TOXICOLOGICAL PROFILE FOR
RDX

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Agency for Toxic Substances and Disease Registry

June 1995

DISCLAIMER

The use of company or product name(s) is for identification only and does not imply endorsement by the Agency for Toxic Substances and Disease Registry.

UPDATE STATEMENT

Toxicological profiles are revised and republished as necessary, but no less than once every three years. For information regarding the update status of previously released profiles, contact ATSDR at:

Agency for Toxic Substances and Disease Registry
Division of Toxicology/Toxicology Information Branch
1600 Clifton Road NE, E-29
Atlanta, Georgia 30333

FOREWORD

This toxicological profile is prepared in accordance with guidelines developed by ATSDR and the Environmental Protection Agency (EPA) and in support of Department of Defense information needs. The original guidelines were published in the Federal Register on April 17, 1987. Each profile will be revised and republished as necessary.

The ATSDR toxicological profile succinctly characterizes the toxicologic and adverse health effects information for the hazardous substance being described. Each profile identifies and reviews the key literature (that has been peer-reviewed) that describes a hazardous substance's toxicologic properties. Other pertinent literature is also presented, but described in less detail than the key studies. The profile is not intended to be an exhaustive document; however, more comprehensive sources of specialty information are referenced.

Each toxicological profile begins with a public health statement, which describes in nontechnical language a substance's relevant toxicological properties. Following the public health statement is information concerning levels of significant human exposure and, when known, significant health effects. The adequacy of information to determine a substance's health effects is described in a health effects summary. Data needs that are significant to protect public health will be identified by ATSDR and the EPA. The focus of the profiles is on health and toxicologic information; therefore, we have included this information in the beginning of the document.

Each profile must include the following:

(A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a hazardous substance in order to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects.

(B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine levels of exposure that present a significant risk to human health of acute, subacute, and chronic health effects.

(C) When appropriate, identification of toxicologic testing needed to identify the types or levels of exposure that might present significant risk of adverse health effects in humans.

The principal audiences for the toxicological profiles are health professionals at the federal, state, and local levels, interested private sector organizations and groups, and members of the public.

The toxicological profiles are developed in response to the Superfund Amendments and Reauthorization Act (SARA) of 1986 (Public Law 99-499) which amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund). Section 211 of SARA also amended Title 10 of the U. S. Code, creating the Defense Environmental Restoration Program. Section 2704(a) of Title 10 of the U. S. Code directs the Secretary of Defense to notify the Secretary of Health and Human Services of not less than 25 of the most commonly found unregulated hazardous substances at defense facilities.

Section 2704(b) of Title 10 of the U. S. Code directs the Administrator of the Agency for Toxic Substances and Disease Registry (ATSDR) to prepare a toxicological profile for each substance on the list provided by the Secretary of Defense under subsection (b).

Foreword

This profile reflects our assessment of all relevant toxicologic testing and information that has been peer reviewed. It has been reviewed by scientists from ATSDR, the Centers for Disease Control and Prevention (CDC), and other federal agencies. It has also been reviewed by a panel of nongovernment peer reviewers and was made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.

David Satcher, M.D., Ph.D.
Administrator
Agency for Toxic Substances and
Disease Registry

CONTRIBUTORS

CHEMICAL MANAGER(S)/AUTHOR(S):

Cassandra Smith-Simon, M.S.
ATSDR, Division of Toxicology, Atlanta, GA

Susan Goldhaber, M.P.H.
Research Triangle Institute, Research Triangle Park, NC

THE PROFILE HAS UNDERGONE THE FOLLOWING ATSDR INTERNAL REVIEWS:

1. Green Border Review. Green Border review assures consistency with ATSDR policy.

2. Health Effects Review. The Health Effects Review Committee examines the health effects chapter of each profile for consistency and accuracy in interpreting health effects and classifying end points.

3. Minimal Risk Level Review. The Minimal Risk Level Workgroup considers issues relevant to substance-specific minimal risk levels (MRLs), reviews the health effects database of each profile, and makes recommendations for derivation of MRLs.

4. Quality Assurance Review. The Quality Assurance Branch assures that consistency across profiles is maintained, identifies any significant problems in format or content, and establishes that Guidance has been followed.

PEER REVIEW

A peer review panel was assembled for RDX. The panel consisted of the following members:

1. Dr. Gordon Edwards, ToxiCon Associates, Natick, Maine;

2. Dr. Vincent Garry, University of Minnesota, Minneapolis, Minnesota;

3. Dr. Barry Levine, University of Illinois at Chicago, Chicago, Illinois; and

4. Dr. Ronald Spanggord, SRI International, Menlo Park, California.

These experts collectively have knowledge of RDX's physical and chemical properties, toxicokinetics, key health end points, mechanisms of action, human and animal exposure, and quantification of risk to humans. All reviewers were selected in conformity with the conditions for peer review specified in Section 104(i)(13) of the Comprehensive Environmental Response, Compensation, and Liability Act, as amended.

Scientists from the Agency for Toxic Substances and Disease Registry (ATSDR) have reviewed the peer reviewers' comments and determined which comments will be included in the profile. A listing of the peer reviewers' comments not incorporated in the profile, with a brief explanation of the rationale for their exclusion, exists as part of the administrative record for this compound. A list of databases reviewed and a list of unpublished documents cited are also included in the administrative record.

The citation of the peer review panel should not be understood to imply its approval of the profile's final content. The responsibility for the content of this profile lies with the ATSDR.

CONTENTS

LIST OF FIGURES

LIST OF TABLES

1. PUBLIC HEALTH STATEMENT

This statement was prepared to give you information about RDX and to emphasize the human health effects that may result from exposure to it. The Environmental Protection Agency (EPA) has identified 1,397 hazardous waste sites as the most serious in the nation. These sites make up the National Priorities List (NPL) and are the sites targeted for long-term federal clean-up activities. RDX has been found in at least 16 of the sites on the NPL. However, the number of NPL sites evaluated for RDX is not known. As EPA evaluates more sites, the number of sites at which RDX is found may increase. This information is important because exposure to RDX may cause harmful health effects and because these sites are potential or actual sources of human exposure to RDX.

When a substance is released from a large area, such as an industrial plant, or from a container, such as a drum or bottle, it enters the environment. This release does not always lead to exposure. You can be exposed to a substance only when you come in contact with it. You may be exposed by breathing, eating, or drinking substances containing the substance or by skin contact with it.

If you are exposed to a substance such as RDX, many factors will determine whether harmful health effects will occur and what the type and severity of those health effects will be. These factors include the dose (how much), the duration (how long), the route or pathway by which you are exposed (breathing, eating, drinking, or skin contact), the other chemicals to which you are exposed, and your individual characteristics such as age, sex, nutritional status, family traits, lifestyle, and state of health.

1.1 WHAT IS RDX?

RDX stands for Royal Demolition Explosive. It is also known as cyclonite or hexogen. The chemical name for RDX is 1,3,5-trinitro-1,3,5-triazine. It is a white powder and is very explosive. It is used as an explosive and is also used in combination with other ingredients in

explosives. Its odor and taste are unknown. It is a synthetic product that does not occur naturally in the environment. It creates fumes when it is burned with other substances. For more information, see Chapters 3 and 4.

1.2 WHAT HAPPENS TO RDX WHEN IT ENTERS THE ENVIRONMENT?

RDX particles can enter the air when it is disposed of by burning. RDX can enter the water from disposal of waste water from Army ammunition plants, and can enter water or soil from spills or leaks from improper disposal at these plants or at hazardous waste sites. RDX dissolves very slowly and to a limited extent in water, and it also evaporates very slowly from water. It does not cling to soil very strongly and can get into the groundwater from soil. RDX can be broken down in air and water in a few hours, but it breaks down more slowly in soil. RDX does not build up in fish or in people. See Chapters 4 and 5 for more information on RDX in the environment.

1.3 HOW MIGHT I BE EXPOSED TO RDX?

Few people will be exposed to RDX. Less than 500 people are known to work with RDX, but these people can breathe dust with RDX in it or get RDX on their skin. You may be exposed to RDX by drinking contaminated water or by touching contaminated soil if you live near factories that produce RDX. RDX has been found in water and soil at some ammunition plants. Surface water samples contained from nondetectable to 36.9 parts of RDX per 1 million parts (ppm) of water. Groundwater samples had levels of 0.001-14.1 ppm. RDX is present at higher levels in soil, with concentrations ranging from less than 5 ppm to 602 ppm. You may be exposed to RDX in the water or soil if it is disposed of improperly. We do not know how much inight be in food or drinking water or how much is in the air. -See Chapter 5 for more information on exposure to RDX.

1. PUBLIC HEALTH STATEMENT

1.4 HOW CAN RDX ENTER AND LEAVE MY BODY?

RDX can get into your lungs if you breathe in the fumes of burning RDX or breathe in the dust from powdered RDX. It can also enter your body if it is in water that you drink. Soldiers have accidentally eaten it when they used it as cooking fuel and it got on their food. It may also pass through the skin into the bloodstream or enter through cuts or breaks in the skin. If you consume RDX, it enters your bloodstream very slowly. We do not know how much can enter through the lungs or skin. The most likely route of exposure at or near hazardous waste sites is contaminated drinking water. We know that it changes into other chemicals in your body, but we do not know which chemicals it changes to. Some of these other chemicals may be hazardous to your health. RDX will leave your body in the breath and urine within a few days. For more information, see Chapter 2.

1.5 HOW CAN RDX AFFECT MY HEALTH?

RDX can cause seizures (a problem of the nervous system) in humans and animals when large amounts are inhaled or eaten. We do not know the effects of long-term, low-level exposure on the nervous system. No other significant health effects have been seen in humans. Rats and mice have had decreased body weights and slight liver and kidney damage from eating RDX for 3 months or more. We do not know if RDX causes cancer in people, but it did cause liver tumors in mice. We do not know whether RDX causes birth defects in humans; it did not cause birth defects in rabbits, but it did result in smaller offspring in rats. We also do not know whether RDX affects reproduction in people. For more information, see Chapter 2.

1.6 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE-BEEN EXPOSED TO RDX?

Medical tests are available to determine whether you have been exposed to RDX. These tests measure RDX levels in your blood or urine. However, these tests can only be used if you have come in contact with RDX in the last few days. These tests can determine if you have

has been exposed to RDX, but they cannot be used to determine how much RDX entered your body. The tests are not routinely available in the doctor's office, but may be ordered by the doctor. They cannot be used to determine long-term health effects from RDX. The usual immediate health effects are seizures, muscle twitching, or vomiting from very high exposures. These would probably occur before you had the blood or urine test.

1.7 WHAT RECOMMENDATIONS HAS THE FEDERAL GOVERNMENT MADE TO PROTECT HUMAN HEALTH?

The government has developed regulations and guidelines for RDX to protect the public from potential harmful health effects of the chemical. The Department of Transportation has many regulations on the transportation of explosives, and the Environmental Protection Agency (EPA) has recommended a drinking water guideline of 2 micrograms per liter μg/L) for RDX.

The Occupational Safety and Health Administration (OSHA) regulates levels of RDX in the workplace. The maximum allowable amount of RDX in workroom air during an 8-hour workday, 40-hour workweek, is 1.5 milligrams per cubic meter (mg/m^3). People's health will probably not be affected by being exposed to this amount of RDX. The National Institute of Occupational Safety and Health (NIOSH) recommends guidelines for RDX in the workplace. The NIOSH recommended exposure limit (REL) for RDX during an &hour workday, 40-hour workweek is 1.5 mg/m 3. The NIOSH short-term exposure limit (STEL), which is the highest level of RDX that they recommend workers be exposed to for 15 minutes, is 3.0 mg/m^3. See Chapter 7 for more information on these and other regulations and guidelines concerning RDX.

1.8 WHERE CAN I GET MORE INFORMATION?

If you have any more questions or concerns, please contact your community or state health or environmental quality department or:

1. PUBLIC HEALTH STATEMENT

Agency for Toxic Substances and Disease Registry
Division of Toxicology
1600 Clifton Road NE, E-29
Atlanta, Georgia 30333

This agency can also provide you with information on the location of the nearest occupational and environmental health clinic. These clinics specialize in the recognition, evaluation, and treatment of illnesses resulting from exposure to hazardous substances.

2. HEALTH EFFECTS

2.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective of the toxicology of RDX and a depiction of significant exposure levels associated with various adverse health effects. It contains descriptions and evaluations of studies and presents levels of significant exposure for RDX based on toxicological studies and epidemiological investigations.

A glossary and list of acronyms, abbreviations, and symbols can be found at the end of this profile.

2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

To help public health professionals address the needs of persons living or working near hazardous waste sites, the information in this section is organized first by route of exposure-inhalation, oral, and dermal-and then by health effect-death, systemic, immunological, neurological, developmental, reproductive, genotoxic, and carcinogenic effects. These data are discussed in terms of three exposure periods-acute (14 days or less), intermediate (15-364 days), and chronic (365 days or more).

Levels of significant exposure for each route and duration are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowestobserved-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELs have been classified into “less serious” or “serious” effects. These distinctions are intended to help the users of the document identify the levels of exposure at which adverse health effects start to appear. They should also help to determine whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

The significance of the exposure levels shown in the tables and figures may differ depending on the user’s perspective. For example, physicians concerned with the interpretation of clinical findings in exposed persons may be interested in levels of exposure associated with “serious” effects. Public health officials and project managers concerned with appropriate actions to take at hazardous waste sites may want information on levels of exposure associated with more subtle effects in humans or

animals (LOAEL) or exposure levels below which no adverse effects (NOAEL) have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels, MRLs) may be of interest to health professionals and citizens alike.

Levels of exposure associated with the carcinogenic effects of RDX are indicated in Table 2-l and Figure 2-l. Because cancer effects could occur at lower exposure levels, Figure 2-l also shows a range for the upper bound of estimated excess risks, ranging from a risk of 1 in 10,000 to 1 in 10,000,000 (10^{-4} to 10^{-7}), as developed by EPA.

Estimates of exposure levels posing minimal risk to humans (MRLs) have been made, where data were believed reliable, for the most sensitive noncancer effect for each exposure duration. MRLs include adjustments to reflect human variability and extrapolation of data from laboratory animals to humans.

Although methods have been established to derive these levels (Barnes and Dourson 1988; EPA 1990b), uncertainties are associated with these techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of the procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for health effects that are delayed in development or are acquired following repeated acute insults, such as hypersensitivity reactions, asthma, or chronic bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.
A User's Guide has been provided at the end of this profile (see Appendix A). This guide should aid in the interpretation of the tables and figures for Levels of Significant Exposure and the MRLs.

2.2.1 Inhalation Exposure

2.2.1.l Death

No studies were located regarding death in humans after inhalation exposure to RDX. Death attributed to impairment of the respiratory system was observed in rabbits and guinea pigs exposed to an unspecified concentration of RDX (Sunderman 1944).

2.2.1.2 Systemic Effects

Very few studies were located regarding systemic effects in humans after inhalation exposure to RDX alone. The available studies have reported gastrointestinal, hematological, hepatic, and renal effects in workers exposed to C-4 (a cooking fuel composed of 91% RDX) or RDX dusts via inhalation. Since the exposure concentration and/or duration were not described for these studies, they are not presented in tables or figures. No studies were located regarding respiratory, cardiovascular, musculoskeletal, dermal, ocular, or other systemic effects in humans after inhalation exposure to RDX. Case reports are available regarding systemic effects in workers exposed to unknown levels of RDX via the inhalation or oral routes (Ketel and Hughes 1972). These studies are also discussed in Section 2.2.2.2. Only one study is available regarding systemic effects in animals after inhalation exposure to RDX (Sunder-man 1944). This study is limited by insufficient numbers of animals tested, no controls, and no data on exposure levels. No studies were located regarding gastrointestinal, hepatic, or dermal effects in animals.

Respiratory Effects. Three of 6 rabbits died from bronchopneumonia; death of 7 of 18 guinea pigs was attributed to pneumonia and pulmonary congestion (Sunderman 1944). Results of this study are preliminary and/or inconclusive since no other inhalation animal studies have been performed.

Cardiovascular Effects. Histopathology revealed the absence of striations in the cardiac muscle of guinea pigs exposed to unspecified levels of RDX for 4-67 days (Sunderman 1944).

Gastrointestinal Effects. Soldiers who were exposed to an unspecified amount of C-4 (91% RDX) as a cooking fuel for an unknown duration experienced nausea and vomiting (Hollander and Colbach 1969; Ketel and Hughes 1972). No studies were located regarding gastrointestinal effects in animals after inhalation exposure to RDX.

Hematological Effects. Two studies of workers exposed to RDX dusts are available, but neither revealed any adverse hematological effects. In one study, workers who were presumably exposed acutely to unknown levels of RDX dusts had normal blood counts (Kaplan et al. 1965). In the other study, workers exposed to an average of 0.3 mg/m3 of RDX dusts in the workplace, presumably for a chronic period, showed no hematological changes compared to controls (Hathaway and Buck 1977). Transient elevation of the white blood count was frequently observed in individuals exposed to C-4

(91% RDX). Normal red blood count, leukocytes, and hemoglobin were reported in rats following intermediate exposure to RDX. However, in the same study, hemoglobin counts were decreased in guinea pigs (Sunderman 1944).

Hepatic Effects. No liver toxicity was revealed by blood or urine analyses of workers exposed to RDX in the air for chronic durations (Hathaway and Buck 1977). No studies were located regarding hepatic effects in animals after inhalation exposure to RDX.

Renal Effects. Blood and urine analyses of workers exposed to RDX in the air for acute (Kaplan et al. 1965) or chronic durations (Hathaway and Buck 1977) did not reveal any kidney toxicity. Although no renal toxicity was observed after exposure to RDX dust, there were some manifestations of renal damage after possible inhalation exposure to C-4 (91% RDX): transient oliguria and proteinuria in two patients and acute renal failure in one case (Ketel and Hughes 1972).
There was no kidney pathology in rats or guinea pigs exposed to RDX, but degeneration of the kidneys was found in rabbits exposed to unspecified levels of RDX for an intermediate period (Sunderman 1944). This study is limited in that no controls were used, and details of the study were not specified.

2.2.1.3 Immunological and Lymphoreticular Effects

Workers at a U.S. Army ammunition plant who were exposed to an average of 0.3 mg/m^3 of RDX dusts for an unknown period of time showed no significant differences in a test for antinuclear antibodies as compared to nonexposed workers. The results of this test provide no evidence of autoimmune disease (Hathaway and Buck 1977). No other immunological function tests were performed.

No studies were located regarding immunological effects in animals after inhalation exposure to RDX.

2.2.1.4 Neurological Effects

Convulsions and unconsciousness, accompanied by headache, dizziness, and vomiting, were noted in 5 out of 26 workers who were exposed to unknown levels of RDX dust in the air (Kaplan et al. 1965).

Similar findings, such as convulsions, muscle twitching, and confusion, have been reported in five case studies of men exposed to C-4 fumes (91% RDX) when it was used as a cooking fuel (Hollander and Colbach 1969). The men from both studies recovered a few days after they were removed from the source of exposure. Other detailed tests of neurological function were not performed.

No studies were located regarding neurological effects in animals after inhalation exposure to RDX.

No studies were located regarding the following effects in humans or animals after inhalation exposure to RDX:

2.2.1.5 Reproductive Effects

2.2.1.6 Developmental Effects

2.2.1.7 Genotoxic Effects

Genotoxicity studies are discussed in Section 2.4.

2.2.1.8 Cancer

No studies were located regarding cancer in humans or animals after inhalation exposure to RDX.

2.2.2 Oral Exposure

2.2.2.1 Death

No studies were located regarding death in humans after oral exposure to RDX.

Deaths were reported in animals following acute, intermediate, and chronic exposures to'RDX. Three out of 12 rats died during induced seizures following acute exposure to 50 mg/kg RDX which was administered by gavage (Burdette et al. 1988). LD_{50} values for single gavage doses in rats range from 71 to 118 mg/kg, and in mice they range from 86 to 97 mg/kg (Army 1978b, 1980b). Miniature swine died following single gavage doses of 100 mg/kg (Schneider et al. 1977). Rat dams that were fed 20 mg/kg/day of RDX during gestation had mortality rates of 30% (Army 1980b, 1986d).

2. HEALTH EFFECTS

In 90-day feeding studies, levels as low as 25 mg/kg/day (von Oettingen et al. 1949) and 100 mg/kg/day, caused deaths in rats (Levine et al. 1990), and levels of 320 mg/kg/day caused deaths in mice (Army 1980b). Levels of 10 mg/kg/day did not cause deaths in dogs (Navy 1974a) or monkeys (Navy 1974b). In chronic-duration studies, rats exposed to 40 mg/kg/day for l-2 years had excessive deaths compared to controls (Army 1983a). However, excessive deaths were not observed in rats administered 10 mg/kg/day of RDX (Navy 1976). The LD_{50} values and all reliable LOAEL values for death are recorded in Table 2-l and plotted in Figure 2-l.

2.2.2.2 Systemic Effects

No studies were located regarding respiratory, cardiovascular, musculoskeletal, or dermal/ocular effects in humans after acute oral exposure to RDX. No studies were located regarding systemic effects in humans after intermediate or chronic oral exposure to RDX. The highest NOAEL values and all reliable LOAEL values for systemic effects in each species and duration category are recorded in Table 2- 1 and plotted in Figure 2-l.

Respiratory Effects. Adverse respiratory effects were not observed in animals following acute, intermediate, or chronic exposure. An acute-duration study in anesthetized dogs showed no changes in breathing rate when RDX was administered by gavage (von Oettingen et al. 1949). No histopathology was seen in the lungs, trachea, or bronchi of rats exposed for 3-13 weeks to 30-300 mg/kg/day of RDX in the food (Levine et al. 1990). These findings are supported by the lack of histopathology at lower dose levels (Army 1980b, 1983a; Levine et al. 1981; von Oettingen et al. 1949). No histopathological changes in the respiratory system were reported in mice (Army 1980b, 1984c), dogs (Navy 1974a; von Oettingen et al. 1949), or monkeys (Navy 1974b). Chronic-duration studies also revealed no histopathology in rats (Army 1983a; Navy 1976) or mice (Army 1984c).

Cardiovascular Effects. Few, if any, changes were observed in cardiovascular parameters measured in animals exposed to RDX. An acute-duration study in anesthetized dogs showed no changes in heart rate when RDX was administered by gavage (von Oettingen et al. 1949). Intermediate-duration studies revealed no histopathology in the heart of rats exposed to 20-100 mg/kg/day of RDX (Levine et al. 1981; Schneider et al. 1978; von Oettingen et al. 1949). Slight myocardial degeneration was observed in rats exposed to 40 mg/kg/day and mice exposed to 320 mg/kg/day in the food (Army 1980b). No pathology was seen in the hearts of dogs (Navy 1974a

TABLE 2-1. Levels of Significant Exposure to RDX - Oral

Key to[a] figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
	ACUTE EXPOSURE						
	Death						
1	Rat (Sprague-Dawley)	once (GO)				71 M (LD50)	Army 1978b
2	Rat (Fischer 344)	once (G)				119 (LD50)	Army 1980b
3	Rat (Fischer 344)	Gd6-19 (GW)				20 F (6/25 died)	Army 1980b
4	Rat (Sprague-Dawley)	Gd6-15 (GW)				20 F (31% died)	Army 1986d
5	Rat (Long- Evans)	once (GW)				50 M (3/12 died during seizures)	Burdette et al. 1988
6	Mouse (Swiss-Webster)	once (GO)				86 F (LD50) 75 M (LD50)	Army 1978b
7	Mouse (B6C3F1)	once (G)				97 M (LD50) 59 F (LD50)	Army 1980b
8	Pig (NS)	once (GW)				100 F (2/10 died)	Schneider et al. 1977

TABLE 2-1. Levels of Significant Exposure to RDX - Oral (continued)

Key to figure[a]	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
	Systemic						
9	Human	NS	Hemato		2571 M (hematuria)		Stone et al. 1969
			Hepatic		2571 M (elevated SGOT)		
			Renal		357 M (azotemia and proteinuria)		
10	Rat (Fischer 344)	Gd 6-19 (GW)	Hepatic		20 F (decreased liver weight)		Army 1980b
			Bd Wt			20 F (12% decrease in body weight)	
	Neurological						
11	Human	NS				357 M (seizures)	Stone et al. 1969
12	Rat (Fischer 344)	Gd6-19 (GW)		2 F		20 F (convulsions and hyperactivity in dams)	Army 1980b
13	Rat (Sprague-Dawley)	once (GW)			12.5 (decreases in motor activity and learning)		Army 1985b
14	Rat (Sprague-Dawley)	Gd6-15 (GW)		6[b] F		20 F (convulsions, prostration in dams)	Army 1986d
15	Rat (Long- Evans)	once (GW)		12.5 M		25 M (spontaeous seizures)	Burdette et al. 1988
16	Rat (Sprague-Dawley)	once (GW)				50 (convulsions)	Schneider et al. 1977

TABLE 2-1. Levels of Significant Exposure to RDX - Oral (continued)

Key to figure[a]	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
17	Pig (NS)	once (GW)				100 F (convulsions)	Schneider et al. 1977
	Developmental						
18	Rat (Fischer 344)	Gd6-19 (GW)		2			Army 1980b
19	Rat (Sprague-Dawley)	Gd6-15 (GW)		6	20 (decreased fetal weight (9%) and length (5%))		Army 1986d
	INTERMEDIATE EXPOSURE						
	Death						
20	Rat (Fischer 344)	13 wk (F)				100 (13/20 died)	Levine et al. 1990
21	Rat (NS)	90 d (F)				25 (8/20 died)	von Oettingen et al. 1949
22	Mouse (B6C3F1)	90 d (F)				320 M (4/10 died)	Army 1980b

TABLE 2-1. Levels of Significant Exposure to RDX - Oral (continued)

Key to figure[a]	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
	Systemic						
23	Rat (Fischer 344)	90 d (F)	Resp	40			Army 1980b
			Cardio	28 F	40 F (decreased absolute heart wt, myocardial degeneration)		
			Gastro	40			
			Hemato	40			
			Musc/skel	40			
			Hepatic	20	28M (significantly decreased SGPT levels)		
			Renal	40			
			Endocr	40			
			Derm	40			
			Ocular	40			
			Bd Wt	28	40M (12% decrease in body wt gain)		
24	Rat (Fischer 344)	6 mo (F)	Resp	40			Army 1983a
			Cardio	40			
			Gastro	40			
			Hemato	40			
			Musc/skel	40			
			Hepatic	40			
			Renal	40			
			Endocr	40			
			Derm	40			
			Ocular	40			
			Bd Wt	8	40 (17% decrease in body wt. gain)		
			Metabolic	40			

TABLE 2-1. Levels of Significant Exposure to RDX - Oral (continued)

Key to figure[a]	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
25	Rat (Fischer 344)	13 wk (F)	Resp	100			Levine et al. 1981
			Cardio	100			
			Gastro	100			
			Hemato		10 F (increased leukocyte counts)		
			Musc/skel	100			
			Hepatic	30	100 F (significant increase in absolute & relative liver wts)		
			Renal	100			
			Bd Wt	30	100M (17% weight loss)		
			Metabolic		10 (10 - 14% decrease in serum triglycerides)		
26	Mouse (B6C3F1)	90 d (F)	Cardio	160	320M (slight myocardial degeneration)		Army 1980b
			Hemato	80	160M (12% decrease in eryrocyte count & 7% decrease in hemoglobin concentration)		
			Hepatic	160	320M (hepatocellular vacuolizaton)		
			Renal	160	320M (mild tubular nephrosis)		
			Endocr	160	320 F (mild fat infiltration)		
			Bd Wt	320			

TABLE 2-1. Levels of Significant Exposure to RDX - Oral (continued)

Key to figure[a]	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
27	Mouse (B6C3F1)	6 mo (F)	Resp	100			Army 1984c
			Cardio	100			
			Gastro	100			
			Hemato	100			
			Musc/skel	100			
			Hepatic	100			
			Renal	100			
			Endocr	100			
			Ocular	100			
28	Dog (NS)	6 wk 6 d/wk (C)	Resp	50			von Oettingen et al. 1949
			Cardio	50			
			Hemato	50			
			Hepatic	50			
			Renal	50			
			Endocr	50			
			Bd Wt		50 (weight loss, unspecified amount)		
			Metabolic	50			
	Immunological/Lymphoreticular						
29	Rat (Fischer 344)	6 mo (F)		40			Army 1983a
30	Rat (Fischer 344)	10 wk (F)		100			Levine et al. 1990

TABLE 2-1. Levels of Significant Exposure to RDX - Oral (continued)

Key to figure[a]	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
31	Mouse (B6C3F1)	90 d (F)		320			Army 1980b
32	Dog (NS)	6 wk 6d/wk (C)		50			von Oettingen et al. 1949
	Neurological						
33	Rat (Fischer 344)	25 wk (F)		8		40 (tremor, convulsions)	Army 1983a
34	Rat Fischer 344	13 wk (F)		30	100 (hyperactive)		Levine et al. 1981
35	Rat (Fischer 344)	10 wk (F)		30	100 (hyperactive)		Levine et al. 1990
36	Rat (NS)	90 d (F)		15		25 (convulsions, hyperirritability & fighting)	von Oettingen et al. 1949
37	Rat (NS)	10 wk (F)		15		50 (hyperirritability & convulsions)	von Oettingen et al. 1949
38	Dog (NS)	6 wk 6d/wk (C)				50 F (hyperactivity, tonic convulsions in 7/7 dogs)	von Oettingen et al. 1949
	Reproductive						
39	Rat (Fischer 344)	6 mo (F)		8[c] M	40 M (testicular degeneration)		Army 1983a

TABLE 2-1. Levels of Significant Exposure to RDX - Oral (continued)

Key to[a] figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
40	Rat (Fischer 344)	3-13 wk (F)		100			Levine et al. 1990
41	Dog Beagles	90 d (F)		10			Navy 1974a
	Developmental						
42	Rabbit (NS)	Gd7-29 (GW)		20			Army 1980b
	CHRONIC EXPOSURE						
	Death						
43	Rat (Fischer 344)	2 yr (F)				40 M (88% died)	Army 1983a

TABLE 2-1. Levels of Significant Exposure to RDX - Oral (continued)

Key to[a] figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
	Systemic						
44	Rat (Fischer 344)	1 & 2 yr (F)	Resp	40			Army 1983a
			Cardio	40			
			Gastro	40			
			Hemato	8	40 (anemia)		
			Musc/skel	40			
			Hepatic	8	40 (hepatomegaly, increase relative liver wt)		
			Renal	8		40 (renal papillary necrosis with increased BUN)	
			Endocr	8		40 (enlarged adrenals)	
			Ocular	8 F		40 F (cataracts)	
			Bd Wt	8		40 (20% less weight gain)	
45	Mouse (B6C3F1)	1 & 2 yr (F)	Resp	100			Army 1984c
			Cardio	35	100 (increased relative heart wt)		
			Gastro	100			
			Hemato	100			
			Musc/skel	100			
			Hepatic	100			
			Renal	35	100 (increased relative kidney wts & reversible cytoplasmic vacuolization)		
			Ocular	100			
			Bd Wt	100			

TABLE 2-1. Levels of Significant Exposure to RDX - Oral (continued)

Key to[a] figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
	Neurological						
46	Rat (Fischer 344)	1 & 2 yr (F)		8		40 (tremors, convulsions)	Army 1983a
	Reproductive						
47	Mouse (B6C3F1)	1 & 2 yr (F)		7 M 100 F	35 M (testicular degeneration)		Army 1984c
	Cancer						
48	Mouse (B6C3F1)	1 & 2 yr (F)				7 F (CEL: hepatocellular carcinomas & adenomas)	Army 1984c

[a]The number corresponds to entries in Figure 2-1

[b]Used to derive an acute oral Minimal Risk Level (MRL) of 0.06 mg/kg/day; dose divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability)

[c]Used to derive an intermediate oral MRL of 0.03 mg/kg/day; dose divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability) and an additional modifying factor of 3 for database deficiencies.

Bd Wt = body weight; BUN = blood urea nitrogen; (C) = capsule; Cardio = cardiovascular; CEL = cancer effect level; d = day(s); Derm = dermal; Endocr = endocrine; F = female; (F) = feed; (G) = gavage; Gastro = gastrointestinal; Gd = gestational day(s); (GO) = gavage in oil; (GW) = gavage in water; Hemato = hematological; Immuno./Lymphor = immunological/lymphoreticular; LD50 = lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male; mo = month(s); Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; NS = not specified; Resp = respiratory; SGOT = serum glutamic oxaloacetic transaminase; wk = week(s); yr = year(s)

FIGURE 2-1. Levels of Significant Exposure to RDX – Oral

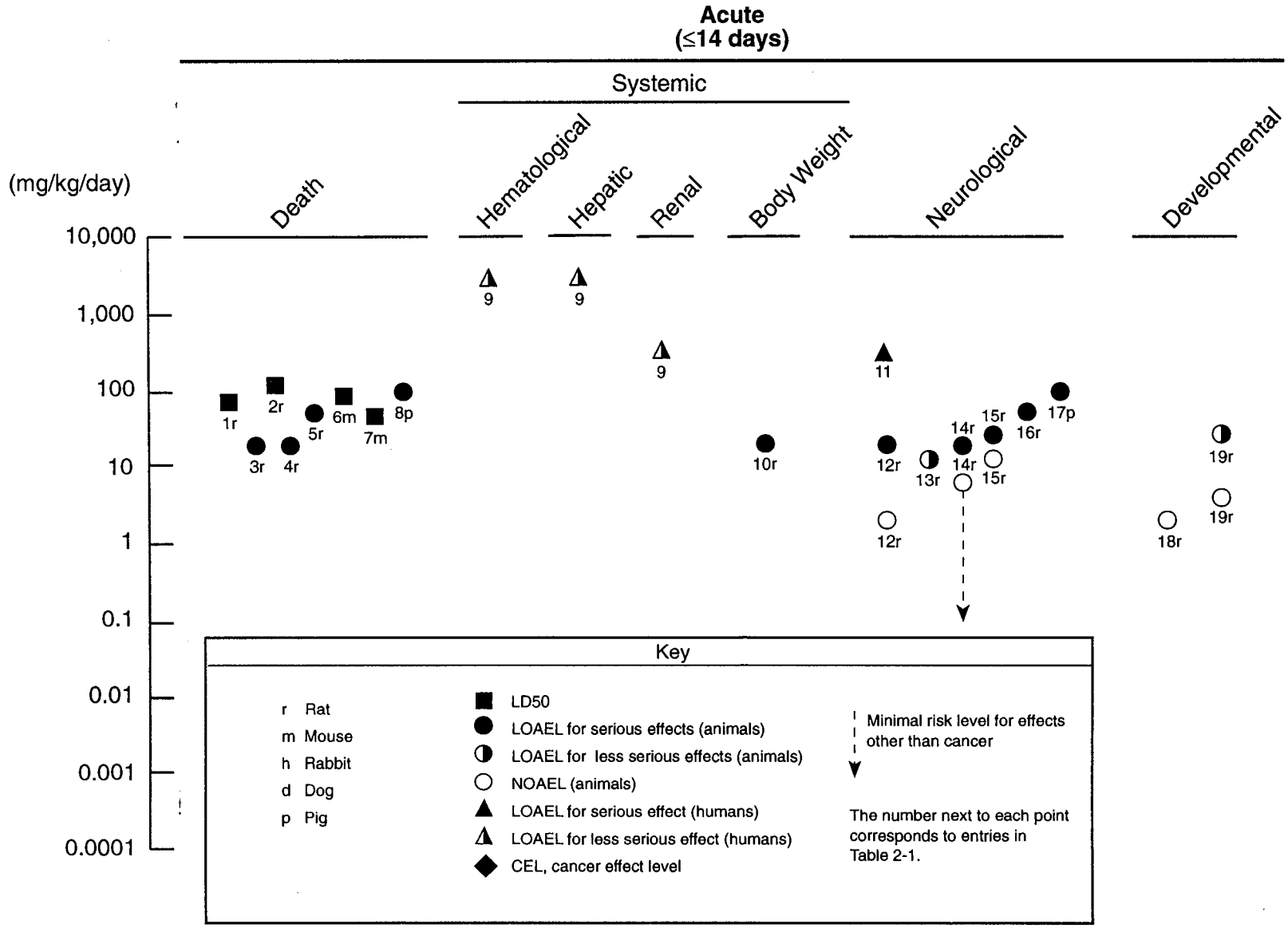


FIGURE 2-1. Levels of Significant Exposure to RDX – Oral (Continued)

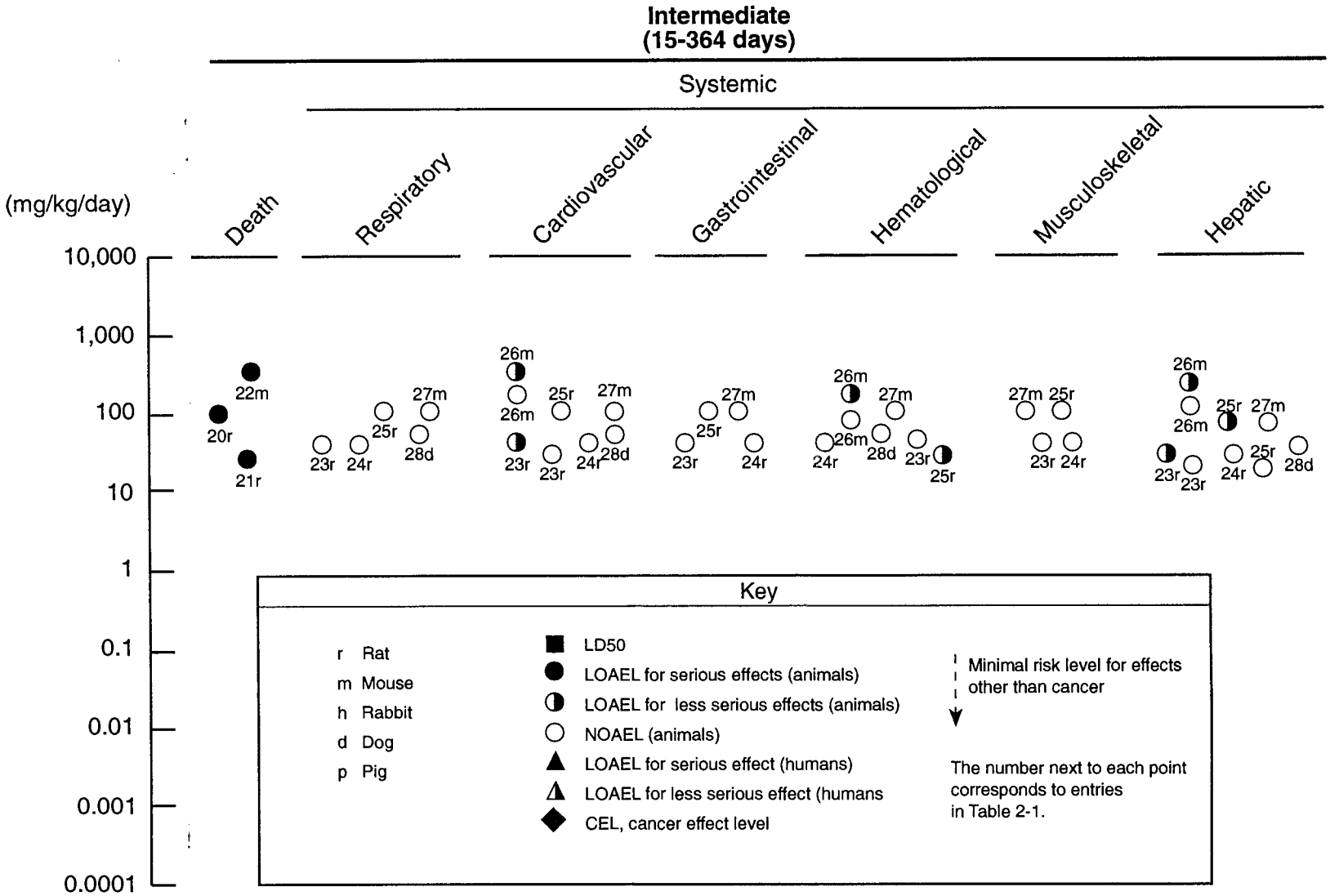


FIGURE 2-1. Levels of Significant Exposure to RDX – Oral (Continued)

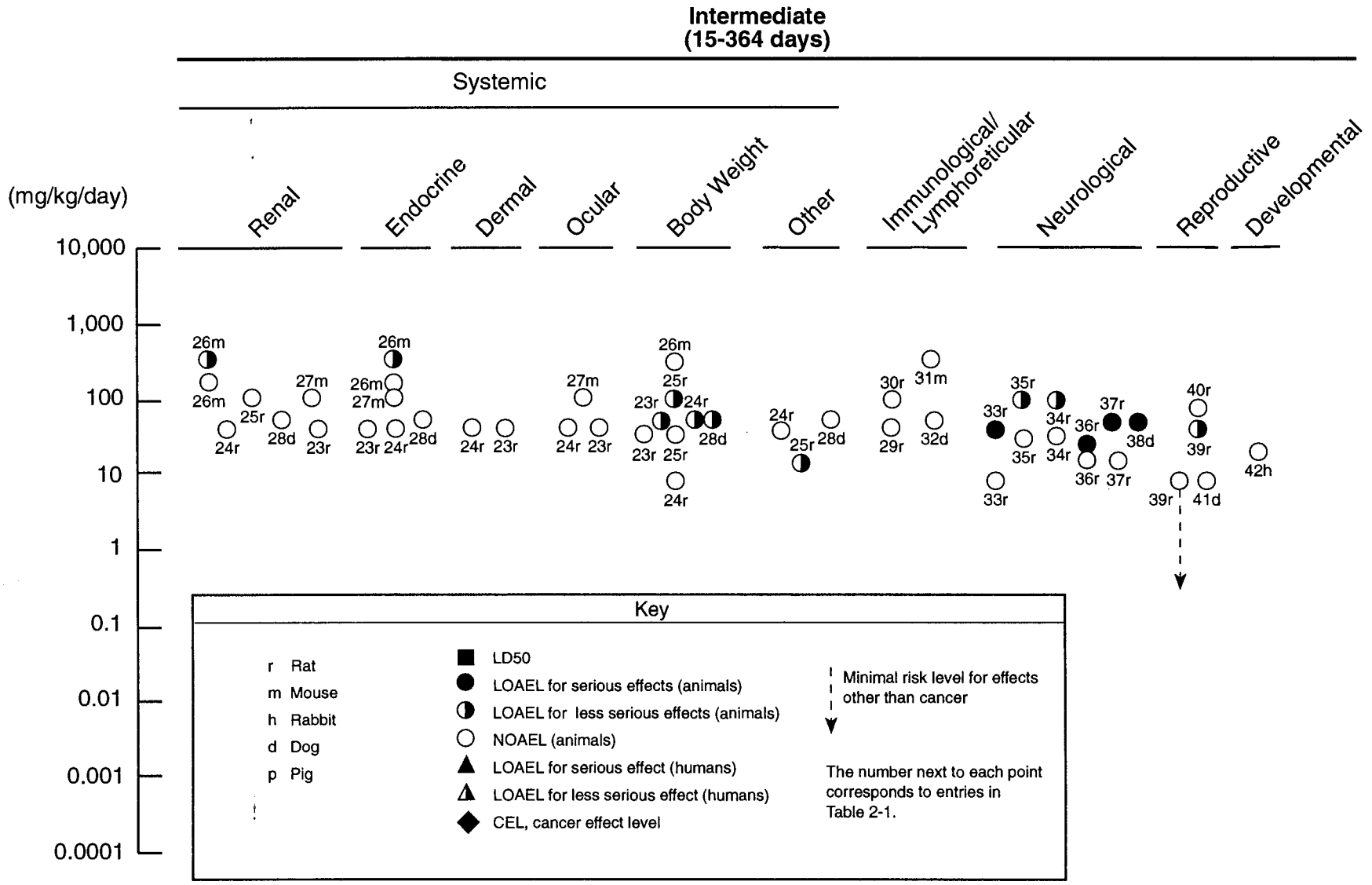
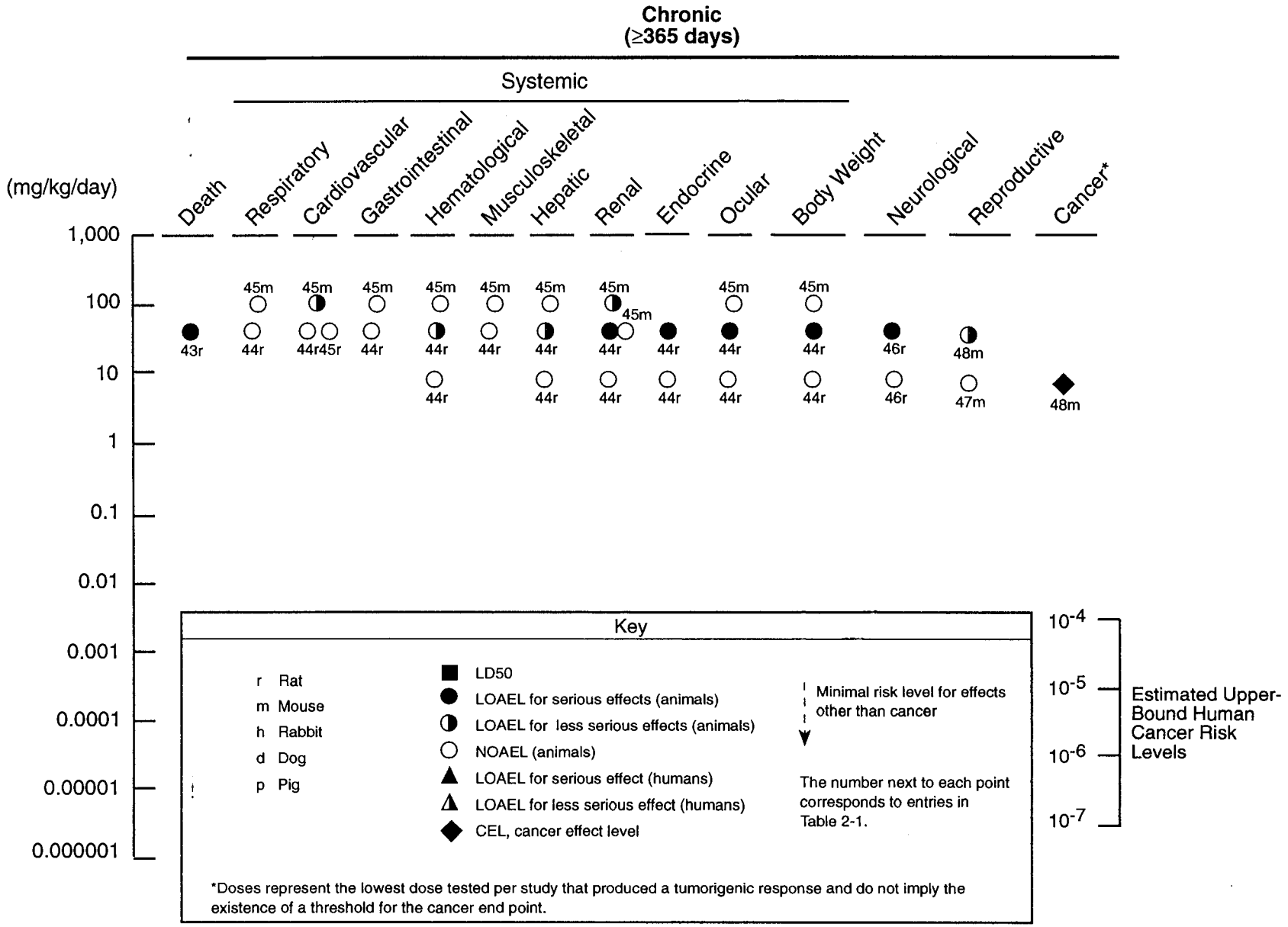


FIGURE 2-1. Levels of Significant Exposure to RDX – Oral (Continued)



von Oettingen et al. 1949) or monkeys (Navy 1974b) exposed to RDX for intermediate periods. Hyaline degeneration of the heart muscles was observed in rats following intermediate exposure to 50 mg/kg/day of RDX (Sunderman 1944). Chronic exposure produced no cardiac histopathology in rats (Army 1983a; Navy 1976), but it increased relative heart weights in mice (Army 1984c).

Gastrointestinal Effects. Humans who accidentally consumed unknown levels of RDX for an acute period had nausea and vomiting (Ketel and Hughes 1972). It is also possible that these individuals were exposed to RDX fumes from using C-4 as a cooking fuel.

Vomiting was reported in dogs acutely exposed to 100 mglkglday and 300 mglkglday of RDX (Sunderman 1944). Following intermediate exposure of rats to 50 mg/kg/day RDX, mild congestion of the intestines was reported (Sunderman 1944). No histopathology was seen in the stomachs or intestines of rats (Army 1980b, 1983a; Levine et al. 1981, 1990; Schneider et al. 1978), mice (Army 1980b, 1984c), dogs (Navy 1974a; von Oettingen et al. 1949), or monkeys (Navy 1974b). Chronic exposure also did not produce histopathology in rats (Army 1983a; Navy 1976) or mice (Army 1984c).

Hematological Effects. Humans who accidentally consumed unknown levels of RDX for an acute-duration period generally had normal blood counts (Ketel and Hughes 1972; Woody et al. 1986). Temporary anemia and leukocytosis were reported in a study of six men who consumed unknown levels of RDX by using cooking utensils that were exposed to RDX fumes (Knepshield and Stone 1972).

No hematological abnormalities were observed in rats exposed to RDX in the food for 90 days (Army 1983a; Levine et al. 1990), except for marginal leukocytosis (Levine et al. 1981) and an increase in reticulocytes, platelets, and hemoglobin without corresponding alterations in the spleen (Army 1980b). Hematological parameters were normal in mice (Army 1980b, 1984c) and dogs (Navy 1974a; von Oettingen et al.- 1949). Necrotic and degenerative megakaryocytes were observed in thebone marrow of monkeys given 10 mg/kg/day of RDX for 90 days (Navy 1974b). Chronic administration of 40 mg/kg/day of RDX in the diet for l-2 years produced decreased hematocrit, hemoglobin, and red blood cells in male rats, but the effects were slight and there were no compensatory responses (Army 1983a). No such effects were seen in mice (Army 1984c).

2. HEALTH EFFECTS

Musculoskeletal Effects. No histopathology was observed in muscle or skeletal tissue of rats (Army 1980b, 1983a; Levine et al. 1981, 1990), mice (Army 1980b, 1984c), or dogs (Navy 1974a) exposed for intermediate periods. Muscles and bones were also normal in rats (Army 1983a; Navy 1976) and mice (Army 1984c) exposed for chronic periods.

Hepatic Effects. Humans who accidentally consumed unknown levels of RDX after using C-4 as a cooking fuel for an acute-duration period had normal liver enzymes (Ketel and Hughes 1972) or slightly elevated serum glutamic oxaloacetic transaminase (Knepshield and Stone 1972; Merrill 1968; Stone et al. 1969). Liver biopsies were normal (Stone et al. 1969), and hepatomegaly was not observed (Knepshield and Stone 1972).

Adverse hepatic effects have been noted in some animal studies. No gross or microscopic lesions were observed in rats exposed for intermediate durations (Levine et al. 1981; Schneider et al. 1978; von Oettingen et al. 1949). Blood and urine parameters were also normal. A decrease in serum glutamic pyruvic transaminase was observed at 28 mg/kg/day (Army 1980b). Significantly increased liver weights were noted in rats at 30 to 300 mg/kg/day (Levine et al. 1981, 1990), while increases in liver weight and hepatocellular vacuolization were observed in mice at doses of 320 mg/kg/day (Army 1980b) and fatty degeneration was reported in the liver of rats exposed to 50 mg/kg/day for 78 days (Sunderman 1944). Normal blood, urine, gross, and histological parameters of liver function were seen in dogs exposed to 50 mg/kg/day or less (Navy 1974a; von Oettingen et al. 1949) and monkeys at 10 mg/kg/day (Navy 1974b). Chronic studies in rats revealed hepatomegaly and increased liver weights at 40 mg/kg/day (Army 1983a). Liver effects were not apparent at 10 mg/kg/day (Navy 1976). Enlarged livers and hypercholesterolemia were observed in mice given 100 mg/kg/day (Army 1984c).

Renal Effects. Humans who accidentally consumed unknown levels of RDX for an acute-duration period showed no (Woody et al. 1986) or only slight (Ketel and Hughes 1972; Knepshield and Stone 1972; Merrill 1968; Stone et al. 1969) changes in renal function parameters.

Few adverse renal effects were reported in animals. No kidney histopathology was observed in rats following intermediate exposure periods (Army 1980b, 1983a; Levine et al. 1981, 1990; Schneider et al. 1978; von Oettingen et al. 1949). Normal kidney parameters were also observed in dogs (Navy 1974a; von Oettingen et al. 1949) and monkeys (Navy 1974b). In contrast, tubular nephrosis was

reported in mice given high doses (320 mg/kg/day) in the food for 13 weeks, but was not seen at lower doses (160 mg/kg/day) (Army 1980b). Following chronic exposure to 40 mg/kg/day of RDX in food, increased kidney weights, urinary bladder distention, renal papillary necrosis, and elevated blood urea nitrogen were observed in rats, which indicates serious renal dysfunction (Army 1983a). These effects were not observed at 8 mg/kg/day. Other studies showed normal renal parameters in rats at lower levels (10 mg/kg/day) (Navy 1976). Increased kidney weights but no other signs of kidney toxicity were observed in mice chronically exposed to 100 mg/kg/day (Army 1984c).

Endocrine Effects. No histopathology was observed in the adrenal glands of rats (Army 1980b, 1983a; Navy 1976), mice (Army 1984c), dogs (Navy 1974a), or monkeys (Navy 1974a) exposed for intermediate periods. One study (Army 1980b) observed mild fat infiltration in the adrenal glands of female mice exposed to 320 mg/kg/day RDX for 90 days, while another study (Army 1983a) observed enlarged adrenals, with no microscopic changes, after exposure to RDX at 40 mg/kg/day for 1 year.

Dermal Effects. No skin lesions were seen in rats (Army 1980b, 1983a), dogs (Navy 1974a), or monkeys (Navy 1974b) exposed for .intermediate periods to RDX in the food.

Ocular Effects. Female rats exposed to 40 mg/kg/day of RDX in their food for 2 years had cataracts (Army 1983a), but this was not seen in mice exposed to a higher level (100 mg/kg/day) (Army 1984c).

Body Weight Effects. Decreased weight gain occurred in rat dams exposed to 20 mg/kg/day during gestation (Army 1980b). Weight loss or lack of weight gain of more than 10% was seen in rats fed 25-40 mg/kg/day (Army 1980b; Levine et al. 1981, 1990; von Oettingen et al. 1949) and dogs fed 50 mg/kg/day (von Oettingen et al. 1949) for an intermediate duration, and in rats receiving 40 mg/kg/day RDX (Army 1983a) and mice receiving 100 mg/kg/day (Army 1984c) for a chronic period. In all cases, the weight changes were minimal.

Metabolic Effects. Decreases in serum triglycerides were noted in rats exposed to 30 mg/kg/day RDX for 13 weeks (Levine et al. 1981, 1990).

2.2.2.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological effects in humans after oral exposure to RDX.

No studies were located regarding immunological effects in animals after acute oral exposure to RDX. Studies of intermediate duration (6-13 weeks) failed to reveal pathology in the spleen, thymus, or lymph nodes in rats (Army 1980b; Levine et al. 1990), mice (Army 198Ob), dogs (Navy 1974a; von Oettingen et al. 1949), or monkeys (Navy 1974b). One study did show splenic extramedullary hematopoiesis (without increased organ weight) after rats were exposed to 40 mg/kg/day of RDX in the feed for 6 months (Army 1983a). No immunological function tests were performed. A chronicduration study showed increased levels of a hemosiderin-like pigment deposited in the spleen of rats exposed to 1.5 mg/kg/day of RDX in the feed (Army 1983a). These changes are not adverse, and no other immunological function tests were performed. The authors stated that these were secondary effects and were probably not treatment related. The highest NOAEL values for immunological effects in each species and duration category are recorded in Table 2-l and plotted in Figure 2-l.

2.2.2.4 Neurological Effects

The available studies have identified the neurological system as a target system in humans following oral exposure to RDX. Numerous case reports are available that describe seizures in men (Hollander and Colbach 1969; Ketel and Hughes 1972; Knepshield and Stone 1972; Merrill 1968; Stone et al. 1969) and in one child (Woody et al. 1986) after accidental consumption of unknown quantities of RDX for acute periods. The RDX was almost always mixed with other components in the form of the explosive C-4 which is 91% RDX (mixed with polyisobutylene, motor oil, and an inert plasticizer). Recovery occurred within a few days or weeks. Accompanying complaints included disorientation, nausea, restlessness, muscle twitching, and lethargy. No other neurological evaluations were performed. An approximate dose could be determined in two cases (Stone et al. 1969); this dose is presented as a serious LOAEL in Table 2- 1 and Figure 2- 1. No intermediate- or chronic-duration exposure data have been reported for humans.

Animal studies have also shown that the neurological system is a target system for animals following oral exposure to RDX. Seizures were observed in acute gavage studies in rats receiving 25 or 50 mg/kg (Burdette et al. 1988; Schneider et al. 1977) and miniature swine receiving 100 mg/kg

(Schneider et al. 1977). Rat dams that were given 20 mg/kg/day by gavage during gestation showed hyperactivity (Army 1980b) and convulsions (Army 1986d). No effects were observed in rats exposed to 6 mg/kg/day of RDX (Army 1986d). This study (Army 1986d) was used to calculate an acute oral MRL. Less severe behavioral changes were observed at a lower dose (12.5 mg/kg) in rats (Army 1985b). Intermediate-duration studies have also shown seizures in rats exposed to 25 mg/kg/day (von Oettingen et al. 1949) and 40 mg/kg/day of RDX in their diet (Army 1983a). Seizures have also been seen in dogs at 50 mg/kg/day (von Oettingen et al. 1949) and monkeys at 10 mg/kg/day (Navy 1974b). In animals that have not had seizures, hyper-reactivity and increased fighting is often observed (Levine et al. 1990). Behavioral tests at a lower dose (10 mg/kg/day for 30 days) showed no adverse effects in rats (Army 1985b). Seizures have also been reported in rats chronically exposed to 40 mg/kg/day of RDX in food. The histopathology reports for the neurological system were negative (Army 1983a). The highest NOAEL values and all reliable LOAEL values for neurological effects in each species and duration category are recorded in Table 2- 1 and plotted in Figure 2-l.

2.2.2.5 Reproductive Effects

No studies were located regarding reproductive effects in humans after oral exposure to RDX.

Toxicity studies lasting 13 weeks showed no pathology in the gonads or uteri of rats (Army 1980b, 1983a; Levine et al. 1981, 1990), dogs (Navy 1974a), or mice (Army 1984c) exposed to RDX. No functional tests were performed. One study did report spermatic granulomas in the prostates of rats exposed to 40 mg/kg/day for 6 months (Army 1983a). No effects were observed in rats exposed to 8 mg/kg/day of RDX for 6 months (Army 1983a); this study was used to derive an intermediate oral MRL.

Histological examinations of rats exposed to 1.5 mg/kg/day for l-2 years in the feed revealed inflammation and pus in the prostate (Army 1983a). The observed toxicity in RDX treated rats may have been due to bacterial infection of the urinary tract, possibly secondary to a diminished ability of the prostate to respond to normal bacterial flora. This is plausible because bladder distention and cystitis were also noted. The pathology reports of this study state that a no-effect level from RDX could not be determined from this study; however, this was not in agreement with the report summary which stated that the no-effect-level was 0.3 mg/kg/day. The prostate pathology was not replicated in other studies in rats (Navy 1976) or in mice (Army 1984c). The rats showed no histopathology in the

testes, ovaries, or uterus, but the mice had testicular degeneration at 35 mg/kg (Army 1984c). A twogeneration study of rats was inconclusive because of excessive mortality at the high dose (50 mg/kg/day), with decreased fertility, viability, and lactation at 50 mg/kg/day (Army 1980b). The highest NOAEL values and all reliable LOAEL values for reproductive effects in each species and duration category are recorded in Table 2-l and plotted in Figure 2- 1.

2.2.2.6 Developmental Effects

No studies were located regarding developmental effects in humans after oral exposure to RDX.

There are two available developmental studies in rats (exposed for 9 or 13 days during gestation) that are inconclusive because of excessive maternal toxicity at the high dose (20 mg/kg/day). In one study, no excessive gross, visceral, or skeletal anomalies were found in fetuses when the dams were exposed to 2 mg/kg/day of RDX (Army 1980b). High maternal lethality, decreased maternal body weights, and adverse maternal neurotoxic effects precluded judgement regarding fetal toxicity at 20 .mg/kg/day. The other rat study also showed high maternal toxicity at 20 mg/kg/day. However, a slight decrease in fetal weights (4%) and lengths (2%) were reported in rats exposed to 2 mg/kg/day (Army 1986d). It appears that there was an overlap in the standard deviations for the fetal body weight and length values; however, the authors stated that the differences in these measurements were statistically significant between controls and each of the dose groups. In contrast to rats, rabbits (exposed for 22 days during gestation) showed no fetal or maternal toxicity at 20 mg/kg/day (Army 1980b). The highest NOAEL values and all reliable LOAEL values for developmental effects for each species and duration category are recorded in Table 2-l and plotted in Figure 2-l.

2.2.2.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans after oral exposure to RDX.

One dominant lethal mutation study was located for RDX exposure in male CD rats (Army 1980b). RDX was administered to the rats through their diets in doses of 0, 5, 16, or 50 mg/kg/day for 15 weeks. The males in each exposure group were allowed to mate with untreated females for 2 weeks. The resulting pregnancies were normal; no dominant lethal mutations were observed (Army 1980b). Other genotoxicity studies are discussed in Section 2.4.

2.2.2.8 Cancer

No studies were located regarding cancer in humans after oral exposure to RDX.

RDX was not found to be carcinogenic when fed to Fischer-344 rats (Army 1983a) or Sprague-Dawley rats (Navy 1976) for chronic periods. Adequate doses, numbers of animals, and survival rates were achieved for both of these studies. Only female B6C3F, mice showed an increased incidence of combined hepatocellular adenomas and carcinomas when compared to concurrent or historical controls (Army 1984c). This study is found in Table 2-l and Figure 2-l as a cancer effect level (CEL) end point. However, these tumors (adenomas and carcinomas in mice) have been shown to be poor predictors for malignancy in other species. No other type of tumor achieved statistically significant increases in this study.

2.2.3 Dermal Exposure

2.2.3.1 Death

No studies were located regarding death in humans after dermal exposure to RDX.
Deaths were reported in rabbits exposed to repeated doses of 33% RDX mixed with dimethylsulfoxide but no gross pathological effects were seen (Army 1974). Because of the lack of data presented, it is difficult to determine whether RDX alone was responsible for the deaths reported in this study.

2.2.3.2 Systemic Effects

No studies were located regarding respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, or renal effects in humans after dermal exposure to RDX. Two older studies of dermal and ocular effects were located for humans following dermal exposure to RDX. One study described a man who was dermally exposed (a 1 cm^2 patch of skin) to RDX, with no irritation noted two days later (von Oettingen et al. 1949). The other study involved workers exposed to RDX fumes of unknown levels and for an unknown duration. The workers reported dermatitis and conjunctivitis (Sunderman 1944).

2. HEALTH EFFECTS

One study describes dermal effects in rabbits, guinea pigs, and dogs following topical exposure to RDX dissolved in dimethyl sulfoxide, acetone, or cyclohexanone (Army 1974). RDX did not produce effects greater than those occurring after exposure to the solvents alone. The highest NOAEL values and all reliable LOAEL values for systemic effects in each species and duration category are recorded in Table 2-2.

Respiratory Effects. No effects were noted in the respiratory rates of dogs following single or multiple dermal exposures to RDX (Army 1974). No lesions were noted in the lungs of rabbits exposed to 16.5 mg/kg of RDX for 4 weeks.

Cardiovascular Effects. No effects were seen on blood pressure, heart rate, or electrocardiograms of dogs dermally exposed for acute or intermediate durations (Army 1974). No lesions were seen in the hearts of rabbits exposed for 4 weeks.

Gastrointestinal Effects. Necropsy did not reveal any lesions in the intestines of rabbits exposed to 165 mg/kg for 4 weeks (Army 1974).

Hematological Effects. Blood samples taken from rabbits after acute exposure to RDX revealed no changes in blood component values (Army 1974).

Musculoskeletal Effects. Necropsy did not reveal pathology in the muscle or bone tissue of rabbits exposed to 165 mg/kg for 4 weeks (Army 1974).

Hepatic Effects. No adverse blood or urine indicators were found in rabbits after acute dermal exposure to RDX. Also, no pathology was noted in the liver of rabbits exposed for 4 weeks (Army 1974).

Renal Effects: No adverse blood or urine indicators were found in rabbits after acute-duration exposure to RDX. Also, no pathology was noted in the kidneys of rabbits exposed for 4 weeks (Army 1974).

TABLE 2-2. Levels of Significant Exposure to RDX - Dermal

Species/ (Strain)	Exposure/ Duration/ Frequency/ (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
ACUTE EXPOSURE						
Systemic						
Dog (NS)	3 d once/day	Cardio	480			Army 1974
Dog (NS)	once	Resp	289			Army 1974
		Cardio	289			
Rabbit (NS)	once	Hemato	165			Army 1974
		Hepatic	165			
		Renal	165			
		Derm		165 (dermatitis)		
Gn pig (NS)	once	Derm	510	1000 (erythema)		Army 1974
INTERMEDIATE EXPOSURE						
Death						
Rabbit (NS)	4 wk 5d/wk				165 (deaths)	Army 1974
Systemic						
Dog (NS)	4 wk 5d/wk	Resp	289			Army 1974
		Cardio	289			

TABLE 2-2. Levels of Significant Exposure to RDX - Dermal (continued)

Species/ (Strain)	Exposure/ Duration/ Frequency/ (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference
				Less Serious (mg/kg/day)	Serious (mg/kg/day)	
Rabbit (NS)	4 wk 5d/wk	Resp	165			Army 1974
		Cardio	165			
		Gastro	165			
		Musc/skel	165			
		Hepatic	165			
		Renal	165			
Gn pig (NS)	3 wk 3d/wk	Derm	165			Army 1974
		Ocular	165			

Cardio = cardiovascular; d = day(s); Derm = dermal; Gastro = gastrointestinal; Gn pig = guinea pig; Hemato = hematological; LOAEL = lowest-observed-adverse-effect level; Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; NS = not specified; Resp = respiratory; wk = week(s)

2. HEALTH EFFECTS

Dermal Effects. One human volunteer had a patch of skin covered with dry RDX for 2 days. No irritation was observed following removal of the gauze coverings (von Oettingen et al. 1949). An accurate dose could not be determined because of the lack of information provided in the study. Another study reported dermatitis in workers exposed to RDX fumes of unknown levels and for unknown duration (Sunder-man 1944).

Rabbits exposed once to 165 mg/kg RDX displayed dermatitis (Army 1974). Erythema was noted in guinea pigs exposed to 1,000 mg/kg one time (Army 1974). Guinea pigs exposed once to an unspecified amount of RDX had exudative dermatitis with edema (Sunderman 1944). The lesions healed promptly after the guinea pigs were removed from the source of exposure. No sensitization was noted in guinea pigs with multiple exposures (Army 1974).

Ocular Effects. Cataracts were observed in guinea pigs exposed through cutaneous or intradermal applications of RDX in solvents. However, the incidence of cataracts did not appear to be greater than that found after exposure to the solvents alone. This suggests that RDX itself did not contribute to cataract formation (Army 1974). Sunder-man (1944) reported conjunctivitis in workers exposed to RDX fumes of unknown levels and for an unknown duration.

Two older studies of dermal and ocular effects were located for humans following dermal exposure to RDX. One study described a man who was dermally exposed (a 1 cm^2 patch of skin) to RDX, with no irritation noted two days later (von Oettingen et al. 1949). The other study involved workers exposed to RDX fumes of unknown levels and for an unknown duration. The workers reported dermatitis and conjunctivitis (Sunder-man 1944).

Body Weight Effects. A small, transient decrease in body weight was observed in rabbits after a single dermal exposure to 2,000 mg/kg of RDX. However, by the end of the observation period, most of the surviving animals showed weight gain (Army 1984b).

2. HEALTH EFFECTS

No studies were located regarding the following effects in humans or animals after dermal exposure to RDX:

2.2.3.3 Immunological and Lymphoreticular Effects

2.2.3.4 Neurological Effects

2.2.3.5 Reproductive Effects

2.2.3.6 Developmental Effects

2.2.3.7 Genotoxic Effects

Genotoxicity studies are discussed in Section 2.4.

2.2.3.8 Cancer

No studies were located regarding cancer in humans or animals after dermal exposure to RDX.

2.3 TOXICOKINETICS

2.3.1 Absorption

No studies specifically designed to study absorption were located for humans. However, humans have suffered toxic effects from ingestion of RDX, indicating that the material is indeed absorbed through the gastrointestinal system (Hollander and Colbach 1969; Kaplan et al. 1965; Ketel and Hughes 1972; Merrill 1968; Stone et al. 1969). One study is available showing peak plasma concentrations 24 hours postingestion for a child (Woody et al. 1986), indicating a fairly slow absorption rate. Since the ingestion levels were not known, the extent of absorption could not be determined. Neurotoxic effects in humans were observed following inhalation exposure (Kaplan et al. 196.5), indicating that RDX may be absorbed in the lungs. One study showed that, following dermal exposure, 90% of the RDX was no longer detected on the skin 1 hour later, and none was detected after 48 hours (Twibell et al. 1984).

2. HEALTH EFFECTS

High concentrations of RDX were found in the stomachs and intestines of miniature swine 24 hours after a single gavage dose of RDX, suggesting poor gastrointestinal absorption (Schneider et al. 1977). No inhalation or dermal data are available for animals.

2.3.2 Distribution

Only one pharmacokinetic study is available regarding distribution of RDX in a child (Woody et al. 1986). The only tissues measured in this case were cerebrospinal fluid, plasma, urine, and feces, and the samples were not taken consistently. RDX was found in the cerebrospinal fluid 24 hours after ingestion and peaked in the plasma at this time as well. RDX was also detectable in feces for 144 hours following ingestion.

No studies were located in animals regarding distribution following exposure via the inhalation or dermal routes. The only data are from the oral route of exposure, and these studies were inadequate to reveal a specific target organ for the distribution of RDX. In rats given RDX by gavage, levels in the plasma and brain reached a steady state for 2-24 hours and then disappeared 3 days postexposure, but no other tissues were sampled (Army 1985b). Miniature swine showed no preferential distribution to brain, heart, liver, kidney, or fat (Schneider et al. 1977). Rats given RDX once by gavage showed the highest levels of RDX in the kidney, with less in the brain and heart, and the least amount in the plasma and liver. However, these findings were not replicated in longer-term studies, which showed no preferential distribution in rats given RDX by gavage or in the drinking water for 90 days (Schneider et al. 1978).

2.3.3 Metabolism

There are no studies available regarding RDX metabolites in humans following inhalation, oral, or dermal exposure.

The specific types of RDX metabolites have not been established in experiments in animals, but excretion experiments indicate that over 90% of a gavage dose of radiolabeled RDX is broken down within 4 days (Schneider et al. 1977).

2.3.4 Excretion

Only one study is available that provides data on excretion in humans after oral exposure (Woody et al. 1986). RDX values peaked 48 hours postexposure in the urine and 96 hours postexposure in the feces. No data are available for excretion in humans following inhalation or dermal exposure. RDX was also detectable in feces for 144 hours following ingestion.

There are no data regarding excretion of RDX following inhalation or dermal exposure in animals. Rats given a single radiolabeled gavage dose eliminated 43% in the breath, 34% in the urine, and 3% in the feces within 4 days (Schneider et al. 1977). A longer-term study showed similar excretion patterns; during a continuous drinking water study, 50% was eliminated in the breath, 34% in the urine, and 5% in the feces (Schneider et al. 1978). There was no evidence that RDX accumulated in the tissues during longer-term exposure.

2.3.5 Mechanisms of Action

The limited available toxicokinetic data show that RDX is absorbed through the gastrointestinal system, lungs, and skin, and is distributed to the cerebrospinal fluid, plasma, urine, and feces. No information is available on the metabolism of RDX, and it appears to be excreted in the urine and feces following oral exposure. No further information is available on the mechanisms of action of RDX in either humans or animals.

2.4 RELEVANCE TO PUBLIC HEALTH

For the general population, exposure to RDX is probably limited to the immediate vicinity of Army ammunition plants. The most likely routes of exposure for populations living nearby are ingestion of contaminated drinking water or skin contact with water or soil that contain RDX. Inhalation is also a possible route of exposure.

The most serious effect that has been shown to occur in humans is seizures associated with the accidental consumption of large amounts of RDX, indicating that the nervous system is the target organ. There are no human studies showing that RDX poses a risk for cancer. One study in mice (Army 1984c) shows increased incidences of liver tumors (adenomas/carcinomas) following chronic

oral exposure. This study was used by EPA to classify RDX as a possible human carcinogen. It is also possible that humans exposed to RDX would develop less serious effects. Although effects such as dermal irritation, decreased weight gain, or minor hematological abnormalities have been noted in a few animal studies, they have not been found in humans exposed to RDX.

Minimal Risk Levels for RDX.

Inhalation MRLs.

No acute, intermediate, or chronic inhalation MRLs were derived for RDX because of the limitations associated with the available studies. There were several human studies with limitations such as small sample size, exposure to other chemicals, incomplete exposure concentration or duration data, or lack of controls. The one available animal study is limited by insufficient number of animals tested, no controls, and no data on exposure levels.

Oral MRLs.

- An MRL of 0.06 mg/kg/day has been derived for acute-duration oral exposure (14 days or less) to RDX.

This MRL was derived from a NOAEL of 6 mg/kg/day in a study where doses of 0, 2, 6, and 20 mg/kg/day were administered to pregnant female rats during gestation days 6-15 (Army 1986d). Mortality was high among the rats receiving 20 mg/kg/day, with 31% dying during the test period. Several surviving females at the 20 mg/kg/day dose displayed convulsions; nasal, oral, and urogenital discharge; and alopecia and hyperactivity. The 20 mg/kg/day dose was identified as a serious LOAEL based on neurological effects (i.e., convulsions) and 6 mg/kg/day was identified as the NOAEL. This NOAEL was used with an uncertainty factor of 100 to derive the MRL.

- An MRL of 0.03 mg/kg/day has been derived for intermediate-duration oral exposure (15-364 days) to RDX.

This MRL was derived from a NOAEL of 8 mg/kg/day in a study where 10 male and 10 female rats were given 0, 0.3, 1.5, 8, or 40 mg/kg/day RDX (Army 1983a). These rats were sacrificed after

6 months, with testicular degeneration and spermatic granulomas in the prostate observed at 40 mg/kg/day. The 8 mg/kg/day dose was identified as the NOAEL based on reproductive effects noted at 40 mg/kg/day. This NOAEL was used with an uncertainty factor of 100 and an additional modifying factor of 3, for database deficiencies, to derive an MRL. Neurological effects, such as tremors and convulsions, were also noted in the Army (1983a) study at 40 mg/kg/day. These neurological effects have been identified as co-critical end points for the derivation of this MRL.

A chronic oral MRL was not derived because of the limitations and deficiencies of the database. The available studies did not clearly define levels where adverse effect have been noted in animals.

Death. No deaths have been known to occur in humans following inhalation, oral, or dermal exposure to RDX. Oral exposures to high levels have caused deaths in animals (Army 1978b, 1980b, 1983a, 1986d; Burdette et al. 1988; Levine et al. 1990). It is unlikely that levels of RDX in the air or water at or near hazardous waste sites will cause death in humans.

Systemic Effects.

Respiratory Effects. No human data are available regarding respiratory effects by any route or duration of exposure. Animals exposed to RDX by the oral or dermal routes showed no adverse respiratory effects (Army 1980b, 1983a, 1984c; Levine et al. 1981; von Oettingen et al. 1949). There are no other data to indicate that respiratory effects may be of concern to humans exposed to RDX at or near hazardous waste sites.

Cardiovascular Effects. No human data are available regarding cardiovascular effects in humans for any route or duration of exposure. Animals exposed to RDX by the oral or dermal routes showed no changes in heart rate (Army 1983a, 1984c; Levine et al. 1981; von Oettingen et al. 1949). A few, but not all, of the oral studies of intermediate duration showed slight myocardial degeneration. This effect was not seen following chronic exposure. These data indicate that cardiovascular effects' are not likely to be of concern to humans exposed to RDX via the oral or dermal routes at or near hazardous waste sites. No data are available regarding the inhalation route.

Gastrointestinal Effects. Human studies revealed nausea and vomiting following inhalation or oral exposure to unknown levels of RDX (Ketel and Hughes 1972; Hollander and Colbach 1969), but

animal studies do not support the identification of the gastrointestinal system as a target for RDX toxicity. No histopathology was noted in the gastrointestinal organs of animals exposed by the oral or dermal routes (Army 1980b, 1983a), and nausea and vomiting cannot be monitored in rodents. No animal data are available regarding the inhalation route of exposure. It is possible that humans exposed to RDX in the air or in the drinking water near hazardous waste sites would experience nausea and vomiting, but the available studies suggest that it is unlikely that any serious gastrointestinal effects will occur after exposure to RDX.

Hematological Effects. Adverse hematological effects were not seen in humans exposed to RDX by the inhalation or oral routes for acute or chronic periods (Hathaway and Buck 1977; Kaplan et al. 1965). Similarly, no significant effects were seen in most studies in animals (Army 198Ob, 1983a, 1984c; Levine et al. 1990). However, two studies did show evidence of possible anemic effects (Army 1983a; Sunder-man 1944). Also, necrotic and degenerative megakaryocytes in bone marrow were observed in monkeys after oral exposure (Navy 1974b). These changes suggest possible thrombocytopenia. These data indicate that hematological effects might be of concern to humans exposed orally to RDX at or near hazardous waste sites.

Musculoskeletal Effects. No human data are available regarding musculoskeletal effects in humans. No musculoskeletal effects were seen in animals exposed via the oral or dermal routes (Army 1980b, 1983a, 1984c; Levine et al. 1981, 1990; Navy 1974a, 1976); no animal data are available regarding the inhalation route. Musculoskeletal effects are not likely to be of concern to humans exposed to RDX at or near hazardous waste sites.

Hepatic Effects. Adverse hepatic effects were not seen in humans exposed by the inhalation or oral routes for acute or chronic periods (Hathaway and Buck 1977; Kaplan et al. 1965; Ketel and Hughes 1972). However, the doses that the people were exposed to are not known. Adverse hepatic effects have been seen in animals exposed via the oral route (Army 1983a, 1980b; Sunderman 1944). Hepatomegaly Was‘observed in a study where rats were exposed to 40 mg/kg/day RDXfor a chronic duration (Army 1983a). These data indicate that hepatic effects might be of concern to humans exposed orally to RDX at or near hazardous waste sites.

Renal Effects. Adverse renal effects were not seen in humans exposed to RDX by the inhalation or oral routes for acute periods (Hathaway and Buck 1977; Kaplan et al. 1965; Ketel and Hughes 1972;

Stone et al. 1969). Few serious effects were seen in animals exposed by the oral or dermal routes for acute, intermediate, or chronic periods (Army 1980b, 1984c; Levine et al. 1981, 1990; Navy 1974a, 1974b, 1976; von Oettingen et al. 1949). Renal papillary necrosis and increased blood urea nitrogen were observed in rats orally exposed to RDX for chronic durations (Army 1983a). These data indicate that renal effects may be of concern to humans exposed to RDX at or near hazardous waste sites.

Endocrine Effects. One study (Army 1980b) observed mild fat infiltration in the adrenal glands of mice and another study (Army 1983a) reported enlarged adrenals after exposure to RDX for one year. The significance of these findings with regard to human exposure is unclear.

Dermal Effects. No studies are available regarding dermal effects in humans following inhalation or oral exposure to RDX. However, it is possible that direct contact with RDX may be irritating to the skin of some people. No skin lesions were seen in animals exposed by the oral route (Army 1980b, 1983a; Navy 1974a, 1974b), but dermatitis was observed in animals following dermal exposure to low levels of RDX, and erythema was seen following exposure to high levels (Army 1974; Sunder-man 1944). These data indicate that dermal effects might be of concern to humans exposed to RDX at or near hazardous waste sites.

Ocular Effects. No studies are available regarding ocular effects in humans following inhalation or oral exposure to RDX.

Female rats exposed to high levels of RDX in the feed had cataracts, but these findings were not replicated in mice (Army 1983a, 1984c). Since cataracts are considered to be a serious effect, this ocular effect may be of concern to humans exposed to RDX at or near hazardous waste sites.

Body Weight Effects. Effects on body weight have not been reported in humans exposed to RDX. Animals exposed to RDX in the food often show decreased weight gain, suggesting generalized toxicity (Army198Ob, 1983a, 1984c; Levine et al. 1981, 1990; von Oettingen et al. 1949). The significance of this observation with regard to human exposures is unknown.

Metabolic Effects. Decreases in serum triglycerides have been noted in rats (Levine et al. 1981, 1990). It is unknown whether this effect may be significant for human exposure to RDX.

2. HEALTH EFFECTS

Immunological and Lymphoreticular Effects. One study is available that tested for immunological effects in humans following long-term exposure to RDX in the air. This study found no adverse immunological effects in RDX workers (Hathaway and Buck 1977). Animal studies revealed no important adverse histopathology in the spleen, thymus, or lymph nodes of animals exposed to RDX via the oral route (Army 1980b; Levine et al. 1990; Navy 1974a; von Oettingen et al. 1949). No other functional studies are available. No data are available regarding these effects following exposure via the dermal route. The information available is insufficient to determine whether immunotoxicity is likely to be of concern to humans exposed to RDX near hazardous waste sites.

Neurological Effects. Humans exposed to RDX by the inhalation or oral routes suffered from seizures, convulsions, confusion, muscle twitching, marked hyperirritability, and amnesia (Hollander and Colbach 1969; Kaplan et al. 1965; Ketel and Hughes 1972; Knepshield and Stone 1972; Merrill 1968; Stone et al. 1969; Woody et al. 1986). Once the individuals were removed from the source of exposure, they recovered. Animals also had seizures following oral exposure (Army 1980b, 1985b, 1986d; Burdette et al. 1988; Levine et al. 1990; Navy 1974b; Schneider et al. 1977). Seizures in rats (Army 1986d) were used as the critical end point for the acute oral MRL. No histopathology was found in the animals, and no other sensitive tests of neurological function were performed in humans. Although the levels of RDX in the air, water, and soil that might cause seizures or other adverse neurological effects in humans are not known, it is possible that these effects may occur in persons living near hazardous waste sites.

Reproductive Effects. No studies are available regarding reproductive effects in humans following inhalation, oral, or dermal exposure to RDX. No studies are available regarding reproductive effects in animals after inhalation or dermal exposure to RDX. Studies regarding oral exposure in animals reveal no damage to the testes, ovaries, or uterus, but prostate lesions were observed in a rat study following intermediate exposure to RDX (Army 1983a). This study was used as the basis for-the intermediate oral MRL. Significantly increased incidences of inflammation and pus in the prostate were observed in rats chronically exposed to 1.5 mg/kg/day or greater of RDX in the feed. No effects were seen at 0.3 mg/kg/day. However, bladder distention and cystitis were also noted, which is consistent with a possible urinary tract bacterial infection (Army 1983a). This study was used by EPA (IRIS 1994) to develop an oral reference dose (RfD). A two-generation functional study in rats had inconclusive results (Army 1980b). It is unknown whether humans exposed to RDX

would be likely to develop pathology in the prostate, or whether they would have adverse reproductive outcomes following exposure to RDX near hazardous waste sites.

Developmental Effects. No studies are available regarding developmental effects in humans following inhalation, oral, or dermal exposure to RDX. No studies are available in animals regarding exposure via the inhalation or dermal routes. When rat dams were given 2 mg/kg/day of RDX orally during gestation, the fetuses had slightly decreased body weights (4%) and lengths (2%) (Army 1986d). Another study in rats showed no changes in fetal parameters when the dams were given 2 mg/kg/day (Army 1980b). Oral studies in rabbits indicate that RDX is not fetotoxic (Army 1980b). It is possible that adverse developmental effects from RDX may occur in human populations exposed to RDX near hazardous waste sites.

Genotoxic Effects. There were no studies involving human exposure to RDX in viva. (In viva studies are listed in Table 2-3). One *in vitro* study was located in which human fibroblasts (WI-38 cells) were incubated in the presence of RDX and tritiated thymidine (3H-TdR) to measure unscheduled deoxyribonucleic acid (DNA) synthesis (Army 1978b). (In *vitro* studies are listed in Table 2-4). Unscheduled DNA synthesis (UDS) occurs when DNA is damaged. Therefore, measuring the amount of UDS activity is an indirect measurement of the amount of DNA damage. RDX was tested in concentrations ranging from 250 to 4,000 yg/mL both with and without metabolic activation (i.e., addition of liver metabolizing enzymes). RDX was not found to significantly increase the rate of UDS in the cells of any exposure group regardless of whether or not metabolic activators were present. Therefore, RDX was not observed to cause DNA damage in human fibroblasts within this particular concentration range (Army 1978b). Although this is the only available study involving human cells, the combined evidence from this and other nonhuman studies suggests that RDX is not genotoxic to humans.

One *in vivo* animal study was located (Table 2-3). This experiment investigated the effects of oral doses of RDX on dominant lethal mutations (Army 1980b). Male CD rats were exposed to RDX through their food and allowed to mate with unexposed females for a 2-week period. No significant effects on the number of corpora lutea, implants or of live or dead embryos were observed (Army 1980b). Therefore, at these doses (50 mg/kg/day or less), RDX does not appear to cause dominant lethal mutations in rats.

TABLE 2-3. Genotoxicity of RDX *In Vivo*

Species (test system)	End point	Results	Reference
Mammalian cells:			
Rat mutation	Dominant lethal	–	Army 1980b

– = negative result

TABLE 2-4. Genotoxicity of RDX *In Vitro*

Species (test system)	End point	Results		
		With activation	Without activation	
Prokaryotic organisms:				
Salmonella typhimurium	Gene mutation	–	–	Army 1980b
S. typhimurium	Gene mutation	No data	–	Army 1977b
S. typhimurium	Gene mutation	–	–	Whong et al. 1980
Eukaryotic organisms:				
Fungi:				
Saccharomyces cerevisiae	Gene mutation	No data	–	Army 1977b
Mammalian cells:				
Human fibroblasts	DNA damage	–	–	Army 1978b

– = negative result; DNA = deoxyribonucleic acid

2. HEALTH EFFECTS

The effect of RDX on gene mutation was studied in *Salmonella typhimurium* and *Saccharomyces cerevisiae* by several researchers. The results have been consistently negative. In one Ames test, five *S. typhimurium* strains (TA-1535, TA-1537, TA-1538, TA-98, and TA-100) were exposed to 0, 1, 10, 100, 300, or 1,000 pg RDX/plate (Army 1980b). Each exposure group was tested both with and without metabolizing enzymes. The number of revertants (gene mutations) observed in all strains and exposure groups (with and without metabolic activation) did not differ significantly from the controls (Army 1980b). In another Ames test using the same *S. typhimurium* strains, RDX was also not observed to be mutagenic with or without metabolic activation at doses up to 2.5 mg/plate (Whong et al. 1980). Another mutagenicity assay testing the effects of RDX on both *S. typhimurium* and *S. cerevisiae* produced negative results for both organisms (Army 1977b). It is not clear from this paper whether or not RDX was tested in the presence of metabolizing enzymes, but mutagenicity tests were performed before and after chlorination. The results were negative for both organisms after chlorination as well (Army 1977b). These experiments strongly suggest that RDX is not a mutagenic chemical.

Cancer. No studies are available regarding cancer in humans or animals following inhalation or dermal exposure to RDX. No human oral studies are available, but there are a few animal oral studies. Two chronic exposure studies in rats reveal no evidence of neoplasms (Army 1983a; Navy 1976). One study in mice found statistically increased incidences of combined hepatocellular adenomas and carcinomas in females (Army 1984c). However, the results of this study are preliminary and suggestive, since no human data are available and carcinogenic effects were not noted in rat studies. More data are needed to better evaluate the carcinogenic potential of RDX. The study in mice (Army 1984c) was used by the EPA (IRIS 1994) to develop an oral slope factor of 0.1 mg/kg/day. A concentration of 30 μg/L in the drinking water is estimated to produce an increased risk in 1 out of 10,000 persons. The weight of evidence (no human data, positive animal responses in only one sex of one animal species) was used by the EPA (IRIS 1994) to classify RDX in Group C--possible human carcinogen.

2.5 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility (NAUNRC 1989).

2. HEALTH EFFECTS

A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself or substance-specific metabolites in readily obtainable body fluid(s) or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time biologic samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to RDX are discussed in Section 25.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAWNRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are often not substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by RDX are discussed in Section 2.5.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism’s ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, biologically effective dose, or target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 2.7, Populations That Are Unusually Susceptible.

2.5.1 Biomarkers Used to Identify or Quantify Exposure to RDX

RDX has been detected in the serum, urine, and feces of one child who consumed unknown levels of RDX in the form of C-4 (91% RDX). RDX was measured in the serum for 120 hours and in the

feces for 144 hours after the presumed time of ingestion (Woody et al. 1986). The metabolites of RDX have only been found in animals by using a radiolabel (^{14}C) (Schneider et al. 1977). Although this study found the radiolabel in the breath, urine, and feces, the chemical identity of the metabolites was not described. Therefore, metabolites cannot currently be used as biomarkers. In the one available human case study, RDX was found in the body following a single exposure, but no data are available regarding intermediate or chronic exposures.

The data are insufficient to characterize a level of RDX in the urine or blood that may be associated with an exposure level.

2.5.2 Biomarkers Used to Characterize Effects Caused by RDX

Very high oral doses of RDX are known to produce seizures in humans (Hollander and Colbach 1969; Kaplan et al. 1965; Ketel and Hughes 1972; Merrill 1968; Stone et al. 1969; Woody et al. 1986) and animals (Army 1983a; Burdette et al. 1988; Navy 1974b; Schneider et al. 1977; von Oettingen et al. 1949), but this effect is not specific to RDX. Thus, there are no known sensitive biomarkers that could be used to characterize effects caused by inhalation, oral, or dermal exposure to RDX.

For more information on biomarkers for renal and hepatic effects of chemicals see ATSDR/CDC Subcommittee Report on Biological Indicators of Organ Damage (1990) and for information on biomarkers for neurological effects see OTA (1990).

2.6 INTERACTIONS WITH OTHER CHEMICALS

Many of the human studies on the accidental inhalation or ingestion of RDX involved composition C-4, which was used for demolition by the U.S. Armed Forces during the Vietnam War. Composition C-4 was 91% RDX, with the other components consisting of polyisobutylene, motor oil, and 2-ethylhexyl sebacate. Minimal information is available on the toxicological properties-df these components of C-4, and it is not known whether they may contribute to the effects seen from exposure to C-4. However, since RDX is the primary component of C-4, the assumption has been made that the major effects noted from C-4 are due to RDX. In addition, the human and animal reports of ingested RDX usually are not limited to pure RDX, but are almost always reports of RDX contaminated with octahydro-1,3,5,7-tetranitro-1,3,5,7-tetrazocine (HMX) or other substances. There

are no studies regarding the interactions of these substances. However, there are several studies in which the oral toxicity of trinitrotoluene (TNT) and RDX were investigated. In one study (Levine et al. 1990) TNT and RDX were coadministered in the feed of rats for 13 weeks. This co-administration potentiated the decrease in body weight gain as compared to RDX alone. TNT antagonized the lethal effects and the hypotriglyceridemia induced by RDX. RDX antagonized the hypercholesterolemia, splenomegaly, testicular atrophy, hepatocytomegaly, degeneration of the seminiferous tubules, and pigmentation of renal cortices induced by TNT. Dilley et al. (1982) investigated the effects of a mixture of 10% RDX and 0.32% TNT in dogs, rats, and mice. All three species showed depression of body weight gain, depressed food intake, and alterations in the spleen, liver, and testes at the highest dose levels. However, RDX was not tested alone.

2.7 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to RDX than will most persons exposed to the same level of RDX in the environment. Reasons include genetic makeup, developmental stage, health and nutritional status, and chemical exposure history. These parameters result in decreased function of the detoxification and excretory processes (mainly hepatic and renal) or the pre-existing compromised function of target organs. For these reasons we expect the elderly with declining organ function and the youngest of the population with immature and developing organs will generally be more vulnerable to toxic substances than healthy adults. Populations who are at greater risk due to their unusually high exposure are discussed in Section 5.6, Populations With Potentially High Exposure.

There are no known populations that would be unusually susceptible to RDX toxicity because of their genetic make-up, developmental stage, health status, nutritional status, or chemical exposure history.

2.8 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to RDX. However, because some of the treatments discussed may be experimental and unproven, this section should not be used as a guide for treatment of exposures to RDX. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice.

The only information known on the mitigation of RDX toxicity is that washing the hands removes most of the RDX deposited there (Twibell et al. 1984). No specific antidotes are known, but the seizures produced by overingestion of RDX should be treated by appropriate methods. Activated charcoal or cathartics can be used to decrease gastrointestinal absorptions (HSDB 1994).

2.8.1 Reducing Peak Absorption Following Exposure

No information was located on methods for reducing peak absorption following exposure to RDX.

2.8.2 Reducing Body Burden

No information was located on methods for reducing the body burden of RDX.

2.8.3 Interfering with the Mechanism of Action for Toxic Effects

No information was located on interfering with the mechanism of action for the toxic effects of RDX.

2.9 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of RDX is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of RDX.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and -EPA. They are defined as substance-specific informational needs that, if met, would reduce or eliminate the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda may be proposed.

2. HEALTH EFFECTS

2.9.1 Existing Information on Health Effects of RDX

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to RDX are summarized in Figure 2-2. The purpose of this figure is to illustrate the existing information concerning the health effects of RDX. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not imply anything about the quality of the study or studies. Gaps in this figure should not be interpreted as "data needs." A data need, as defined in ATSDR's Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles (ATSDR 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

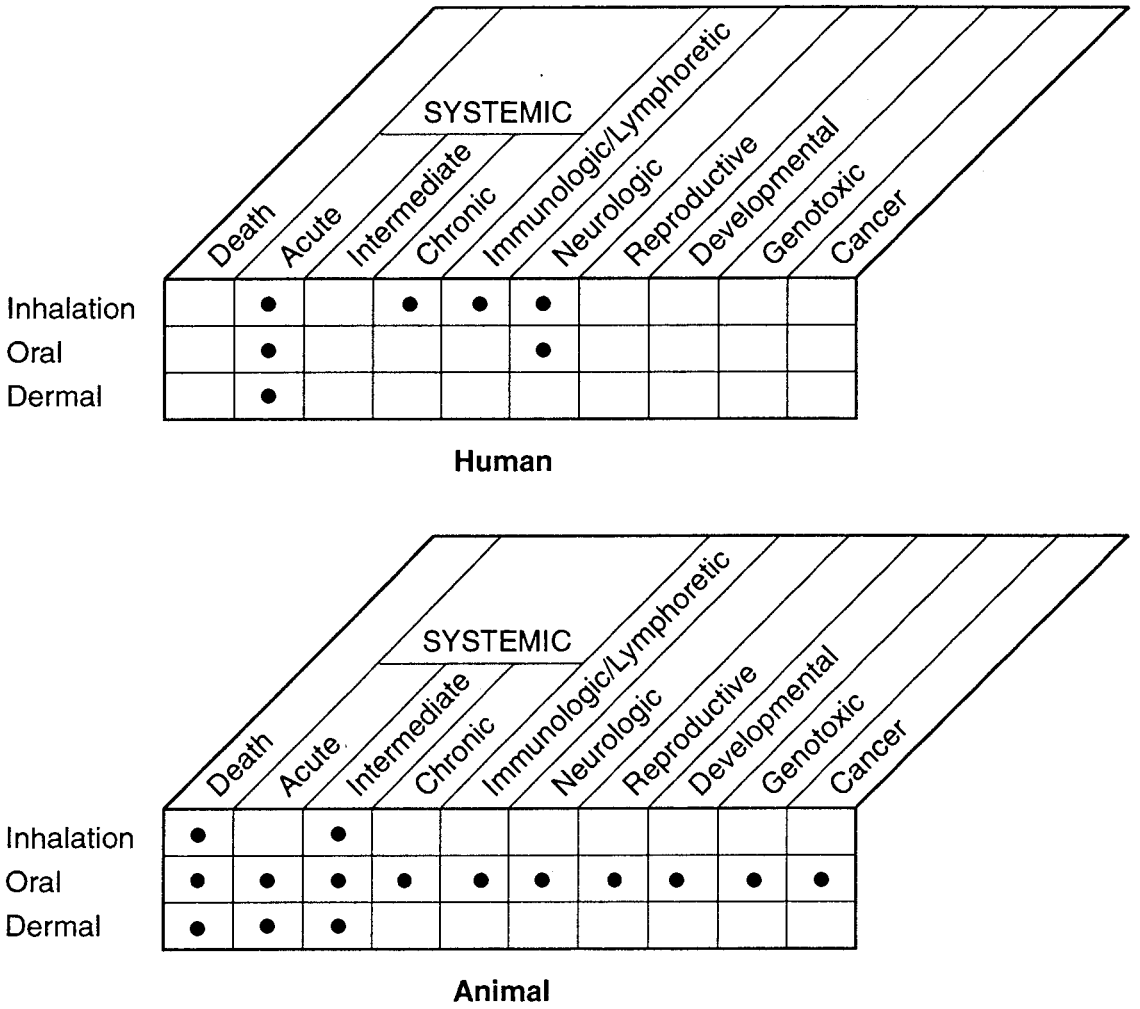
Case studies are available regarding systemic effects in humans following acute exposures to RDX via all three routes. One study in the workplace provides information on immunological and neurological effects following inhalation exposure for chronic periods. Neurological effects have also been described following acute oral exposures to RDX.

Animal data on inhalation exposure is limited to one study. Oral animal data are available for all exposure durations and for all end points. Dermal data on death and systemic effects are available for animals exposed to RDX for acute and intermediate exposure periods.

2.9.2 Identification of Data Needs

Acute-Duration Exposure. The nervous system is one of the main targets for RDX toxicity in humans exposed by the inhalation (Hollander and Colbach 1969) or oral (Hollander and Colbach 1969; Ketel and Hughes 1972; Knepshield and Stone 1972; Merrill 1968; Stone et al. 1969; Woody et al. 1986) routes, and animal studies support this finding (Army 1985b; Burdette et al. 1988; Schneider et al. 1977). This is further described in the section on Neurotoxicity below. One animal-study suggests that the skin is a target organ for RDX following dermal exposure (Army 1974). However, the use of solvents confounded the results. No acute inhalation MRLs could be derived because of the lack of human and animal studies with accurate exposure estimates. An acute oral MRL of 0.06 mg/kg/day was derived from a study showing seizures in rats at 20 mg/kg/day (Army 1986d). One study (Army 1986d) observed slightly decreased fetal weights and lengths in rat dams exposed to 2 mg/kg/day;

FIGURE 2-2. Existing Information on Health Effects of RDX



● Existing Studies

however, the results are questionable due to problems with the statistical analysis. Further acute inhalation and oral studies on the developmental and neurological effects of RDX would be useful in determining levels that may cause harm to humans living near hazardous waste sites. No acute dermal MRLs were derived because of a lack of appropriate methodology for deriving such levels.

Intermediate-Duration Exposure. The nervous system is the target organ for RDX toxicity in animals exposed by the oral route for intermediate periods (Army 1983a, 1985b; Levine et al. 1990; Navy 1974b; von Oettingen et al. 1949). This is further described in the section on Neurotoxicity below. Studies involving intermediate dermal exposure to RDX did not identify a target organ (Army 1974). No intermediate-duration inhalation MRL could be derived because of the lack of human and animal studies with accurate exposure estimates. An intermediate oral MRL of 0.03 mg/kg/day was derived from a study showing reproductive effects in rats exposed to 40 mg/kg/day (Army 1983a). This study is further described in the section on reproductive effects below. Further inhalation studies on the neurological effects of RDX would be useful in determining levels that may cause harm to humans who live near hazardous waste sites.

Chronic-Duration Exposure and Cancer. Only one human study was located for chronicinhalation exposure. This study revealed no adverse health effects following chronic exposures to unknown levels of RDX in the air (Hathaway and Buck 1977). No animal studies concerning chronic inhalation exposure were located. No chronic inhalation MRLs could be derived because of the lack of human and animal studies with accurate exposure estimates. Therefore, further inhalation studies would be useful to identify target organs and define the potential for human health risks.

No human studies concerning chronic oral exposure were located. The most sensitive target organ for adverse effects in animals following chronic oral exposure has not been well defined. Chronicduration oral animal studies provide information regarding death in rats (Army 1983a; Navy 1976), mild adverse systemic effects in rats (Army 1983a; Navy 1976) and mice (Army 1984c), and a lack of adverse immunological effects in rats (Army 1983a). The other significant adverse effect-found in oral animal studies was seizures, which is further described in the section on Neurotoxicity below. Only one human study was located for chronic dermal exposure (Sunderman 1944). This study reported dermatitis in workers exposed to RDX, but no dose levels were reported. No animal studies concerning chronic dermal exposure were located. No chronic MRL was derived due to the limitations of the

available data. Additional chronic oral and dermal studies would be useful to better define dose levels which may cause a risk to humans.

Increased incidences of combined hepatocellular adenomas and carcinomas were found in female mice orally exposed to RDX (Army 1984c). These results were not supported by oral studies of rats (Army 1983a; Navy 1976). No studies are available regarding cancer in humans following any route of exposure. The risk of developing cancer by the inhalation or dermal routes has not been investigated. Genotoxicity data were consistently negative. Further inhalation, oral, or dermal carcinogenicity studies would be useful to determine whether RDX, poses a risk of cancer for humans.

Genotoxicity. Data from microbial mutagenicity studies using *S. typhimurium* and *S. cerevisiae* have consistently produced negative results (Army 1977b, 1980b; Whong et al. 1980). Therefore, additional research in this area would not be useful at the present time. Studies involving humans and mammalian species are few. The two mammalian studies available were negative for DNA damage (Army 1978b) and dominant lethal mutations (Army 1980b) in humans and rats, respectively. Epidemiological studies involving humans exposed occupationally or militarily to RDX may help to confirm its status as a human genotoxin. However, considering the evidence available, it is unlikely that RDX poses a serious genotoxic threat to humans.

Reproductive Toxicity. No data are available on the reproductive toxicity of RDX in humans via inhalation, oral, or dermal routes of exposure. No inhalation or dermal studies are available for animals. The only available chronic study was a two-generation oral study in rats that was seriously flawed because of excessive deaths in the parental generation (Army 1980b). An oral study in mice (Army 1984c) and one in rats (Navy 1976) revealed no histopathology in the ovaries, testes, or uterus. One oral study did reveal testicular degeneration and spermatic granulomas in the prostate of rats after 6 months exposure. This study was used as the basis for the intermediate oral MRL (Army 1983a). No pharmacokinetic data are available that can be used to determine whether the reproductive system is likely to be a target for RDX toxicity. Therefore, further studies to determine whether the prostate is indeed the most sensitive organ are important. A properly conducted two-generation reproductive study in animals via the oral route would provide valuable information regarding possible adverse reproductive effects in humans exposed to RDX at or near hazardous waste sites.

2. HEALTH EFFECTS

Developmental Toxicity. No human studies on developmental effects are available for exposure to RDX via inhalation, oral, or dermal routes. No inhalation or dermal studies are available for animals. Maternal deaths were observed in rats exposed to 20 mg/kg/day of RDX (Army 1980b, 1986d). The one available oral study in rabbits revealed no fetotoxicity (Army 1980b). No pharmacokinetic data are available that can be used to determine whether the developmental system is likely to be a target organ. Further developmental studies via the oral route are important to determine whether humans exposed to RDX at or near hazardous waste sites are at risk of experiencing adverse developmental effects.

Immunotoxicity. The only available immunological study in humans reveals no changes in the antinuclear antibodies of workers exposed to RDX in the air (Hathaway and Buck 1977). No other functional tests were performed. An intermediate-duration study in rats revealed an increase in extramedullary hematopoiesis apparently secondary to a mild anemia (Army 1983a), but this effect was not considered adverse. No histopathology was found in the spleen, thymus, or lymph nodes of other groups of rats (Army 1980b; Levine et al. 1990) or mice (Army 1980b), or in the spleens of dogs (Navy 1974a; von Oettingen et al. 1949) or monkeys (Navy 1974b), after intermediate exposure via the oral route. An increase in hemosiderin-like pigment was found in rats exposed to RDX in the food for 2 years (Army 1983a), but this change was secondary to mild anemia and not considered adverse. A study by Levine et al. (1981) demonstrated mild leukocytosis, where mild anemia was seen in the two-year chronic toxicity study (Army 1983a). Further oral studies would be useful to determine whether the changes seen in the rat spleen are linked to other adverse effects. In addition, inhalation and dermal studies would help determine whether exposure to RDX at or near hazardous waste sites would affect the human immune system.

Neurotoxicity. The nervous system is a major target organ for RDX toxicity. Seizures have been reported in humans exposed for acute periods by inhalation (Kaplan et al. 1965), ingestion (Merrill 1968; Stone et al. 1969; Woody et al. 1986), or a combination of the inhalation and oral routes (Hollander and Colbach 1969; Ketel and Hughes 1972). Oral studies in animals have supported this finding for acute (Burdette et al. 1988; Schneider et al. 1977), intermediate (Army 1983a; Navy 1974b; von Oettingen et al. 1949), and chronic (Army 1983a) exposure durations. There is one study on behavioral effects in rats; however, no adverse effects were noted (Army 1985b). More sensitive neurological tests in animals via inhalation, oral, or dermal routes would be helpful in establishing definite less serious LOAELs.

2. HEALTH EFFECTS

Epidemiological and Human Dosimetry Studies. There is one human study that tested blood chemistry and hematology in 70 workers exposed to an average of 0.3 mg/m3 of RDX in the air (Hathaway and Buck 1977). All the other human studies are individual case reports. No epidemiology studies are available for exposure in drinking water. If populations with appropriate exposures could be identified, it would be useful to conduct epidemiologic and human dosimetry studies to establish cause and effect relationships and to plan future monitoring of individuals living near hazardous waste sites.

Biomarkers of Exposure and Effect. Urine or blood levels of RDX are the only known biomarkers of exposure for RDX. These biomarkers have only been demonstrated in a single case report of a child exposed one time (Woody et al. 1986). Therefore, the exposure level cannot be correlated to the levels in the body fluids for other people. Metabolites of RDX cannot be detected unless they are radiolabeled (Schneider et al. 1977). Further studies on determining the correlation between exposure and RDX levels in blood or urine would be useful in developing these levels as biomarkers.

There is no known sensitive biomarker for the effects of RDX. The most prominent effects are seizures in humans (Hollander and Colbach 1969; Kaplan et al. 1965; Ketel and Hughes 1972; Merrill 1968; Stone et al. 1969; Woody et al. 1986) or animals (Army 1983a; Burdette et al. 1988; Navy 1974b; Schneider et al. 1977; von Oettingen et al. 1949), but seizures can be evoked by a large number of substances and disease states. Further neurological tests would be useful in identifying a sensitive biomarker for effects.

Absorption, Distribution, Metabolism, and Excretion. There is only one study available regarding distribution of RDX. In this study, RDX was measured in the cerebrospinal fluid, blood, urine, and feces of a child following a single acute exposure to an unknown amount of RDX (Woody et al. 1986). Since there was only one child and incomplete data were provided, the rate and extent of absorption, distribution, metabolism, and excretion cannot be extrapolated to other indiv%uals. Neurotoxic effects in humans were observed following inhalation exposure, indicating that RDX may be absorbed in the lungs (Hollander and Colbach 1969; Kaplan et al. 1965). Humans have also suffered toxic effects from ingestion of RDX, indicating that RDX is absorbed through the gastrointestinal system (Hollander and Colbach 1969; Kaplan et al. 1965; Ketel and Hughes 1972; Merrill 1968; Stone et al. 1969; Woody et al. 1986). Other studies described some parameters of

absorption, distribution, and elimination in rats and miniature swine administered RDX via gavage (Schneider et al. 1977, 1978). Insufficient data are available to characterize RDX metabolism, or to give more than preliminary estimates of other kinetic parameters, including rate and extent of absorption, distribution, and excretion in animals. Further animal studies regarding these parameters following exposure via all routes would be useful to define the effects of RDX in the human body.

Comparative Toxicokinetics. Very few data are available to compare human and animal kinetics since only one human clinical case (Woody et al. 1986) and two animal studies in rats and miniature swine (Schneider et al. 1977, 1978) are available. Target organs for distribution are not known in either humans or animals. It is unknown whether rats, miniature swine, or any other animal are a good model for human kinetic properties. Establishing which animal species serves as the best model for extrapolating results to humans would be a useful first step in investigating comparative toxicokinetics. There is no available information regarding differences in toxicokinetics according to route of exposure.

Methods for Reducing Toxic Effects. There are no known mitigation measures for RDXinduced toxicity, other than removing it from the skin by washing (Twibell et al. 1984). Information on techniques to mitigate low-level, long-term effects would be useful for determining the safety and effectiveness of possible methods for treating RDX-exposed populations in the vicinity of hazardous waste sites. Further information on mitigation would rely on characterizing the mechanisms for RDX's effects.

2.9.3 Ongoing Studies

There are no known ongoing studies on the toxicity of RDX.

3. CHEMICAL AND PHYSICAL INFORMATION

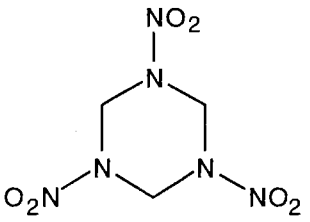
3.1 CHEMICAL IDENTITY

Information regarding the chemical identity of RDX is located in Table 3-l.

3.2 PHYSICAL AND CHEMICAL PROPERTIES

Information regarding the physical and chemical properties of RDX is located in Table 3-2.

TABLE 3-1. Chemical Identity of RDX

Characteristic	Information	Reference
Chemical name	RDX	HSDB 1994
Synonym(s)	Cyclonite; 1,3,5-triaza1,3,5,-trinitro-cyclohexane; hexahydro1,3,5-trinitro-1,3,5-triazine; 1,3,5-trinitrohexahydro-1,3,5-triazine; cyclotrimethylenenitramine;hexogen; hexolite; PBX	HSDB 1994
Registered trade name(s)	No data	
Chemical formula	$C_3H_6N_6O_6$	HSDB 1994
Chemical structure		Merck 1989
Identification numbers:		
CAS registry	121-82-4	Sax and Lewis 1987
NIOSH RTECS	XY9450000	HSDB 1994
EPA hazardous waste	No data	
OHM/TADS	No data	
DOT/UN/NA/IMCO shipping	UN0072; IMO1.1	HSDB 1994
HSDB	2079	HSDB 1994
NCI	No data	

CAS = Chemical Abstracts Services; DOT/UN/NA/IMCO = Department of Transportation/United Nations/North America/International Maritime Dangerous Goods Code; EPA = Environmental Protection Agency; HSDB = Hazardous Substances Data Bank; NCI = National Cancer Institute; NIOSH = National Institute for Occupational Safety and Health; OHM/TADS = Oil and Hazardous Materials/Technical Assistance Data System; RTECS = Registry of Toxic Effects of Chemical Substances

TABLE 3-2. Physical and Chemical Properties of RDX

Property	Information	Reference
Molecular weight	222.26	Merck 1989
Color	White	Sax and Lewis 1987
Physical state	Solid	Sax and Lewis 1987
Melting point	205–206 °C	Merck 1989
Boiling point	Decomposes	Miyares and Jenkins 1991
Density at 20 °C	1.82 g/mL	Merck 1989
Odor	No data	
Odor threshold:		
Water	No data	
Air	No data	
Solubility:		
Water at 20 °C	38.4–38.9 mg/L; 60 mg/L	Army 1983b; Miyares and Jenkins 1991
Organic solvent(s)	Slightly soluble in methanol, ether, ethyl acetate, glacial acetic acid	Merck 1989
Partition coefficients:		
Log K_{ow}	0.87[a]	HSDB 1994
Log K_{oc}	1.80[b]	Army 1987a
Vapor pressure at 20 °C	$1x10^{-9}$ mm Hg (Torr)	Army 1987a
Henry's law constant (atm-m^3/mol)	$1.2x10^{-5}$	McKone and Layton 1986
Autoignition temperature	No data	
Flashpoint	No data	
Flammability limits (explosive limits) (vol % in air)	No data	
Conversion factors	1 mg/m^3 = 9.1 ppm	HSDB 1994
Explosive limits	Class A explosive; explosion may be prompted by sudden shock, high temperature, or combination of both	

[a]Estimate value
[b]Calculated value

HSDB = Hazardous Substance Data Bank; vol % = percent volume

4. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

4.1 PRODUCTION

RDX has been produced several ways, but the most common method of manufacture used in the United States is the continuous Bachmann process (Army 1986a; Merck 1989). The Bachmann process involves reacting hexamine with nitric acid, ammonium nitrate, glacial acetic acid, and acetic anhydride (Army 1978c, 1986e). The crude product is filtered and recrystallized to form RDX (Army 1986a). A second process that has been used to manufacture RDX, the direct nitration of octahydro-1,3,5,7-tetranitro-1,3,5,7-tetrazocine (HMX), has not yielded a percentage of RDX as high as the percentage produced in the Bachmann process (Army 1978; Merck 1989).

Production of RDX peaked in the 1960s when it was ranked third in explosive production by volume in the United States (Army 1986e). The average volume of RDX produced from 1969 to 1971 was 15 million pounds per month. However, production of RDX decreased to a yearly total of 16 million pounds for 1984.

RDX is not produced commercially in the United States (HSDB 1994). Production in the United States is limited to Army ammunition plants such as Holston Army ammunition plant in Kingsport, Tennessee, which has been operating at lo-20% capacity (Army 1986e). Several Army ammunition plants, such as Louisiana (Shreveport, Louisiana), Lone Star (Texarkana, Texas), Iowa (Middletown, Iowa), and Milan (Milan, Tennessee), also handle and package RDX.

Since the release of RDX is not required to be reported under SARA Section 313, there are no data on RDX in the Toxics Release Inventory (TRI 1993).

4.2 IMPORT/EXPORT

No information is available regarding the import or export of RDX.

4. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

4.3 USE

RDX is a nitrate explosive compound (Turley and Brewster 1987). RDX has both military and civilian applications. As a military explosive, RDX can be used alone as a base charge for detonators or mixed with another explosive such as TNT to form cyclotols, which produce a bursting charge for aerial bombs, mines, and torpedoes (Sax and Lewis 1989; Stokinger 1982). Common military uses of RDX have been as an ingredient in plastic bonded explosives, or plastic explosives which have been used as explosive fill in almost all types of munition compounds (Gibbs and Popolato 1980). The plasticized form of RDX, composition C-4, contains 91% RDX, 2.1% polyisobutylene, 1.6% motor oil, and 5.3% 2-ethylhexyl sebacate (Turley and Brewster 1987). Civilian applications of RDX include use in fireworks, in demolition blocks, as a heating fuel for food rations (Turley and Brewster 1987), and as an occasional rodenticide (HSDB 1994). Combinations of RDX and HMX, another explosive, have been the chief ingredients in approximately 75 products (Army 1978c).

4.4 DISPOSAL

Waste-water treatment sludges resulting from the manufacture of RDX are classified as hazardous wastes and are subject to EPA regulations (EPA 1990a). For more information on regulations that apply to RDX, see Chapter 7.

Munitions such as RDX have been disposed of in the past by dumping in deep sea water (Hoffsommer and Rosen 1972). By-products of military explosives such as RDX have also been openly burned in many Army ammunition plants in the past. There are indications that in recent years as much as 80% of waste munitions and propellants have been disposed of by incineration (Army 1986a). Wastes containing RDX have been incinerated by grinding the explosive wastes with a flying knife cutter and spraying the ground material with water to form a slurry. The types of incineration used to dispose of waste munitions containing RDX include rotary kiln incineration, fluidized bed incineration, and pyrolitic incineration (Army 1986a). The primary disadvantage of open burning or incineration is that explosive contaminants are often released into the air, water, and soils (Army 1986c).

RDX wastes found in soils and sediments have been degraded in composts using substances such as hay, horse feed, sewage sludge, wood shavings, animal manure, and fruit and vegetable wastes (Army 1986b; Greist et al. 1993; Williams et a1.1992). In a mechanically stirred amended compost, the

concentration of RDX in soil was reduced from <800 mg/kg to 39 mg/kg after 44 days (Griest et al. 1993). RDX has been removed from munitions waste waters and contaminated groundwater by activated carbon columns (Army 1987c; Bricka and Sharp 1992; Wujcik et al. 1992). No RDX was detected when a contaminated groundwater containing 487 μg/L of RDX was passed through granular activated carbon (GAC) columns at a loading rate of 7.11 gpm/ft, flow rate of 0.7 gpm and an empty-bed contact time of 4.2 minutes (Wujcik et al. 1992). Once carbon columns were saturated with explosive, they were traditionally destroyed by open burning. Since this practice is no longer allowed in many areas, other disposal alternatives for spent carbons, such as thermal reactivation for reuse, oxidative incineration with ash burial, and thermal deactivation with carbon burial, have been investigated (Army 1987c). In a feasibility study, UV irradiation was found to provide effective treatment of RDX-contaminated groundwater (Bricka and Sharp 1992).

5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

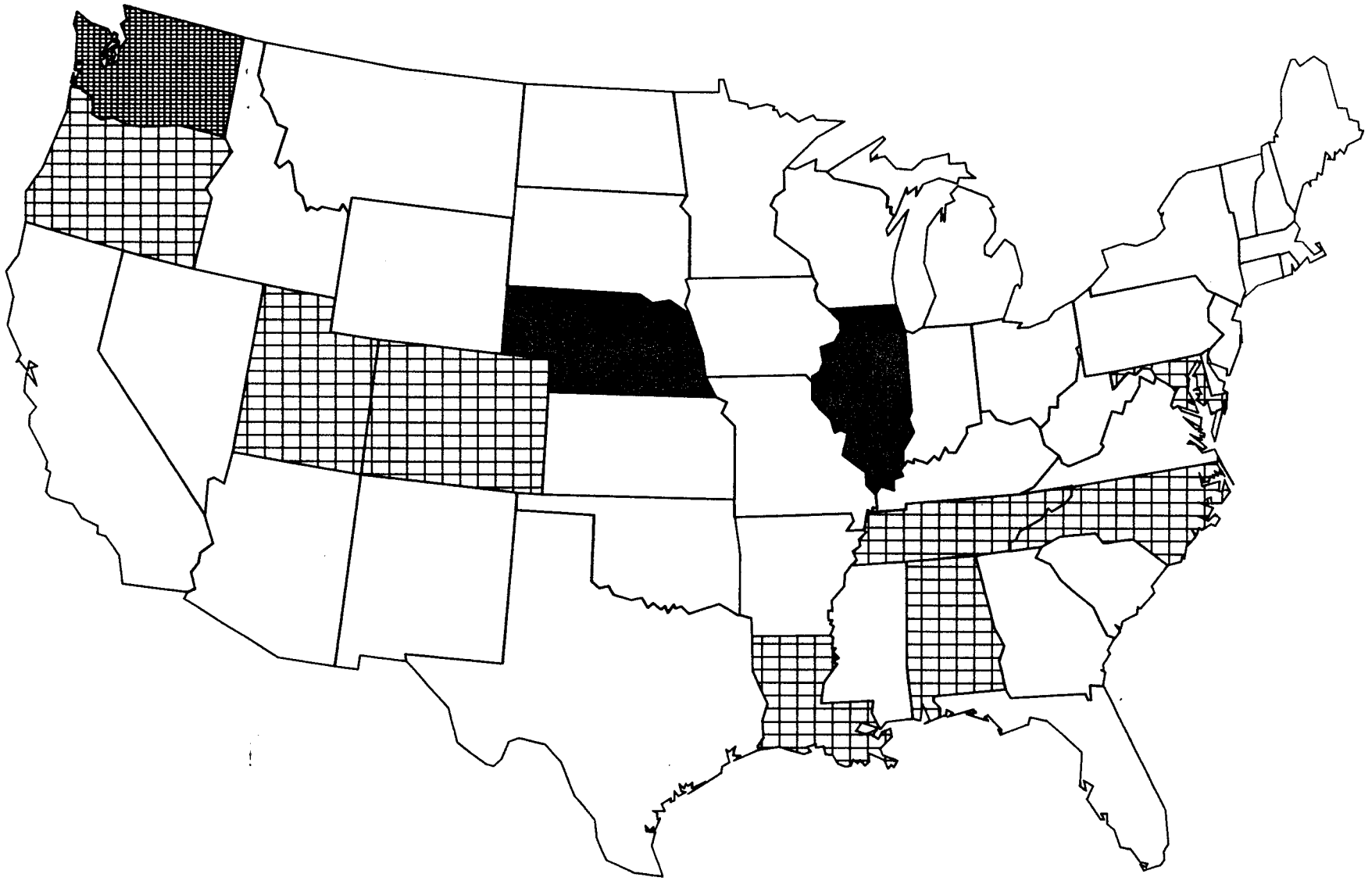
RDX is a widely used military explosive. It is a synthetic compound and is not known to exist in nature. Effluents and emissions from Army ammunition plants are responsible for the release of RDX into the environment. When released to the atmosphere, RDX may be removed by reaction with photochemically generated hydroxyl radicals (half-life = 1.5 hours). When released to water, RDX is subject to photolysis (half-life = 9-13 hours). Photoproducts include formaldehyde and nitrosamines. RDX undergoes biodegradation in water and soil under anaerobic conditions. Its biodegradation products include hexahydro-1-nitroso-3,5-dinitro-1,3,5-triazine; hexahydro-1,3-dinitroso-5-nitro-1,3,5-triazine (DNX); hexahydro-1,3,5-trinitroso-1,3,5-triazine (TNX); hydrazine; l,l-dimethyl-hydrazine, 1,2-dimethyl-hydrazine; formaldehyde; and methanol. RDX is mobile in soil and can leach into groundwater, and can be transported from soils to plants.

For the general population, exposure to RDX is limited to areas around Army ammunition plants where it is manufactured, converted to munitions, packed, loaded, or released through the demilitarization of antiquated munitions. The most likely route of exposure is ingestion of contaminated drinking water. Inhalation exposure of contaminated particulate matter produced during incineration of RDX-containing waste material is also a possible route of exposure. Occupational exposure to RDX can occur when workers handle RDX at Army ammunition plants. According to the National Occupational Exposure Survey (NOES) of 1981-1983 conducted by NIOSH, the estimated number of workers potentially exposed to RDX in the United States was 488 (NOES 1990).

RDX has been identified in 16 of the 1,397 hazardous waste sites that have been proposed for inclusion on the National Priorities List (NPL) (HazDat 1994). The frequency of these sites within the United States can be seen in Figure 5-l.

Since RDX releases are not required to be reported under SARA Section 313, there are no data on RDX in the Toxics Release Inventory (TRI 1993).

FIGURE 5-1. FREQUENCY OF NPL SITES WITH RDX CONTAMINATION *



*Derived from HazDat 1994

5. POTENTIAL FOR HUMAN EXPOSURE

5.2 RELEASES TO THE ENVIRONMENT

5.2.1 Air

RDX can enter the air through the release of contaminated particulate matter formed during the incineration of RDX-containing mixtures (Army 1984a). RDX can also enter the air through evaporation from aquatic effluent streams or waste storage lagoons (Army 1984a).

5.2.2 Water

RDX can be released to water in waste discharge effluents from Army ammunition production, formulation, manufacturing, loading, assembly, and packing, and through the demilitarization of antiquated munitions (Army 1980a, 1984a, 1984f).

5.2.3 Soil

Manufacturing, packing, and use of RDX have often resulted in contamination of soil. RDX can enter soil by leaching from waste lagoons and from improper disposal of contaminated sludge (Army 1984a). RDX can also enter the soil from spills during manufacture, transportation, and storage. Releases can also occur from the settling of airborne particulates from manufacturing and incineration onto soil surfaces (Army 1984a).

5.3 ENVIRONMENTAL FATE

5.3.1 Transport and Partitioning

RDX has a vapor pressure of 1.0×10^{-6} mm Hg (Army 1987a). It may exist in both the vapor phase and particulate phase in the atmosphere (Eisenreich et al. 1981). The solubility of RDX in water is low to negligible (Merck 1989; HSDB 1994). However, the following water solubility values have been reported: 21.8-21.9 mg/L at 10 °C, 38.4-38.9 mg/L at 20 °C, and 66.7-67 mg/L at 30 °C (Army 1983b). RDX is slightly soluble in methanol, ether, ethyl acetate, and glacial acetic acid (Merck 1989). The Henry's law constant for RDX (1.2×10^{-5} atm-m^3/mol) (McKone and Layton 1986)

indicates that RDX tends to partition equally between the atmosphere and water (Eisenreich et al. 1981) and that volatilization is a slow transport process (Lyman et al. 1982).

The calculated soil sorption coefficient (K_{OC}) values for RDX range from 63.1 (Army 1987a) to 270 (Army 1983b). These K_{OC} values are indicative of medium-to-high mobility in soil (Swarm et al. 1983); therefore, RDX can be expected to leach into groundwater. Experimental data have shown that RDX is not readily bound or retained in soil as evidenced by its early breakthrough in column leachates (Army 1985a). A lysimeter study of the migration of RDX in soil showed that RDX was found in leachate from the soil columns (Navy 1982). Based on these K_{OC} values and the experimental data, adsorption to sediment and particulate matter in the aquatic environment should not be significant (Army 1980a). Although RDX does not significantly adsorb to sediment, greater adsorption occurs with an increase in organic matter or clay content (Army 1980a). However, the clay content seems to be more important than organic matter content in influencing the amount of RDX adsorbed (Army 1980a). In a later study sponsored by the U.S. Army Medical Research and Development Command (USAMRDC), the adsorption rate constant of RDX in soil was found to be low (k_d of <l mg/g). The adsorption constant was linearly correlated with a combination of soil properties, such organic carbon and clay content, pH, and cation exchange capacity (Ainsworth et al. 1993). It appears that sorption of RDX in soils is not solely the result of hydrophobic partitioning of RDX to the organic carbon phase of the soils.

The logarithm of the octauol/water partition coefficient (log K_{OW}) is a useful preliminary indicator of potential bioaccumulation of a compound. The log K_{OW} for RDX was estimated to be 0.87 (HSDB 1994), indicating RDX is not very lipid soluble and therefore has a low potential for bioaccumulation. Experimental bioconcentration factors in edible tissue for bluegill *(Lepomis macrochirus),* channel catfish *(Ictalurus punctatus),* and fathead minnow *(Pimephales promelas)* were 1.9-6.4, 1.2-5.5, and 1.4-5.9, respectively (Army 1984a). These factors indicate that bioaccumulation in aquatic organisms is not an important fate process.

Data indicate that RDX can be taken up by plants (Army 1990a; Harvey et al. 1991). Studies of bean plants grown in 10 ppm RDX hydroponic solutions and exposed for 1 or 7 days indicated that uptake of RDX readily occurred. Following uptake, translocation of the compounds to the aerial tissue occurred, resulting in foliar concentrations of 20 ppm and 97 ppm for the 1 and 7 day exposures, respectively. Metabolism of RDX to polar metabolites was observed in plants exposed for 7 days

(Harvey et al. 1991). Additional studies of hydroponic plant-culture systems indicated that RDX (l-10 ppm) was also absorbed by the roots of blando brome and wheat and that plant absorption was concentration-dependent (Army 1990a). In a later study, plants were grown in soils containing 10 ppm RDX for a period of 60 days, and the extent of plant uptake was found to be dependent both on soil type and plant species (Cataldo et al. 1993). RDX was transported unchanged from soils to plants and the plant uptake increased as the organic matter content of soil decreased. In bush bean plants, RDX was mostly concentrated in leaves and seed, but less in roots, stems and pods. In case of wheat and blando brome, RDX mostly concentrated in leaves and roots, but very little or none in seeds (Cataldo et al. 1993). After plant uptake, RDX in storage tissues of plants (i.e., roots and stems) mostly metabolized to unidentified polar metabolites or non-extractable products, while RDX remained mostly unchanged (>50%) in leaves and seed tissues (Cataldo et al. 1993).

5.3.2 Transformation and Degradation

5.3.2.1 Air

When released to the atmosphere, RDX is degraded by reacting with photochemically generated hydroxyl radicals (Atkinson 1987; HSDB 1994). The half-life for this reaction in the vapor phase was estimated to be 1.5 hours (Atkinson 1987; HSDB 1994). No data were located on photolysis of RDX in the atmosphere. However, it is expected that photolysis of RDX is an important fate process in the atmosphere since RDX absorbs ultraviolet wavelengths between 240 and 350 nm (Army 1986e) and it undergoes rapid photolysis in water (Army 1980a).

5.3.2.2 Water

In a hydrolysis study of RDX in seawater (pH 8.1) at 25 °C, 11.6% of initial RDX hydrolyzed in 112 days (Hoffsommer and Rosen 1973). Other data found that RDX was stable to hydrolysis in an aqueous solution at a pH range normally found in natural waters (Army 1980a). Therefore, hydrolysis is not expected to significantly influence the environmental fate of RDX.

The primary physical mechanism that degrades RDX in aqueous solutions is photolysis (Army 1986e). The range of ultraviolet wavelengths that causes photolytic reactions with RDX is generally between 240 and 350 nm (Army 1986e). RDX in waste water (23.9 mg/L) exposed to ultraviolet radiation

decomposed with a half-life of 3.7 minutes (Burrows et al. 1984). Photolysis of an aqueous solution of RDX in natural sunlight is fairly rapid with an experimental half-life of 9-13 hours. Consequently, RDX is not expected to persist for a long period of time in surface waters (Army 1980a). Formaldehyde and nitrosamines were identified as photoproducts. Nitrosamines may be of environmental importance because of their potential mutagenicity/carcinogenicity. Conversion to this product, however, occurs only to a limited extent since the product itself is photoreactive (Army 1980a). The rate constants for photolytic transformation of RDX in the waste-water lagoon of a Louisiana Army ammunition plant were determined as 0.016 cm/day in the winter and 0.076 cm/day in the summer (Army 1983b). The half-life of RDX was estimated to range from over 2,000 days in winter to 456 days in summer in a lagoon 50 cm deep (Army 1983b). The slow photolysis rate can be attributed to the high absorptivity of light by surface water of the lagoon, which allowed little light to penetrate deeper into the lagoon water (Army 1983b).

The biodegradation of RDX has been studied under aerobic and anaerobic conditions. RDX did not undergo aerobic biodegradation using a variety of inocula and nutrients (Osmon and Klausmeier 1973). However, microbial degradation studies were carried out using water and sediment samples collected from the Holston River and the waste-water effluents from the Holston Army ammunition plant showed some degradation (Army 1980a). Only the addition of river sediments appeared to stimulate the aerobic biodegradation of RDX in samples of river water containing either 5.5 or 11.5 ppm of RDX. The half-life for the disappearance of RDX in water samples supplemented with sediment was approximately 7 days. A lag period of 2-3 weeks was observed before a noticeable degradation of RDX occurred. The results showed that biodegradation of RDX leads to mineralization of the molecule (Army 1980a). No degradation of RDX was observed during a 90-day aerobic experiment with RDX in the lagoon water alone, with added yeast extract, or with 1% of bottom sediment (Army 1983b). Concentrations of RDX remained unchanged when cultures were inoculated with aerobic activated sludge and incubated aerobically. No RDX disappeared in uninoculated controls (McCormick et al. 1981).

Data are available indicating that biodegradation of RDX occurs under anaerobic conditions (Army 1984f; McCormick et al. 1981; Walker and Kaplan 1992). RDX (50 or 100 yg/mL) disappeared rapidly from nutrient broth cultures inoculated with anaerobic sewage sludge and incubated anaerobically. Biodegradation of RDX was complete after 4 days (McCormick et al. 1981). The disappearance of RDX was accompanied by the appearance of several products identified as the

mono-, di-, and trinitroso derivatives of RDX formed by sequential reductions of the nitro groups to nitroso groups (McCormick et al. 1981; Walker and Kaplan 1992). Anaerobic biodegradation products included hexahydro-1-nitroso-3,5-dinitro-1,3,5-triazine (MNX); hexahydro-1,3-dinitroso-5-nitro-1,3,5-triazine (DNX); hexahydro-1,3,5-trinitroso-1,3,5-triazine (TNX); hydrazine; l,l-dimethyl-hydrazine; 1,2-dimethyl-hydrazine; formaldehyde; and methanol. The nitroso intermediates are known to be hazardous. Both l,l- and 1,2-dimethylhydrazine, as well as hydrazine, are known mutagens and/or carcinogens (McCormick et al. 1981), but may be found naturally in the environment (e.g., certain mushrooms).

After an incubation period of 5 days, 97% of RDX was anaerobically degraded by a mixed population of purple photosynthetic bacteria of the genera *Chromatium, Rhodospirillum,* and *Rhodopseudomonas,* and possibly others (Navy 1973). Sixty percent of RDX was anaerobically degraded by *Chromatium* alone (Navy 1973). These photosynthetically active cultures, which do not release oxygen, were supplemented with sodium acetate and ammonium chloride. It was hypothesized that RDX was not actually metabolized, but rather was being reduced and modified as a result of the active electron transfer brought about by the anaerobic photosynthetic activity of the organisms.

RDX (13 ppm) in lagoon waste water at the Louisiana Army ammunition plant did not undergo anaerobic degradation for approximately 90 days with yeast extract repeatedly added as a nutrient (Army 1983b). The RDX concentration dropped to 2.9 ppm at day 90 and to 1.4 ppm at day 92. The authors reported that the repeated addition of yeast extract acclimated RDX-utilizing organisms. The RDX-acclimated organisms then degraded 9.1 ppm of RDX 93% after 5 days of anaerobic incubation (Army 1983b).

5.3.2.3 Sediment and Soil

Three soils containing 0.5%-7.2% organic matter were amended with 60 ppm (mg/kg) RDX and incubated for 60 days under aerobic conditions (Cataldo et al. 1993). After 60 days, >95% were extractable and remained unchanged as parent RDX; only <2% remained non-extractable in the soils. No significant transformation products of RDX were observed in the soils. These results indicate that RDX may not be easily amenable to aerobic biodegradation in soils. However, significant biotransformation may occur under certain conditions. The degradation of pink water compounds in soil was studied (Army 1985a). Pink water is a generic term used for colored waters that may contain

some explosive compounds, including RDX. A simulated pink water containing RDX (30 mg/L) was continuously applied to a series of soil columns at different flow rates, with and without carbon supplementation. The columns were inoculated with combined samples of microorganisms from activated sludge, anaerobic sludge digest, and garden soil. Concentrations of RDX and biotransformation products were monitored on a weekly basis. There appeared to be a significant decrease in RDX recovery in the leachate of the column with slow and fast flow with carbon supplement, indicating microbial activity. The mononitroso derivative (MNX) and the dinitroso derivatives of RDX were identified in the leachate of the column with fast flow (100 ml/day) and carbon supplement (2.0 g/L glucose). MNX was also identified in the leachates from the columns with slow flow (40 ml/day) with and without carbon supplement (Army 1985a). Since the nitroso derivatives are intermediates in the anaerobic biodegradation of RDX in aqueous systems (Walker and Kaplan 1992), it is likely that the observed products resulted from anaerobic biodegradation of RDX. The authors reported that land treatment or land farming of pink water should not be considered as a treatment option for pink water. Hazardous biotransformation intermediates and unchanged concentrations of some of the pink water compounds would contaminate groundwater and soil.

5.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

5.4.1 Air

No data are available regarding levels of RDX in outdoor air. However, indoor air samples collected at Holtson Army ammunition plant in Kingsport, Tennessee in 1974 contained RDX levels ranging from not detected (<0.5 mg/m^3 [4.5 ppm]) to 60 mg/m^3 (546 ppm) (Army 1975). A more recent study found that RDX was detected at a concentration of 0.032 mg/m^3 (0.29 ppm) in the particulate fraction of one indoor air sample taken from the incorporation area of Holtson Army ammunition plant in 1986 (Bishop et al. 1988).

5.4.2 Water

Seawater samples taken in 1971 from a munitions dumping area 85 miles west of Cape Flattery, Washington, and similar samples taken 172 miles south-southeast of Charleston, South Carolina, were analyzed for RDX (Navy 1972). No RDX was found in any of the samples examined (detection limit of 5 ppt). RDX was found on-site at the Savanna Army Depot in Illinois in surface water samples at

a maximum reported concentration of 36.9 ppm (ATSDR 1989c). The Savanna Army Depot is on the NPL. It is an Army munitions plant engaged in munitions renovation, loading, demolition, and burning. On-site groundwater sampling at the Milan Army ammunition plant in Tennessee identified RDX at concentrations ranging from not detected to 11.24 ppm (detection limit not reported) (ATSDR 1989b). Maximum concentrations of RDX detected in water at the Cornhusker Army ammunition plant (Nebraska) were 0.307 and 0.371 ppm from on-site and off-site wells, respectively (ATSDR 1989a). A plume of RDX-contaminated groundwater, which stretched 6.5 km, was found near the Cornhusker Army ammunition plant. The concentrations ranged from 9 to >l00 μg/L (Spalding and Fulton 1988). The Louisiana Army ammunition plant is a shell manufacturing and explosives load, assembly, and pack facility (Army 1988). From 1951 to 1980, waste waters were trucked to and discharged into a series of artificial leaching pits, which resulted in contamination of soil, sediments, and groundwater. Levels of RDX measured in groundwater at the Louisiana Army ammunition plant ranged from 1.3 to 14,100 μg/L (Army 1988).

5.4.3 Sediment and Soil

Ocean floor sediment samples taken in 1971 from a munitions dumping area 85 miles west of Cape Flattery, Washington, and similar samples taken 172 miles south-southeast of Charleston, South Carolina, were analyzed for RDX (Navy 1972). No RDX was found in any of the sediment samples analyzed. RDX was found on-site at the Savanna Army Depot in Illinois in soil samples at a maximum concentration of 12.3 ppm (ATSDR 1989c). RDX was found at the Louisiana Army ammunition plant in soil and drainage sediments at concentrations ranging from <5 to 602 mg/kg (Army 1988).

5.4.4 Other Environmental Media

Ocean floor fauna samples (rat tail fish and sea cucumbers) taken in 1971 from munitions dumping areas in the Atlantic and Pacific oceans contained no RDX residues (detection limit of 0.123 μg/kg) (Navy 1972).

5.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

For the general population, exposure to RDX is most likely limited to areas around Army ammunition plants where RDX is manufactured, converted to munitions, or released through the demilitarization of antiquated munitions (Army 1980a, 1984a, 1984f). The most likely route of exposure for populations living in the vicinity of Army ammunition plants is ingestion of contaminated drinking water. Inhalation exposure of contaminated particulate matter produced during incineration of RDXcontaining waste material is a possible route of exposure. However, since no monitoring data were located regarding levels of RDX in air, the extent of exposure by this route is not known. Dermal contact with contaminated soil is also a possible route of exposure. However, since no absorption data following dermal exposure to RDX were located, the extent of exposure by this route is also not known.

Occupational exposure to RDX can occur when workers handle RDX in explosive plants (Hathaway and Buck 1977; Kaplan et al. 1965). Inhalation exposure of workers to RDX has occurred as a result of release of dust into the workroom air, principally during dumping of dried RDX powder, screening and blending, and clean-up of spilled material (Kaplan et al. 1965). Exposure to RDX can also occur through dermal contact during manufacture, handling, and clean-up of RDX (Kaplan et al. 1965). RDX was detected at a concentration of 0.052 mg/m^3 (0.47 ppm) in the particulate fraction of one indoor air sample taken from the incorporation area of Holston Army Ammunition Plants in Tennessee in 1986 (Bishop et al. 1988). Based on the observed concentration, the authors considered the potential for exposure to RDX to be very low.

According to the NOES (1981-1983), the estimated number of workers potentially exposed to RDX in the United States was 488 (NOES 1990)

5.6 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Workers involved in the production and use of RDX at Army ammunition plants constitute a group at risk because of the potential for occupational exposure. Persons living near Army ammunition plants or hazardous waste sites may have a higher risk of exposure to RDX resulting from inhalation of dusts or fumes, ingestion of contaminated drinking water, or contact with contaminated soil.

5.7 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of RDX is available. where adequate information is not available, ATSDR, in conjunction with NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of RDX.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that, if met, would reduce or eliminate the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda may be proposed.

5.7.1 Identification of Data Needs

Physical and Chemical Properties. The physical and chemical properties of RDX are sufficiently characterized to permit estimation of its environmental fate (Army 1986e, 1987a; HSDB 1994; Merck 1989; McKone and Layton 1986).

Production, Import/Export, Use, Release and Disposal. RDX is not produced commercially in the United States (HSDB 1994). Production in the United States is limited to Army ammunition plants such as Holston Army Ammunition Plants in Kingsport, Tennessee, which has been operating at 10-20s capacity (Army 1986e). Several Army ammunition plants also handle and package RDX such as Louisiana (Shreveport, Louisiana), Lone Star (Texarkana, Texas), Iowa (Middletown, Iowa), and Milan (Milan, Texas) (Army 1986e). Current import/export data for RDX are not available. RDX is primarily used as a high explosive, although it has been used occasionally as a rat poison or for civilian uses, such as in fireworks or as heating fuel for food rations (Merck 1989; HSDB 1994; Turley and Brewster 1987). RDX is primarily found in water, groundwater, and soil around Army ammunition plants (Army 1988; ATSDR 1989a, 1989b, 1989c; Spalding and Fulton 1988). Data on the most commonly used disposal methods are sufficient (Army 1986a, 1986c; Hoffsommer and Rosen

1972); however, more data on the amounts of RDX being disposed of and on alternative disposal methods would be useful. RDX wastes produced in manufacturing and processing are classified as hazardous wastes and are subject to EPA regulations (EPA 1990a).

Environmental Fate. RDX released to the environment partitions into air, water, and soil (Army 1980a, 1983b, 1987a; Eisenreich et al. 1981; Lyman et al. 1982). RDX is transported in soil, surface water, and groundwater (Army 1983b, 1985a; 1986e, 1987a; Swann et al. 1983). Volatilization is expected to be a slow transport process (Lyman et al. 1982). No data were located in the literature regarding atmospheric transport of RDX. RDX is degraded in the atmosphere by reacting with photochemically generated hydroxyl radicals (half-life = 1.5 hours) (Atkinson 1987; HSDB 1994). Experimental data are needed regarding photolysis of RDX in the atmosphere. Photolysis is the primary mechanism of RDX degradation in water (half-life = 9-13 hours) (Army 1980a, 1986e). Biodegradation of RDX occurs in water and soil, principally under anaerobic conditions (Army 1984f, 1985a; McCormick et al. 1981; Osmon and Klausmeier 1973). Biodegradation half-life data for RDX and its breakdown products in water and soil are needed. This information will be helpful in better identifying the most important pathways of human exposure to RDX.

Bioavailability from Environmental Media. Absorption data regarding dermal exposure in humans are not available. Very limited data indicate that RDX is absorbed following inhalation exposure (Kaplan et al. 1965). RDX is absorbed through the gastrointestinal system following ingestion of the compound (Hollander and Colbach 1969; Ketel and Hughes 1972; Merrill 1968; Stone et al. 1969). The oral and dermal routes of exposure may be of concern to humans because of the potential for RDX to contaminate drinking water and soil. More information regarding all absorption routes, particularly on the absorption of RDX following ingestion of contaminated drinking water and soil or plants grown in contaminated environments, is needed to better characterize the bioavailability of RDX.

Food Chain Bioticcumulation. Based on a low log K_{ow} and a low experimental BCF, RDX has a low bioconcentration potential in aquatic organisms (Army 1984a; HSDB 1994). Limited data were located regarding bioaccumulation of RDX in plants (Harvey et al. 1991). No data were located regarding bioconcentration potential in animals. Data are needed regarding bioconcentration/ biomagnification potential in terrestrial food chains.

5. POTENTIAL FOR HUMAN EXPOSURE

Exposure Levels in Environmental Media. RDX has been detected in surface water, groundwater, and soil at Army ammunition plants (ATSDR 1989a, 1989b, 1989c; Spalding and Fulton 1988). Data are needed regarding levels of RDX in ambient air and occupational air. No data were located regarding human intake estimates for each media. Reliable monitoring data are needed for levels of RDX in contaminated media at hazardous waste sites. The information on RDX levels in the environment and the resulting body burden of RDX can be used to assess the potential risk of adverse health effects in populations living in the vicinity of hazardous waste sites.

Exposure Levels in Humans. Very limited data indicate that RDX has been found in human cerebrospinal fluid, plasma, urine, and feces (Woody et al. 1986). Biological monitoring data are needed for occupationally exposed populations and populations living in the vicinity of Army ammunition plants and hazardous waste sites. This information is necessary for assessing the need to conduct health studies on these populations.

Exposure Registries. No exposure registries for RDX were located. This substance is not currently one of the substances for which a subregistry has been established in the National Exposure Registry. The substance will be considered in the future when chemical selection is made for subregistries to be established. The information that is amassed in the National Exposure Registry facilitates the epidemiological research needed to assess adverse health outcomes that may be related to the exposure to this substance.

5.7.2 Ongoing Studies

The Department of Energy is sponsoring a project to study plant physiology. The process by which plant cells take up, degrade, or modify certain explosive compounds (i.e., RDX, TNT, and HMX) will be investigated. This work is being performed at the Los Alamos National Laboratory by P.J. Jackson (FEDRIP 1994).

6. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting and/or measuring and monitoring RDX in environmental media and in biological samples. The intent is not to provide an exhaustive list of analytical methods that could be used to detect and quantify RDX. Rather, the intention is to identify well-established methods that are used as the standard methods of analysis. Many of the analytical methods used to detect RDX in environmental samples are the methods approved by federal organizations such as EPA and the National Institute for Occupational Safety and Health (NIOSH). Other methods presented in this chapter may be those that are approved by groups such as the Association of Official Analytical Chemists (AOAC) and the American Public Health Association (APHA). Additionally, analytical methods may be included that refine previously used methods to obtain lower detection limits, and/or to improve accuracy and precision.

6.1 BIOLOGICAL SAMPLES

Analytical methods specifically used for the determination of RDX in biological fluids and tissues are limited. Methods were located which discussed the analysis of RDX in blood, tissues, urine, and hand swabs. The separation methods employed were either high-performance liquid chromatography (HPLC) or gas chromatography (GC). These were combined with detection by thermal energy analyzer (TEA), ultraviolet (UV), electrochemical detector (ED), or electron capture detector (ECD). Both HPLC and high-resolution gas chromatography (HRGC) can rapidly separate RDX from other explosives, but HPLC has the advantage of being run at ambient temperature, which helps prevent breakdown of the analyte. Sample preparation for RDX analytical methods is relatively simple, consisting of collection, one or two extraction/clean-up steps, and concentration of the sample. Pertinent data on the these methods are presented in Table 6- 1.

Detection of RDX in human and animal plasma and human urine and cerebrospinal fluid has been accomplished by HPLC/TEA and HPLC/UV (Army 1981a; Fine et al. 1984; Turley and Brewster 1987). While both methods provide relatively rapid sample turn-around times, HPLC/TEA is the most sensitive and selective of the two, and requires little sample preparation (Fine et al. 1984). The older HPLCU/UV method (Army 1981a) had the problem of coelution of a plasma component with the RDX peak. This was eradicated by clean-up on a C_{18} bonded-phase extraction column (Turley and Brewster 1987: Woody et al. 1986), but the sensitivity of HPLC/UV was still several orders of magnitude less

TABLE 6-1. Analytical Methods for Determining RDX in Biological Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Plasma	Extract with methylene chloride and pentane; filter; concentrate	HPLC/TEA	100 ng/L	No data	Fine et al. 1984
Plasma	Add NaCl/acetic acid solution to sample; extract with toluene; add water; evaporate organic phase; combine aqueous phase with acetonitrile-containing internal standard; filter	HPLC/UV	146 mg/L	87.7	Army 1981a
Serum and urine	Mix sample with internal standard; clean up on C_{18}-bonded-phase extraction column, eluting with methanol; concentrate	HPLC/UV	100 µg/L	90–101 (serum); 98–101 (urine)	Turley and Brewster 1987
Kidney	Add NaCl/acetic acid solution to sample; extract with toluene; add water; evaporate organic phase; combine aqueous phase with acetonitrile-containing internal standard; filter	HPLC/UV	95 ng/g	99.5	Army 1981a
Muscle/fat	Homogenize sample; extract with acetonitrile; concentrate; add internal standard and purified water; filter	HPLC/UV	62 ng/g	102.9	Army 1981a
Liver	Homogenize sample; add NaCl/acetic acid solution; evaporate; redissolve in acetonitrile-containing internal standard; filter	HPLC/UV	150 ng/g	87.7	Army 1981a
Hand swabs	Wipe hand with swab soaked in acetone; squeeze out acetone and concentrate	HPLC/TEA; HRGC/TEA	10 pg/inj	No data	Fine et al. 1984
Hand swabs	Wipe hand with swab soaked in ether; extract with ether; centrifuge to remove debris; decant supernatant and evaporate; redissolve in pentane; clean up on Amberlite XAD-7 beads, eluting with ethyl acetate; evaporate; redissolve in pentane and repeat Amberlite XAD-7 clean-up	GC/ECD	50 ng/swab (1.7 ng/inj)	47	Douse 1982
		TLC	20 ng/swab	No data	
Hand swabs, standards	Wipe hand with dry swab; extract with methanol/potassium phosphate; directly inject standards	HPLC/PMDE	8 pg/inj (standards)	No data	Lloyd 1983

ECD = electron capture detection; GC = gas chromatography; HPLC = high-performance liquid chromatography; HRGC = high-resolution gas chromatography; inj = injection; NaCl = sodium chloride; PMDE = pendant mercury drop electrode; TEA = thermal energy analyzer; TLC = thin layer chromatography; UV = ultraviolet detection

(limit of detection in low ppb) than that of HPLC/TEA (limit of detection in low ppt). Reported recoveries, which ranged from 87.7 to 101%, were excellent (Army 1981a; Turley and Brewster 1987; Woody et al. 1986). Precision was comparable and ranged from 0.65 to 10% coefficient of variation (CV).

A single method of analyzing feces for RDX was located (Woody et al. 1986). This method used HPLC/UV and required extraction of the sample with acetonitrile and sonication. The limit of detection was not reported but, based on the data presented, is assumed to be in the low ppb. Accuracy and precision were comparable with similar measurements in serum, urine, and cerebrospinal fluid.

Only one method was located for analysis of tissue samples. The method used HPLC/UV to analyze bovine kidney, muscle/fat, and liver samples for RDX, but it could be used to analyze human tissues (Army 1981a). Optimal sample preparation methods varied slightly for the different tissues, as did detection limits and precision. In general, the detection limit was in the low ppb and recovery was excellent (range of 87.7-102.9). Precision ranged from 7 to 16% CV. The primary problem with analysis of tissue using this method is the variation in selectivity. Minor differences in sample extraction and contamination from unknown sources can create interferences that drastically affect interpretation of results and may also adversely affect the sensitivity.

The only other methods for biological matrices located were for analysis of hand swabs. These are of primary importance in forensics, but they could also be used to determine if dermal exposure of workers has occurred. Methods that have been used for the determination of trace amounts of RDX on hands include HPLC with TEA or electrochemical detection and HRGC with TEA or ECD (Douse 1982; Fine et al 1984; Lloyd 1983). Thin-layer chromatography has also been tested, but because of the large amounts of sample that are required for the analysis, it is useful only as a confirmatory test (Douse 1982). Separation of the sample by HPLC and HRGC are comparable, but reported recovery for HRGC is low (Douse 1982). This is likely because of decomposition of the sample;‘but the data are not available to adequately compare the recovery of the two methods. The nature of the detector seems to be the most important factor in determining which of the reported methods is most useful for the analysis of RDX in hand-swab extracts. ECD appears to be less sensitive (ng amounts) than either electrochemical detection using the pendant mercury drop electrode (PMDE) or TEA (pg amounts). In addition, in the method reported, clean-up was required to prevent matrix interference (Douse 1982).

For both the PMDE and TEA methods, clean-up of the sample was not required, and both methods were rapid, selective, and of high precision (Fine et al. 1984; Lloyd 1983).

6.2 ENVIRONMENTAL SAMPLES

A large variety of methods have been described for the detection of RDX in environmental samples. These primarily include HRGC combined with ECD, TEA, mass spectrometry (MS), or flame ionization detection (FID); HPLC combined with UV, TEA, MS, photoconductivity (PD), or electrochemical detection; and several stand-alone MS techniques. Other methods have also been proposed, including fluorescent quenching; supercritical fluid (SFC) with UV; liquid chromatography (LC) with thermospray (TSP) and MS; and bioassays based on chemical oxygen demand (COD) and total oxygen demand (TOD). Table 6-2 is a summary of several representative methods for determining RDX in various environmental media.

Several methods for determining RDX in air have been investigated. Based on the limited data available, the two most common methods are GC/ECD and MS. The data reported are not sufficient to make comparisons of sensitivity and reliability between the methods. However, GC/ECD appears to have good sensitivity (low ppb), accuracy, and precision (Bishop et al. 1981, 1988). The sensitivity of this method (mid ppb) is approximately 30 times greater than that achieved with GC/FID (Army 1975), and precision is also better (±4% CV for GC/ECD versus ±15% CV for GC/FID). An alternate method based on spectrophotometry also provided very good results for accuracy and precision (±12.4% CV) and had a detection limit of the same order of magnitude as that reported using GC/ECD (Eminger and Vejrostova 1984). MS methods with sensitivity in the sub-ppb range have been described, but specific information on their reliability is limited. MS is generally accepted to be highly selective. Of the two MS methods described, isotope dilution MS (IDMS) (St. John et al. 1975) and MS/MS with atmospheric pressure chemical ionization (APCI) (Tanner et al. 1983), the latter (APCI/MS/MS) is the most rapid and simple to perform because the sample of air containing RDX vapors is-directly injected into the instrument. The high sensitivity and selectivity of MS/MS allow the air sample to be injected without prior treatment or concentration. However, the method as presented appears to be primarily useful as a screening technique to determine if more rigorous quantitative analysis is required. IDMS requires some sample preparation in order to incorporate the known amount of labeled analyte in with the sample containing the unknown amount of RDX. IDMS has been used to measure the vapor pressure of RDX, which is in the sub-ppb range.

TABLE 6-2. Analytical Methods for Determining RDX in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Air	Collect sample on Tenax-plus-filter tubes; desorb with acetonitrile	HRGC/ECD	17 µg/m^3	No data	Bishop et al. 1988
Air	Collect sample on Tenax-GC; desorb with acetonitrile	HRGC/ECD	No data	93–102	Bishop et al. 1981
Air	Collect sample on glass-fiber filter; extract with ethyl acetate	GC/FID	0.5 mg/m^3	No data	Army 1975
Air	Collect sample in sampling tube of glass-microfibers and silica gel; transfer to H_2SO_4 solution and react with dihydroxynapthalene-disulfonic acid and water; dilute with water	Spectrophotometry	40 µg/m^3	95.7–97.3	Eminger and Vefrostova 1984
Air	Incorporate sample into bulb containing isotopically-labeled RDX; extract with benzene; transfer to capillary tube and evaporate	IDMS	Sub-ppb	No data	St. John et al. 1975
Air	Inject sample directly into instrument	APCI/MS/MS	Sub-ppb	No data	Tanner et al. 1983
Waste-water effluents	Add internal standard to sample; elute from reverse-phase column with methanol/water	HPLC/UV	0.2 mg/L	72–103	Army 1983c
Groundwater, waste-water effluents	Dilute sample with methanol/acetonitrile; filter; elute from reverse-phase column with water/aceto-nitrile/methanol	HPLC/UV	22 µg/L	101	Army 1985c; Jenkins et al. 1986
Groundwater	Collect sample on Hayesep R solid sorbent cartridge; elute with acetone; concentrate; add internal standards; dilute with methanol/water	HPLC/UV/UV/PD	5–7.5 µg/L	104–121	Army 1989a

TABLE 6-2. Analytical Methods for Determining RDX in Environmental Samples (continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Surface water, well water	Collect sample on Porapak resin; rinse sorbent with distilled water and elute with acetone; concentrate; add ethanol; concentrate; add methanol/water	HPLC/ED	≈1 µg/L	57–63	Maskarinec et al. 1984
Water	Collect sample on XAD-4 resin; elute with ethyl acetate; concentrate	HRGC/ECD	<0.1 µg/L	97	Richard and Junk 1986
Groundwater, drinking water	Extract sample with isoamyl acetate	HRGC/ECD	0.3 µg/L	56–84	Hable et al. 1991
Sea water	Add internal standard to sample; extract with benzene; evaporate; redissolve in benzene	GC/ECD	5 ng/L	70	Hoffsommer and Rosen 1972
Groundwater, drinking water	Extract sample with isoamyl acetate	HRGC/ECD	0.3 µg/L	56–84	Hable et al. 1991
Sea water	Add internal standard to sample; extract with benzene; evaporate; redissolve in benzene	GC/ECD	5 ng/L	70	Hoffsommer and Rosen 1972
Water	Evaporate sample; redissolve in acetone; filter; concentrate	HRGC/ECD	60 ng/L	85	Haas et al. 1990
Water	Inject sample directly into instrument	MS (CI)	4 mg/L	No data	Yinon and Laschever 1982
Groundwater	Add sample to cyclo-hexanone/pyrenebutyric acid/cellulose triacetate/isodecyl diphenylphosphate membrane in cuvette	Fluorescense quenching	≈10 mg/L	No data	Jian and Seitz 1990

TABLE 6-2. Analytical Methods for Determining RDX in Environmental Samples (continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Soil	Air-dry, grind, and sieve sample; extract with acetonitrile in ultrasonic bath; add $CaCl_2$; filter; elute from reverse-phase column with water/methanol	HPLC/UV	0.74 µg/g	84–112	Army 1987b; Bauer et al. 1990; Jenkins and Grant 1987; Jenkins et al. 1989 (interim AOAC method)
Soil	Adjust sample moisture to 20–30%; homogenize and sieve; extract with acetonitrile and sonication; centrifuge and filter; elute from reverse-phase column with methanol/water	HPLC/UV	0.6 µg/g	103.7	Bongiovanni et al. 1984
Soil	Air-dry sample; extract with acetonitrile; filter; evaporate; redissolve in acetonitrile; elute from reverse-phase column with acetonitrile/water	HPLC/UV	0.005 µg/g	No data	Lyter 1983
Soil	Homogenize sample; extract with acetone; filter	HRGC/ECD	75 ng/g	95	Haas et al. 1990
Soil	Homogenize sample; extract with acetone; evaporate; react with diphenylamine/H_2SO_4	Spectrophotometry	5 mg/L	No data	Haas et al. 1990
Explosive preparations	Elute from HPLC column with isooctane/ethanol	HPLC/TEA	No data	98–102	Lafleur and Morriseau 1980
Explosives, explosion debris	Dissolve sample in acetone; dilute in methanol	HPLC/TEA HRGC/TEA	Low pg	No data	Fine et al. 1984

TABLE 6-2. Analytical Methods for Determining RDX in Environmental Samples (continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Explosives	Extract sample with acetone; elute from HPLC column with methanol/potassium phosphate	HPLC/EC (PDME)	8 pg/g	No data	Lloyd 1983
Explosion debris	Extract sample in acetone; clean up on cyclohexyl column; eluting with methylene chloride/hexane; clean up on cyanopropyl column; eluting with acetonitrile/water	HPLC/UV	No data	99	Strobel and Tontarski 1983
Munitions products	Dissolve sample in acetonitrile; add water; elute from reverse-phase column with methanol/water	HPLC/UV	No data	No data	Burrows and Brueggemann 1985
Explosives	Extract with acetone; evaporate; redissolve in dichloroethane; elute from HPLC column with dichloroethane/hexane	HPLC/MS (CI)	≈1 ng	No data	Vouros et al. 1977
Explosives, explosive residues	Dissolve in acetone or methanol; elute from HPLC column with methanol/ammonium acetate	HPLC/TSP/MS	Low pg	No data	Berberich et al. 1988

APCI = atmospheric pressure chemical ionization; AOAC = Association of Official Analytical Chemists; $CaCl_2$ = calcium chloride; CI = chemical ionization; EC = electrochemical detection; ECD = electron capture detection; ED = electrochemical detection; FID = flame ionization detection; GC = gas chromatography; HPLC = high-performance liquid chromatography; HRGC = high-resolution gas chromatography; H_2SO_4 = sulfuric acid; IDMS = isotope dilution mass spectrometry; MS = mass spectrometry; PD = photoconductivity detection; PDME = pendant mercury drop electrode; TEA = thermal energy analyzer; TSP = thermospray; UV = ultraviolet detection

6. ANALYTICAL METHODS

The primary analytical methods for determining RDX in water are HPLC/UV and GC/ECD. These methods have been used to determine the chemical in waste-water effluents, groundwater, well water, drinking water, and sea water. The critical step in the analysis of RDX by HPLC/UV is separation of the sample on a reverse-phase column, which provides good selectivity without risk of thermal breakdown of the analyte (Army 1983c, 1985c; Jenkins et al. 1986). The method is simple, quick, and reproducible. Sensitivity is in the low- to mid-ppb range, with very good recovery and excellent precision (2-7.6% CV). The use of HPLC in combination with photodiode-array detection improves the reliability of peak identification (Emmrich et al. 1993). The HPLC-photodiode-array detection method can provide a detection limit of 0.09 ppb for RDX in aqueous samples concentrated l,000-fold by liquid-liquid extraction or by solid phase extraction (C-18) (Levsen et al. 1993). The extraction efficiency of RDX from water to acetonitrile can be improved by using salting out agents (Miyares and Jenkins 1991). The sensitivity and selectivity of RDX detection was improved by combining a solid sorbent cartridge to concentrate RDX from water and HPLC-tandem ultraviolet and photoconductivity detection (HPLC/UV/UV/PD) (Army 1989a). The serial use of the three detectors effectively differentiated RDX from other explosives and from contaminants in the solid sorbent cartridge. In addition, the sensitivity was improved by a factor of about 3, and the accuracy and precision (±13-19.6% CV) were only slightly less than HPLC/UV values. To prevent negative baseline drift and random spikes in the PD, only highly purified water must be used, and the effluent must be exhaustively degassed. For analysis by GC/ECD, water samples may be solvent-extracted (Belkin et al. 1985; Haas et al. 1990; Hable et al. 1991; Hoffsommer and Rosen 1972) or collected on a solid sorbent (Richard and Junk 1986). Solvent extraction is most commonly used, but solid sorbent collection has the advantages of being faster and cheaper than solvent extraction (Richard and Junk 1986). Sensitivity for the GC/ECD methods ranges from low to mid ppt, and the recovery and precision are acceptable. Use of the solid sorbent improved recovery and precision compared to solvent-extraction methods (Richard and Junk 1986). Substitution of electrochemical detection (ED), using a gold-mercury electrode, improved selectivity compared to ECD detection. Sensitivity was not as good, but it remained within an order of magnitude of that found with GC/ECD (Maskarinec et al. 1984). Recove-Q and precision were comparable. Other methods that have been used to determine RDX in water are MS, fluorescence quenching, chemical oxygen demand (COD), and total organic carbon (TOC) (Jian and Seitz 1990; Roth and Murphy 1978; Yinon and Laschever 1982). COD and TOC (Roth and Murphy 1978) are well-established standard methods for determining organic pollution in water, but they are not selective for RDX. MS with chemical ionization (CI) permits direct injection of the water sample into the analytical instrument, but the sensitivity is substantially less than

with the HPLC and GC methods (Yinon and Laschever 1982). Fluorescence quenching also lacks sensitivity, and the method is still under development. However, it does permit *in situ* measurement of samples, and further improvements in the technology may make it a desirable field method (Jian and Seitz 1990).

The few methods that were located for detection of RDX in soil are based primarily on HPLC/UV analysis (Army 1987b; Bauer et al. 1990; Bongiovanni et al. 1984; Jenkins and Grant 1987; Jenkins et al. 1989; Lyter 1983). All the methods involve extraction of the sample with acetonitrile, separation using a reverse-phase column, and in most cases, elution with acetonitrile/water. Sensitivity for these methods is in the sub- to low-ppm range with good recovery (84-l 12%) and precision (2.3-24% CV). A variation of the method, which involves the soil sample being extracted with acetonitrile in an ultrasonic bath, has been approved on an interim basis by the AOAC (Jenkins et al. 1989). The only other methods located were based on GC/ECD and spectrophotometry (Haas et al. 1990). For both of these, the sample was extracted with acetone. The detection limit for spectrophotometric determination of RDX in soil was in the low-ppm range, while the detection limit for GC/ECD was in the mid-ppb range. No information on accuracy and precision were given for the spectrophotometric method; however, the accuracy of GC/ECD was comparable to HPLCAJV.

Several methods have been used to detect and measure RDX in explosive materials and debris from explosions. The most common separation procedure is HPLC, but HRGC has also been used. These methods have been paired with several types of detectors, including TEA, MS, electrochemical detection, and UV. The TEA is very selective for nitroso compounds and when paired with either HPLC or HRGC gives excellent selectivity, recovery, and precision and high sensitivity (Fine et al. 1984; Lafleur and Morriseau 1980). The limited reports of analysis of materials using HPLC and electrochemical detection indicate detection limits in the low ppb and good reliability (Krull et al. 1984; Lloyd 1983). UV detection has also been used with HPLC separation, but few data are available for comparison with other methods (Burrows and Brueggemann 1985; Strobe1 and Tontarski 1983). The data suggest that this method has very good accuracy and precision; however, the selectivity may not be as good as that obtained with other detectors. GC/MS has been used for confirmation of RDX in samples (Burrows and Brueggemann 1985), and HPLC/MS and MS/MS have been investigated as screening methods for explosives (McLucky et al. 1985; Vouros et al. 1977). A sophisticated method linking HPLC, thermospray (TSP), and MS or MS/MS (with both positive and negative chemical ionization) has also been proposed as an extremely sensitive (low pg range) and

selective method for detecting RDX in explosive residues (Berberich et al. 1988; Verweij et al. 1993). However, there is no evidence that any MS-based method is currently used to quantitatively measure RDX in explosives or explosion debris. A relatively new method being investigated uses supercritical fluid extraction chromatography (SFC) to separate RDX from other analytes and contaminants followed by detection by UV/FID (Griest et al. 1989). The method is slower but more selective than HPLC/UV. The precision for standard solutions was excellent. However, more work is needed to improve the mobile phase and column packing material before samples in complex matrices can be analyzed.

6.3 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of RDX is available. Where adequate information is not available, ATSDR, in conjunction with NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of RDX.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that, if met, would reduce or eliminate the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda may be proposed.

6.3.1 Identification of Data Needs

Methods for Determining Biomarkers of Exposure and Effect. Few methods-exist for monitoring exposure to RDX. Methods have been reported for detection of the analyte in plasma (Army 1981a; Fine et al. 1984; Turley and Brewster 1987; Woody et al. 1986), urine (Turley and Brewster 1987; Woody et al. 1986) cerebrospinal fluid (Woody et al. 1986), feces (Woody et al. 1986), and tissues (Army 1981a), as well as on hands (Douse 1982; Fine et al. 1984; Lloyd 1983). The available methods can detect levels in urine and plasma from exposure to concentrations below

those that would be encountered in most manufacturing situations. In general, these methods are reliable and accurate; however, the development of the LC-MS methodology could be useful as a definitive method to validate the specificity of the HPLC methods. The data are insufficient to permit correlation of RDX levels in the urine or blood with exposure levels (see Section 2.5.1). Therefore, the level of RDX in urine or blood cannot be used as a biomarker of exposure.

There are no known sensitive biomarkers of effect for RDX. Therefore, no methods recommendations can be made for this chemical.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. Methods exist to detect and quantify RDX in air (Army 1974; Bishop et al. 1988; Eminger and Vejrostova 1984; St. John et al. 1975; Tanner et al. 1983), water (Army 1983c, 1985c, 1989a; Haas et al. 1990; Hable et al. 1991; Jian and Seitz 1990; Maskarinec et al. 1984; Richard and Junk 1986; Yinon and Laschever 1982), soil (Army 1987b; Bongiovanni et al. 1984; Haas et al. 1990), explosive materials (Burrows and Brueggemann 1985; Fine et al. 1984; Lafleur and Morriseau 1980; Lloyd 1983), and debris from explosions (Fine et al. 1984; Strobe1 and Tontarski 1983). These methods are relatively sensitive and reliable and can be used to detect levels of the compound in the environment that cause known adverse health effects. There are some problems involving reduced sensitivity and selectivity with all the commonly used methods. Several proposed improvements in current methods, such as combining various analytical methods to increase selectivity, sensitivity, reliability, and/or accuracy (Army 1989a; Berberich et al. 1988; Krull et al. 1984), and investigations of new methods (Griest et al. 1989; Jian and Seitz 1990) will be useful in forensics and in monitoring environmental contamination from manufacture and disposal of RDX.

6.3.2 Ongoing Studies

No ongoing methods studies were located.

7. REGULATIONS AND ADVISORIES

The international, national, and state regulations and guidelines regarding RDX in air, water, and other media are summarized in Table 7- 1.

An acute oral MRL of 0.06 mg/kg/day was derived. The MRL is based on a NOAEL value of 6 mg/kg/day for seizures in rats administered RDX on gestation days 6-15 in a developmental study (Army 1986d).

An intermediate oral MRL of 0.03 mg/kg/day was derived. The MRL is based on a NOAEL value of 8 mg/kg/day for reproductive effects in rats after 6 months of exposure (Army 1983a).

A chronic oral reference dose (RfD) of 0.003 mg/kg/day has been derived by EPA for RDX (IRIS 1994). The RfD is based on a NOAEL for reproductive effects (inflammation of the prostate) in rats fed 0.3 mg/kg/day of RDX.

EPA (IRIS 1994) has assigned RDX a weight-of-evidence carcinogenic classification of C, which indicates that RDX is a possible human carcinogen.

The transportation of explosives, including RDX, must be in accordance with the Department of Transportation hazardous material regulations (49 CFR 171-190) and the motor carrier safety regulations (49 CFR 390-398). Numerous states have established regulations on explosives for air quality control, solid waste disposal, storage, manufacture, and use.

Table 7-1. Regulations and Guidelines Applicable to RDX

Agency	Description	Information	Reference
NATIONAL			
Regulations:			
a. Air:			
OSHA	PEL TWA (skin designation)	1.5 mg/m^3	OSHA 1989 (29 CFR 1910.1000)
b. Water:			
EPA/ODW	Drinking Water Guideline	2.0 µg/L	FSTRAC 1994
EPA/OW	Explosives Manufacturing Point Source Category	none	EPA 1976 (40 CFR 457.11)
c. Other			
DOT	Class A Explosive (high explosive); domestic transportation limited to road and water (cargo only, in magazines)	Yes	DOT 1989 (49 CFR 172.101)
DOT	Designated as a hazardous substance subject to requirements for packaging, labeling, and transportation	Yes	DOT 1989 (49 CFR 172.101 Appendix A)
Guidelines:			
a. Air			
ACGIH	TLV TWA (skin designation)	1.5 mg/m^3	ACGIH 1994
NIOSH	REL - TWA (skin)	1.5 mg/m^3	NIOSH 1992
	STEL (skin)	3.0 mg/m^3	
b. Other			
EPA	RfD (oral)	3.0x10^{-3} mg/kg/day	IRIS 1994
	Carcinogen classification	C[a]	IRIS 1994
	Unit risk (air)	ND	IRIS 1994
	Unit risk (water)	3.1x10^{-6} µg/L	IRIS 1994
STATE			
Regulations and Guidelines:			
a. Air:			
	Acceptable Ambient Air Concentrations		NATICH 1991
CT	8 hr avg. time	30.0 µg/m^3	
FL- Pinellas	8 hr avg. time	15.0 mg/m^3	
FL-Pinellas	24 hr avg. time	3.60 µg/m^3	
MD		0.00	

Table 7-1. Regulations and Guidelines Applicable to RDX (continued)

Agency	Description	Information	Reference
STATE (cont.)			
ND	8 hr avg. time	0.015 mg/m^3	
NV	8 hr avg. time	0.036 mg/m^3	
OK	24 hr avg. time	30.0 µg/m^3	
TX	30 min avg. time	15.0 µg/m^3	
TX	Annual avg. time	1.5 µg/m^3	
VA	24 hr avg. time	25.0 µg/m^3	
KY	Significant emission levels of toxic air pollutants	3.827×10^{-4} pounds/hour	NREPC 1986 (410 KAR 63:022)
b. Other			
	Transportation of explosives is in accordance with the U.S. Department of Transportation hazardous materials regulations (49 CFR 171-190) and the motor carrier safety regulations (49 CFR 390-398) with some exceptions or additional requirements that vary from state to state		CELDs 1994
AL		Yes	
AK		Yes	
AZ		Yes	
CA		Yes	
CT		Yes	
CO		Yes	
DE		Yes	
FL		Yes	
GA		Yes	
HI		Yes	
ID		Yes	
IN		Yes	
IA		Yes	
LA		Yes	
MD		Yes	
MA		Yes	
MI		Yes	
MN		Yes	
MS		Yes	

Table 7-1. Regulations and Guidelines Applicable to RDX (continued)

Agency	Description	Information	Reference
STATE (cont.)			
MO		Yes	
MT		Yes	
NE		Yes	
NJ		Yes	
NM		Yes	
NC		Yes	
ND		Yes	
NY		Yes	
OH		Yes	
OR		Yes	
RI		Yes	
SD		Yes	
TN		Yes	
TX		Yes	
UT		Yes	
VA		Yes	
VT		Yes	
WA		Yes	
WA-DC		Yes	
WV		Yes	
WI		Yes	
WY		Yes	
	Rules and regulations for air quality control and/or solid waste disposal have been established for explosives in general; regulations vary from state to state		CELDs 1994
AL	Pretreatment standards for discharge Hazardous waste: thermal treatment	Yes	
AR	Solid waste collection	Yes	
AR	Solid waste storage and collection	Yes	
CO	Fugitive dust	Yes	
CT	Hazardous waste: thermal treatment	Yes	
FL	Hazardous waste: thermal treatment	Yes	
GA	Open burning	Yes	

Table 7-1. Regulations and Guidelines Applicable to RDX (continued)

Agency	Description	Information	Reference
STATE (cont.)			
IL	Sewer discharge	Yes	
IN	Open burning	Yes	
KY	Hazardous waste management	Yes	
LA	Open burning	Yes	
MN	Hazardous waste management	Yes	
NH	Open burning	Yes	
NJ	Hazardous waste management	Yes	
NM	Hazardous waste management	Yes	
NV	Hazardous waste management	Yes	
NC	Hazardous waste management	Yes	
ND	Fugitive emissions	Yes	
PA	Fugitive emissions	Yes	
SC	Open burning	Yes	
TN	Hazardous waste: thermal treatment	Yes	
UT	Hazardous waste management	Yes	
VT	Open burning	Yes	
VA	Solid waste management	Yes	
WI	Open burning and malodorous emissions	Yes	
	Explosive control laws regulating storage, manufacture, and use; regulations vary from state to state		CELDs 1994
AK		Yes	
CA		Yes	
CT		Yes	
GA		Yes	
HI		Yes	
IN		Yes	
IA		Yes	
KS		Yes	
NJ		Yes	
MA		Yes	
NE		Yes	
NJ		Yes	

Table 7-1. Regulations and Guidelines Applicable to RDX (continued)

Agency	Description	Information	Reference
STATE (cont.)			
OK		Yes	
OR		Yes	
WA-DC		Yes	
WV		Yes	
WI		Yes	

NOTE: Units in table reflect values and units of measure designated by each agency in its regulations or advisories.

a Possible human carcinogen

ACGIH = American Conference of Governmental and Industrial Hygienists; CELDs = Comprehensive Environmental Legislative Database; CFR = Code of Federal Regulations; DOT = Department of Transportation; EPA = Environmental Protection Agency; FSTRAC = Federal-State Toxicology and Regulatory Alliance; IRIS = Integrated Risk Information System; NATICH = National Air Toxics Information Clearinghouse; ND = No data; NIOSH = National Institute of Occupational Safety and Health; NREPC = Natural Resources and Environmental Protection Cabinet (KY); ODW = Office of Drinking Water; OSHA = Occupational Safety and Health Administration; OSW = Office of Solid Waste; OW = Office of Water; PEL = Permissible Exposure Limit; REL = Recommended Exposure Level; RfD = Reference Dose; STEL = Short-term Exposure Limit; TLV = Threshold Limit Value; TWA = Time Weighted Average

8. REFERENCES

ACGIH. 1986. Documentation of the threshold limit values and biological exposure indices. Fifth edition. American Conference of Governmental Industrial Hygienists, Cincinnati, OH.

*ACGIH. 1994. Threshold limit values and biological exposure indices for 1994-1995. American Conference of Governmental Industrial Hygienists, Cincinnati, OH.

*Ainsworth CC, Harvey SD, Szecsody JE, et al. 1993. Relationship between the leachability characteristics of unique energetic compounds and soil properties. U.S. Army Medical Research and Development Command, Fort Detrick, Frederick, MD. AD-A-267-580.

Andren RK, Nystron JM, McDonnell RP, et al. 1977. Explosives removal from munitions wastewater. Proceedings of the Industrial Waste Conference 30816-825.

*Army. 1974. The toxicology of cyclotrimethylenetrinitramine (RDX) and cyclotetramethylenetetranitramine (HMX) solutions in dimethylsulfoxide (DMSO), cyclohexanone, and acetone. Edgewood Arsenal technical report EB-TR-73040. Aberdeen Proving Ground, MD: U.S. Army, Edgewood Arsenal. Document no. AD 788010. (author: McNamara BP et al.)

*Army. 1975. Development of industrial hygiene sampling and analytical methodology for evaluation of exposures to TNT and associated explosives. Contract no. DADA17-73-C-3167. Washington, DC: U.S. Army Medical Research and Developmental Command. Document no. AD-A008 399. (author: Saltzman BE et al.)

Army 1976. Adverse health effects of selected explosives (TNT, RDX). Report no. USAEHH-32-049-75/76. Aberdeen Proving Ground, MD: U.S. Arrny Environmental Hygiene Agency. Document no. ADB010943.

Army 1977a. Laboratory evaluation of the toxicity of cyclotrimethylene trinitramine (RDX) to aquatic organisms. Contract no. DAMD-17-74-C-4101. Frederick, MD: U.S. Army Medical Research and Development Command, Fort Detrick. Document no. ADA061730.

*Army. 1977b. Mutagenicity of some munition wastewater chemicals and chlorine test reagents. Contract no. DAMD17-76-C-6013. Frederick, MD: U.S. Army Medical Research and Development Command, Fort Detrick. (author: Simmon VF et al.)

Army. 1978a. The hazard ranking and allocation methodology: Evaluation of TNT wastewaters for continuing research. efforts. Technical report 7808. Frederick, MD: U.S. Army Medical Research and Development Command, Fort Detrick. Document no. AD A061770. (author: Small MJ).

*Army. 1978b. Mammalian toxicological evaluation of TNT wastewaters. Volume II: Acute and subacute mammalian toxicity of TNT and the LAP mixture. Contract no. DAMD17-76-C-6050. Frederick, MD: U.S. Army Medical Research and Development Command, Fort Detrick. (author: Dilley JV et al.)

*Cited in text

8. REFERENCES

*Army. 1978c. Specific air pollutants from munitions processing and their atmospheric behavior. Volume 2: RDX/HMX production. Contract no. DAMD17-76-C-6067. Frederick, MD: U.S. Army Medical Research and Development Command, Fort Detrick. Document no. AD A060122. (author: Carpenter BH et al.)

Army. 1979. Evaluation of the environmental fate of munition compounds in soil. Contract no. DAMD17-76-C-6065. Frederick, MD: U.S. Army Medical Research and Development Command, Fort Detrick. Document no. AD A082874. (author: Hale VQ et al.)

*Army. 1980a. Environmental fate of RDX and TNT. Report no. TR 81-538. Contract no. DAMD17-77-C-7026. Frederick, MD: U.S. Army Medical Research and Development Command, Fort Detrick. (author: Sikka HC et al.)

*Army. 1980b. Mammalian toxicological evaluation of RDX. Contract no. DAMD17-78-C-8027. Frederick, MD: U.S. Army Medical Research and Development Command, Fort Detrick. Document no. AD A092531. (author: Cholakis et al.)

Army. 1980c. Environmental fate studies on certain munition wastewater constituents: Phase II--Laboratory studies. Contract no. DAMD17-78-8081. Frederick, MD: U.S. Army Medical Research and Development Command, Fort Detrick. Document no. AD A099256. (author: Spanggord et al.)

*Army. 1981a. Identification or development of chemical analysis methods for plants and animal tissues. Contract no. DAAKll-79-C-0110. Aberdeen Proving Ground, MD: U.S. Army Armament Research and Development Command, Edgewood Area. Document no. AD A107346. (author: Lakings and Gan).

Army. 1981b. Preliminary pollutant limit values for Alabama Army Ammunition Plant. Technical report 8105. Frederick, MD: U.S. Army Medical Research and Development Command, Fort Detrick. Document no. AD A104203. (author: Rosenblatt and Small).

*Army. 1983a. Determination of the chronic mammalian toxicological effects of RDX: Twenty-four month chronic toxicity/carcinogenicity study of hexahydro-1,3,5-trinitro-1,3,5-triazine (RDX) in the Fischer 344 rat: Phase V. Vol. 1. Contract no. DAMD17-C-9161. Frederick, MD: U.S. Army Medical Research and Development Command, Fort Detrick. Document no. AD A160774. (authored by Levine BS et al.)

*Army. 1983b. Environmental fate studies on certain munitions wastewater constituents: Phase IV--Lagoon model studies. Contract no. DAMD17-78-C-8081. Frederick, MD: U.S. Army Medical Research and Development Command, Fort Detrick. Document no. AD A138550. (authored by Spanggord RJ et al,) -.

*Army. 1983c. HPLC analysis of SEX, HMX, TAX, RDX, and TNT in wastewater. Technical report 8206. Frederick, MD: U.S. Army Medical Research and Development Command, Fort Detrick. Document no. AD 127348. (authored by Brueggemann EE).

*Army. 1984a. Database assessment of the health and environmental effects of munition production waste products. Frederick, MD: U.S. Army Medical Research and Development Command, Fort Detrick. Document no. AD-Al45 417. (authored by Ryon MG et al.)

8. REFERENCES

*Army. 1984b. Determination of the chronic mammalian toxicological effects of RDX: Acute dermal toxicity test of hexahydro-1,3,5-trinitro-1,3,5triazine (RDX) in rabbits. Contract no. DAMD17-79-C-9161. Frederick, MD: U.S. Army Medical Research and Development Command, Fort Detrick. (authored by Furedi-Machacek EM et al.)

*Army. 1984c. Determination of the chronic mammalian toxicological effects of RDX: Twenty-four month chronic toxicity/carcinogenicity study of hexahydro-1,3,5-trinitro-1,3,5-triazine (RDX) in the B6C3Fl hybrid mouse: Phase VI. Vol. 1. Contract no. DAMD17-79-C-9161. Frederick, MD: U.S. Army Medical Research and Development Command, Fort Detrick. (authored by Lish PM et al.)

Army. 1984d. Development of novel decontamination techniques for explosive contaminated facilities. Contract no. DAAKll-Sic-0101. U.S. Army Toxic and Hazardous Material Agency. Document no. AD-PO04 880. (authored by Benecke HP et al.)

Army. 1984e. Reverse phase HPLC method for analysis of TNT, RDX, HMX, and 2,4-DNT in munitions wastewater. CRREL report 84-29. Aberdeen Proving Ground, MD: U.S. Army Toxic and Hazardous Materials Agency. Report no. DRXTH-TE-TR-84301. (authored by Jenkins TF et al.)

*Army. 1984f. The anaerobic biotransformation of RDX, HMX, and their acetylated derivatives. Technical report NATICWTR-85/007. Aberdeen Proving Ground, MD: U.S. Army Toxic and Hazardous Materials Agency. Document no. AD-Al49 464. (authored by McCormick NG et al.)

Army. 1984g. The fate of hexahydro-1,3,5-trinitro-1,3,5-triazine (RDX) and related compounds in anaerobic denitrifying continuous culture systems using simulated waste water. Technical report NATICWTR-85/008. Aberdeen Proving Ground, MD: U.S. Army Toxic and Hazardous Materials Agency. Document no. AD-149 462. (authored by McCormick NG et al.)

*Army. 1985a. Degradation of pink water compounds in soil - TNT, RDX, HMX. Technical report NATICWTR-85/046. Aberdeen Proving Ground, MD: U.S. Army Toxic and Hazardous Materials Agency. Document no. AD-Al57 954. (authored by Greene B et al.)

*Army. 1985b. Neurotoxicology of cyclotrimethylenetrinitramine (RDX). Frederick, MD: U.S. Army Medical Research and Development Command, Fort Detrick. AD-A168266. (authored by MacPhail RC et al.)

*Army. 1985c. Suitability of polyvinyl chloride pipe for monitoring TNT, RDX, HMX, and DNT in groundwater. Aberdeen Proving Ground, MD: U.S. Army Toxic and Hazardous Materials Agency. Report no. AMX-TH-TE-85037. (authored by Parker LV et al.)

*Army. 1986a. Database assessment of pollution.control in the military explosives and propellants production industry. Frederick, MD: U.S. Army Medical Research and Development Command, Fort Detrick. (authored by Pal BC and Ryon MG).

*Army. 1986b. Cornposting explosives/organics contaminated soils. Contract no. DAAKll-84-C-0057. Aberdeen Proving Ground, MD: U.S. Army Toxic and Hazardous Materials Agency. Document no. AD-Al69 994. (authored by Doyle RC et al.)

8. REFERENCES

*Army. 1986c. Demilitarization of conventional ordnance: Priorities for data-base assessments of environmental contaminants. Frederick, MD: U.S. Army Medical and Development Command, Fort Detrick. Document no. AD-Al82 922. (authored by Layton DW, et al.)

*Army. 1986d. Teratological assessment of trinitro - RDX in rats. Aberdeen Proving Ground, MD: Department of the Army, U.S. Army Environmental Hygiene Agency. Document no. AD-Al66 249. (authored by Angerhofer et al.)

*Army. 1986e. Water quality criteria for hexahydro-1,3,5-trinitro-1,3,5triazine (RDX). Frederick, MD: U.S. Army Medical Research and Development Command, Fort Detrick. (authored by Etnier EL).

*Army. 1987a. Conventional weapons demilitarization: A health and environmental effects data base assessment: Phase II. Explosives and their co-contaminants. Frederick, MD: U.S. Army Medical Research and Development Command, Fort Detrick. Document no. AD-A220 588. (authored by Layton D et al.)

*Army. 1987b. Development of an analytical method for explosive residues in soil. CRREL report 87-7. Aberdeen Proving Ground, MD: U.S. Army Toxic and Hazardous Materials Agency. Document no. AD-Al83 738. (authored by Jenkins TF and Walsh ME).

*Army. 1987c. Treatment alternatives for explosive-laden spent carbons. Contract no. DAAKl l-85-D-0008. Aberdeen Proving Ground, MD: U.S. Army Toxic and Hazardous Materials Agency. Document no. AD/A199 506. (authored by Balasco AA et al.)

*Army. 1988. Residual explosives criteria for treatment of area P soil, Louisiana Army Ammunition Plant. Technical report 8807. Frederick, MD: U.S. Army Medical Research and Development Command, Fort Detrick. Document no. AD-Al97 799. (authored by Small MJ).

*Army. 1989a. Evaluation of four well casing materials for monitoring selected trace level organics in ground water. CRREL report 89-18. Aberdeen Proving Ground, MD: U.S. Army Toxic and Hazardous Materials Agency. Report no. CETHA-TE-CR-89209. (authored by Parker et al.)

Army. 1989b. Validation of a sorbent tube/high performance liquid chromatographic procedure for the determination of eight explosives in water. Aberdeen Proving Ground, MD: U.S. Army Toxic and Hazardous Materials Agency. Document no. AD-A210 777. (authored by Valis RJ et al.)

*Army. 1990a. An evaluation of the environmental fate and behavior of munitions material (TNT, RDX) in soil and plat systems: Environmental fate and behavior of RDX. Pacific Northwest Laboratory-7529. Project order no. 88PP8853. Frederick, MD: U.S. Army Biomedical Research and Development Laboratory, Fort Detrick.

Army. 1990b. Environmental transformation products of nitroaromatics and nitramines: Literature review and recommendations for analytical method development. Special report 90-2. Aberdeen Proving Ground, MD: U.S. Army Toxic and Hazardous Materials Agency. (authored by Walsh ME).

*Atkinson R. 1987. A structure-activity relationship for the estimation of rate constants for the gas-phase reactions of OH radicals with organic compounds. International Journal of Chemical Kinetics 19:799-828.

8. REFERENCES

*ATSDR. 1989. Decision guide for identifying substance-specific data needs related to toxicological profiles. Agency for Toxic Substances and Disease Registry, Division of Toxicology, Atlanta GA.

*ATSDR. 1989a. Health assessment for Cornhusker Army Ammunition Plant, Grand Island, Nebraska, Region 7. Agency for Toxic Substances and Disease Registry, Atlanta GA. CERCLIS 'No. NE2213820234. Issue 02.

*ATSDR. 1989b. Health assessment for Milan Army Plant, Carrol and Gibson Counties, Tennessee, Region 4. Agency for Toxic Substances and Disease Registry, Atlanta GA. CERCLIS no. TND210020582. Issue 07.

*ATSDR. 1989c. Health assessment for Savanna Army Depot, Savanna, Carroll County, Illinois, Region 5. Agency for Toxic Substances and Disease Registry, Atlanta GA. CERCLIS no. ILO213820376. Issue 01.

*ATSDR/CDC. 1990. Subcommittee report on biological indicators of organ damage. Agency for Toxic Substances and Disease Registry, Centers for Disease Control and Prevention, Atlanta GA.

*Barnes DG, Dourson M. 1988. Reference dose (RfD): Description and use in health risk assessments. Regul Toxic01 Pharmacol 8:471-486.

Barsotti M, Crotti G. 1949. [Epileptic attacks as manifestations of industrial intoxication caused by trimethylenetrinitroamine (T4).] Med Lav 40: 107-l 12. (Italian)

Bauer CF, Grant CL, Jenkins TF. 1986. Inter-laboratory evaluation of high-performance liquid-chromatographic determination of nitro-organics in munition plant waste water. Anal Chem 58:176-182.

*Bauer CF, Koza SM, Jenkins TF. 1990. Liquid chromatographic method for determination of explosive residues in soil: Collaborative study. J Assoc Off Anal Chem 73:541-552.

*Belkin F, Bishop RW, Sheely MV. 1985. Analysis of explosives in water by capillary gas chromatography. J Chromatogr Sci 23:532-534.

*Berberich DW, Yost RA, Fetterolf DD. 1988. Analysis of explosives by liquid chromatography/ thermospray/mass spectrometry. J Forensic Sci 33:946-959.

*Bishop RW, Ayers TA, Rinehart DS. 1981. The use of a solid sorbent as a collection medium for TNT and RDX vapours. Am Ind Hyg Assoc J 42:586-589.

*Bishop RW, Kennedy JL, Podolak GE, et al. 1988. A field evaluation of air sampling-methods for TNT and RDX. Am Ind Hyg Assoc J 49:635-638.

*Bongiovanni R, Podolak GE, Clark LD, et al. 1984. Analysis of trace amounts of six selected poly-nitro compounds in soils. Am Ind Hyg Assoc J 45:222-226.

*Bricka RM, Sharp W. 1992. Treatment of groundwater contaminated with low levels of military munitions. 47th Purdue Industrial Waster Conference Proceedings. Chelsea, MI: Lewis Publishers, 199-204.

8. REFERENCES

Brown D. 1975. The acute and chronic biochemical and behavioral effects of cyclotrimethylenetriamine. Baltimore, MD: Maryland University School of Pharmacy. Document no. AD-A024415/2.

Brown JM, Spanggord RJ, Jorgenson TA. 1988. Chronic mammalian toxicological effects of LAP wastewater. Issue 08.

*Burdette LJ, Cook LL, Dyer RS. 1988. Convulsant properties of cyclotrimethylenetrinitramine (RDX): Spontaneous audiogenic, and amygdaloid kindled seizure activity. Toxic01 Appl Pharmacol 92:436-444.

*Burrows EP, Brueggemann EE. 1985. Reversed-phase gradient high-performance liquid chromatography of nitramine munitions and characterization of munitions process samples by gas chromatography-mass spectrometry. J Chromatogr 329:285-289.

*Burrows WD, Chyrek RH, Noss CI, et al. 1984. Treatment for removal of munition chemicals from army industrial wastewaters. In: LaGrega MD, Long DA, eds. Toxic and hazardous wastes: Proceedings of the 16th Mid-Atlantic Industrial Waste Conference, Bucknell University, 1984. Lancaster, PA: Technomic Publishing Co., Inc., 331-342.

Carrol JW, Guinivan TL, Tuggle RM. 1979. Assessment of hazardous air pollutants from disposal of munitions in a prototype fluidized bed incinerator. Am Ind Hyg Assoc J 40:147-158.

*Cataldo DA, Harvey SD, Fellows RJ. 1993. The environmental behavior and chemical fate of energetic compounds (TNT, RDX, tetryl) in soil and plant systems. Prepared by Pacific Northwest Laboratory, Richland, WA under DOE contract. DE 93-019614.

*CELDS. 1994. Computer-Environmental Legislative Data Systems. University of Illinois, Urbana, IL.

*Dilley JV, Tyson CA, Spanggord RJ, et al. 1982. Short-term oral toxicity of a 2,4,6-trinitrotoluene and hexahydro-1,3,5-trinitro-1,3,5-triazine mixture in mice, rats, and dogs. J Toxic01 Environ Health 9:587-610.

*DOT. 1989. Hazardous materials table. Department of Transportation. Code of Federal Regulations. 49 CFR 172.101.

*Douse JMF. 1982. Trace analysis of explosives in hand-swab extracts using amberlite XAD-7, porous polymer beads, silica capillary-column gas chromatography with electron capture detection and thin-layer chromatography. J Chromatogr 234:415-425.

Doyle RC, Isbister JD, Forgacs TW, et al. 1985. Cornposting explosives contaminated sediments. American Defense Preparedness Association 14:40-44.

Edwards BH, Paullin JN, Coghlan-Jordan K. 1983. Emerging technologies for the control of hazardous wastes: Project summary. Park Ridge, NJ: Noyes Data Corporation.

*Eisenreich SJ, Looney BB, Thornton JD. 1981. Airborne organic contaminants in the Great Lakes ecosystem. Environ Sci Technol 15:30-38.

8. REFERENCES

*Eminger S, Vejrostova M. 1984. Photometric determination of microgram quantities of 1,3,5-trinitro-1,3,5-triazacyclohexane in air. Collection of Czechoslovak Chem Commun 49:1464-1467.

*Emmrich M, Kaiser M, Rueden H, et al. 1993. Determination of RDX, 2,4,6-trinitrotoluene and other nitroaromatic compounds by high-performance liquid chromatography with photoiodide-array detection. J Chromatogr 645 (1): 89-94.

*EPA. 1976. Explosives manufacturing point source category. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 457.11.

EPA. 1988. Health advisory for hexahydro-1,3,5-trinitro-1,3,5-triazine (RDX). Washington, DC: U.S. Environmental Protection Agency, Office of Drinking Water, Criteria and Standards Division.

*EPA. 1990a. Hazardous wastes from specific sources. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 261.32.

*EPA. 1990b. Interim methods for development of inhalation reference concentrations. Washington DC: U.S. Environmental Protection Agency. EPA/600/890/066A.

Etnier EL. 1989. Water quality criteria for hexahydro-1,3,5-trinitro-1,3,5-triazine (RDX). Regul Toxico1 Pharmacol 9:147-157.

Etnier EL, Hartley WR. 1990. Comparison of water quality criterion and lifetime health advisory for hexahydro-1,3,5-trinitro-1,3,5-triazine (RDX). Regul Toxic01 Pharmacol 11:118-122.

*FEDRIP. 1994. Federal Research in Progress: RDX. Dialog Information Service, Inc

*Fine DH, Yu WC, Goff EU, et al. 1984. Picogram analyses of explosive residues using the thermal energy analyzer (TEA). J Forensic Sci 29:732-746.

French JE, Bradley SL, Schneider NR, et al. 1976. Cyclotrimethylenetrinitramine (RDX)-induced ultrastructural changes in rat liver and kidney [Abstract]. Toxic01 Appl Pharmacol 37:122.

*FSTRAC. 1994. Summary of state and federal drinking water standards and guidelines. U.S. Environmental Protection Agency. Chemical Communication Subcommittee, Federal State Toxicology and Regulatory Alliance Committee (FSTRAC).

*Gibbs TR, Popolato A, eds. 1980. LASL explosive property data. Berkeley, CA: University of California Press, 141-143.

Glish GL, McLuckey SA, Carter JA. 1984. Mass spectrometry/mass spectrometry as a screening method for detecting explosive vapors. Nucl Mater Manage 13:216-219.

*Griest WH, Guzman C, Dekker M. 1989. Packed-column supercritical fluid chromatographic separation of highly explosive compounds. J Chromatogr 467:423-429.

*Griest, WH, Stewart AJ, Tyndall et al. 1993. Chemical and toxicological testing of composted explosives-contaminated soil. Environ. Toxicol. Chem. 12: 1105-l 116

8. REFERENCES

*Haas R, Schreiber I, Von Loew E, et al. 1990. Conception for the investigation of contaminated munition plants: 2. Investigation of former RDX-plants and filling stations. Fresenius' Journal of Analytical Chemistry 338:41-45.

*Hable M, Stem C, Asowata C, et al. 1991. The determination of nitroaromatics and nitramines in ground and drinking water by wide-bore capillary gas chromatography. J Chromatogr Sci 29: 131-135.

*Harvey SD, Fellows RJ, Cataldo DA, et al. 1991. Environmental chemistry: Fate of the explosive hexahydro-1,3,5triazine (RDX) in soil and bioaccumulation in bush bean hydroponic plants. Environmental Toxicology and Chemistry 10845855.

*Hathaway JA, Buck CR. 1977. Absence of health hazards associated with RDX manufacture and use. J Occup Med 19:269-272.

*HazDat. 1994. Agency for Toxic Substances and Disease Registry, Atlanta GA.

*Hoffsommer JC, Rosen JM. 1972. Analysis of explosives in sea water. Bull Env Contam Toxic01 7:177-181.

*Hoffsommer JC, Rosen JM. 1973. Hydrolysis of explosives in sea water. Bull Env Contam Toxic01 10:78-79.

*Hollander AI, Colbach EM. 1969. Composition C-4 induced seizures: A report of five cases. Milit Med 134:1529-1530.

*HSDB. 1994. Hazardous Substances Data Bank. National Library of Medicine, National Toxicology Information Program, Bethesda, MD. May, 1991.

*IRIS. 1994. Integrated Risk Information Systems. U.S. Environmental Protection Agency, Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH.

Isbister JD, Anspach GL, Kitchens JF, et al. 1984. Cornposting for decontamination of soils containing explosives. Microbiologica 7:47-73.

*Jenkins TF, Grant CL. 1987. Comparison of extraction techniques for munitions residues in soil. Anal Chem 59:1326-1331.

*Jenkins TF, Leggett DC, Grant CL, et al. 1986. Reversed-phase high-performance liquid chromatographic determination of nitroorganics in munitions wastewater. Anal Chem 58: 170- 175.

*Jenkins TF, Walsh ME, Schumacher PW, et al. 1989. Liquid chromatographic methodfor determination of extractable nitroaromatic and nitramine residues in soil. J Assoc Off Anal Chem 72:890-899.

*Jian C, Seitz WR. 1990. Membrane for in situ optical detection of organic nitro compounds based on fluorescence quenching. Anal Chim Acta 237:265-271.

*Kaplan AS, Berghout CF, Peczenik A. 1965. Human intoxication from RDX. Arch Environ Health 10:877-883.

8. REFERENCES

Kayser EG, Burlinson NE. 1988. Migration of explosives in soil: Analysis of RDX, TNT, tetryl from a 14C lysimeter study. Journal of Energetic Materials 6:45-71.

*Ketel WB, Hughes JR. 1972. Toxic encephalopathy with seizures secondary to ingestion of an explosive material composition C-4: A clinical and electroencephalographic study. Neurology 22:871-876.

*Knepshield JH, Stone WJ. 1972. Toxic effects following ingestion of C-4 plastic explosive. In: Keup W, ed. Drug abuse: Current concepts and research. Springfield, IL: Charles C. Thomas, 296-301.

*Krull IS, Ding XD, Selavka C, et al. 1984. Explosives and other nitro compounds determined by liquid chromatography with photolysis-electrochemical detection. Methodological Surveys in Biochemistry and Analysis 14:365-366.

*Lafleur AL, Morriseau BD. 1980. Identification of explosives at trace levels by high-performance liquid chromatography with a nitrosyl-specific detector. Anal Chem 52: 13 13-l 3 18.

*Levine BS, Furedi EM, Gordon DE, et al. 1981. Thirteen-week toxicity study of hexahydro-1,3,5-trinitro-1,3,5-triazine (RDX) in Fischer 344 rats. Toxic01 Lett 8:241-245.

*Levine BS, Furedi EM, Gordon DE, et al. 1990. Toxic interactions of the munitions compounds TNT and RDX in F344 rats. Fundam Appl Toxic01 15:373-380.

*Levsen K, Mussmann E, Berger E, et al. 1993. Analysis of nitroaromatics and nitramines in ammunition waste water and in aqueous samples from former ammunition plants and other military sites. Acta Hydrochim Hydrobiol 21:153-166.

*Lloyd JBF. 1983. High-performance liquid chromatography of organic explosives components with electrochemical detection at a pendent-mercury-drop electrode. J Chromatogr 257:227-236.

*Lyman WJ, Reehl WF, Rosenblatt DH. 1982. Handbook of chemical property estimation methods: Environmental behavior of organic compounds. New York, NY: McGraw-Hill Book Company.

*Lyter AH. 1983. A high performance liquid chromatographic (HPLC) study of seven common explosive materials. J Forensic Sci 28:446-450.

*Maskarinec MP, Manning DL, Harvey RW. 1984. Determination of munitions components in water by resin adsorption and high-performance liquid chromatography-electrochemical detection. J Chromatogr 302:51-63.

*McCormick N-G, Cornell JH, Kaplan AM. 1981. Biodegradation of hexahydro-1,3,5-trinitro-1,3,5-triazine. Appl Environ Microbial 42:8 17-823.

McDiarmid MA, Weaver V. 1993. Fouling One's Own Nest Revisited. Am J Ind Med 24(l): l-9.
*McKone TE, Layton DW. 1986. Screening the potential risks of toxic substances using a multimedia compartment model: Estimation of human exposure. Regul Toxic01 Pharmacol 6:359-380.

8. REFERENCES

*McLuckey SA, Glish GL, Carter JA. 1985. The analysis of explosives by tandem mass spectrometry. J Forensic Sci 30:773-788.

*Merck. 1989. The Merck index: An encyclopedia of chemical, drugs, and biologicals. Eleventh edition. Budavari S, O'Neil MJ, Smith A, et al., eds. Rahway, NJ: Merck & Co., Inc.

*Merrill SL. 1968. Ingestion of an explosive material, composition C-4: A report of two cases. U.S. ARV Med Bull 35-l 1.

Meyer R. 1977. Explosives. Weinheim, New York: Verlag Chemie, 150-152.

*Miyares PH, Jenkins TF. 1991. Improved salting out extraction-preconcentration determination of nitroaromatics and nitramines in water. U.S. Army Corps of Engineers, Cold Regions Research and Engineering Lab, Special Report 91-l 8. AD-AD-A245 49 1.

*NAS/NRC. 1989. Biologic markers in reproductive toxicology. National Academy of Sciences/National Research Council. Washington, DC: National Academy Press, 15-35.

*NATICH. 1991. National Air Toxics Information Clearinghouse. Data base report on state, local, and EPA air toxics activities. U.S. Environmental Protection Agency, Office of Air Quality Planning and Standards, Washington, DC: September 17, 1990.

*Navy. 1972. Analysis of explosives in sea water and in ocean floor sediment and fauna. Silver Springs, MD: Naval Ordinance Laboratory. Document no. AD 757778. (authored by Hoffsommer et al.)

*Navy. 1973. Microbial degradation of cyclonite (RDX). Naval Weapons Center technical publication 5525. China Lake, CA: Naval Weapons Center. Document no. AD-762 751. (authored by Soli G.)

*Navy. 1974a. Subacute toxicity of RDX and TNT in dogs. Contract no. N00014-73-C-0162. Arlington, VA: Office of Naval Research. (authored by Hart ER.)

*Navy. 1974b. Subacute toxicity of RDX and TNT in monkeys. Contract no. N00014-73-C-0162, NR108-985. Arlington, VA: Office of Naval Research. Document no. AD 044650. (authored by Martin and Hart).

*Navy. 1976. Two-year feeding study in rats. Contract no. NOOO14-73-C-0162, NR 202-043. Arlington, VA: Office of Naval Research. Document no. AD-A040 161. (authored by Hart ER).

Navy. 1979. Photolysis of RDX in aqueous solution, with and without ozone. Naval Surface Weapons Center/White Oak Laboratory technical report 78-175. Silver Spring, MD: Naval Surface Weapons Center. Document no. AD A080195. (authored by Glover and Hoffsommer).

*Navy. 1982. Migration of explosives in soil. Naval Surface Weapons Center technical report 82-566. Silver Spring, MD: Naval Surface Weapons Center. Document no. AD-A135417. (authored by Kayser EG and Burlinson NE.)

8. REFERENCES

*NIOSH. 1992. Recommendations for occupational safety and health. Compendium of policy documents and statements. U.S. Department of Health and Human Services, National Institute of Occupational Safety and Health, Cincinnati, OH.

*NOES. 1990. National Occupational Exposure Survey (1981-83): RDX. U.S. Department of Health and Human Services, National Institute for Occupational Safety and Health, Cincinnati, OH.
NRC. 1982. Evaluation of the health risks of ordnance disposal waste in drinking water.

Washington, D.C: National Research Council, Assembly of Life Sciences, Board on Toxicology and Environmental Health Hazards, National Academy Press.

*NREPC. 1986. New or modified sources emitting toxic air pollutants. Proposed regulations. Frankfort, KY: Department for Environmental Protection, Natural Resources and Environmental Protection Cabinet. 401 KAR 63:022.

*OSHA. 1989. Air contaminants. U.S. Department of Labor, Occupational Safety and Health Administration. Code of Federal Regulations. 29 CFR 1910.1000.

*Osmon JL, Klausmeier RE. 1973. The microbial degradation of explosives. Developments in Industrial Microbiology 14:247-252.

*OTA. 1990. Neurotoxicity: Identifying and controlling poisons of the nervous system. Office of Technology Assessment, Washington, DC. OTA-BA-438.

Pach J, Groszek B, Bogusz M, et al. 1980. Acute forced poisoning with explosives. Archiwum Medycyny Sadowej I Krjminologii 30:321-325.

*Richard JJ, Junk GA. 1986. Determination of munitions in water using macroreticular resins. Anal Chem 58:723-725.

*Roth M, Murphy JM Jr. 1978. Correlation of oxygen demand and total organic carbon tests on wastewaters from ammunition plants. Proceedings of the Industrial Waste Conference 32:674-688.

*Sax NI, Lewis RJ Sr. 1987. Hawley’s condensed chemical dictionary. Eleventh edition. New York, NY: Van Nostrand Reinhold Co.

*Sax NI, Lewis RJ Sr. 1989. Dangerous properties of industrial materials. Seventh edition. Volume III. New York, NY: Van Nostrand Reinhold Co.

Schneider NR, Bradley SL, Anderson ME. 1976a. Metabolism of carbon-14 cyclotrimethylenetrinitramine in the rat [Abstract]. Toxic01 Appl Pharmacol 37:137.

Schneider NR, Bradley SL, Anderson ME. 1976b. Toxicology of cyclotrimethylenetrinitramine (RDX): Distribution and metabolism in the rat and the miniature swine. Bethesda, MD: Armed Forces Radiobiology Research Institute, Defense Nuclear Agency. Document no. AD A026892.

*Schneider NR, Bradley SL, Anderson ME. 1977. Toxicology of cyclotrimethylenetrinitramine: Distribution and metabolism in the rat and the miniature swine. Toxic01 Appl Pharmacol 39:531-541.

8. REFERENCES

*Schneider NR, Bradley SL, Anderson ME. 1978. The distribution and metabolism of cyclotrimethylenetrinitramine (RDX) in the rat after subchronic administration. Toxic01 Appl Pharmacol 46:163-171.

Scott DH, Fellows RJ, Cataldo DA, et al. 1991. Fate of the explosive hexahydro- 1,3,5trinitro- 1,3,5triazine (RDX) in soil and bioaccumulation in bush bean hydroponic plants. Environ Toxic01 Chem 10:845-855.

Shen Z, Wang W. 1983. [Rapid cathode-ray polarographic (linear-sweep chronoamperometric) determination of micro amounts of hexahydro- 1,3,5-trinitro- 1,3,5-triazine in water.] Fenxi Huaxue 11:289-290. (Chinese)

*Spalding RF, Fulton JW. 1988. Groundwater munition residues and nitrate near Grand Island, Nebraska, USA. Journal of Contaminant Hydrology 2: 139-153.
Spanggord RJ, Mabey WR, Mill T, et al. 1981. Environmental fate studies on certain munition wastewater constituents: Phase 3, part 2. Laboratory studies. NTIS AD-Al31 90. Menlo Park, CA: SRI International, 58.

*St. John GA, McReynolds JH, Blucher WG, et al. 1975. Determination of the concentration of explosives in air by isotope dilution analysis. Forensic Sci 6:53-66.

*Stokinger HE. 1982. Aliphatic nitro compounds, nitrates, nitrites. In: Clayton GD, Clayton FE, eds. Patty's industrial hygiene and toxicology. Vol. 2C. 3rd revised ed. New York, NY: John Wiley & Sons, 4141,4196-4197.

*Stone WJ, Paletta TL, Heiman EM, et al. 1969. Toxic effects following ingestion of C-4 plastic explosive. Arch Intern Med 124:726-730.

*Strobe1 RA, Tontarski RE. 1983. Organic solvent extracts of explosive debris: Clean-up procedures using bonded phase sorbents. Proceedings of the International Symposium on the Analysis and Detection of Explosives, FBI Academy, Quantico, VA, March 29-31, 1983. Washington, DC: U.S. Department of Justice, Federal Bureau of Investigation, 67-70.

*Sunderman FW. 1944. Hazards to the health of individuals working with RDX(B). OSRD Report No. 4147. National Defense Research Committee of the Office of Scientific Research and Development.

*Swann RL, Laskowski DA, McCall PJ. 1983. A rapid method for the estimation of the environmental parameters 0ctanoVwater partition coefficient, soil sorption constant, water to air ratio, and water solubility. Residue Rev 85:17-28.

*Tanner SD, Davidson WR, Fulford JE. 1983. The instantaneous detection of explosives by tandem mass spectrometry. In: Proceedings of the International Symposium on the Analysis and Detection of Explosives, FBI Academy, Quantico, VA, March 29-31, 1983. Washington, DC: U.S. Department of Justice, Federal Bureau of Investigation, 409-417.

*TRI. 1993. Toxic Chemical Release Inventory. National Library of Medicine, National Toxicology Information Program, Bethesda, MD.

8. REFERENCES

*Turley CP, Brewster MA. 1987. Liquid-chromatographic analysis of cyclotrimethylenetrinitramine in biological fluids using solid-phase extraction. J Chromatogr Biomed Appl 421:430-433.

*Twibell JD, Turner SL, Smalldon KW, et al. 1984. The persistence of military explosives on hands. J Forensic Sci 29:284-290.

Unkefer PJ, Alvarez MA, Hanners JL, et al. 1990. Bioremediation of explosives. U.S. Department of Energy contract no. W-740.5ENG-36. Los Alamos, NM: Los Alamos National Laboratory. NTIS/DE9001 1989.

*Verweij A, De Bruyn P, et al. 1993. Liquid chromatographic, thermospray/negative ion, tandem mass spectrometic analysis (Ic/tsp/ms/ms) of some exposives. Forensic Sci. Int. 60:7-13.
Vogel W. 1951. [Hexogen poisoning in human beings.] Zentralkl Arbeitsmed Arbeitsschutz 151-54; Abstracted in Industrial Hygiene Digest 16:29-30 (1959). (German)

*von Oettingen WF, Donahue DD, Yagoda H, et al. 1949. Toxicity and potential dangers of cyclotrimethylenetrinitramine (RDX). Journal of Industrial Hygiene and Toxicology 3 1:21-3 1.

*Vouros P, Petersen BA, Colwell L, et al. 1977. Analysis of explosives by high performance liquid chromatography and chemical ionization mass spectrometry. Anal Chem 49:1039-1044.

Wakabayashi K, Okuzu M. 1970. [Inhibitory effects of s-triazines on nitrification in soils: IV. Hydroxy-S-triazines and their derivatives, miscellaneous S-triazines, and hydro-S-triazines.] Nippon Dojo Hiryogaku Zasshi 41:237-245. (Japanese)

*Walker JE, Kaplan DL. 1992. Biological degradation of explosives and chemical agents. Biodegradation 3:369-385.

Weigel K. 1955. An explosive as a new rodenticide. Seifen, Oele, Fette, Wachse 81:95-96.

*Whong W-Z, Speciner ND, Edwards GS. 1980. Mutagenic activity of tetryl, a nitroaromatic explosive, in three microbial test systems. Toxic01 Lett (Amst) 5:11-17.

Williams RT, Ziegenfuss PS, Mohrman GB, et al. 1989. Composting of explosives and propellant contaminated sediments. Hazardous and Industrial Waste 21:599-611.

*Williams RT, Ziegenfuss PS, Sisk WE. 1992. Composting of explosives and propellent contaminated soils under thermophilic and mesophilic conditions. J Ind Microbial 9:137-144.

*Woody RC, Keams GL, Brewster MA, et al. 1986. The neurotoxicity of cyclotrimethylenetrinitramine (RDX) in a child: A clinical and pharmacokinetic evaluation. Clin Toxic01 24:305-319.

*Wujcik WJ, Lowe WL, Marks PJ, et al. 1992. Granular activated carbon pilot treatment studies for explosives removal from contaminated groundwater. Environmental Progress 11:178-l 89.

8. REFERENCES

Yang Y, Li W, Yin P, et al. 1986. Biological treatment for mixed 2,4,6-trinitrotoluenecyclotrimethylene-trinitroamine wastewater by screened bacteria strains. Acta Microbiologica Sinica 26:53-59.

Yang Y, Wang X, Yin P, et al. 1983. 3 Strains of corynebacterium degrading cyclotrimethylenetrinitroamine.
Acta Microbiologica Sinica 23:251-256.

*Yinon J, Laschever M. 1982. Direct-injection chemical ionization mass spectrometry of explosives in water. European Journal of Mass Spectrometry in Biochemistry, Medicine and Environmental Research 2:101-104.

9. GLOSSARY

Acute Exposure -- Exposure to a chemical for a duration of 14 days or less, as specified in the Toxicological Profiles.

Adsorption Coefficient (K_{OC}) -- The ratio of the amount of a chemical adsorbed per unit weight of organic carbon in the soil or sediment to the concentration of the chemical in solution at equilibrium.

Adsorption Ratio (Kd) -- The amount of a chemical adsorbed by a sediment or soil (i.e., the solid phase) divided by the amount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed in micrograms of chemical sorbed per gram of soil or sediment.

Bioconcentration Factor (BCF) -- The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same period.

Cancer Effect Level (CEL) -- The lowest dose of chemical in a study, or group of studies, that produces significant increases in the incidence of cancer (or tumors) between the exposed population and its appropriate control.

Carcinogen -- A chemical capable of inducing cancer.

Ceiling Value -- A concentration of a substance that should not be exceeded, even instantaneously.

Chronic Exposure -- Exposure to a chemical for 365 days or more, as specified in the Toxicological Profiles.

Developmental Toxicity -- The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

Embryotoxicity and Fetotoxicity -- Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the insult occurred. The terms, as used here, include malformations and variations, altered growth, and in utero death.

EPA Health Advisory -- An estimate of acceptable drinking water levels for a chemical substance based on healtheffects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

Immediately Dangerous to Life or Health (IDLH) -- The maximum environmental concentration of a contaminant from which one could escape within 30 min without any escape-impairing symptoms or irreversible health effects.

Intermediate Exposure -- Exposure to a chemical for a duration of 15364 days, as specified in the Toxicological Profiles.

9. GLOSSARY

Immunologic Toxicity -- The occurrence of adverse effects on the immune system that may result from exposure to environmental agents such as chemicals.

In Vitro -- Isolated from the living organism and artificially maintained, as in a test tube.

In Vivo -- Occurring within the living organism.

Lethal Concentration$_{(LO)}$ (LC_{LO}) -- The lowest concentration of a chemical in air which has been reported to have caused death in humans or animals.

Lethal Concentration$_{(50)}$ (LC_{50}) -- A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

Lethal Dose$_{(LO)}$ (LD_{LO}) -- The 1 owest dose of a chemical introduced by a route other than inhalation that is expected to have caused death in humans or animals.

Lethal Dose$_{(50)}$ (LD_{50}) -- The dose of a chemical which has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time$_{(50)}$ (LT_{50}) -- A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

Lowest-Observed-Adverse-Effect Level (LOAEL) -- The lowest dose of chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

Malformations -- Permanent structural changes that may adversely affect survival, development, or function.

Minimal Risk Level -- An estimate of daily human exposure to a dose of a chemical that is likely to be without an appreciable risk of adverse noncancerous effects over a specified duration of exposure.

Mutagen -- A substance that causes mutations. A mutation is a change in the genetic material in a body cell. Mutations can lead to birth defects, miscarriages, or cancer.

Neurotoxicity -- The occurrence of adverse effects on the nervous system following exposure to chemical.

No-Observed-Adverse-Effect Level (NOAEL) -- The dose of chemical at which there were no statistically or biologically significant increases in frequency or severity of adverse effe_cts seen between the exposed population and its appropriate control. Effects may be produced at this dose, but they are not considered to be adverse.

Octanol-Water Partition Coefficient (K_{OW}) -- The equilibrium ratio of the concentrations of a chemical in n-octanol and water, in dilute solution.

Permissible Exposure Limit (PEL) -- An allowable exposure level in workplace air averaged over an g-hour shift.

9. GLOSSARY

q_1* -- The upper-bound estimate of the low-dose slope of the dose-response curve as determined by the multistage procedure. The q_1* can be used to calculate an estimate of carcinogenic potency, the incremental excess cancer risk per unit of exposure (usually μg/L for water, mg/kg/day for food, and $\mu g/m^3$ for air).

Reference Dose (RfD) -- An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure of the human population to a potential hazard that is likely to be without risk of deleterious effects during a lifetime. The RfD is operationally derived from the NOAEL (from animal and human studies) by a consistent application of uncertainty factors that reflect various types of data used to estimate RfDs and an additional modifying factor, which is based on a professional judgment of the entire database on the chemical. The RfDs are not applicable to nonthreshold effects such as cancer.

Reportable Quantity (RQ) -- The quantity of a hazardous substance that is considered reportable under CERCLA. Reportable quantities are (1) 1 pound or greater or (2) for selected substances, an amount established by regulation either under CERCLA or under Sect. 3 11 of the Clean Water Act. Quantities are measured over a 24-hour period.

Reproductive Toxicity -- The occurrence of adverse effects on the reproductive system that may result from exposure to a chemical. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

Short-Term Exposure Limit (STEL) -- The maximum concentration to which workers can be exposed for up to 15 min continually. No more than four excursions are allowed per day, and there must be at least 60 min between exposure periods. The daily TLV-TWA may not be exceeded.

Target Organ Toxicity -- This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

Teratogen -- A chemical that causes structural defects that affect the development of an organism.

Threshold Limit Value (TLV) -- A concentration of a substance to which most workers can be exposed without adverse effect. The TLV may be expressed as a TWA, as a STEL, or as a CL.

Time-Weighted Average (TWA) -- An allowable exposure concentration averaged over a normal Shour workday or 40-hour workweek.

Toxic Dose (TD_{50}) -- A calculated dose of a chemical, introduced by a route other than-inhalation, which is expected to cause a specific toxic effect in 50% of a defined experimental animal population.

Uncertainty Factor (UF) -- A factor used in operationally deriving the RfD from experimental data. Ufs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using LOAEL data rather than NOAEL data. Usually each of these factors is set equal to 10.

APPENDIX A

USER'S GUIDE

Chapter 1

Public Health Statement

This chapter of the profile is a health effects summary written in non-technical language. Its intended audience is the general public especially people living in the vicinity of a hazardous waste site or chemical release. If the Public Health Statement were removed from the rest of the document, it would still communicate to the lay public essential information about the chemical.

The major headings in the Public Health Statement are useful to find specific topics of concern. The topics are written in a question and answer format. The answer to each question includes a sentence that will direct the reader to chapters in the profile that will provide more information on the given topic.

Chapter 2

Tables and Figures for Levels of Significant Exposure (LSE)

Tables (2-1, 2-2, and 2-3) and figures (2-l and 2-2) are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species, minimal risk levels (MRLs) to humans for noncancer endpoints, and EPA's estimated range associated with an upper-bound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. Use the LSE tables and figures for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of No-Observed-Adverse-Effect Levels (NOAELs), Lowest-Observed-Adverse-Effect Levels (LOAELs), or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE Table 2-l and Figure 2-l are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

LEGEND

See LSE Table 2-1

1) Route of Exposure One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. When sufficient data exists, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure, i.e., inhalation, oral, and dermal (LSE Table 2-1, 2-2, and 2-3, respectively). LSE figures are limited to the inhalation (LSE Figure 2-l) and oral (LSE Figure 2-2) routes. Not all substances will have data on each route of exposure and will not therefore have all five of the tables and figures.

APPENDIX A

2) Exposure Period Three exposure periods - acute (less than 15 days), intermediate (15-364 days), and chronic (365 days or more) are presented within each relevant route of exposure. In this example, an inhalation study of intermediate exposure duration is reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.

3) Health Effect The major categories of health effects included in LSE tables and figures are death, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the "System" column of the LSE table (see key number 18).

4) Key to Figure Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 18 has been used to derive a NOAEL and a Less Serious LOAEL (also see the 2 " 18r" data points in Figure 2-l).

5) Species The test species, whether animal or human, are identified in this column. Section 2.4, "Relevance to Public Health," covers the relevance of animal data to human toxicity and Section 2.3, "Toxicokinetics," contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.

6) Exposure Frequency/Duration The duration of the study and the weekly and daily exposure regimen are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18), rats were exposed to toxaphene via inhalation for 6 hours per day, 5 days per week, for 3 weeks. For a more complete review of the dosing regimen refer to the appropriate sections of the text or the original reference paper, i.e., Nitschke et al. 1981.

7) System This column further defines the systemic effects. These systems include: respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. "Other" refers to any systemic effect (e.g., a decrease in body weight) not covered in these systems. In the example of key number 18, 1 systemic effect (respiratory) was investigated.

8) NOAEL A No-Observed-Adverse-Effect Level (NOAEL) is the highest exposure level at which no harmful effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system which was used to derive an intermediate exposure, inhalation MRL of 0.005 ppm (see footnote "b").

9) LOAEL -A Lowest-Observed-Adverse-Effect Level (LOAEL) is the lowest dose used in the study that caused a harmful health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific endpoint used to quantify the adverse effect accompanies the LOAEL. The respiratory effect reported in key number 18 (hyperplasia) is a Less serious LOAEL of 10 ppm. MRLs are not derived from Serious LOAELs.

10) Reference The complete reference citation is given in chapter 8 of the profile.

APPENDIX A

11) CEL A Cancer Effect Level (CEL) is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases.

12) Footnotes Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. Footnote "b" indicates the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

LEGEND

See Figure 2-1

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure concentrations for particular exposure periods.

13) Exposure Period The same exposure periods appear as in the LSE table. In this example, health effects observed within the intermediate and chronic exposure periods are illustrated.

14) Health Effect These are the categories of health effects for which reliable quantitative data exists. The same health effects appear in the LSE table.

15) Levels of Exposure concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m^3 or ppm and oral exposure is reported in mg /kg/day.

16) NOAEL In this example, 18r NOAEL is the critical endpoint for which an intermediate inhalation exposure MRL is based. As you can see from the LSE figure key, the open-circle symbol indicates to a NOAEL for the test species-rat. The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the Table) to the MRL of 0.005 ppm (see footnote "b" in the LSE table).

17) CEL Key number 38r is 1 of 3 studies for which Cancer Effect Levels were derived. The diamond symbol refers to a Cancer Effect Level for the test species-mouse. The number 38 corresponds to the entry in the LSE table.

18) Estimated Upper-Bound Human Cancer Risk Levels This is the range associated with the upper-bound for lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. These risk levels are derived from the EPA's Human Health Assessment Group's upper-bound estimates of the slope of the cancer dose response curve at low dose levels (q_1*).

19) Key to LSE Figure The Key explains the abbreviations and symbols used in the figure.

SAMPLE

1 → **TABLE 2-1. Levels of Significant Exposure to [Chemical x] – Inhalation**

Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
2 → INTERMEDIATE EXPOSURE							
	5	6	7	8	9		10
3 → Systemic	↓	↓	↓	↓	↓		↓
4 → 18	Rat	13 wk 5d/wk 6hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
CHRONIC EXPOSURE							
					11		
					↓		
Cancer							
38	Rat	18 mo 5d/wk 7hr/d			20	(CEL, multiple organs)	Wong et al. 1982
39	Rat	89–104 wk 5d/wk 6hr/d			10	(CEL, lung tumors, nasal tumors)	NTP 1982
40	Mouse	79–103 wk 5d/wk 6hr/d			10	(CEL, lung tumors, hemangiosarcomas)	NTP 1982

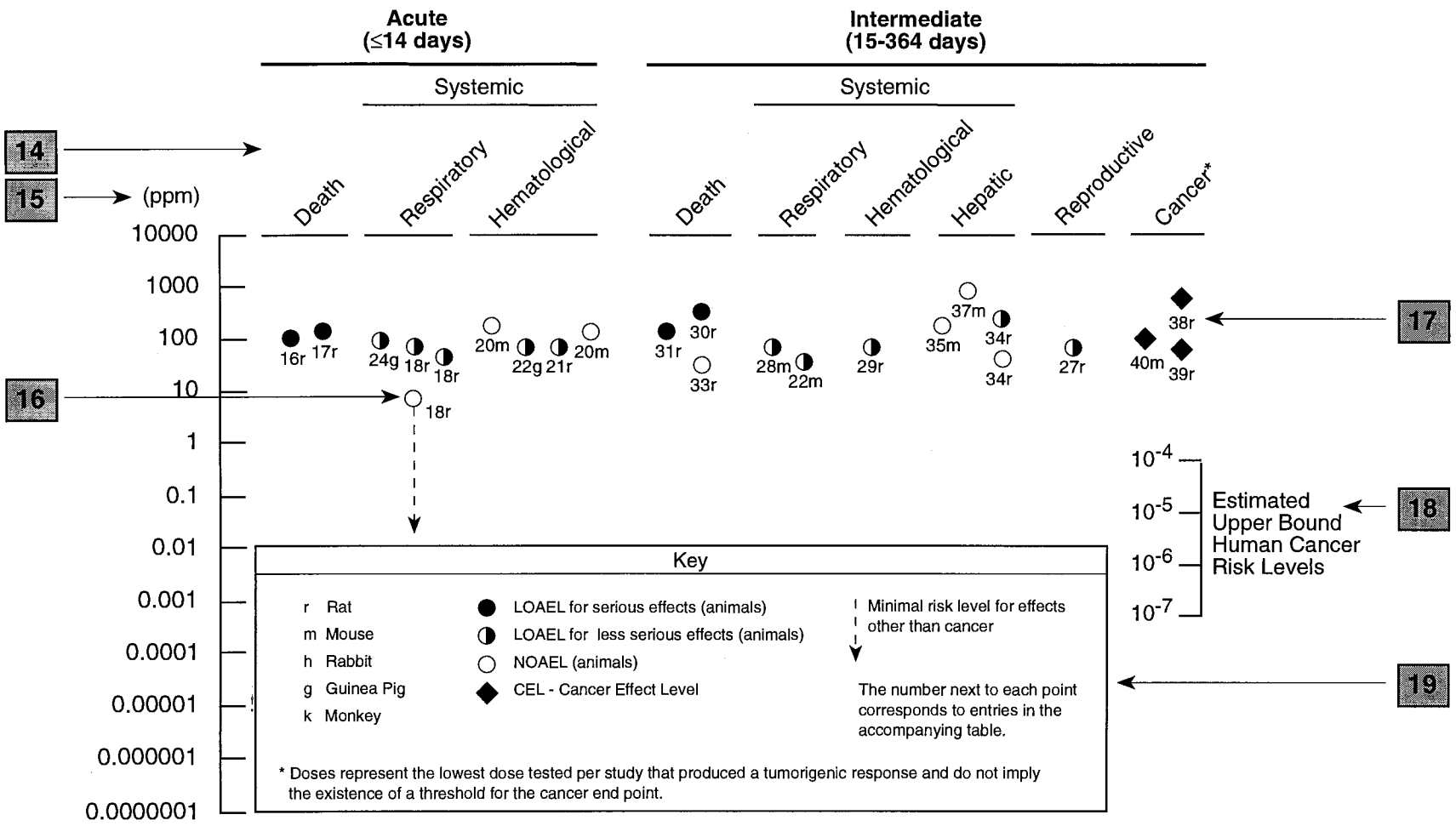
[a] The number corresponds to entries in Figure 2-1.

12 → [b] Used to derive an intermediate inhalation Minimal Risk Level (MRL) of 5 x 10^{-3} ppm; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

CEL = cancer effect level; d = days(s); hr = hour(s); LOAEL = lowest-observed-adverse-effect level; mo = month(s); NOAEL = no-observed-adverse-effect level; Resp = respiratory; wk = week(s)

SAMPLE

13 → **Figure 2-1. Levels of Significant Exposure to [Chemical X] – Inhalation**



APPENDIX A

Chapter 2 (Section 2.4)

Relevance to Public Health

The Relevance to Public Health section provides a health effects summary based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information. This summary is designed to present interpretive, weight-of-evidence discussions for human health endpoints by addressing the following questions.

1. What effects are known to occur in humans?

2. What effects observed in animals are likely to be of concern to humans?

3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

The section covers endpoints in the same order they appear within the Discussion of Health Effects by Route of Exposure section, by route (inhalation, oral, dermal) and within route by effect. Human data are presented first, then animal data. Both are organized by duration (acute, intermediate, chronic). *In vitro* data and data from parenteral routes (intramuscular, intravenous, subcutaneous, etc.) are also considered in this section. If data are located in the scientific literature, a table of genotoxicity information is included.

The carcinogenic potential of the profiled substance is qualitatively evaluated, when appropriate, using existing toxicokinetic, genotoxic, and carcinogenic data. ATSDR does not currently assess cancer potency or perform cancer risk assessments. Minimal risk levels (MRLs) for noncancer endpoints (if derived) and the endpoints from which they were derived are indicated and discussed.

Limitations to existing scientific literature that prevent a satisfactory evaluation of the relevance to public health are identified in the Data Needs section.

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information is available, we have derived minimal risk levels (MRLs) for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not meant to support regulatory action; but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans. They should help physicians and public health officials determine the safety of a community living near a chemical emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Chapter 2.4, “Relevance to Public Health,” contains basic information known about the substance. Other sections such as 2.6, “Interactions with Other Substances,” and 2.7, “Populations that are Unusually Susceptible” provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses for lifetime exposure (RfDs).

APPENDIX A

To derive an MRL, ATSDR generally selects the most sensitive endpoint which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen endpoint are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest NOAEL that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor (UF) of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MRL are provided in the footnotes of the LSE Tables.

APPENDIX B

ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ADME	Absorption, Distribution, Metabolism, and Excretion
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
BCF	bioconcentration factor
BSC	Board of Scientific Counselors
C	Centigrade
CDC	Centers for Disease Control
CEL	Cancer Effect Level
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
CLP	Contract Laboratory Program
cm	centimeter
CNS	central nervous system
d	day
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DOL	Department of Labor
ECG	electrocardiogram
EEG	electroencephalogram
EPA	Environmental Protection Agency
EKG	see ECG
F	Fahrenheit
F_1	first filial generation
FAO	Food and Agricultural Organization of the United Nations
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
fpm	feet per minute
ft	foot
FR	Federal Register
g	gram
GC	gas chromatography
gen	generation
HPLC	high-performance liquid chromatography
hr	hour
IDLH	Immediately Dangerous to Life and Health
IARCC	International Agency for Research on Cancer
ILO	International Labor Organization
in	inch
Kd	adsorption ratio
kg	kilogram
kkg	metric ton
K_{OC}	organic carbon partition coefficient
K_{OW}	octanol-water partition coefficient

APPENDIX B

L	liter
LC	liquid chromatography
LC_{LO}	lethal concentration, low
LC_{50}	lethal concentration, 50% kill
LD_{LO}	lethal dose, low
LD_{50}	lethal dose, 50% kill
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
m	meter
mg	milligram
min	minute
mL	milliliter
mm	millimeter
mm Hg	millimeters of mercury
mmol	millimole
mo	month
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectrometry
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
ng	nanogram
nm	nanometer
NHANES	National Health and Nutrition Examination Survey
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPL	National Priorities List
NRC	National Research Council
NTIS	National Technical Information Service
NTP	National Toxicology Program
OSHA	Occupational Safety and Health Administration
PEL	permissible exposure limit
pg	picogram
pmol	picomole
PHS	public Health Service
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
REL	recommended exposure limit
RfD	Reference Dose
RTECS	Registry of Toxic Effects of Chemical Substances
sec	second
SCE	sister chromatid exchange
SIC	Standard Industrial Classification
SMR	standard mortality ratio

APPENDIX B

STEL	short term exposure lirnit
STORET	STORAGE and RETRIEVAL
TLV	threshold limit value
TSCA	Toxic Substances Control Act
TRI	Toxics Release Inventory
TWA	time-weighted average
U.S.	United States
UF	uncertainty factor
yr	year
WHO	World Health Organization
wk	week
>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
δ	delta
γ	gamma
μm	micron
μg	microgram

☆U.S. GOVERNMENT PRINTING OFFICE: 638-643