TOXICOLOGICAL PROFILE FOR
HMX

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UPDATE STATEMENT

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

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

FOREWORD

This toxicological profile is prepared in accordance with guidelines* developed by the Agency for Toxic Substances and Disease Registry (ATSDR) and the Environmental Protection Agency (EPA). The original guidelines were published in the *Federal Register* on April 17, 1987. Each profile will be revised and republished as necessary.

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

The focus of the profiles is on health and toxicologic information; therefore, each toxicological profile begins with a public health statement that describes, in nontechnical language, a substance's relevant toxicological properties. Following the public health statement is information concerning levels of significant human exposure and, where known, significant health effects. The adequacy of information to determine a substance's health effects is described in a health effects summary. Data needs that are of significance to protection of public health are identified by ATSDR and EPA.

Each profile includes the following:

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

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

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

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

This profile reflects ATSDR's assessment of all relevant toxicologic testing and information that has been peer-reviewed. Staff of the Centers for Disease Control and Prevention and other Federal scientists have also reviewed the profile. In addition, this profile has been peer-reviewed by a nongovernmental panel and was made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.

David Satcher, M.D., Ph.D.
Administrator
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Disease Registry

*Legislative Background

The toxicological profiles are developed in response to the Superfund Amendments and Reauthorization Act (SARA) of 1986 (Public Law 99-499) which amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund). Section 211 of SARA also amended Title 10 of the U. S. Code, creating the Defense Environmental Restoration Program. Section 2704(a) of Title 10 of the U. S. Code directs the Secretary of Defense to notify the Secretary of Health and Human Services of not less than 25 of the most commonly found unregulated hazardous substances at defense facilities. Section 2704(b) of Title 10 of the U. S. Code directs the Administrator of the Agency for Toxic Substances and Disease Registry (ATSDR) to prepare a toxicological profile for each substance on the list provided by the Secretary of Defense under subsection (b).

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THE PROFILE HAS UNDERGONE THE FOLLOWING ATSDR INTERNAL REVIEWS:

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

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

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

PEER REVIEW

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

1. Dr. Tim Borges, Technical Information Analyst, Clinton, Tennessee
2. Mr. Bruce Jacobs, Director, General Physics Corporation, Edgewood, Maryland
3. Dr. Ronald Spanggord, Director of Bio-Analytical Chemistry, SRI International, Menlo Park, California

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

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

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

CONTENTS

LIST OF FIGURES

LIST OF TABLES

1. PUBLIC HEALTH STATEMENT

This Statement was prepared to give you information about HMX and to emphasize the human health effects that may result from exposure to it. The Environmental Protection Agency (EPA) has identified 1,416 hazardous waste sites as the most serious in the nation. These sites make up the National Priorities List (NPL) and are the sites targeted for long-term federal cleanup activities. HMX has been found in at least 10 of the sites on the NPL. However, the number of NPL sites evaluated for HMX is not known. As EPA evaluates more sites, the number of sites at which HMX is found may increase. This information is important because exposure to HMX may cause harmful health effects and because these sites are potential or actual sources of human exposure to HMX.

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

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

1.1 WHAT IS HMX?

HMX, an acronym for High Melting eXplosive, is also known as octogen and cyclotetramethylene-tetranitramine, as well as by other names. It is a colorless solid that dissolves slightly in water. Only a very small amount of HMX will evaporate into the air; however, it can occur in air attached to suspended particles or dust. The taste and smell of HMX are not known.

HMX is a manmade chemical and does not occur naturally in the environment. It is made from other chemicals known as hexamine, ammonium nitrate, nitric acid, and acetic acid. HMX explodes

violently at high temperatures (534°F and above). Because of this property, HMX is used in nuclear devices, plastic explosives, rocket fuels, and burster chargers. A small amount of HMX is also formed in making cyclotrimethylene-trinitramine (RDX), another explosive similar in structure to HMX. The amount of HMX made and used in the United States at present is not known, but it is believed to be greater than 30 million pounds per year.

More information about the chemical names, properties, and uses of HMX is in Chapters 3 and 4.

1.2 WHAT HAPPENS TO HMX WHEN IT ENTERS THE ENVIRONMENT?

Most of the HMX that enters the environment is released into waste water from places that make or use HMX. A small amount of HMX can be released to the air as dust or ash from facilities that burn waste contaminated with HMX. Some HMX may be released to soil as a result of accidental spills, the settling of HMX-containing dust particles from the air, or the disposal of waste that contains HMX in landfills.

Dust particles containing HMX may be carried by the wind for some distance. The distance depends on a number of factors, including particle size, wind velocity, and weather conditions. Eventually, these particles settle to the earth, depositing on soil and surface waters. The length of time that HMX remains in the air is not known.

In surface water, HMX does not evaporate or bind to sediments to any large extent. Sunlight breaks down most of the HMX in surface water into other compounds, usually in a matter of days to weeks. The amount of time HMX remains in surface water depends on how much light-absorbing material is present. A small amount of HMX may also be broken down by bacteria in the water. Some of the breakdown products of HMX (nitrite, nitrate, formaldehyde, l,l-dimethylhydrazine) are also harmful to your health, although the amounts you may be exposed to as a result of HMX in your drinking water are not expected to be above trace levels.

Laboratory studies show that HMX is likely to move from soil into groundwater, particularly in sandy soils. For most soils, however, the movement of HMX into groundwater is expected to be slow. Bacteria in the soil are not expected to break down HMX to any large extent. Exactly how long HMX

will remain in the environment is not known; however, HMX in soil and groundwater is expected to stay there for a long time.

It is not known if plants, fish, or animals living in areas contaminated with HMX build up high levels of the chemical in their tissues.

More information on what happens to HMX when it enters the environment is in Chapters 4 and 5.

1.3 HOW MIGHT I BE EXPOSED TO HMX?

There is no information on how often you might be exposed to HMX in the environment or to how much. Most people, however, probably won't be exposed to HMX from the environment. People who work at facilities that make or use HMX or RDX, such as military personnel, may be exposed. These workers may be exposed by inhaling dusts that contain HMX or by getting HMX-containing liquids on their skin. People who live near facilities that make or use HMX, or near hazardous waste sites that contain HMX, may also be exposed. For these residents, exposure (if any) is most likely to occur from contaminated groundwater. However, exposures to small amounts of HMX from contaminated surface water, soil, and air are also possible.

More information on how you can be exposed to HMX is in Chapter 5.

1.4 HOW CAN HMX ENTER AND LEAVE MY BODY?

HMX can enter your body if you breathe contaminated air, swallow contaminated water or soil, or get substances that contain HMX on your skin. Very little is known about how much and how fast HMX enters your body after you are exposed.

Limited information from laboratory studies in animals suggests that if you swallow HMX, only a small amount (less than 5 percent) will be absorbed into your blood. The rest of the HMX that is not absorbed leaves your body in your feces, usually within a day or two after you are exposed. Your blood carries the small amount of absorbed HMX to your tissues. Animal studies suggest that the

resulting concentrations of HMX in your lungs, liver, heart, and kidneys may be slightly higher than the concentrations in other tissues.

HMX does not remain in any of your tissues for very long. Information from animal studies suggests that your body can transform HMX into other compounds called metabolites. At present, the identity and toxicity of these metabolites are not known. Most of these metabolites leave your body in your urine, usually within a few days after you are exposed. Smaller amounts of these metabolites may be released in your feces or in the air you breathe out.

More information on how HMX enters and leaves your body is in Chapter 2.

1.5 HOW CAN HMX AFFECT MY HEALTH?

Information on the adverse health effects of HMX is limited. In one human study, no adverse effects were reported in workers exposed to HMX in air. However, the concentrations of HMX in the workplace air were not reported in this study, and only a small number of workers and effects were investigated.

Studies in rats, mice, and rabbits indicate that HMX may be harmful to your liver and central nervous system if it is swallowed or gets on your skin. The lowest dose producing any effects in animals was 100 milligrams per kilogram of body weight per day (mg/kg/day) orally and 165 mg/kg/day on the skin. Limited evidence suggests that even a single exposure to these dose levels harmed rabbits. The mechanism by which HMX causes adverse effects on the liver and nervous system is not understood.

The reproductive and developmental effects of HMX have not been well studied in humans or animals. At present, the information needed to determine if HMX causes cancer is insufficient. Due to the lack of information, EPA has determined that HMX is not classifiable as to its human carcinogenicity.

More information on how HMX can affect your health is in Chapter 2.

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

You can find out if you have been exposed to HMX by having your blood, urine, or feces tested for HMX. Since HMX is poorly absorbed after it is swallowed, the levels of HMX in your blood and urine are likely to be lower than those in your feces. For best results, tests for HMX should be done within a few days after you are exposed. These tests cannot be used to tell how much HMX you have been exposed to or to predict whether or not you will experience adverse health effects. These tests are not usually done in a doctor's office, but require that the samples be sent to a laboratory for testing.

More information on medical tests to determine whether you have been exposed to HMX is in Chapters 2 and 6.

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

The federal government has made several regulations and guidelines to protect human health. EPA recommends that the concentration of HMX in an adult's drinking water be less than 0.40 milligrams per liter (mg/L) for a lifetime exposure. EPA regulates waste containing HMX as hazardous and has set restrictions on its disposal in landfills. The Department of State regulates the exportation of HMX, and the Department of Transportation regulates its transportation. The Bureau of Alcohol, Tobacco, and Firearms regulates the importation, manufacture, distribution, and storage of HMX.

More information on government regulations and guidelines for HMX is in Chapter 7.

1.8 WHERE CAN I GET MORE INFORMATION?

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

Agency for Toxic Substances and Disease Registry
Division of Toxicology
1600 Clifton Road NE, E-29
Atlanta, Georgia 30333
(404) 639-6000

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

2. HEALTH EFFECTS

2.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective on the toxicology of HMX. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxokinetic data to public health.

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 and others 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, reproductive, developmental, 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. “Serious” effects are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). “Less serious” effects are those that are not expected to cause significant dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether an end point should be classified as a NOAEL, “less serious” LOAEL, or “serious” LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify

these end points. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between “less serious” and “serious” effects. The distinction between “less serious” effects and “serious” effects is considered to be important because it helps the users of the profiles to identify levels of exposure at which major health effects start to appear. LOAELs or NOAELs should also help in determining 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 Levels of Significant Exposure (LSE) tables and figures may differ depending on the user’s perspective. Public health officials and others 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 or exposure levels below which no adverse effects have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels or MRLs) may be of interest to health professionals and citizens alike.

Estimates of exposure levels posing minimal risk to humans (Minimal Risk Levels or MRLs) have been made for HMX. An MRL is defined as an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (noncarcinogenic) over a specified duration of exposure. MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration within a given route of exposure. MRLs are based on noncancerous health effects only and do not consider carcinogenic effects. MRLs can be derived for acute, intermediate, and chronic duration exposures for inhalation and oral routes. Appropriate methodology does not exist to develop MRLs for dermal exposure.

Although methods have been established to derive these levels (Barnes and Dourson 1988; EPA 1990), 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 B). 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 or animals after inhalation exposure to HMX.

2.2.1.2 Systemic Effects

No studies were located regarding respiratory, cardiovascular, gastrointestinal, musculoskeletal, dermal, or ocular effects in humans or animals after inhalation exposure to HMX. Data regarding the hematological, hepatic, and renal effects of HMX in humans are limited to a single study. This study is discussed below.

Hematological Effects. A single study investigated the hematological effects of HMX in 24 male munitions workers who were also exposed to cyclotrimethylenetrinitramine (RDX) (Hathaway and Buck 1977). Compared to an unexposed control group (237 males), there were no significant differences in hemoglobin, hematocrit, and reticulocyte count in blood samples from workers exposed to HMX and RDX. Although levels of RDX in air were measured in this study (mean = 0.28 mg/m^3), the levels of HMX in the air of the munitions plant were not determined.

No studies were located regarding hematological effects in animals after inhalation exposure to HMX.

Hepatic Effects. A single study investigated the hepatic effects of HMX in 24 male munitions workers who were also exposed to a mean concentration of 0.28 mg/m^3 RDX (Hathaway and Buck 1977). Compared to an unexposed control group (237 males), there were no significant differences in lactate dehydrogenase, alkaline phosphatase, serum glutamic oxaloacetic transaminase, or serum glutamic pyruvic transaminase activities. Since this study was originally conducted to investigate the effects of RDX, the levels of HMX in the air of the munitions plant were not determined.

No studies were located regarding hepatic effects in animals after inhalation exposure to HMX.

Renal Effects. A single study investigated the renal effects of HMX in 24 male munitions workers who were also exposed to a mean concentration of 0.28 mg/m^3 RDX (Hathaway and Buck 1977). Compared to an unexposed control group (237 males), there were no significant differences in blood urea nitrogen concentration. Since this study was originally conducted to investigate the effects of RDX, the levels of HMX in the air of the munitions plant were not determined.

No studies were located regarding renal effects in animals after inhalation exposure to HMX.

2.2.1.3 Immunological and Lymphoreticular Effects

A single study investigated the immunological effects of explosives in a group of 558 male and female munitions workers (Hathaway and Buck 1977). The study was prompted by the occurrence of three cases of lupus erythematosus at one munitions plant within a 2-year period. The workers were exposed to RDX and HMX either alone or in combination with other explosives such as trinitrotoluene. Compared to an unexposed control group (863 males and females), the prevalence of antinuclear antibodies (a biomarker for lupus erythematosus) was not significantly different in exposed workers. Although the levels of RDX were determined to range up to 1.57 mg/m^3 (mean = 0.28 mg/m^3) in the air of one munitions plant, the levels of HMX in air were not determined.
No studies were located regarding immunological and lymphoreticular effects in animals after inhalation exposure to HMX.

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

2.2.1.4 Neurological Effects

2.2.1.5 Reproductive Effects

2.2.1.6 Developmental Effects

2.2.1.7 Genotoxic Effects

Genotoxicity studies are discussed in Section 2.5.

2.2.1.8 Cancer

No studies were located regarding carcinogenic effects in humans and animals after inhalation exposure to HMX.

2.2.2 Oral Exposure

2.2.2.1 Death

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

Several studies in animals indicate that acute and intermediate oral exposure to HMX can be lethal. For single exposures, LD_{50} values of 5,500 and 6,400 mg/kg HMX were reported for male and female rats, respectively (Army 1985h). In mice, the LD_{50} values were 1,700 and 3,200 mg/kg HMX for males and females, respectively (Army 1985h). Limited evidence suggests that rabbits may be more sensitive to the lethal effects of HMX than rodents. Deaths in rabbits were observed following single oral doses of 100 mg/kg or more (Army 1985h). However, there are several deficiencies in this Army (1985h) study that preclude establishing a definitive conclusion. For instance, the gavage administration of the HMX may have contributed to the apparent greater susceptibility of the rabbits as a result of a bolus effect. Also, only a small number of rabbits were tested (two per group), and no control group was run concurrently. The authors concluded that HMX was relatively nontoxic to rats, slightly toxic to mice, and toxic to rabbits. Deaths were observed in rats exposed to 3,055-8,054 mg/kg/day HMX and in mice exposed to 300-800 mg/kg/day for 14 days (Army 1985d, 1985e). In mice, the males appeared to be more sensitive to the lethal effects of HMX since 5/6 males died following exposure to 300 mg/kg/day, whereas only 2/6 females died following exposure to 800 mg/kg/day. In rats, the females appeared to be more sensitive than male rats to the lethal effects of HMX, since 6/6 females died following exposure to 3,055 mg/kg/day, compared to 5/6 males following exposure to 8,504 mg/kg/day. No treatment-related deaths were observed in rats exposed to up to 4,000 mg/kg/day HMX for 13 weeks (Army 1985b). However in mice, deaths were noted in 13/20 males exposed to 200 mg/kg/day and in 12/20 females exposed to 250 mg/kg/day HMX for 13 weeks (Army 1985b). All LOAEL values from each reliable study for death are recorded in Table 2-l and plotted in Figure 2-l.

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

Key [a] to figure	Species (strain)	Exposure duration/ frequency (specific route)	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference
	ACUTE EXPOSURE						
	Death						
1	Rat Fischer 344	14 d ad lib (F)				3055 F (death in 6/6)	Army 1985e
2	Rat Fischer 344	Once[b] (G)				5500 M (LD50) 6400 F (LD50)	Army 1985h
3	Mouse B6C3F1	14 d ad lib (F)				300 M (5/6 deaths) 800 F (2/6 deaths)	Army 1985d
4	Mouse B6C3F1	Once[b] (G)				1700 M (LD50) 3200 F (LD50)	Army 1985h
	Systemic						
5	Rat Fischer 344	14 d ad lib (F)	Hepatic		1280 F (hepatocyte hyperplasia and cytoplasmic eosinophilia in the liver)	8504 M (toxic centrilobular degeneration)	Army 1985e
			Renal		1280 F (congestion of the kidney)		

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

Key [a] to figure	Species (strain)	Exposure duration/ frequency (specific route)	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference
6	Rat Fischer 344	Once[b] (G)	Resp	3632	5447 ("reddening" of the lungs)		Army 1985h
			Gastro	3632	5447 (presence of "white fluid" in the gastrointestinal tract)		
			Renal	3632	5447 ("pale" kidneys)		
7	Mouse B6C3F1	14 d ad lib (F)	Cardio	5000 F			Army 1985d
			Hepatic		300 M (hepatocellular hyperplasia and cytoplasmic eosinophilia)		
			Renal	5000 F			
8	Mouse NS	Once[b] (G)	Resp	956	1626 ("reddening" of the lungs)		Army 1985h
			Gastro	956	1626 (presence of "white fluid" in the gastrointestinal tract)		
	Immunological/Lymphoreticular						
9	Rat Fischer 344	14 d ad lib (F)			1280 F (lymphocyte depletion in thymus and spleen)		Army 1985e

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

Key [a] to figure	Species (strain)	Exposure duration/ frequency (specific route)	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference
10	Mouse B6C3F1	14 d ad lib (F)			300 M (lymphocyte depletion in the thymus and spleen)		Army 1985d
	Neurological						
11	Rat Fischer 344	14 d ad lib (F)		3474		8504 M (congestion and hemorrhage in the brain)	Army 1985e
12	Rat Fischer 344	Once (G)			2421 (hyperkinesia, piloerection)	5447 (ataxia)	Army 1985h
13	Mouse B6C3F1	14 d ad lib (F)			100 [c] M (hyperkinesia)	300 M (convulsions, hunched posture, and increased sensitivity to audio stimuli)	Army 1985d
14	Mouse B6C3F1	Once [b] (G)			956 (hyperkinesia)	1626 (piloerection, ataxia)	Army 1985h

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

Key [a] to figure	Species (strain)	Exposure duration/ frequency (specific route)	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference
	INTERMEDIATE EXPOSURE						
	Death						
15	Mouse B6C3F1	13 wk ad lib (F)				200 M (13/20 deaths) 250 F (12/20 deaths)	Army 1985b
	Systemic						
16	Rat Fischer 344	13 wk ad lib (F)	Hemato		1500 F (decreased hemoglobin and packed cell volume, slight increase in methemoglobin)		Army 1985c
			Hepatic	50 [d] M	150 M (enlarged centrilobular cells with dark cytoplasm)		
			Renal	115 F	270 F (focal tubular atrophy, dilatation, and increased kidney weights)		
			Ocular	4000 M			

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

Key [a] to figure	Species (strain)	Exposure duration/ frequency (specific route)	System	NOAEL (mg/kg/day)		LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference
17	Mouse B6C3F1	13 wk ad lib (F)	Resp	90	F			Army 1985b
			Cardio	90	F			
			Gastro	90	F			
			Hemato	750	F			
			Musc/skel	90	F			
			Hepatic	90	F			
			Renal	90	F			
			Ocular	90	F			
			Bd Wt	750	F			
	Reproductive							
18	Mouse B6C3F1	13 wk ad lib (F)		90	F			Army 1985b

[a] The number corresponds to entries in Figure 2-1.
[b] HMX was administered in a carboxymethylcellulose solution.
[c] Used to derive an acute oral Minimal Risk Level (MRL) of 0.1 mg/kg/day; dose divided by an uncertainty factor of 1,000 (10 for use of an LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability).
[d] Used to derive an intermediate oral Minimal Risk Level (MRL) of 0.05 mg/kg/day; dose divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability) and a modifying factor of 10 for use of a "limited database."

ad lib = ad libitum; Bd Wt = body weight; Cardio = cardiovascular; d = day(s); F = female; (F) = feed; (G) = gavage (not specified); Gastro = gastrointestinal; Hemato = hematological; LD50 = lethal dose (50% kill); LOAEL = lowest-observed-adverse-effect level; M = male; Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; NS = not specified; Resp = respiratory; wk = week(s); " " = indicates an ambiguous term used by study authors

Figure 2-1. Levels of Significant Exposure to HMX - Oral

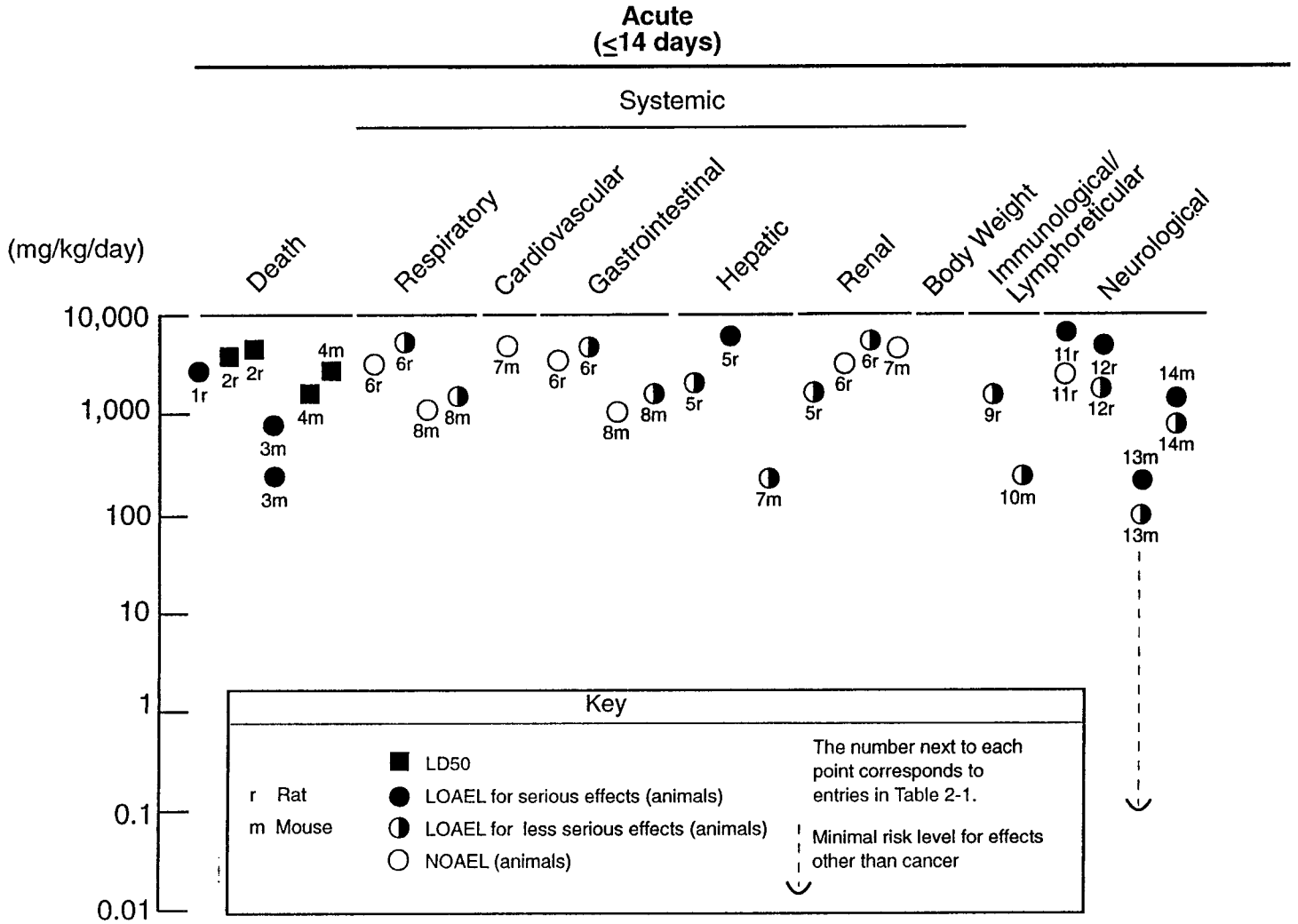
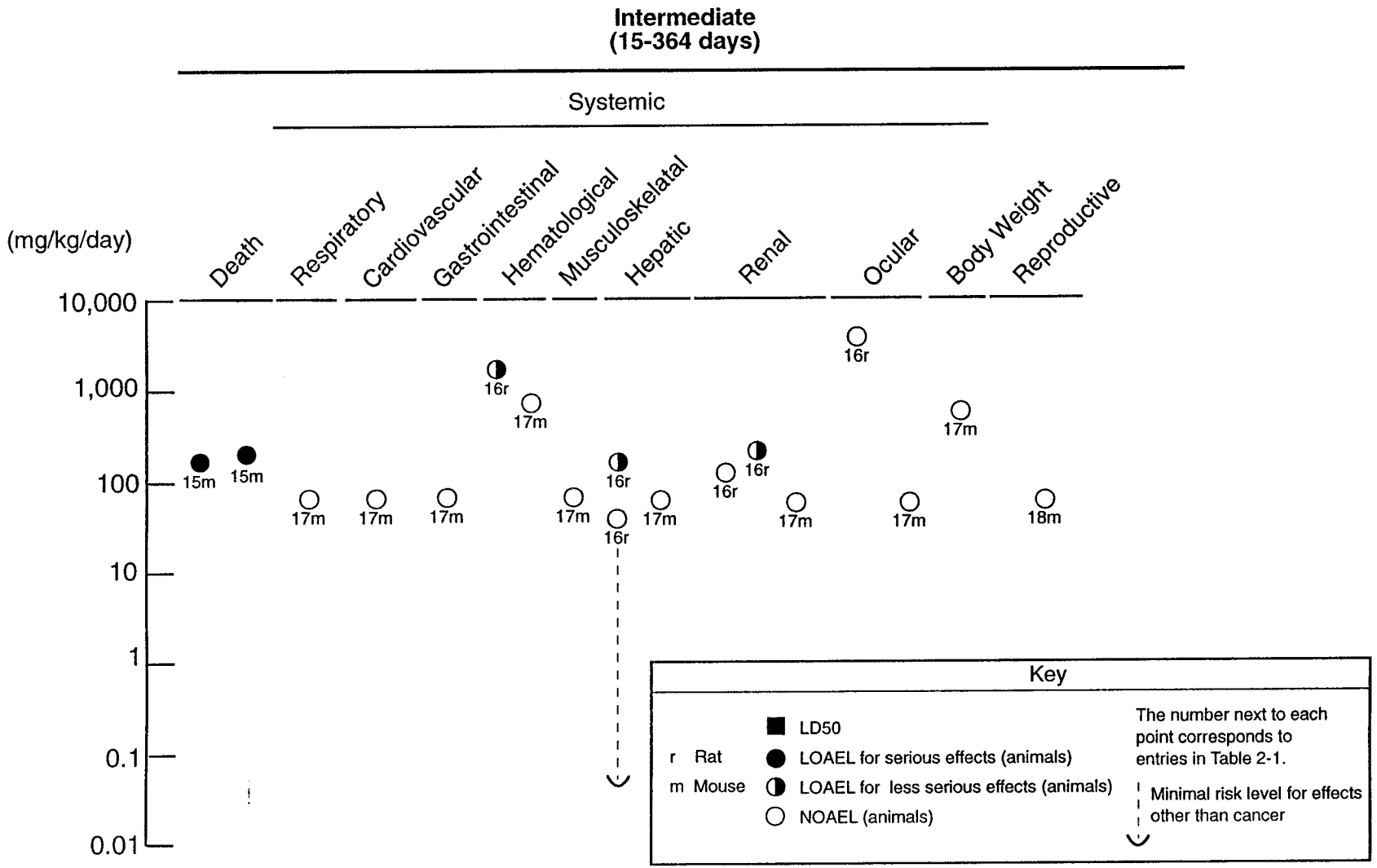


Figure 2-1. Levels of Significant Exposure to HMX - Oral (continued)



2.2.2.2 Systemic Effects

No studies were located regarding systemic effects in humans after oral exposure to HMX. Studies regarding systemic effects in animals are summarized below. The highest NOAEL values and all LOAEL values from each reliable study for systemic effects in animals are recorded in Table 2-1 and plotted in Figure 2- 1.

Respiratory Effects. No studies were located regarding respiratory effects in humans after oral exposure to HMX. Following exposure to a single oral dose of 5,447, 1,626, and 50 mg/kg HMX in rats, mice, and rabbits, respectively, a "reddening" of the lungs was observed (Army 1985h). White nodules were also noted in the lungs of one exposed rabbit. Both lesions were not described further by the authors; therefore, their significance is uncertain. Furthermore, the rabbit study contained a number of design limitations (small number of animals, no control group). No gross or histopathological lesions were observed in the lungs of mice exposed to 90 mg/kg/day HMX in the diet for 13 weeks (Army 1985b). Pulmonary function was not investigated in any of the animals. The data are too limited to draw firm conclusions, but suggest that rabbits may be more susceptible than rats and mice to the acute pulmonary effects of HMX.

Cardiovascular Effects. No studies were located regarding cardiovascular effects in humans after oral exposure to HMX. No gross or histopathological lesions of the heart were observed in mice exposed to 5,000 mg/kg/day HMX for 14 days (Army 1985d). Similarly, no effects were noted on the heart in mice exposed to 90 mg/kg/day HMX for 13 weeks (Army 1985b). The data suggest that the heart is not a critical target of HMX toxicity.

Gastrointestinal Effects. No studies were located regarding gastrointestinal effects in humans after oral exposure to HMX. A "white fluid" was noted in the gastrointestinal tract of rats and mice exposed to a single oral dose of 5,447 and 1,626 mg/kg HMX, respectively (Army 198%). The fluid was not described further; therefore its significance is uncertain. No gross or histopathological lesions were observed in the gastrointestinal tract of mice exposed to 90 mg/kg/day HMX in the diet for 13 weeks (Army 1985b). Although the data suggest that high doses of HMX may adversely affect the gastrointestinal system, the gastrointestinal tract may not be affected by relatively low doses of HMX.

Hematological Effects. No studies were located regarding hematological effects in humans after oral exposure to HMX. A statistically significant decrease in hemoglobin and packed cell volume, and a nonsignificant increase in methemoglobin were noted in female rats exposed to 1,500 mg/kg/day in the diet for 13 weeks (Army 1985c). A significant elevation in methemoglobin concentration was observed in male rats exposed to 4,000 mg/kg/day (Army 1985c). No significant hematological effects were noted in mice exposed to 750 mg/kg/day HMX for 13 weeks (Army 1985b). The data suggest that mild hematological effects may occur following exposure to large doses of HMX, but that these effects may not be of concern following exposure to relatively low doses of HMX.

Musculoskeletal Effects. No studies were located regarding musculoskeletal effects in humans after oral exposure to HMX. Data regarding the musculoskeletal effects of HMX in animals are limited to a single study. No gross or histopathological lesions were noted in the bones or skeletal muscle of mice exposed to 90 mg/kg/day HMX for 13 weeks (Army 1985b). The data suggest that musculoskeletal effects are not of concern following exposure to relatively low doses of HMX, but this has not been well studied.

Hepatic Effects. No studies were located regarding hepatic effects in humans after oral exposure to HMX. Several studies have reported hepatic effects in animals following exposure to HMX. Hepatocyte hyperplasia and cytoplasmic eosinophilia were noted in rats and mice exposed to 1,280 and 300 mg/kg/day HMX, respectively, for 14 days (Army 1985d, 1985e). Clear evidence of hepatotoxicity was observed at a higher dose of 8,504 mg/kg/day HMX, which resulted in centrilobular degeneration in male rats exposed for 14 days (Army 1985e). Hepatic effects were not observed in control animals. The centrilobular cells of male rats exposed to 150 mg/kg/day HMX for 13 weeks were enlarged with pale nuclei and dark cytoplasm (Army 1985c). Higher doses of 1,500 mg/kg/day (females) and 4,000 mg/kg/day (males) produced significant elevations in serum alkaline phosphatase levels in rats, while serum aspartate aminotransferase, serum alanine amino transferase, and lactate dehydrogenase levels showed no consistent change. No hepatic effects were observed in male and female rats exposed to 50 mg/kg/day HMX, in female mice exposed to 90 mg/kg/day HMX, and in male mice exposed to 75 mg/kg/day HMX for 13 weeks (Army 1985b, 1985c). Histopathology was not performed on mice exposed to doses greater than 90 mg/kg/day (females) or 75 mg/kg/day (males). Since deaths occurred in these animals, a histological examination may have indicated whether or not there were any hepatic lesions.

Some of the hepatic effects observed in animals (hepatocyte hyperplasia, cytoplasmic eosinophilia, centrilobular cell enlargement) may represent an adaptive response of the liver rather than a toxic response. Adaptive responses may result in changes that are beneficial or potentially detrimental to the host. However, given that the borderline between adaptive physiology and toxicity is not always well defined, and that such changes may be predictive of effects which are clearly toxic (centrilobular degeneration), it is best to consider these changes as less serious adverse effects. Collectively, the data from animal studies indicate that the liver is adversely affected by exposure to moderate to high doses of HMX. Based on the NOAEL of 50 mg/kg/day in rats, an intermediate oral MRL of 0.05 mg/kg/day was calculated as described in footnote "d" of Table 2-l.

Renal Effects. No studies were located regarding renal effects in humans after oral exposure to HMX. Data regarding the renal effects of HMX in animals are limited. The kidneys of rats administered a single dose of 5,447 mg/kg HMX were "pale" in appearance (Army 1985h). This effect was not described further by the authors, therefore its significance is uncertain. Congestion of the kidney was noted in some rats exposed to 1,280 mg/kg/day or more (Army 1985e). However, no gross or histopathological lesions of the kidney developed in mice exposed to up to 5,000 mg/kg/day HMX for 14 days (Army 1985d). Focal tubular atrophy, dilatation, and increased kidney weights were observed in female rats exposed to 270 mg/kg/day HMX, while blood urea nitrogen was elevated in female rats exposed to 1,500 mg/kg/day HMX in the diet for 13 weeks (Army 1985c). In the same study, decreased pH, increased volume, and crystal formation was observed in the urine of male and female rats exposed to 1,500-4,000 mg/kg/day HMX. No gross or histopathological lesions of the kidney were observed in female rats exposed to 115 mg/kg/day or in female mice exposed to 90 mg/kg/day for 13 weeks (Army 1985b, 1985c). No gross or histopathological effects were observed in male rats exposed to 4,000 mg/kg/day HMX or in male mice exposed to 75 mg/kg/day HMX for 13 weeks. Histopathological examinations were not performed in male mice exposed to doses greater than 75 mg/kg/day HMX, or female mice exposed to doses greater than 90 mg/kg/day. The data suggest that moderate to high doses of HMX may adversely affect the kidney, but that relatively low doses of HMX are without effect.

Dermal Effects. No studies were located regarding dermal effects in humans after oral exposure to HMX. Data regarding the dermal effects of HMX in animals are limited to one study. No gross or histopathological lesions of the skin developed in mice exposed to 90 mg/kg/day HMX for 13 weeks

(Army 1985b). Data suggest that the skin is not an important target of HMX toxicity following ingestion.

Ocular Effects. No studies were located regarding ocular effects in humans after oral exposure to HMX. Data regarding the ocular effects of HMX in animals are limited to one study. Ophthalmoscopic examinations did not reveal any treatment-related effects on the eyes of rats exposed to up to 4,000 mg/kg/day HMX for 13 weeks (Army 1985c).

Body Weight Effects. No studies were located regarding body weight effects in humans after oral exposure to HMX. A decrease in body weight gain of 19% was observed in rats exposed to 370 mg/kg/day HMX in the diet for 14 days (Army 1985e). Body weights were decreased in a dosedependent manner in male and female rats exposed to 50-4,000 mg/kg/day for 13 weeks (Army 1985c). However, the dose at which this effect became significant could not be determined. Food intake of the animals in both studies was depressed. Although food intake was also decreased in mice exposed to 750 mg/kg/day HMX for 13 weeks, no significant change in body weight gain was noted (Army 1985b). These data are inconsistent, therefore no firm conclusions can be made.

2.2.2.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological and lymphoreticular effects in humans after oral exposure to HMX.

Lymphocytic depletion of the thymus and spleen was noted in rats and mice exposed to 1,280 and 300 mg/kg/day, respectively for 14 days (Army 1985d, 1985e). Effects were not observed in animals in the control group. The absolute and relative spleen weights were decreased in a dose-dependent manner in male rats exposed to 50 mg/kg/day HMX or more for 13 weeks (Army 1985c). However, significant body weight changes occurred in these animals, and therefore these effects are difficult to interpret. Collectively, the data suggest that perhaps even low doses of HMX can adversely affect organs important to the immune system; however, none of the studies investigated the effects of HMX on immune system function. The highest NOAEL values and all LOAEL values for immunological effects in animals are recorded in Table 2-l and plotted in Figure 2-l.

2.2.2.4 Neurological Effects

No studies were located regarding neurological effects in humans after oral exposure to HMX. Several studies have reported neurological effects in animals after acute exposure to HMX. A single dose of 2,421 or 956 mg/kg HMX produced hyperkinesia in rats and mice, respectively (Army 1985h). The authors of this study also reported hypokinesia and ataxia in rats and mice exposed to higher doses (5,447 and 1,626 mg/kg, respectively) of HMX. Mild convulsions, hyperkinesia, and mydriasis (dilated pupils) occurred in rabbits following a single oral dose of 50 mg/kg HMX or more (Army 1985h). However, limitations in this study (only a small number of rabbits were tested and no control group was run concurrently) detract from the significance of these findings. In addition, gavage administration of the HMX may have contributed to the apparent greater susceptibility of the rabbits as a result of a bolus effect. Congestion and hemorrhaging of the blood vessels in the brain was noted in some rats exposed to 8,504 mg/kg/day HMX for 14 days (Army 1985e). Hyperkinesia and excitability when aroused were noted in mice exposed to 100 mg/kg/day HMX in the diet for 14 days (Army 1985d). A NOAEL was not identified in this study. Doses of 300 mg/kg/day HMX produced convulsions, a hunched posture, piloerection, and increased sensitivity to audio stimuli in some of the mice from this study. Collectively, these data suggest that the central nervous system is an important target of HMX toxicity. Based on the LOAEL of 100 mg/kg/day in mice, an acute oral MRL of 0.1 mg/kg/day was calculated as described in footnote “c” of Table 2-l. All LOAEL values for neurological effects in animals are recorded in Table 2-l 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 HMX.

No gross or histopathological lesions were observed in the ovaries or testes of mice exposed to 90 mg/kg/day HMX in the diet for 13 weeks (Army 1985b). Mice exposed to higher doses of HMX in this study were not histopathologically examined. Reproductive function was not assessed in this study, therefore no firm conclusions can be made regarding the potential of HMX in producing reproductive effects. The NOAEL value for reproductive organ histopathology is recorded in Table 2-l and plotted in Figure 2-l.

2.2.2.6 Developmental Effects

No studies were located regarding developmental effects in humans or animals after oral exposure to HMX.

2.2.2.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans or animals after oral exposure to HMX.

Genotoxicity studies are discussed in Section 2.5.

2.2.2.8 Cancer

No studies were located regarding carcinogenic effects in humans or animals after oral exposure to HMX.

2.2.3 Dermal Exposure

2.2.3.1 Death

No studies were located regarding death in humans after dermal exposure to HMX.

The dermal LD_{50} values for HMX in rabbits were reported to be 634 mg/kg in males and 7 19 mg/kg in females (Army 1985h). The LD_{50}values were slightly higher (and therefore less toxic) in rabbits with abraded skin. The reason for this unexpected difference in HMX toxicity between rabbits with abraded versus nonabraded skin is not readily apparent. No deaths were observed in rabbits and rats exposed to 372 and 4,230 mg/kg HMX, respectively (Army 1985h). Exposure to 165 mg/kg/day HMX in dimethylsulfoxide for up to 5 days caused deaths in 3/10 exposed rabbits (Army' 1974). The same dose produced 3/6 deaths in rabbits exposed for 4 weeks (Army 1974). The data indicate that dermal exposure to HMX can be lethal to rabbits. All LOAEL values for death in animals are recorded in Table 2-2.

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

Species (strain)	Exposure duration/ frequency	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)		LOAEL (effect) Serious (mg/kg/day)		Reference
ACUTE EXPOSURE								
Death								
Rabbit NS	1-5 d 1x/d					165	(3/10 deaths)	Army 1974
Rabbit New Zealand	Once					634 M (LD50) 719 F (LD50)		Army 1985h
Systemic								
Dog Beagle	1-5 d 1x/d	Cardio	480					Army 1974
Rabbit NS	Once	Hemato	165					Army 1974
		Dermal	165					
Rabbit New Zealand	Once	Resp		168	(congestion and "reddening" of the lungs and trachea)			Army 1985h
		Hepatic	168	372	(congested and "mottled" liver with fissures prominent)			
		Renal				168	(tubular dilation, fibrosis, and atrophy; glomerular atrophy)	
Rabbit New Zealand	Once	Dermal		109	(mild irritation of the skin)			Army 1985h
		Ocular		109	(mild irritation of the conjunctiva)			

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

Species (strain)	Exposure duration/ frequency	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)		LOAEL (effect) Serious (mg/kg/day)		Reference
Gn pig NS	1-3 d 1x/d	Dermal	510	1000	(slight erythema)			Army 1974
Gn pig Dunkin-Hartley	Once	Dermal	357 F					Army 1985h
Immunological/Lymphoreticular								
Rabbit New Zealand	Once			168	(enlarged spleen)			Army 1985h
Neurological								
Dog Beagle	1-5 d 1x/d		480					Army 1974
Rabbit New Zealand	Once					168	(convulsions, hyperkinesia, hypokinesia, and aggression)	Army 1985h
INTERMEDIATE EXPOSURE								
Death								
Rabbit NS	4 wk 5d/wk 1x/d					165	(3/6 deaths)	Army 1974
Systemic								
Dog Beagle	4 wk 5d/wk 1x/d	Cardio	289					Army 1974

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

Species (strain)	Exposure duration/ frequency	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference
Rabbit	4 wk	Resp	165			Army 1974
NS	5d/wk					
	1x/d	Cardio	165			
		Musc/skel	165			
		Hepatic	165			
		Renal	165			
		Dermal		16.5 (dermatitis)		
Gn pig	3 wk	Dermal	196			Army 1974
NS	3d/wk					
	1x/d					
Neurological						
Dog	4 wk		289			Army 1974
Beagle	5d/wk					
	1x/d					

Cardio = cardiovascular; d = day(s); F = female; Gn pig = guinea pig; Hemato = hematological; LD50 = lethal dose (50% kill); LOAEL = lowest-observed-adverse-effect level; M = male; Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; NS = not specified; Resp = respiratory; wk = week(s); x = time(s); " " = indicates an ambiguous term used by study authors

2.2.3.2 Systemic Effects

No studies were located regarding systemic effects in humans after dermal exposure to HMX. Data regarding the systemic effects of HMX in animals are discussed below. The highest NOAEL values and all LOAEL values for systemic effects in animals are recorded in Table 2-2.

Respiratory Effects. No studies were located regarding respiratory effects in humans after dermal exposure to HMX. Congestion and "reddening" of the trachea and lungs were observed in rabbits dermally exposed to a single dose of 168 mg/kg HMX (Army 1985h). The nature of the "reddening" was not discussed further by the authors, therefore its significance is uncertain. Pulmonary function was not evaluated in these animals. No gross or histopathological lesions of the lungs were noted in three rabbits that died following exposure to 165 mg/kg/day HMX solution for 4 weeks (Army 1974). These data are too limited to draw firm conclusions regarding the respiratory effects of HMX after dermal exposure.

Cardiovascular Effects. No studies were located regarding cardiovascular effects in humans after dermal exposure to HMX. Data regarding the cardiovascular effects of HMX in animals are limited to a single study. Consistent changes in blood pressure, heart rate, and electrocardiogram readings were not observed in groups of l-2 dogs exposed to up to 480 mg/kg/day for l-5 days or 289 mg/kg/day for 4 weeks (Army 1974). No gross or histopathological lesions of the heart were noted in three rabbits that died after exposure to 165 mg/kg/day HMX in solution for 4 weeks (Army 1974). However, due to the small number of animals tested, these studies may not have had the statistical power to detect any subtle effects of HMX on the cardiovascular system. These data are too limited to draw firm conclusions on the potential cardiovascular effects of HMX, but suggest that the heart is not particularly sensitive.

Gastrointestinal Effects. No studies were located regarding gastrointestinal effects in humans or animals after dermal exposure to HMX.

Hematological Effects. No studies were located regarding hematological effects in humans after dermal exposure to HMX. Data regarding the hematological effects of HMX in animals are limited to a single study. No changes were noted for a large number of hematological parameters in rabbits exposed to a single dermal exposure to 165 mg/kg of HMX in solution (Army 1974). Although limited, the data from this study suggest that the blood is not particularly sensitive to the toxic effects of HMX.

Musculoskeletal Effects. No studies were located regarding musculoskeletal effects in humans after dermal exposure to HMX. Data regarding the musculoskeletal effects of HMX in animals are limited to a single study. No gross or histopathological lesions were observed in the muscle or bone of rabbits exposed to 165 mg/kg/day of an HMX solution for 4 weeks (Army 1974). The data are too limited to draw firm conclusions, but suggest that muscle and bone tissue are not important targets of HMX toxicity.

Hepatic Effects. No studies were located regarding hepatic effects in humans after dermal exposure to HMX. The livers of rabbits administered a single dermal dose of 372 mg/kg HMX were congested and mottled in appearance with prominent fissures (Army 1985h). No gross or histopathological lesions of the liver were observed in rabbits exposed to a single dose of 168 mg/kg HMX (Army 1985h) or to 165 mg/kg/day HMX for 4 weeks (Army 1974). These data are too limited to make firm conclusions, but suggest that dermal exposure to HMX may adversely affect the liver.

Renal Effects. No studies were located regarding renal effects in humans after dermal exposure to HMX. Following exposure to a single dermal dose of 168 mg/kg HMX, the kidneys of rabbits showed tubular dilation, fibrosis, and atrophy (Army 198511). Atrophy of the glomerulus was also noted. No gross or histopathological lesions of the kidney were observed in rabbits exposed to 165 mg/kg/day HMX for 4 weeks (Army 1974). Although limited, these data suggest that the kidney may be adversely affected following dermal exposure to HMX.

Dermal Effects. No studies were located regarding dermal effects in humans after dermal exposure to HMX. Several studies have reported dermal effects in animals following dermal exposure to HMX. Mild irritation of the skin was noted in rabbits after a single dermal exposure to 109 mg/kg HMX as a 60% solution in dimethylsulfoxide (Army 1985h). Slight erythema was noted in guinea pigs after dermal application of 1,000 mg/kg/day HMX for l-3 days (Army 1974). No evidence of skin

irritation was observed in guinea pigs exposed to dermal doses of 510 mg/kg/day HMX for l-3 days or in rabbits receiving a single dose of 165 mg/kg HMX (Army 1974). In addition, no evidence of dermal sensitization was noted in guinea pigs previously exposed to HMX and challenged with a single dermal dose of 357 mg/kg HMX (Army 1985h). Dermatitis was observed in rabbits administered 16.5 mg/kg/day HMX for 4 weeks, but not in guinea pigs receiving topical or intradermal doses of 196 mg/kg/day HMX, 3 times/week for 3 weeks (Army 1974). Although some studies reported dermal effects in animals exposed to HMX, some of these effects were attributed to the solvents used in HMX solutions (e.g., dimethylsulfoxide). Collectively, the data indicate that HMX may cause a mild irritation of the skin following direct exposure.

Ocular Effects. No studies were located regarding ocular effects in humans after dermal exposure to HMX. Mild irritation of the conjunctiva was noted in rabbits after a single dermal exposure to 109 mg/kg HMX as a 60% solution in dimethylsulfoxide (Army 1985h).

2.2.3.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological and lymphoreticular effects in humans after dermal exposure to HMX.

A single study reported no evidence of dermal sensitization in guinea pigs challenged with a single application of a 60% solution of HMX (see Section 2.2.3.2). A single study reported a pale appearance and enlargement of the spleen in rabbits administered a single dermal dose of 168 mg/kg HMX or more (Army 1985h). Higher doses depleted the spleen of lymphocytes, red pulp, and white pulp. No other studies regarding the immunological effects of HMX in animals were located. The LOAEL value for immunological effects in animals is recorded in Table 2-2.

2.2.3.4 Neurological Effects

No studies were located regarding neurological effects in humans after dermal exposure to HMX. A number of neurological effects including hyperkinesia, hypokinesia, clonic convulsions, and changes in aggressive behavior were noted in rabbits administered a single dose of 168 mg/kg HMX or more (Army 1985h). An increase in the severity of the convulsions, hindleg paralysis, and perivascular

cuffing in the brain was observed in rabbits exposed to 372 mg/kg HMX in this study. Other studies detected no consistent electroencephalogram abnormalities in beagle dogs exposed to 480 mg/kg/day for 3 days or to 289 mg/kg/day for 4 weeks (Army 1974); however, only a small number of dogs were used in this study. The data are too limited to draw firm conclusions, but suggest that the central nervous system may be a target of HMX toxicity. In addition, rabbits may be more sensitive than beagle dogs to the neurological effects of HMX. The highest NOAEL values and all LOAEL values from each reliable study for neurological effects in animals are recorded in Table 2-2.

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

2.2.3.5 Reproductive Effects

2.2.3.6 Developmental Effects

2.2.3.7 Genotoxic Effects

Genotoxicity studies are discussed in Section 2.5.

2.2.3.8 Cancer

No studies were located regarding carcinogenic effects in humans or animals after dermal exposure to HMX.

2. 3 TOXICOKINETICS

No studies were located regarding toxicokinetics in humans after exposure to HMX. Limited information is available from studies in animals exposed to HMX by the oral and parenteral routes. These studies suggest that HMX is poorly absorbed in the gastrointestinal tract. Most of, an orally administered dose is excreted in the feces as unchanged HMX. The small amount of HMX that is absorbed in the body may be temporarily found at higher concentrations, particularly in the lungs, liver, heart, and kidneys. However, the levels of HMX in these tissues do not remain elevated for very long. Limited data indicate that HMX is readily metabolized to polar intermediates; however, these metabolites have not been identified. Most of an absorbed dose of HMX is excreted in the urine

within 4 days. The mechanism of action for HMX in producing adverse effects may involve the formation of toxic metabolites; however, data regarding this possibility are generally lacking.

2.3.1 Absorption

2.3.1 .1 Inhalation Exposure

No studies were located regarding absorption in humans or animals after inhalation exposure to HMX.

2.3.1.2 Oral Exposure

No studies were located regarding absorption in humans after oral exposure to HMX.

Several studies investigated the oral absorption of HMX in animals. In rats and mice exposed to a single oral dose of 500 mg/kg HMX, peak plasma levels of 6-10 μg/mL were reached by 6 hours after exposure. These peak levels corresponded to <0.1% of the administered dose (Army 1986). Based on urinary and fecal excretion data, less than 15% of the dose was absorbed by rats, and less than 30% of the dose was absorbed by mice exposed to a single oral dose of 500 mg/kg (Army 1986). Based on a comparison of the levels of HMX in the plasma and urine following oral and intravenous exposures, the authors also concluded that <5% of the oral dose was absorbed. Plasma levels of HMX were relatively low and were not dependent on dose in rats administered 50-4,000 mg/kg/day HMX for 13 weeks (Army 19858). The authors concluded that most of the administered dose was not systemically absorbed. Indirect evidence of a low absorption fraction for HMX can be inferred from the fact that LD_{50} values for intravenously administered HMX in rats are several orders of magnitude lower than those reported for oral exposures (Army 1985h). Collectively, the data from animal studies indicate that HMX is not well absorbed by the gastrointestinal tract. However, the absorption of HMX has not been investigated in what appears to be the most sensitive species, rabbits. Species differences in absorption may be responsible in part for differences observed in sensitivity to HMX.

2.3.1.3 Dermal Exposure

No studies were located regarding absorption in humans or animals after dermal exposure to HMX.

2.3.2 Distribution

2.3.2.1 Inhalation Exposure

No studies were located regarding distribution in humans or animals after inhalation exposure to HMX.

2.3.2.2 Oral Exposure

No studies were located regarding distribution in humans after oral exposure to HMX.
Limited information regarding the distribution of HMX is available from animal studies. Four days after a single oral dose of 500 mg/kg HMX, approximately 0.7% and 0.6% of the dose was retained in the bodies of exposed rats and mice, respectively (Army 1986). Plasma levels in rats administered 50-4,000 mg/kg/day for 13 weeks ranged from 0.91-3.76 μg/mL, but were not increased in a dosedependent manner (Army 19858). However, in this study, low levels of HMX were also detected in the plasma of unexposed control rats. The authors offered no explanation for this occurrence; therefore, the validity of the results is questionable. Information regarding levels of HMX measured in specific organs was not provided.

2.3.2.3 Dermal Exposure

No studies were located regarding distribution in humans or animals after dermal exposure to HMX.

2.3.2.4 Other Routes of Exposure

No studies were located regarding distribution in humans after other routes of exposure to HMX.

Data regarding distribution in animals after parenteral exposure to HMX are limited to a single study. Two minutes after a single intravenous dose of 2 mg/kg radiolabeled ^{14}C-HMX was administered to rats, the highest levels of radioactivity (expressed in terms of μg/g) were detected in the lungs (15.39), while lower levels were detected in the heart (5.18), liver (4.25), kidney (3.96), whole blood (2.15), ovaries and uterus (2.03), spleen (1.87), thymus (1.74), plasma (1.58), skeletal muscle (1.28), bone

(1.25), and gastrointestinal tract (1.23) (Army 1986). The lowest levels of radioactivity were detected in the fat (0.48), testes and seminal vesicles (0.22), and brain (0.22). By 96 hours after exposure, levels of radioactivity dropped considerably. Detectable levels were found in the kidney (0.36), thymus (0.30), and liver (0.26), while lower levels were found in the lung (0.19), spleen (0.18), ovaries and uterus (0.15), heart (0.13), fat (O.10), and bone (0.10). The lowest levels of radiolabel were detected in the testes and seminal vesicles (0.09), gastrointestinal tract (0.08), skeletal muscle (0.08), whole blood (0.07), plasma (0.05), and brain (0.04). Although the data are limited, they suggest that there is some preferential distribution of HMX in the body, particularly in the lungs, liver, heart, and kidney, but that these tissue levels do not remain elevated for very long after exposure.

2.3.3 Metabolism

No studies were located regarding metabolism in humans after exposure to HMX.
Data regarding the metabolism of HMX in animals are extremely limited. A single study reported rapid metabolism of HMX in rats injected intravenously with 2 mg/kg ^{14}C-HMX (Army 1986). Analysis of urine, feces, plasma, and tissues revealed the presence of very polar metabolites of HMX. Although these metabolites were not identified, chromatographic analysis of the urine revealed the presence of at least two metabolites. Following doses of 5-750 mg/kg/day HMX in the diet for 13 weeks, the stomach contents of exposed mice were analyzed for nitrite content (Army 1985a). The nitrite content of the stomach (0.1-l .l μg/g) was not elevated above levels expected to arise from normal dietary contributions. The authors concluded that nitrite was not released from HMX in the stomach to any significant extent. However, the extent to which nitrite is released after HMX is absorbed into the blood was not investigated. No other studies were located regarding the metabolism of HMX.

2.3.4 Excretion

2.3.4.1 Inhalation Exposure

No studies were located regarding excretion in humans or animals after inhalation exposure to HMX.

2.3.4.2 Oral Exposure

No studies were located regarding excretion in humans after oral exposure to HMX.

Four days after a single oral dose of 500 mg/kg ^{14}C-HMX, most of the dose (approximately 85% and 70%) was excreted in the feces of exposed rats and mice, respectively (Army 1986). Smaller fractions of the dose were eliminated in the urine (3-4%) and expired air (0.5-l%) of exposed animals. Although these studies suggest that most of an administered dose of HMX is excreted in the feces, fecal excretion most likely represents the fraction of the dose that is not absorbed in the gastrointestinal tract. Other studies indicate that the majority of an absorbed dose of HMX is excreted in the urine (see Section 2.3.4.4).

2.3.4.3 Dermal Exposure

No studies were located regarding excretion in humans or animals after dermal exposure to HMX.

2.3.4.4 Other Routes of Exposure

No studies were located regarding excretion in humans after other routes of exposure to HMX. Data regarding excretion in animals injected with HMX are limited to a single study. In rats administered a single intravenous dose of 2 mg/kg HMX, approximately 3% of the dose was excreted in the feces, 61% was excreted in the urine within 4 days, and 6% of the dose was released in expired air within 2 days after exposure (Army 1986). Although 24% of the dose was not accounted for in this study, the data suggest that most of an absorbed dose of HMX is excreted in the urine. Biliary excretion does not appear to contribute significantly to the fecal excretion of HMX after oral exposure.

2.4 MECHANISMS OF ACTION

The mechanism of action for the absorption and distribution of HMX has not been studied. Based on the physical properties of HMX (see Chapter 3), these processes most likely occur by passive diffusion.

The mechanism of action for HMX in producing adverse effects has not been studied in humans or animals. One possible mechanism of action involves the generation of toxic intermediates during the metabolism of HMX. Although the metabolites of HMX have not been characterized, some possible metabolites include nitrite and hydrazines. Speculative mechanisms involving the formation of these metabolites are discussed below.

Potentially, four molecules of nitrite could be released from each molecule of HMX as a result of cleavage of the nitrogen-nitrogen bond at the l-, 3-, 5-, and 7-positions. Studies in animals have reported methemoglobin formation (Army 1985c) and cardiovascular collapse (Army 1974) following exposure to HMX. Both effects are similar to effects observed in animals exposed to nitrite. Although the stomach contents of HMX-exposed mice did not contain levels of nitrite that were elevated above levels detected in control mice (Army 1985a), the possibility remains for the liberation of nitrite after HMX is absorbed and metabolized in the body.

Hydrazines such as l,l-dimethylhydrazine, 1-methylhydrazine, and hydrazine could be formed as a result of nitroreduction of the nitro groups in HMX to amines, followed by ring cleavage at the carbon-nitrogen bonds. Some microorganisms are capable of forming l,l-dimethylhydrazine from HMX (see Section 5.3.2.2), therefore it is possible that some mammalian enzyme systems possess similar metabolic abilities. Hydrazines are known to adversely affect the central nervous system and the liver (ATSDR 1993). Reactions with pyridoxine (vitamin B6) and the generation of reactive intermediates have been implicated in the mechanism of action for hydrazines (ATSDR 1993). It is possible that the neurological and hepatic effects of HMX are attributable to the formation of hydrazines in the body. This mechanism is purely speculative and has not been studied, yet it parallels that observed for the structurally related explosive, RDX.

2.5 RELEVANCE TO PUBLIC HEALTH

HMX is used in the manufacture of explosives. People may be exposed to HMX if they .work at facilities which manufacture, process, or use HMX. People who live near these facilities, near accidental spills, or near hazardous waste sites contaminated with HMX may also be exposed.

The toxicity of HMX in humans has not been well studied. A single human study reported no adverse effects in munitions workers exposed to an undetermined concentration of HMX in air. However, the number of subjects and end points evaluated in this study were limited.

The toxicity of HMX has been investigated in animals primarily exposed by the oral route. These studies indicate that the central nervous system and liver are the primary targets of HMX toxicity following acute and intermediate exposures. Neurological effects noted include hyperkinesia, hypokinesia, and convulsions. Hepatic effects noted include hepatocyte hyperplasia, cytoplasmic eosinophilia, mottled appearance, and centrilobular degeneration. The mechanism by which HMX produces these effects is not well understood. There appear to be some species- and sex-dependent differences regarding the sensitivity to HMX-mediated lethal and neurological effects. However, since these effects have only been described in animals, their relevance to human exposures to HMX is uncertain.

The potential of HMX to cause reproductive and developmental effects has not been well investigated in animals. In addition, the toxicokinetic data for HMX are very limited. A limited number of *in vitro* studies report that HMX is not mutagenic. However, other genotoxic end points have not been studied.

Minimal Risk Levels for HMX

Inhalation

No studies were located regarding adverse health effects in humans or animals after inhalation exposure to HMX that provide quantitative information regarding exposure levels. Therefore, no inhalation MRLs were derived for HMX.

Oral

- An MRL of 0.1 mg/kg/day has been derived for acute oral exposure to HMX. This MRL is based on a LOAEL of 100 mg/kg/day for neurological effects (hyperkinesia) in mice exposed to HMX in the diet for 14 days (Army 1985d). A NOAEL was not identified in this study. The LOAEL value of 100 mg/kg/day for hyperkinesia in mice was divided by an uncertainty factor of

1,000 (10 for use of a LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability). Other studies in animals support the contention that the central nervous system is a target for HMX after acute oral exposure (Army 1985e, 1985h). Uncertainty in the acute oral MRL arises from the fact that serious neurological effects (convulsions) were observed in rabbits administered a single dose of 50 mg/kg HMX by gavage (Army 1985h). While this study suggests that rabbits may be the most sensitive species, it has a number of limitations that detract from the confidence in the findings, including lack of a control group and the small number of animals tested (two animals per exposure group). In addition, gavage administration of HMX may have contributed to the apparent greater susceptibility of the rabbits as a result of a bolus effect. Nevertheless, if the neurological effects observed in rabbits represent true manifestations of HMX toxicity, the current acute oral MRL of 0.1 may not be protective of neurological effects. ATSDR recognizes this uncertainty, but maintains greater confidence in the results of the mouse study (Army 1985d) than in the rabbit study (Army 1985h). It is possible that rabbits are more sensitive to the effects of HMX than other species, but based on current information, this conclusion cannot be made with certainty. Further study into this possibility is warranted.

An MRL of 0.05 mg/kg/day has been derived for intermediate duration oral exposure to HMX. This MRL is based on a NOAEL of 50 mg/kg/day for hepatic effects in rats exposed to HMX in the diet for 13 weeks (Army 1985c). The NOAEL value was divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability) and by a modifying factor of 10 for use of a “limited database” and of data indicating that mice may be more sensitive than rats. In this study, doses of 150 mg/kg/day HMX produced enlarged centrilobular cells with dark cytoplasm in the livers of exposed rats. These changes were relatively mild and may represent an adaptive response of the liver rather than a toxic response. However, given that the borderline between adaptive physiology and toxicity is not always well defined, it is best to consider these changes as a less serious adverse effect. Higher doses of 1,500 mg/kg/day (females) and 4,000 mg/kg/day (males) produced significant elevations in the serum alkaline phosphatase levels in rats. Support for the MRL comes from a study that reported no evidence of systemic toxicity in mice maintained on diets providing 90-750 mg/kg/day for 13 weeks (Army 1985b). However, mortality was greater than 50% in mice exposed to 200-250 mg/kg/day (Army 1985b), suggesting that mice may be more sensitive than rats to the lethal effects of HMX.

No studies were located regarding the adverse health effects of HMX after chronic oral exposures.

Death. Data regarding the lethal effects of HMX are limited to studies in animals exposed by oral, dermal, and parenteral routes. Deaths have been observed in rats, mice, guinea pigs, and rabbits following acute exposure to 50-8,054 mg/kg by the oral route (Army 1985d, 1985e, 1985h), 634-719 mg/kg by the dermal route (Army 1985h), and l0-38 mg/kg HMX by the parenteral route (Army 1974, 1985h). Deaths were also noted in animals following intermediate-duration exposure to 200-250 mg/kg/day HMX by the oral route (Army 1985b) and 165 mg/kg/day by the dermal route (Army 1974).

The lethal dose of HMX appears to depend greatly on the route of exposure and to some extent on the species and sex of the animal exposed. The LD_{50} values for HMX in rats and mice following intravenous exposure were 170-220-fold and 60-110 fold lower than their respective oral LD,, values (Army 1974, 1985h), suggesting that HMX is not well absorbed in the gastrointestinal tract. Rabbits appeared to be more sensitive to the lethal effects of HMX than other species following oral, dermal, and intravenous exposures (Army 1985h). Sex differences were also observed. In most cases, lethal doses tended to be slightly lower for male animals than female animals (Army 1985h); however, these differences may not be significant.

Although there have been no reports of human fatalities following exposure to HMX, the animal data suggest that oral and dermal exposure to HMX at sufficient doses can be lethal.

Systemic Effects

Respiratory Effects. Data regarding the respiratory effects of HMX are limited to a few studies in animals exposed by the oral and dermal routes. Respiratory effects (“reddening” of the lungs, congestion, white nodules) have been observed in rats, mice, and/or rabbits acutely exposed to 50-5,447 mg/kg HMX by the oral route and in rabbits acutely exposed to 168 mg/kg HMX by the dermal route (Army 1985h). It is not known if this discoloration is the result of irritation in the lung; therefore the significance of these observations is uncertain. Other studies have reported no gross or histopathological lesions in the lungs of mice orally exposed to 90 mg/kg/day HMX (Army 1985b) or in rabbits dermally exposed to 165 mg/kg/day HMX for intermediate durations (Army 1974).

Although the data are limited, they suggest that respiratory effects are not of primary concern for humans exposed dermally or orally to HMX.

Cardiovascular Effects. Several animal studies have reported no significant effect on the cardiovascular system following oral exposure to 90-5,000 mg/kg/day HMX (Army 1985b, 1985d) and dermal exposure to 165-480 mg/kg/day HMX (Army 1974). These studies suggest that cardiovascular effects are not of concern to humans exposed to HMX by oral and dermal routes. However, intravenous injection of a single dose of 1.55 mg/kg HMX or more produced cardiovascular collapse in beagle dogs (Army 1974). Since HMX is known to be poorly absorbed in the gastrointestinal tract, it is possible that following oral and dermal exposure, the amount of HMX absorbed into the body is generally not sufficient to produce cardiovascular effects but that large absorbed doses of HMX could adversely affect the cardiovascular system of humans; however, this is not certain.

Gastrointestinal Effects. Data regarding the gastrointestinal effects of HMX are limited to studies in animals after oral exposure. Although large doses of HMX (1,626-5,447 mg/kg) result in the presence of a white fluid in the gastrointestinal tract of exposed animals (Army 1985h), lower doses of HMX (90 mg/kg/day) do not result in the formation of histopathological lesions (Army 1985b). However, the white fluid was not analyzed; therefore its significance is uncertain. The data, although limited, suggest that gastrointestinal effects are not of concern for humans exposed to HMX by the oral route.

Hematological Effects. No evidence of any hematological effects were observed in 24 male munitions workers exposed to an undetermined concentration of HMX in workplace air (Hathaway and Buck 1977). A single study in animals reported hematological effects (decreased hemoglobin and packed cell volume, increased methemoglobin) in rats exposed to 1,500 mg/kg/day for 13 weeks (Army 1985c). Other studies have not observed hematological effects in rats and mice exposed to 620-750 mg/kg/day HMX by the oral route (Army 1985b, 1985c) or in rabbits exposed to 165 mg/kg HMX by the dermal route (Army 1974). The data suggest that hematological effects may be of concern in humans exposed to large doses of HMX.

Musculoskeletal Effects. Data regarding the musculoskeletal effects of HMX are limited to studies in animals exposed by the oral and dermal route. Gross or histopathological lesions of the bones and skeletal muscle were not observed in mice exposed orally to 90 mg/kg/day HMX (Army 1985b) or in

rabbits exposed dermally to 165 mg/kg/day for intermediate durations (Army 1974). The data suggest that musculoskeletal effects are not of concern for humans orally or dermally exposed to HMX.

Hepatic Effects. No evidence of hepatotoxicity was noted in 24 male munitions workers exposed to an undetermined concentration of HMX (Hathaway and Buck 1977). Several studies have reported hepatic effects in laboratory animals following oral exposure to 150-8,504 mg/kg/day HMX (Army 1985c, 1985d, 1985e) or dermal exposure to 372 mg/kg HMX (Army 1985h). Hepatic effects were relatively mild (hepatocellular hyperplasia, cytoplasmic eosinophilia, pale nuclei, dark cytoplasm, congestion, mottled appearance) at the lower end of the effective dose range and may represent an adaptive response. However, the effects were more serious (centrilobular degeneration) at the upper end of the dose range. Other animal studies did not report any significant effects on the liver following oral exposure to 50-90 mg/kg/day HMX (Army 1985b, 1985c) or dermal exposure to 165-168 mg/kg/day (Army 1974, 1985h). However, histopathological examinations were not performed in female mice exposed to doses greater than 90 mg/kg/day or in male mice exposed to doses greater than 75 mg/kg/day. An intermediate MRL of 0.05 mg/kg/day was derived for HMX based on a NOAEL of 50 mg/kg/day for hepatic effects in rats (Army 1985c). The data from animal studies suggests that hepatic effects may be of concern in humans exposed to moderate-to-high doses of HMX at the workplace or at hazardous waste sites.

Renal Effects. No evidence of renal toxicity was observed in 24 male munitions workers exposed to an undetermined concentration of HMX in workplace air (Hathaway and Buck 1977). Renal effects (focal tubular atrophy, dilatation, congestion, pale and/or mottled appearance) were noted in animals after oral doses of 270-3,632 mg/kg/day HMX (Army 1985c, 1985e, 1985h) or dermal doses of 168 mg/kg HMX (Army 1985h). Elevated blood urea nitrogen levels were noted in male and female rats following oral doses of 1,500-4,000 mg/kg/day HMX (Army 1985c). Other studies did not report renal effects in animals exposed to 90-115 mg/kg/day HMX (Army 1985b, 1985c) by the oral route or 165 mg/kg/day HMX by the dermal route (Army 1974). The animal data suggest that renal effects may be of concern in humans exposed to moderate-to-high doses (i.e., doses well above-the MRL) of HMX by the oral and dermal routes.

Dermal Effects. Data regarding the dermal effects of HMX are limited to studies in animals exposed by the oral and dermal routes. Repeated oral doses of 90-4,000mg/kg/day produced no effects on the skin of exposed animals (Army 1985b, 1985c). However, direct exposure of the skin to doses of

16.5-1,000 mg/kg/day HMX often produces mild irritation at the site of application (Army 1974, 1985h). The data from animal studies suggest that humans exposed to HMX by the dermal route may be at risk for dermal effects, but that these effects are relatively mild.

Ocular Effects. Data regarding the ocular effects of HMX are limited. Direct exposure of the eyes of guinea pigs and rabbits to doses of 16.5-1,000 mg/kg/day HMX produced mild irritation at the site of application (Army 1974, 1985h).

Body Weight Effects. Decreased body weight gain and food intake occurred in rats following doses of 2370 mg/kg/day in the diet (Army 1985c, 1985e), but not in mice following doses of 750 mg/kg/day (Army 1985b). These data are too limited to make firm conclusions regarding body weight effects in humans exposed to HMX.

Immunological and Lymphoreticular Effects. No evidence of lupus erythematosus was observed in a group of 558 male and female munitions workers exposed to an unspecified concentration of explosives, including HMX, in workplace air (Hathaway and Buck 1977). Changes in the thymus and spleen (decreased organ weight or lymphocyte depletion) were noted in laboratory animals orally exposed to 50-1,280 mg/kg/day (Army 1985d, 1985e). Spleen enlargement was noted in rabbits following a single dermal dose of 168 mg/kg HMX (Army 1985h). However, it is not known if immune function was affected in these animals. Dermal exposure to 357 mg/kg HMX did not produce an allergic reaction in guinea pigs exposed previously to HMX (Army 1985h). The animal data are too limited to make firm conclusions, but suggest that immunological effects may be of concern for humans exposed to HMX.

Neurological Effects. Several studies have reported neurological effects in animals after acute oral, dermal, and intravenous exposure to HMX. Hyperkinesia, hypokinesia, convulsions, mydriasis, congestion, and/or hemorrhaging of the brain were noted in laboratory animals following oral doses of 50-8,504 mg/kg/day HMX (Army 1985d, 1985e, 1985h) and dermal application of 168 mg/kg HMX (Army 198511). In addition, intravenous doses of l-28.9 mg/kg HMX have produced similar effects (convulsions, hyperkinesia, paralysis, coma) in rats, mice, rabbits, guinea pigs, and dogs (Army 1974, 1985h). Rabbits appeared to be the most sensitive to the neurological effects of HMX following oral and dermal exposures. However, as discussed previously, there are several deficiencies in the Army 1985h study that preclude a definitive conclusion. In this regard, gavage administration of the HMX

may have contributed to the apparent greater susceptibility of the rabbits as a result of a bolus effect. However, very little difference was observed between species following intravenous exposures. The data suggest that species differences in absorption and/or first-pass metabolism may underlie the species differences observed for the adverse health effects of HMX. An acute oral MRL of 0.1 mg/kg/day was derived for HMX based on a LOAEL of 100 mg/kg/day for neurological effects (hyperkinesia) in mice exposed to HMX in the diet for 14 days (Army 1985d). The data from animal studies suggest that the central nervous system may be a target for HMX toxicity and that neurological effects may be of concern for humans exposed to HMX either occupationally or at hazardous waste sites.

Reproductive Effects. Data regarding the reproductive effects of HMX are limited to studies in animals exposed by the oral route. Histopathological lesions were not observed in ovaries or testes of mice exposed to 90 mg/kg/day HMX for 13 weeks (Army 1985b). However, reproductive function was not evaluated in this study. The animal data are too limited to make firm conclusions regarding the risk of reproductive effects in humans exposed to HMX.

Developmental Effects. No studies were located regarding developmental effects in humans or animals following exposure to HMX.

Genotoxic Effects. No studies were located regarding genotoxic effects in humans or animals after exposure to HMX *in vivo*. Data regarding the genotoxic effects of HMX are limited to a few *in vitro* studies. The results of these studies are summarized in Table 2-3 and are discussed below.
Three studies did not detect an increased mutation frequency with HMX in several strains of *Salmonella typhimurium* (TA98, TA100, TA1535, TA1537, TA1538), both in the presence and absence of an activation system (Army 1977c; Tan et al. 1992; Whong et al. 1980). Chlorination or composting had no effect on the mutagenicity of HMX (Army 1977c; Tan et al. 1992). Waste waters that contained HMX from an ammunition plant did not produce a significant increase ofmutation frequency in several strains of *Salmonella typhimurium* (Army 1977a). The authors generally concluded that HMX was not mutagenic under the conditions of these assays. In addition, the frequency of mitotic recombination was not significantly increased in *Saccharomyces cerevisiae* (Army 1977c). Although the data are limited in the number of end points investigated, they suggest that HMX is not genotoxic.

TABLE 2-3. Genotoxicity of HMX *In Vitro*

Species (test system)	End point	Results: With activation	Results: Without activation	Reference
Prokaryotic organisms:				
Salmonella typhimurium	Reverse mutation	–	–	Army 1977c
S. typhimurium	Reverse mutation	–	–	Army 1977a
S. typhimurium	Reverse mutation	–	–	Tan et al. 1992
S. typhimurium	Reverse mutation	–	–	Whong et al. 1980
Saccharomyces cerevisiae	Mitotic recombination	–	–	Army 1977c

– = negative result

Cancer. There is some indirect evidence that suggests HMX may be carcinogenic. RDX, another explosive polynitramine that is similar in structure to HMX, is known to produce hepatocellular adenomas and carcinomas in female mice (IRIS 1995). In addition, some of the potential metabolites of HMX (hydrazines, nitrosamines) are carcinogenic. However, the carcinogenic effects of HMX have not been studied in humans or animals. Based on the lack of appropriate cancer bioassays and epidemiological studies, EPA has determined that HMX is not classifiable as to its human carcinogenicity (Group D) (IRIS 1995).

2.6 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 (NAS/NRC 1989).

Due to a nascent understanding of the use and interpretation of biomarkers, implementation of biomarkers as tools of exposure in the general population is very limited. 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 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 HMX are discussed in Section 2.6.1.

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 (NAS/NRC 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 not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by HMX are discussed in Section 2.6.2.

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, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 2.8, Populations That Are Unusually Susceptible.

2.6.1 Biomarkers Used to Identify or Quantify Exposure to HMX

Studies in animals show that biological samples (plasma, tissues, urine, feces) can be analyzed for HMX content (Army 1958g, 1986). These studies suggest HMX is poorly absorbed by the oral route (Army 1986), and therefore levels of HMX in plasma, tissues, and urine are likely to be very low. Higher levels are more likely to be detected in the feces following oral exposure, but only for the first l-2 days after exposure ceases. Since the metabolites of HMX have not been well characterized, they cannot be used as biomarkers of exposure for HMX.

2.6.2 Biomarkers Used to Characterize Effects Caused by HMX

Studies in animals indicate that the critical effects of HMX are on the liver, the kidney, and the central nervous system (see Section 2.2) (Army 1985d, 1985h). Measurement of enzymes in the blood that are indicative of liver damage (alkaline phosphatase, lactate dehydrogenase, serum glutamic oxaloacetic transaminase, serum glutamic pyruvic transaminase), measurement of blood meal nitrogen levels to assess renal damage, or monitoring electroencephalogram readings may serve as biomarkers of effect for HMX. However, these biomarkers are by no means specific for HMX, as many exogenous compounds and endogenous diseases are capable of producing similar effects.

2.7 INTERACTIONS WITH OTHER SUBSTANCES

No studies were located regarding interactions with other substances in humans or animals after exposure to HMX.

2.8 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to HMX than will most persons exposed to the same level of HMX in the environment. Reasons include genetic make-up, developmental stage, age, health and nutritional status (including dietary habits that may increase susceptibility, such as inconsistent diets or nutritional deficiencies), and substance exposure history (including smoking). These parameters may result in decreased function of the detoxification and excretory processes (mainly hepatic, renal, and respiratory) or the pre-existing compromised function of target organs (including effects or clearance rates and any resulting end-product metabolites). 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.

No studies were located regarding susceptible populations in humans or animals exposed to HMX. Since studies in animals indicate that the liver, kidney, and central nervous system are the most sensitive targets of HMX toxicity, people with liver damage (cirrhosis, hepatitis), kidney damage, or neurological disorders (Parkinson’s disease, epilepsy) may be more susceptible to the effects of HMX. Since HMX appears to be poorly absorbed in the gastrointestinal tract (Army 1986), persons with increased absorption capacity, either due to stomach ulcers, open wounds on the skin, or for some other reason, may also be more susceptible to the effects of HMX. However, these possibilities have not been studied.

2.9 METHODS FOR REDUCING TOXIC EFFECTS

This section describes clinical practice and research concerning methods for reducing toxic effects of exposure to HMX. 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 HMX. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice.

2.9.1 Reducing Peak Absorption Following Exposure

No studies were located for reducing absorption in humans or animals exposed to HMX. However, standard methods exist to reduce the absorption of chemicals such as HMX following oral exposure, including gastrointestinal lavage, induced emesis, and cathartics (Ellenhom and Barceloux 1988). However, since studies in animals suggest HMX is not well absorbed in the gastrointestinal tract (Army 1986), these methods may not have a significant effect. For situations in which a larger fraction of HMX may be absorbed (for example, when in solution, or at low doses) activated charcoal may be useful in slowing absorption. Oils have been contraindicated for use as a lavage or cathartic, because oils may increase the gastrointestinal absorption of HMX (Ellenhom and Barceloux 1988). Common methods for reducing dermal absorption of HMX include removing contaminated clothes and washing contacted skin with soap and water (Ellenhom and Barceloux 1988). Oils have been contraindicated for cleaning the skin, since oils may increase the dermal absorption of HMX (Ellenhom and Barceloux 1988). Following eye contact with HMX, it has been suggested that contact lenses (if present) be removed and eyes flushed with copious amounts of water (Ellenhorn and Barceloux 1988).

2.9.2 Reducing Body Burden

No studies were located regarding methods to reduce body burden in humans or animals after exposure to HMX. Activated charcoal, given in serial doses, has been suggested to minimize enterohepatic recirculation of toxic chemicals. Unfortunately, the enterohepatic recirculation of HMX has not been investigated, therefore it is not known whether or not serial doses of activated charcoal would have a significant effect.

2.9.3 Interfering with the Mechanism of Action for Toxic Effects

Although the mechanism of action of HMX is not known, this mechanism may involve the formation of nitrite or hydrazines during the metabolism of HMX. Efforts to inhibit the enzyme systems responsible for the formation of these intermediates could interfere with the mechanism of action for the toxic effects of HMX. Methylene blue and pyridoxine have been suggested for interfering with the mechanisms of action for nitrite and hydrazines, respectively (Ellenhorn and Barceloux 1988). If the formation of nitrite or hydrazines is involved in the mechanism of action for HMX, then treatment with methylene blue and pyridoxine may also be useful in treating individuals exposed to HMX. It should be noted that treatment with methylene blue or pyridoxine is not without risk, as these agents are capable of producing adverse effects themselves.

2.10 ADEQUACY OF THE DATABASE

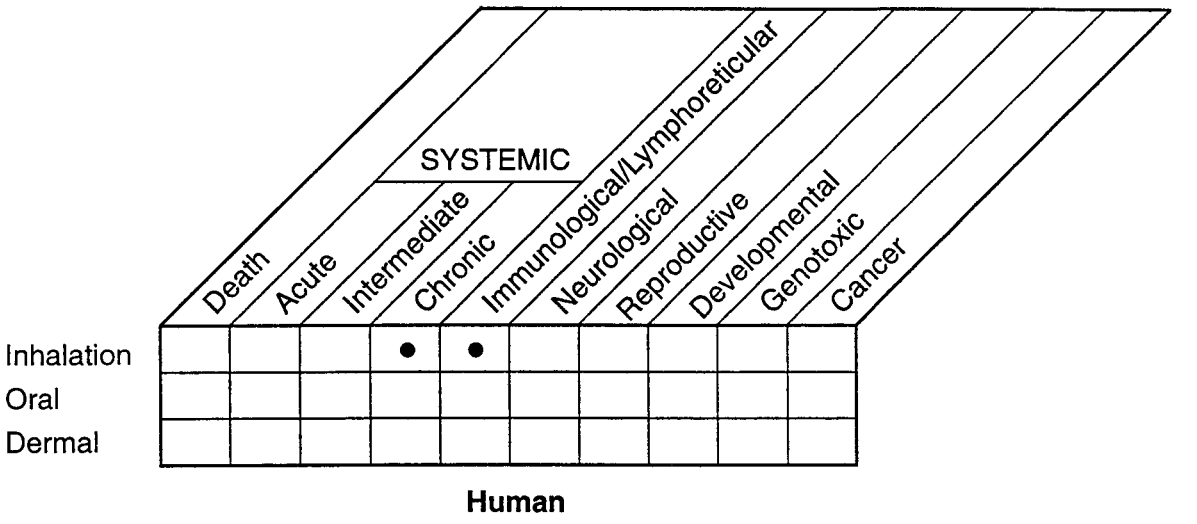
Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of HMX is available. Where adequate information is not available, 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 HMX.

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 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 will be proposed.

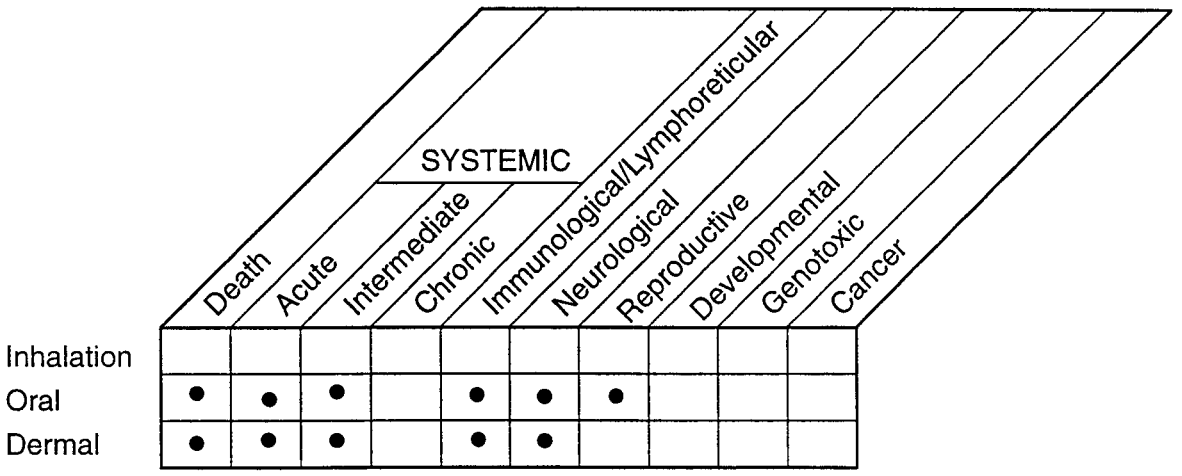
2.10.1 Existing Information on Health Effects of HMX -.

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to HMX are summarized in Figure 2-2. The purpose of this figure is to illustrate the existing information concerning the health effects of HMX. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not necessarily imply anything

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



Human



Animal

● Existing Studies

about the quality of the study or studies, nor should missing information in this figure be interpreted as a "data need." 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.

As shown in Figure 2-2, information in humans is limited to a single study that investigated systemic and immunologic effects after chronic inhalation exposure to HMX.

2.10.2 Identification of Data Needs

Acute-Duration Exposure. No human data were located regarding acute-duration exposure to HMX by any route. In addition, no animal data were located regarding acute inhalation exposure to HMX. Studies in several animal species suggest that the central nervous system may be a target of HMX toxicity after oral (Army 1985d, 1985e, 1985h), dermal (Army 1985h), and parenteral (Army 1974, 1985h) routes of exposure. The data are sufficient to support the derivation of an acute oral MRL of 0.1 mg/kg/day. This MRL is based on a LOAEL of 100 mg/kg/day for neurological effects in mice (Army 1985d). Uncertainty in the acute oral MRL arises from the fact that serious neurological effects (convulsions) were observed in rabbits administered a single dose of 50 mg/kg HMX by gavage (Army 1985h). Additional acute studies in animals exposed to HMX by all three routes are needed to better define the threshold dose at which neurological effects occur. Such studies may be useful in predicting the risk of neurological effects in humans acutely exposed to HMX by similar routes, either occupationally or at hazardous waste sites. Case studies of accidental human exposure to HMX may serve to indicate whether or not the effects observed in animals are also observed in humans and may be useful in selecting the most appropriate animal model for HMX toxicity.

Intermediate-Duration Exposure. No human data were located regarding intermediate-duration exposure to HMX by any route. Studies in animals are limited, but suggest that the liver, kidney, and skin are targets of HMX toxicity following oral and dermal exposures (Army 1974, 1985b). The data are sufficient to support the derivation of an intermediate oral MRL of 0.05 mg/kg/day. This MRL is based on a NOAEL of 50 mg/kg/day for hepatic effects observed in rats (Army 1985c). Additional animal studies (particularly those in mice and rabbits) that confirm the critical effects of HMX

following inhalation, oral, and dermal exposure and better define the threshold dose at which these effects occur would be useful in predicting the risk of adverse health effects in humans exposed at the workplace or at hazardous waste sites by similar routes. Epidemiological studies of humans occupationally exposed to HMX that quantitate exposure may serve to indicate whether the effects observed in animals are also observed in humans.

Chronic-Duration Exposure and Cancer. In a single human study, no signs of hematological, hepatic, kidney, or immunological effects were reported in munitions workers exposed to an unspecified concentration of HMX in air (Hathaway and Buck 1977). No other studies were located regarding adverse effects in humans after exposure to HMX by any route. Additional epidemiological studies which quantitate human exposure and employ larger study populations may be useful in defining the threshold dose for HMX-related effects. No studies were located regarding adverse health effects in animals following exposure to HMX by any route. Studies in animals that investigate the adverse health effects associated with chronic exposure to HMX by all routes would be useful in predicting the risk of adverse health effects in humans exposed at the workplace or hazardous waste sites for similar durations.

There are no human or animal data regarding any potential carcinogenic effects of HMX. Epidemiological studies and chronic studies in animals exposed by all three routes would be useful in determining if humans exposed to HMX in the workplace or at hazardous waste sites are at increased risk for developing cancer.

Genotoxicity. No human or animal data were located regarding the genotoxicity of HMX following exposure by any route. A limited number of in vitro studies indicate that HMX does not increase the frequency of mutations or mitotic recombinations (Army 1977c; Tan et al. 1992; Whong et al. 1980). Studies in humans occupationally exposed to HMX and in animals exposed to HMX by all three exposure routes may confirm the findings of *in vitro* studies. Additional *in vitro* studies which evaluate other end points of genotoxicity (for example, sister chromatid exchange and chromosomal aberrations) would be useful in providing a complete profile of the genotoxicity of HMX.

Reproductive Toxicity. No human data were located regarding the reproductive effects of HMX. Limited data from animal studies indicate that HMX does not produce histopathological lesions of the ovaries or testes following oral exposure (Army 1985b). Epidemiological studies of male and female workers exposed to HMX and additional animal studies that investigate the effects of HMX on reproductive function would help determine if reproductive effects are of concern for humans exposed to HMX in occupational settings or at hazardous waste sites.

Developmental Toxicity. No human or animal data were located regarding the developmental effects of HMX. Epidemiological studies that investigate infants and children born of parents exposed to HMX in the workplace would be useful in determining if developmental effects are of concern for humans exposed to HMX occupationally or at hazardous waste sites. Studies in animals exposed to HMX by all three exposure route could help define the threshold dose at which potential developmental effects may occur.

Immunotoxicity. A single human study reported no evidence of lupus erythematosus in munitions workers, some of whom were exposed to an unspecified concentration of HMX in workplace air (Hathaway and Buck 1977). Effects were noted in the thymus and spleen of animals exposed to HMX by the oral and dermal routes (Army 1985a, 1985d, 1985h), but the effects on immunological function were not determined. Additional studies of humans occupationally exposed to HMX that investigate other immunological parameters, and additional studies in animals exposed via all routes which investigate the effects of HMX on immunological function would help determine if immunological effects are of concern for humans exposed to HMX.

Neurotoxicity. No human data were located regarding the neurological effects of HMX. Studies in animals have reported neurological effects (hyperkinesia, hypokinesia, convulsions) following acute oral (Army 1985d, 1985e, 1985h), dermal (Army 1985h), and parenteral (Army 1974, 198511) exposures to HMX. Although one study suggests that rabbits may be more sensitive than other species following oral or dermal exposure to HMX, there are numerous limitations in this rabbit study. These limitations include the lack of a control group, a small number of animals tested, and the possibility that gavage administration may have contributed to the apparently greater susceptibility of the rabbit as result of a bolus effect. Case studies of humans which report neurological effects following accidental exposure to HMX would determine if the effects observed in animals are also observed in humans. Additional animal studies, particularly those in rabbits, that better define the threshold dose

for neurological effects for all three exposure routes would be helpful in predicting the potential for neurological effects in humans exposed to HMX in the workplace or at hazardous waste sites.

Epidemiological and Human Dosimetry Studies. A single human study reported no evidence of adverse health effects in munitions workers exposed to an unspecified concentration of HMX in workplace air (Hathaway and Buck 1977). Additional studies of munitions workers exposed to HMX which employ larger study populations, quantify exposure, and determine the resulting levels of HMX or its metabolites in plasma, urine, and feces may be useful in estimating exposure to humans living near hazardous waste sites.

Biomarkers of Exposure and Effect

Exposure. The levels of HMX have been determined in the plasma, tissues, urine, and feces in animals shortly following oral and parenteral exposure to HMX (Army 1985g, 1986). Additional studies which identify and quantify the metabolites of HMX in biological samples could lead to the development of biomarkers which are also specific to HMX exposures and could be used for future medical surveillance. Such efforts could lead to early detection and possible treatment.

Effect. Measurements can be made for serum enzyme activities (alkaline phosphatase, lactate dehydrogenase, serum glutamic oxaloacetic transaminase, serum glutamic pyruvic transaminase) or for brain wave alterations (electroencephalograph) to determine the magnitude of the hepatic and neurological effects of HMX. However, these biomarkers are not specific for exposures to HMX. Studies which provide insight into the mechanism of action of HMX could lead to the development of biomarkers of effect that are specific to HMX.

Absorption, Distribution, Metabolism, and Excretion. There are no data regarding the toxicokinetics of HMX in humans. Studies in animals exposed to HMX by the oral and parenteral route suggest that HMX is poorly absorbed from the gastrointestinal tract (Army 1985g,--1986), and may preferentially distribute to the lungs, liver, heart, and kidney, and that most of an absorbed dose of HMX is excreted in the urine (Army 1986). The data regarding the metabolism of HMX are extremely limited, and data regarding the mechanism of action of HMX are purely speculative. Studies in animals which investigate the toxicokinetics of HMX following inhalation and dermal exposure would be useful in predicting the risk of adverse health effects following exposure to HMX

by these routes. Studies which provide insight into the metabolism and mechanism of action of HMX could lead to the development of sensitive biomarkers and effective treatments for the toxic effects of HMX.

Studies that investigate the absorption, distribution, metabolism, and excretion of HMX in animals (particularly rabbits) following single and repeated exposures to HMX for a wide range of doses by all three routes may provide important information regarding the time- and dose-dependency of the toxicokinetics of HMX.

Comparative Toxicokinetics. There are no human data regarding the toxicokinetics of HMX. Animal studies regarding the toxicokinetics of HMX are too limited to indicate any species differences. However, species differences have been observed for the toxic effects of HMX (Army 1985h). Additional animal studies which investigate potential species differences in absorption, distribution, metabolism, and/or excretion of HMX would be useful in understanding the mechanism underlying the species differences in sensitivity to the adverse health effects of HMX. Studies of humans following occupational or accidental exposure to HMX would be useful in determining which animal species are good models. *In vitro* studies which investigate the metabolism of HMX using microsomal fractions from human and animal tissues may indicate important species differences and/or similarities across species.

Methods for Reducing Toxic Effects. There are no data regarding the reduction of toxic effects of HMX in humans or animals. Although standard methods exist for reducing the absorption of chemicals such as HMX following oral or dermal exposure, studies which investigate the mechanism by which HMX is absorbed could lead to the development of methods which are specific for exposure to HMX. Data regarding the toxicokinetics of HMX are limited. Additional studies which better define the metabolism and mechanism of action of HMX could lead to the development of methods for reducing body burden and interfering with the mechanism of action of HMX.

2.10.3 On-going Studies

No information was located regarding on-going studies on HMX.

3. CHEMICAL AND PHYSICAL INFORMATION

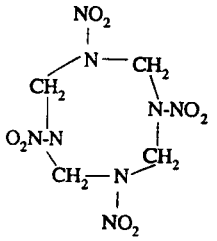
3.1 CHEMICAL IDENTITY

Table 3-l lists common synonyms, trade names, and other pertinent identification information for HMX.

3.2 PHYSICAL AND CHEMICAL PROPERTIES

Table 3-2 lists important physical and chemical properties of HMX.

TABLE 3-1. Chemical Identity of HMX

Characteristic	Information	Reference
Chemical name	HMX	
Synonym(s)	1,3,5,7-Tetranitro-1,3,5,7,-tetraazocyclooctane; cyclotetramethylenetetranitramine; tetramethylenetetranitramine; octahydro-1,3,5,7-tetranitro-1,3,5,7-tetrazocine; octogen; and others	HSDB 1995; IRIS 1995
Registered trade name(s)	No data	
Chemical formula	$C_4H_8N_8O_8$	HSDB 1995
Chemical structure		Bongiovanni et al. 1984
Identification numbers:		
CAS registry	2691-41-0	HSDB 1995
NIOSH RTECS	XF 7450000	HSDB 1995
EPA hazardous waste	No data	
OHM/TADS	No data	
DOT/UN/NA/IMCO shipping	UN0226	HSDB 1995
HSDB	5893	HSDB 1995
NCI	No data	

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

TABLE 3-2. Physical and Chemical Properties of HMX

Property	Information	Reference
Molecular weight	296.20	HSDB 1995
Color	Colorless	EPA 1988
Physical state	Solid	EPA 1988
Melting point	276–286°C	Army 1989; EPA 1988
Boiling point	No data	
Density:		
at 25°C	1.90 g/cm^3	Army 1989
Odor	No data	
Odor threshold:		
Water	No data	
Air	No data	
Solubility:		
Water at 20°C	6.63 mg/L	EPA 1988
Water at 25°C	5 mg/L	Army 1989
Water at 83°C	140 mg/L	EPA 1988
Organic solvent(s)	Soluble in dimethyl sulfoxide, acetone, cyclohexanone, acetic anhydride	EPA 1988
Partition coefficients:		
Log K_{ow}	0.26; 0.06	Army 1989
Log K_{oc}	0.54	Army 1989
Vapor pressure at 25°C	3.33×10^{-14} mmHg	Army 1989
at 100°C	3×10^{-9} mmHg	EPA 1988
Henry's law constant:		
at 25°C	2.60×10^{-15} atm-m^3/mol	Army 1989
Autoignition temperature	No data	
Flashpoint	No data	
Flammability limits	No data	
Conversion factors	No data	
Explosive limits	Decomposes violently at 279°C	Sax and Lewis 1989

4. PRODUCTION, IMPORT, USE, AND DISPOSAL

4.1 PRODUCTION

HMX is produced by the nitration of hexamine with ammonium nitrate and nitric acid in an acetic acid/acetic anhydride solvent at 44°C. The raw materials are mixed in a two-step process and the product is purified by recrystallization. This is a modification of the Bachmann Process used to produce RDX, another explosive. The yield of HMX is about 55-60%, with RDX as an impurity. RDX produced by the Bachmann Process usually contains about 8-12% HMX as an acceptable byproduct (Army 1984a, 1989; EPA 1986, 1988).

HMX is currently produced at only one facility in the United States, the Holston Army Ammunition Plant in Kingsport, Tennessee. Estimated production volume of HMX was about 30 million pounds annually between 1969 and 1971. No estimates of current production volume were located, but it is estimated that its use is increasing (Army 1984a, 1989; EPA 1986).
Processing may occur at load, assemble, and pack (LAP) facilities operated by the military (Army 1984a; EPA 1988). There were 10 facilities engaged in LAP operations in the United States in 1976 (Army 1984a).

4.2 IMPORT/EXPORT

No information was located regarding import or export of HMX in the United States. Export of this chemical is regulated by the U.S. State Department (see Table 7-l) (Department of State 1992).

4.3 USE

HMX is used to implode fissionable material in nuclear devices to achieve critical mass and as a component of plastic-bonded explosives, solid fuel rocket propellants, and as burster chargers in military munitions (EPA 1988). The use of HMX as a propellant and in maximum-performance explosives is increasing (Army 1989). Data on quantities of HMX currently consumed for these uses were not located.

4.4 DISPOSAL

Wastes from explosive manufacturing processes are classified as hazardous wastes by EPA. Generators of these wastes must conform to EPA regulations for treatment, storage, and disposal (see Chapter 7). The waste water treatment sludges from processing of explosives are listed as hazardous wastes by EPA based only on reactivity (EPA 1986). Waste water treatment may involve filtering through activated charcoal, photolytic degradation, and biodegradation (EPA 1988). Rotary kiln or fluidized bed incineration methods are acceptable disposal methods for HMX-containing wastes.

At the Holston facility, waste waters are generated from the manufacturing areas and piped to an industrial water treatment plant on site. Following neutralization and nutrient addition, sludge is aerobically digested and dewatered. It was estimated that the facility generates a maximum of 3,800 tons (7.6 million pounds) of treated, dewatered sludge annually. Based on demonstration by Holston that this sludge is nonhazardous, the EPA proposed granting a petition to exclude the sludge from hazardous waste control (EPA 1986). HMX is not listed on the Toxics Release Inventory (TRI) database, because it is not a chemical for which companies are required to report discharges to environmental media.

5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

HMX is a high explosive chemical which does not occur naturally. Most of the HMX entering environmental media is from discharge of waste waters from manufacture and processing of the chemical into aquatic environments. Treatment and disposal of other HMX-containing wastes also contributes to the environmental concentrations of this chemical.

HMX is persistent in the environment, with little transport from water to other media. Volatilization, sorption, and bioconcentration are not expected to be important. The primary transformation process is photolysis, with a half-life of about 17 days in river water. Biodegradation may occur in waste water and in water enriched with nutrients under aerobic and anaerobic conditions, but is not expected to be significant in ambient waters.

Exposure of the general population to HMX, if it occurs at all, is expected to be low. If exposure does occur, it is most likely to arise from drinking or showering with HMX-contaminated water at or near processing facilities or hazardous waste sites.

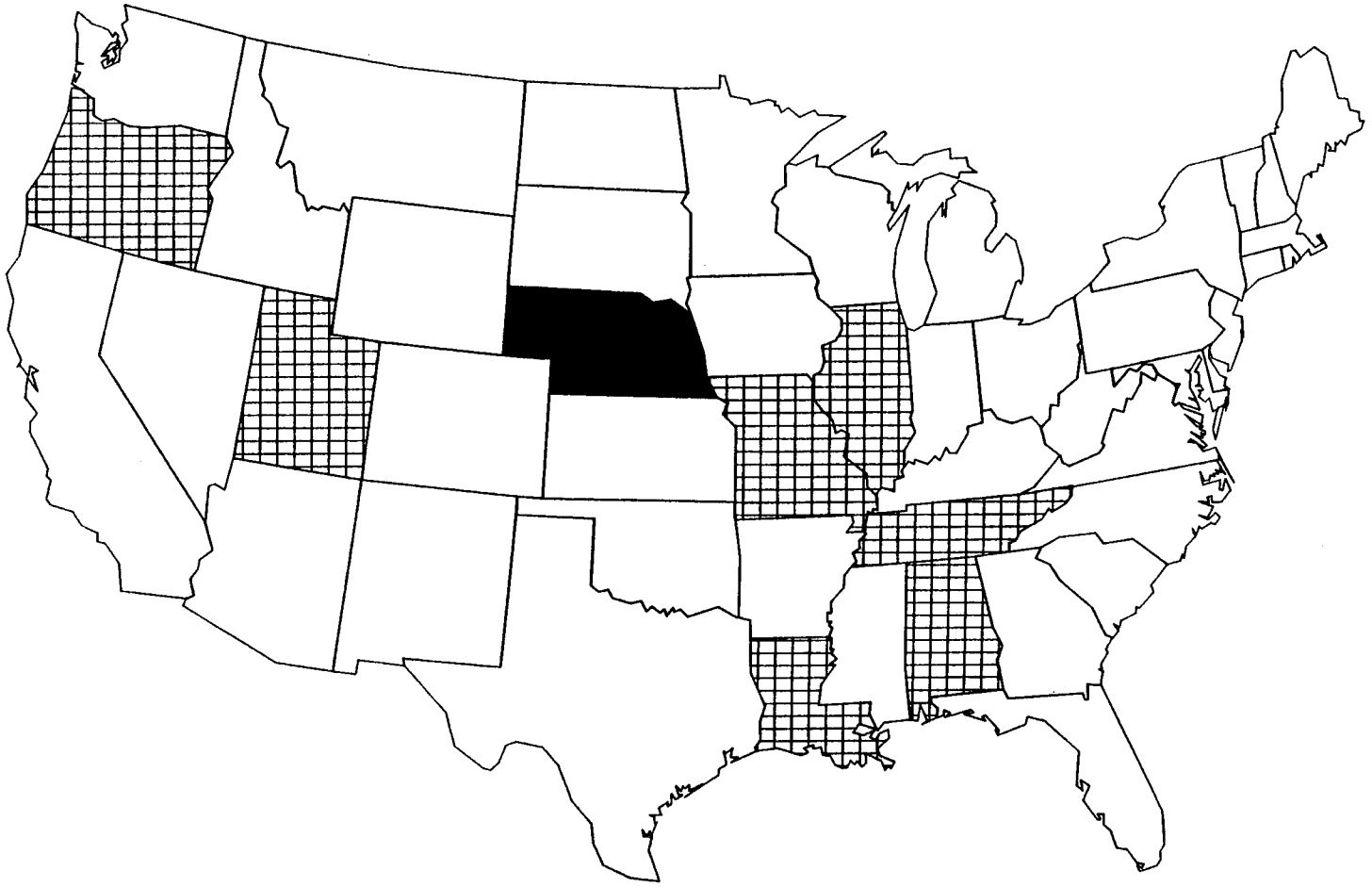
HMX has been identified in at least 10 of the 1,416 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (HazDat 1995). However, the number of sites evaluated for HMX is not known. The frequency of these sites within the United States can be seen in Figure 5-l.

5.2 RELEASES TO THE ENVIRONMENT

5.2.1 Air

Although no data were located, it is unlikely that substantial quantities of HMX are released to air. The chemical is not volatile, but, based on detection of RDX on particulate emissions (Army 1984a), may adsorb to particulates generated during burning of HMX-containing materials. Concentrations of

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



*Derived from HazDat 1995

HMX released to air in this manner are expected to be low. HMX is not listed on the TRI database, so estimates of environmental release of this chemical are not available from this source.

5.2.2 Water

Releases of HMX to surface water may occur from discharge of waste waters from production and processing of the chemical. In the past, reported concentrations of HMX in manufacturing effluents ranged from 0.09 to 3.59 mg/L (Army 1983, 1984a). Based on these concentrations, it was estimated that the Holston facility discharged about 45-123 pounds per day of HMX into the Holston River (Army 1984a). Waste waters from LAP operations such as washdown, explosive melting, and reject warhead steam cleaning may also contain HMX (EPA 1988). However, based on data for RDX, waste water treatment may reduce HMX concentrations by one to two orders of magnitude (Army 1984a). No information on the current status of waste water treatment at facilities generating waste waters containing HMX was located.

5.2.3 Soil

HMX may be released to soil by industrial sources and from hazardous waste sites at which this chemical has been detected. Releases may be via deposition of airborne particles from manufacture or incineration, spills occurring during manufacture, transportation, or storage, or landfilling of explosive wastes or explosive-generated incineration ashes (Army 1984a; EPA 1988). No data regarding quantities of HMX released to soil by these processes were located.

5.3 ENVIRONMENTAL FATE

5.3.1 Transport and Partitioning

HMX released to water or soil may volatilize into air or sorb onto soil and sediments. However, neither volatilization nor sorption are expected to be major removal mechanisms for HMX. The volatilization rate constant from aquatic systems was estimated at about 2.4×10^{-4} to 7.2×10^{-4} day^{-1}, resulting in a volatilization half-life of about 3,000-1,000 days for HMX (Army 1984a). In aquatic environments, adsorption to suspended solids and partitioning to sediments may occur, but is not

considered a major fate process (EPA 1988). Thus, HMX may be transported for a considerable distance in water.

Based on the calculated soil adsorption factor (log $K_{oc}$of 0.54), HMX is expected to have high mobility in soil. Results of laboratory studies indicate that HMX was present in leachate from various types of soils and is likely to migrate into groundwater (Army 1982b, 1984b). However, the extent of migration to groundwater is limited by the relatively low solubility of HMX in water (6.63 mg/L) (EPA 1988). Therefore, the migration of HMX through soil is expected to be slow, resulting in low concentrations in groundwater (EPA 1988). The highest migration rate was reported in coarse, loamy soil (Army 1984a). More recently, a study was conducted on the migration of HMX in soil obtained from the Milan Army Ammunition Plant in Milan, Tennessee (Checkai et al. 1993). Experiments involved leaching soil columns with synthetic rainwater for up to 243 days. HMX, at an average concentration of 0.4 mg/L, was detected in the leachate samples. No biodegradation products of HMX were detected. HMX had migrated the full soil-core length by 19.5 weeks.

Atmospheric transport of HMX may occur, based on persistence of munitions compounds in air (Army 1984a), but no data were located to support this hypothesis.

No data regarding the bioconcentration potential of HMX were located. Bioaccumulation of HMX is not expected to be significant, based on bioconcentration and elimination studies on RDX, an HMX analog, in several species (Army 1984a).

5.3.2 Transformation and Degradation

5.3.2.1 Air

No data were located on HMX transformations in the atmosphere.

5.3.2.2 Water

HMX is relatively stable in the aquatic environment. Neither hydrolysis nor oxidation of HMX in water are expected to be important removal processes (EPA 1988). Direct photolysis is probably the primary transformation pathway for HMX in aquatic systems. Photolysis rate constants reported for

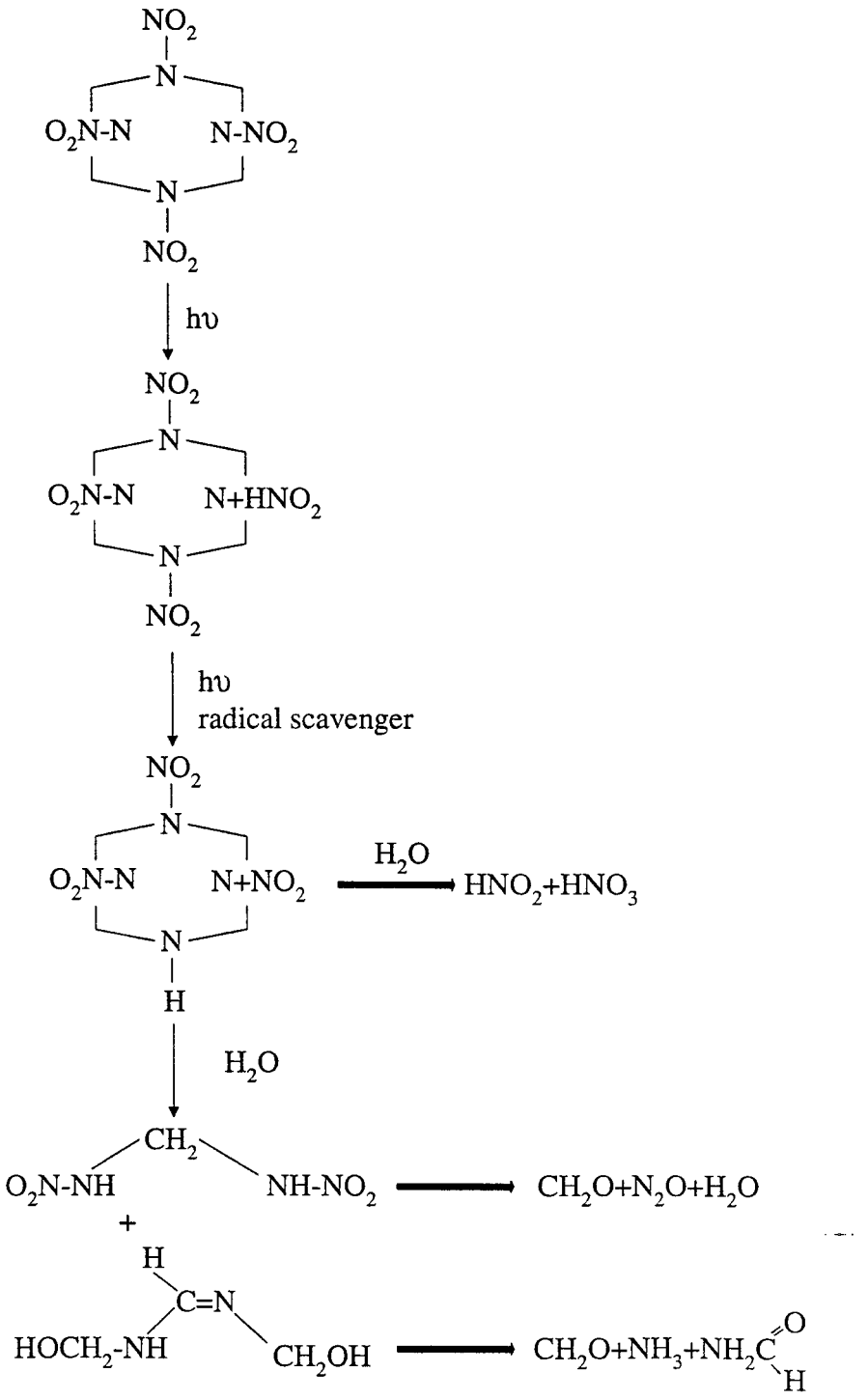
HMX were 0.19, 0.166, and 0.0099 day^{-1} in pure water, Holston River water, and Louisiana Army Ammunition Plant (LAAP) lagoon water, respectively (Army 1983). The resulting photolytic halflives for HMX were 1.4, 1.7, and 70 days, respectively. The major difference affecting the photolysis rate in these laboratory experiments appeared to be light attenuation by ultraviolet absorbing species in the lagoon water. The rate did not appear to be affected by co-substrates in solution. The observed stable end products of HMX photolysis were nitrate, nitrite, and formaldehyde. Since the nitrate and nitrite ions accounted for only 50% of the nitro groups per mole of HMX consumed, the authors proposed a photolysis mechanism, summarized in Figure 5-2, which includes dinitrogen oxide, ammonia, and formamide as additional end products. Modeling of Holston River and LAAP lagoon waters, including such factors as water flow, depth, and seasonal changes in rate constants, indicated that the average half-life of HMX would be 17 days in the Holston River and 7,900 days in the LAAP lagoon. Dilution served as the primary mechanism for reduction of HMX concentration, with photolysis contributing losses of l-5%. The authors concluded that HMX may persist in the Holston River for a significant distance (more than 20 km) from the Holston plant.

Biodegradation does not appear to be significant in ambient waters; however, some studies indicate that biodegradation may be an important removal process for HMX in manufacturing effluents and in waters containing organic nutrients. Aerobic and anaerobic biotransformation was reported in waste water and river water enriched with nutrients. The transformation products included mono- through tetra-nitroso derivatives of HMX, which eventually were metabolized to l,l-dimethylhydrazine (Army 1983). Transformation was not significant in the Holston River water or the LAAP lagoon water. The authors postulated that the levels of organisms and nutrients in the water were too low to support the biotransformation of HMX (Army 1983). Other studies confirmed the anaerobic, but not aerobic, biotransformation of HMX in nutrient broth culture systems inoculated with sewage sludge (Army 1984d).

5.3.2.3 Sediment and Soil

No data were located regarding HMX transformation in soil or sediment. Based on data for RDX and HMX transformations in water, microbial degradation does not proceed rapidly and the chemical may be persistent in soil and sediments (Army 1984a).

FIGURE 5-2. Proposed Mechanism for the Solar Photolysis of HMX in Water*



*Adapted from Army 1983

5.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

5.4.1 Air

No monitoring data for HMX in ambient air were located.

5.4.2 Water

HMX has been detected in groundwater samples at the northern facility boundary of the Milan Army Ammunition Plant in Milan, Tennessee (EPA 1994). Concentrations of 0.53-821.0 μg/L HMX were detected in monitoring well groundwater samples. HMX has also been detected in surface waters receiving effluents from HMX manufacturing and processing facilities. HMX was detected at a concentration of 67 μg/L in the Holston River, one mile downstream of the last plant effluent (Army 1984a).

5.4.3 Sediment and Soil

At the Joliet Army Ammunition Plant located in Joliet, Illinois, HMX has been detected in soil samples at concentrations of 5-3,054 μg/g (Phillips et al. 1994). HMX, at a concentration of 13 μg/g, was detected by high-performance liquid chromatography (HPLC) in soil obtained from the Milan Army Ammunition Plant, Milan, Tennessee (Phillips et al. 1993). High levels could be present in limited areas as a result of releases from manufacture and processing as well as from waste disposal in landfills (Army 1984a).

5.4.4 Other Environmental Media

No data were located regarding HMX in foods or other environmental media.

5.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

Exposure of the general population to HMX is expected to be extremely low, but data are insufficient for exposure estimates. The chemical has only been detected in environmental media in the vicinity of

manufacturing or processing facilities or hazardous waste sites. If exposure of the general population to HMX occurred, water would be the most likely source (Army 1989).

Workers in military facilities manufacturing or processing HMX may be exposed to the chemical. Plant personnel may handle HMX dissolved in various solvents (Army 1984a). The National Occupational Exposure Survey (NOES) estimated that six technicians for research and development laboratories were potentially exposed to HMX in the United States between 1981-1983 (Sieber et al. 1991). The NOES database does not contain data on the frequency, duration, concentration, or route of exposure of workers to chemicals.

5.6 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Residents or workers near hazardous waste sites containing HMX wastes or manufacturing or processing facilities handling explosives are at greater risk of exposure to HMX than the general population.

5.7 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of HMX is available. Where adequate information is not available, ATSDR, in conjunction with the 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 HMX.

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 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 will be proposed.

5.7.1 Identification of Data Needs

Physical and Chemical Properties. The physical and chemical properties of HMX are sufficiently well characterized to allow estimation of its environmental fate (see Table 3-2) (Army 1989; EPA 1988; HSDB 1995). On this basis, it does not appear that further research in this area is required.

Production, Import/Export, Use, Release, and Disposal. HMX is manufactured by only one facility in the United States (Army 1984a, 1989; EPA 1986). Current production volumes, both as a primary product and as a by-product in RDX, and import and export information are not available. Current amounts of this chemical consumed by each use were not located. Current information on the amounts of HMX released to the environment and disposed by various treatment methods are also not available. This information would be helpful in assessing potential exposure to workers and the general population.

According to the Emergency Planning and Community Right-to-Know Act of 1986, 42 U.S.C. Section 11023, industries are required to submit substance release and off-site transfer information to the EPA. The Toxics Release Inventory (TRI), which contains this information for 1992, became available in May of 1994. This database will be updated yearly and should provide a list of industrial production facilities and emissions. However, HMX is currently not listed in the TRI database.

Environmental Fate. The environmental fate of HMX has been investigated in several studies (Army 1982b, 1983, 1984b, 1984d). The chemical is relatively unreactive and degrades slowly in environmental media. It is not likely that exposure to the general population is of concern. Nevertheless, because it appears to be persistent in aquatic and terrestrial environments and may migrate to groundwater (Army 1982b, 1984b), additional studies might be useful to assess the potential for transport of this chemical from hazardous waste sites. In addition, determining the effect of chlorination on HMX degradation rates would be useful in predicting potential exposure via drinking water.

Bioavailability from Environmental Media. No studies were located regarding the bioavailability of HMX from environmental media. However, studies in rodents indicate that HMX is not well absorbed (<5%) in the gastrointestinal tract following exposure by gavage or in the diet (Army 1985g, 1986). Based on a log K_{oc} value of 0.54 (Army 1989), interactions between HMX and soil may decrease bioavailability to some extent, but this is not expected to be significant. Studies which investigate the bioavailability of HMX from environmental media would be useful in estimating exposure to persons who live near hazardous waste sites contaminated with HMX.

Food Chain Bioaccumulation. No data on bioconcentration of HMX by aquatic organisms were located. Based on data for RDX, food chain bioaccumulation is unlikely, but information on the bioconcentration potential of this chemical would be useful to confirm this assumption.

Exposure Levels in Environmental Media. Reliable monitoring data for the levels of HMX in contaminated media at hazardous waste sites are needed so that the information obtained on levels of HMX in the environment can be used in combination with the known body burden of HMX to assess the potential risk of adverse health effects in populations living in the vicinity of hazardous waste sites. Monitoring data were not located for HMX in ambient air or soil. The chemical has been detected in surface waters receiving effluents from HMX manufacturing and processing facilities. Since this chemical is not expected to be prevalent in the environment and exposure of the general population is not expected to be of concern, monitoring of ambient environmental media does not appear to be required. However, monitoring of environmental media (particularly tap water from surface water sources) in the vicinity of HMX manufacturing and processing facilities, and at hazardous waste sites at which HMX has been detected, would help determine potential sources and magnitude of exposure.

Exposure Levels in Humans. No data were located regarding exposure levels of HMX to humans. This information is necessary for assessing the need to conduct health studies on these populations. Since HMX does not appear to be well absorbed, analyzing blood or urine of workers potentially exposed to the chemical is unlikely to provide useful information unless the exposure levels are very large. Analysis of feces, although impractical for large scale monitoring, might provide documentation of oral exposure.

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

5.7.2 On-going Studies

Current research on the environmental fate of HMX involves studies of biological waste management including the anaerobic degradation of HMX and the effectiveness of white rot fungus in degrading HMX for bioremediation of contaminated soil and water (FEDRIP 1995).

6. ANALYTICAL METHODS

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

6.1 BIOLOGICAL MATERIALS

Reverse-phase high performance liquid chromatography (HPLC) is the preferred method for detecting and quantifying HMX in rodent plasma (Army 1985g), and has also been used to analyze rodent urine and fecal samples (Army 1986). This method should be applicable to analysis of human biological samples, as well. The liquid chromatograph separates mixtures of organics and allows individual compounds to be identified and quantified by a detector. An ultraviolet (UV) detector is used for quantitation of HMX. Thin layer chromatography (TLC) has also been used for analysis of ^{14}C-HMX in urine and fecal samples, but this method is not applicable to unlabeled HMX analysis (Army 1986).

Prior to analysis, HMX must be separated from the biological sample matrix and prepared for introduction into the analytical instrument. Separation from plasma is accomplished by extraction with methylene chloride, followed by drying to remove the solvent, and dissolution in a mixture of perchloric acid and acetonitrile prior to injection onto the HPLC column (Army 1985g). Extraction with acetonitrile separates HMX from urine and fecal samples (Army 1986). Details of methods for HMX analysis in biological samples are summarized in Table 6- 1.

TABLE 6-1. Analytical Methods for Determining HMX in Biological Materials

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Plasma (rodent)	Extract with methylene chloride; dry under nitrogen stream; dissolve residue in perchloric acid/acetonitrile	HPLC/UV	20 ng/mL	105–108	Army 1985g
Urine/feces (rodent)	Extract with acetonitrile; dry; dissolve in methanol/water; elute with acetonitrile/water	HPLC/UV	No data	No data	Army 1986

HPLC = high performance liquid chromatography; UV = ultraviolet detector

6.2 ENVIRONMENTAL SAMPLES

Several methods have been developed to detect HMX in water and soil. Representative methods for quantifying HMX in these media are summarized in Table 6-2. Only one analytical method for HMX in air was located (OSHA 1987). This method has been only partially evaluated and is presented for information and trial use. The method is summarized in Table 6.2.

The primary method for determining HMX in water and soil samples is by HPLC analysis (Army 1984c, 1985i, 1991c; Bauer et al. 1986, 1990; Jenkins et al. 1986, 1989; Maskarinec et al. 1984; Phillips et al. 1994). The U.S. EPA has issued a reverse-phase high-performance liquid chromatographic (RP-HPLC) method (Method 8330) for the determination of nitroaromatic and nitramine explosives in environmental samples (EPA 1992). The American Society for Testing and Materials (see ASTM 1991) and the Association of Official Analytical Chemists (AOAC 1990) have also adopted an HPLC method as the standard method for determining explosive residues in soil and water (AOAC 1990; Army 1984c; Bauer et al. 1986, 1990; Jenkins et al. 1986, 1989). Gas chromatography (GC) and thin-layer chromatography (TLC) may also be employed (Glover and Hoffsommer 1973; Hable et al. 1991).

Separation of HMX from environmental samples is usually accomplished by extraction with an organic solvent such as methanol, isoamyl acetate, or acetonitrile (Army 1984c, 1985i; Bauer et al. 1986, 1990; Bongiovanni et al. 1984; Jenkins et al. 1989; Phillips et al. 1994). Method 8330 recommends a salting-out procedure with sodium chloride and acetonitrile for low concentrations of explosive residues in surface or groundwater, direct injection for water samples of higher concentrations, and extraction by acetonitrile in an ultrasonic bath for soil and sediment samples (EPA 1992). Research to improve these extraction methods is still in progress. A recent study was conducted to evaluate the use of supercritical fluids for the extraction of explosive residues from soils in an attempt to improve the efficiency, specificity, and time and solvent requirements of extraction (Thorne 1994). This study, however, concluded that supercritical fluid extraction was not a practical method for the routine extraction of explosive residues from soils.

Identification and quantification is most frequently done by UV (Army 1984c, 1985i; Bauer et al. 1986, 1990; Bongiovanni et al. 1984; Glover and Hoffsommer 1973; Jenkins et al. 1989), but an

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

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Air	Draw air through fiber filter; extract with acetone	HPLC/UV	10.5 ng/injection	93–96	OSHA 1987
Water	Adsorb on Porapak resin; desorb with acetone; exchange with ethanol	HPLC/ED	≈1 µg/L[a]	No data	Maskarinec et al. 1984
Water	Adsorb on Porapak resin; desorb with acetonitrile dilute with reagent grade water	Reverse-phase HPLC	0.21 µg/L	107	Jenkins 1992
Water	Filter through Empore styrene-divinyl benzene disk; extract with aceto-nitrile; dilute with reagent grade water	Reverse-phase HPLC	0.33 µg/L	81	Jenkins 1992
Water	Extract with benzene; dry; dissolve in acetone; elute with benzene/acetone	TLC/UV	20 µg/L	5–15	Glover and Hoffsommer 1973
Water	Extract with sodium chloride and acetonitrile; evaporate and exchange to water; elute with water/methanol/tetra-hydrofuran	Reverse-phase HPLC/UV	0.271 µg/L	118	Army 1991c
Water	Adjust pH to 6; mix with	HPLC/UV	No data	29	Major 1992

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

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
	sodium chloride; trap with C18 disposable cartridge; elute with methanol				
Water	Extract with acetonitrile and sodium chloride; mix with salt water; separate acetonitrile phase; dilute with reagent grade water	Reverse-phase HPLC	0.19 µg/L	106	EPA 1992; Jenkins 1992
Waste water	Mix with methanol/acetonitrile; elute with water/methanol/ acetonitrile	Reverse-phase HPLC/UV	26 µg/L	95	Bauer et al. 1986; AOAC 1990; Army 1984c; Jenkins et al. 1986; EPA 1992
Drinking water	Extract with isoamyl acetate; inject using direct flash injection technique	Capillary column GC/ECD	6 µg/L	81–92 (avg. = 86)	Hable et al. 1991
Soil	Grind soil sample with mortar and pestle; extract with acetonitrile in ultrasonic bath; dilute with aqueous calcium chloride	Reverse-phase HPLC/UV	1.27 µg/g	80–95	Bauer et al. 1986, 1990; Jenkins et al. 1989; EPA 1992

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

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Soil	Grind soil sample; extract with acetonitrile containing 1,3-dinitrobenzene in sonic bath; dilute with aqueous calcium chloride	HPLC/UV	0.15 mg/L	99–112	Major 1992
Soil	Extract with acetonitrile, with sonication; elute with methanol/water	HPLC/UV	0.45 µg/g (ppm)	109.7	Bongiovanni et al. 1984
Soil/Sediment	Freeze or air dry, as required; extract with acetonitrile/methanol/water	Reverse-phase HPLC/UV	≈1 µg/g	92–104	Army 1985i
Food (rodent diet)	Extract with acetonitrile; elute with acetonitrile/water	HPLC/UV	1,250 µg/g (ppm)	94.2–102	Army 1985f

[a] For explosives; not specific for HMX

ECD = electron capture detection; ED = electrochemical detection; GC = gas chromatrography; HPLC = high performance liquid chromatography; TLC = thin layer chromatography; UV = ultraviolet detection

electron capture detector (ECD), thermal energy analyzer (TEA), or electrochemical detector (ED) may also be used (Fine et al. 1984; Hable et al. 1991; Maskarinec et al. 1984). When unequivocal confirmation is required, mass spectrometry (MS) may be employed (Hable et al. 1991).

Accurate determination of HMX in environmental samples is complicated by its low vapor pressure and susceptibility to thermal degradation (EPA 1988), thus compromising the usefulness of GC methods for separation of this compound from complex mixtures. This problem has recently been overcome by limiting contact of the compound with metal parts in the injection port, deactivating the injection port liner by acid treatment, and employing direct flash rather than splitless injection (Hable et al. 1991).

Due to lack of experimental data for HMX, EPA specified a maximum holding time (MHT) for preextraction samples of seven days (the same as for semivolatile organics) (EPA 1992). Subsequently, the stability of HMX in laboratory samples was evaluated (Army 1991b; Grant et al. 1993a, 1993b). The MHT for HMX was experimentally evaluated in reagent-grade water, groundwater, and surface water (Grant et al. 1993a). Samples were held for a period of up to 70 days at both room temperature (22°C) and under refrigeration (2°C). HMX was stable over the entire period for all waters under both storage temperatures (Grant et al. 1993a). Studies to evaluate the MHT in soils demonstrated that HMX was stable over the 56-day study period under all conditions (Grant et al. 1993b). Further studies on MHT for both water samples and soil samples were conducted by Makarinec, Bayne, and Johnson (Army 1991). Based on these studies, the recommended MHT for surface water, groundwater, and soil samples prior to analysis for HMX were 30 days, 50 days, and 56 days respectively (Army 1991b; Grant et al. 1993a, 1993b). All samples should be refrigerated during storage.

6.3 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of HMX is available. Where adequate information is not available, ATSDR, in conjunction with the 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 HMX.

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 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 will be proposed.

6.3.1 Identification of Data Needs

Methods for Determining Biomarkers of Exposure and Effect

Exposure. Methods exist for determining the levels of HMX in plasma, tissues, urine, and feces in animals (Army 1985g, 1986), which are presumably applicable to human exposures, as well. These methods are reasonably accurate, reliable, and specific for determining exposures to HMX. Since HMX is poorly absorbed in the gastrointestinal tract, the levels in plasma, tissues, and urine are likely to be lower than those detected in the feces following oral exposure. The data are too limited to determine if these methods are sufficiently sensitive for measuring the levels at which biological effects are expected to occur. Most people are not exposed to HMX; therefore the background levels of HMX in the general population are not expected to be detectable. Since HMX is metabolized to polar intermediates in the body, studies which identify these intermediates, in conjunction with studies which develop sensitive and reliable methods for detecting and quantifying these intermediates, would be useful for medical surveillance in the future.

Effect. Methods exist for measuring serum enzyme activities and brain wave alterations which could be used as biomarkers of the hepatic and neurological effects of HMX. These methods are sufficiently sensitive for measuring background levels in unexposed populations and could be used to determine the levels at which biological effects occur. However, these types of effects are common to exposures to a large number of exogenous compounds and endogenous diseases and illnesses and, therefore, are not specific biomarkers of effect for HMX exposure. Studies which identify specific biomarkers of effect for HMX, in conjunction with studies that develop sensitive and reliable methods for detecting these biomarkers, would be useful in determining if significant exposure to HMX has occurred.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. Analytical methods are available to detect and quantify HMX in water and soil (Army 1984c, 1985i, 1991c; Bauer et al. 1986, 1990; Bongiovanni et al. 1984; EPA 1992; Glover and Hoffsommer 1973; Hable et al. 1991; Jenkins et al. 1986, 1989, 1992; Major 1992; Maskarinec et al. 1984). Water is the medium of most concern for human exposure to this chemical. Exposure may also occur from soil or sediments in the vicinity of hazardous waste sites or from manufacturing or processing sources. The existing analytical methods can provide determinations for HMX at levels sufficiently low to meet water quality guidelines and below which health effects may occur (Army 1991c; Hable et al. 1991). However, improved methods of extraction and analysis that minimize interferences and decomposition would enhance recovery of lower levels of HMX that may be present in soil and in drinking water at hazardous waste sites and at military manufacturing and processing facilities. Research to improve the available methods is in progress (see Section 6.3.2). No information was located on specific analytical methodology for HMX in air samples. Development of a simple method for sampling and analyzing workplace air would be helpful in assessing the potential for human exposure from this source.

Methods are also available to measure degradation products of HMX in environmental samples (Army 1983), but these products (mainly nitrate, nitrite, and formaldehyde) are released to the environment from many other sources and are therefore not useful determinants of the environmental impact of this chemical.

6.3.2 On-going Studies

On-going research to improve analytical methods for HMX and related compounds includes studies to facilitate efficient elution of HMX using mobile phase modifiers and/or more inert capillary columns, thus enabling detection and quantitation of HMX by these methods. Research continues on developing improved techniques for extraction, concentration, and elution of HMX (Army 1991c; Bauer et al. 1990; Berberich et al. 1988; Hable et al. 1991). These improvements are designed to oVercome problems with sample preparation and increase sensitivity and reliability of the analyses.

7. REGULATIONS AND ADVISORIES

Because of its potential to cause adverse health effects in exposed people, numerous regulations and advisories have been established for HMX by various national agencies. Major regulations and advisories pertaining to HMX are summarized in Table 7- 1.

ATSDR has derived an acute oral MRL of 0.1 mg/kg/day for HMX. The MRL is based on a LOAEL of 100 mg/kg/day for neurological effects in mice exposed for 14 days (Army 1985d). The LOAEL value was divided by an uncertainty factor of 1,000 (10 for use of a LOAEL, 10 for extrapolation from animal to humans, and 10 for human variability).

ATSDR has derived an intermediate oral MRL of 0.05 mg/kg/day for HMX. The MRL is based on a NOAEL of 50 mg/kg/day for hepatic effects in rats exposed for 13 weeks (Army 1985c). The NOAEL value was divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans 10 for human variability) and a modifying factor of 10 for use of a “limited database” and data indicating that mice may be more sensitive than rats.

EPA has derived a chronic oral RfD of 0.05 mg/kg/day for HMX (IRIS 1995; EPA 1995). This value is based on a NOAEL of 50 mg/kg/day for liver lesions in rats exposed for 13 weeks (Army 1985c). The NOAEL was divided by an uncertainty factor of 1,000 to account for extrapolation from animals to humans, uncertainty in the threshold for sensitive humans, and extrapolation from subchronic exposure to chronic exposure.

TABLE 7-1. Regulations and Guidelines Applicable to HMX

Agency	Description	Information	References
NATIONAL			
Regulations:			
a. Other:			
EPA OSW	Hazardous Waste Wastewater treatment sludges and wastewater from the manufacturing and processing of explosives	Yes	EPA 1986 (40 CFR 261)
	Land Disposal Restrictions	Yes	EPA 1990 (22520) (40 CFR 268)
Department of State	Arms Export Regulations U.S. Munitions List	Yes	Department of State 1992 (22 CFR 121.12)
Bureau of Alcohol, Tobacco and Firearms	Importation, Manufacture, Distribution and Storage of Explosive Materials - List of Explosive Materials	Yes	ATF 1993 (18 U.S.C. 40)
DOT RSPA	Hazardous Materials Regulations Transport of Explosives	Yes	DOT 1990 (49 CFR 117-173)
Guidelines:			
a. Water:			
EPA ODW	Health Advisories		EPA 1995, IRIS 1995
	1-day (10-kg child)	5 mg/L	
	10-day (10-kg child)	5 mg/L	
	Longer term (10-kg child)	5 mg/L	
	Longer term (adult)	20 mg/L	
	Lifetime (adult)	0.40 mg/L	
	DWEL	2 mg/L	
b. Other:			
EPA	RfD (oral)	$5x10^{-2}$ mg/kg/day	EPA 1995; IRIS 1995
	Carcinogenic Classification	Group D[a]	EPA 1995; IRIS 1995

[a]Group D = not classifiable as to human carcinogenicity

DOT = Department of Transportation; DWEL = drinking water equivalence level; EPA = Environmental Protection Agency; ODW = Office of Drinking Water; OSW = Office of Solid Waste; RfD = reference dose; RSPA = Research and Special Programs Administration

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9. GLOSSARY

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

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

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

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

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

Carcinogen -- A chemical capable of inducing cancer.

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

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

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

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

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

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

Intermediate Exposure -- Exposure to a chemical for a duration of 15-364 days, as specified in the Toxicological Profiles.

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

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

In Vivo -- Occurring within the living organism.

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

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

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

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

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

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

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

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

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

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

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

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

Permissible Exposure Limit (PEL) -- An allowable exposure level in workplace air averaged over an 8-hour shift.

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

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

Reportable Quantity (RQ) -- The quantity of a hazardous substance that is considered reportable under CERCLA. Reportable quantities are (1) 1 pound or greater or (2) for selected substances, an amount established by regulation either under CERCLA or under Sect. 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

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

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

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

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

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

Time-Weighted Average (TWA) -- An allowable exposure concentration averaged over a normal 8-hour workday or 40-hour workweek. -.

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

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

APPENDIX A

MINIMAL RISK LEVEL WORKSHEETS

Chemical Name: HMX
CAS Number: 2691-41-0
Date: June 6, 1997
Profile Status: Final (Post-Public Comment)
Route: [ ] Inhalation [xl Oral
Duration: [xl Acute [ ] Intermediate [ ] Chronic
Graph Key: 13
Species: Mouse

Minimal Risk Level:

0.1 [X] mg/kg/day [ ] ppm

Reference:

Army. 1985d. HMX: 14-day toxicity study in mice by dietary administration. Ft. Detrick, MD: Research and Development Command, U.S. Army Medical Bioengineering Research and Development Laboratory. AD-A171 597 (authored by Greenough RJ, McDonald P).

Experimental design:

Groups of 6 male and 6 female B6C3Fl mice were administered HMX in the feed for 14 days at the following doses: 0 , 100, 300, 900, and 2700 mg/kg/day for males; and 0 , 320, 800, 2000, and 5000 mg/kg/day for females.

Effects noted in studv and corresponding doses:

HMX-treated animals exhibited hyperkinesia when aroused at doses of 100 mg/kg/day. Convulsions were observed in two males exposed to 300 mg/kg/day. Other effects including piloerection, hunched posture, and increased sensitivity to auditory stimuli were also noted in animals exposed to this dose. No mention was made by the authors whether or not convulsions were observed in animals given higher doses. Necropsy of the brain did not reveal any abnormalities.

Dose and end point used for MRL derivation: 100 mg/kg/day hyperkinesia

[ ] NOAEL [x] LOAEL

Uncertaintv factors used in MRL derivation:

[XI 10 for use of a LOAEL
[X] 10 for extrapolation from animals to humans
[X] 10 for human variability

Was a conversion used from npm in food or water to a mg/bodv weight dose? If so explain:

NA

If an inhalation study in animals, list the conversion factors used in determining human equivalent dose:

NA

MRL Calculation:

LOAEL: 100 mg/kg/day
MRL = LOAEL/UF = 100/1000 = 0.1 mg/kg/day

Chemical Name: HMX
CAS Number: 2691-41-0
Date: June 6, 1997
Profile Status: Final (Post-Public Comment)
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Graph Key: 16
Species: Rat

Minimal Risk Level:

0.05 [X] mg/kg/day [ ] ppm

Reference:

Army. 1985c. HMX: 13 week toxicity study in rats by dietary administration. Ft. Detrick, MD: US. Army Medical Research and Development Command, U.S. Army Medical Bioengineering Research and Development Laboratory. (authored by Everett et al.)

Experimental design:

Groups of 20 male and 20 female Fischer rats were administered HMX in the feed for 13 weeks at the following doses: 0 , 50, 150, 450, 1,350, and 4,000 mg/kg/day for males; 0 , 50, 115, 270, 620, and 1,500 mg/kg/day for females.

Effects noted in study and corresponding doses:

A NOAEL was established for hepatic effects at 50 mg/kg/day. Hepatic effects including enlarged centrilobular cells with pale nuclei and dark cytoplasm were observed in males exposed to 150 mglkgiday or more. In females administered 270 mg/kg/day or more, focal atrophy of the kidney tubules and dilatation was observed. Only high-dose animals (1,500 mg/kg/day for females, 4,000 mg/kg/day for males) were evaluated for serum chemistry parameters. Decreases in hemoglobin, packed cell volume, and blood urea nitrogen, and an increase in methemoglobin were observed in both males and females, although the elevation in methemoglobin levels was significant in males only. In addition, urinary pH was decreased while urinary volume was increased in females administered the highest dose. Crystals were observed in the urine of males administered the highest dose. Significant body weights were decreased in a dose-dependent manner, and many organ weights (adrenal, brain, heart, kidney, spleen, liver, lungs, and ovaries) were affected in a dose-dependent manner, however, the dose at which these changes became significant could not be determined. Histological effects were seen only in the liver and the kidneys. The results of this study indicate the liver and the kidneys as target organs. Ophthalmoscopic examination did not reveal any significant effects on the eyes that could be attributed to HMX treatment. Food intake did not show a consistent dose-related trend, but was reduced in treated animals as compared to controls.

Dose and end point used for MRL derivation: 50 mg/kg/day- Hepatic

[Xl NOAEL [ ] LOAEL

Uncertainy factors used in MRL derivation:

[X] 10 for extrapolation from animals to humans
[X] 10 for human variability

Modifving factors used in MRL derivation:

[X] 10 for use of a “limited database” and of data indicating that mice may be more sensitive than rats

Supporting studies:

Hepatocyte hyperplasia and cytoplasmic eosinophilia were noted in rats and mice exposed to 1,280 and 300 mg/kg/day HMX, respectively, for 14 days (Army 1985d, 1985e). No hepatic effects were observed in mice exposed to 90 mg/kg/day HMX (Army 1985b).

Was a conversion used from ppm in food or water to a mg/bodv weight dose? If so explain:

NA

If an inhalation study in animals, list the conversion factors used in determining human equivalent dose:

NA

MRL Calculation:

NOAEL: 50 mg/kg/day

MRL = (NOAEL/UF)/ MF = (50/100)/10 = 0.05 mg/kg/day

APPENDIX B

USER'S GUIDE

Chapter 1

Public Health Statement

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

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

Chapter 2

Tables and Figures for Levels of Significant Exposure (LSE)

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

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

LEGEND

See LSE Table 2-1

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

(2) Exposure Period Three exposure periods - acute (less than 15 days), intermediate (15-364 days), and chronic (365 days or more) are presented within each relevant route of exposure. In this example, an inhalation study of intermediate exposure duration is reported. For quick reference to

health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.

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

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

(5) Species The test species, whether animal or human, are identified in this column. Section 2.5, "Relevance to Public Health," covers the relevance of animal data to human toxicity and Section 2.3, "Toxicokinetics," contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.

(6) Exposure Frequency/Duration The duration of the study and the weekly and daily exposure regimen are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18), rats were exposed to 1,1,2,2-tetrachloroethane via inhalation for 6 hours per day, 5 days per week, for 3 weeks. For a more complete review of the dosing regimen refer to the appropriate sections of the text or the original reference paper, i.e., Nitschke et al. 1981.

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

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

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

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

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

APPENDIX B

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

LEGEND

See Figure 2-1

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

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

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

(15) Levels of Exposure concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m3 or ppm and oral exposure is reported in mg/kg/day.

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

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

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

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

SAMPLE

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

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

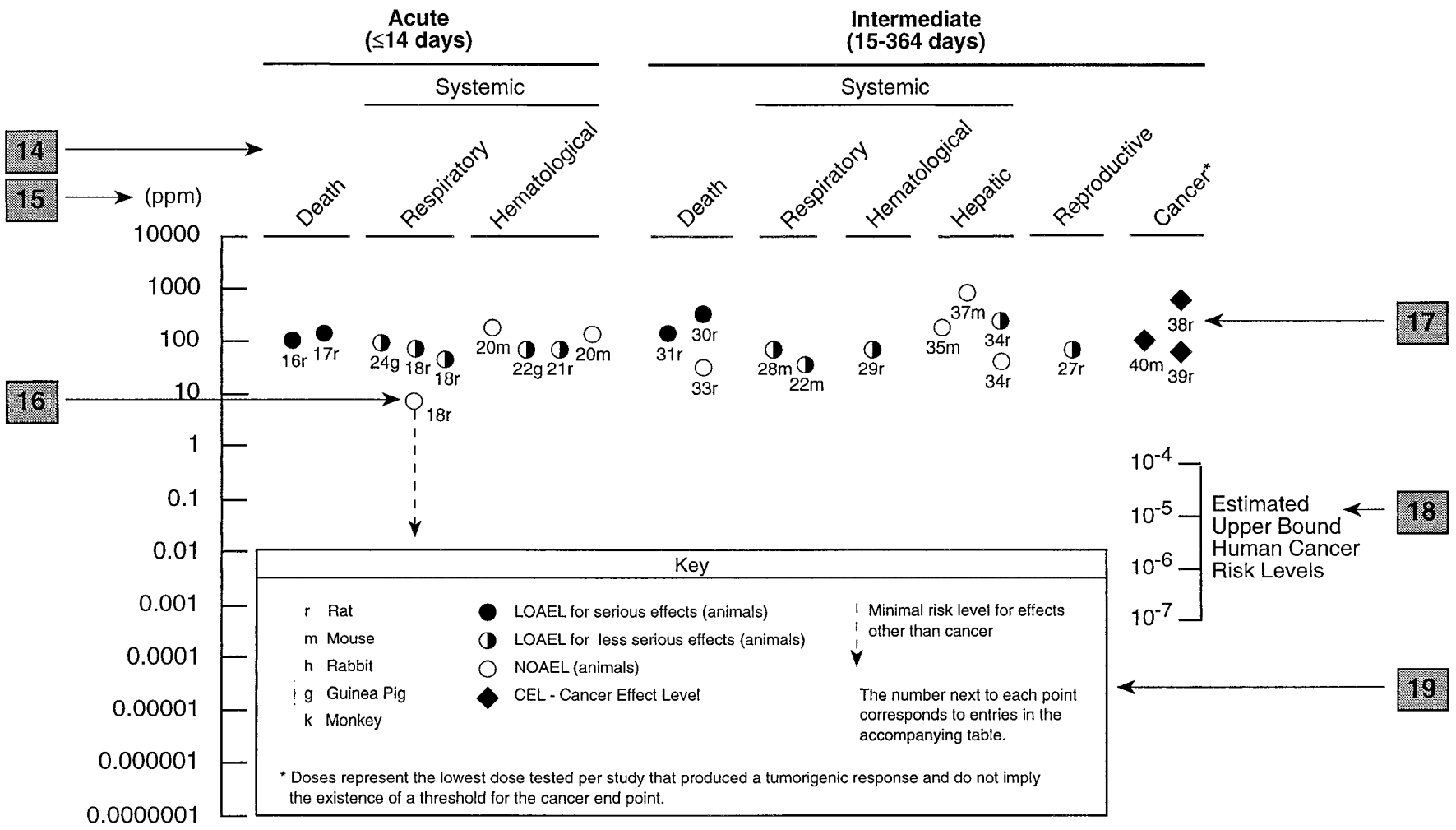
[a] The number corresponds to entries in Figure 2-1.

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

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

SAMPLE

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



Chapter 2 (Section 2.5)

Relevance to Public Health

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

1. What effects are known to occur in humans?

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

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

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

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

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

Interpretation of Minimal Risk Levels

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

MRL users should be familiar with the toxicologic information on which the number is based. Chapter 2.5, “Relevance to Public Health,” contains basic information known about the substance. Other sections such as 2.7, “Interactions with Other Substances,” and 2.8, “Populations that are Unusually Susceptible” provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses for lifetime exposure (RfDs).
To derive an MRL, ATSDR generally selects the most sensitive end point which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR

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

APPENDIX C

ACRONYMS, ABBREVIATIONS, AND SYMBOLS

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

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

SCE	sister chromatid exchange
SIC	Standard Industrial Classification
SMR	standard mortality ratio
STEL	short term exposure limit
STORET	STORAGE and RETRIEVAL
TLV	threshold limit value
TSCA	Toxic Substances Control Act
TRI	Toxics Release Inventory
TWA	time-weighted average
UMDNJ	University of Medicine and Dentistry New Jersey
U.S.	United States
UF	uncertainty factor
yr	year
WHO	World Health Organization
wk	week

>	greater than
≥	greater than or equal to
=	equal to
≈	approximately equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
δ	delta
γ	gamma
μm	micrometer
μg	microgram