Hexahydro-1,3,5-trinitro-1,3,5-triazine (RDX); CASRN 121-82-4

Human health assessment information on a chemical substance is included in the IRIS database only after a comprehensive review of toxicity data, as outlined in the IRIS assessment development process. Sections I (Health Hazard Assessments for Noncarcinogenic Effects) and II (Carcinogenicity Assessment for Lifetime Exposure) present the conclusions that were reached during the assessment development process. Supporting information and explanations of the methods used to derive the values given in IRIS are provided in the guidance documents located on the IRIS website.

STATUS OF DATA FOR RDX

File First On-Line 09/26/1988

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<th>Last Revised</th>
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<td>09/26/1988</td>
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<td>Carcinogenicity Assessment (II.)</td>
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I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

I.A. Reference Dose for Chronic Oral Exposure (RfD)

Substance Name — Hexahydro-1,3,5-trinitro-1,3,5-triazine (RDX)
CASRN — 121-82-4
Last Revised — 09/26/1988

The oral Reference Dose (RfD) is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. It is expressed in units of mg/kg-day. In general, the RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Please refer to the Background Document for an elaboration of these concepts. RfDs can also be derived for the noncarcinogenic health effects of
substances that are also carcinogens. Therefore, it is essential to refer to other sources of information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

I.A.1. Oral RfD Summary

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<th>MF</th>
<th>RfD</th>
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<tr>
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<td>LOAEL: 1.5 mg/kg/day</td>
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<td>2-Year Rat Feeding Study</td>
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*Conversion Factors: None

I.A.2. Principal and Supporting Studies (Oral RfD)


The U.S. Department of Defense (U.S. DOD, 1983) commissioned a study to evaluate the chronic effects of RDX in groups of 85 male and female Fischer 344 rats fed doses of 0, 0.3, 1.5, 8.0, or 40.0 mg/kg/day for 24 months. RDX purity ranged from 89.2 to 98.7%, and particle size ranged from <22 um (51.7%) to 440 um. Mortality was increased in high-dose males and females throughout the study (e.g., 88 and 41%, respectively, at week 88 as compared with 32 and 33% for respective controls). Tremors and convulsions were frequently observed prior to deaths of high-dose males and females beginning at week 25. Behavioral hypersensitivity to stimuli resulted in fighting among cohabited high-dose males. Histologic evaluation failed to detect lesions of the central nervous system. The incidence of cataracts was significantly increased (p<0.05) in high-dose females at weeks 78 and 104; the eyes of high- dose males appeared normal. These observations were considered to be treatment-related. Hepatotoxicity, primarily at 40 mg/kg/day, was evidenced by hepatomegaly (although histological changes were not reported to be apparent), hypocholesteremia, hypotriglyceridemia, reduced serum albumin/total protein levels, and increased lactic dehydrogenase (LDH) levels. Compound-
induced renal toxicity was found primarily in high-dose males. Absolute kidney weights were significantly increased in high-dose females, and relative kidney weights were significantly increased in high-dose males throughout the study. Absolute and relative kidney weights were sporadically increased in males and females receiving 8 mg/kg/day at 12 months or in any controls. In males receiving 1.5, 8.0, and 40.0 mg/kg/day, there was increased pigment in the spleen (possibly a hematopoietic response and not adverse) and suppurative inflammation of the prostate. The only significant (p<0.05) histologic change in females was an increase in lenticular cataracts (32/48 in the high-dose group compared with 15/53 in controls). Based on suppurative inflammation of the prostate of males receiving 1.5 mg/kg/day and above, the LOAEL was 1.5 mg/kg/day and the NOEL was 0.3 mg/kg/day.

Schneider et al. (1978) dosed 30 Sprague-Dawley rats (sex not specified) orally with RDX in an isotonic saline slurry at 20 mg/kg/day for 90 days. Eight dosed rats died between days 42 and 77, apparently from exacerbation of chronic respiratory disease.

Groups of 10 male and 12 female mice were fed 0, 40, 60, or 80 mg/kg/day RDX in the diet for 2 weeks, followed by 0, 80, 160, or 320 mg/kg/day RDX, respectively, for 11 weeks. The LOAEL for the study based on anemia in males was 160 mg/kg/day, and the NOAEL was 80 mg/kg/day. In the 13-week study with Fischer 344 rats (U.S. DOD, 1980), 60 male and 60 female rats were divided into six groups, each consisting of 10 males and 10 females. The groups were fed diets that provided an RDX intake of 0, 10, 14, 20, 28, or 40 mg/kg/day. Based on anemia, the LOAEL was 28 mg/kg/day and the NOAEL was 20 mg/kg/day.

Levine et al. (1981) fed RDX in the diet to groups of 10 male and 10 female Fischer 344 rats for 13 weeks at doses of 0, 10, 30, 100, 300, or 600 mg/kg/day. Based on effects on liver weights, the LOAEL was 100 mg/kg/day and the NOAEL 30 mg/kg/day.

Von Oettingen et al. (1949) conducted short-term toxicity studies with RDX in rats (strain and sex not specified), and dogs (breed not specified). Groups of 15 rats received RDX in the feed at doses of 0, 15, 50, or 100 mg/kg/day for 10 weeks. Based on CNS effects, the LOAEL was 50 mg/kg/day and the NOAEL was 15 mg/kg/day. In a follow-up study, groups of 20 rats were administered RDX in the diet at doses to provide an intake of 0, 15, 25, or 50 mg/kg RDX/day for 12 weeks. The LOAEL based on mortality and body weight loss was 25 mg/kg/day, and the NOAEL was 15 mg/kg/day. In the dog study, seven healthy females were force-fed 50 mg/kg/day RDX (molded in a moistened pellet), 6 days/week for 6 weeks. One treated dog that died at the end of week 5 had many congested areas on the walls of the small intestines. Treatment caused hyperirritability, convulsions, and weight loss. The gross and microscopic changes in the organs and tissues were negligible.
Groups of three male and three female dogs were fed 0, 0.1, 1, or 10 mg/kg/day RDX for 90 days (U.S. DOD, 1974a). No signs of toxicity, except for temporary episodes of emesis, were seen.

Groups of three male and three female monkeys were administered oral gavage doses of 0, 0.1, 1, or 10 mg/kg RDX in a 1% aqueous solution of methylcellulose daily for 90 days (U.S. DOD, 1974b). Based on effects on the CNS, the LOAEL was 10 mg/kg/day and the NOAEL was 1 mg/kg/day.

Male and female Sprague-Dawley rats were fed RDX at doses of 0, 1.0, 3.1, or 10 mg/kg/day for 24 months (U.S. DOD, 1976). Survival was comparable to controls in high-dose males and females. The LOAEL is 3.1 mg/kg/day and the NOAEL is 1 mg/kg/day based on decreased body weights in females.

The chronic effects of RDX were evaluated for groups of 85 male and female B6C3F1 mice fed doses of 0, 1.5, 7.0, 35.0, or 100 mg/kg/day for 24 months (U.S. DOD, 1984). The major toxic effects included weight loss, increased liver weights, and testicular degeneration. Based on testicular degeneration in males, the LOAEL for systemic toxicity was 35 mg/kg/day, and the NOAEL was 7.0 mg/kg/day.

I.A.3. Uncertainty and Modifying Factors (Oral RfD)

UF — The UF of 100 allows for uncertainty in the extrapolation of dose levels from laboratory animals to humans (10A) and uncertainty in the threshold for sensitive humans (10H).

MF — None

I.A.4. Additional Studies/Comments (Oral RfD)

A two-generation reproduction study was conducted with Fischer 344 rats (U.S. DOD, 1980). The initial group of parental animals (F0), consisting of 22 males and 22 females, was fed RDX in the diet at nominal doses of 0, 5, 16, or 50 mg/kg/day for 13 weeks. After treatment, the animals were mated and the dams were allowed to litter. After weaning, groups of 26 males and 26 females (F1) were fed the same dietary concentrations of RDX as their parents for 13 weeks and were allowed to mate following completion of treatment. The LOAEL for reproductive effects was 50 mg/kg/day, and the NOAEL was 16 mg/kg/day. The LOAEL for developmental toxicity was 16 mg/kg/day, and the NOAEL was 5 mg/kg/day.

Developmental toxicity studies were conducted with Fischer 344 rats and New Zealand rabbits (U.S. DOD, 1980). In the study with rats, groups of 24 or 25 rats received 0, 0.2, 2, or 20 mg/kg/day RDX, by gavage on days 6 through 19 of gestation. Teratogenicity was not
demonstrated at any of the dose levels tested. Based on embryotoxicity and maternal toxicity, the LOAEL was 20 mg/kg/day and the NOAEL was 2 mg/kg/day. In the study with rabbits, dams (number not reported) were dosed with 0, 0.2, 2, or 20 mg/kg/day RDX, by gavage, on days 7 through 29 of gestation, and 11 to 12 litters/group were delivered by cesarean section on day 30. Based on maternal toxicity and developmental effects, the LOAEL was 20 mg/kg/day and the NOAEL was 2.0 mg/kg/day.

Angerhofer et al. (1986) investigated the developmental toxic effects of RDX in rats. The authors conducted a range-finding study using groups of six pregnant rats treated with RDX, by gavage, at dose levels of 0, 10, 20, 40, 80, or 120 mg/kg/day on gestational days 6 through 15. No teratogenic effects were noted in this study. Based on maternal deaths and toxicity and a decrease in fetal weight length, the LOAEL was 20 mg/kg/day and the NOAEL was 6 mg/kg/day.

I.A.5. Confidence in the Oral RfD

Study — High  
Database — High  
RfD — High

The principal study was a well-designed and well-executed long-term study with a large number of dose groups using an adequate number of animals. A clear NOEL and LOAEL were established. The database is extensive, covering all important toxicological endpoints, but lacking a chronic study for a nonrodent species. However, short-term data suggests that dogs and monkeys are not more sensitive than rats. High confidence in the RfD follows.

I.A.6. EPA Documentation and Review of the Oral RfD

Source Document — This assessment is not presented in any existing U.S. EPA document.

Other EPA Documentation — U.S. EPA, 1988

Agency Work Group Review — 04/20/1988

Verification Date — 04/20/1988

I.A.7. EPA Contacts (Oral RfD)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (FAX) or hotline.iris@epa.gov (internet address).
I.B. Reference Concentration for Chronic Inhalation Exposure (RfC)

Substance Name — Hexahydro-1,3,5-trinitro-1,3,5-triazine (RDX)
CASRN — 121-82-4

Not available at this time.

II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name — Hexahydro-1,3,5-trinitro-1,3,5-triazine (RDX)
CASRN — 121-82-4
Last Revised — 08/01/1990

Section II provides information on three aspects of the carcinogenic assessment for the substance in question; the weight-of-evidence judgment of the likelihood that the substance is a human carcinogen, and quantitative estimates of risk from oral exposure and from inhalation exposure. The quantitative risk estimates are presented in three ways. The slope factor is the result of application of a low-dose extrapolation procedure and is presented as the risk per (mg/kg)/day. The unit risk is the quantitative estimate in terms of either risk per ug/L drinking water or risk per ug/cu.m air breathed. The third form in which risk is presented is a drinking water or air concentration providing cancer risks of 1 in 10,000, 1 in 100,000 or 1 in 1,000,000. The rationale and methods used to develop the carcinogenicity information in IRIS are described in The Risk Assessment Guidelines of 1986 (EPA/600/8-87/045) and in the IRIS Background Document. IRIS summaries developed since the publication of EPA's more recent Proposed Guidelines for Carcinogen Risk Assessment also utilize those Guidelines where indicated (Federal Register 61(79):17960-18011, April 23, 1996). Users are referred to Section I of this IRIS file for information on long-term toxic effects other than carcinogenicity.

II.A. Evidence for Human Carcinogenicity

II.A.1. Weight-of-Evidence Characterization

Classification — C; possible human carcinogen

Basis — Hepatocellular adenomas and carcinomas in female B6C3F1 mice.
II.A.2. Human Carcinogenicity Data

None.

Hexahydro-1,3,5-trinitro-1,3,5-triazine, an explosive polynitramine, is commonly known as RDX (British code name for Research Department Explosive or Royal Demolition Explosive). Epidemiological studies of munitions workers have not been conducted. There is no carcinogenicity information in the human health effects database.

II.A.3. Animal Carcinogenicity Data

The carcinogenic potential of RDX has been evaluated in Fischer 344 rats [U.S. Department of Defense (U.S. DOD, 1983), Sprague-Dawley rats (Hart, 1976) and B6C3F1 mice (U.S. DOD, 1984). RDX was not found to be carcinogenic when fed to either strain of rats. It was found to produce significant increases in the combined hepatocellular adenomas/carcinomas in B6C3F1 female mice.

RDX was not found to be oncogenic in male and female Sprague-Dawley rats (100 rats/sex/dose) fed RDX in the diet at doses of 1.0, 3.1, or 10 mg/kg/day for 24 months (Hart, 1976). The percent survival among the groups was comparable (the range was between 60% and 73%).

U.S. DOD (1983) evaluated the carcinogenicity of RDX in male and female Fischer 344 rats (85 rats/sex/dose) fed doses of 0.3, 1.5, 8.0, or 40.0 mg/kg/day RDX for 24 months. Ten rats/sex/dose were killed at 6 and 12 months and the remaining animals killed after 24 months of treatment. The major toxic effects observed included anemia with secondary splenic lesions, hepatotoxicity, and urogenital lesions. Based on adverse systemic effects at 1.5 mg/kg/day, the MTD was achieved. RDX was not found to be oncogenic in this study.

U.S. DOD (1984) evaluated the incidence of tumors in groups of 85 male and female B6C3F1 mice fed doses of 1.5, 7.0, 35.0, or 100 mg/kg/day RDX for 24 months. The combined incidence of hepatocellular carcinomas and adenomas was statistically significantly increased in females receiving 7.0, 35.0, and 100.0 mg/kg RDX (14.1, 18.8, and 19.4%, respectively) when compared with concurrent (1.5%) or historical (7.9%) controls. These findings were considered to be compound-related in females. Historically, the combined incidence of hepatocellular adenomas and carcinomas in untreated male B6C3F1 mice is 31.6% as compared with 7.9% for untreated B6C3F1 females (Haseman et al., 1984). In addition, the incidence of hepatocellular adenomas in females receiving 7.0 and 35.0, but not 100 mg/kg/day, was statistically significantly increased when compared with historical controls. The incidence of combined hepatocellular adenomas and carcinomas in high-dose males was 48.1% as compared with 33.3% for the concurrent control group; the increase was not statistically significant. The incidence of benign
and malignant tumors was not distinguished. Increases in alveolar and bronchiolar carcinomas in high-dose males and females, and in lung histiocytes of high-dose females were not statistically significant. Malignant lymphoma of the kidney was reported to be slightly increased (not statistically significant) in males receiving 1.5, 7.0, and 35.0 mg/kg when compared with concurrent controls. This finding was not seen in female mice. The high dose was lowered from 175 mg/kg/day to 100 mg/kg/day during week 11 because of the high mortality in both sexes. This mortality substantially reduced the number of high-dose animals. The RDX used contained 3 to 10% octahydro-1,3,5,7-tetranitro-1,3,5,7-toluene (HMX). The increase in the incidence of hepatocellular adenomas or carcinomas was not statistically significant (when compared with concurrent controls) in dosed females when analyzed separately, but was significant only when the two groups were combined. Percent survival for the groups is not stated. Mean survival time was statistically significantly lower for the highest male (14.6 months) and female (20.6 months) dose groups and for the male dose group receiving 1.5 mg/kg/day (21 months). The mean survival times for the male and female control groups were 22.3 months and 22 months, respectively.

II.A.4. Supporting Data for Carcinogenicity

RDX gave negative results in all genotoxicity studies cited. The mutagenic potential of RDX was evaluated in two studies using the Salmonella/microsomal preincubation assay. Salmonella strains TA98, TA100, TA1535, and TA1538 were exposed to RDX at concentrations of 1, 10, 100, 300, or 1000 ug/plate in one study (U.S. DOD, 1980), and at 0.625 or 1.25 mg/plate in the second study (Whong et al., 1980). The assays were conducted with and without the addition of hepatic homogenates. In both studies, RDX was not mutagenic.

U.S. DOD (1977) tested the mutagenicity of several munitions wastewater chemicals before and after chlorination or ozone treatment. RDX was evaluated in Salmonella strains TA98, TA100, TA1535, TA1537, and TA1538 at several concentrations ranging from 0.24 to 14 ug/plate, and in Saccharomyces cerevisiae strain D3 at concentrations ranging from 0.00004 to 0.0023%. The assays were conducted with or without hepatic homogenates. RDX was not mutagenic before or after chlorination in these assays.

RDX gave negative results in an unscheduled DNA synthesis (UDS) assay using WI-38 (human fibroblasts) when tested at a maximum concentration of 4000 ug/mL, with or without the addition of hepatic homogenates (U.S. DOD, 1978).
II.B. Quantitative Estimate of Carcinogenic Risk from Oral Exposure

II.B.1. Summary of Risk Estimates

Oral Slope Factor — 1.1E-1 per (mg/kg)/day

Drinking Water Unit Risk — 3.1E-6 per (ug/L)

Extrapolation Method — Linearized multistage procedure, extra risk

Drinking Water Concentrations at Specified Risk Levels:

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<td>E-5 (1 in 100,000)</td>
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<td>E-6 (1 in 1,000,000)</td>
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II.B.2. Dose-Response Data (Carcinogenicity, Oral Exposure)

Tumor Type: liver, hepatocellular carcinoma, and adenomas (combined)
Test animals: mouse/B6C3F1, female
Route: diet
Reference: U.S. DOD, 1984

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<th>Human Equivalent Dose (mg/kg)/day</th>
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II.B.3. Additional Comments (Carcinogenicity, Oral Exposure)

The animal study dose is divided by the ratio of the human weight (70 kg) to the mouse weight (0.040 kg) raised to the 1/3 power. The high-dose data was not used in the slope factor calculation since it was lowered from 175 mg/kg/day to 100 mg/kg/day during week 11 due to low survival.

The unit risk should not be used if the water concentration exceeds 3E+3 ug/L, since above this concentration the slope factor may differ from that stated.

II.B.4. Discussion of Confidence (Carcinogenicity, Oral Exposure)

RDX was found to be carcinogenic in the female B6C3F1 mice. This study had some previously discussed technical problems but is clearly positive for liver carcinomas and adenomas combined. Adequate number of animals were treated for a period of time approximating lifetime.

II.C. Quantitative Estimate of Carcinogenic Risk from Inhalation Exposure

Not available.

II.D. EPA Documentation, Review, and Contacts (Carcinogenicity Assessment)

II.D.1. EPA Documentation


The risk assessment in the 1988 Health Advisory on Hexahydro-1,3,5-trinitro- 1,3,5-triazine (RDX) is a final document and has received Agency Review.
II.D.2. EPA Review (Carcinogenicity Assessment)


Verification Date — 11/30/1988

II.D.3. EPA Contacts (Carcinogenicity Assessment)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (FAX) or hotline.iris@epa.gov (internet address).

III. [reserved]
IV. [reserved]
V. [reserved]

VI. Bibliography

Substance Name — Hexahydro-1,3,5-trinitro-1,3,5-triazine (RDX)
CASRN — 121-82-4

VI.A. Oral RfD References


VI.B. Inhalation RfC References

None

VI.C. Carcinogenicity Assessment References


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**VII. Revision History**

Substance Name — Hexahydro-1,3,5-trinitro-1,3,5-triazine (RDX)
CASRN — 121-82-4

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VIII. Synonyms

Substance Name — Hexahydro-1,3,5-trinitro-1,3,5-triazine (RDX)
CASRN — 121-82-4
Last Revised — 09/26/1988

- 121-82-4
- cyclonite
- cyclotrimethylenenitramine
- cyclotrimethylenetrinitramine
- CYKLNIT
- ESAIDRO-1,3,5-TRINITRO-1,3,5-TRIAZINA
- HEKSOGEN
- HEXAHYDRO-1,3,5-TRINITRO-1,3,5-TRIAZIN
- Hexahydro-1,3,5-trinitro-1,3,5-triazine
- HEXAHYDRO-1,3,5-TRINITRO-s-TRIAZINE
- HEXOGEN
- HEXOGEN
- HEXOGEN 5W
- HEXOLITE
- HEXOLITE, dry or containing, by weight, less than 15% water
- PBX(AF) 108
- PBXW 108(E)
- RDX
- T4
- 1,3,5-TRIAZINE, HEXAHYDRO-1,3,5-TRINITRO-s-triazine, hexahydro-1,3,5-trinitro-
- TRIMETHYLEENTRINITRAMINE
- TRIMETHYLENETRINITRAMINE
- sym-TRIMETHYLENETRINITRAMINE
- TRINITROCYCLOTRIMETHYLENE TRIAMINE
- 1,3,5-TRINITROHEXAHYDRO-s-TRIAZINE
- 1,3,5-TRINITRO-1,3,5-TRIAZACYCLOHEXANE
- UN 0072
- UN 0118