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

2.2.1.1 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).

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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[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						
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 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						
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)		7M 100 F	35M (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

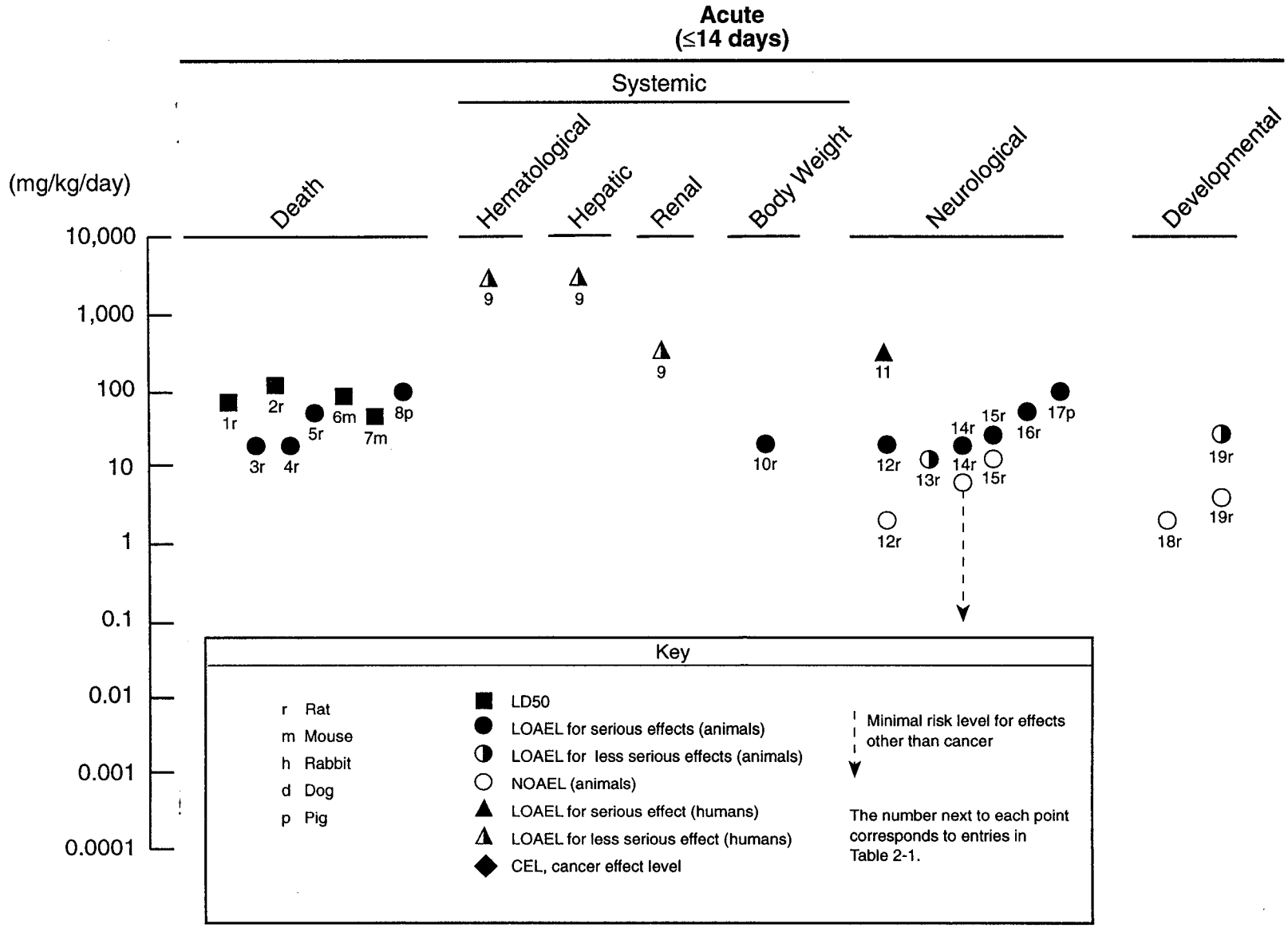


FIGURE 2-1. Levels of Significant Exposure to RDX – Oral (Continued)

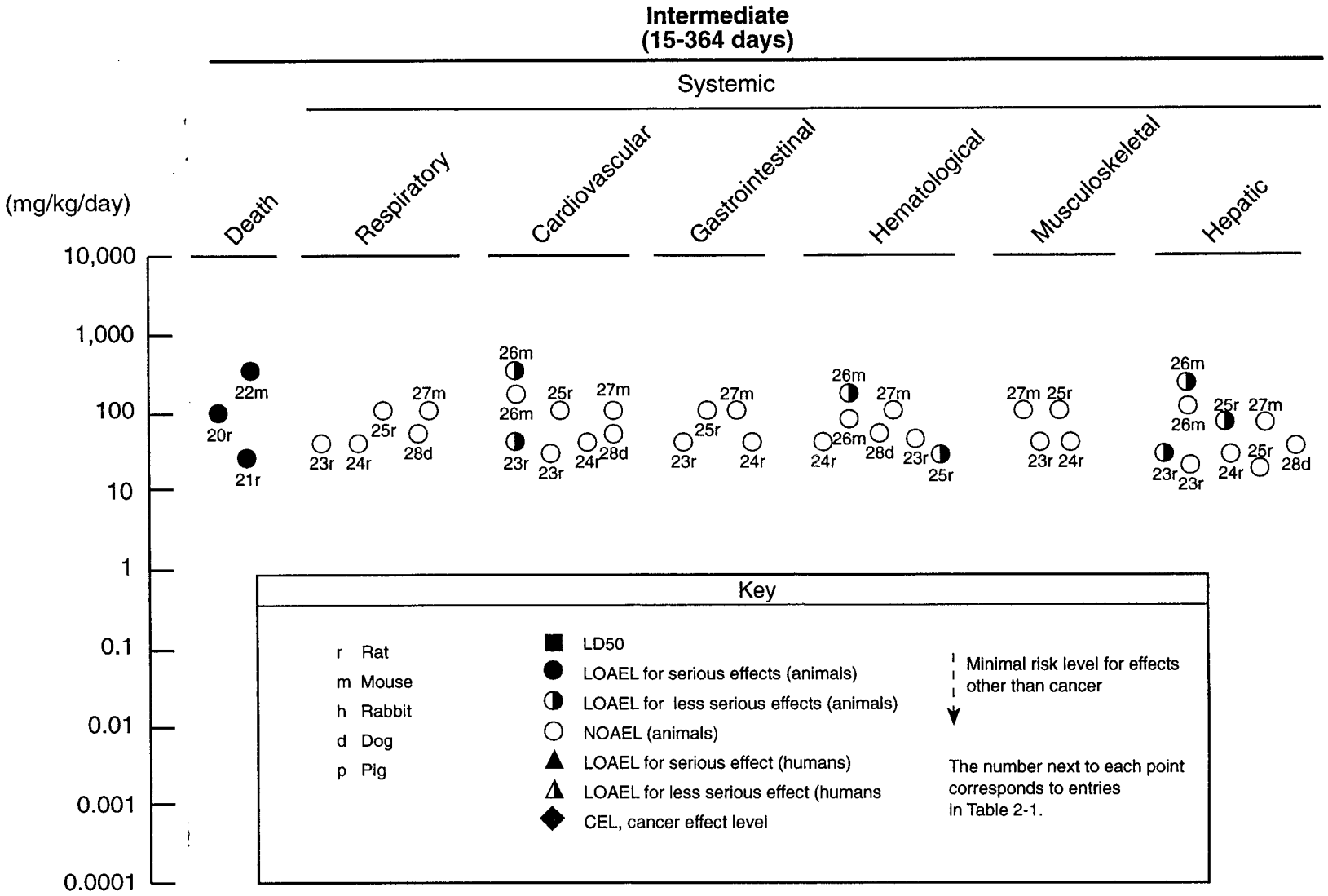


FIGURE 2-1. Levels of Significant Exposure to RDX – Oral (Continued)

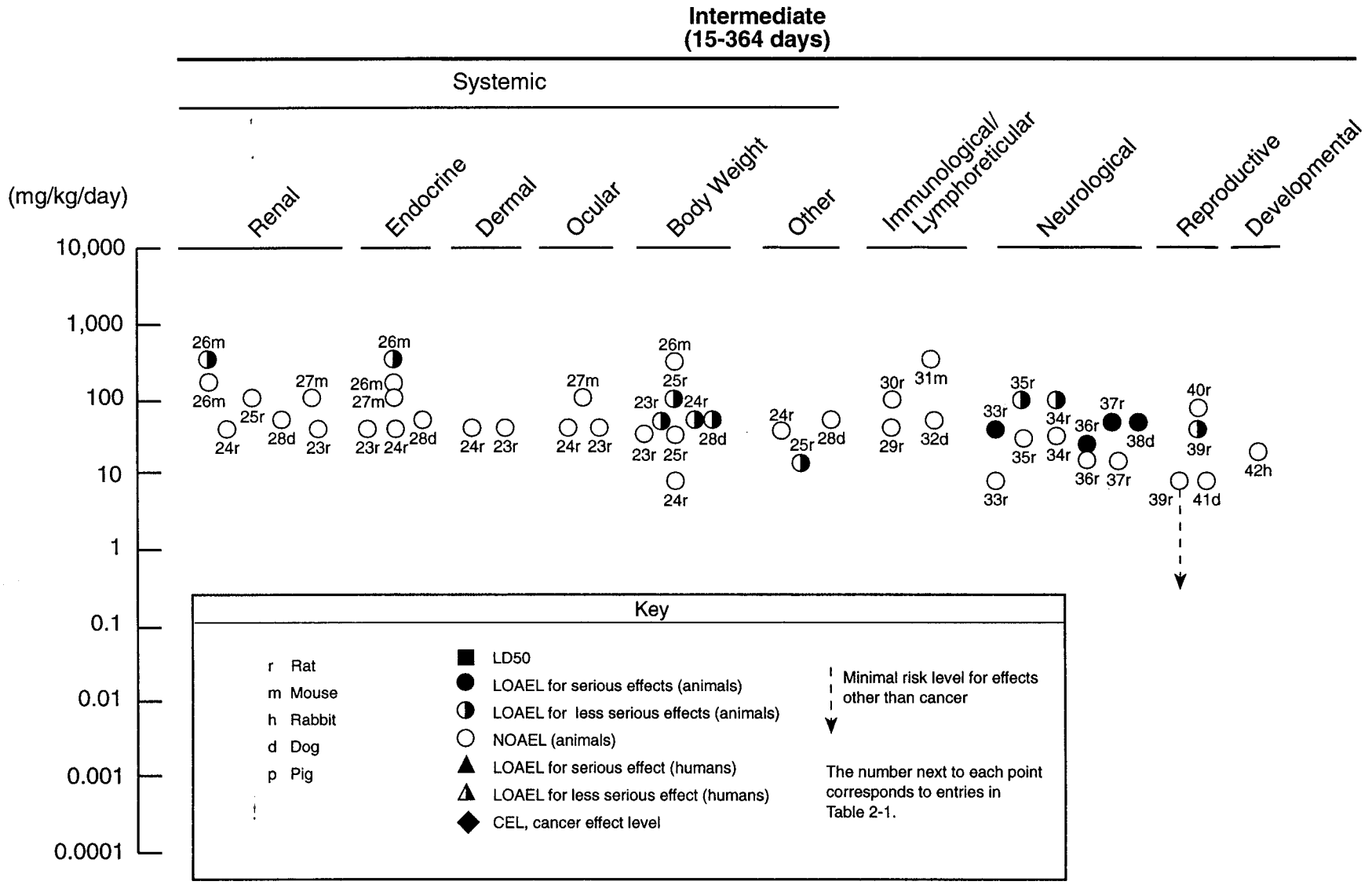
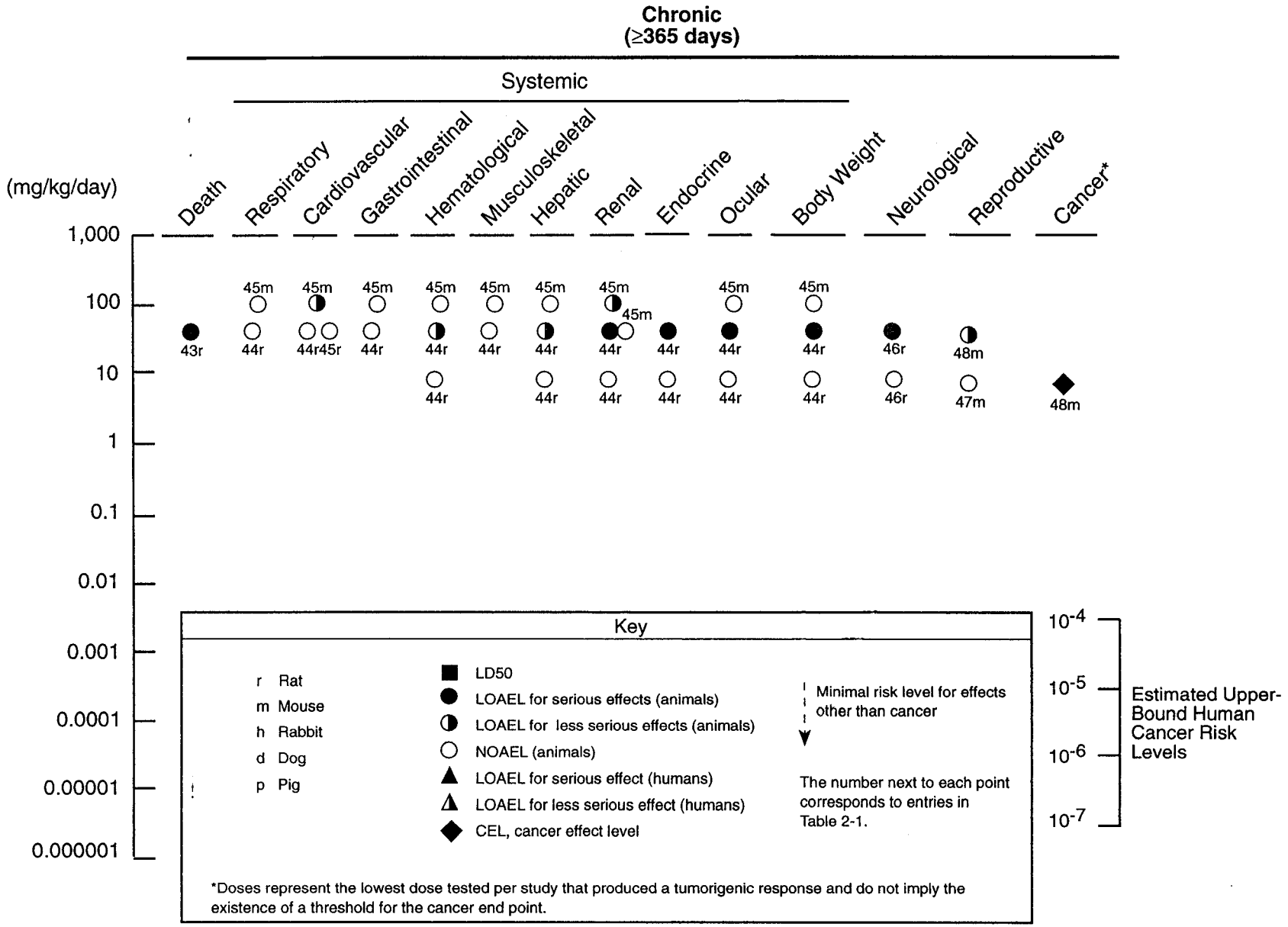


FIGURE 2-1. Levels of Significant Exposure to RDX – Oral (Continued)



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).

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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.

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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

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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).

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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.

2.9.1 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.

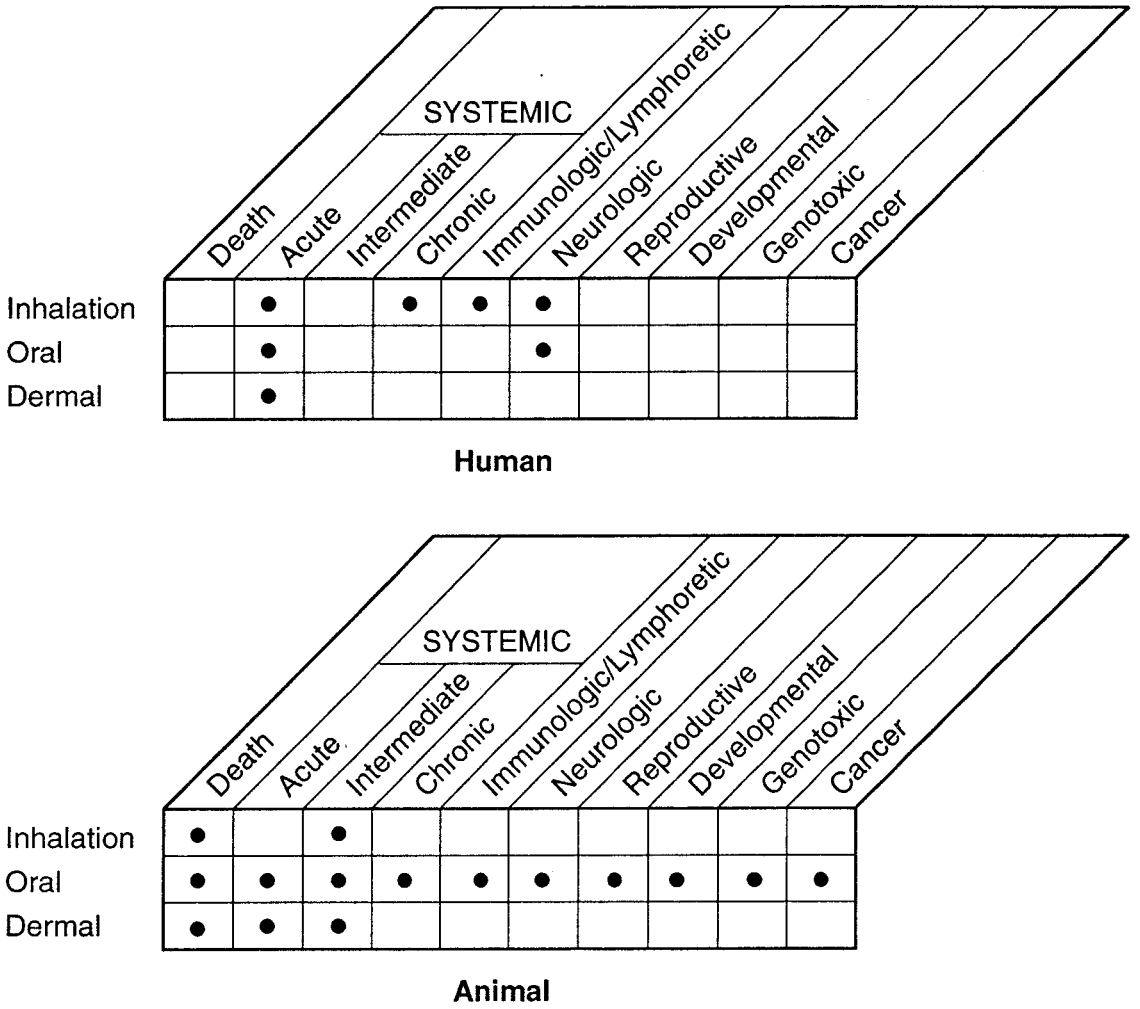
Case studies are available regarding systemic effects in humans following acute exposures to RDX via all three routes. One study in the workplace provides information on immunological and neurological effects following inhalation exposure for chronic periods. Neurological effects have also been described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

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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.

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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.