR "1,3,5-Trinitrohexahydro-1,3,5-triazine" OR "1,3,5-Trinitrohexahydro-s-triazine" OR "1,3,5-Trinitroperhydro-1,3,5-triazine" OR "Esaidro-1,3,5-trinitro-1,3,5-triazina" OR "Hexahydro-1,3,5-trinitro-1,3,5-triazin" OR "Perhydro-1,3,5-trinitro-1,3,5-triazine" OR Cyclotrimethylenenitramine OR Trimethylenetrinitramine OR "Trimethylene trinitramine" OR Trimethyleentrinitramine OR "Trinitrocyclotrimethylene triamine" OR Trinitrotrimethylenetriamine OR "CX 84A" OR Cyklonit OR Geksogen OR Heksogen OR Hexogeen OR Hexolite OR "KHP 281" OR "PBX (af) 108" OR "PBXW 108(E)" OR "Pbx(AF) 108")AND (chronic OR immunotox? OR neurotox? OR toxicokin? OR biomarker? OR neurolog? OR pharmacokin? OR subchronic OR pbpk OR epidemiology/st,ct, it) OR acute OR subacute OR ld50# OR lc50# OR (toxicity OR adverse OR poisoning)/st,ct,it OR inhal? OR pulmon? OR nasal? OR lung? OR respir? OR occupation? OR workplace? OR worker? OR oral OR orally OR ingest? OR gavage? OR diet OR diets OR dietary OR drinking(w)water OR (maximum and concentration? and (allowable OR permissible)) OR (abort? OR abnormalit? OR embryo? OR cleft? OR fetus? OR foetus? OR fetal? OR foetal? OR fertil? OR malform? OR ovum OR ova OR ovary OR placenta? OR pregnan? OR prenatal OR perinatal? OR postnatal? OR reproduc? OR steril? OR teratogen? OR sperm OR spermac? OR spermag? OR spermati? OR spermas? OR spermatob? OR spermatoc? OR spermatog? OR spermatoi? OR spermatol? OR spermator? OR spermatox? OR spermatoz?	337

Database	Set #	Terms	Hits
		OR spermatu? OR spermi? OR spermo? OR neonat? OR newborn OR development OR developmental? OR zygote? OR child OR children OR adolescen? OR infant OR wean? OR offspring OR age(w)factor? OR dermal? OR dermis OR skin OR epiderm? OR cutaneous? OR carcinog? OR cocarcinog? OR cancer? OR precancer? OR neoplas? OR tumor? OR tumour? OR oncogen? OR lymphoma? OR carcinom? OR genetox? OR genotox? OR mutagen? OR genetic(w)toxic? OR nephrotox? OR hepatotox? OR endocrin? OR estrogen? OR androgen? OR hormon? OR rat OR rats OR mouse OR mice OR muridae OR dog OR dogs OR rabbit? OR hamster? OR pig OR pigs OR swine OR porcine OR goat OR goats OR sheep OR monkey? OR macaque? OR marmoset? OR primate? OR mammal? OR ferret? OR gerbil? OR rodent? OR lagomorpha OR baboon? OR bovine OR canine OR cat OR cats OR feline OR pigeon? OR occupation? OR worker? OR epidem?) AND (biosis/fs AND py>1999 AND (caplus/fs AND 4-?/cc) Duplicates were removed; Biosis subfile results were date limited to avoid extensive overlap with Toxline	
Merged Reference Set	1	Including additional strategies and DTIC (after duplicate removal)	924

1

2 **Table 1-3. Summary of detailed search strategies for RDX (DTIC)**

Database	Set #	Terms	Hits
DTIC **Search date: 2/11/2013**	2A1	key:((toxicity OR phramacokinetics OR toxicology OR pharmacology OR poisoning OR toxic hazards OR radiation hazards OR radiation effects OR toxic diseases OR toxic agents OR lethal agents OR antidotes OR death OR "signs and symptoms" OR cancer OR carinogens OR physiology OR biochemistry OR body weight OR anatomy OR body fluids OR metabolism OR immunology OR mutagens OR teratogenic compounds OR mutations OR antimetabolites) NOT (aquatic animals OR Invertebrates OR venomous animals OR wildlife OR biodegradation)) and ("121-82-4" OR Cyclonite OR RDX OR Cyclotrimethylenetrinitramine OR "cyclotrimethylene trinitramine" OR "Hexahydro-1,3,5-trinitro-1,3,5-triazine" OR "Hexahydro-1,3,5-trinitro-s-triazine" OR Hexogen OR Cyclotrimethylenenitramine OR Trimethylenetrinitramine OR "Trimethylene trinitramine" OR Trimethyleentrinitramine OR "Trinitrocyclotrimethylene triamine" OR Trinitrotrimethylenetriamine OR Hexolite) and distco:(A) | Report Date: All dates	504 (8 selected and added to HERO)
	2A2	Searched for: distco:(govt) and key:((toxicity OR phramacokinetics OR toxicology OR pharmacology OR poisoning OR toxic hazards OR radiation hazards OR radiation effects OR toxic diseases OR toxic agents OR lethal agents OR antidotes OR death OR "signs and symptoms" OR cancer OR carinogens OR physiology OR biochemistry OR body weight OR anatomy OR body fluids OR metabolism OR immunology OR mutagens OR teratogenic compounds OR mutations OR antimetabolites) NOT (aquatic animals OR Invertebrates OR venomous animals OR wildlife OR biodegradation)) and ("121-82-4" OR Cyclonite OR RDX OR	304 (7 selected for further consideration)

Database	Set #	Terms	Hits
		Cyclotrimethylenetrinitramine OR "cyclotrimethylene trinitramine" OR "Hexahydro-1,3,5-trinitro-1,3,5-triazine" OR "Hexahydro-1,3,5-trinitro-s-triazine" OR Hexogen OR Cyclotrimethylenenitramine OR Trimethylenetrinitramine OR "Trimethylene trinitramine" OR Trimethyleentrinitramine OR "Trinitrocyclotrimethylene triamine" OR Trinitrotrimethylenetriamine OR Hexolite) | Report Date: All dates	
	2A3	Searched for: distco:(dod) and key:((toxicity OR phramacokinetics OR toxicology OR pharmacology OR poisoning OR toxic hazards OR radiation hazards OR radiation effects OR toxic diseases OR toxic agents OR lethal agents OR antidotes OR death OR "signs and symptoms" OR cancer OR carinogens OR physiology OR biochemistry OR body weight OR anatomy OR body fluids OR metabolism OR immunology OR mutagens OR teratogenic compounds OR mutations OR antimetabolites) NOT (aquatic animals OR Invertebrates OR venomous animals OR wildlife OR biodegradation)) and ("121-82-4" OR Cyclonite OR RDX OR Cyclotrimethylenetrinitramine OR "cyclotrimethylene trinitramine" OR "Hexahydro-1,3,5-trinitro-1,3,5-triazine" OR "Hexahydro-1,3,5-trinitro-s-triazine" OR Hexogen OR Cyclotrimethylenenitramine OR Trimethylenetrinitramine OR "Trimethylene trinitramine" OR Trimethyleentrinitramine OR "Trinitrocyclotrimethylene triamine" OR Trinitrotrimethylenetriamine OR Hexolite) | Report Date: All dates	50 (3 selected for further consideration)
Merged	2		858 (8 added to HERO; see text)

1

Table 1-4. Processes used to augment the search of core databases for RDX

System Used	Selected Key Reference(s) or Sources	Date	Additional References Identified
Web of Science, forward search	Sweeney, LM; Gut, CP, Jr.; Gargas, ML; Reddy, G; Williams, LR; Johnson, MS. (2012). Assessing the non-cancer risk for RDX (hexahydro-1,3,5-trinitro-1,3,5-triazine) using physiologically based pharmacokinetic (PBPK) modeling. 62: 107-114. 1 search result	3/2013	0 citations added
	Sweeney, LM; Okolica, MR; Gut, CP, Jr; Gargas, ML. (2012). Cancer mode of action, weight of evidence, and proposed cancer reference value for hexahydro-1,3,5-trinitro-1,3,5-triazine (RDX). Regul Toxicol Pharmacol 64: 205-224 0 search results	3/2013	0 citations added
Web of Science, backward search	Sweeney, LM; Gut, CP, Jr.; Gargas, ML; Reddy, G; Williams, LR; Johnson, MS. (2012). Assessing the non-cancer risk for RDX (hexahydro-1,3,5-trinitro-1,3,5-triazine) using physiologically based pharmacokinetic (PBPK) modeling. 62: 107-114. 35 cited papers	3/2013	0 citations added
	Sweeney, LM; Okolica, MR; Gut, CP, Jr; Gargas, ML. (2012). Cancer mode of action, weight of evidence, and proposed cancer reference value for hexahydro-1,3,5-trinitro-1,3,5-triazine (RDX). Regul Toxicol Pharmacol 64: 205-224 69 cited papers	3/2013	3 citations added
Background Check	Combination of CASRN and synonyms searched on the following websites: ATSDR http://www.atsdr.cdc.gov/substances/index.asp (Note: the reference list for the ATSDR toxicological profile for RDX was compared to the search results and relevant references were added) CalEPA (Office of Environmental Health Hazard Assessment) (http://www.oehha.ca.gov/risk.html) eChemPortal (http://www.echemportal.org/echemportal/participant/page.action?pageID=9) EPA Acute Exposure Guideline Levels (http://www.epa.gov/oppt/aegl/pubs/chemlist.htm) EPA – IRISTrack/New Assessments and Reviews (http://cfpub.epa.gov/ncea/iristrac/) to find dates (http://www.epa.gov/ncea/iris/index.html) to find data EPA NSCEP (http://www.epa.gov/ncepihom/) EPA Science Inventory (http://cfpub.epa.gov/si/) Federal Docket www.regulations.gov Health Canada First Priority List Assessments	4/11/2012	15 citations added

	(http://www.hc-sc.gc.ca/ewh-semt/pubs/contaminants/psl1-lsp1/index-eng.php) Health Canada Second Priority List Assessments (http://www.hc-sc.gc.ca/ewh-semt/pubs/contaminants/psl2-lsp2/index-eng.php) IARC (http://monographs.iarc.fr/htdig/search.html) IPCS INCHEM (http://www.inchem.org/) NAS via NAP (http://www.nap.edu/) NCI (http://www.cancer.gov) NCTR (http://www.fda.gov/AboutFDA/CentersOffices/OC/OfficeofScientificandMedicalPrograms/NCTR/default.htm) National Institute for Environmental Health Sciences (NIEHS) http://www.niehs.nih.gov/ NIOSHTIC 2 (http://www2a.cdc.gov/nioshtic-2/) NTP - RoC, status, results, and management reports (http://ntpsearch.niehs.nih.gov/query.html) WHO assessments – CICADS, EHC (http://www.who.int/ipcs/assessment/en/)		

Table 1-5. Summary disposition of DTIC database citations

Criteria	Percent of Citations
Exclusion - Not chemical-specific	~50%
Exclusion - Bioremediation or biodegradation	5%
Exclusion - Chemical/physical properties of explosive properties	<5%
Exclusion - Physical or chemical treatment	<5%
Exclusion - Miscellaneous, including: • Superfund RODs for which the abstract did not specify whether RDX was a contaminant of concern • Meeting minutes and conference proceedings for which only general categories of topics were included in the DTIC record • DTIC records containing only a title containing inadequate information with which to classify the citation	~35%
Exclusion Total	*98% (841 total)*
Additional Resource – Regulatory documents	<5%
Additional Resource – Reviews	<5%
Additional Resource – Ecosystem effects	<5%
Additional Resource – Risk assessments	<5%
Additional Resource – Exposure levels	<5%

Additional Resource – Measurement methods	<5%
Additional Resource – Mixture only	<5%
Additional Resource – Toxicokinetics	<5%
Possible Further Review – No abstract	<5%
Possible Further Review – inadequate reporting in abstract	<5%
Inclusion Total	*~2% (17 total)*
TOTAL NUMBER OF DTICS CITATIONS (including 10 limited distribution for further review)	**858**

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1.2. List of References Based on Search Strategy for RDX

Citations for excluded references are not listed here, but can be found on the Health and Environmental Research Online (HERO) Web site (http://hero.epa.gov/RDX).

1.2.1. Primary Sources of Health Effects Data

Data from citations in **bold** are displayed in tabular or graphical form in Section 2. See Section 2.1 for a description of the process of selecting these studies for evidence tables and exposure-response arrays.

Human Health Effects (21 citations)

1. ATSDR. (1996). Symptom and disease prevalence with biomarkers health study Cornhusker Army Ammunition Plant Hall County, Nebraska. Atlanta, GA. Div. of Health Studies.
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14. **Ma, B., & Li, H. (1992). Neurobehavioral effects of hexogen. *Gongye Weisheng yu***

***Zhiyebin / Industrial health and occupational diseases, 19*(1), 20-23.**
15. Merrill, S. L. (1968). Ingestion of an explosive material, composition C-4: A report of two cases. *U.S. Army Vietnam Medical Bulletin, 8*, 5-11.
16. Stone, W., Paletta, T., Heiman, E., Bruce, J. I., & Knepshield, J. H. (1969). Toxic effects following ingestion of C-4 plastic explosive. *Archives of Internal Medicine, 124*(6), 726-730.
17. Testud, F., Glancaude, J. M., Imperatori, J., Le Meur, B., & Descotes, J. (1996). Acute poisoning from occupational exposure to hexogen, a novel nitrate explosive. *Medicina y Seguridad del Trabajo*(171), 119-127.
18. Testud, F., Glanclaude, J., Imperatori, J., Le Meur, B., & Descotes, J. (1996). [Acute hexogen poisoning after occupational exposure, report of 2 cases]. *Archives des Maladies Professionnelles de Medecine du Travail et de Securite Sociale, 57*(5), 342-346.
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<u>*Animal Health Effects*</u> (26 citations)

1. Angerhofer, R., Davis, G., & Balezewski, L. (1986). Teratological assessment of Trinitro-RDX in rats. Aberdeen Proving Ground: U.S. Army Environmental Hygiene Agency.
2. Brown, D. (1975). The acute and chronic biochemical and behavioral effects of cyclotrimethylenetrinitramine. Baltimore, MD: Maryland University Baltimore School of Pharmacy.
3. Burdette, L., Cook, L., & Dyer, R. (1988). Convulsant properties of cyclotrimethylenetrinitramine (RDX): Spontaneous, audiogenic, and amygdaloid kindled seizure activity. *Toxicology and Applied Pharmacology, 92*(3), 436-444. doi: 10.1016/0041-008x(88)90183-4
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triazine (RDX) in rabbits. Chicago, IL: IIT Research Institute.
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1.2.2. Not Primary Source of Health Effects Data, but Kept as Additional Resources

<u>*Regulatory Documents*</u> (8 citations)

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<u>*Inadequate reporting in abstract*</u> (4 citations)

1. . Final report on occupational health and safety at the plants of "Les Produits Chimiques Expro Inc." (1983) (Vol. Government of Quebec): Gouvernement du QuÃ¢ebec.
2. Berry, A., Arbuckle, J., & Nicol, J. (1983). Cyclonite poisoning in a dog. *Veterinary Record, 113*(19), 449.
3. De Cramer, K. G., & Short, R. P. (1992). Plastic explosive poisoning in dogs. *Journal of the South African Veterinary Medical Association, 63*(1), 30-31.
4. Wang, Y., Yan, C., Xia, B., & Tang, H. (2001). Study on health standard of octogen in air of workplaces. *Gongye Weisheng yu Zhiyebin / Industrial health and occupational diseases, 27*(3), 134-136.

2. PRELIMINARY EVIDENCE TABLES AND EXPOSURE-RESPONSE ARRAYS

2.1. Data Extraction: Preparation of Preliminary Evidence Tables and Exposure-Response Arrays

The 47 references identified as primary sources of health effects data were considered for data extraction to evidence tables and exposure-response arrays. References were first collated with respect to exposure route, exposure duration, and type of endpoint, to identify those most pertinent for evaluating the human health effects from chronic oral or inhalation exposure to RDX. As a result, data from 27 studies with one or more of the following characteristics were not extracted into evidence tables or exposure-response arrays:

- The study involved human case reports, dermal exposure or intravenous/intraperitoneal exposure;
- The study only involved acute or short-term exposures (less than 30 days), and it was not conducted in the context of immune, developmental, neurological or reproductive toxicity;
- The data in the study only included endpoints related to possible mechanisms of toxicity;
- No effects were associated with exposure to RDX for the endpoints evaluated in the study, nor were RDX-related effects observed for those endpoints in any of the other available references.

Data from the 20 remaining references were summarized in preliminary evidence tables. No studies were excluded based on study quality considerations, so as to allow for public input on methodological considerations that could affect the interpretation of, or confidence in, each study's results. In some instances, references are grouped together as "related" references because they represent pilot (e.g., range-finding), unpublished (e.g., technical reports, some with multiple volumes), and/or published (e.g., journal article) versions of the same study. The tables for noncarcinogenic effects appear first and are arranged in the order from the health effect with the most data to the health effect with the least data. The tables for carcinogenic effects follow, along with other systemic effects, which are those with little data to determine hazard. Finally, tables present data on genotoxic effects of RDX and its metabolites. Within each endpoint, the studies are presented beginning with chronic studies followed by those with subchronic exposures. The information in the preliminary evidence tables is displayed graphically in preliminary exposure-response arrays. In these arrays, a significant effect (indicated by a filled datapoint) is based on statistical significance, with the exception of the arrays for mortality and neurological endpoints.

For these two endpoints, it was determined that the severity of the endpoints (seizures and death) warranted identification based on biological significance. A study with a low number of animals per dose group may preclude identifying a change from the control as statistically significant when the incidence is low; however, given the severity of the effect, the observed effect was identified as biologically significant.

2.2. Neurological Effects Evidence Tables and Array

Table 2-1. Evidence pertaining to neurological effects in humans following exposure to RDX

<table>
<tr><th>Reference and Study Design</th><th colspan="4">Results</th></tr>
<tr><td rowspan="8">Ma and Li (1992) (China)

Cross-sectional study, 60 workers exposed to RDX (30 in Group A [26 males; 4 females]; 30 in Group B [24 males; 6 females]), compared to 32 workers with similar age, education level, and length of employment from same plant with no exposure to RDX (27 males; 5 females).

Exposure measures: Details of exposure measurement were not provided; exposed workers were divided into two groups based on RDX concentration in the air:

Concentration (mg/m^3)
Group A 0.407 (± 0.332)
Group B 0.672 (± 0.556)

Effect measures[a]: Five neurobehavioral function tests and five additional memory subtests.

Analysis: Variance (F-test); unadjusted linear regression, multiple regression, and correlation analysis.</td><td colspan="4">Neurobehavioral function tests, scaled scores (mean, standard deviation):</td></tr>
<tr><td>Test</td><td>Group A</td><td>Group B</td><td>Control</td></tr>
<tr><td>Memory retention*</td><td>96.9 (9.6)</td><td>91.1 (10.3)</td><td>111.3 (9.3)</td></tr>
<tr><td>Simple reaction time</td><td>539 (183)</td><td>578 (280)</td><td>493 (199)</td></tr>
<tr><td>Choice reaction time</td><td>775 (161)</td><td>770 (193)</td><td>763 (180)</td></tr>
<tr><td>Block design*</td><td>16.0 (4.3)</td><td>13.5(6.7)</td><td>18.0 (5.4)</td></tr>
<tr><td>Letter cancellation</td><td>1449 (331)</td><td>1484 (443)</td><td>1487 (343)</td></tr>
<tr><td colspan="4">*p < 0.01 (overall F-test); no statistically significant differences between Group A and Group B.
Lower score indicates worse performance.

Memory retention subtests, scaled scores (mean, standard deviation):</td></tr>
<tr><td>Subtest</td><td>Group A</td><td>Group B</td><td>Control</td></tr>
<tr><td>Directional memory*
Associative learning*
Image free recall*
Recognition of nonsense pictures*
Associative recall of portrait characteristics*</td><td>17.2 (4.9)
20.0 (4.3)
20.9 (4.1)
23.2 (4.9)
20.3 (4.4)</td><td>18.1 (5.7)
18.5 (4.6)
20.4 (3.3)
21.6 (4.3)
18.5 (4.3)</td><td>23.5 (3.6)
24.9 (5.1)
24.1 (3.8)
26.3 (3.6)
26.3 (3.3)</td></tr>
<tr><td colspan="4">*p < 0.01 (overall F-test); no statistically significant differences between Group A and Group B.
Lower score indicates worse performance.
Total behavioral score negatively correlated with exposure index (high exposure correlated with poor performance).</td></tr>
</table>

[a]Symptom data were not included in evidence table because of incomplete reporting.

Table 2-2. Evidence pertaining to neurological effects in animals following oral exposure to RDX

Reference and Study Design	Results
Lish et al. (1984); Levine et al. (1984) Mice, B6C3F$_1$, 85/sex/group; interim sacrifices (10/sex/group) at 6 and 12 mo 0, 1.5, 7.0, 35, or 175/100 mg/kg-d (high dose reduced to 100 mg/kg-d in wk 11 due to excessive mortality) Diet 24 mo	One male mouse in the 35 mg/kg-d dose group and one female mouse in the 175/100 mg/kg-d[a] group convulsed near the end of the study.
Hart (1976) Rats, Sprague-Dawley, 100/sex/group 0, 1.0, 3.1, or 10 mg/kg-d Diet 2 yrs	No neurological effects, as evidenced by clinical signs or changes in appearance or behavior, were reported.
Levine et al. (1983); Thompson (1983) Rats, F344, 75/sex/group; interim sacrifices (10/sex/group) at 6 and 12 mo 0, 0.3, 1.5, 8.0, or 40 mg/kg-d Diet 24 mo	Tremors, convulsions, and hyper-responsiveness to stimuli were noted at 40 mg/kg-d[a]; no incidence data were reported.
Cholakis et al. (1980) Mice, B6C3F$_1$, 10–12/sex/group 0, 40, 60, or 80 mg/kg-d for 2 wks followed by 0, 320, 160, or 80 mg/kg-d (TWA doses of 0, 79.6, 147.8, or 256.7 mg/kg-d for males and 0, 82.4, 136.3, or 276.4 mg/kg-d for females)[b] Diet 13 wks	Hyperactivity and/or nervousness observed in 50% of the high-dose males; no signs observed in females[a]; no incidence data were reported.
Cholakis et al. (1980) Rats, F344, 10/sex/group 0, 10, 14, 20, 28, or 40 mg/kg-d Diet 13 wks	No neurological effects, as evidenced by clinical signs or changes in appearance or behavior, were reported.

Reference and Study Design	Results
Cholakis et al. (1980) Rats, CD, two-generation study; F0: 22/sex/group; F1: 26/sex/group; F2: 10/sex/group F0 and F1 parental animals: 0, 5, 16, or 50 mg/kg-d Diet 13 wks	No neurological effects were reported.
Crouse et al. (2006) Rats, F344, 10/sex/group 0, 4, 8, 10, 12, or 15 mg/kg-d Gavage 90 d	Doses: 0 / 4 / 8[a] / 10 / 12 / 15 *Convulsions (incidence)* M: 0/10 / 0/10 / 1/10 / 3/10 / 8/10 / 7/10 F: 0/10 / 0/10 / 2/10 / 3/10 / 5/10 / 5/10 *Tremors (incidence)* M: 0/10 / 0/10 / 0/10 / 0/10 / 2/10 / 3/10 F: 0/10 / 0/10 / 0/10 / 0/10 / 0/10 / 1/10
Levine et al. (1990); Levine et al. (1981a); Levine et al. (1981b) Rats, F344, 10/sex/group; 30/sex for control 0, 10, 30, 100, 300, or 600 mg/kg-d Diet 13 wks	Hyper-reactivity to approach was observed in groups receiving ≥100 mg/kg-d[a]; no incidence data were reported. Tremors and convulsions were observed prior to death in some animals receiving 600 mg/kg-d; no incidence data were reported.
Von Oettingen et al. (1949) Rats, sex/strain not specified, 20/group 0, 15, 25, or 50 mg/kg-d Diet 3 mo	Hyperirritability and convulsions were observed in the 25 and 50 mg/kg-d groups[a]; no incidence data were reported.
Hart (1974) Dogs, Beagle, 3/sex/group 0, 0.1, 1, or 10 mg/kg-d Diet 90 d	No neurological effects, as evidenced by clinical signs or changes in appearance or behavior, were reported.
Martin and Hart (1974) Monkeys, Cynomolgus or Rhesus, 3/sex/group 0, 0.1, 1, or 10 mg/kg-d Gavage 90 d	Doses: 0 / 0.1 / 1 / 10[a] *CNS effects characterized as trembling, shaking, jerking, or convulsions (incidence)* M: 0/3 / 0/3 / 0/3 / 2/3 F: 0/3 / 0/3 / 0/3 / 2/3

Reference and Study Design	Results
Von Oettingen et al. (1949) Dogs, breed not specified, 5 females/group (control); 7 females/group (exposed) 0 or 50 mg/kg-d Diet 6 d/wk for 6 wks	Treated dogs exhibited convulsions, excitability, ataxia, and hyperactive reflexes[a]; no incidence data were reported.
MacPhail et al. (1985) Rats, Sprague-Dawley derived CD, 8–10 males or females/group 0, 1, 3, or 10 mg/kg-d Gavage 30 d	No changes in motor activity, flavor aversion, scheduled-controlled response, or acoustic startle-response were reported.
Cholakis et al. (1980) Rats, F344, 24–25 females/group 0, 0.2, 2.0, or 20 mg/kg Gavage GDs 6–19	Convulsions and hyperactivity in 18/25 dams at 20 mg/kg[a]; one female at 2.0 mg/kg-d exhibited convulsions.
Angerhofer et al. (1986) (range-finding study) Rats, Sprague-Dawley, 6 pregnant females/group 0, 10, 20, 40, 80, or 120 mg/kg-d Gavage GDs 6–15	Convulsions preceding death were observed at ≥40 mg/kg-d[a]; no incidence data were reported.
Angerhofer et al. (1986) Rats, Sprague-Dawley, 39–51 mated females/group 0, 2, 6, or 20 mg/kg-d Gavage GDs 6–15	Convulsions and hyperactivity[a] were observed at 20 mg/kg-d; no incidence data were reported.

[a]Mortality was reported in some RDX-treated groups in this study; see mortality evidence tables for additional details.
[b]Doses were calculated by the study authors.

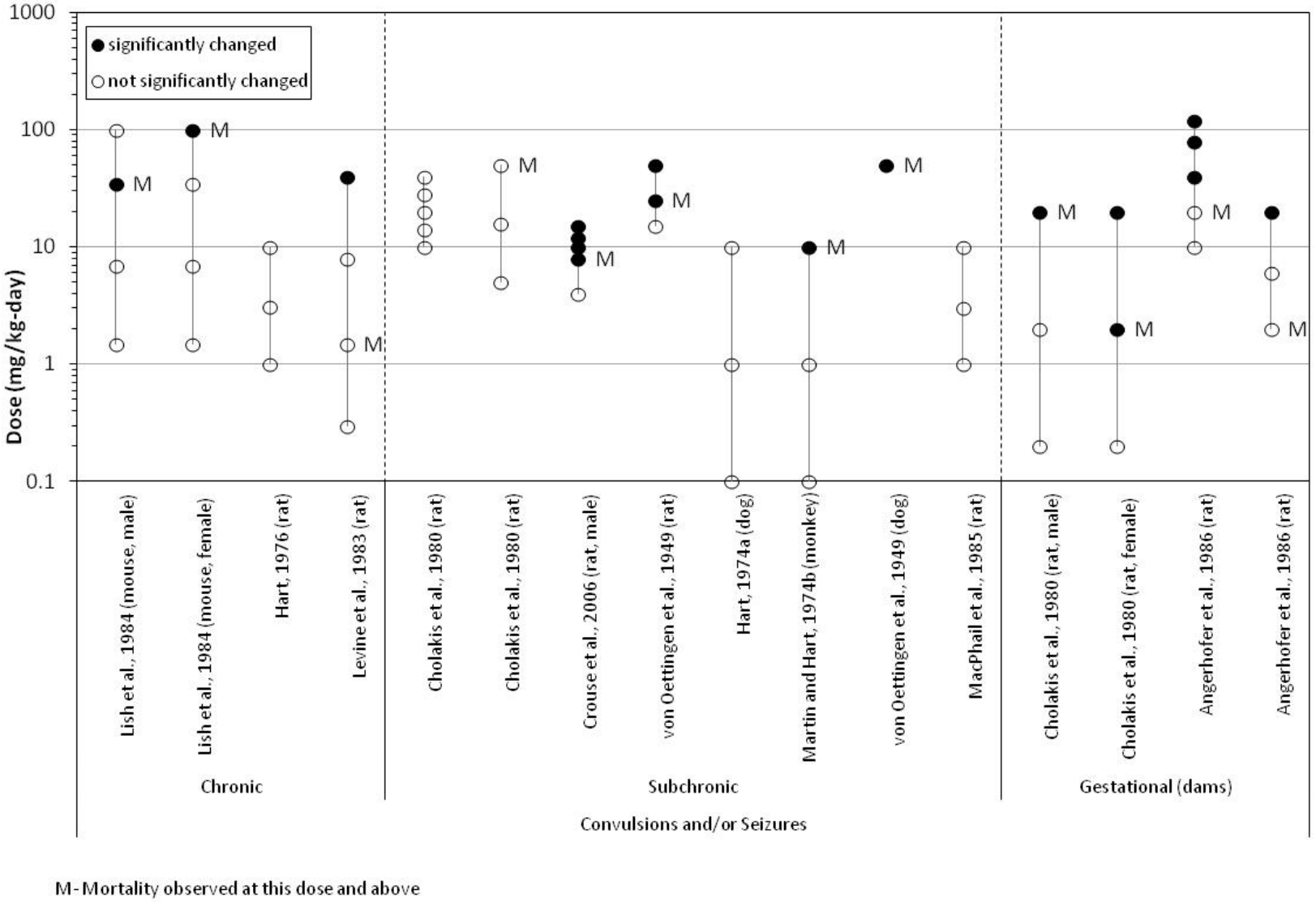


Figure 2-1. Exposure-response array of neurological effects following oral exposure to RDX

2.3. Mortality Evidence Table and Array

Table 2-3. Evidence pertaining to mortality following oral exposure to RDX

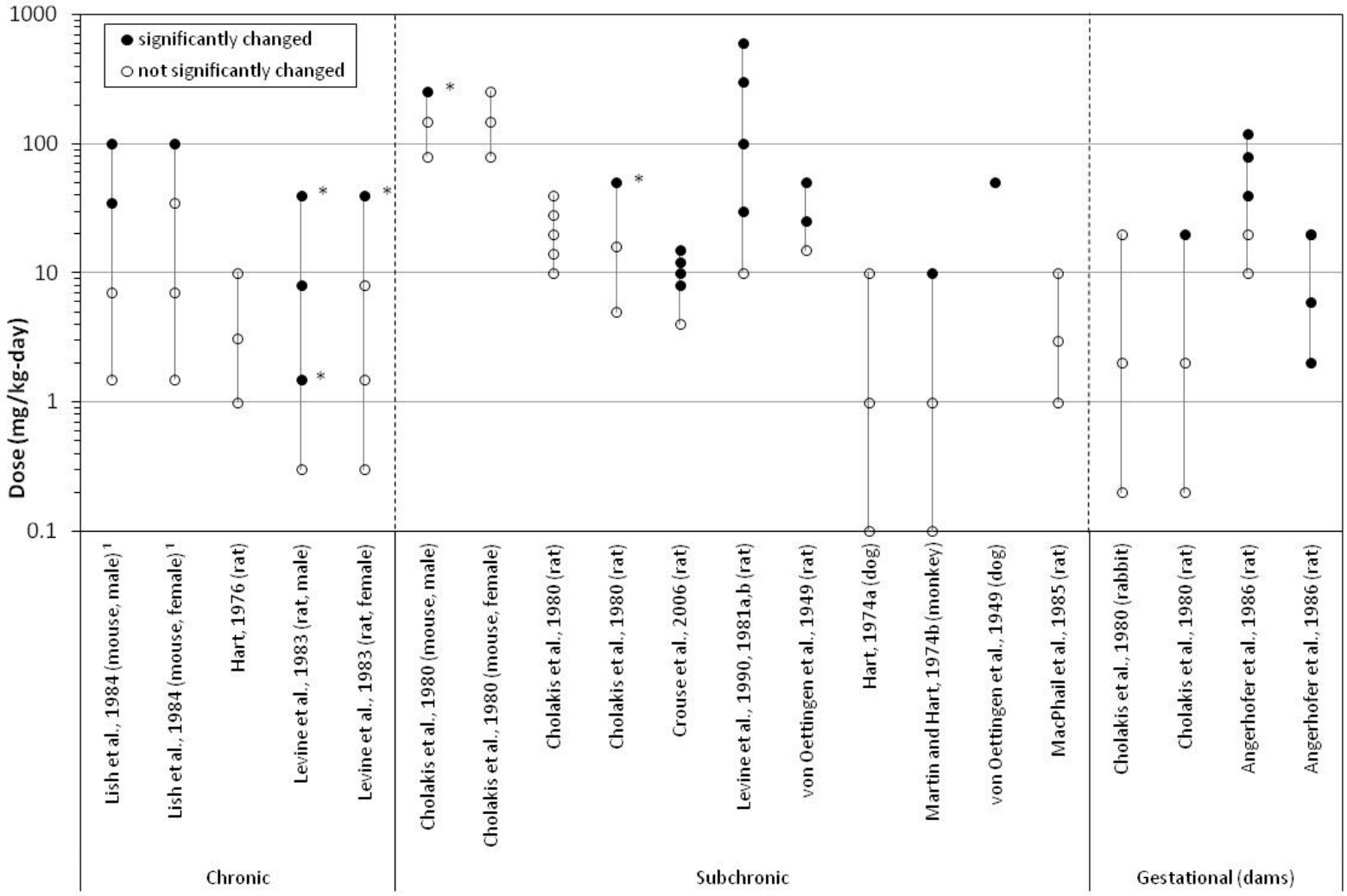
Reference and Study Design	Results					
Lish et al. (1984); Levine et al. (1984) Mice, B6C3F$_1$, 85/sex/group; interim sacrifices (10/sex/group) at 6 and 12 mo 0, 1.5, 7.0, 35, or 175/100 mg/kg-d (high dose reduced to 100 mg/kg-d in wk 11 due to excessive mortality) Diet 24 mo	Doses	0	1.5	7.0	35	175/100
	Mortality (incidence)[a]					
	M	20/65	23/65	25/65	29/65	41/65
	F	16/65	21/65	14/65	21/65	42/65
	After the high dose was reduced to 100 mg/kg-d, survival was similar to controls.					
Hart (1976) Rats, Sprague-Dawley, 100/sex/group 0, 1.0, 3.1, or 10 mg/kg-d Diet 2 yrs	Doses	0	1.0	3.1	10	
	Mortality (incidence)[b]					
	M	34/94	30/95	25/86	33/92	
	F	20/83	32/95	29/100	33/96	
Levine et al. (1983); Thompson (1983) Rats, F344, 75/sex/group; interim sacrifices (10/sex/group) at 6 and 12 mo 0, 0.3, 1.5, 8.0, or 40 mg/kg-d Diet 24 mo	Doses	0	0.3	1.5	8.0	40
	Mortality (incidence)[a]					
	M	17/55	19/55	30/55*	26/55	51/55*
	F	12/55	10/55	13/55	14/55	27/55*
Cholakis et al. (1980) Mice, B6C3F$_1$, 10–12/sex/group 0, 40, 60, or 80 mg/kg-d for 2 wks followed by 0, 320, 160, or 80 mg/kg-d (TWA doses of 0, 79.6, 147.8, or 256.7 mg/kg-d for males and 0, 82.4, 136.3, or 276.4 mg/kg-d for females)[c] Diet 13 wks	Doses	0	80	160	320	
	Mortality (incidence)					
	M	0/10	0/10	0/10	4/10*	
	F	0/11	0/12	0/10	2/12	
Cholakis et al. (1980) Rats, F344, 10/sex/group 0, 10, 14, 20, 28, or 40 mg/kg-d Diet 13 wks	Doses	0	10	14	20	28	40
	Mortality (incidence)						
	M	0/10	0/10	0/10	0/10	0/10	0/10
	F	1/10	0/10	0/10	0/10	0/10	0/10

Reference and Study Design	Results						
Cholakis et al. (1980) Rats, CD, two-generation study; F0: 22/sex/group; F1: 26/sex/group; F2: 10/sex/group F0 and F1 parental animals: 0, 5, 16, or 50 mg/kg-d Diet 13 wks	Doses	0	5	16	50		
	Mortality in F0 adults (incidence)[d]						
	M	0/22	0/22	0/22	2/22		
	F	0/22	0/22	0/22	6/22		
	M&F	0/44	0/44	0/44	8/44*		
Crouse et al. (2006) Rats, F344, 10/sex/group 0, 4, 8, 10, 12, or 15 mg/kg-d Gavage 90 d	Doses	0	4	8	10	12	15
	Mortality (incidence)						
	M	0/10	0/10	1/10	3/10	2/10	3/10
	F	0/10	0/10	1/10	2/10	5/10	4/10
Levine et al. (1990); Levine et al. (1981a); Levine et al. (1981b) Rats, F344, 10/sex/group; 30/sex for control 0, 10, 30, 100, 300, or 600 mg/kg-d Diet 13 wks	Doses	0	10	30	100	300	600
	Mortality (incidence)[e]						
	M	0/30	0/10	0/10	8/10	10/10	10/10
	F	0/30	1/10	0/10	5/10	10/10	10/10
Von Oettingen et al. (1949) Rats, sex/strain not specified, 20/group 0, 15, 25, or 50 mg/kg-d Diet 3 mo	Doses	0	15	25	50		
	Mortality (incidence)						
		0/20	1/20[f]	8/20	8/20		
Hart (1974) Dogs, Beagle, 3/sex/group 0, 0.1, 1, or 10 mg/kg-d Diet 90 d	Doses	0	0.1	1	10		
	Mortality (incidence)						
	M	0/3	0/3	1/3[g]	0/3		
	F	0/3	0/3	0/3	0/3		
Martin and Hart (1974) Monkeys, Cynomolgus or Rhesus, 3/sex/group 0, 0.1, 1, or 10 mg/kg-d Gavage 90 d	Doses	0	0.1	1	10		
	Mortality (incidence)						
	M	0/3	0/3	0/3	0/3		
	F	0/3	0/3	0/3	1/3[h]		

Reference and Study Design	Results					
Von Oettingen et al. (1949) Dogs, breed not specified, 5 females/group (control); 7 females/group (exposed) 0 or 50 mg/kg-d Diet 6 d/wk for 6 wks	Doses	0			50	
	Mortality (incidence)					
	F	0/5			1/7	
MacPhail et al. (1985) Rats, Sprague-Dawley derived CD, 8–10 males or females/group 0, 1, 3, or 10 mg/kg-d Gavage 30 d	No mortality was reported (incidence data were not provided).					
Cholakis et al. (1980) Rabbits, New Zealand white, 11–12 pregnant females/group 0, 0.2, 2.0, or 20 mg/kg-d Diet GDs 7–29	Doses	0	0.2	2.0	20	
	Mortality (incidence)					
	F	0/11	0/11	0/11	0/12	
Cholakis et al. (1980) Rats, F344, 24–25 females/group 0, 0.2, 2.0, or 20 mg/kg-d Gavage GDs 6–19	Doses	0	0.2	2.0	20	
	Mortality (incidence)					
	F	0/24	0/24	0/23	7/24[i]	
Angerhofer et al. (1986) (range-finding study) Rats, Sprague-Dawley, 6 pregnant females/group 0, 10, 20, 40, 80, or 120 mg/kg-d Gavage GDs 6–15	Doses	0	10	20	40	80	120
	Mortality (incidence)						
	F	0/6	0/6	0/6	6/6	6/6	6/6
Angerhofer et al. (1986) Rats, Sprague-Dawley, 39–51 mated females/group 0, 2, 6, or 20 mg/kg-d Gavage GDs 6–15	Doses	0	2	6	20		
	Mortality (incidence)						
	F	0/39	1/40	1/40	16/51		

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

[a]Interim sacrifices (10 animals/sex/dose) were performed at 27 and 53 weeks (Levine et al., 1983) or 26 and 53 weeks (Lish et al., 1984); these animals were not included in the mortality incidences.
[b]A malfunctioning heating system resulted in the premature deaths of 59 animals across groups; these animals were omitted from mortality results.
[c]Doses were calculated by the study authors.
[d]Data for male and female rats were combined for statistical analysis.
[e]Animals receiving 300 mg/kg-day died by week 3 of the study; animals receiving 600 mg/kg-day died by week 1 of the study.
[f]The study authors noted that the single death at 15 mg/kg-day was probably not treatment-related and noted that a large encapsulated cyst had replaced a lobe of the lung.
[g]The study authors stated that the animal died from bacteremia derived from a lesion unrelated to RDX treatment.
[h]The affected animal exhibited severe neurological effects following RDX administration and was euthanized.
[i]Includes one rat that was accidentally killed.



* changes identified as statisically significant based on analysis by study authors

[1] during the first 11 weeks of the study, mortality was observed at a dose of 175 mg/kg-day, the dose was lowered to 100 mg/kg-day for the remainder of the study. See the mortality evidence table.

Figure 2-2. Exposure-response array of mortality following oral exposure to RDX

2.4. Reproductive and Developmental Effects Evidence Tables and Array

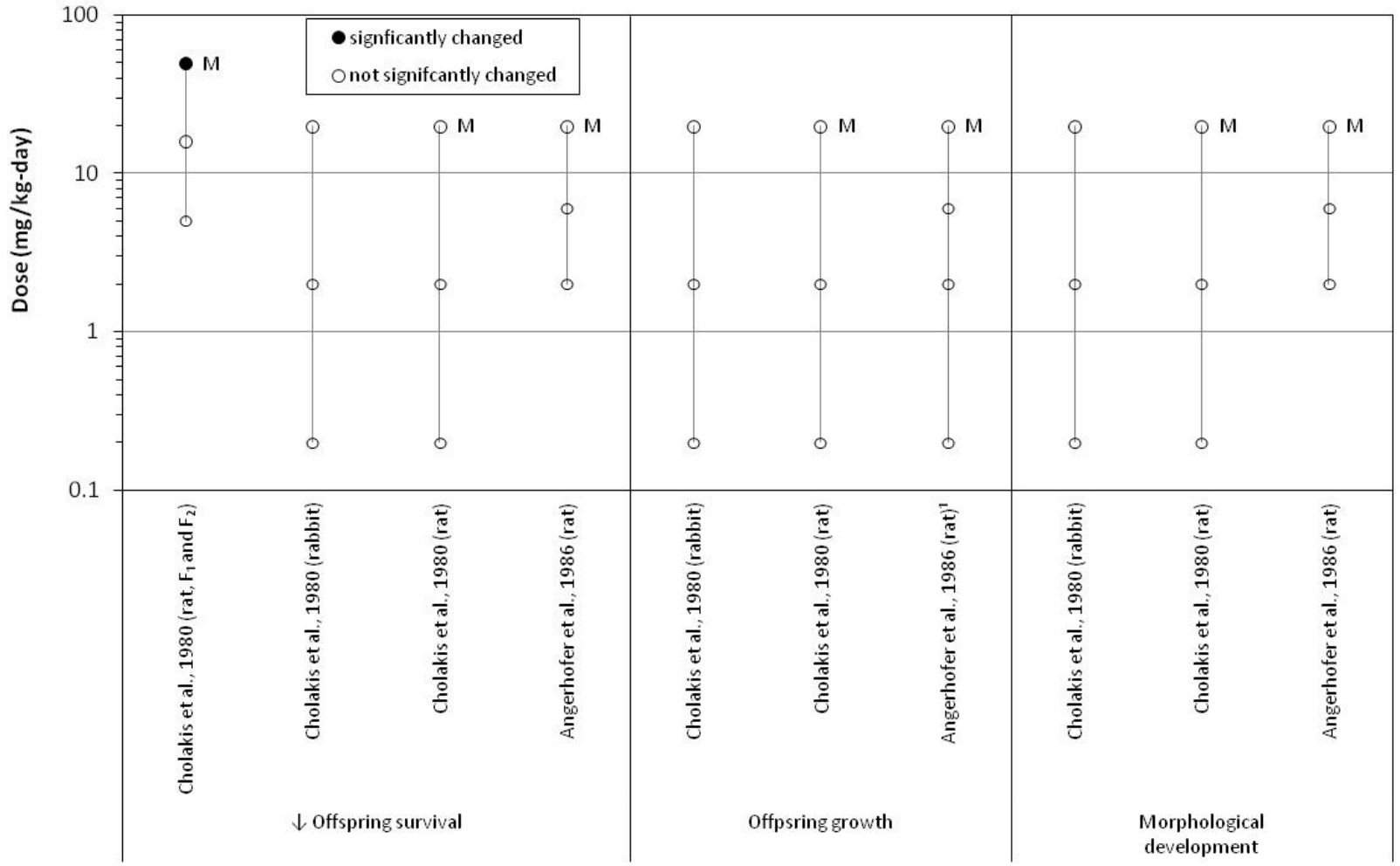
Table 2-4. Evidence pertaining to reproductive and developmental effects in animals following oral exposure to RDX

Reference and Study Design	Results				
Offspring survival					
Cholakis et al. (1980) Rats, CD, two-generation study; F0: 22/sex/group; F1: 26 sex/group; F2: 10 sex/group F0 and F1 parental animals: 0, 5, 16, or 50 mg/kg-d Diet 13 wks	Doses	0	5	16	50
	Stillborn pups (incidence)				
	F1	8/207	6/296	4/259	16/92*
	F2	6/288	6/290	2/250	24/46*
	Offspring survival at birth (percent of fetuses)				
	F1	96%	98%	98%	83*%
	F2	98%	98%	99%	48*%
	F0 maternal deaths occurred at 50 mg/kg-d. Only six F1 females in this group survived to serve as parental animals; none of the six died during subsequent treatment.				
Cholakis et al. (1980) Rabbits, New Zealand white, 11–12/group 0, 0.2, 2.0, or 20 mg/kg-d Gavage GDs 7–29	Doses	0	0.2	2	20
	Early resorptions (mean percent per dam)				
		6%	5%	4%	1%
	Late resorptions (mean percent per dam)				
		8%	5%	3%	3%
	Complete litter resorptions (number of litters)				
		0	0	0	2
	Viable fetuses (mean percent per dam):				
		85%	82%	77%	94%
Cholakis et al. (1980) Rats, F344, 24–25 females/group 0, 0.2, 2.0, or 20 mg/kg-d Gavage GDs 6–19	Doses	0	0.2	2.0	20
	Early resorptions (mean percent per dam)				
		6.0%	2.5%	4.8%	15.3%
	Late resorptions (mean percent per dam)				
		0.5%	0.5%	0.3%	1.6%
	Complete litter resorptions (number of litters)				
		0	0	0	2
	Viable fetuses (mean percent per dam)				
		93.2%	97.6%	94.9%	81.4%
	Significant maternal mortality (7/24 dams) occurred at 20 mg/kg-d.				

Reference and Study Design	Results				
Angerhofer et al. (1986) Rats, Sprague-Dawley, 39–51 mated females/group (25–29 pregnant dams/group) 0, 2, 6, or 20 mg/kg-d Gavage GDs 6–15	Doses	0	2	6	20
	Resorptions (percent of total implantations)				
		4.8%	6.1%	5.9%	6.4%
	Early resorptions (percent of total implantations)				
		4.8%	6.1%	5.9%	6.2%
	Late resorptions (percent of total implantations)				
		0%	0%	0%	0.27%
	Live fetuses (mean percent per litter)				
		100%	100%	100%	100%
	Significant maternal mortality (16/51) occurred at 20 mg/kg-d.				
Offspring growth					
Cholakis et al. (1980) Rabbits, New Zealand white, 11–12/group 0, 0.2, 2.0, or 20 mg/kg-d Gavage GDs 7–29	Doses	0	0.2	2.0	20
	Fetal body weight (percent change compared to control)				
		0%	19%	24%	15%
Cholakis et al. (1980) Rats, F344, 24–25 females/group 0, 0.2, 2.0, or 20 mg/kg-d Gavage GDs 6–19	Doses	0	0.2	2.0	20
	Fetal body weight (percent change compared to control)				
		0%	2%	3%	-7%
	Significant maternal mortality (7/24 dams) occurred at 20 mg/kg-d.				
Angerhofer et al. (1986) Rats, Sprague-Dawley, 39–51 mated females/group (25–29 pregnant dams/group) 0, 2, 6, or 20 mg/kg-d Gavage GDs 6–15	Doses	0	2	6	20
	Fetal body weight (percent change compared to control)				
		0%	-4%	-2%	9%[a]
	Fetal body length (percent change compared to control)				
		0%	-1%	-1%	-5%[a]
	Significant maternal mortality (16/51) occurred at 20 mg/kg-d.				
Morphological development					
Cholakis et al. (1980) Rabbits, New Zealand white, 11–12/group 0, 0.2, 2.0, or 20 mg/kg-d Gavage GDs 7–29	Doses	0	0.2	2.0	20
	Spina bifida (incidence)				
	Fetuses	0/88	0/99	0/94	3/110
	Litters	0/11	0/11	0/11	2/12
	Misshapen eye bulges (incidence)				
	Fetuses	0/88	0/99	0/94	3/110
	Litters	0/11	0/11	0/11	1/12
	Cleft palate (incidence)				
	Fetuses	0/39	1/46	2/44	2/52
	Litters	0/11	1/11	1/11	1/12

Reference and Study Design	Results				
	Enlarged front fontanel (incidence)				
	Fetuses	0/49	5/53	2/50	8/58
	Litters	0/11	2/11	2/11	2/12
Cholakis et al. (1980) Rats, F344, 24–25 females/group 0, 0.2, 2.0, or 20 mg/kg-d Gavage GDs 6–19	No gross or soft-tissue anomalies were seen in any exposure group. No treatment-related increase in the incidence of litters with skeletal anomalies was observed. Significant maternal mortality (7/24 dams) occurred at 20 mg/kg-d.				
Angerhofer et al. (1986) Rats, Sprague-Dawley, 39–51 mated females/group (25–29 pregnant dams/group) 0, 2, 6, or 20 mg/kg-d Gavage GDs 6–15	No treatment-related increase in the incidence of anomalies was observed.				
	Doses	0	2	6	20
	Total malformations (percent of fetuses with malformations)				
		1%	1%	0%	2%
	Significant maternal mortality (16/51) occurred at 20 mg/kg-d.				

*Statistically significant ($p < 0.05$) based on analysis by study authors.
[a]Statistically significant dose-related trend ($p \leq 0.05$) by Jonckheere-Terpstra test, performed for this assessment. Average fetal weights or lengths for each litter comprised the sample data for this test.



M - Maternal mortality observed at the highest dose
[1] Statistically signficant dose-related trend (p <= 0.05) by Jonckheere-Terpstra test, performed for this assessment.

Figure 2-3. Exposure-response array of reproductive and developmental effects following oral exposure to RDX.

Table 2-5. Evidence pertaining to male reproductive effects in animals following oral exposure to RDX

Reference and Study Design	Results					
Lish et al. (1984); Levine et al. (1984) Mice, B6C3F$_1$, 85/sex/group; interim sacrifices (10/sex/group) at 6 and 12 mo 0, 1.5, 7.0, 35, or 175/100 mg/kg-d (high dose reduced to 100 mg/kg-d in wk 11 due to excessive mortality) Diet 24 mo	Doses	0	1.5	7.0	35	175/100
	Testicular degeneration (incidence)					
		0/63	2/60	2/62	6/59	3/27[a]
	Absolute testes weight; wk 105 (percent change compared to control)					
		0%	-6%	0%	-2%	-6%
	Relative testes weight; wk 105 (percent change compared to control)					
		0%	-4%	2%	-2%	-2%
	Prostate was examined microscopically in control and 175/100 mg/kg-d groups; no effects were observed.					
Hart (1976) Rats, Sprague-Dawley, 100/sex/dose 0, 1.0, 3.1, or 10 mg/kg-d Diet 2 yrs	Doses	0	1.0	3.1	10	
	Absolute testes (with epididymis) weight; wk 104					
		0%	-2%	2%	5%	
	Relative testes (with epididymis) weight; wk 104					
		0%	-1%	7%	9%	
	Testes were examined microscopically in control and 10 mg/kg-d groups; no degeneration or other treatment-related effects were observed. Prostate was not examined microscopically.					
Levine et al. (1983); Thompson (1983) Rats, F344, 75/sex/group; interim sacrifices (10/sex/group) at 6 and 12 mo 0, 0.3, 1.5, 8.0, or 40 mg/kg-d Diet 24 mo	Doses	0	0.3	1.5	8.0	40
	Testes, germ cell degeneration; 12 mo[b] (incidence)					
	SS	0/10	0/10	0/10	0/10	4/10*
	SDMS	–	–	1/3	–	4/19
	Testes, germ cell degeneration; 24 mo (incidence)					
	SS	0/38	0/36	0/25	0/29	0/4
	SDMS	0/16	0/19	0/27	0/26	0/27
	Prostate, suppurative prostatitis; 24 mo (incidence)					
	SS	0/38	1/36	2/25*	4/29*	0/4
	SDMS	2/16	3/19	7/27*	8/26	19/27*
	Testes weights were not measured at termination due to testicular masses in nearly all males. SDMS = spontaneous death or moribund sacrifice; SS = scheduled sacrifice					

Reference and Study Design	Results						
Cholakis et al. (1980) Mice, B6C3F$_1$, 10–12/sex/group Experiment 1: 0, 10, 14, 20, 28, or 40 mg/kg-d Diet 13 wks	Doses	0	10	14	20	28	40
	Absolute testes weight (percent change compared to control)						
		0%	–	–	–	-4%	-4%
	Relative testes weight (percent change compared to control)						
		0%	–	–	–	2%	-1%
Experiment 2: 0, 40, 60, or 80 mg/kg-d for 2 wks followed by 0, 320, 160, or 80 mg/kg-d (TWA doses of 0, 79.6, 147.8, or 256.7 mg/kg-d for males and 0, 82.4, 136.3, or 276.4 mg/kg-d for females)[a] Diet 13 wks	Doses	0		80	160		320
	Absolute testes weight (percent change compared to control)						
		0%		4%	-4%		-8%
	Relative testes weight (percent change compared to control)						
		0%		1%	-4%		-9%
	Testes were examined microscopically in control and 320 mg/kg-d groups; no effects were observed.						
Cholakis et al. (1980) Rats, F344, 10/sex/dose 0, 10, 14, 20, 28, or 40 mg/kg-d Diet 13 wks	Doses	0	10	14	20	28	40
	Absolute testes weight (percent change compared to control)						
		0%	–	–	–	-2%	0%
	Relative testes weight (percent change compared to control)						
		0%	–	–	–	2%	9%
	Testes were examined microscopically in control and 40 mg/kg-d groups; no effects were observed. Prostate was not weighed or examined microscopically.						
Cholakis et al. (1980) Rats, CD, two-generation study; F0: 22/sex/group; F1: 26/sex/group; F2: 10/sex/group F0 and F1 parental animals: 0, 5, 16, or 50 mg/kg-d Diet 13 wks	In F2 offspring of 0, 5, and 16 mg/kg-d groups. No high-dose F2 animals available.						
	Doses	0		5	16		50
	Absolute testes weight (percent change compared to control)						
		0%		3%	-31%		–
	Testes were examined microscopically in all F2 groups; no effects observed.						
Crouse et al. (2006) Rats, F344, 10/sex/group 0, 4, 8, 10, 12, or 15 mg/kg-d Gavage 90 d	Doses	0	4	8	10	12	15
	Absolute testes weight (percent change compared to control)						
		0%	-3%	-5%	-4%	-4%	-8%
	Relative testes weight (percent change compared to control)						
		0%	4%	5%	0%	-6%	-10*%
	Prostate, mild subacute inflammation (incidence)						
		0/10	–	–	–	–	1/8

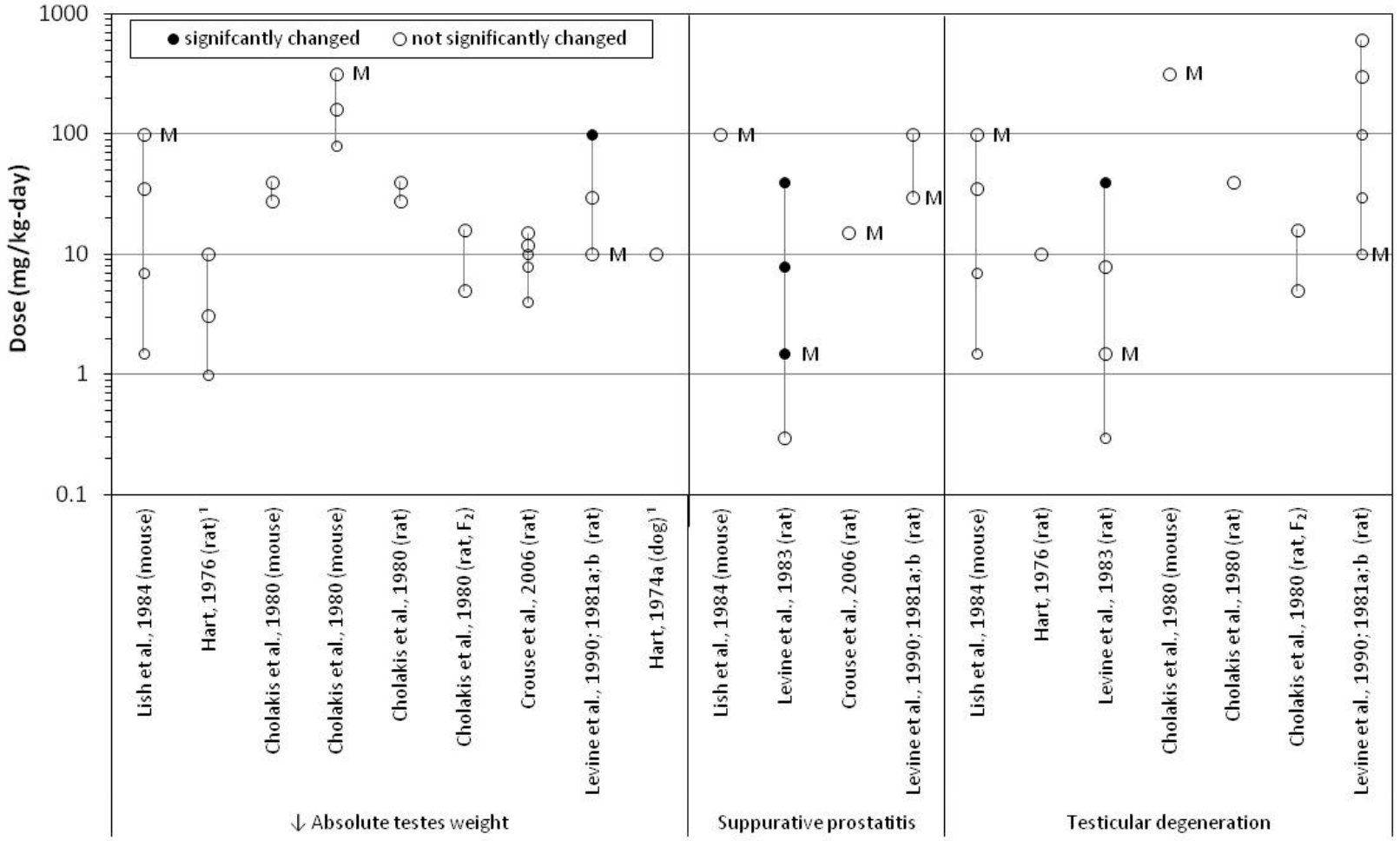
Reference and Study Design	Results						
Levine et al. (1990); Levine et al. (1981a); Levine et al. (1981b) Rats, F344, 10/sex/group; 30/sex for control 0, 10, 30, 100, 300, or 600 mg/kg-d Diet 13 wks	Doses	0	10	30	100	300	600
	Testes, germ cell degeneration (incidence)						
		0/10	0/10	0/10	0/10	1/9	1/10
	Absolute testes weight (percent change compared to control)						
		0%	1%	1%	-2%	–	–
	Relative testes weight (percent change compared to control)						
		0%	4%	5%	19*%	–	–
	Prostate was examined microscopically in control, 30, and 100 mg/kg-d groups; no effects were observed.						
Hart (1974) Dogs, Beagle, 3/sex/dose 0, 0.1, 1, or 10 mg/kg-d Diet 90 d	Doses	0		0.1	1		10
	Absolute testes (with epididymis) weight (percent change compared to control)						
		0%		–	–		51%
	Testes and prostate were not examined microscopically.						

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

[a]Although the study authors did not observe a statistically significant increase in the incidence of testicular degeneration, they determined that the incidences at the 35 and 175/100 mg/kg-day dose groups were "notable" when compared to concurrent (0%) and historical (1.5%) incidences.

[b]Testicular atrophy was observed at 12 months, along with a statistically reduced mean testes weight (compared with controls). By 24 months, all male rats (including controls) had testicular masses; testes weights were not recorded, and an increased incidence of testicular degeneration was not observed.

1



[1]increased absolute weight of testes and epididymis

Figure 2-4. Exposure-response array of male reproductive effects following oral exposure to RDX.

2.5. Liver Effects Evidence Tables and Array

Table 2-6. Evidence pertaining to liver effects of RDX in humans

Reference and Study Design	Results			
Hathaway and Buck (1977) (United States) Cross-sectional study, 2,022 workers, 1,491 participated (74% response rate). Analysis group: limited to whites; 69 exposed to RDX alone and 24 exposed to RDX and HMX; 338 not exposed to RDX, HMX, or TNT. **Exposure measures:** Exposure determination based on job title and industrial hygiene evaluation. Exposed subjects assigned to two groups: less than the limit of detection (LOD) or ≥0.01 mg/m^3 (mean 0.28 mg/m^3). **Effect measures:** Liver function tests. **Analysis:** Types of statistical tests were not reported (assumed to be t-tests for comparison of means and χ^2 tests for comparison of proportions).	*Liver function tests in men; mean (standard deviation not reported)*			
	Test	Referent (n = 237)	RDX exposed: Undetected (n = 22)	RDX exposed: >0.01 mg/m^3 (n = 45)
	LDH	173	191	174
	Alkaline phosphatase	82	78	80
	ALA (SGOT)	22	25	21
	AST (SGPT)	21	26	18
	Bilirubin	0.5	0.4	0.4
	No differences were statistically significant. Similar results in women.			
	Liver function tests in men: prevalence of abnormal values			
	Test (abnormal range)	Referent	RDX exposed: Undetected	RDX exposed: >0.01 mg/m^3
	LDH (>250)	2/237	1/22	0/45
	Alkaline phosphatase (>1.5)	34/237	1/22	6/45
	AST (SGOT) (>35)	20/237	4/22	2/45
	ALT (SGPT) (>35)	15/237	2/22	0/45
	Bilirubin (>1.0)	5/237	1/22	1/45
	No differences were statistically significant. Similar results in women.			

Table 2-7. Evidence pertaining to liver effects in animals following oral exposure to RDX

Reference and Study Design	Results					
Liver weight						
Lish et al. (1984); Levine et al. (1984) Mice, B6C3F$_1$, 85/sex/group; interim sacrifices (10/sex/group) at 6 and 12 mo 0, 1.5, 7.0, 35, or 175/100 mg/kg-d (high dose reduced to	Doses	0	1.5	7.0	35	175/100
	Absolute liver weight at 104 wks (percent change compared to control)					
	M	0%	28*%	11%	12%	35*%
	F	0%	7%	7%	15%	18*%
	Relative liver weight at 104 wks (percent change compared to control)					
	M	0%	32*%	12%	14%	46*%
	F	0%	6%	8%	18%	45*%

Reference and Study Design	Results					
100 mg/kg-d in wk 11 due to excessive mortality) Diet 24 mo	Note: Percent change in liver weights of male and female mice was reduced in all dose groups when mice with liver tumors were removed from the analysis.					
Hart (1976) Rats, Sprague-Dawley, 100/sex/group 0, 1.0, 3.1, or 10 mg/kg-d Diet 2 yrs	Doses	0	1.0	3.1	10	
	Absolute liver weight (percent change compared to control)					
	M	0%	-6%	-6%	-6%	
	F	0%	7%	-11%	1%	
	Relative liver weight (percent change compared to control)					
	M	0%	-5%	-2%	-3%	
	F	0%	17%	-2%	13%	
Levine et al. (1983); Thompson (1983) Rats, F344, 75/sex/group; interim sacrifices (10/sex/group) at 6 and 12 mo 0, 0.3, 1.5, 8.0, or 40 mg/kg-d Diet 24 mo	Doses	0	0.3	1.5	8.0	40
	Absolute liver weight at 105 wks (percent change compared to control)					
	M	0%	3%	-7%	1%	-8%
	F	0%	1%	-4%	3%	0%
	Relative liver weight at 105 wks (percent change compared to control)					
	M	0%	1%	0%	2%	11%
	F	0%	1%	-2%	6%	18*%
Cholakis et al. (1980) Mice, B6C3F_1, 10–12/sex/group Experiment 1: 0, 10, 14, 20, 28, or 40 mg/kg-d Diet 13 wks	Doses	0	10	14	20	28	40
	Absolute liver weight (percent change compared to control)						
	M	0%	–	–	–	-6%	-5%
	F	0%	–	–	–	-4%	-1%
	Relative liver weight (percent change compared to control)						
	M	0%	–	–	–	-4%	-4%
	F	0%	–	–	–	-6%	1%

Reference and Study Design	Results						
Experiment 2: 0, 40, 60, or 80 mg/kg-d for 2 wks followed by 0, 320, 160, or 80 mg/kg-d (TWA doses of 0, 79.6, 147.8, or 256.7 mg/kg-d for males and 0, 82.4, 136.3, or 276.4 mg/kg-d for females)[a] Diet 13 wks	Doses	0		80	160		320
	Absolute liver weight (percent change compared to control)						
	M	0%		2%	12%		26*%
	F	0%		4%	9%		29*%
	Relative liver weight (percent change compared to control)						
	M	0%		0%	9%		25*%
	F	0%		4%	4%		22*%
Cholakis et al. (1980) Rats, F344, 10/sex/group 0, 10, 14, 20, 28, or 40 mg/kg-d Diet 13 wks	Doses	0	10	14	20	28	40
	Absolute liver weight (percent change compared to control)						
	M	0%	–	–	–	-2%	-5%
	F	0%	–	–	–	6%	4%
	Relative liver weight (percent change compared to control)						
	M	0%	–	–	–	2%	3%
	F	0%	–	–	–	10%	11%
Cholakis et al. (1980) Rats, CD, two-generation study; F0: 22/sex/group; F1: 26/sex/group; F2: 10/sex/group F0 and F1 parental animals: 0, 5, 16, or 50 mg/kg-d Diet 13 wks	Doses	0		5	16		50
	Absolute liver weight (percent change compared to control)						
	M	0%		7%	-16%		–
	F	0%		0%	-14%		–
Crouse et al. (2006) Rats, F344, 10/sex/group 0, 4, 8, 10, 12, or 15 mg/kg-d Gavage 90 d	Doses	0	4	8	10	12	15
	Absolute liver weight (percent change compared to control)						
	M	0%	-6%	-9%	0%	7%	5%
	F	0%	1%	7%	18*%	15%	28*%
	Relative liver weight (percent change compared to control)						
	M	0%	0%	-1%	2%	5%	2%
	F	0%	1%	-2%	2%	-3%	2%
Levine et al. (1990); Levine et al. (1981a); Levine et al. (1981b) Rats, F344, 3–4 wks old; 10/sex/group; 30/sex/group for controls 0, 10, 30, 100, 300, or 600 mg/kg-d Diet 13 wks	Data were not reported for rats in the 300 or 600 mg/kg-d dose groups because all of the rats died before the 13-wk necropsy.						
	Doses	0	10	30	100	300	600
	Absolute liver weight (percent change compared to control)						
	M	0%	5%	-1%	-2%	–	–
	F	0%	2%	4%	16*%	–	–
	Relative liver weight (percent change compared to control)						
	M	0%	8%	6%	1%	–	–
	F	0%	3%	5%	19*%	–	–

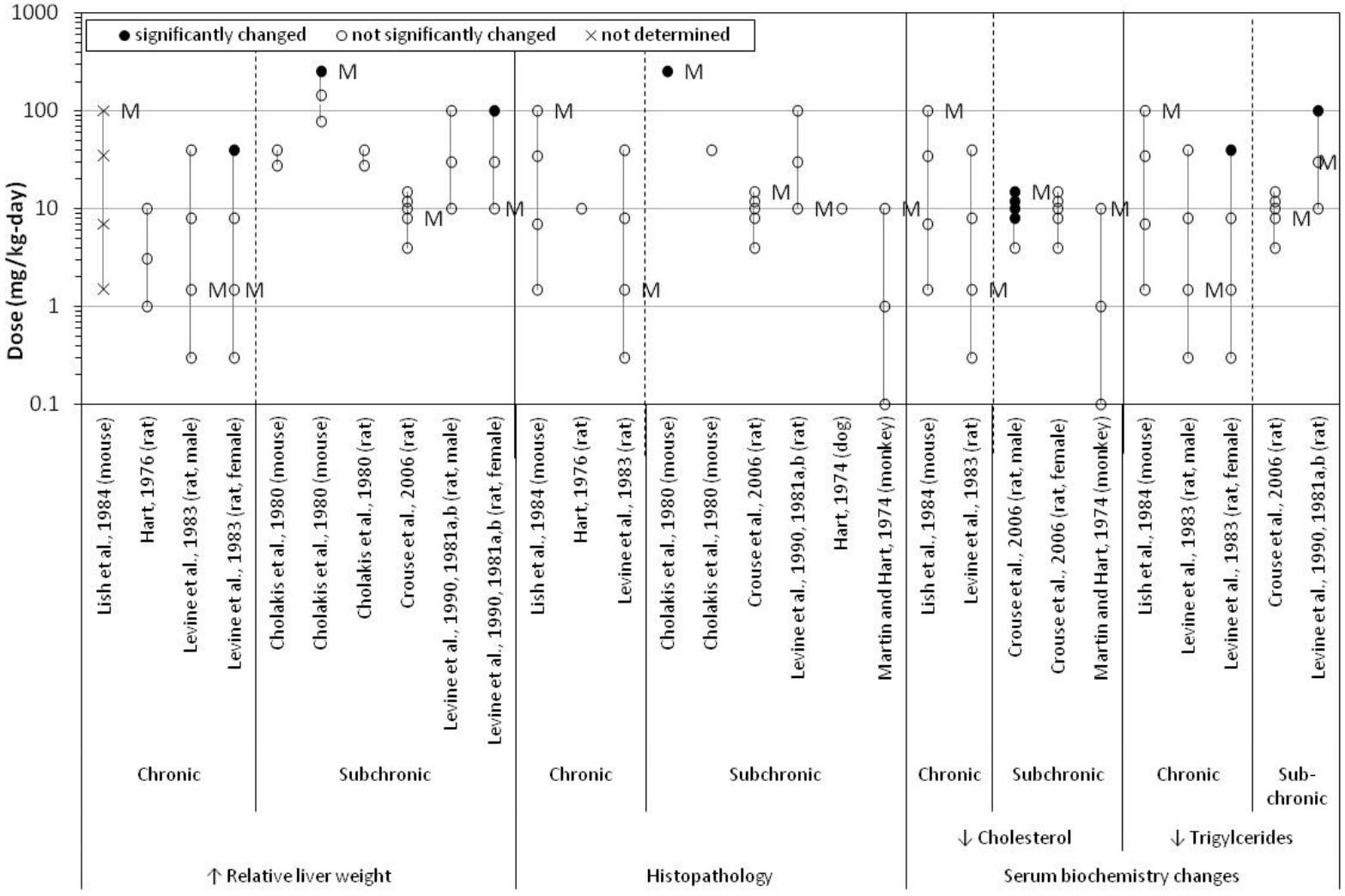
Reference and Study Design	Results				
Hart (1974) Dogs, Beagle, 3/sex/group 0, 0.1, 1, or 10 mg/kg-d Diet 90 d	Doses	0	0.1	1	10
	Absolute liver weight (percent change compared to control)				
	M	0%	–	–	53%
	F	0%	–	–	3%
Martin and Hart (1974) Monkeys, Cynomolgus or Rhesus, 3/sex/group 0, 0.1, 1, or 10 mg/kg-d Gavage 90 d	Doses	0	0.1	1	10
	Absolute liver weight (percent change compared to control)				
	M+F	0%	2%	6%	16%
Histopathological lesions					
Lish et al. (1984); Levine et al. (1984) Mice, B6C3F_1, 85/sex/group; interim sacrifices (10/sex/group) at 6 and 12 mo 0, 1.5, 7.0, 35, or 175/100 mg/kg-d (high dose reduced to 100 mg/kg-d in wk 11 due to excessive mortality) Diet 24 mo	Histopathological lesions in liver other than adenomas and carcinomas were not significantly different compared to controls.				
Hart (1976) Rats, Sprague-Dawley, 100/sex/group 0, 1.0, 3.1, or 10 mg/kg-d Diet 2 yrs	Histopathological examination performed only for controls and 10 mg/kg-d rats; no significant differences compared to controls were reported.				
Levine et al. (1983); Thompson (1983) Rats, F344, 3–4 wks old; 75/sex/group; interim sacrifices (10/sex/group) at 6 and 12 mo 0, 0.3, 1.5, 8.0, or 40 mg/kg-d Diet 24 mo	Doses	0	0.3	1.5	8.0	40
	Microgranulomas (incidence)					
	M	0/38	0/36	0/25	0/29	0/4
	F	10/43	19/45	12/42	17/41	4/28

Reference and Study Design	Results					
Cholakis et al. (1980) Mice, B6C3F$_1$, 10–12/sex/group 0, 80, 60, or 40 mg/kg-d for 2 wks followed by 0, 80, 160, or 320 mg/kg-d (TWA doses of 0, 79.6, 147.8, or 256.7 mg/kg-d for males and 0, 82.4, 136.3, or 276.4 mg/kg-d for females)[a] Diet 13 wks	Doses	0	80	160	320	
	Liver microgranulomas; mild (incidence)					
	M	2/10	–	–	1/9	
	F	2/11	–	–	7/11*	
	Increased karyomegaly of hepatocytes					
	M	0/10	–	–	5/9*	
	F	–	–	–	–	
Cholakis et al. (1980) Rats, F344, 10/sex/group 0, 10, 14, 20, 28, or 40 mg/kg-d Diet 13 wks	Doses	0	10	14	20	28	40
	Liver granulomas; mild (incidence)						
	M	0/10	–	–	–	–	1/10
	F	–	–	–	–	–	–
	Liver portal inflammation						
	M	2/10	–	–	–	–	3/10
	F	1/10	–	–	–	–	7/10
Crouse et al. (2006) Rats, F344, 10/sex/group 0, 4, 8, 10, 12, or 15 mg/kg-d Gavage 90 d	Histopathology examination of the 15 mg/kg-d group showed one male rat with mild liver congestion and one female rat with a moderate-sized focus of basophilic cytoplasmic alteration; neither finding was attributed to treatment with RDX.						
Levine et al. (1990); Levine et al. (1981a); Levine et al. (1981b) Rats, F344, 10/sex/group; 30/sex for control 0, 10, 30, 100, 300, or 600 mg/kg-d Diet 13 wks	Histopathological examination of liver did not reveal any significant differences compared to controls.						
Hart (1974) Dogs, Beagle, 3/sex/group 0, 0.1, 1, or 10 mg/kg-d Diet 90 d	Histopathological examination performed only for controls and 10 mg/kg-d dogs; no significant differences compared to controls were reported.						
Martin and Hart (1974) Monkeys, Cynomolgus or Rhesus, 3/sex/group 0, 0.1, 1, or 10 mg/kg-d Gavage 90 d	An increase in the amount of iron-positive material in liver cord cytoplasm was reported in monkeys treated with 10 mg/kg-d RDX; however, the study authors considered the toxicological significance to be uncertain.						

Reference and Study Design	Results						
Serum chemistry							
Lish et al. (1984); Levine et al. (1984) Mice, B6C3F$_1$, 85/sex/group; interim sacrifices (10/sex/group) at 6 and 12 mo 0, 1.5, 7.0, 35, or 175/100 mg/kg-d (high dose reduced to 100 mg/kg-d in wk 11 due to excessive mortality) Diet 24 mo	Doses	0	1.5	7.0	35	175/100	
	Serum cholesterol at 105 wks (percent change compared to control)						
	M	0%	11%	-11%	5%	39%	
	F	0%	5%	15%	25%	38%	
	Serum triglycerides at 105 wks (percent change compared to control)						
	M	0%	21%	-20%	10%	-25%	
	F	0%	34%	28%	41%	28%	
Levine et al. (1983); Thompson (1983) Rats, F344, 75/sex/group; interim sacrifices (10/sex/group) at 6 and 12 mo 0, 0.3, 1.5, 8.0, or 40 mg/kg-d Diet 24 mo	Doses	0	0.3	1.5	8.0	40	
	Serum cholesterol at 104 wks (percent change compared to control)						
	M	0%	15%	38%	19%	-6%	
	F	0%	6%	3%	-7%	-9%	
	Serum triglycerides at 104 wks (percent change compared to control)						
	M	0%	14%	-15%	-12%	-52%	
	F	0%	18%	5%	-42%	-51*%	
Crouse et al. (2006) Rats, F344, 10/sex/group 0, 4, 8, 10, 12, or 15 mg/kg-d Gavage 90 d	Doses	0	4	8	10	12	15
	Serum cholesterol (percent change compared to control)						
	M	0%	-3%	-10*%	-16*%	-18*%	-11*%
	F	0%	-1%	-8%	-4%	-4%	-1%
	Serum triglycerides (percent change compared to control)						
	M	0%	1%	1%	-7%	-2%	-19%
	F	0%	-16%	-21%	7%	-37%	18%
Levine et al. (1990); Levine et al. (1981a); Levine et al. (1981b) Rats, F344, 10/sex/group; 30/sex for control 0, 10, 30, 100, 300, or 600 mg/kg-d Diet 13 wks	Data were not reported for 300 and 600 mg/kg-d dose groups because all of the animals died before the 13-wk blood sampling.						
	Doses	0	10	30	100	300	600
	Serum triglyceride levels (percent change compared to control)						
	M	0%	-14%	-34%	-62*%	–	–
	F	0%	-12%	-29%	-50*%	–	–

Reference and Study Design	Results				
Martin and Hart (1974) Monkeys, Cynomolgus or Rhesus, 3/sex/group 0, 0.1, 1, or 10 mg/kg-d Gavage 90 d	Serum biochemistry analysis revealed scattered deviations, but they appear to have no toxicological significance.				
	Doses	0	0.1	1	10
	Serum cholesterol (percent change compared to control)				
	M	0%	-17%	-2%	-7%
	F	0%	7%	7%	7%

*Statistically significant ($p < 0.05$) based on analysis by study authors.
[a]Doses were calculated by the study authors.



X- not determined due to confounding caused by presence of tumors
These studies were excluded from array because only absolute liver weight was reported: Cholakis, 1980 (2-gen rat); Hart, 1974; Martin and Hart, 1974
M - Mortality observed at this dose and above

Figure 2-5. Exposure-response array of liver effects following oral exposure to RDX.

2.6. Kidney Effects Evidence Tables and Array

Table 2-8. Evidence pertaining to renal effects of RDX in humans

Reference and Study Design	Results			
Hathaway and Buck (1977) Cross-sectional study, 2,022 workers, 1,491 participated (74% response rate). Analysis group: limited to whites; 69 workers exposed to RDX alone and 24 workers exposed to RDX and HMX, compared to 338 workers not exposed to RDX, HMX, or TNT. **Exposure measures:** Exposure determination based on job title and industrial hygiene evaluation; exposed subjects assigned to two groups: undetected (<LOD) or ≥0.01 mg/m^3 (mean 0.28 mg/m^3). **Effect measures:** Renal function tests (blood) **Analysis:** Types of statistical tests werenot reported (assumed to be t-tests for comparison of means and χ^2 tests for comparison of proportions).	*Renal function tests in men: mean (standard deviation not reported)*			
			RDX exposed	
	Test	Referent (n = 237)	Undetected (n = 22)	>0.01 mg/m^3 (n = 45)
	Blood urea nitrogen	15.5	15.6	16.4
	Total protein	7.2	7.2	7.3
	No differences were statistically significant. Similar results in women.			

Table 2-9. Evidence pertaining to renal effects in animals following oral exposure to RDX

Reference and Study Design	Results					
Kidney weights						
Lish et al. (1984); Levine et al. (1984) Mice, B6C3F$_1$, 85/sex/group; interim sacrifices (10/sex/group) at 6 and 12 mo 0, 1.5, 7.0, 35, or 175/100 mg/kg-d (high dose reduced to 100 mg/kg-d in wk 11 due to excessive mortality) Diet 24 mo	Doses	0	1.5	7.0	35	175/100
	Absolute kidney weight at 104 wks (percent change compared to control)					
	M	0%	-1%	4%	9*%	19*%
	F	0%	3%	1%	1%	-2%
	Relative kidney weight at 104 wks (percent change compared to control)					
	M	0%	3%	6%	11*%	27*%
	F	0%	1%	1%	2%	19*%

Reference and Study Design	Results					
Hart (1976) Rats, Sprague-Dawley, 100/sex/group 0, 1.0, 3.1, or 10 mg/kg-d Diet 2 yrs	Doses	0	1.0	3.1	10	
	Absolute kidney weight (percent change compared to control)					
	M	0%	-3%	-7%	2%	
	F	0%	14%	-4%	8%	
	Relative kidney weight (percent change compared to control)					
	M	0%	-1%	-4%	4%	
	F	0%	22%	3%	18%	
Levine et al. (1983); Thompson (1983) Rats, F344, 75/sex/group; interim sacrifices (10/sex/group) at 6 and 12 mo 0, 0.3, 1.5, 8.0, or 40 mg/kg-d Diet 24 mo	Doses	0	0.3	1.5	8.0	40
	Absolute kidney weight at 105 wks (percent change compared to control)					
	M	0%	2%	-7%	1%	0%
	F	0%	3%	3%	2%	2%
	Relative kidney weight at 105 wks (percent change compared to control)					
	M	0%	1%	0%	2%	20*%
	F	0%	3%	6%	5%	21*%
Cholakis et al. (1980) Mice, B6C3F$_1$, 10–12/sex/group Experiment 1: 0, 10, 14, 20, 28, or 40 mg/kg-d Diet 13 wks	Doses	0	10	14	20	28	40
	Absolute kidney weight (percent change compared to control)						
	M	0%	–	–	–	18%	2%
	F	0%	–	–	–	-8%	-5%
	Relative kidney weight (percent change compared to control)						
	M	0%	–	–	–	29%	0%
	F	0%	–	–	–	-8%	-3%
Experiment 2: 0, 40, 60, or 80 mg/kg-d for 2 wks followed by 0, 320, 160, or 80 mg/kg-d (TWA doses of 0, 79.6, 147.8, or 256.7 mg/kg-d for males and 0, 82.4, 136.3, or 276.4 mg/kg-d for females)[a] Diet 13 wks	Doses	0	80	160	320	
	Absolute kidney weight (percent change compared to control)					
	M	0%	8%	11%	13%	
	F	0%	-5%	-3%	0%	
	Relative kidney weight (percent change compared to control)					
	M	0%	5%	9%	10%	
	F	0%	-5%	-4%	-5%	
Cholakis et al. (1980) Rats, F344, 10/sex/group 0, 10, 14, 20, 28, 40 mg/kg-d Diet 13 wks	Doses	0	10	14	20	28	40
	Absolute kidney weight (percent change compared to control)						
	M	0%	–	–	–	-2%	-5%
	F	0%	–	–	–	1%	0%
	Relative kidney weight (percent change compared to control)						
	M	0%	–	–	–	1%	5%
	F	0%	–	–	–	6%	6%

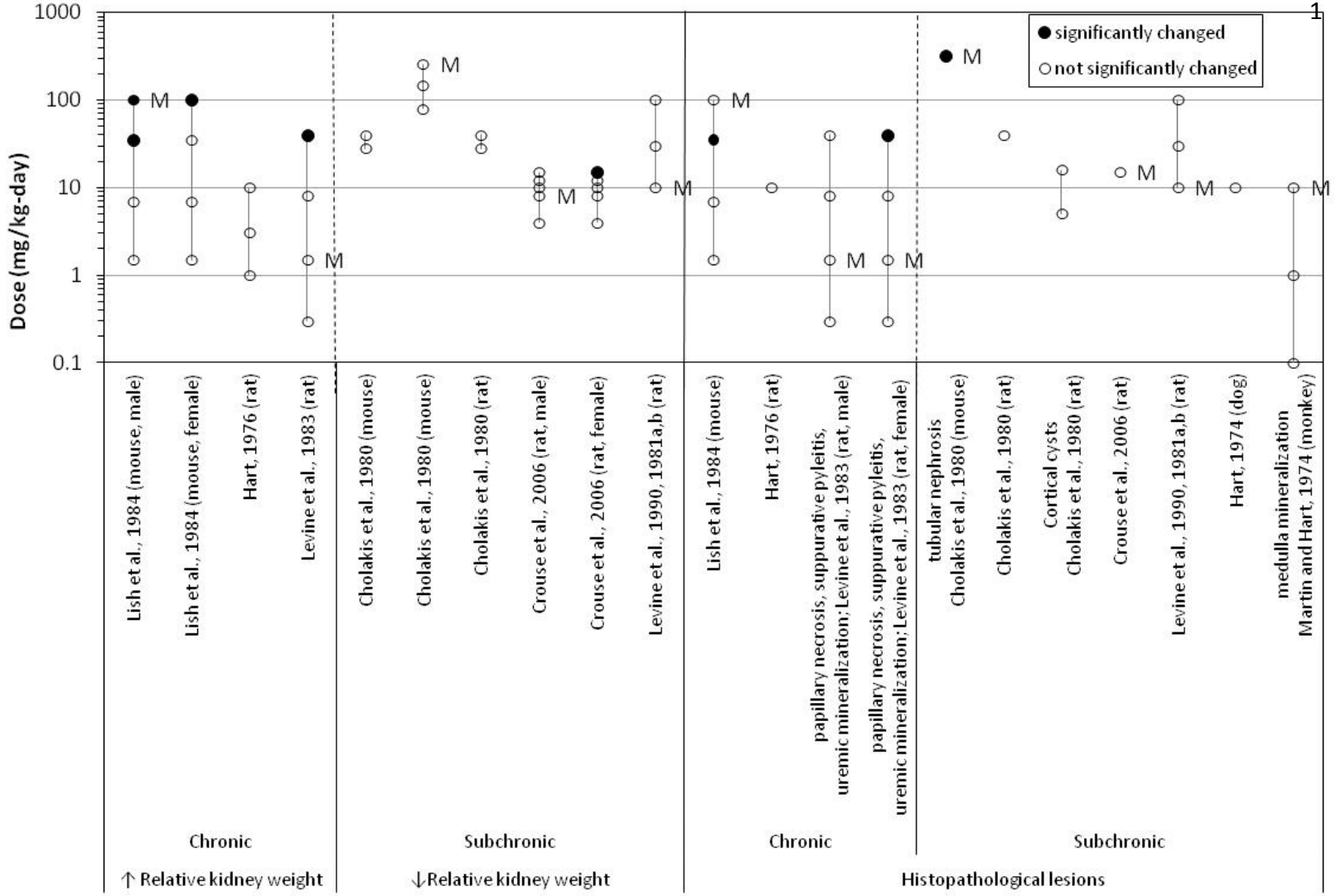
Reference and Study Design	Results						
Cholakis et al. (1980) Rats, CD, two-generation study; F0: 22/sex/group; F1: 26/sex/group; F2: 10/sex/group F0 and F1 parental animals: 0, 5, 16, 50 mg/kg-d Diet 13 wks	Doses	0	5	16	50		
	Absolute kidney weight (percent change compared to control)						
	M	0%	6%	-12%	–		
	F	0%	-4%	-21*%	–		
Crouse et al. (2006) Rats, F344, 10/sex/group 0, 4, 8, 10, 12, or 15 mg/kg-d Gavage 90 d	Doses	0	4	8	10	12	15
	Absolute kidney weight (percent change compared to control)						
	M	0%	-3%	-4%	-1%	3%	5%
	F	0%	2%	5%	13*%	10%	15*%
	Relative kidney weight (percent change compared to control)						
	M	0%	3%	6%	2%	1%	3%
	F	0%	1%	-3%	-1%	-6%	-7*%
Levine et al. (1990); Levine et al. (1981a); Levine et al. (1981b) Rats, F344, 10/sex/group; 30/sex for control 0, 10, 30, 100, 300, or 600 mg/kg-d Diet 13 wks	Data were not reported for rats in the 300 or 600 mg/kg-d groups because all of the rats died before the 13-wk necropsy.						
	Doses	0	10	30	100	300	600
	Absolute kidney weight (percent change compared to control)						
	M	0%	1%	1%	-9%	–	–
	F	0%	1%	3%	-1%	–	–
	Relative kidney weight (percent change compared to control)						
	M	0%	5%	7%	10%	–	–
	F	0%	3%	5%	2%	–	–
Hart (1974) Dogs, Beagle, 3/sex/group 0, 0.1, 1, or 10 mg/kg-d Diet 90 d	Numerical values given only for control and 10 mg/kg-d groups.						
	Doses	0	0.1	1	10		
	Absolute kidney weight (percent change compared to control)						
	M	0%	–	–	38%		
	F	0%	–	–	-18%		
Martin and Hart (1974) Monkeys, Cynomolgus or Rhesus, 3/sex/group 0, 0.1, 1, or 10 mg/kg-d Gavage 90 d	Doses	0	0.1	1	10		
	Absolute kidney weight (percent change compared to control)						
	M+F	0%	-2%	-3%	4%		
Histopathological lesions							

Reference and Study Design	Results
Lish et al. (1984); Levine et al. (1984) Mice, B6C3F$_1$, 85/sex/group; interim sacrifices (10/sex/group) at 6 and 12 mo 0, 1.5, 7.0, 35, or 175/100 mg/kg-d (high dose reduced to 100 mg/kg-d in wk 11 due to excessive mortality) Diet 24 mo	The incidence of cytoplasmic vacuolization of renal tubules was greater for RDX-treated males than the control group males after 6 mo of treatment. However, at 12 and 24 mo of treatment, this lesion was observed as frequently in control animals as animals treated with RDX.
Hart (1976) Rats, Sprague-Dawley, 100/sex/group 0, 1.0, 3.1, or 10 mg/kg-d Diet 2 yrs	Histopathological examination of kidney did not reveal any significant differences compared to controls; lesions observed were not attributed to RDX treatment; incidence data were reported only for control and 10 mg/kg-d groups.
Levine et al. (1983); Thompson (1983) Rats, F344, 75/sex/group; interim sacrifices (10/sex/group) at 6 and 12 mo 0, 0.3, 1.5, 8.0, or 40 mg/kg-d Diet 24 mo	Data were analyzed separately for animals sacrificed on schedule (SS) and those that died spontaneously or were sacrificed moribund (SDMS); incidence data were not reported for females. Doses: 0 / 0.3 / 1.5 / 8.0 / 40 *Medullary papillary necrosis; 24 mo (incidence)* M (SS): 0/38 / 0/36 / 0/25 / 0/29 / 0/4 F (SDMS): 0/17 / 1/19 / 0/27 / 0/26 / 18/27* *Suppurative pyelitis; 24 mo (incidence)* M (SS): 0/38 / 0/36 / 0/25 / 0/29 / 0/4 F (SDMS): 0/17 / 1/19 / 0/27 / 1/26 / 5/27* *Uremic mineralization; 24 mo (incidence)* M (SS): 1/38 / 0/36 / 0/25 / 0/29 / 0/4 F (SDMS): 0/17 / 1/19 / 2/27 / 0/26 / 13/27
Cholakis et al. (1980) Mice, B6C3F$_1$, 10–12/sex/group 0, 80, 60, 40 mg/kg-d for 2 wks followed by 0, 80, 160, or 320 mg/kg-d (TWA doses of 0, 79.6, 147.8, or 256.7 mg/kg-d for males and 0, 82.4, 136.3, or 276.4 mg/kg-d for females)[a] Diet 13 wks	Incidence data reported only for controls and the 320 mg/kg-d group. Doses: 0 / 80 / 160 / 320 *Tubular nephrosis (incidence)* M: 0/10 / – / – / 4/9* F: 0/11 / – / – / 1/11
Cholakis et al. (1980) Rats, F344, 10/sex/group 0, 10, 14, 20, 28, or 40 mg/kg-d Diet 13 wks	Histopathological examination of kidney did not reveal any significant differences compared to controls; incidence data were reported only for control and 40 mg/kg-d groups.

Reference and Study Design	Results				
Cholakis et al. (1980) Rats, CD, two-generation study; F0: 22/sex/group; F1: 26/sex/group; F2: 10/sex/group F0 and F1 parental animals: 0, 5, 16, or 50 mg/kg-d Diet 13 wks	Data were reported only for F2 generation controls and 5 and 16 mg/kg-d groups.				
	Doses	0	5	16	50
	Cortical cysts (incidence)				
	M	4/10	4/10	8/10	–
	F	3/10	4/10	8/10	–
Crouse et al. (2006) Rats, F344, 10/sex/group 0, 4, 8, 10, 12, or 15 mg/kg-d Gavage 90 d	Histopathological examination of kidney did not reveal any significant differences compared to controls; incidence data were reported only for control and 15 mg/kg-d groups.				
Levine et al. (1990); Levine et al. (1981a); Levine et al. (1981b) Rats, F344, 10/sex/group; 30/sex for control 0, 10, 30, 100, 300, or 600 mg/kg-d Diet 13 wks	Histopathological examination of kidney did not reveal any significant differences compared to controls.				
Hart (1974) Dogs, Beagle, 3/sex/group 0, 0.1, 1, or 10 mg/kg-d Diet 90 d	Histopathological examination of kidney did not reveal any significant differences compared to controls; incidences were reported only for control and 10 mg/kg-d groups.				
Martin and Hart (1974) Monkeys, Cynomolgus or Rhesus, 3/sex/group 0, 0.1, 1, or 10 mg/kg-d Gavage 90 d	Doses	0	0.1	1	10
	Medulla; mineralization, minimal to mild (incidence)				
	M+F	0/6	1/6	0/6	4/6

*Statistically significant ($p < 0.05$) based on analysis by study authors.
[a]Doses were calculated by the study authors.

1



The following studies were excluded from array because absolute kidney weight was reported: Cholakis, 1980 (2-gen rat); Hart, 1974; Martin and Hart, 1974
M - Mortality observed at this dose and above

Figure 2-6. Exposure-response array of renal effects following oral exposure to RDX.

2.7. Carcinogenicity Evidence Tables

Table 2-10. Liver tumors observed in chronic animal bioassays following oral exposure to RDX

Reference and Study Design	Results					
Lish et al. (1984); Levine et al. (1984) Mice, B6C3F$_1$, 85/sex/group; interim sacrifices (10/sex/group) at 6 and 12 mo 0, 1.5, 7.0, 35, or 175/100 mg/kg-d (high dose reduced to 100 mg/kg-d in wk 11 due to excessive mortality) Diet 24 mo	Doses	0	1.5	7.0	35	175/100
	Hepatocellular adenomas (incidence)					
	M	8/63	6/60	1/62*	7/59	7/27
	F	1/65	1/62	6/64	6/64	3/31[a]
	Hepatocellular carcinomas (incidence)					
	M	13/63	20/60	16/62	18/59	6/27
	F	0/65	4/62	3/64	6/64	3/31[a]
	Hepatocellular adenoma or carcinoma combined (incidence)					
	M	21/63	26/60	17/62	25/59	13/27
	F	1/65	5/62	9/64*	12/64*	6/31*[a]
	Pathology workgroup reanalysis of liver lesion slides from female mice (Parker et al., 2006; Parker, 2001)[b]					
	Doses	0	1.5	7.0	35	175
	Hepatocellular adenomas (incidence)					
	F	1/67	3/62	2/63	8/64	2/31[a]
	Hepatocellular carcinomas (incidence)					
	F	0/67	1/62	3/63	2/64	2/31[a]
	Hepatocellular adenoma or carcinoma combined (incidence)					
	F	1/67[b]	4/62	5/63[b]	10/64	4/31[a]
Hart (1976) Rats, Sprague-Dawley, 100/sex/group 0, 1.0, 3.1, or 10 mg/kg-d Diet 2 yrs	*Hepatocellular adenomas (incidence)* None reported by the study authors.					
	Doses	0	1.0	3.1	10	
	Hepatocellular carcinomas (incidence)					
	M	1/82	–	–	1/77	
	F	1/72	–	–	1/81	
Levine et al. (1983); Thompson (1983) Rats, F344, 75/sex/group; interim sacrifices (10/sex/group) at 6 and 12 mo 0, 0.3, 1.5, 8.0, or 40 mg/kg-d Diet 24 mo	*Hepatocellular adenomas (incidence):* None reported by the study authors					
	Doses	0	0.3	1.5	8.0	40
	Hepatocellular carcinomas (incidence)					
	M	1/55	0/55	0/52	2/55	2/31
	F	0/53	1/55	0/54	0/55	0/48
	Hepatocellular adenoma or carcinoma combined (incidence): Not determined.					

*Statistically significant difference compared to the control group ($p < 0.05$), identified by the authors.
[a]Statistically significant trend ($p < 0.05$) was identified using Cochran-Armitage trend tests performed by EPA.
[b]It is not clear why the numbers of animals at risk in the control group (n = 67) and 7 mg/kg-day dose group (n = 63) differed from the numbers reported in the original study (n = 65 and 64, respectively).

Table 2-11. Lung tumors observed in chronic animal bioassays following oral exposure to RDX

Reference and Study Design	Results					
Lish et al. (1984); Levine et al. (1984) Mice, B6C3F$_1$, 85/sex/group; interim sacrifices (10/sex/group) at 6 and 12 mo 0, 1.5, 7.0, 35, or 175/100 mg/kg-d (high dose reduced to 100 mg/kg-d in wk 11 due to excessive mortality) Diet 24 mo	Doses	0	1.5	7.0	35	175/100
	Alveolar/bronchiolar adenomas (incidence)					
	M	6/63	5/60	5/62	7/59	1/27
	F	4/65	2/62	5/64	9/64	3/31[a]
	Alveolar/bronchiolar carcinomas (incidence)					
	M	3/63	6/60	3/62	7/59	5/27[a]
	F	3/65	1/62	3/64	3/64	4/31
	Alveolar/bronchiolar adenoma or carcinoma combined (incidence)					
	M	9/63	11/60	8/62	14/59	6/27
	F	7/65	3/62	8/64	12/64	7/31[a]
Hart (1976) Rats, Sprague-Dawley, 100/sex/group 0, 1.0, 3.1, or 10 mg/kg-d Diet 2 yrs	Doses	0	1.0	3.1	10	
	Alveolar/bronchiolar adenoma (incidence)					
	M	2/83	–	–	1/77	
	F	0/73	–	–	0/82	
	Alveolar/bronchiolar carcinoma (incidence): None reported by study authors.					
Levine et al. (1983); Thompson (1983) Rats, F344, 75/sex/group; interim sacrifices (10/sex/group) at 6 and 12 mo 0, 0.3, 1.5, 8.0, or 40 mg/kg-d Diet 24 mo	Doses	0	0.3	1.5	8.0	40
	Alveolar/bronchiolar adenomas (incidence)					
	M	1/55	0/15	1/17	0/16	1/31
	F	3/53	0/7	0/8	1/10	0/48
	Alveolar/bronchiolar carcinomas (incidence)					
	M	–	–	–	–	–
	F	0/53	0/7	1/8	0/10	0/48
	Alveolar/bronchiolar adenoma or carcinoma combined (incidence)					
	M	–	–	–	–	–
	F	3/53	0/7	1/8	1/10	0/48

[a]Statistically significant trend ($p < 0.05$) was identified using Cochran-Armitage trend test performed by EPA.

2.8. Other Systemic Effects Evidence Tables

Table 2-12. Evidence pertaining to other systemic effects (hematological) of RDX in humans

Reference and Study Design	Results			
Hematological Effects				
West and Stafford (1997) (United Kingdom) Case-control study, 32 cases with abnormal and 322 controls with normal hematology test drawn from 1991 study of 404 workers at ammunitions plant; participation rate 97% of cases, 93% of controls. Analysis limited to men (29 cases, 282 controls). **Exposure measures:** Exposure determination based on employee interviews and job title analysis; data included frequency (hours/day, days/year), duration (years), and intensity (low [1–10 ppm], moderate [10–100 ppm], and high [100–1,000 ppm], based on ventilation considerations). **Effect measures:** Hematology tests; blood disorder defined as neutropenia (2.0 x 109/l), low platelet count (<150 x 109/l), or macrocytosis (mean corpuscular volume = 99 fl or >6% macrocytes). **Analysis:** Unadjusted odds ratio.	*Odds ratio (95% CI) [number of exposed cases] of blood disorder and RDX*			
	Low intensity, 50 hr-duration	1.7 (0.7,4.2) [22]		
	Medium intensity, 50-hr duration	1.6 (not reported) [5]		
	High intensity, 50-hr duration	1.2 (0.3, 5.3) [2]		
Hathaway and Buck (1977) (United States) Cross-sectional study, 2,022 workers, 1,491 participated (74% response rate). Analysis limited to whites; 69 exposed to RDX alone and 24 exposed to RDX and HMX; 338 not exposed to RDX, HMX, or TNT. **Exposure measures:** Exposure determination based on job title and industrial hygiene evaluation. Exposed subjects assigned to two groups: <LOD or ≥0.01 mg/m^3 (mean 0.28 mg/m^3). **Effect measures:** Hematology tests. **Analysis:** Types of statistical tests were not reported (assumed to be t-tests for comparison of means and χ^2 tests for comparison of proportions).	*Hematology tests in men; mean (standard deviation not reported)*			
	Test	Referent (n = 237)	RDX exposed: Undetected (n = 22)	RDX exposed: >0.01 mg/m^3 (n = 45)
	Hemoglobin	15.2	14.7	15.2
	Hematocrit	42	45.6	47
	Reticulocyte count	0.7	0.9	0.7
	No differences were statistically significant. Similar results in women. *Hematology tests in men: prevalence of abnormal values*			
	Test (abnormal range)	Referent	RDX exposed: Undetected	RDX exposed: >0.01 mg/m^3
	Hemoglobin (<14)	15/237	3/22	4/45

Reference and Study Design	Results			
	Hematocrit (<40)	1/237	1/22	1/45
	Reticulocyte count (>1.5)	18/237	3/22	2/45
	No differences were statistically significant. Similar results in women.			

Table 2-13. Evidence pertaining to other systemic effects in animals following oral exposure to RDX

Reference and Study Design	Results					
Ocular effects						
Lish et al. (1984); Levine et al. (1984) Mice, B6C3F$_1$, 85/sex/group; interim sacrifices (10/sex/group) at 6 and 12 mo 0, 1.5, 7.0, 35, or 175/100 mg/kg-d (high dose reduced to 100 mg/kg-d in wk 11 due to excessive mortality) Diet 24 mo	Doses	0	1.5	7.0	35	175/100
	Cataracts; 103 wks (incidence)[a]					
	M	2/47	2/41	0/41	2/37	2/16
	F	2/50	1/37	6/52	0/46	1/26
Levine et al. (1983); Thompson (1983) Rats, F344, 75/sex/group; interim sacrifices (10/sex/group) at 6 and 12 mo 0, 0.3, 1.5, 8.0, or 40 mg/kg-d Diet 24 mo	Doses	0	0.3	1.5	8.0	40
	Cataracts; 103 wks (incidence)					
	M	8/40	6/39	6/31	8/35	2/6
	F	14/44	4/48	11/44	8/43	22/30*
Cholakis et al. (1980) Rats, F344, 10/sex/group 0, 10, 14, 20, 28, or 40 mg/kg-d Diet 13 wks	No ocular effects were observed (gross examination of eye was performed in all animals, and microscopic examination in control and 40 mg/kg-d animals).					

Reference and Study Design	Results					
Crouse et al. (2006) Rats, F344, 10/sex/group 0, 4, 8, 10, 12, or 15 mg/kg-d Gavage 90 d	No ocular effects were observed (opthalmic examinations were performed in all animals within 1 wk of sacrifice, and microscopic examination of the eye was performed in control and 15 mg/kg-d animals).					
Martin and Hart (1974) Monkeys, Cynomolgous or Rhesus, 3/sex/group 0, 0.1, 1, or 10 mg/kg-d Gavage 90 d	No ocular effects were observed (opthalmoscopic examination was performed at the end of exposure).					
Cardiovascular effects						
Lish et al. (1984); Levine et al. (1984) Mice, B6C3F$_1$, 85/sex/group; interim sacrifices (10/sex/group) at 6 and 12 mo 0, 1.5, 7.0, 35, or 175/100 mg/kg-d (high dose reduced to 100 mg/kg-d in wk 11 due to excessive mortality) Diet 24 mo	Doses	0	1.5	7.0	35	175/100
	Absolute heart weight; 104 wks (percent change compared to control)					
	M	0%	4%	4%	5%	7%
	F	0%	1%	5%	2%	-5%
	Relative heart-to-body weight; 104 wks (percent change compared to control)					
	M	0%	7%	5%	5%	13*%
	F	0%	0%	6%	4%	17*%
	Body weight was significantly lower at termination in males and females exposed to 175/100 mg/kg-d (-5 and -19%, respectively).					
Hart (1976) Rats, Sprague-Dawley, 100/sex/group 0, 1.0, 3.1, or 10 mg/kg-d Diet 2 yrs	Doses	0	1.0	3.1	10	
	Myocardial fibrosis (percent incidence; number not reported)					
	M	20%	–	–	5%	
	F	5%	–	–	1%	
	Endocardial disease (percent incidence; number not reported)					
	M	1%	–	–	3%	
	F	0%	–	–	0%	
	Absolute heart weight; 104 wks (percent change compared to control)					
	M	0%	-6%	-2%	-5%	
	F	0%	13%	3%	15%	
	Relative heart-to-body weight; 104 wks (percent change compared to control)					
	M	0%	-2%	4%	1%	
	F	0%	23%	13%	27%	

Reference and Study Design	Results						
Levine et al. (1983); Thompson (1983) Rats, F344, 75/sex/group; interim sacrifices (10/sex/group) at 6 and 12 mo 0, 0.3, 1.5, 8.0, or 40 mg/kg-d Diet 24 mo	Doses	0	0.3	1.5	8.0	40	
	Absolute heart weight; 104 wks (percent change compared to control)						
	M	0%	3%	-2%	-2%	1%	
	F	0%	-1%	0%	-4%	-3%	
	Relative heart-to-body weight; 104 wks (percent change compared to control)						
	M	0%	2%	6%	0%	22%	
	F	0%	-2%	3%	-1%	15%	
Cholakis et al. (1980) Mice, B6C3F$_1$, 10–12/sex/group Experiment 1: 0, 10, 14, 20, 28, or 40 mg/kg-d Diet 13 wks	Doses	0	10	14	20	28	40
	Absolute heart weight (percent change compared to control)						
	M	0%	–	–	–	7%	7%
	F	0%	–	–	–	0%	0%
	Relative heart weight (percent change compared to control)						
	M	0%	–	–	–	6%	0%
	F	0%	–	–	–	-4%	0%
Experiment 2: 0, 40, 60, or 80 mg/kg-d for 2 wks followed by 0, 320, 160, or 80 mg/kg-d (TWA doses of 0, 79.6, 147.8, or 256.7 mg/kg-d for males and 0, 82.4, 136.3, or 276.4 mg/kg-d for females)[b] Diet 13 wks	Doses	0	80	160	320		
	Focal myocardial degeneration (incidence):						
	M**	0/10	–	–	5/10*		
	F***	0/11	–	–	2/11		
	Absolute heart weight (percent change compared to control)						
	M	0%	0%	0%	8%		
	F	0%	0%	0%	8%		
	Relative heart-to-body weight (percent change compared to control)						
	M	0%	0%	-2%	6%		
	F	0%	0%	-2%	2%		
	**Includes one affected and three unaffected animals that died prematurely. ***Includes one unaffected animal that died prematurely.						
Cholakis et al. (1980) Rats, F344, 10/sex/group 0, 10, 14, 20, 28, or 40 mg/kg-d Diet 13 wks	Doses	0	10	14	20	28	40
	Focal myocardial degeneration (incidence)						
	M	3/10	–	–	–	–	1/10
	F	2/10	–	–	–	–	6/10
	Absolute heart weight (percent change compared to control)						
	M	0%	–	–	–	0%	-8*%
	F	0%	–	–	–	-6%	-11*%
	Relative heart-to-body weight (percent change compared to control)						
	M	0%	–	–	–	3%	0%
	F	0%	–	–	–	-3%	-8%
	Relative heart-to-brain weight (percent change compared to control)						

Reference and Study Design	Results						
	M	0%	–	–	–	-4%	-10*%
	F	0%	–	–	–	-5%	-11*%
Cholakis et al. (1980) Rats, CD, two-generation study; F0: 22/sex/group; F1: 26/sex/group; F2: 10/sex/group F0 and F1 parental animals: 0, 5, 16, or 50 mg/kg-d Diet 13 wks	No cardiac effects were observed (microscopic examination of heart was performed in randomly selected F2 animals). Heart weight data were reported only for F2 generation controls, 5 and 16 mg/kg-d groups.						
	Doses	0		5	16		50
	Absolute heart weight (percent change compared to control)						
	F2 M	0%		3.2%	-6.5%		–
	F2 F	0%		15%	-3.7%		–
Crouse et al. (2006) Rats, F344, 10/sex/group 0, 4, 8, 10, 12, or 15 mg/kg-d Gavage 90 d	Doses	0	4	8	10	12	15
	Cardiomyopathy (incidence)						
	M	2/10	–	–	–	–	3/8
	F	0/10	–	–	–	–	1/6
	Absolute heart weight (percent change compared to control)						
	M	0%	-2%	-7%	-1%	1%	11%
	F	0%	-2%	0%	8%	7%	6%
	Relative heart-to-body weight (percent change compared to control)						
	M	0%	4%	2%	1%	-1%	8%
	F	0%	-2%	-7%	-6%	-9%	-16*%
Levine et al. (1990); Levine et al. (1981a); Levine et al. (1981b) Rats, F344, 10/sex/group; 30/sex for control 0, 10, 30, 100, 300, or 600 mg/kg-d Diet 13 wks	All animals in the 300 and 600 mg/kg-d groups died prior to study termination.						
	Doses	0	10	30	100	300	600
	Chronic focal myocarditis (incidence)						
	M	8/30	8/10	6/10	1/10	1/10	0/10
	F	8/30	3/10	1/10	1/10	1/10	1/9
	Absolute heart weight (percent change compared to control)						
	M	0%	-2%	-10%	-15%	–	–
	F	0%	-3%	0%	-5%	–	–
	Relative heart-to-body weight (percent change compared to control)						
	M	0%	2%	-4%	3%	–	–
	F	0%	-2%	0%	-3%	–	–
Von Oettingen et al. (1949) Rats (sex/strain not specified); 20/group 0, 15, 25, or 50 mg/kg-d Diet 3 mo	The study authors reported that there were no cardiac effects (microscopic examination of the heart was performed in all rats; data were not shown).						

Reference and Study Design	Results				
Hart (1974) Dogs, Beagle, 3/sex/group 0, 0.1, 1, or 10 mg/kg-d Diet 90 d	Doses	0	0.1	1	10
	Focal hyalinization of the heart (incidence)				
	M	0/3	–	–	0/3
	F	0/3	–	–	1/3
	Absolute heart weight (percent change compared to control)				
	M	0%	–	–	31%
	F	0%	–	–	5.7%
Martin and Hart (1974) Monkeys, Cynomolgous or Rhesus, 3/sex/group 0, 0.1, 1, or 10 mg/kg-d Gavage 90 d	Doses	0	0.1	1	10
	Myocarditis (incidence in control and 10 mg/kg-d groups)				
	M	1/3	–	–	1/3
	F	0/3	–	–	0/3
	Absolute heart weight (percent change compared to control)				
	M	0%	7%	-1%	5%
	F	0%	10%	12%	-12%
Immune effects					
Lish et al. (1984); Levine et al. (1984) Mice, B6C3F$_1$, 85/sex/group; interim sacrifices (10/sex/group) at 6 and 12 mo 0, 1.5, 7.0, 35, or 175/100 mg/kg-d (high dose reduced to 100 mg/kg-d in wk 11 due to excessive mortality) Diet 24 mo	No immune effects were observed with routine hematology, clinical chemistry, or histopathology evaluations.				
	Doses	0	1.5	7.0	35	175/100
	WBC count; 105 wks (percent change compared to control)					
	M	0%	-13%	-8%	-16%	-30%
	F	0%	12%	39*%	28%	0%
	Absolute spleen weight; 105 wks (percent change compared to control)					
	M	0%	24%	31%	-10%	-28%
	F	0%	4%	15%	-17%	16%
	Relative spleen weight; 105 wks (percent change compared to control)					
	M	0%	26%	32%	-11%	-21%
	F	0%	4%	15%	-17%	44%
Hart (1976) Rats, Sprague-Dawley, 100/sex/group 0, 1.0, 3.1, or 10 mg/kg-d Diet 2 yrs	Doses	0	1.0	3.1	10
	WBC count; 104 wks (percent change compared to control)				
	M	0%	-13%	-22*%	-34*%
	F	0%	5%	-32*%	-12%
	Absolute spleen weight; 104 wks (percent change compared to control)				
	M	0%	-11%	-16%	-4%
	F	0%	58%	8%	37%
	Relative spleen weight; 104wks (percent change compared to control)				
	M	0%	-11%	-14%	1%
	F	0%	77%	19%	55%

Reference and Study Design	Results					
Levine et al. (1983); Thompson (1983) Rats, F344, 75/sex/group; interim sacrifices (10/sex/group) at 6 and 12 mo 0, 0.3, 1.5, 8.0, or 40 mg/kg-d Diet 24 mo	No immune effects were observed with routine hematology, clinical chemistry and histopathology evaluations.					
	Doses	0	0.3	1.5	8.0	40
	WBC count; 105 wks (percent change compared to control)					
	M	0%	-11%	103[c] %	184[c] %	15%
	F	0%	7%	12%	354[c] %	251[c]%
	Absolute spleen weight; 105 wks (percent change compared to control)					
	M	0%	5%	-10%	-32%	-49%
	F	0%	-28%	-44%	-35%	17%
	Relative spleen weight; 105 wks (percent change compared to control)					
	M	0%	9%	4%	-29%	-38%
	F	0%	-34%	-45%	-36%	9%
Cholakis et al. (1980) Mice, B6C3F$_1$, 10–12/sex/group Experiment 1: 0, 10, 14, 20, 28, or 40 mg/kg-d Diet 13 wks	Doses	0	10	14	20	28	40
	Absolute spleen weight (percent change compared to control)						
	M	0%	–	–	–	18%	13%
	F	0%	–	–	–	-2%	-8%
	Relative spleen weight (percent change compared to control)						
	M	0%	–	–	–	24%	14%
	F	0%	–	–	–	-3%	-5%
Experiment 2: 0, 40, 60, 80 mg/kg-d for 2 wks followed by 0, 320, 160, or 80 mg/kg-d (TWA doses of 0, 79.6, 147.8, or 256.7 mg/kg-d for males and 0, 82.4, 136.3, or 276.4 mg/kg-d for females)[b] Diet 13 wks	Doses	0	80	160	320
	WBC count (percent change compared to control)				
	M	0%	-27%	-12%	30%
	F	0%	-17%	3%	-3%
	Absolute spleen weight (percent change compared to control)				
	M	0%	17%	0%	-17%
	F	0%	-22%	0%	0%
	Relative spleen weight (percent change compared to control)				
	M	0%	25%	5%	0%
	F	0%	-12%	0%	-3%

Reference and Study Design	Results						
Cholakis et al. (1980) Rats, F344, 10/sex/group 0, 10, 14, 20, 28, or 40 mg/kg-d Diet 13 wks	Doses	0	10	14	20	28	40
	WBC count (percent change compared to control)						
	M	0%	–	–	–	-12%	7%
	F	0%	–	–	–	17%	30%
	Absolute spleen weight (percent change compared to control)						
	M	0%	–	–	–	2%	-4%
	F	0%	–	–	–	-10%	-12*%
	Relative spleen weight (percent change compared to control)						
	M	0%	–	–	–	5%	5%
	F	0%	–	–	–	-8%	-8%
Cholakis et al. (1980) Rats, CD, two-generation study; F0: 22/sex/group; F1: 26/sex/group; F2: 10/sex/group F0 and F1 parental animals: 0, 5, 16, or 50 mg/kg-d Diet 13 wks	No immune effects were observed upon routine histopathology evaluation.						
Crouse et al. (2006) Rats, F344, 10/sex/group 0, 4, 8, 10, 12, or 15 mg/kg-d Gavage 90 d	No effects were observed on thymus or spleen histology, red and white blood cell populations, or lymphocyte populations.						
	Doses	0	4	8	10	12	15
	WBC count (percent change compared to control)						
	M	0%	-5%	-12%	-7%	1%	-3%
	F	0%	22%	45%	12%	52%	29%
	Absolute spleen weight (percent change compared to control)						
	M	0%	-3%	-6%	3%	1%	5%
	F	0%	1%	8%	23*%	17*%	24*%
	Relative spleen weight (percent change compared to control)						
	M	0%	3%	4%	7%	-1%	2%
	F	0%	1%	0%	6%	-1%	-2%
	Absolute thymus weight (percent change compared to control)						
	M	0%	-1%	3%	-10%	-12%	-25%
	F	0%	-7%	12%	19%	32%	19%
	Relative thymus weight (percent change compared to control)						
	M	0%	-1%	3%	-10%	-12%	-25%
	F	0%	-7%	4%	4%	12%	-6%

Reference and Study Design	Results						
Levine et al. (1990); Levine et al. (1981a); Levine et al. (1981b) Rats, F344, 10/sex/group; 30/sex for control 0, 10, 30, 100, 300, or 600 mg/kg-d Diet 13 wks	Data were not reported for rats in the 300 or 600 mg/kg dose groups because all of the rats died before the 13-wk necropsy.						
	Doses	0	10	30	100	300	600
	WBC count (percent change compared to control)						
	M	0%	4%	7%	15%	–	–
	F	0%	23*%	24*%	62*%	–	–
	Absolute spleen weight (percent change compared to control)						
	M	0%	-11%	-16%	-34%	–	–
	F	0%	2%	12%	0%	–	–
	Relative spleen weight (percent change compared to control)						
	M	0%	-9%	-12%	-21%	–	–
	F	0%	2%	12%	3%	–	–
Von Oettingen et al. (1949) Rats, sex/strain not specified, 20/group 0, 15, 25, or 50 mg/kg-d Diet 3 mo	Doses	0		15	25		50
	WBC count (percent change compared to control)						
	M	0%		-30%	7%		-6%
Hart (1974) Dogs, Beagle, 3/sex/group 0, 0.1, 1, or 10 mg/kg-d Diet 90 d	Doses	0		0.1	1		10
	WBC count (percent change compared to control)						
	M	0%		5%	2%		-19%
	F	0%		-2%	24%		6%
	Absolute spleen weight (percent change compared to control)						
	M	0%		–	–		123%
	F	0%		–	–		-11%
Martin and Hart (1974) Monkeys, Cynomolgous or Rhesus, 3/sex/group 0, 0.1, 1, or 10 mg/kg-d Gavage 90 d	Doses	0		0.1	1		10
	WBC count (percent change compared to control)						
	M	0%		-32%	0%		-3%
	F	0%		-38%	-1%		-41%

Reference and Study Design	Results
Gastrointestinal (GI) effects	
Lish et al. (1984); Levine et al. (1984) Mice, B6C3F$_1$, 85/sex/group; interim sacrifices (10/sex/group) at 6 and 12 mo 0, 1.5, 7.0, 35, or 175/100 mg/kg-d (high dose reduced to 100 mg/kg-d in wk 11 due to excessive mortality) Diet 24 mo	No GI effects were observed as clinical signs or on gross pathology or histopathology examination.
Levine et al. (1983); Thompson (1983) Rats, F344, 75/sex/group; interim sacrifices (10/sex/group) at 6 and 12 mo 0, 0.3, 1.5, 8.0, or 40 mg/kg-d Diet 24 mo	No GI effects were observed as clinical signs or on gross pathology or histopathology examination.
Crouse et al. (2006) Rats, F344, 10/sex/group 0, 4, 8, 10, 12, or 15 mg/kg-d Gavage 90 d	No GI effects were observed on gross pathology or histopathology examination. Increased salivation and blood stains around the mouth were noted (affected doses and incidences were not reported); it is not clear whether these effects occurred in animals also experiencing convulsions.
Von Oettingen et al. (1949) Rats (sex/strain not specified); 20/group 0, 15, 25, or 50 mg/kg-d Diet 3 mo	Congestion of the GI tract was observed in 50 and 100 mg/kg-d rats that also exhibited mortality (40%) and severe neurotoxicity.

Reference and Study Design	Results					
Martin and Hart (1974) Monkeys (Cynomolgus or Rhesus); 3/sex/group 0, 0.1, 1, or 10 mg/kg-d Gavage 90 d	Vomiting was observed more frequently in the 1 and 10 mg/kg-d groups compared to the control or 0.1 mg/kg-d groups, although some episodes occurred during the intubation procedure.					
Hart (1974) Dogs, Beagle, 3/sex/group 0, 0.1, 1, or 10 mg/kg-d Diet 90 d	Some nausea and vomiting were reported (incidences and affected dose groups were not reported).					
Hematological effects						
Lish et al. (1984); Levine et al. (1984) Mice, B6C3F$_1$, 85/sex/group; interim sacrifices (10/sex/group) at 6 and 12 mo 0, 1.5, 7.0, 35, or 175/100 mg/kg-d (high dose reduced to 100 mg/kg-d in wk 11 due to excessive mortality) Diet 24 mo	Doses	0	1.5	7.0	35	175/100
	RBC count; 105 wks (percent change compared to control)					
	M	0%	-4%	3%	-3%	14%
	F	0%	4%	-7%	5%	3%
	Hemoglobin; 105 wks (percent change compared to control)					
	M	0%	-6%	3%	-5%	9%
	F	0%	2%	-7%	3%	1%
	Hematocrit; 105 wks (percent change compared to control)					
	M	0%	-4%	3%	-4%	9%
	F	0%	3%	-6%	3%	1%
	Platelets; 105 wks (percent change compared to control)					
	M	0%	33%	9%	21%	27%
	F	0%	-14%	-7%	1%	5%
Hart (1976) Rats, Sprague-Dawley, 100/sex/group 0, 1.0, 3.1, or 10 mg/kg-d Diet 2 yrs	Doses	0	1.0	3.1	10	
	RBC count; 104 wks (percent change compared to control)					
	M	0%	3%	7%	-2%	
	F	0%	-14%	7%	2%	
	Reticulocyte count; 104 wks (percent change compared to control)					
	M	0%	250[c]%	500*[c]%	850*[c]%	
	F	0%	180*[c]%	-40%	20%	
	Hemoglobin; 104 wks (percent change compared to control)					
	M	0%	3%	4%	0%	
	F	0%	-1%	1%	-2%	
Levine et al. (1983); Thompson (1983) Rats, F344, 75/sex/group; interim sacrifices	Doses	0	0.3	1.5	8.0	40
	Hemoglobin levels; 105 wks (percent change compared to control)					
	M	0%	6%	6%	3%	-13%
	F	0%	-5%	1%	-9%	-14%

Reference and Study Design	Results					
(10/sex/group) at 6 and 12 mo 0, 0.3, 1.5, 8.0, or 40 mg/kg-d Diet 24 mo	*RBC count; 105 wks (percent change compared to control)*					
	M	0%	5%	2%	-1%	-9%
	F	0%	-2%	2%	-9%	-13%
	Platelet count; 105 wks (percent change compared to control)					
	M	0%	6%	-4%	-10%	-7%
	F	0%	14%	-4%	5%	22%
	Hematocrit; 105 wks (percent change compared to control)					
	M	0%	5%	5%	2%	-7%
	F	0%	-5%	0%	-8%	-12%
Cholakis et al. (1980) Mice, B6C3F$_1$, 10–12/sex/group 0, 80, 60, or 40 mg/kg-d for 2 wks followed by 0, 80, 160, or 320 mg/kg-d (TWA doses of 0, 79.6, 147.8, or 256.7 mg/kg-d for males and 0, 82.4, 136.3, or 276.4 mg/kg-d for females)[b] Diet 13 wks	Doses	0	80	160	320	
	RBC count (percent change compared to control)					
	M	0%	-5%	-12*%	-2%	
	F	0%	-10%	-1%	1%	
	Reticulocytes (percent change compared to control)					
	M	0%	-36%	-13%	15%	
	F	0%	21%	25%	-19%	
	Hematocrit (percent change compared to control)					
	M	0%	-1%	-6%	0%	
	F	0%	-8%	2%	1%	
	Hemoglobin (percent change compared to control)					
	M	0%	-2%	-7*%	-3%	
	F	0%	-5%	4%	1%	
	Platelets (percent change compared to control)					
	M	0%	33%	28%	22%	
	F	0%	3%	9%	39%	
Cholakis et al. (1980) Rats, F344, 10/sex/group 0, 10, 14, 20, 28, or 40 mg/kg-d Diet 13 wks	Doses	0	10	14	20	28	40
	RBC count (percent change compared to control)						
	M	0%	–	–	–	3%	-1%
	F	0%	–	–	–	-1%	-7%
	Hemoglobin (percent change compared to control)						
	M	0%	–	–	–	2%	-1%
	F	0%	–	–	–	-1%	-1%
	Platelet (percent change compared to control)						
	M	0%	–	–	–	11%	16*%
	F	0%	–	–	–	-23%	-13%
	Reticulocytes (percent change compared to control)						
	M	0%	–	–	–	26%	76*%
	F	0%	–	–	–	-2%	17%
	Hematocrit (percent change compared to control)						

Reference and Study Design	Results						
	M	0%	–	–	–	3%	0%
	F	0%	–	–	–	0%	-2%
Crouse et al. (2006)	Doses	0	4	8	10	12	15
Rats, F344, 10/sex/group	*RBC count (percent change compared to control)*						
0, 4, 8, 10, 12, or 15 mg/kg-d	M	0%	1%	-7%	-2%	-4%	-5%
Gavage	F	0%	3%	3%	-1%	2%	-2%
90 d	*Hemoglobin (percent change compared to control)*						
	M	0%	-1%	-5%	0%	-1%	-6%
	F	0%	2%	4%	-1	4%	-4%
	Platelet count (percent change compared to control)						
	M	0%	21%	11%	13%	-8%	34%
	F	0%	6%	40%	47%	34%	-36%
	Hematocrit (percent change compared to control)						
	M	0%	2%	-5%	0%	-1%	-4%
	F	0%	3%	4%	0%	4%	-2%
Levine et al. (1990); Levine et al. (1981a); Levine et al. (1981b)	Data were not reported for rats in the 300 or 600 mg/kg dose groups because all of the rats died before the 13-wk necropsy.						
Rats, F344, 10/sex/group; 30/sex for control	Doses	0	10	30	100	300	600
0, 10, 30, 100, 300, or 600 mg/kg-d	*Hematocrit (percent change compared to control)*						
Diet	M	0%	-2%	-1%	-5%	–	–
13 wks	F	0%	0%	-4%	-7%	–	–
	Hemoglobin (percent change compared to control)						
	M	0%	-3%	-1%	-6%	–	–
	F	0%	0%	-4%	-8*%	–	–
	RBC count (percent change compared to control)						
	M	0%	-2%	-2%	-5%	–	–
	F	0%	-1%	-4%	-5%	–	–
	Reticulocytes (percent change compared to control)						
	M	0%	-4%	10%	28%	–	–
	F	0%	9%	73%	71%	–	–
Von Oettingen et al. (1949)	Doses	0		15	25		50
Rats, sex/strain not specified, 20/group	*RBC count (percent change compared to control)*						
0, 15, 25, or 50 mg/kg-d	M+F	0%		-23%	-12%		-14%
Diet	*Hemoglobin (percent change compared to control)*						
3 mo	M+F	0%		-25%	-7%		-11%
Hart (1974)	Doses	0		0.1	1		10
Dogs, Beagle, 3/sex/group	*RBC count (percent change compared to control)*						
	M	0%		-3%	3%		2%

Reference and Study Design	Results				
0, 0.1, 1, or 10 mg/kg-d Diet 90 d	F	0%	13%	7%	11%
	Reticulocyte count (percent change compared to control)				
	M	0%	-66%	0%	-50%
	F	0%	-17%	-50%	0%
	Hematocrit (percent change compared to control)				
	M	0%	-4%	2%	0%
	F	0%	6%	1%	7%
	Hemoglobin (percent change compared to control)				
	M	0%	5%	-2%	0%
	F	0%	8%	-2%	8%
Martin and Hart (1974) Monkeys, Cynomolgous or Rhesus, 3/sex/group 0, 0.1, 1, or 10 mg/kg-d Gavage 90 d	Histopathological examination revealed increased numbers of degenerate or necrotic megakaryocytes in all bone marrow sections.				
	Doses	0	0.1	1	10
	RBC count (percent change compared to control)				
	M	0%	-3%	2%	-3%
	F	0%	0%	-1%	2%
	Reticulocyte count (percent change compared to control)				
	M	0%	-33%	-50%	-50%
	F	0%	-18%	-36%	45%
	Hematocrit (percent change compared to control)				
	M	0%	-7%	-4%	-1%
	F	0%	10%	7%	3%
	Hemoglobin (percent change compared to control)				
	M	0%	-10%	-8%	-6%
	F	0%	6%	6%	3%

*Statistically significantly different compared to the control, as determined by study authors ($p < 0.05$).
[a]Incidence counts exclude individuals from which blood was obtained via the orbital sinus.
[b]Doses were calculated by the study authors.
[c]Standard deviations accompanying the mean response in a given dose group were high, suggesting uncertainty in the accuracy of the reported percent change compared to control.

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2.9. Genotoxic Effects

Table 2-14. Summary of in vitro studies of RDX genotoxicity

Endpoint	Test system	Dose/ concentration[a]	Results[b]		Comments	Reference
			Without activation	With activation		
Genotoxicity studies in prokaryotic organisms						
Reverse mutation	*Salmonella. typhimurium* TA1535, TA1537, TA1538, TA98, TA100	1,000 µg/plate	–	–	Metabolic activation with S9	Cholakis et al. (1980)
Reverse mutation	*S. typhimurium* TA1535, TA1537, TA1538 TA100, TA98	14 µg/plate	–	–	Effect of disinfection treatments on mutagenicity tested: RDX was not mutagenic in any strain before or after disinfection treatment with chlorine or ozone	Simmon et al. (1977)
Reverse mutation	*S. typhimurium* TA98, TA100	250 µg/plate	–	–	Study authors noted that results were consistent with literature	George et al. (2001)
Reverse mutation	*S. typhimurium* TA98, TA100	1 mg/plate	–	–	Metabolic activation with S9	Tan et al. (1992)
Reverse mutation	*S. typhimurium* TA98, TA100	1,090 µg/plate	–	–	High S9 activation (9%) used	Pan et al. (2007)
Reverse mutation	*S. typhimurium* TA97a	32.7 µg/plate	–	±	High S9 activation (9%) used; study authors concluded that RDX "required intensive metabolic activation" to exhibit mutagenicity in this strain	Pan et al. (2007)
Reverse mutation	*Vibrio fischeri*	0.004 µg/tube	±	+	Mutatox assay with metabolic activation (S9)	Arfsten et al. (1994)
Reverse mutation (*umu* test)	*Salmonella choleraesius subsp. chol.* (prior *Salmonella typhimurium*) TA1535/pSK1002;	20.6 µg/mL	–	–	No observed effect concentration; tested at highest concentration where the induction rate was below 1.5 for the first time and the growth factor was below 0.5	Neuwoehner et al. (2007)
Reverse mutation (NM2009 test)	*S. choleraesius subsp. chol.* NM2009, TA1535/pSK1002/pNM12	20.6 µg/mL	–	–	No observed effect concentration; tested at highest concentration where the induction rate was below 1.5 for the first time and the growth factor was below 0.5	Neuwoehner et al. (2007)

Endpoint	Test system	Dose/ concentration[a]	Results[b]		Comments	Reference
			Without activation	With activation		
Induction of the *sfiA* gene (SOS chromotest)	*Escherichia. coli* PQ37	20.6 µg/mL	–	–	No observed effect concentration; tested at highest concentration where the induction rate was below 1.5 for the first time and the growth factor was below 0.5	Neuwoehner et al. (2007)
Reverse mutation	*S. typhimurium*, TA98, TA100	24.8 µg/mL	–	–	No observed effect concentration; metabolic activation with S9	Neuwoehner et al. (2007)
Reverse mutation	*S. typhimurium* TA98, TA100	2.6 µg/mL	–	–	No observed effect concentration; metabolic activation with S9	Lachance et al. (1999)
Reverse mutation	*S. typhimurium* TA1535, TA1536, TA1537, TA1538 TA100, TA98	30.8 µg/mL	-	-	Metabolic activation with S9	Cotruvo et al. (1977)
Genotoxicity studies in nonmammalian eukaryotic organisms						
Recombination induction	*S. cerevisiae* D3	23 µg/mL	–	–	Study authors concluded that this microorganism did not appear to be useful for detecting mutagenicity in several compounds tested	Simmon et al. (1977)
Recombination induction	*S. cerevisiae* D3	30.8 µg/mL	-	-	Metabolic activation with S9	Cotruvo et al. (1977)
Genotoxicity studies in mammalian cells						
Forward mutation	Chinese hamster lung fibroblasts V79 cells	40 µg/mL	–	–	Minimal cytotoxicity observed at 40 µg/mL (limit of solubility)	Lachance et al. (1999)
Mutation	L5178Y mouse lymphoma cells	500 µg/mL	–	–	No or low cytotoxicity seen at these concentrations; however, precipitate was observed >250 µg/mL	Reddy et al. (2005)
Unscheduled DNA synthesis; DNA repair	WI-38 cells, human diploid fibroblasts	4,000 µg/mL	-	-	Precipitates were observed at concentrations of RDX ≥40 µg/mL	Dilley et al. (1979)

[a]Lowest effective dose for positive results; highest dose tested for negative results.
[b]+ = positive; ± = equivocal or weakly positive; – = negative

Table 2-15. Summary of in vivo studies of RDX genotoxicity

Endpoint	Test system	Dose/ concentration	Results	Comments	Reference
In vivo genotoxicity studies in mammalian systems					
Micronucleus formation	CD-1 mouse bone marrow	Single dose of 62.5, 125, or 250 mg/kg	No significant decrease in PCE:NCE ratios; no induction of micronucleated PCE at any dose	250 mg/kg was maximum tolerated dose determined in dose range-finding study	Reddy et al. (2005)
Dominant lethal mutations	Male CD rats dosed and mated with untreated female rats	0, 5, 16, or 50 mg/kg-day for 15 wk	No statistically or biologically significant effects on fertility; determined to be negative for the induction of lethal mutations	Males in the high-dose group experienced lower food consumption and weight gain compared with all other groups	Cholakis et al. (1980)

Table 2-16. Summary of in vitro and in vivo studies of RDX metabolite genotoxicity

Endpoint	Test system	Dose/ concentration[a]	Results[b]		Comments	Reference
			Without activation	With activation		
Genotoxicity studies in prokaryotic organisms						
Reverse mutation	*Salmonella typhimurium* TA97a, TA102	22 µg/plate	–	+	Mono and trinitroso metabolites (MNX and TNX); high S9 activation (9%) used	Pan et al. (2007)
Reverse mutation	*S. typhimurium TA1535, TA1537, TA1538, TA98, TA100*	500 ug/plate	+	+	Positive only for TNX; MNX and DNX were negative	George et al. (2001)
Reverse mutation	*S. typhimurium* TA1535, TA1537, TA1538, TA98, TA100	NR[c]	–	–	Mononitroso metabolite, MNX; metabolic activation with S9	Snodgrass (1984)
Genotoxicity studies in mammalian cells—in vitro						
Forward mutation	Mouse lymphoma thymidine kinase	NR[c]	+	+	Mononitroso metabolite, MNX; metabolic activation with S9	Snodgrass (1984)
Chromosomal aberrations	Chinese hamster ovary cells	NR[c]	–	+	Mononitroso metabolite, MNX; metabolic activation with S9	Snodgrass (1984)
Unscheduled DNA synthesis; DNA repair	Primary rat hepatocytes	NR[c]	+		Mononitroso metabolite, MNX; additional metabolic activation not required with S9	Snodgrass (1984)
In vivo genotoxicity studies in mammalian systems						
Dominant lethal mutations	Male mice dosed and mated with untreated female mice	NR[c]	–		Mononitroso metabolite, MNX; additional metabolic activation not required with S9	Snodgrass (1984)

[a]Lowest effective dose for positive results; highest dose tested for negative results.
[b]+ = positive; ± = equivocal or weakly positive; − = negative
[c]NR = not reported