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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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U.S. Environmental Protection Agency
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<br>Toxline<br>TSCATS1<br>WOS<br>Toxcenter<br>DTIC | Chemical CASRN: 121-82-4<br>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"<br><br>Synonym and CASRN search for all databases; Toxcenter, Pubmed, and WOS limited using toxicity-related keywords<br><br><u>Toxicity-related terms (see Table 1-2 for specific keywords)</u><br>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 | |

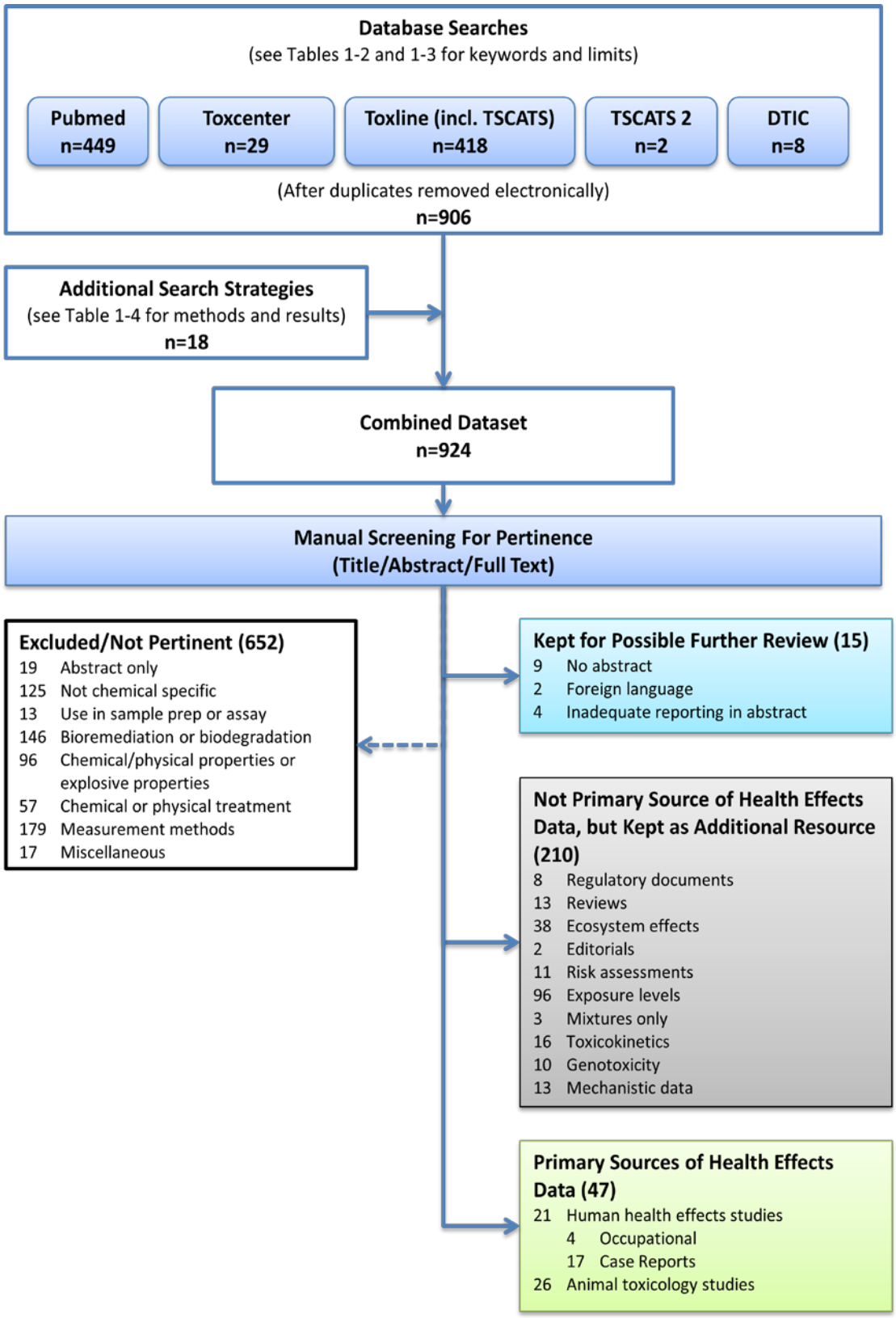


**Figure 1-1. Literature search approach for RDX.**

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

| Database | Set # | Terms | Hits |
|---|---|---|---|
| **PubMed**<br><br>**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**<br><br>**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**<br><br>**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**<br><br>**Date limit: 1907 – 4/2012** | 1B3 | casrn or synonyms<br>-removed invertebrates, aquatic organisms, amphibians, earthworms | 507 |
| **TSCATS** | 1C1 | @term+@rn+121-82-4+@AND+@org+tscats | 4 |
| **Toxcenter**<br><br>**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)<br>Duplicates were removed; Biosis subfile results were date limited to avoid extensive overlap with Toxline | |
| **Toxcenter**<br><br>**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)<br>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**<br><br>**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<br>(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<br>(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.<br>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<br>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.<br>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<br>69 cited papers | 3/2013 | 3 citations added |
| Background Check | Combination of CASRN and synonyms searched on the following websites:<br>ATSDR http://www.atsdr.cdc.gov/substances/index.asp<br>(Note: the reference list for the ATSDR toxicological profile for RDX was compared to the search results and relevant references were added)<br>CalEPA (Office of Environmental Health Hazard Assessment) (http://www.oehha.ca.gov/risk.html)<br>eChemPortal (http://www.echemportal.org/echemportal/participant/page.action?pageID=9)<br>EPA Acute Exposure Guideline Levels (http://www.epa.gov/oppt/aegl/pubs/chemlist.htm)<br>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<br>EPA NSCEP (http://www.epa.gov/ncepihom/)<br>EPA Science Inventory (http://cfpub.epa.gov/si/)<br>Federal Docket www.regulations.gov<br>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)<br>Health Canada Second Priority List Assessments<br>(http://www.hc-sc.gc.ca/ewh-semt/pubs/contaminants/psl2-lsp2/index-eng.php)<br>IARC<br>(http://monographs.iarc.fr/htdig/search.html)<br>IPCS INCHEM<br>(http://www.inchem.org/)<br>NAS<br>via NAP (http://www.nap.edu/)<br>NCI<br>(http://www.cancer.gov)<br>NCTR<br>(http://www.fda.gov/AboutFDA/CentersOffices/OC/OfficeofScientificandMedicalPrograms/NCTR/default.htm)<br>National Institute for Environmental Health Sciences (NIEHS)<br>http://www.niehs.nih.gov/<br>NIOSHTIC 2<br>(http://www2a.cdc.gov/nioshtic-2/)<br>NTP - RoC, status, results, and management reports<br>(http://ntpsearch.niehs.nih.gov/query.html)<br>WHO assessments – CICADS, EHC<br>(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:<br>• Superfund RODs for which the abstract did not specify whether RDX was a contaminant of concern<br>• Meeting minutes and conference proceedings for which only general categories of topics were included in the DTIC record<br>• 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.
2. Barsotti, M., & Crotti, G. (1949). [Attacchi epileptici come manifestazione di intossicazione professionale da trimetilen-trinitroamina (T4)]. *La Medicina del Lavoro, 40*(4), 107-112.
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4. Goldberg, D. J., Green, S. T., Nathwani, D., McMenamin, J., Hamlet, N., & Kennedy, D. H. (1992). RDX intoxication causing seizures and a widespread petechial rash mimicking meningococcaemia. *Journal of the Royal Society of Medicine, 85*(3), 181.
5. Harrell-Bruder, B., & Hutchins, K. L. (1995). Seizures caused by ingestion of composition C-4. *Annals of Emergency Medicine, 26*(6), 746-748.
6. **Hathaway, J. A., & Buck, C. R. (1977). Absence of health hazards associated with RDX manufacture and use. *Journal of Occupational and Environmental Medicine, 19*(4), 269-272.**
7. Hett, D., & Fichtner, K. (2002). A plastic explosive by mouth. *Journal of the Royal Society of Medicine, 95*(5), 251-252. doi: 10.1258/jrsm.95.5.251
8. Hollander, A., & Colbach, E. (1969). Composition C-4 induced seizures: A report of five cases. *Military Medicine, 134*(13), 1529-1530.
9. Kaplan, A. S., Berghout, C. F., & Peczenik, A. (1965). Human intoxication from RDX. *Archives of Environmental Health, 10*, 877-883.
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11. Ketel, W. B., & Hughes, J. R. (1972). Toxic encephalopathy with seizures secondary to ingestion of composition C-4. A clinical and electroencephalographic study. *Neurology, 22*(8), 871-876.
12. Knepshield, J. H., & Stone, W. J. (Eds.). (1972). *Toxic effects following ingestion of C-4 plastic explosive*. Springfield, IL: Charles C. Thomas.
13. Küçükardali, Y., Acar, H. V., Özkan, S., Nalbant, S., Yazgan, Y., Atasoyu, E. M., Danaci, M. (2003). Accidental oral poisoning caused by RDX (cyclonite): A report of 5 cases. *Journal of Intensive Care Medicine, 18*(1), 42-46. doi: 10.1177/0885066602239123
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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**20. West, R. R., & Stafford, D. A. (1997). Occupational exposures and haematological abnormalities among ordnance factory workers: A case control study. *Leukemia Research, 21*(7), 675-680.**
21. Woody, R. C., Kearns, G. L., Brewster, M. A., Turley, C. P., Sharp, G. B., & Lake, R. S. (1986). The neurotoxicity of cyclotrimethylenetrinitramine (RDX) in a child: A clinical and pharmacokinetic evaluation. *Clinical Toxicology, 24*(4), 305-319. doi: 10.3109/15563658608992595

<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.
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triazine (RDX) in rabbits. Chicago, IL: IIT Research Institute.
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9. **Hart, E. (1976). Two-year chronic toxicity study in rats. Kensington, MD: Litton Bionetics, Inc.**
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12. **Levine, B., Furedi, E., Gordon, D., Burns, J., & Lish, P. (1981). Thirteen week oral (diet) toxicity study of trinitrotoluene (TNT), hexahydro-1, 3, 5-trinitro-1, 3, 5-triazine (RDX) and TNT/RDX mixtures in the Fischer 344 rat. Final report. Chicago, IL: IIT Research Institute.**
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Biskup, D. K. (1974). The toxicology of cyclotrimethylenetrinitramine (RDX) and cyclotetramethylenetetranitramine (HMX) solutions in dimethylsulfoxide (DMSO), cyclohexanone, and acetone. Aberdeen Proving Ground, MD: Edgewood Arsenal.

**21. Parker, G. (2001). Attachment 1: Pathology Working Group- Chairperson's report: Reevaluation: Twenty-four month chronic toxicity/carcinogenicity study of hexahydro-1,3,5-trinitro-1,3.5-triazine (RDX) in the B6C3F1 hybrid mouse. Research Triangle Park, NC: National Institute of Environmental Health Sciences.**

**22. Parker, G. A., Reddy, G., & Major, M. A. (2006). Reevaluation of a twenty-four-month chronic toxicity/carcinogenicity study of hexahydro-1,3,5-trinitro-1,3,5-triazine (RDX) in the B6C3F1 hybrid mouse. *International Journal of Toxicology, 25*(5), 373-378. doi: 10.1080/10915810600846245**

23. Stork, C., Kos, S., Langden, B., & Cantor, R. (2000). *Acute canine C-4 explosive ingestion resulting in prolonged status epilepticus*.

**24. Thompson, C. A. (1983). Twenty-four month chronic toxicity/carcinogenicity study of hexahydro-1,3,5-trinitro-1,3,5-triazine (RDX) in the Fischer 344 rat. Twenty-four month interim report. Necropsy observations. 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)

1. . Guidance for characterizing explosives contaminated soils: Sampling and selecting on-site analytical methods. (1996). Idaho Falls; Department of Energy, Washington, DC.: Technical Information Center Oak Ridge Tennessee.
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### 1.2.3. Kept for Possible Further Review

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

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# 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)<br><br>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).<br><br>Exposure measures: Details of exposure measurement were not provided; exposed workers were divided into two groups based on RDX concentration in the air:<br><br>Concentration (mg/m$^3$)<br>Group A 0.407 (± 0.332)<br>Group B 0.672 (± 0.556)<br><br>Effect measures[a]: Five neurobehavioral function tests and five additional memory subtests.<br><br>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.<br>Lower score indicates worse performance.<br><br>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*<br>Associative learning*<br>Image free recall*<br>Recognition of nonsense pictures*<br>Associative recall of portrait characteristics*</td><td>17.2 (4.9)<br>20.0 (4.3)<br>20.9 (4.1)<br>23.2 (4.9)<br>20.3 (4.4)</td><td>18.1 (5.7)<br>18.5 (4.6)<br>20.4 (3.3)<br>21.6 (4.3)<br>18.5 (4.3)</td><td>23.5 (3.6)<br>24.9 (5.1)<br>24.1 (3.8)<br>26.3 (3.6)<br>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.<br>Lower score indicates worse performance.<br>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)**<br>Mice, B6C3F$_1$, 85/sex/group; interim sacrifices (10/sex/group) at 6 and 12 mo<br>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)<br>Diet<br>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)**<br>Rats, Sprague-Dawley, 100/sex/group<br>0, 1.0, 3.1, or 10 mg/kg-d<br>Diet<br>2 yrs | No neurological effects, as evidenced by clinical signs or changes in appearance or behavior, were reported. |
| **Levine et al. (1983); Thompson (1983)**<br>Rats, F344, 75/sex/group; interim sacrifices (10/sex/group) at 6 and 12 mo<br>0, 0.3, 1.5, 8.0, or 40 mg/kg-d<br>Diet<br>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)**<br>Mice, B6C3F$_1$, 10–12/sex/group<br>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]<br>Diet<br>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)**<br>Rats, F344, 10/sex/group<br>0, 10, 14, 20, 28, or 40 mg/kg-d<br>Diet<br>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)**<br>Rats, CD, two-generation study;<br>F0: 22/sex/group; F1: 26/sex/group;<br>F2: 10/sex/group<br>F0 and F1 parental animals: 0, 5, 16, or 50 mg/kg-d<br>Diet<br>13 wks | No neurological effects were reported. |
| **Crouse et al. (2006)**<br>Rats, F344, 10/sex/group<br>0, 4, 8, 10, 12, or 15 mg/kg-d<br>Gavage<br>90 d | Doses: 0 / 4 / 8[a] / 10 / 12 / 15<br>*Convulsions (incidence)*<br>M: 0/10 / 0/10 / 1/10 / 3/10 / 8/10 / 7/10<br>F: 0/10 / 0/10 / 2/10 / 3/10 / 5/10 / 5/10<br>*Tremors (incidence)*<br>M: 0/10 / 0/10 / 0/10 / 0/10 / 2/10 / 3/10<br>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)**<br>Rats, F344, 10/sex/group; 30/sex for control<br>0, 10, 30, 100, 300, or 600 mg/kg-d<br>Diet<br>13 wks | Hyper-reactivity to approach was observed in groups receiving ≥100 mg/kg-d[a]; no incidence data were reported.<br>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)**<br>Rats, sex/strain not specified, 20/group<br>0, 15, 25, or 50 mg/kg-d<br>Diet<br>3 mo | Hyperirritability and convulsions were observed in the 25 and 50 mg/kg-d groups[a]; no incidence data were reported. |
| **Hart (1974)**<br>Dogs, Beagle, 3/sex/group<br>0, 0.1, 1, or 10 mg/kg-d<br>Diet<br>90 d | No neurological effects, as evidenced by clinical signs or changes in appearance or behavior, were reported. |
| **Martin and Hart (1974)**<br>Monkeys, Cynomolgus or Rhesus, 3/sex/group<br>0, 0.1, 1, or 10 mg/kg-d<br>Gavage<br>90 d | Doses: 0 / 0.1 / 1 / 10[a]<br>*CNS effects characterized as trembling, shaking, jerking, or convulsions (incidence)*<br>M: 0/3 / 0/3 / 0/3 / 2/3<br>F: 0/3 / 0/3 / 0/3 / 2/3 |

| Reference and Study Design | Results |
|---|---|
| **Von Oettingen et al. (1949)**<br>Dogs, breed not specified, 5 females/group (control); 7 females/group (exposed)<br>0 or 50 mg/kg-d<br>Diet<br>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)**<br>Rats, Sprague-Dawley derived CD, 8–10 males or females/group<br>0, 1, 3, or 10 mg/kg-d<br>Gavage<br>30 d | No changes in motor activity, flavor aversion, scheduled-controlled response, or acoustic startle-response were reported. |
| **Cholakis et al. (1980)**<br>Rats, F344, 24–25 females/group<br>0, 0.2, 2.0, or 20 mg/kg<br>Gavage<br>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)<br>Rats, Sprague-Dawley, 6 pregnant females/group<br>0, 10, 20, 40, 80, or 120 mg/kg-d<br>Gavage<br>GDs 6–15 | Convulsions preceding death were observed at ≥40 mg/kg-d[a]; no incidence data were reported. |
| **Angerhofer et al. (1986)**<br>Rats, Sprague-Dawley, 39–51 mated females/group<br>0, 2, 6, or 20 mg/kg-d<br>Gavage<br>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.

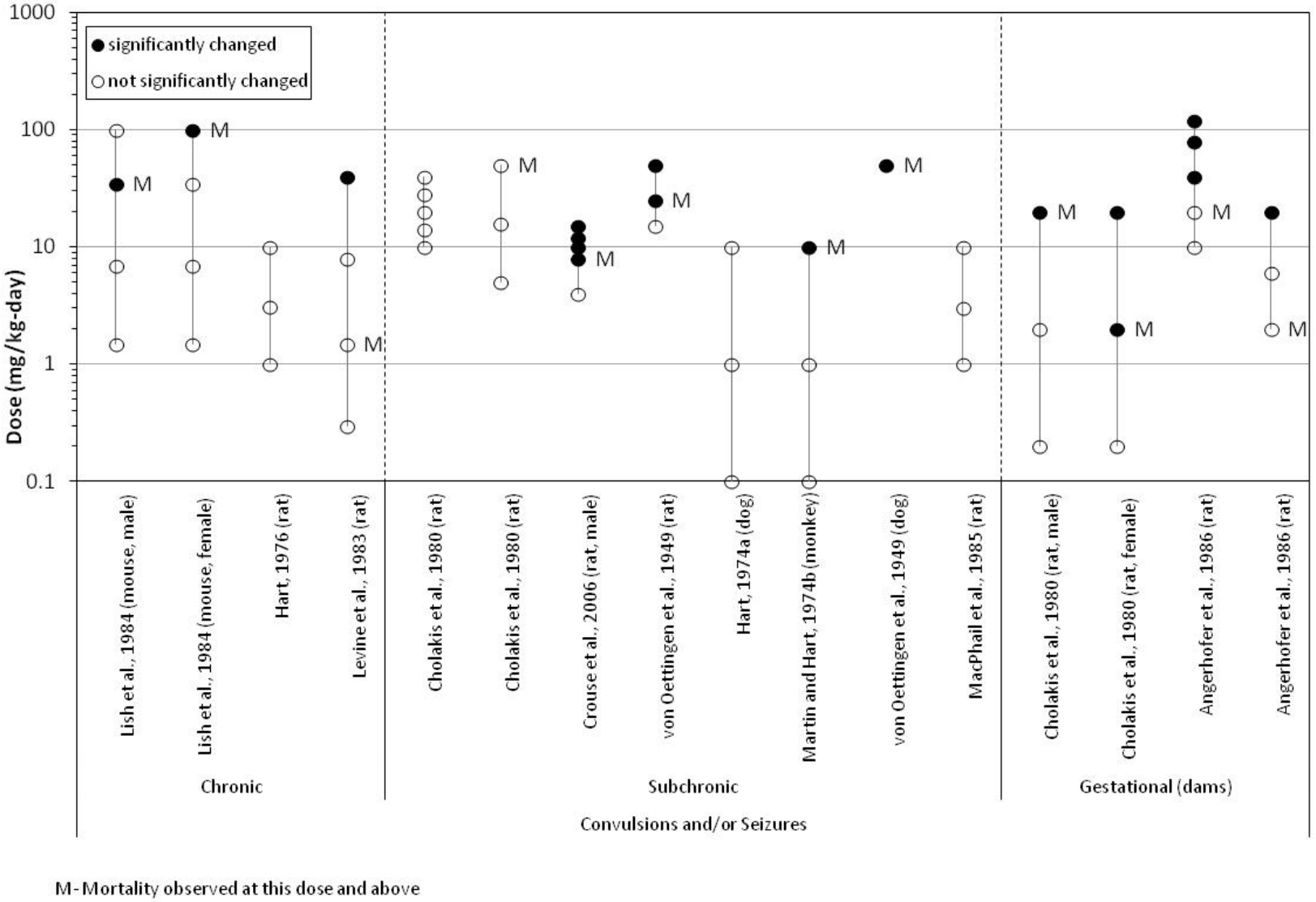



**Figure 2-1. Exposure-response array of neurological effects following oral exposure to RDX**

## 2.3. Mortality Evidence Table and Array

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

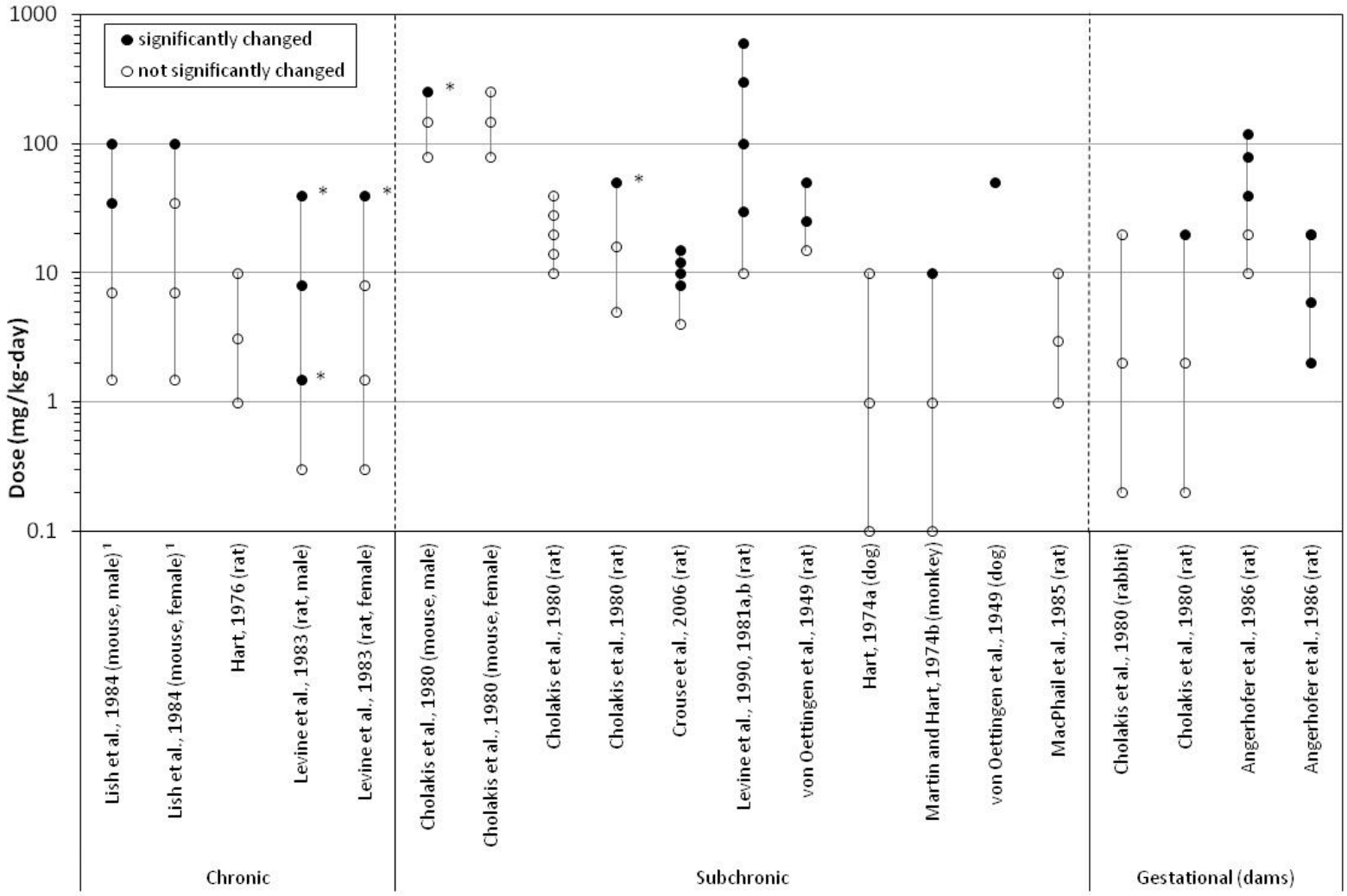
| Reference and Study Design | Results | | | | | |
|---|---|---|---|---|---|---|
| **Lish et al. (1984); Levine et al. (1984)**<br>Mice, B6C3F$_1$, 85/sex/group; interim sacrifices (10/sex/group) at 6 and 12 mo<br>0, 1.5, 7.0, 35, or 175/100 mg/kg-d (high dose reduced to 100 mg/kg-d in wk 11 due to excessive mortality)<br>Diet<br>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)**<br>Rats, Sprague-Dawley, 100/sex/group<br>0, 1.0, 3.1, or 10 mg/kg-d<br>Diet<br>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)**<br>Rats, F344, 75/sex/group; interim sacrifices (10/sex/group) at 6 and 12 mo<br>0, 0.3, 1.5, 8.0, or 40 mg/kg-d<br>Diet<br>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)**<br>Mice, B6C3F$_1$, 10–12/sex/group<br>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]<br>Diet<br>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)**<br>Rats, F344, 10/sex/group<br>0, 10, 14, 20, 28, or 40 mg/kg-d<br>Diet<br>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)<br>Rats, CD, two-generation study; F0: 22/sex/group; F1: 26/sex/group; F2: 10/sex/group<br>F0 and F1 parental animals: 0, 5, 16, or 50 mg/kg-d<br>Diet<br>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)<br>Rats, F344, 10/sex/group<br>0, 4, 8, 10, 12, or 15 mg/kg-d<br>Gavage<br>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)<br>Rats, F344, 10/sex/group; 30/sex for control<br>0, 10, 30, 100, 300, or 600 mg/kg-d<br>Diet<br>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)<br>Rats, sex/strain not specified, 20/group<br>0, 15, 25, or 50 mg/kg-d<br>Diet<br>3 mo | Doses | 0 | 15 | 25 | 50 | | |
| | *Mortality (incidence)* | | | | | | |
| | | 0/20 | 1/20[f] | 8/20 | 8/20 | | |
| Hart (1974)<br>Dogs, Beagle, 3/sex/group<br>0, 0.1, 1, or 10 mg/kg-d<br>Diet<br>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)<br>Monkeys, Cynomolgus or Rhesus, 3/sex/group<br>0, 0.1, 1, or 10 mg/kg-d<br>Gavage<br>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)<br>Dogs, breed not specified,<br>5 females/group (control);<br>7 females/group (exposed)<br>0 or 50 mg/kg-d<br>Diet<br>6 d/wk for 6 wks | Doses | 0 | | | 50 | |
| | *Mortality (incidence)* | | | | | |
| | F | 0/5 | | | 1/7 | |
| MacPhail et al. (1985)<br>Rats, Sprague-Dawley derived CD, 8–10 males or females/group<br>0, 1, 3, or 10 mg/kg-d<br>Gavage<br>30 d | No mortality was reported (incidence data were not provided). | | | | | |
| Cholakis et al. (1980)<br>Rabbits, New Zealand white, 11–12 pregnant females/group<br>0, 0.2, 2.0, or 20 mg/kg-d<br>Diet<br>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)<br>Rats, F344, 24–25 females/group<br>0, 0.2, 2.0, or 20 mg/kg-d<br>Gavage<br>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)<br>Rats, Sprague-Dawley, 6 pregnant females/group<br>0, 10, 20, 40, 80, or 120 mg/kg-d<br>Gavage<br>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)<br>Rats, Sprague-Dawley, 39–51 mated females/group<br>0, 2, 6, or 20 mg/kg-d<br>Gavage<br>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

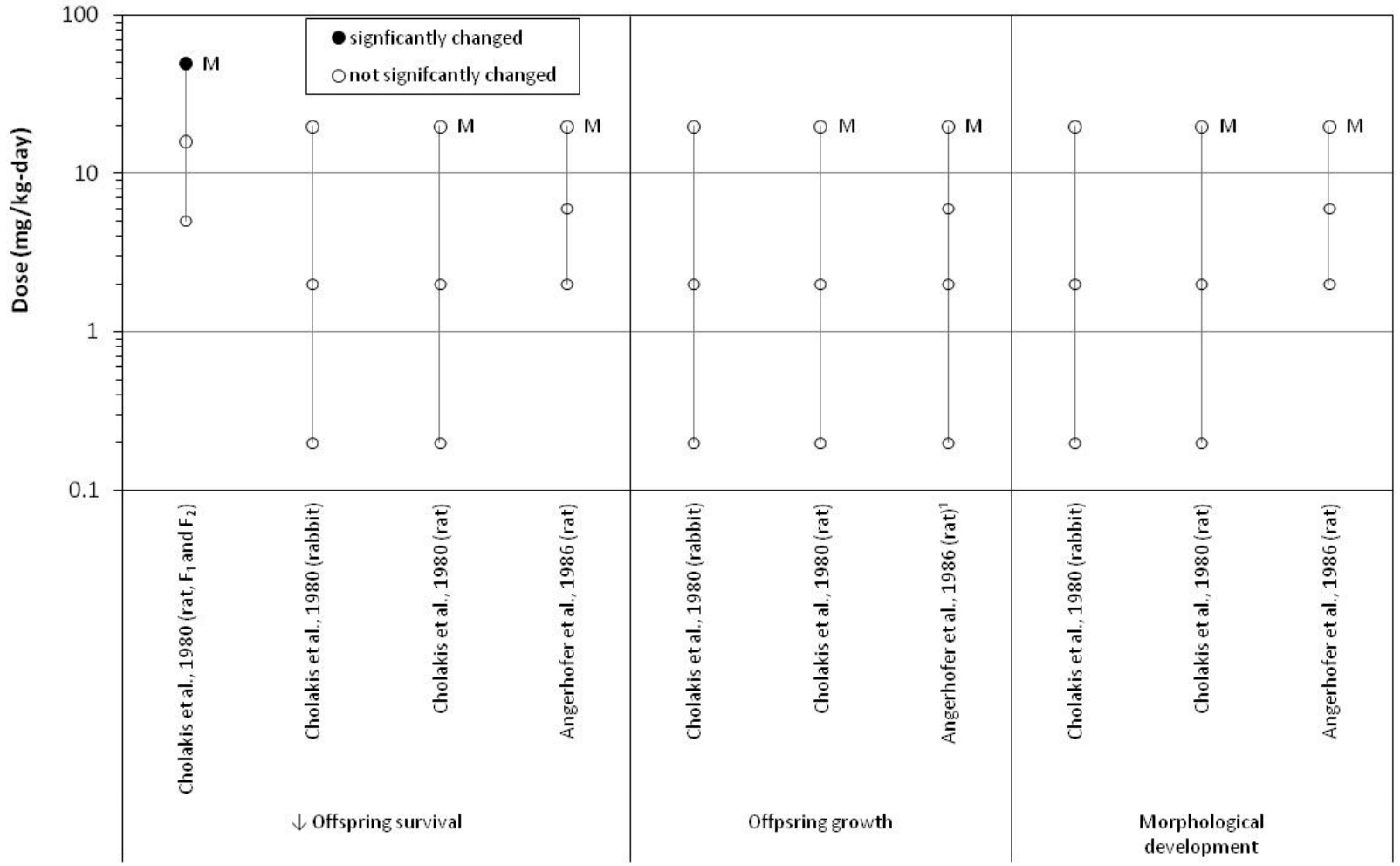
**Table 2-4. Evidence pertaining to reproductive and developmental effects in animals following oral exposure to RDX**

| Reference and Study Design | Results | | | | |
|---|---|---|---|---|---|
| *Offspring survival* | | | | | |
| **Cholakis et al. (1980)**<br>Rats, CD, two-generation study;<br>F0: 22/sex/group; F1: 26 sex/group; F2: 10 sex/group<br>F0 and F1 parental animals: 0, 5, 16, or 50 mg/kg-d<br>Diet<br>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)**<br>Rabbits, New Zealand white, 11–12/group<br>0, 0.2, 2.0, or 20 mg/kg-d<br>Gavage<br>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)**<br>Rats, F344, 24–25 females/group<br>0, 0.2, 2.0, or 20 mg/kg-d<br>Gavage<br>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)<br>Rats, Sprague-Dawley, 39–51 mated females/group (25–29 pregnant dams/group)<br>0, 2, 6, or 20 mg/kg-d<br>Gavage<br>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)**<br>Rabbits, New Zealand white, 11–12/group<br>0, 0.2, 2.0, or 20 mg/kg-d<br>Gavage<br>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)<br>Rats, F344, 24–25 females/group<br>0, 0.2, 2.0, or 20 mg/kg-d<br>Gavage<br>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)<br>Rats, Sprague-Dawley, 39–51 mated females/group (25–29 pregnant dams/group)<br>0, 2, 6, or 20 mg/kg-d<br>Gavage<br>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)**<br>Rabbits, New Zealand white, 11–12/group<br>0, 0.2, 2.0, or 20 mg/kg-d<br>Gavage<br>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)**<br>Rats, F344, 24–25 females/group<br>0, 0.2, 2.0, or 20 mg/kg-d<br>Gavage<br>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.<br><br>Significant maternal mortality (7/24 dams) occurred at 20 mg/kg-d. | | | | |
| **Angerhofer et al. (1986)**<br>Rats, Sprague-Dawley, 39–51 mated females/group (25–29 pregnant dams/group)<br>0, 2, 6, or 20 mg/kg-d<br>Gavage<br>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)<br>Mice, B6C3F$_1$, 85/sex/group; interim sacrifices (10/sex/group) at 6 and 12 mo<br>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)<br>Diet<br>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)<br>Rats, Sprague-Dawley, 100/sex/dose<br>0, 1.0, 3.1, or 10 mg/kg-d<br>Diet<br>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)<br>Rats, F344, 75/sex/group; interim sacrifices (10/sex/group) at 6 and 12 mo<br>0, 0.3, 1.5, 8.0, or 40 mg/kg-d<br>Diet<br>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.<br><br>SDMS = spontaneous death or moribund sacrifice; SS = scheduled sacrifice | | | | | |

| Reference and Study Design | Results | | | | | | |
|---|---|---|---|---|---|---|---|
| **Cholakis et al. (1980)**<br>Mice, B6C3F$_1$, 10–12/sex/group<br>Experiment 1: 0, 10, 14, 20, 28, or 40 mg/kg-d<br>Diet<br>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]<br>Diet<br>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)**<br>Rats, F344, 10/sex/dose<br>0, 10, 14, 20, 28, or 40 mg/kg-d<br>Diet<br>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)**<br>Rats, CD, two-generation study; F0: 22/sex/group; F1: 26/sex/group; F2: 10/sex/group<br>F0 and F1 parental animals: 0, 5, 16, or 50 mg/kg-d<br>Diet<br>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)**<br>Rats, F344, 10/sex/group<br>0, 4, 8, 10, 12, or 15 mg/kg-d<br>Gavage<br>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 |

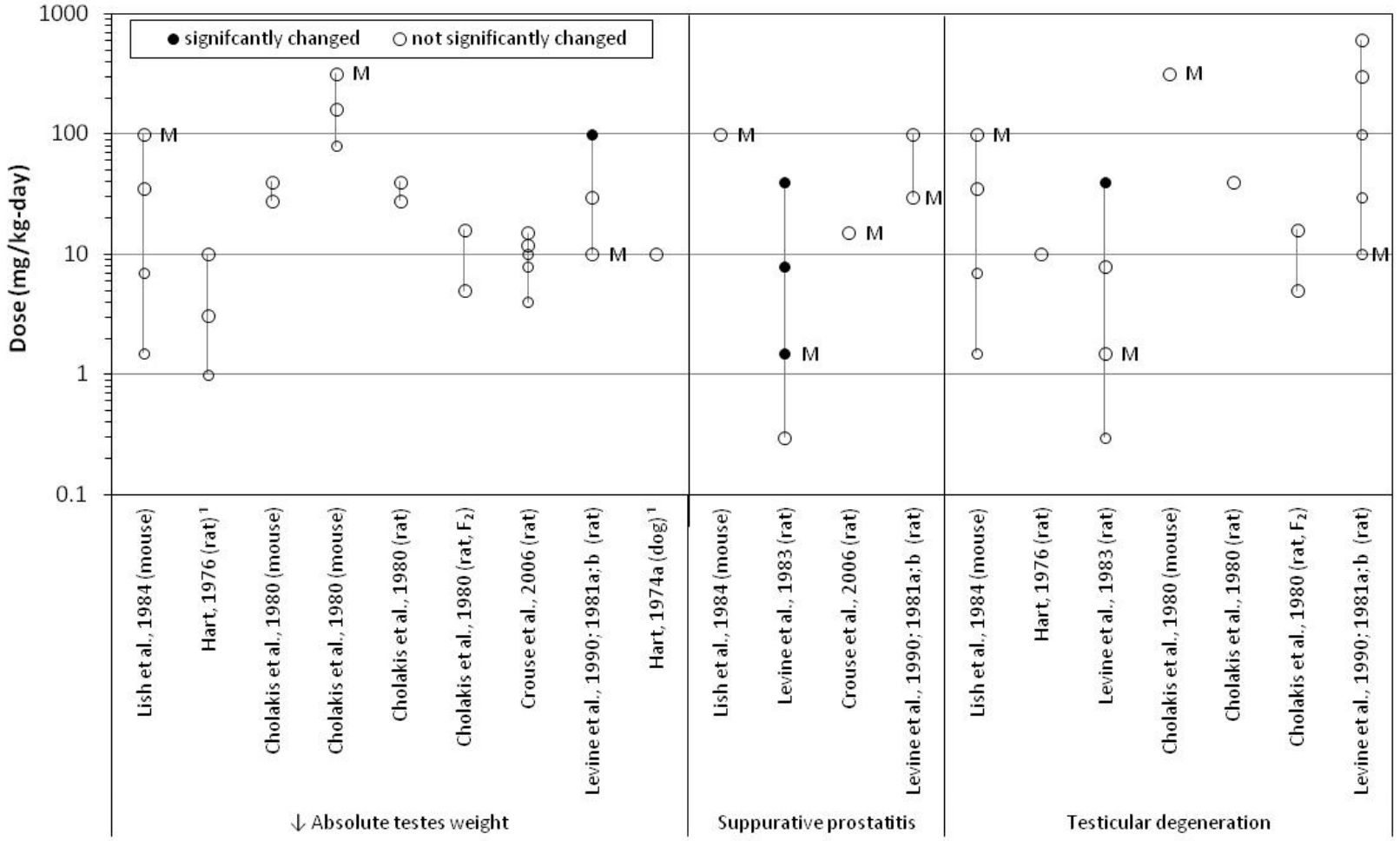
| Reference and Study Design | Results | | | | | | |
|---|---|---|---|---|---|---|---|
| Levine et al. (1990); Levine et al. (1981a); Levine et al. (1981b)<br>Rats, F344, 10/sex/group; 30/sex for control<br>0, 10, 30, 100, 300, or 600 mg/kg-d<br>Diet<br>13 wks | Doses | 0 | 10 | 30 | 100 | 300 | 600 |
| | *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)<br>Dogs, Beagle, 3/sex/dose<br>0, 0.1, 1, or 10 mg/kg-d<br>Diet<br>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)<br><br>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.<br><br>**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$^3$).<br><br>**Effect measures:** Liver function tests.<br><br>**Analysis:** Types of statistical tests were not reported (assumed to be t-tests for comparison of means and $\chi^2$ 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)**<br>Mice, B6C3F$_1$, 85/sex/group; interim sacrifices (10/sex/group) at 6 and 12 mo<br>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)<br>Diet<br>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)**<br>Rats, Sprague-Dawley, 100/sex/group<br>0, 1.0, 3.1, or 10 mg/kg-d<br>Diet<br>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)**<br>Rats, F344, 75/sex/group; interim sacrifices (10/sex/group) at 6 and 12 mo<br>0, 0.3, 1.5, 8.0, or 40 mg/kg-d<br>Diet<br>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)**<br>Mice, B6C3$F_1$, 10–12/sex/group<br>Experiment 1: 0, 10, 14, 20, 28, or 40 mg/kg-d<br>Diet<br>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]<br>Diet<br>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)**<br>Rats, F344, 10/sex/group<br>0, 10, 14, 20, 28, or 40 mg/kg-d<br>Diet<br>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)**<br>Rats, CD, two-generation study;<br>F0: 22/sex/group;<br>F1: 26/sex/group;<br>F2: 10/sex/group<br>F0 and F1 parental animals: 0, 5, 16, or 50 mg/kg-d<br>Diet<br>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)**<br>Rats, F344, 10/sex/group<br>0, 4, 8, 10, 12, or 15 mg/kg-d<br>Gavage<br>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)**<br>Rats, F344, 3–4 wks old; 10/sex/group; 30/sex/group for controls<br>0, 10, 30, 100, 300, or 600 mg/kg-d<br>Diet<br>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*% | – | – |

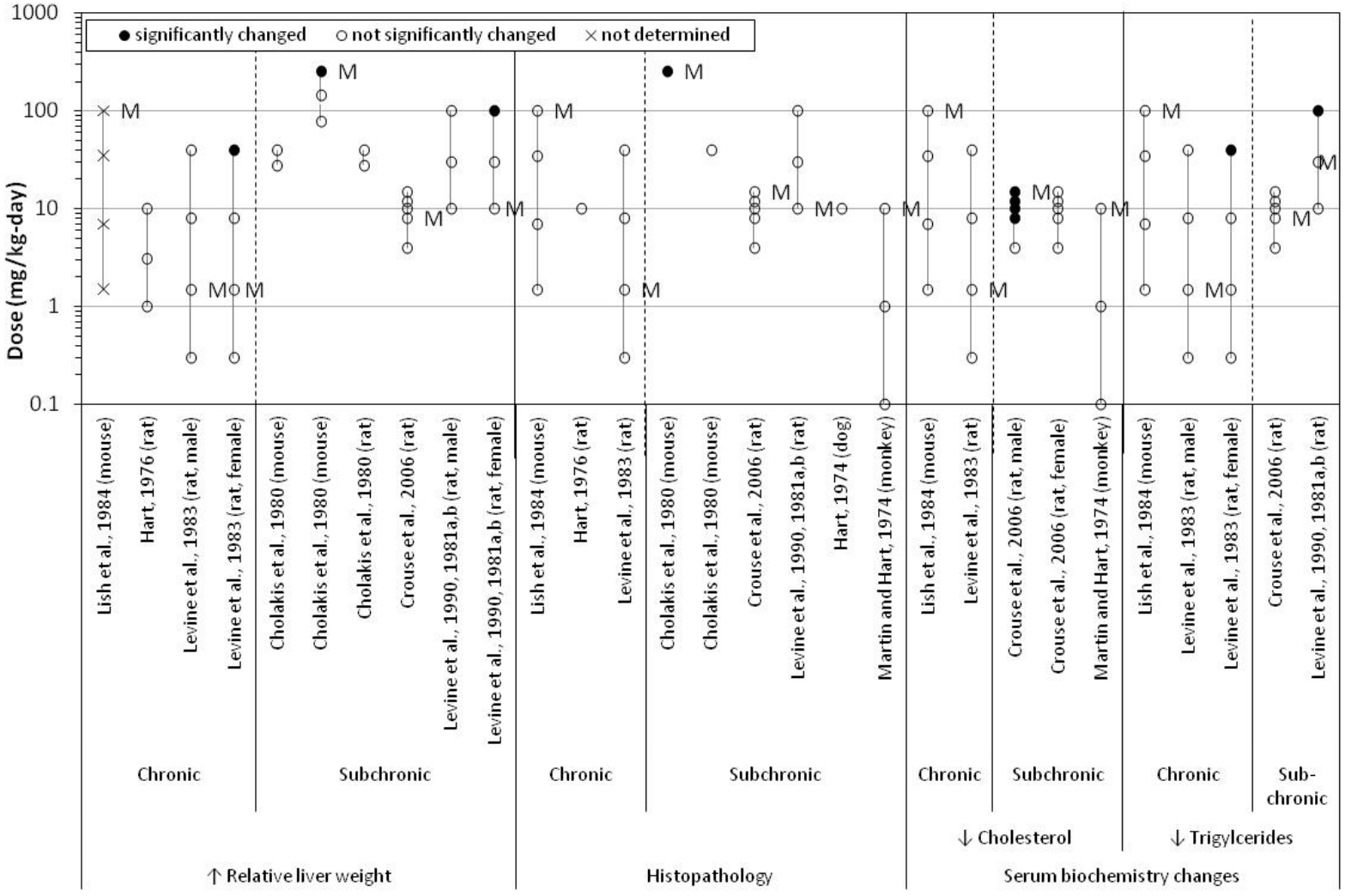
| Reference and Study Design | Results | | | | |
|---|---|---|---|---|---|
| **Hart (1974)**<br>Dogs, Beagle, 3/sex/group<br>0, 0.1, 1, or 10 mg/kg-d<br>Diet<br>90 d | Doses | 0 | 0.1 | 1 | 10 |
| | *Absolute liver weight (percent change compared to control)* | | | | |
| | M | 0% | – | – | 53% |
| | F | 0% | – | – | 3% |
| **Martin and Hart (1974)**<br>Monkeys, Cynomolgus or Rhesus, 3/sex/group<br>0, 0.1, 1, or 10 mg/kg-d<br>Gavage<br>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)**<br>Mice, B6C3$F_1$, 85/sex/group; interim sacrifices (10/sex/group) at 6 and 12 mo<br>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)<br>Diet<br>24 mo | Histopathological lesions in liver other than adenomas and carcinomas were not significantly different compared to controls. | | | | |
| **Hart (1976)**<br>Rats, Sprague-Dawley, 100/sex/group<br>0, 1.0, 3.1, or 10 mg/kg-d<br>Diet<br>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)**<br>Rats, F344, 3–4 wks old; 75/sex/group; interim sacrifices (10/sex/group) at 6 and 12 mo<br>0, 0.3, 1.5, 8.0, or 40 mg/kg-d<br>Diet<br>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)**<br>Mice, B6C3F$_1$, 10–12/sex/group<br>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]<br>Diet<br>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)**<br>Rats, F344, 10/sex/group<br>0, 10, 14, 20, 28, or 40 mg/kg-d<br>Diet<br>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)**<br>Rats, F344, 10/sex/group<br>0, 4, 8, 10, 12, or 15 mg/kg-d<br>Gavage<br>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)**<br>Rats, F344, 10/sex/group; 30/sex for control<br>0, 10, 30, 100, 300, or 600 mg/kg-d<br>Diet<br>13 wks | Histopathological examination of liver did not reveal any significant differences compared to controls. | | | | | | |
| **Hart (1974)**<br>Dogs, Beagle, 3/sex/group<br>0, 0.1, 1, or 10 mg/kg-d<br>Diet<br>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)**<br>Monkeys, Cynomolgus or Rhesus, 3/sex/group<br>0, 0.1, 1, or 10 mg/kg-d<br>Gavage<br>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)**<br>Mice, B6C3F$_1$, 85/sex/group; interim sacrifices (10/sex/group) at 6 and 12 mo<br>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)<br>Diet<br>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)**<br>Rats, F344, 75/sex/group; interim sacrifices (10/sex/group) at 6 and 12 mo<br>0, 0.3, 1.5, 8.0, or 40 mg/kg-d<br>Diet<br>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)**<br>Rats, F344, 10/sex/group<br>0, 4, 8, 10, 12, or 15 mg/kg-d<br>Gavage<br>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)**<br>Rats, F344, 10/sex/group; 30/sex for control<br>0, 10, 30, 100, 300, or 600 mg/kg-d<br>Diet<br>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)**<br>Monkeys, Cynomolgus or Rhesus, 3/sex/group<br>0, 0.1, 1, or 10 mg/kg-d<br>Gavage<br>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)**<br><br>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.<br><br>**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$^3$).<br><br>**Effect measures:** Renal function tests (blood)<br><br>**Analysis:** Types of statistical tests werenot reported (assumed to be t-tests for comparison of means and $\chi^2$ 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)**<br>Mice, B6C3F$_1$, 85/sex/group; interim sacrifices (10/sex/group) at 6 and 12 mo<br>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)<br>Diet<br>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)**<br>Rats, Sprague-Dawley, 100/sex/group<br>0, 1.0, 3.1, or 10 mg/kg-d<br>Diet<br>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)**<br>Rats, F344, 75/sex/group; interim sacrifices (10/sex/group) at 6 and 12 mo<br>0, 0.3, 1.5, 8.0, or 40 mg/kg-d<br>Diet<br>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)**<br>Mice, B6C3F$_1$, 10–12/sex/group<br>Experiment 1: 0, 10, 14, 20, 28, or 40 mg/kg-d<br>Diet<br>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]<br>Diet<br>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)**<br>Rats, F344, 10/sex/group<br>0, 10, 14, 20, 28, 40 mg/kg-d<br>Diet<br>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% |

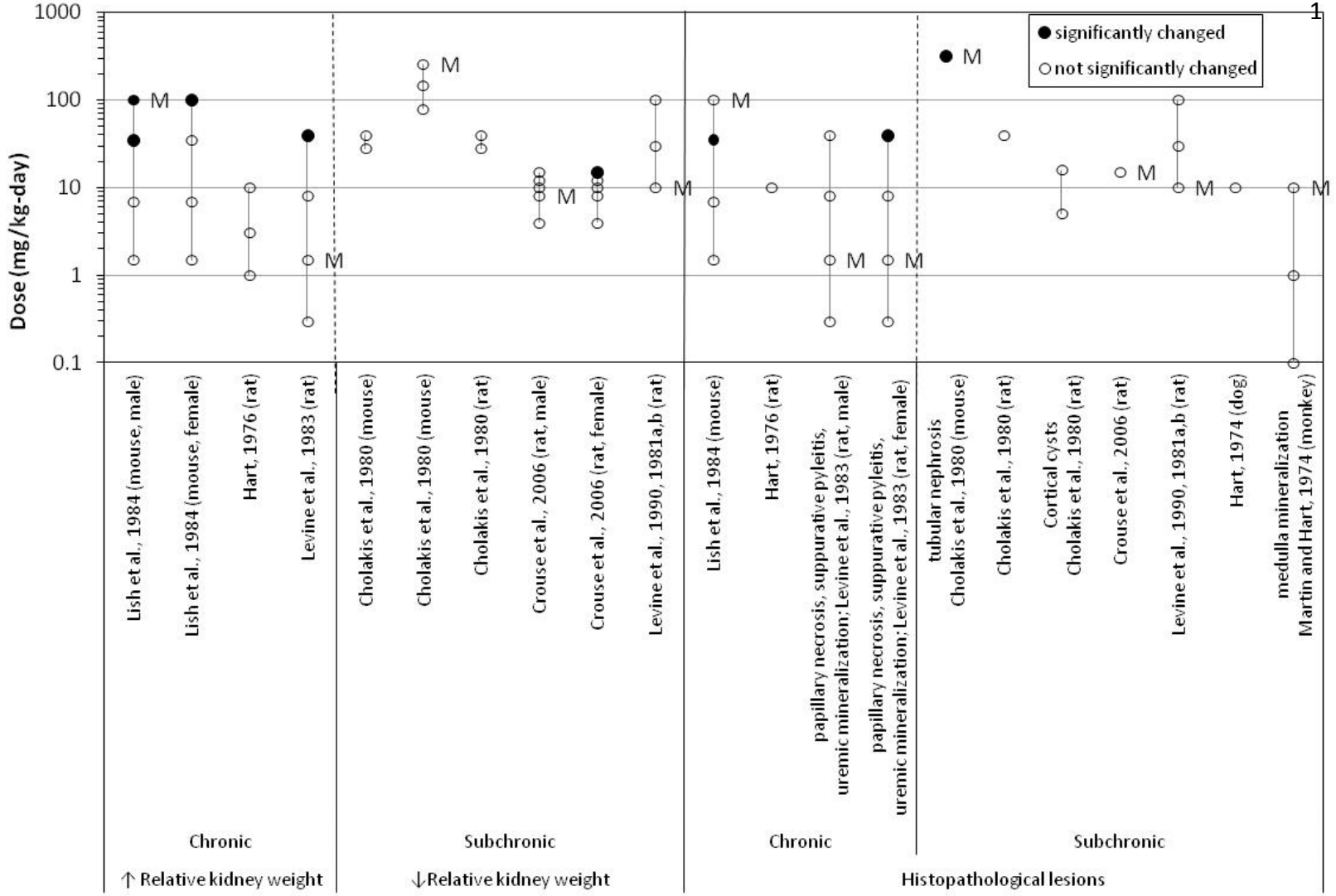
| Reference and Study Design | Results | | | | | | |
|---|---|---|---|---|---|---|---|
| **Cholakis et al. (1980)**<br>Rats, CD, two-generation study;<br>F0: 22/sex/group; F1: 26/sex/group;<br>F2: 10/sex/group<br>F0 and F1 parental animals: 0, 5, 16, 50 mg/kg-d<br>Diet<br>13 wks | Doses | 0 | 5 | 16 | 50 | | |
| | *Absolute kidney weight (percent change compared to control)* | | | | | | |
| | M | 0% | 6% | -12% | – | | |
| | F | 0% | -4% | -21*% | – | | |
| Crouse et al. (2006)<br>Rats, F344, 10/sex/group<br>0, 4, 8, 10, 12, or 15 mg/kg-d<br>Gavage<br>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)**<br>Rats, F344, 10/sex/group; 30/sex for control<br>0, 10, 30, 100, 300, or 600 mg/kg-d<br>Diet<br>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)**<br>Dogs, Beagle, 3/sex/group<br>0, 0.1, 1, or 10 mg/kg-d<br>Diet<br>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)<br>Monkeys, Cynomolgus or Rhesus, 3/sex/group<br>0, 0.1, 1, or 10 mg/kg-d<br>Gavage<br>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)**<br>Mice, B6C3F$_1$, 85/sex/group; interim sacrifices (10/sex/group) at 6 and 12 mo<br>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)<br>Diet<br>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)**<br>Rats, Sprague-Dawley, 100/sex/group<br>0, 1.0, 3.1, or 10 mg/kg-d<br>Diet<br>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)**<br>Rats, F344, 75/sex/group; interim sacrifices (10/sex/group) at 6 and 12 mo<br>0, 0.3, 1.5, 8.0, or 40 mg/kg-d<br>Diet<br>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.<br>Doses: 0 / 0.3 / 1.5 / 8.0 / 40<br>*Medullary papillary necrosis; 24 mo (incidence)*<br>M (SS): 0/38 / 0/36 / 0/25 / 0/29 / 0/4<br>F (SDMS): 0/17 / 1/19 / 0/27 / 0/26 / 18/27*<br>*Suppurative pyelitis; 24 mo (incidence)*<br>M (SS): 0/38 / 0/36 / 0/25 / 0/29 / 0/4<br>F (SDMS): 0/17 / 1/19 / 0/27 / 1/26 / 5/27*<br>*Uremic mineralization; 24 mo (incidence)*<br>M (SS): 1/38 / 0/36 / 0/25 / 0/29 / 0/4<br>F (SDMS): 0/17 / 1/19 / 2/27 / 0/26 / 13/27 |
| **Cholakis et al. (1980)**<br>Mice, B6C3F$_1$, 10–12/sex/group<br>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]<br>Diet<br>13 wks | Incidence data reported only for controls and the 320 mg/kg-d group.<br>Doses: 0 / 80 / 160 / 320<br>*Tubular nephrosis (incidence)*<br>M: 0/10 / – / – / 4/9*<br>F: 0/11 / – / – / 1/11 |
| **Cholakis et al. (1980)**<br>Rats, F344, 10/sex/group<br>0, 10, 14, 20, 28, or 40 mg/kg-d<br>Diet<br>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)<br>Rats, CD, two-generation study; F0: 22/sex/group; F1: 26/sex/group; F2: 10/sex/group<br>F0 and F1 parental animals: 0, 5, 16, or 50 mg/kg-d<br>Diet<br>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)**<br>Rats, F344, 10/sex/group<br>0, 4, 8, 10, 12, or 15 mg/kg-d<br>Gavage<br>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)**<br>Rats, F344, 10/sex/group; 30/sex for control<br>0, 10, 30, 100, 300, or 600 mg/kg-d<br>Diet<br>13 wks | Histopathological examination of kidney did not reveal any significant differences compared to controls. | | | | |
| **Hart (1974)**<br>Dogs, Beagle, 3/sex/group<br>0, 0.1, 1, or 10 mg/kg-d<br>Diet<br>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)**<br>Monkeys, Cynomolgus or Rhesus, 3/sex/group<br>0, 0.1, 1, or 10 mg/kg-d<br>Gavage<br>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)<br>Mice, B6C3F$_1$, 85/sex/group; interim sacrifices (10/sex/group) at 6 and 12 mo<br>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)<br>Diet<br>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)<br>Rats, Sprague-Dawley, 100/sex/group<br>0, 1.0, 3.1, or 10 mg/kg-d<br>Diet<br>2 yrs | *Hepatocellular adenomas (incidence)*<br>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)<br>Rats, F344, 75/sex/group; interim sacrifices (10/sex/group) at 6 and 12 mo<br>0, 0.3, 1.5, 8.0, or 40 mg/kg-d<br>Diet<br>24 mo | *Hepatocellular adenomas (incidence):*<br>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):*<br>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)<br>Mice, B6C3F$_1$, 85/sex/group; interim sacrifices (10/sex/group) at 6 and 12 mo<br>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)<br>Diet<br>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)<br>Rats, Sprague-Dawley, 100/sex/group<br>0, 1.0, 3.1, or 10 mg/kg-d<br>Diet<br>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):*<br>None reported by study authors. | | | | | |
| Levine et al. (1983); Thompson (1983)<br>Rats, F344, 75/sex/group; interim sacrifices (10/sex/group) at 6 and 12 mo<br>0, 0.3, 1.5, 8.0, or 40 mg/kg-d<br>Diet<br>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)<br><br>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).<br><br>**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).<br><br>**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).<br><br>**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)<br>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.<br><br>**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$^3$).<br><br>**Effect measures:** Hematology tests.<br><br>**Analysis:** Types of statistical tests were not reported (assumed to be t-tests for comparison of means and $\chi^2$ 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.<br><br>*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)<br>Mice, B6C3F$_1$, 85/sex/group; interim sacrifices (10/sex/group) at 6 and 12 mo<br>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)<br>Diet<br>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)<br>Rats, F344, 75/sex/group; interim sacrifices (10/sex/group) at 6 and 12 mo<br>0, 0.3, 1.5, 8.0, or 40 mg/kg-d<br>Diet<br>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)<br>Rats, F344, 10/sex/group<br>0, 10, 14, 20, 28, or 40 mg/kg-d<br>Diet<br>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)**<br>Rats, F344, 10/sex/group<br>0, 4, 8, 10, 12, or 15 mg/kg-d<br>Gavage<br>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)**<br>Monkeys, Cynomolgous or Rhesus, 3/sex/group<br>0, 0.1, 1, or 10 mg/kg-d<br>Gavage<br>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)**<br>Mice, B6C3F$_1$, 85/sex/group; interim sacrifices (10/sex/group) at 6 and 12 mo<br>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)<br>Diet<br>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)**<br>Rats, Sprague-Dawley, 100/sex/group<br>0, 1.0, 3.1, or 10 mg/kg-d<br>Diet<br>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)<br>Rats, F344, 75/sex/group; interim sacrifices (10/sex/group) at 6 and 12 mo<br>0, 0.3, 1.5, 8.0, or 40 mg/kg-d<br>Diet<br>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)<br>Mice, B6C3F$_1$, 10–12/sex/group<br>Experiment 1: 0, 10, 14, 20, 28, or 40 mg/kg-d<br>Diet<br>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]<br>Diet<br>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.<br>***Includes one unaffected animal that died prematurely. | | | | | | |
| Cholakis et al. (1980)<br>Rats, F344, 10/sex/group<br>0, 10, 14, 20, 28, or 40 mg/kg-d<br>Diet<br>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)**<br>Rats, CD, two-generation study; F0: 22/sex/group; F1: 26/sex/group; F2: 10/sex/group<br>F0 and F1 parental animals: 0, 5, 16, or 50 mg/kg-d<br>Diet<br>13 wks | No cardiac effects were observed (microscopic examination of heart was performed in randomly selected F2 animals).<br><br>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)**<br>Rats, F344, 10/sex/group<br>0, 4, 8, 10, 12, or 15 mg/kg-d<br>Gavage<br>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)**<br>Rats, F344, 10/sex/group; 30/sex for control<br>0, 10, 30, 100, 300, or 600 mg/kg-d<br>Diet<br>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)**<br>Rats (sex/strain not specified); 20/group<br>0, 15, 25, or 50 mg/kg-d<br>Diet<br>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)**<br>Dogs, Beagle, 3/sex/group<br>0, 0.1, 1, or 10 mg/kg-d<br>Diet<br>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)**<br>Monkeys, Cynomolgous or Rhesus, 3/sex/group<br>0, 0.1, 1, or 10 mg/kg-d<br>Gavage<br>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)**<br>Mice, B6C3F$_1$, 85/sex/group; interim sacrifices (10/sex/group) at 6 and 12 mo<br>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)<br>Diet<br>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)**<br>Rats, Sprague-Dawley, 100/sex/group<br>0, 1.0, 3.1, or 10 mg/kg-d<br>Diet<br>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)<br>Rats, F344, 75/sex/group; interim sacrifices (10/sex/group) at 6 and 12 mo<br>0, 0.3, 1.5, 8.0, or 40 mg/kg-d<br>Diet<br>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)<br>Mice, B6C3F$_1$, 10–12/sex/group<br>Experiment 1: 0, 10, 14, 20, 28, or 40 mg/kg-d<br>Diet<br>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]<br>Diet<br>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)<br>Rats, F344, 10/sex/group<br>0, 10, 14, 20, 28, or 40 mg/kg-d<br>Diet<br>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)<br>Rats, CD, two-generation study; F0: 22/sex/group; F1: 26/sex/group; F2: 10/sex/group<br>F0 and F1 parental animals: 0, 5, 16, or 50 mg/kg-d<br>Diet<br>13 wks | No immune effects were observed upon routine histopathology evaluation. | | | | | | |
| Crouse et al. (2006)<br>Rats, F344, 10/sex/group<br>0, 4, 8, 10, 12, or 15 mg/kg-d<br>Gavage<br>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)<br>Rats, F344, 10/sex/group; 30/sex for control<br>0, 10, 30, 100, 300, or 600 mg/kg-d<br>Diet<br>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)**<br>Rats, sex/strain not specified, 20/group<br>0, 15, 25, or 50 mg/kg-d<br>Diet<br>3 mo | Doses | 0 | | 15 | 25 | | 50 |
| | *WBC count (percent change compared to control)* | | | | | | |
| | M | 0% | | -30% | 7% | | -6% |
| **Hart (1974)**<br>Dogs, Beagle, 3/sex/group<br>0, 0.1, 1, or 10 mg/kg-d<br>Diet<br>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)**<br>Monkeys, Cynomolgous or Rhesus, 3/sex/group<br>0, 0.1, 1, or 10 mg/kg-d<br>Gavage<br>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)**<br>Mice, B6C3F$_1$, 85/sex/group; interim sacrifices (10/sex/group) at 6 and 12 mo<br>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)<br>Diet<br>24 mo | No GI effects were observed as clinical signs or on gross pathology or histopathology examination. |
| **Levine et al. (1983); Thompson (1983)**<br>Rats, F344, 75/sex/group; interim sacrifices (10/sex/group) at 6 and 12 mo<br>0, 0.3, 1.5, 8.0, or 40 mg/kg-d<br>Diet<br>24 mo | No GI effects were observed as clinical signs or on gross pathology or histopathology examination. |
| Crouse et al. (2006)<br>Rats, F344, 10/sex/group<br>0, 4, 8, 10, 12, or 15 mg/kg-d<br>Gavage<br>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)**<br>Rats (sex/strain not specified); 20/group<br>0, 15, 25, or 50 mg/kg-d<br>Diet<br>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)**<br>Monkeys (Cynomolgus or Rhesus); 3/sex/group<br>0, 0.1, 1, or 10 mg/kg-d<br>Gavage<br>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)**<br>Dogs, Beagle, 3/sex/group<br>0, 0.1, 1, or 10 mg/kg-d<br>Diet<br>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)**<br>Mice, B6C3F$_1$, 85/sex/group; interim sacrifices (10/sex/group) at 6 and 12 mo<br>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)<br>Diet<br>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)**<br>Rats, Sprague-Dawley, 100/sex/group<br>0, 1.0, 3.1, or 10 mg/kg-d<br>Diet<br>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)**<br>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<br>0, 0.3, 1.5, 8.0, or 40 mg/kg-d<br>Diet<br>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)<br>Mice, B6C3F$_1$, 10–12/sex/group<br>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]<br>Diet<br>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)<br>Rats, F344, 10/sex/group<br>0, 10, 14, 20, 28, or 40 mg/kg-d<br>Diet<br>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<br>Diet<br>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)**<br>Monkeys, Cynomolgous or Rhesus, 3/sex/group<br>0, 0.1, 1, or 10 mg/kg-d<br>Gavage<br>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.

1

## 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