TOXICITY SUMMARY FOR
HEXAHYDRO-1,3,5-TRINITRO-1,3,5-TRIAZINE (RDX)

February 1995

Prepared by
Rosmarie A. Faust, Ph.D.
Chemical Hazard Evaluation Group
Biomedical and Environmental Information Analysis Section
Health Sciences Research Division
Oak Ridge National Laboratory*
Oak Ridge, Tennessee

Prepared for
U.S. ARMY ENVIRONMENTAL CENTER
Aberdeen Proving Ground, Maryland 21010-5401

Contracting Officer's Representative
Robert L. Muhly
Technology Demonstration and Transfer Branch
Environmental Technology Division
U.S. ARMY ENVIRONMENTAL CENTER
Aberdeen Proving Ground, Maryland 21010-5401

*Managed by Martin Marietta Energy Systems, Inc., for the U.S. Department of Energy under Contract No. DE-AC05-84OR21400
TOXICITY SUMMARY UPDATE

This report is an update of the Toxicity Summary for RDX (Hexahydro-1,3,5-trinitro-1,3,5-triazine (CAS Registry No. 121-82-4). The original summary for this chemical was submitted in June 1991. The update was performed by incorporating any new human health toxicity data published since the original submittal of the report. Pertinent pharmacokinetic, toxicologic, carcinogenic, and epidemiologic data were obtained through on-line searches of the TOXLINE database from 1991 through 1994. In addition, any changes to EPA-approved toxicity values (reference doses, reference concentrations, or cancer slope factors) from the Integrated Risk Information System (IRIS) (current as of December 1994) and/or the Health Effects Assessment Summary Tables, Annual FY-94 and July Supplement No. 1) for this chemical were incorporated in this update.
Hexahydro-1,3,5-trinitro-1,3,5-triazine (RDX) is extensively used in military munitions formulations. RDX can enter the aquatic environment through wastewater discharges from the manufacture and loading of RDX, and migration from settling ponds into soil, with subsequent leaching to groundwater. Direct photochemical degradation is the major removal process in water. Atmospheric releases may occur from incineration of RDX-containing mixtures, with dry or wet deposition as major atmospheric removal processes (Etnier, 1986; U.S. EPA, 1989).

RDX exerts its primary toxic effect on the central nervous system (CNS) of humans. Chronic or subchronic exposure of workers to RDX by inhalation is characterized by generalized convulsions, headaches, nausea, vomiting, and unconsciousness. Seizures may be followed by temporary amnesia, disorientation, and weakness (U.S. EPA, 1988; Kaplan et al., 1965). Acute oral exposure to RDX in the form of Composition C-4 (containing 91% RDX) results in similar symptoms. Recovery appears complete when exposure is discontinued (Stone et al., 1969).

In a life-time feeding study, doses up to 40 mg/kg/day of RDX produced increased mortality, weight loss, hypoglycemia, CNS effects, anemia with secondary splenic lesions, hepatotoxicity, urogenital lesions, and cataracts in rats (Levine et al., 1984). Increased mortality, decreased weight gain, hepatomegaly, increased kidney and heart weights, and testicular degeneration were seen in mice exposed to doses up to 100 mg/kg/day for 2 years (Lish et al., 1984). There is no evidence of teratogenicity, but reproductive effects (decreased fertility) and developmental effects (decreased pup weights) have been observed in rats orally exposed to RDX (Angerhofer et al., 1986; Cholakis et al., 1980).

An oral reference dose (RfD) of 0.003 mg/kg/day was derived for both chronic and subchronic exposure to RDX (U.S. EPA, 1994a,b), based on inflammation of the prostate observed in rats in a 2-year feeding study (Levine et al., 1984). An inhalation reference concentration (RfC) has not been derived for RDX.

RDX was not carcinogenic in rats administered 40 mg/kg/day for 2 years (Levine et al., 1984), but induced a statistically significant (p < 0.05) increase in the incidence of hepatocellular adenomas and carcinomas (combined) in female mice that received ≥7 mg/kg/day for 2 years (Lish et al., 1984).

According to U.S. EPA guidelines, RDX was assigned to weight-of-evidence Group C, possible human carcinogen, based on a significantly increased incidence of liver tumors in female mice. For oral exposure, the slope factor is 1.1E-1 (mg/kg/day)^-1 and the drinking water unit risk is 3.1E-6 (µg/L)^-1 (U.S. EPA, 1994a).
1. INTRODUCTION

Hexahydro-1,3,5-trinitro-1,3,5-triazine (CAS Reg. No. 121-82-4), commonly known as RDX or cyclonite, is a white crystalline solid extensively used by the military as an explosive. RDX is slightly soluble in water and apolar organic solvents and readily soluble in polar organic solvents (Etnier, 1986; Sax and Lewis, 1987).

RDX can enter the aquatic environment through wastewater discharges from the manufacture and loading of RDX, and migration from settling ponds into soil, with subsequent leaching to groundwater. Direct photochemical degradation is the major removal process in translucent waters. Atmospheric releases may occur from incineration of RDX-containing mixtures, with dry or wet deposition as major atmospheric removal processes (Etnier, 1986; U.S. EPA, 1989).

2. METABOLISM AND DISPOSITION

2.1. ABSORPTION

In humans and laboratory animals, RDX is slowly absorbed from the gastrointestinal tract after ingestion and from the lungs after inhalation; absorption through the skin apparently has not been demonstrated (Etnier, 1986; U.S. EPA, 1989). In rats, the absorption from the gastrointestinal tract is nearly complete (U.S. EPA, 1989).

2.2. DISTRIBUTION

Following oral administration, absorbed RDX is rapidly cleared from plasma and distributed to tissues of animals (U.S. EPA, 1989). Schneider et al. (1977) showed that plasma concentration in rats reached a plateau within several hours of RDX administration, was maintained at this level for 24 hours, and then declined over the next 2 days. The concentrations of RDX were highest in kidneys, followed by brain, heart, and liver. Continued exposure to RDX resulted in no significant accumulation in any tissue (U.S. EPA, 1989).

2.3. METABOLISM

RDX metabolism is catalyzed by microsomal enzyme systems and occurs primarily in the liver. Metabolism produces several one-carbon fragments, including CO₂, bicarbonate ion, and formic acid; larger intermediates have not been identified (Schneider et al., 1978).

2.4. EXCRETION

RDX is primarily excreted in the urine or exhaled as carbon dioxide. Rats administered 5-8 mg/kg/day of [¹⁴C]-labelled RDX in drinking water for 90 days excreted 22-35% in urine, 4-5% in feces, and 27-51% as exhaled CO₂. Unmetabolized RDX measured in the urine accounted for only 3-5% of the total urinary activity (Schneider et al., 1978).
3. NONCARCINOGENIC HEALTH EFFECTS

3.1. ORAL EXPOSURES

3.1.1. Acute Toxicity

3.1.1.1. Human

Toxic symptoms have been observed in military personnel accidentally or intentionally ingesting C-4, a plastic explosive containing 91% RDX. Generalized convulsions, muscular twitching, hyperactive reflexes, headaches, severe nausea and vomiting, hematuria, and loss of memory were seen within several hours of ingesting 25-180 g C-4. Although serum AST (aspartate aminotransferase) was elevated, liver function tests were normal. Other abnormal laboratory findings included leukocytosis, increased blood urea nitrogen, proteinuria, and hematuria. There were no fatalities and recovery was complete within 1-2 months (Stone et al., 1969).

CNS effects (convulsions) have been observed in a child following ingestion of approximately 1.23 g RDX. The estimated fatal dose of RDX in humans ranges from 5 to 500 mg/kg (U.S. EPA, 1989). A recent case report documented grand mal seizures accompanied by a widespread petechial rash in a soldier 4 hours after chewing a plastic explosive containing RDX (Goldberg et al., 1992).

3.1.1.2. Animal

Similar symptoms occur in laboratory animals following acute exposure with central nervous system excitation (clonic/tonic convulsions) as the most prominent effect. Other toxic manifestations are gasping and labored breathing. Pathological changes at necropsy, generally non-specific, consist of congestion of various organs, including kidney, liver, and lungs. Oral LD₅₀ values range from 44 to 300 mg/kg for rats, indicating that RDX is moderately to highly toxic to animals following acute exposures (Etnier, 1986). The acute oral toxicity of RDX is dependent on the physical form and also on the method used to dissolve or suspend it (Schneider et al., 1977).

3.1.2. Subchronic Toxicity

3.1.2.1. Human

Information on the subchronic oral toxicity of RDX in humans was not available.

3.1.2.2. Animal

F344 rats and B6C3C₁ mice were administered RDX in the diet at doses ranging from 10 to 40 mg/kg/day for 90 days. In the rat study, the only consistent effect was decreased weight gain and decreased food consumption at the highest dose. No toxic effects were seen in mice at any dose level (Cholakis et al., 1980). In a follow-up study, mice were treated with 0, 40, 60, or 80 mg/kg/day for 2 weeks, and then with 0, 80, 160, or 320 mg/kg/day, respectively, for 11 weeks. Significant toxic effects, seen only at 320 mg/kg/day, included increased mortality, hyperactivity, increased liver weight accompanied by hepatocellular vacuolization (males) and microgranulomas (females), and increased kidney weight with mild tubular nephrosis (males) (Cholakis et al., 1980).
RDX was administered daily to F344 rats at dietary doses of 0, 10, 30, 100, 300, or 600 mg/kg/day for 13 weeks. The RDX contained 3-10% HMX (octahydro-1,3,5,7-tetranitro-1,3,5,7-tetrazocine). All rats administered 300 or 600 mg/kg/day died within 1.5 weeks of dosing; high mortality was also seen in rats dosed with 100 mg/kg/day. All animals receiving lethal doses of RDX exhibited hyperactivity and tremors/convulsions. Slightly increased liver weights in the absence of histological liver lesions were seen at 100 mg/kg/day. Serum cholesterol levels were within the normal range (Levine et al., 1981).

In rhesus monkeys, daily oral doses of 0, 0.1, 1.0, or 10 mg RDX/kg/day for 13 weeks caused signs of CNS toxicity, usually involving clonic convulsions at the highest dose. Except for frequent episodes of vomiting, no other clinical signs of toxicity were observed (Litton Bionetics, 1974).

3.1.3. Chronic Toxicity

3.1.3.1. Human

Information on the chronic oral toxicity of RDX in humans was not available.

3.1.3.2. Animal

Male and female F344 rats were fed RDX (containing 3-10% HMX) at doses of 0, 0.3, 1.5, 8.0, or 40.0 mg RDX/kg/day for 24 months (Levine et al., 1984). Compound-related toxicity was seen at 40.0 mg/kg/day and included increased mortality, hypoglycemia, weight loss, anemia with secondary splenic lesions, hepatotoxicity, possible CNS involvement, cataracts, and urogenital lesions. The incidence of mortality in the high-dose group (68% males; 36% females) was increased throughout the study and was frequently preceded by tremors and convulsions. The incidence of cataracts was significantly increased in high-dose females; the eyes of males appeared normal. Hepatotoxicity (both sexes) was characterized by increased liver weight, increased cholesterol and triglyceride levels, decreased serum albumin/total protein levels, and increased lactic dehydrogenase levels. Kidney weights were increased in males and females receiving 8.0 or 40.0 mg/kg/day. There was increased hemosiderin-like pigment in the spleen and suppurative inflammation of the prostate in male rats receiving 1.5, 8.0, or 40.0 mg/kg/day. No adverse effects were noted at 0.3 mg/kg/day.

Lish et al. (1984) exposed B6C3C1 mice to RDX (containing 3-10% HMX) at dietary doses of 0, 1.5, 7.0, 35.0, or 100 mg/kg/day for 24 months. Mice in the high dose group exhibited increased incidence of mortality, reduction in body weight gain, a high incidence of fighting wounds in males, hepatomegaly, increased cholesterol levels, increased kidney and heart weights, and testicular degeneration. Increased kidney weights and testicular degeneration in males and increased cholesterol levels in females were also seen at 35 mg/kg/day.

In contrast to the results of the Levine et al. (1984) and Lish et al. (1984) studies, no evidence of significant toxicity was found in Sprague-Dawley rats ingesting dietary levels up to 10 mg RDX/kg/day for 2 years (Hart, 1976).

3.1.4. Developmental and Reproductive Toxicity

3.1.4.1. Human

Information on the oral developmental and reproductive toxicity of RDX in humans was not available.
3.1.4.2. Animal

RDX was not teratogenic to F344 rats or New Zealand rabbits administered by gavage 0, 0.2, 2.0, or 20.0 mg/kg/day RDX (containing 9% HMX) on days 6-19 of gestation or in New Zealand rabbits administered the same doses on days 7-29 of gestation. However, the high dose produced maternal toxicity (primarily neurotoxicity), maternal mortality, and embryotoxicity in both species (Cholakis et al., 1980). Decreased fetal weight and maternal mortality was also seen in Sprague-Dawley rats given 20.0 mg RDX/kg/day by gavage on days 6-15 of gestation (Angerhofer et al., 1986).

In a two-generation reproductive study, F344 rats were fed 0, 5, 16, or 50 mg RDX/kg/day for 13 weeks and then mated. Increased incidence of mortality, decreased body weight, and decreased food consumption were seen at the high dose. Reproductive effects included decreased number of pregnancies and poor survival of offspring. Decreased pup weights were seen at 16 and 50 mg/kg/day; there were no adverse effects at the lowest RDX dose (Cholakis et al., 1980).

3.1.5. Reference Dose

3.1.5.1. Subchronic

<table>
<thead>
<tr>
<th>ORAL RfD:</th>
<th>0.003 mg/kg/day (U.S. EPA, 1994b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>UNCERTAINTY FACTOR:</td>
<td>100</td>
</tr>
<tr>
<td>NOAEL:</td>
<td>0.3 mg/kg/day</td>
</tr>
<tr>
<td>LOAEL:</td>
<td>1.5 mg/kg/day</td>
</tr>
</tbody>
</table>

COMMENTS: The chronic RfD was adopted as the subchronic RfD (U.S. EPA, 1994b).

3.1.5.2. Chronic

<table>
<thead>
<tr>
<th>ORAL RfD:</th>
<th>0.003 mg/kg/day (U.S. EPA, 1994a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>UNCERTAINTY FACTOR:</td>
<td>100</td>
</tr>
<tr>
<td>NOAEL:</td>
<td>0.3 mg/kg/day</td>
</tr>
<tr>
<td>LOAEL:</td>
<td>1.5 mg/kg/day</td>
</tr>
</tbody>
</table>

CONFIDENCE: Study High, Data Base High, RfD High

VERIFICATION DATE: 04/20/88

PRINCIPAL STUDY: Levine et al., 1984

COMMENTS: The RfD is based on inflammation of the prostrate seen in a 2-year feeding study with rats. The uncertainty factor accounts for interspecies variability between humans and animals (10) and protection of sensitive individuals (10) (U.S. EPA, 1994a).
3.2. INHALATION EXPOSURES

3.2.1. Acute Toxicity

3.2.1.1. Human

Central nervous system toxicity ranging from confusion to multiple seizures and amnesia were seen in soldiers burning composition C-4 explosives (containing 91% RDX) to heat food in the field. Most individuals experienced frequent nausea and vomiting (U.S. EPA, 1988).

3.2.1.2. Animal

Information on the acute inhalation toxicity of RDX in animals was not available.

3.2.2. Subchronic Toxicity

3.2.2.1. Human

Headache, dizziness, nausea, vomiting, convulsions, and unconsciousness were reported in workers exposed to finely powdered RDX dust within 3 months of start-up of RDX-processing in an explosives plant. The workers generally recovered within one day (U.S. EPA, 1988).

3.2.2.2. Animal

Information on the subchronic inhalation toxicity of RDX in animals was not available.

3.2.3. Chronic Toxicity

3.2.3.1. Human

Chronic intoxication resulting from occupational exposure to RDX in munitions workers has been characterized by generalized convulsions and unconsciousness. Convulsions may occur without warning or may be preceded by insomnia, restlessness, and irritability, and may be followed by temporary amnesia, disorientation, nausea, and weakness. Complete recovery occurs upon removal from exposure (Kaplan et al., 1965). A cross-sectional epidemiological study found no evidence of systemic toxicity in munition workers exposed to RDX at concentrations up to 1.57 mg/m³ (Hathaway and Buck, 1977).

3.2.3.2. Animal

Information on the chronic inhalation toxicity of RDX in animals was not available.

3.2.4. Developmental and Reproductive Toxicity

Information on the developmental and reproductive toxicity in humans or animals following inhalation exposure was not available.

3.2.5. Reference Dose/Concentration

Data were insufficient to derive a reference concentration (RfC) for RDX.
3.3. OTHER ROUTES OF EXPOSURE

3.3.1. Acute Toxicity

3.3.1.1. Human

Information on the acute toxicity of RDX in humans by other routes of exposure was not available.

3.3.1.2. Animal

The acute effects following parenteral administration of RDX are similar to those observed after oral administration, but the onset is more rapid. Intraperitoneal administration of an RDX suspension in saline produced deaths in 9/10 rats at a dose of 100 mg/kg (this dose was nonlethal when administered orally); convulsions were seen at a dose as low as 10 mg RDX/kg. Subcutaneous injections of 100 mg RDX/kg caused convulsions in 3/3 rats and death in 2/3 rats. Severe convulsions and death occurred in a rabbit following an intravenous injection of 18 mg RDX/kg (Sunderman, 1944).

Acute dermal toxicity studies conducted with rabbits, beagle dogs, and guinea pigs indicated that RDX causes no or only slight skin irritation following single or multiple skin applications of RDX. Topical application or intradermal injections of RDX produced no evidence of sensitization in guinea pigs (U.S. EPA, 1988).

3.3.2. Subchronic Toxicity

Information on the subchronic toxicity of RDX in humans or animals by other routes of exposure was not available.

3.3.3. Chronic Toxicity

Information on the chronic toxicity of RDX in humans or animals by other routes of exposure was not available.

3.3.4. Developmental and Reproductive Toxicity

Information on the developmental and reproductive toxicity of RDX in humans or animals by other routes of exposure was not available.

3.4. TARGET ORGANS/Critical EFFECTS

3.4.1. Oral exposures

3.4.1.1. Primary Target Organs

1. Central Nervous System: Hyperactivity, tremors, and convulsions were seen in subchronic and chronic feeding studies with rodents.

2. Urogenital System: Chronic exposure of rats and mice produced suppurative inflammation of the prostate gland in rats and testicular degeneration in both species.

3. Liver: Increased liver weights were seen in subchronic and chronic feeding studies with
rodents. Abnormal laboratory values indicative of hepatotoxicity included increased cholesterol and triglyceride, decreased serum albumin/total protein, and increased lactic dehydrogenase levels.

4. Kidneys: Increased kidney weights were seen in subchronic and chronic feeding studies with rodents.

5. Spleen: Hemosiderin-like pigments of the spleen (a secondary response to a hemolytic anemia) were seen in male rats chronically exposed to RDX.

3.4.1.2. Other Target Organs

1. Eyes: Cataracts resulting from chronic RDX exposure were seen in female rats.

2. Reproductive System: A two-generation reproductive study indicated decreased fertility and developmental effects (decreased pup weights) in rats.

3.4.2. Inhalation Exposures

3.4.2.1. Primary Target Organs

1. Central Nervous System: Subchronic to chronic symptoms reported in workers occupationally exposed to RDX include headache, dizziness, generalized convulsions, and unconsciousness. Convulsions may occur without warning or may be preceded by insomnia, restlessness, and irritability, and may be followed by temporary amnesia, disorientation, nausea, and weakness. Complete recovery occurs upon removal from exposure.

2. Gastrointestinal Tract: Nausea and vomiting may result from subchronic or chronic exposure to RDX.

3.4.2.2. Other Target Organs

Available information indicates that other organ systems are unaffected.

4. CARCINOGENICITY

4.1. ORAL EXPOSURES

4.1.1. Human

Information on the carcinogenicity of RDX in humans following oral exposure was not available.

4.1.2. Animal

Groups of 85 male and female B6C3F1 mice were fed doses of 0, 1.5, 7.0, 35.0, or 100.0 mg/kg/day RDX (containing 3-10% HMX) for 24 months (Lish et al., 1984). There was a statistically significant (p < 0.05) increase of hepatocellular carcinomas and adenomas (combined) in females receiving doses ≥ 7.0 mg/kg/day compared with controls. The incidence of combined hepatocellular adenomas and carcinomas was also increased in high dose males, but the increase was not significant.
Levine et al. (1984) (see Section 3.1.3.2) found no evidence of carcinogenicity in F344 rats fed dietary concentrations up to 40 mg RDX/kg/day for 24 months. RDX gave consistently negative responses in in vitro genotoxicity assays (U.S. EPA, 1989).

4.2. INHALATION EXPOSURES

Information on the carcinogenicity of RDX in humans or animals following inhalation exposure was not available.

4.3. OTHER ROUTES OF EXPOSURE

Information on the carcinogenicity of RDX in humans or animals by other routes of exposure was not available.

4.4. EPA WEIGHT-OF-EVIDENCE

Classification -- C - Possible human carcinogen (U.S. EPA, 1994a)
Basis -- Hepatocellular adenomas and carcinomas in female B6C3F1 mice (U.S. EPA, 1994a)

4.5. CARCINOGENICITY SLOPE FACTORS

4.5.1. Oral

SLOPE FACTOR: 1.1E-1 (mg/kg/day)^-1 (U.S. EPA, 1994a)
DRINKING WATER UNIT RISK: 3.1E-6 (µg/L)^-1 (U.S. EPA, 1994a)
PRINCIPAL STUDY: Lish et al., 1984

4.5.2. Inhalation

An inhalation slope factor has not been calculated.
5. REFERENCES


Litton Bionetics, Inc. 1974. Subacute Toxicity of RDX and TNT in Monkeys. AD-A044650/0. Kensington, MD. (As reported in Etnier, 1986)


