

## 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 lowest observed-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

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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.

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**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<sup>3</sup>), 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<sup>3</sup> 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.

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**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<sup>3</sup> 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<sup>3</sup> (mean = 0.28 mg/m<sup>3</sup>) 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.

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**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<sub>50</sub> values of 5,500 and 6,400 mg/kg HMX were reported for male and female rats, respectively (Army 1985h). In mice, the LD<sub>50</sub> 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 2-1 and plotted in Figure 2-1.

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

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

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

Key <sup>a</sup> to figure	Species (strain)	Exposure duration/ frequency (specific route)	System	NOAEL (mg/kg/day)	LOAEL (effect)		Reference
					Less serious (mg/kg/day)	Serious (mg/kg/day)	
6	Rat Fischer 344	Once <sup>b</sup> (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 <sup>b</sup> (G)	Resp	956	1626	("reddening" of the lungs)	Army 1985h
			Gastro	956	1626	(presence of "white fluid" in the gastrointestinal tract)	
<b>Immunological/Lymphoreticular</b>							
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 <sup>a</sup> to figure	Species (strain)	Exposure duration/ frequency (specific route)	System	NOAEL (mg/kg/day)	LOAEL (effect)		Reference
					Less serious (mg/kg/day)	Serious (mg/kg/day)	
10	Mouse B6C3F1	14 d ad lib (F)			300 M (lymphocyte depletion in the thymus and spleen)		Army 1985d
<b>Neurological</b>							
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 <sup>c</sup> M (hyperkinesia)	300 M (convulsions, hunched posture, and increased sensitivity to audio stimuli)	Army 1985d
14	Mouse B6C3F1	Once <sup>b</sup> (G)			956 (hyperkinesia)	1626 (piloerection, ataxia)	Army 1985h



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

Key <sup>a</sup> to figure	Species (strain)	Exposure duration/ frequency (specific route)	System	NOAEL (mg/kg/day)	LOAEL (effect)		Reference
					Less serious (mg/kg/day)	Serious (mg/kg/day)	
<b>INTERMEDIATE EXPOSURE</b>							
<b>Death</b>							
15	Mouse B6C3F1	13 wk ad lib (F)				200 M (13/20 deaths)  250 F (12/20 deaths)	Army 1985b
<b>Systemic</b>							
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 <sup>d</sup> 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 <sup>a</sup> to figure	Species (strain)	Exposure duration/ frequency (specific route)	System	NOAEL (mg/kg/day)	LOAEL (effect)		Reference
					Less serious (mg/kg/day)	Serious (mg/kg/day)	
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		
<b>Reproductive</b>							
18	Mouse B6C3F1	13 wk ad lib (F)		90	F		Army 1985b

<sup>a</sup> The number corresponds to entries in Figure 2-1.

<sup>b</sup> HMX was administered in a carboxymethylcellulose solution.

<sup>c</sup> 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).

<sup>d</sup> 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

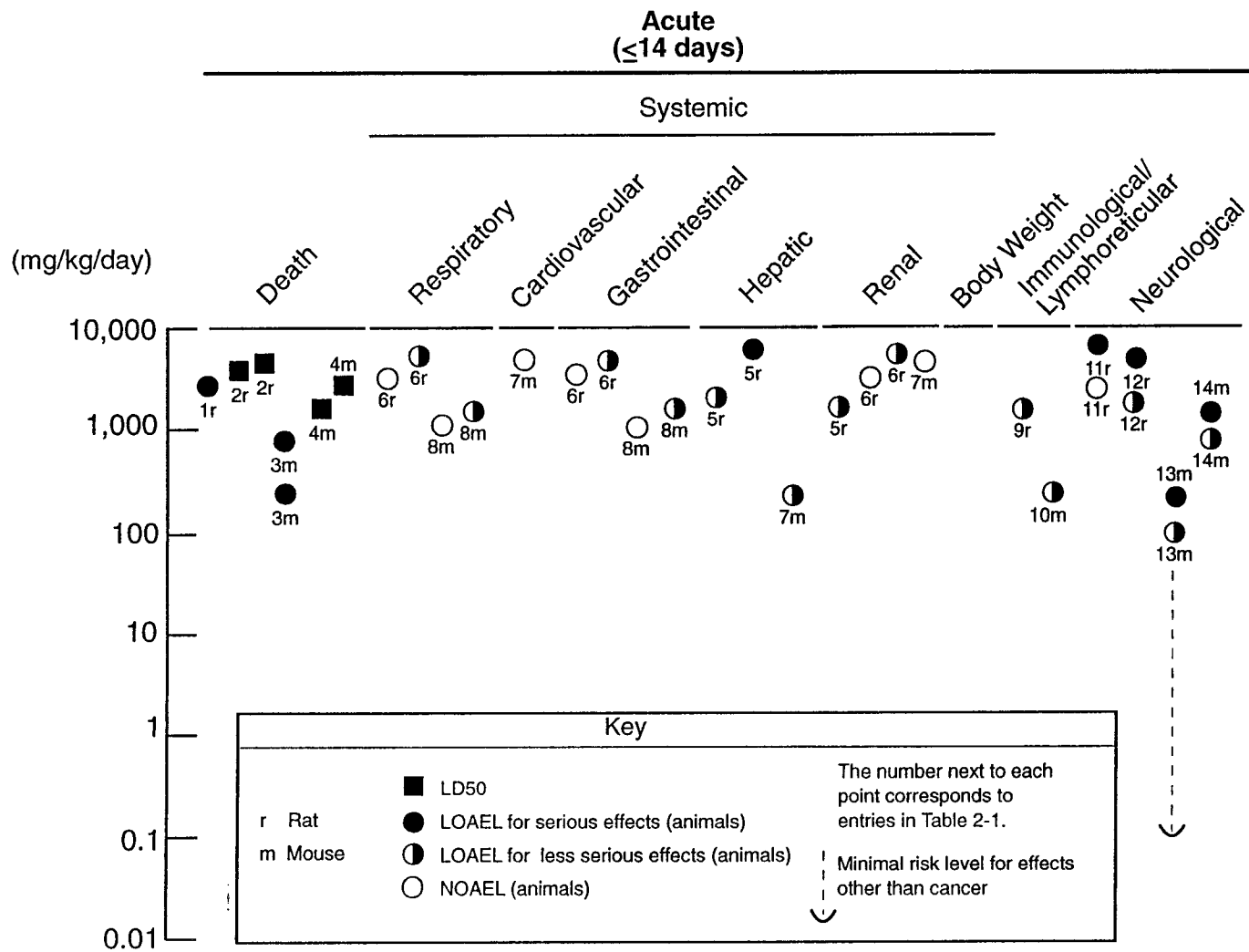
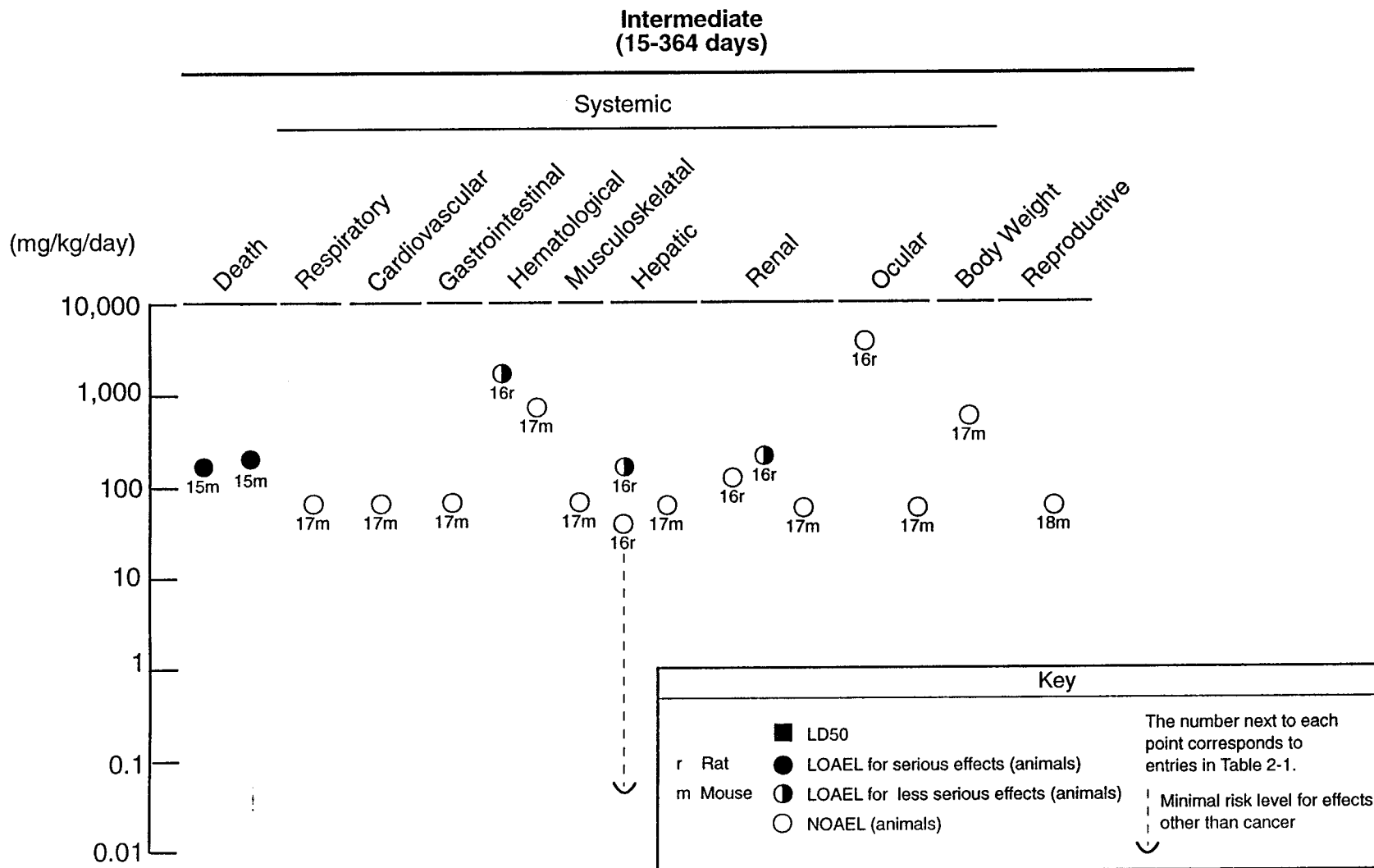


Figure 2-1. Levels of Significant Exposure to HMX - Oral (continued)



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**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.

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**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.

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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 2-1.

**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

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(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 dose-dependent 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 2-1 and plotted in Figure 2-1.



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**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 2-1. All LOAEL values for neurological effects in animals are recorded in Table 2-1 and plotted in Figure 2-1.

**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 2-1 and plotted in Figure 2-1.

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**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<sub>50</sub> values for HMX in rabbits were reported to be 634 mg/kg in males and 719 mg/kg in females (Army 1985h). The LD<sub>50</sub> 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)		Reference
				Less serious (mg/kg/day)	Serious (mg/kg/day)	
<b>ACUTE EXPOSURE</b>						
<b>Death</b>						
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
<b>Systemic</b>						
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)		Reference
				Less serious (mg/kg/day)	Serious (mg/kg/day)	
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
<b>Immunological/Lymphoreticular</b>						
Rabbit New Zealand	Once			168	(enlarged spleen)	Army 1985h
<b>Neurological</b>						
Dog Beagle	1-5 d 1x/d		480			Army 1974
Rabbit New Zealand	Once				168 (convulsions, hyperkinesia, hypokinesia, and aggression)	Army 1985h
<b>INTERMEDIATE EXPOSURE</b>						
<b>Death</b>						
Rabbit NS	4 wk 5d/wk 1x/d				165 (3/6 deaths)	Army 1974
<b>Systemic</b>						
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)		Reference
				Less serious (mg/kg/day)	Serious (mg/kg/day)	
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					
<b>Neurological</b>						
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

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**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 1-2 dogs exposed to up to 480 mg/kg/day for 1-5 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.

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**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 1-3 days (Army 1974). No evidence of skin

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irritation was observed in guinea pigs exposed to dermal doses of 510 mg/kg/day HMX for 1-3 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



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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

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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<sub>50</sub> 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 dose-dependent 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 <sup>14</sup>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

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(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 (0.10), 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 <sup>14</sup>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 (0.1-1.1 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.

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### 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 <sup>14</sup>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 (0.5-1%) 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.

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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 1-, 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 1,1-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 1,1-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.

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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

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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.



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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 10-38 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<sub>50</sub> values for HMX in rats and mice following intravenous exposure were 170-220-fold and 60-110 fold lower than their respective oral LD<sub>50</sub> 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).

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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

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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

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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 1985i). In addition, intravenous doses of 1-28.9 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

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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 of mutation 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		Reference
		With activation	Without activation	
Prokaryotic organisms:				
<i>Salmonella typhimurium</i>	Reverse mutation	-	-	Army 1977c
<i>S. typhimurium</i>	Reverse mutation	-	-	Army 1977a
<i>S. typhimurium</i>	Reverse mutation	-	-	Tan et al. 1992
<i>S. typhimurium</i>	Reverse mutation	-	-	Whong et al. 1980
<i>Saccharomyces cerevisiae</i>	Mitotic recombination	-	-	Army 1977c

- = negative result

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**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

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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 1-2 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.



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### 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 on 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 (Ellenhorn 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 (Ellenhorn and Barceloux 1988). Common methods for reducing dermal absorption of HMX include removing contaminated clothes and washing contacted skin with soap and water (Ellenhorn and Barceloux 1988). Oils have been contraindicated for cleaning the skin, since oils may increase the dermal absorption of HMX (Ellenhorn 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.

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### 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.

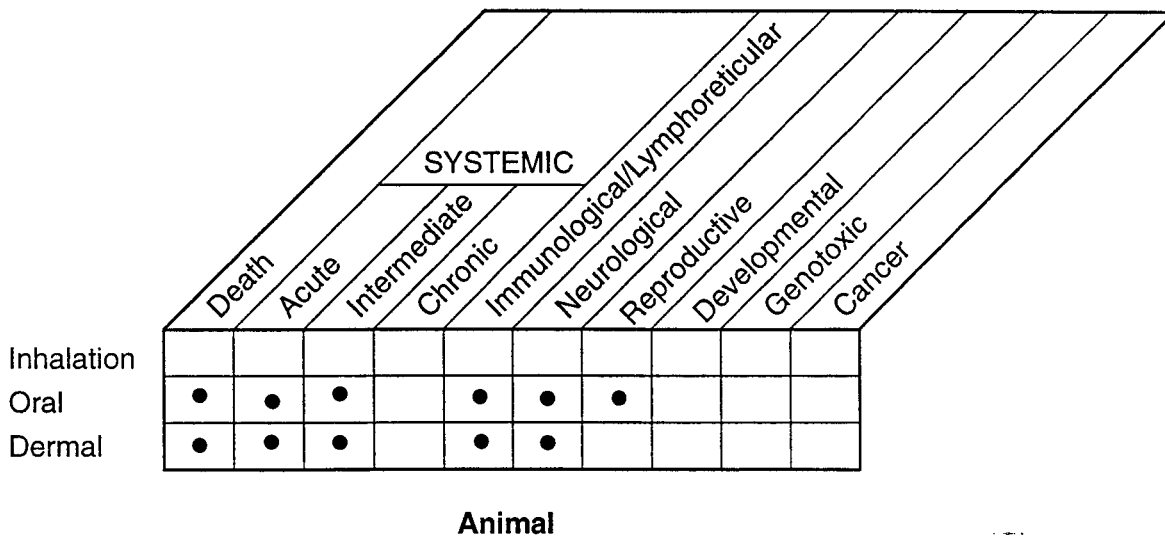
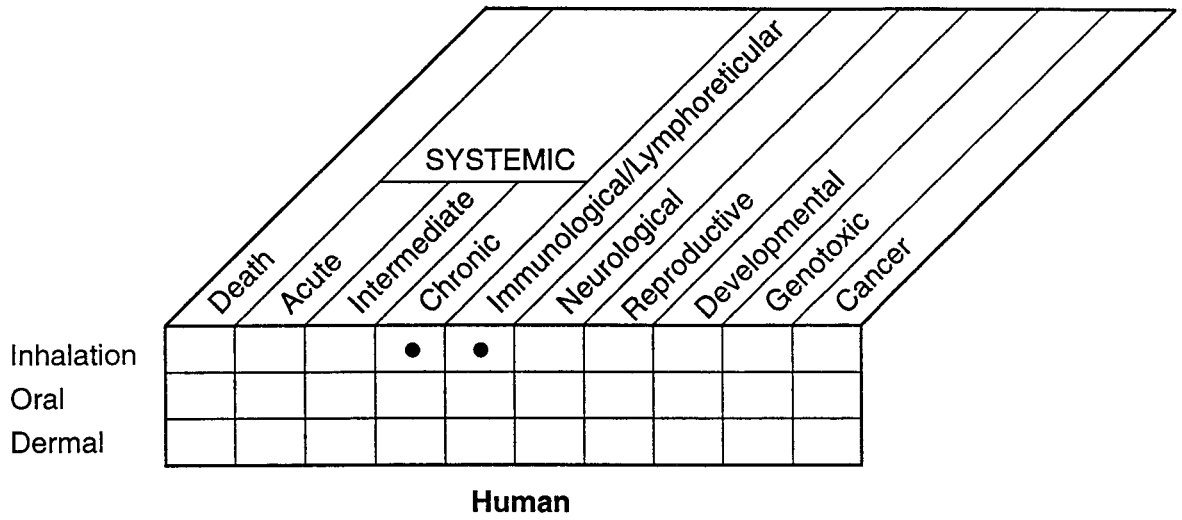
The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean 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

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



● Existing Studies

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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

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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.

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**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

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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



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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.

