2. HEALTH EFFECTS

2.1 INTRODUCTION

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

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

2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

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

Levels of significant exposure for each route and duration are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowestobserved-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELS have been classified into “less serious” or “serious” effects. “Serious” effects are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). “Less serious” effects are those that are not expected to cause significant dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether an end point should be classified as a NOAEL, “less serious” LOAEL, or “serious” LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify these end points. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between “less serious” and “serious” effects. The distinction between “less serious” effects and “serious” effects

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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 (LOAEL) or exposure levels below which no adverse effects (NOAELs) 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 hexamethylene diisocyanate. 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

Inhalation is the most common route of exposure for hexamethylene diisocyanate (HDI). Over 99% of the HDI manufactured in or imported into the United States is used to make HDI prepolymers, also lmown as polyisocyanates. These prepolymers, in turn, are used by paint formulators as hardeners in two-component polyurethane paint systems, used primarily for painting automobiles. The remaining fraction of HDI production (<1%) is sold as solid rocket fuel binders and as paint thickeners (CMA 1997). At the time of manufacture, biuret prepolymer contains about 0.7% monomeric HDI. During storage, the monomeric content can increase to as much as 1.6% due to *in situ* breakdown of the biuret (Hulse 1984). The monomeric content of HDI trimer is 0.2% at the time of manufacture and remains stable at this level during storage. Human inhalation exposures reported in studies discussed in this chapter are typically in the range of 0.001-0.02 ppm; in many cases, a dose could not be determined. Because the vast majority of HDI is used to make prepolymers used in paint systems, most of the reports concerning the respiratory toxicity of HDI focus on that source of exposure. Approximately 50% of HDI prepolymers are biurets, which contain 0.7-1.6% monomer. The other 50% of HDI prepolymers are trimers, which contain 0.2% monomer. Because paint formulators typically add solvents to the prepolymer, the percentage of monomer in the paint hardener is usually less than these percentages. In large painting operations, the paint hardener is mixed with the paint in closed systems, so that workers are exposed only to the mixture, further diluting the percentage of monomer. HDI monomer content in the mixed paints is 0.006-0.5%. As discussed below, workers in the studies discussing the respiratory effects of HDI would have been exposed to a combination of HDI monomeric and polymeric forms, making it difficult to determine whether the observed effects were due to the monomer, polymer, or both.

Monomeric HDI vaporizes quite easily, leading to inhalation and dermal exposures of workers who come in contact with the air containing the HDI vapors. Monomeric HDI, like other diisocyanates, can produce both a local irritation to the nasal and respiratory tract and an asthma-like condition in sensitized people at air vapor concentrations (range, from approximately 0.0002 to 0.02 ppm) (Malo et al. 1983; Tornling et al. 1990). Monomeric HDI also produces clinical signs of respiratory toxicity that are similar to the other diisocyanates (e.g., toluene diisocyanate). At concentrations greater than 0.0006 ppm, burning and irritation of the nose, throat and mucous membranes of the lungs; cough; laryngitis; bronchitis; tightness of the chest; hoarseness; pulmonary edema; emphysema; car pulmonale; and an asthma-like syndrome have also been reported (Grammar et al. 1988; Malo et al. 1983; Von Burg 1993). Other clinical signs

may include more vague symptoms, such as headache, fatigue, and an asthma-like condition (Von Burg 1993). Overall, information on the total health effects of HDI on humans and animals is limited.

As stated earlier, over 99% of the monomeric HDI manufactured in the United States is converted into polymeric forms (biuret and trimer), which are then sold to paint formulators for use in the hardening component of two-component polyurethane paint systems. HDI biuret and trirner can induce respiratory and immunological reactions similar to HDI monomer in both humans (Alexandersson et al. 1987; Belin et al. 1981; Cockcroft and Mink 1979; Grammar et al. 1988; Usui et al. 1992; Vandenplas et al. 1993) and animals (Ferguson et al. 1987; Weyel et al. 1982). Unlike monomeric HDI, polymeric forms typically have a very low vapor pressure, making it very unlikely to vaporize at room or paint shop ambient temperatures. Exposures to polymeric forms, primarily via the inhalation and dermal routes, and secondarily by the oral route, occur when the paint/hardener combination is ejected from the spray nozzle onto a metal surface. During the spraying process, small droplets of the monomeric/polymeric mixture suspended in the surrounding air is inadvertently breathed in by or lands on the skin of an exposed worker. The exposures discussed in many of the reports mentioned earlier that describe the inhalation toxicology of monomeric HDI in humans were probably combination exposures of the monomeric form and polymeric forms of HDI, making it difficult to determine whether the respiratory and immunologic effects observed in humans and laboratory animals are induced by either one or both forms of HDI.

2.2.1.1 Death

No studies were located regarding death in humans after inhalation exposure to HDI.

Several reports of death after inhalation exposures of acute-duration in laboratory animals were located. In one study, the acute inhalation toxicity of the HDI and various HDI pre-polymer was tested on male and female Wistar rats. The rats (n=l0 males and 10 females per group) were exposed to 105, 143,259, 341,383,443,575,589, or 719 mg HDI/m^3 (15.3,20.7,37.6,49.4,55.5,64.2,83.4, 85.4, or 104.3 ppm) in inhalation chambers for 4 hours and observed for 4 weeks after exposure. Deaths approximately followed a dose-response pattern in both sexes. Death was not observed in any of the rats in the 105 or 143 mg HDI/m^3 (15.3, 20.7 ppm) groups. Deaths occurred in 4 of 10 males and 1 of 10 females exposed to 259 mg HDI/m^3 (37.6 ppm); 9 of 10 males and 5 of 10 females exposed to 341 mg HDI/m^3 (49.4 ppm); 7 of 10 males and 6 of 10 females exposed to 383 mg HDI/m^3 (55.5 ppm); 8 of 10 males and 8 of 10 females exposed to 443 mg HDI/m^3 (64.2 ppm); 8 of 10 males and 9 of 10 females exposed to 575 mg

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HDI/m^3 (83.4 ppm); 9 of 10 males and 9 of 10 females exposed to 589 mg HDI/m^3 (85.4 ppm); and 10 of 10 males and 10 of 10 females exposed to 719 mg HDI/m^3 (104.3 ppm). Deaths occurred between 1 and 20 days after exposure. From this data, the concentration of HDI that resulted in death to 50% of the exposed population, (LC_{50}) was calculated to be 3 10 mg/m^3 (45 ppm) (Kimmerle 1976).

Groups of 4 male albino ChR-CD rats were exposed to various concentrations of HDI for 4 or 8 hours. When rats were exposed to 370 ppm, they died after 2-3 hours of exposure. Prior to death, rats showed signs of irritation, gasping, and convulsions. Tracheitis, pleural effusion, and small areas of pulmonary hemorrhage were observed at necropsy but were not considered extensive enough to cause death. Rats survived exposures to 5-72 ppm HDI (Haskell Laboratory 1961). In a similar study, groups of 4 male albino ChR-CD rats were exposed to 30 ppm HDI for 4 hours daily for 10 days over a 2-week period. Two of 4 animals (50%) of the HDI-exposed rats died (one during the 8th exposure and the other 6 days after the last exposure). Bronchitis with purulent obstruction of some bronchial branches was observed in the rat that died during exposure. Bronchopneumonia was observed in the rat that died after exposure (Haskell Laboratory 1961).

In another study, male albino Sprague-Dawley rats were exposed to HDI air concentrations of 3,4,6,11, 22,44, or 88 ppm for 6 hours. At 44 ppm, 1 of 6 rats failed to survive the exposure, while 1 additional rat died within 7 days after exposure to 44 ppm of HDI. All of the rats at the 88 ppm dose died during exposure. No other deaths were reported at either 7 or 15 days after exposure in any of the other treatment groups. In the rat that died immediately after exposure to 44 ppm of HDI, lung changes were limited to moderate congestion; the rats that died at 88 ppm exposure to HDI had moderate-to-severe pulmonary edema and congestion, which may be indicative of acute irritation and/or heart failure (Dow Chemical Co. 1964)

Male English smooth-haired guinea pigs were exposed to 0.5 ppm HDI for 6 hours, 1.8 ppm for 2 hours, or 4 ppm for 3 hours. At the 4 ppm dose level, 50% of the animals died within 1 hour during exposure (Karol et al. 1984).

Fewer studies were located on death in laboratory animals exposed for intermediate and chronicdurations. One study by Mobay Corporation (1984) determined the toxicity of HDI via inhalation exposures in Sprague-Dawley rats over a 3-week period. Male and female rats were exposed (head-only) to HDI vapors at average concentrations of 0.005,0.0175,0.15, or 0.3 ppm for 5 hours a day, 5 days a

week for 3 weeks. No mortality was observed in any of the treatment groups at any time during or after exposures. In another unrelated study of longer duration, Fischer 344 rats of both sexes were exposed to HDI (whole body exposure) over a period of 90 days. Rats were exposed to 0, 0.011,0.041, or 0.143 ppm HDI in air for 6 hours per day for 66-69 days over a period of approximately 13 weeks. No deaths occurred in any of the treatment groups during or after exposures (Mobay Corporation 1988).

One study was identified that described the death rates of rats exposed to HDI for a chronic duration. Groups of 60 male and 60 female Fischer 344 rats were exposed (whole body) to 0,0.005,0.025, or 0.175 ppm HDI for 2 years. None of the three inhaled concentrations of HDI was shown to have an effect on mortality in exposed rats compared to control animals (Mobay Corporation 1989).
The LOAEL values resulting in mortality in all species are recorded in Table 2-l and plotted in Figure 2-l.

2.2.1.2 Systemic Effects

Studies regarding the systemic effects that have been observed in humans and animals after inhalation exposure to HDI are discussed below. The highest NOAEL values and all LOAEL values from each reliable study for each systemic effect in each species and duration category are recorded in 2-l and plotted in Figure 2- 1.

Respiratory Effects. Respiratory effects due to inhalation of HDI are the subject of most of the literature on HDI toxicity, with most reports on humans based on individual case studies (Belin et al. 1981; Cockcroft and Mink 1979; Patterson et al. 1990; Vandenplas et al. 1993). One report described the case of a 56-year-old man who worked as a foreman in a garage where automobile painting was done and consequently was exposed intermittently to paints containing HDI for 5-6 years. He reported having developed respiratory and systemic reactions after exposure to paints (which contained 7% polymeric HDI) used in the garage. Episodes of shortness of breath, wheezing, malaise, and chills were reported, with symptoms occurring in the late afternoons of working days and lasting for several hours thereafter. In an attempt to confum that HDI was the compound responsible, the man was removed from the garage environment for several weeks and lung parameters were measured, including forced expiratory volume-l second (FEV_1), forced vital capacity (FVC), vital capacity (VC), forced residual capacity (FRC), total lung capacity (TLC), among others. Body temperature and blood samples were also

Table 2-1. Levels of Significant Exposure to Hexamethylene Diisocyanate - Inhalation

Key to figure[a]	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
ACUTE EXPOSURE							
Death							
1	Rat (Sprague-Dawley)	6 hr				44 M (1/6 rats died)	Dow Chemical Co. 1964 HDI
2	Rat (CD)	4 or 8 hr				370 M (death in 4/4 within 2-3 hrs)	Haskell Laboratory 1961 HDI
3	Rat (CD)	2 wk 10 x 4 hr/x				30 M (2/4 died)	Haskell Laboratory 1961 HDI
4	Rat (Wistar)	4 hr				45 M (LC50)	Kimmerle 1976 HDI
5	Gn Pig (English)	2-6 hr				4.0 M (2/4 died within 1 hr)	Karol et al. 1984 HDI
Systemic							
6	Human	5 min	Resp		0.02 M (cough, inspiratory crackles, decreased FVC, PaO_2, TLC, and VC)		Malo et al. 1983 polymeric HDI
			Hemato		0.02 M (elevated WBC count)		
			Metab		0.02 M (chills, increased body temperature)		
7	Rat (Sprague-Dawley)	6 hr	Resp		3 M (nasal irritation)	88 M (moderate to severe pulmonary edema and congestion)	Dow Chemical Co. 1964 HDI
			Bd Wt	88 M			

Table 2-1. Levels of Significant Exposure to Hexamethylene Diisocyanate - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
8	Rat (CD)	4 or 8 hr	Resp	5 M	11 M (labored breathing)	72 M (gasping, bronchopneumonia, bronchiectasis)	Haskell Laboratory 1961 HDI
			Gastro	11 M	27 M (chronic gastritis)		
			Hemato	27 M	72 M (cyanosis)		
			Bd Wt	27 M	72 M (unspecified decreased body weight)		
9	Rat (CD)	2 wk 10 x 4 hr/x	Resp			30 M (bronchitis, bronchopneumonia, labored breathing)	Haskell Laboratory 1961 HDI
			Ocular		30 M (corneal ulcer)		
			Bd Wt	30 M			
10	Rat (Wistar)	4 hr	Resp		15.3 (labored breathing)	37.6 (lung edema, pneumonia)	Kimmerle 1976 HDI
11	Rat (Fischer- 344)	30 min	Resp		0.11 M (21% decreased respiratory rate)		Mobay 1982 HDI
12	Mouse (Swiss)	3 min	Resp		0.36 M (50% decrease in respiratory rate)		E.I. Dupont de Nemours 1978 HDI
13	Mouse (Swiss-Webster)	30-180 min	Resp		0.17 (RD_{50} for 180 min exposure)		Sangha et al. 1981 HDI
14	Gn Pig (English)	2-6 hr	Resp	0.5 M	1.8 M (slowed respiratory rate and labored breathing)	4.0 M (severe respiratory distress)	Karol et al. 1984 HDI

Table 2-1. Levels of Significant Exposure to Hexamethylene Diisocyanate - Inhalation (continued)

Key to figure[a]	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
15	Dog (Beagle)	10 d 6 x 2 hr/x	Resp		0.27 F (severe nose and throat irritation, cough up foamy material)		Haskell Laboratory 1961 HDI
			Gastro		0.27 F (vomiting)		
			Ocular		0.27 F (irritation and lacrimation)		
			Metab	1.43 F			
			Bd Wt	0.27 F			
Immunological/Lymphoreticular							
16	Human	5 min			0.02 M (increased airway hyperexcitablity and increased specific IgG against HDI-HSA)		Malo et al. 1983 polymeric HDI
Neurological							
17	Rat (CD)	4 or 8 hr			11 M (irritation)	370 M (convulsions)	Haskell Laboratory 1961 HDI
18	Gn Pig (English)	2-6 hr		4.0 M			Karol et al. 1984 HDI

Table 2-1. Levels of Significant Exposure to Hexamethylene Diisocyanate - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
INTERMEDIATE EXPOSURE							
Systemic							
19	Rat (Sprague-Dawley)	3 wk 5 d/wk 5 hr/d	Resp	0.005 [b]	0.0175 (hemorrhage, inflammatory exudate, epithelial changes in nasal cavity)		Mobay 1984 HDI
			Cardio	0.3			
			Gastro	0.3			
			Hemato	0.3			
			Musc/skel	0.3			
			Hepatic	0.15 F 0.3 M	0.3 F (decreased absolute and relative liver weight)		
			Renal	0.15	0.3 (decreased absolute and relative kidney weight)		
			Endocr	0.3			
			Dermal	0.3			
			Ocular	0.005	0.0175 (ocular irritation)		
			Bd Wt	0.3			
20	Rat (Fischer- 344)	66-69 d 5 d/wk 6 hr/d	Resp	0.011	0.041 (hyperplasia and/or squamous metaplasia, mucous cell hyperplasia and inflammation in the anterior nasal cavity)		Mobay 1988 HDI
			Cardio	0.143			
			Hemato	0.143			
			Hepatic	0.143			
			Metab	0.011 M 0.143 F	0.041 M (increase urinary ketone)		
			Ocular		0.011 (ocular irritation with subsequent lacrimation)		
			Bd Wt	0.143			

Table 2-1. Levels of Significant Exposure to Hexamethylene Diisocyanate - Inhalation (continued)

Key to figure[a]	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
Immunological/Lymphoreticular							
21	Rat (Sprague-Dawley)	3 wk 5 d/wk 5 hr/d		0.3			Mobay 1984 HDI
22	Rat (Fischer- 344)	66-69 d 5 d/wk 6 hr/d		0.143			Mobay 1988 HDI
Neurological							
23	Rat (Sprague-Dawley)	3 wk 5 d/wk 5 hr/d		0.3			Mobay 1984 HDI
24	Rat (Fischer- 344)	66-69 d 5 d/wk 6 hr/d		0.143			Mobay 1988 HDI
Reproductive							
25	Rat (Sprague-Dawley)	3 wk 5 d/wk 5 hr/d		0.3			Mobay 1984 HDI
26	Rat (Fischer- 344)	66-69 d 5 d/wk 6 hr/d		0.143			Mobay 1988 HDI

Table 2-1. Levels of Significant Exposure to Hexamethylene Diisocyanate - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
CHRONIC EXPOSURE							
Systemic							
27	Human	7 yrs	Resp		0.006 M (increase in % closing volume)		Alexandersson et al. 1987 HDIt
28	Human	7 yrs	Resp		0.0001 M (increase in % closing volume)		Alexandersson et al. 1987 HDI
29	Human	24-51 mo	Resp		0.0006 M (chest tightness and cough)		Grammer et al. 1988 HDI
30	Human	16.5 yrs	Resp		0.0002 M (increase in wheezing; decrease in FVC, FEV_1, VC)		Tornling et al. 1990 HDI
31	Human	16.5 yrs	Resp		0.005 M (increase in wheezing; decrease in FVC, FEV_1, VC)		Tornling et al. 1990 HDIt

Table 2-1. Levels of Significant Exposure to Hexamethylene Diisocyanate - Inhalation (continued)

Key to figure[a]	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
32	Rat (Fischer- 344)	1 and 2 yrs 5 d/wk 6 hr/d	Resp		0.005[c] F (nasal cavity epithelial hyperplasia; hyperkeratosis)		Mobay 1989 HDI
			Cardio	0.175			
			Gastro	0.175			
			Hemato	0.025	0.175 (reticulocytosis)		
			Musc/skel	0.175			
			Hepatic	0.175			
			Renal	0.175			
			Endocr	0.175			
			Dermal	0.175 M			
			Ocular	0.025 M 0.175 F	0.175 M (eye irritation)		
			Bd Wt	0.175			
Immunological/Lymphoreticular							
33	Human	24-51 mo		0.0006			Grammer et al. 1988 HDI
34	Human	16.5 yrs		0.0002 M			Tornling et al. 1990 HDI
35	Human	16.5 yrs		0.005 M			Tornling et al. 1990 HDI
36	Rat (Fischer- 344)	1 and 2 yrs 5 d/wk 6 hr/d		0.175			Mobay 1989 HDI
Neurological							
37	Rat (Fischer- 344)	1 and 2 yrs 5 d/wk 6 hr/d		0.175			Mobay 1989 HDI

Table 2-1. Levels of Significant Exposure to Hexamethylene Diisocyanate - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
Reproductive							
38	Rat (Fischer- 344)	1 and 2 yrs 5 d/wk 6 hr/d		0.175			Mobay 1989 HDI

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

[b] Used to derive an intermediate inhalation minimal risk level (MRL) of 0.00003 ppm (3×10^{-5}) using the regional gas dose ratio (ventilation to respiratory surface areas, animal:human) divided by an uncertainty factor of 30 (3 for extrapolation from animals to humans, and 10 for human variability).

[c] Used to derive a chronic inhalation MRL of 0.00001 ppm (1×10^{-5}) using the regional gas dose ratio (ventilation to respiratory surface areas, animal:human); concentration divided by an uncertainty factor of 90 (3 for use of a minimal LOAEL, 3 for extrapolation from animals to humans, and 10 for human variability).

Bd Wt = body weight; Cardio = cardiovascular; d = day(s); Endocr = endocrine; F = female; FVC = forced vital capacity; Gastro = gastrointestinal; Gn Pig = guinea pig; Hemato = hematological; HDI = hexamethylenediisocyanate; HDIt= hexamethylene diisocyanate biuret trimer; hr = hour(s); HSA = human serum albumin; IgG = immunoglobulin G; LOAEL = lowest-observed-adverse-effect level; M = male; min = minute(s); mo = month(s); Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; PaO_2 = oxygen partial pressure; Resp = respiratory; TLC = total lung capacity; VC = vital capacity; WBC = white blood count; wk = week(s); x = times; yr = year(s)

Figure 2-1. Levels of Significant Exposure to Hexamethylene Diisocyanate - Inhalation

Acute (≤14 days)

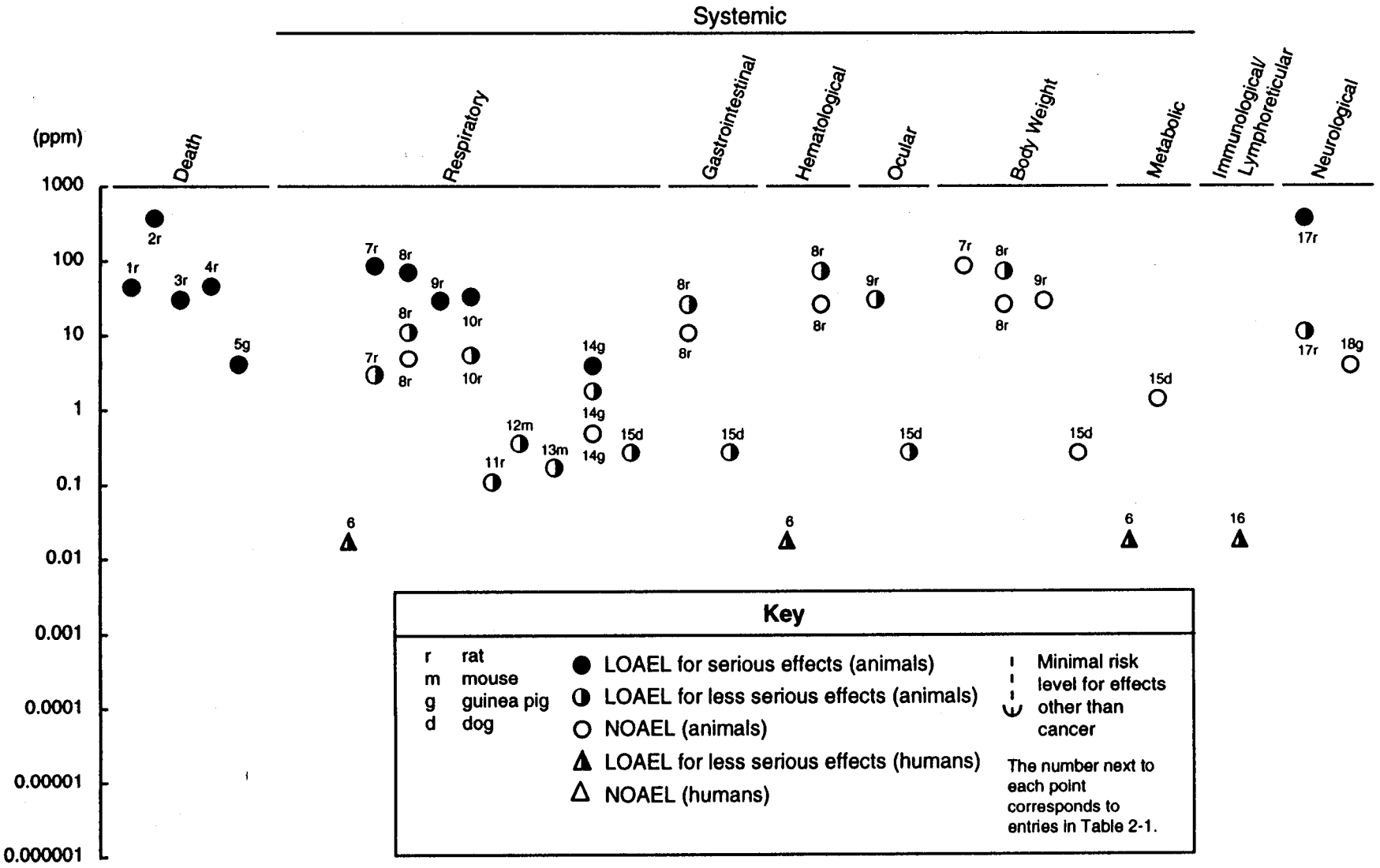


Figure 2-1. Levels of Significant Exposure to Hexamethylene Diisocyanate - Inhalation (cont.)

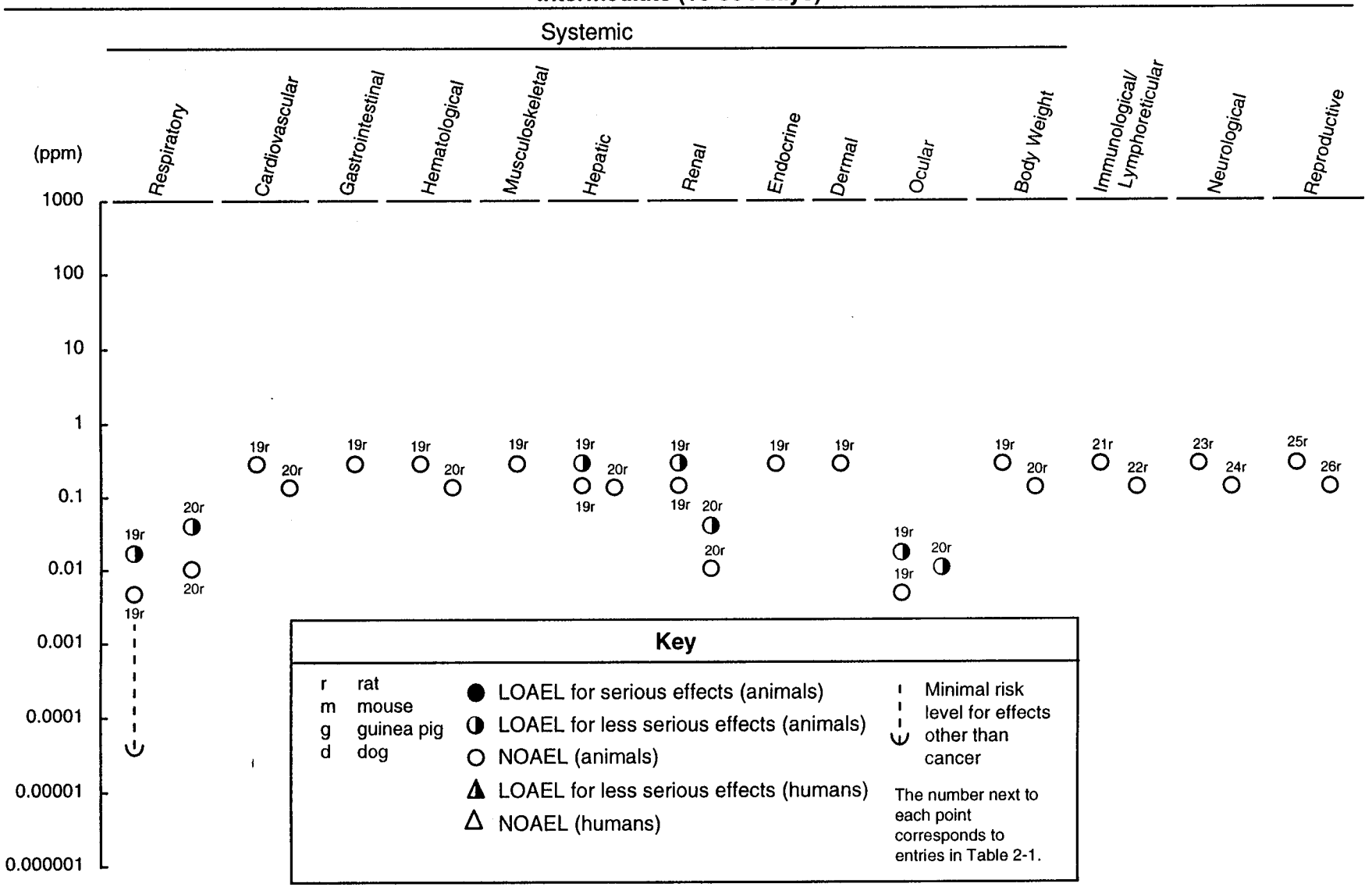
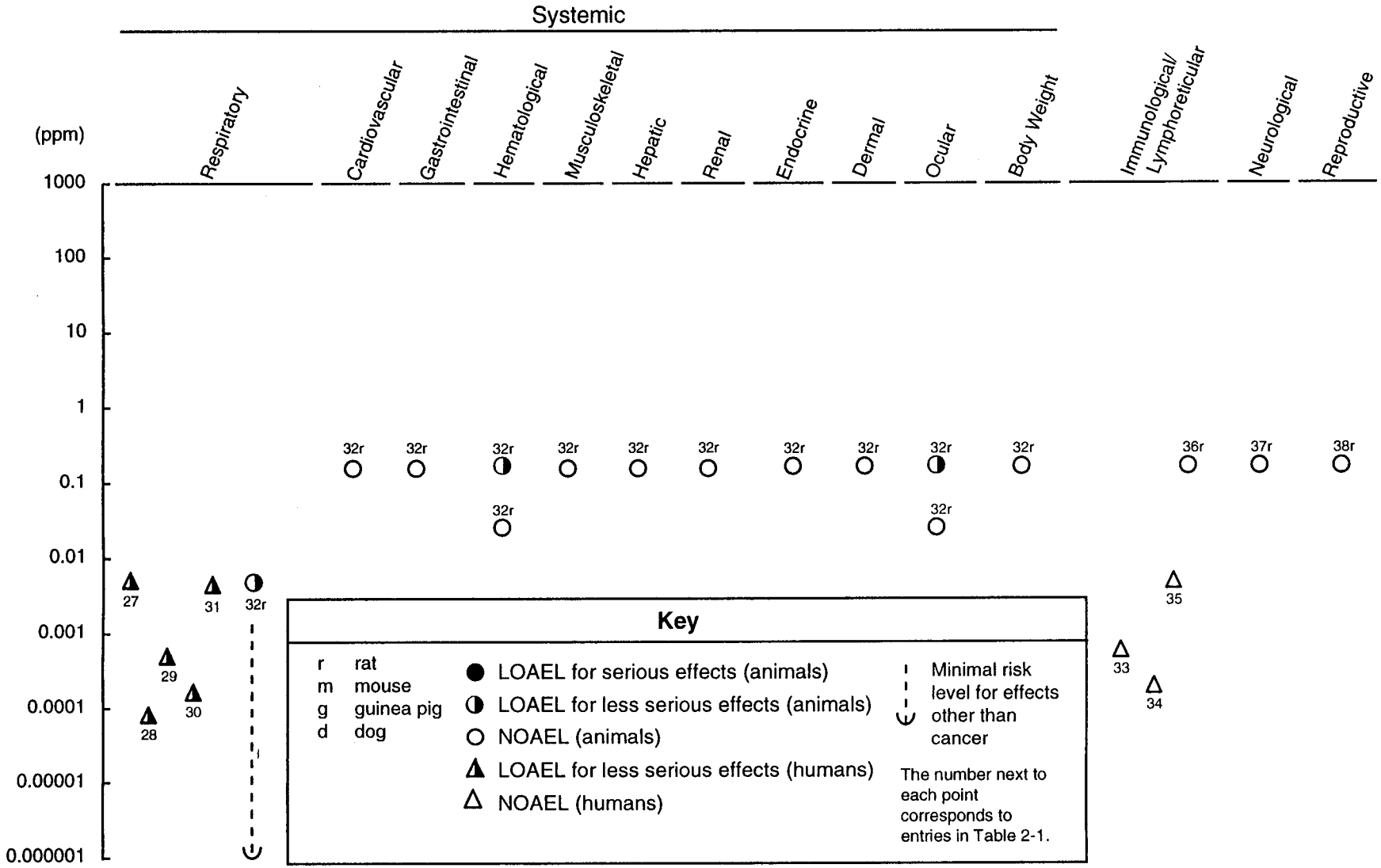


Figure 2-1. Levels of Significant Exposure to Hexamethylene Diisocyanate - Inhalation (cont.)

Chronic (≥365 days)



collected. In an inhalation test exposure to one of the spray paints in which the HDI concentration was measured to be 0.02 ppm (polymeric forms of HDI were not measured), no abnormalities in clinical signs or lung parameters were noted during the first hour after exposure. At one hour, a burning sensation began to occur in his chest, followed by a cough, and a drop in FVC (but no change in FEV_1/FVC ratio). A productive cough was later noted with progression to chills, headache, and malaise at the third hour after exposure. The man was prostrate at 6 hours after exposure. Other clinical signs included bibasal inspiratory crackles and an increase in body temperature, an elevated white blood cell (WBC) count, and a normal chest radiograph. Lung functions at 6 hours after exposure showed decreased TLC and VC, while FRC was higher. Six hours after exposure, clinical signs improved. One day after exposure, lung volumes and FEV_1 also improved. This report suggested that the HD1 and/or the HDI prepolymer is capable of inducing both an alveolar reaction (characterized by fever, inspiratory crackles, elevated WBC count and a drop in PaO_2) and a bronchial reaction (characterized by drops in FEV_1/FVC ratio and an increase in FRC). The reaction was classified as a late obstructive and restrictive breathing defect after exposure to HDI (Malo et al. 1983).

Another case involving an auto spray painter who was assumed to have been exposed to HDI was reported. He worked most of his life as a spray painter (primarily of automobiles). The worker spent about 25-33% of his time spraying paint on vehicles in a poorly ventilated shop, but he did wear a respirator with an outside air supply. At one point during his work he began to notice shortness of breath, chest tightness and wheezes, and dry cough, but no nasal problems. Symptoms occurred shortly after he began spraying paint and would generally worsen through the night. Attacks could persist for a week before resolving. The worker identified three paints that he had used that seemed to contribute the most to his symptomatology, all three of which had a hardener consisting of dimeric HDI. The worker was challenged by breathing 0.0034 ppm HDI for 15 minutes, 0.0167 ppm for 15 minutes, and 0.007 ppm for 60 minutes and respiratory parameters (FEV, and methacholine challenge) were measured. The study failed to induce a bronchoconstriction response in the worker after exposure to HDI. Challenge with methacholine induced a 20% decline in FEV, after 340 units; however, a subsequent challenge with methacholine following all of the HDI exposures gave a 20% decline in FEV_1 with 360 units. These . results indicated that the worker had a mild broncho-hyperresponsiveness which did not change significantly after exposures to HDI. Either the worker is not allergic to HDI and/or the HDI dimer, or the worker is allergic to just the HDI dimer, which went undetected in this study because the patient was not tested with the dimer (Tulane Medican 1982a). The authors also indicate that the worker was involved in the preparatory bodywork prior to spray painting for which he used epoxy resins which he

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both applied and sanded. It has been lmown for a considerable time that many amine curing agents for epoxy resins are skin sensitizers; some, such as diethylene triamine, have been shown to be sensitizers to both skin and respiratory tract (ACGIH 1994). This study illustrates the difficulty of relating a specific effect in humans to the complex exposure situations often encountered in the workplace.

Short-term pulmonary function studies were performed to determine the daily and weekly changes in pulmonary function of a group of isocyanate/solvent-exposed workers in a urethane molding department (n=17) when compared with non-exposed workers (n=20). The average age was 30 ±7 years for the exposed workers and 35 ±10 years for controls; 47% of the exposed workers were smokers compared to 15% of the controls. Mean personal air samples indicated exposure to 1.55 ±I.63 ppb (approximately 0.002 ppm) HDI in exposed workers compared to 0.67 ±0.25 ppb (approximately 0.0007 ppm) in controls. Mold operators were exposed to both isocyanates and volatile organic compounds (VOC) as the urethane paint was sprayed. While spraying the paint, mold operators wore half-face respirators with cartridges and pre-filters for protection against organic vapors. Gloves, hearing protection, and safety glasses were also worn. Pre- and post-shift pulmonary function tests, including forced vital capacity (PVC), forced expiratory volume in 1 second (FEV_1), and FEV_1% FVC, were performed on 5-7 people from the exposed group and 5-7 people from the control group on the Monday and Friday of each week. All FVC and FEV_1 actual values were above the predicted values. There were no significant differences between groups in pulmonary function parameters. A higher prevalence of respiratory symptoms were reported by controls than exposed workers. There were no significant changes in FVC values for either exposed or control workers during the work shift on Monday or during the workweek. FVC values for female workers in the exposed group did increase during the work shift in comparison to females in the control group, however, this was increase was not considered significant ($p<0.l$). This increase resulted in a significant increase in FVC values for the entire exposed group for Friday in comparison to controls ($p<0.05$). No significant FEV_1 changes were observed. Based upon the workplace survey, it appeared that exposures were well controlled. The authors suggested that this may have contributed to the negative findings. In the same report, a group of workers with similar population characteristics, but with longer-term exposure (minimum of 1 year but not more than 2.5 years) showed a significant long-term reduction in their FVC ($P<0.05$) and FEV_1 ($p<0.00l$). Mean air samples indicated exposure to 0.0010 ±0.0004 ppm HDI, 0.29 ±0.35 ppm HDI polyisocyanate, and 0.00045 ppm in these isocyanate/solvent exposed workers. These changes were not observed in non-exposed or solvent exposed groups. A significantly greater proportion of isocyanate/solvent-exposed workers developed respiratory symptoms than non-exposed (Akbar-Khanzadeh and Rivas 1996).

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Several experimental studies have described the respiratory effects of HDI after acute inhalation exposures in laboratory animals. The acute inhalation toxicity of the aerosols of HDI and various pre-polymer products were tested on male and female Wistar rats exposed to 105, 143,259, 341, 383,443, 575,589, or 719 mg HDI/m^3 (15.3,20.7,37.6,49.4,55.5,64.2, 83.4, 85.4, 104.3 ppm) ininhalationchambers for 4 hours. All HDI-exposed rats exhibited signs of labored breathing at all exposure concentrations. Lung edema and pneumonia were observed upon necropsy (Kimmerle 1976).

Male English smooth-haired guinea pigs were exposed to 0.5 ppm HDI for 6 hours, 1.8 ppm for 2 hours, or 4 ppm for 3 hours. Animals exposed to 1,8 ppm displayed severe respiratory irritation as evidenced by slowed respiratory rate and labored breathing, with high death rates at the highest dose (Karol et al. 1984).

The time-response and concentration-response relationships of HDI as sensory irritants was evaluated in Male Swiss Webster mice (4 per group). Respiratory rates were recorded by plethysmography prior to, during, and following exposure. With the time-response relationships, the response was gradual with time, reaching a first maximum within l0-20 minutes of exposure and continuing to increase slowly, reaching a plateau within 180 minutes. Recovery was rapid with short exposures and very slow for longer exposures, regardless of the level of response induced in each exposure group. For concentration-response relationships, values for HDI that produced a 50% decrease in respiration rate (RD_{50}) were 0.96,0.35,0.35,0.22, and 0.17 ppm for the 10-, 30-, 60-, 120-, and 18Ominute exposures, respectively (Sangha et al. 1981).

The mouse sensory irritation potentials of HDI, toluene-2,4diisocyanate (TDI), isocyanatoethyl methacrylate (IEM), and isocyanatoethyl propionate (IEP) were determined in another study, Male Swiss albino CD- 1 mice were exposed for a 2minute control period with room air, 3 minutes of exposure to one of 4 isocyanate vapors, then 2 minutes of recovery with room air. The range of concentrations tested were: 0-0.82 ppm for HDI, 0-3.44 ppm for TDI, 0-2.5 1 ppm for IEM, and 0 -l.95 ppm for IEP. The concentration that produced RD_{50} was determined. HDI was determined to be approximately 3 times more irritating than TDI, IEM, and IEP, with an RD_{50} of 0.36 ppm for a 3-minute exposure. Even though HDI was the most irritating, recovery from exposure was rapid and respiration rate was essentially normal at all test concentrations 2 minutes post-exposure. TDI, IEM, and IEP vapors were similar in sensory irritation potential with RD_{50} values of 1.28 ppm, 1.14 ppm, and 0.98 ppm, respectively, for

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3-minute exposures. Exposed mice recovered slowly from TDI exposure (E.I. DuPont de Nemours 1978).

In another acute study of slightly longer duration, male Fischer 344 rats were exposed to 0.11, 0.18, 0.30, 0.88, 1.75, 2.46, or 5.58 ppm concentration of HDI for 30 minutes. The only clinical signs monitored for HDI-induced respiratory irritation were changes in the average respiratory rate normalized to control rats. The concentration associated with an RD_{50} was calculated using the data obtained from changes in respiratory rates in all exposure groups. The inhalation 30-minute RD_{50} of HDI in rats was calculated to be 1.42 ppm, with 95% confidence intervals from 1.03 to 2.09 ppm, with a correlation coefficient of 0.99. Overall, the time-response curves showed that the onset of the response was rapid, with a major decrease in respiratory rate occurring within the first 5 minutes. After this time, tolerance to HDI was observed, manifested by slow increases in respiratory rates, but still considerably lower than those observed in control animals. The pattern was most clear at the middle concentration tested (1.75 ppm). Decreases in average respiratory rates were dose-dependent, ranging from 2 to 66% (Mobay Corporation 1982).

Male albino ChR-CD rats were exposed to 5, 11,26,27, or 370 ppm HDI for 4 or 8 hours. When rats were exposed to 370 ppm, they died after 2-3 hours of exposure. Prior to death, rats showed signs of irritation, gasping, and convulsions. Tracheitis, pleural effusion, and small areas of pulmonary hemorrhage were observed, but were not considered extensive enough to cause death. Rats survived a 4-hour exposure to 72 ppm but showed severe respiratory impairment, cyanosis, and signs of respiratory irritation during exposure. The respiratory impairment progressed to labored breathing and gasping during the exposure. Bronchopneumonia and bronchiectasis were observed in all of the rats exposed to this HDI concentration when sacrificed 14-16 days later. Rats also survived exposure to 27 and 26 ppm for 4 and 8 hours, respectively, but showed similar, though less severe, clinical and histopathological signs of toxicity. Rats exposed to 11 ppm for 4 hours showed the same, though less severe, clinical signs of toxicity seen at higher concentrations without tissue changes (Haskell Laboratory 1961).

In another study of longer duration, 4 male albino ChR-CD rats were exposed to 30 ppm HDI for 4 hours daily for 10 days over a 2-week period. In the 2 rats that died (one during the 8th exposure and the other 6 days after the last exposure), bronchitis with purulent obstruction of some bronchial branches was observed in the rat that died during exposure; bronchopneumonia was observed in the other dead rat. Respiratory impairment was observed, which included labored breathing and irritation (Haskell Laboratory 1961).

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Male albino Sprague-Dawley rats were exposed to HDI air concentrations of 3, 4, 6, 11,22,44, or 88 ppm for 6 hours. Surviving animals were kept as long as 15 days after the single exposure, with some animals sacrificed between 0 and 15 days after exposure to determine lung damage due to HDI toxicity. At all exposure concentrations, except 88 ppm, nasal irritation was observed clinically at the beginning of exposure but did not progress during the exposure period. Gross necropsies showed hemorrhagic areas of the lungs in rats exposed to 88 ppm HDI. Animals sacrificed at timed-intervals up to 2 weeks after exposure found no histopathological changes in the lung related to HDI exposure in the 3,4, 6, 11, 22, or 44 ppm exposure groups; however, in the one rat that died immediately after exposure to 44 ppm of HDI, lung changes were limited to moderate congestion. The rats that died at 88 ppm exposure to HDI had moderate to severe pulmonary edema and congestion which may be indicative of acute irritation and/or heart failure (Dow Chemical Co. 1964).

HDI exposures have also been conducted in dogs. Two female Beagle dogs were exposed to <2 ppm of HDI 6 times (2 hours each) over a 10-day period (the frequency between exposures was not reported). Average HDI concentrations were 0.28, 0.32, 0.39, 0.55, 0.89, and 1.07 ppm for each trial. Severe nose, throat, and eye irritation was observed in the dogs at all concentrations of HDI tested (0.27-l.43 ppm). Generally, the severity of these signs of irritation was directly correlated to the inhaled HDI concentration. Recovery was complete by the end of each exposure day (Haskell Laboratory 1961).

A study by Ferguson et al. (1987) reported on HDI polymer exposure for acute-duration periods. In one study, groups of male English short-haired guinea pigs were exposed to 8-121 mg/lm^3 (0.4-6.2 ppm) HDI trimer for 3 hours by inhalation. Tidal volume and respiratory frequency were measured during inhalation of room air (5 minutes before and after challenge) and during a 7-minute challenge with 10% CO, in 20% O_2 and 70% N, as indicators of ventilatory response. Particle sizes had a mass median diameter of 0.38 pm at low concentrations of HDI polymer and 0.73 pm at high exposures, with 98% of all particles (by weight) measuring <3 μm. Four animals were exposed to 22 mg/m^3 (1.l ppm) and 84 mg/m^3 (4.3 ppm) HDI trimer for 3 hours per day for one exposure, challenged with CO_2 immediately after exposure; 7 hours after exposure, the animals were sacrificed, and the lungs and trachea removed and weighed. Another set was exposed identically, sacrificed at 24 hours, and organs extracted and weighed. The animals displayed a concentration-dependent increase in respiratory rate and decrease in tidal volume when challenged with CO_2 as well as coughing and apnea. Their ventilatory response to 10% CO_2 was abnormal and characteristic of a lung restriction response. Some airflow limitation was seen during expiration, but this occurred more often during air breathing than during CO_2 challenge. No

significant changes in lung weights were noted in either exposure group compared to controls exposed to acetone only or to controls exposed to air only. Similar decreases in respiratory rates were found in male Swiss Webster mice acutely exposed to 1.3-6.7 ppm HDI trimer (Weyel et al. 1982).

In the same study (Ferguson et al. 1987), groups of 4 male English short-haired guinea pigs were exposed to HDI trimer via inhalation for 3 hours per day for 5 or 11 consecutive days. On days 12 and 13, the animals received no exposure or challenge and then were exposed for 3 hours on day 14. A final exposure was performed on day 25. The exposure concentration during the 5-day exposure ranged from 27.5 to 34.4 mg/m^3 (1.4 ppm-1.8 ppm) and during the 1l-day exposure ranged from 65.1 to 74.4 mg/m^3 ((3.3-3.8 ppm). Tidal volume and respiratory frequency were measured during inhalation of room air (5 minutes before and after challenge) and during a 7-minute challenge with 10% CO_2 in 20% O_2 and 70% N_2, as indicators of ventilator-y response as before. With daily exposures repeated for 11 consecutive days, guinea pigs began to adapt to the exposures as indicated by a return to a normal ventilator-y response to CO_2. This adaptation occurred within the first 5 days of exposure, with a maximum change in tidal volume and respiratory frequency occurring 24 hours after the first exposure. From days 6 to 11, there was a demonstrable effect, but the level of response was much less than that following the first exposure. No cumulative effect could be demonstrated. No significant changes in lung weights were noted in either exposure group compared to controls.

One clinical report of a human exposed to HDI for an intermediate-duration was reported. A 60-year-old male automobile paint sprayer was examined following health complaints, which included shortness of breath, a productive cough, and an intermittent fever (usually about 6 hours after he finished work) of l-month duration. Symptoms were reported to subside on weekends. He had used paint materials containing HD1 for about one month and had worked without a protective mask. Clinical signs were noted to have begun when he started to use a paint containing HDI. A chest X-ray taken after exposure showed diffuse ground-glass infiltrates, with focal fine nodular infiltrates. A transbronchial lung biopsy revealed chronic inflammatory cells diffusely infiltrating the lung interstitium and cellular bronchiolitis. Non-necrotizing granulomas were not found. Increased number of activated cytotoxic T lymphocytes in the bronchoalveolar lavage fluid (BALF) were also discovered. A gradual improvement in his symptoms was observed once the worker began wearing a mask containing activated charcoal during exposure to HDI (Usui et al. 1992).

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Compared to the acute studies, there are fewer reported studies on the toxicity of inhaled HDI for an intermediate-duration in laboratory animals. Male and female Sprague-Dawley rats were exposed (head-only) to HDI vapors at average concentrations of 0.005, 0.0175, 0.15, or 0.3 ppm for 5 hours a day, 5 days a week for 3 weeks. Five animals per sex per exposure concentration were sacrificed at the end of the exposure period; the balance of the animals were allowed a 2-week period to recover from the exposures and then sacrificed. All animals exposed to all concentrations of HDI exhibited varying degrees of irritation of eyes and/or noses during exposure and at 1 hour post-exposure, with all animals appearing normal the following morning. No clinical signs of toxicity were observed during the nonexposure days (weekends). All animals exposed to 0.15 ppm were sneezing during the last week of exposure while the animals exposed to 0.3 ppm started to sneeze at the end of the first week of exposure and then sneezed randomly during the second and third week of exposure. The author attributed the sneezing to a local and severe irritation of the nasal cavity. The severity of the irritation in the animals exposed to the 0.005 ppm level was similar to that of controls (slightly irritated eyes and/or noses at 1 hour post-exposure). Histologic changes in the nasal cavity, trachea, and larynx were noted. Changes in the nasal tract included hemorrhage, inflammatory exudate, and epithelial changes; the epithelial changes varied from vacuolation and disruption of epithelial cells to a more chronic squamous metaplasia, characterized by a loss of cilia and change from the normal ciliated pseudostratified columnar cell type to a more flattened (squamous) type of epithelium with minimal-to-mild keratinization. Changes in the larynx included focal accumulations of inflammatory cells in the submucosa and a minimal-to-mild hyperplasia of the epithelium. The nasal changes occurred in a dose-related manner. At 0.3 ppm, 80-90% of the animals were affected with moderate severity, while at 0.15 ppm, 50-70% were affected with a slightly milder severity. At 0.005 and 0.0175 ppm, the changes were minimal-to-mild in severity and similar to controls, even though the incidence was slightly higher in the 0.0175 ppm males. The severity of the changes in the trachea and larynx was not dose-related (Mobay Corporation 1984). The NOAEL of 0.005 ppm was used to derive an intermediate-duration inhalation MRL of $3.0x10^{-5}$ ppm.

Fischer 344 rats were exposed to 0, 0.011, 0.041, or 0.143 ppm HDI in air for 6 hours a day 66-69 days over a period of approximately 13 weeks. Animals were exposed to HDI in 2-cubic-meter-chambers (whole body). All rats were sacrificed at week 14. Rhinorrhea and ocular opacity were observed in all groups of rats tested, including control animals, and animals did not exhibit a concentration-dependent response. No compound-related toxic effects were noted by changes in lung weights or lung weight to body weight ratios at gross necropsy. Although many histopathologic lesions were found in the many organs examined in this study, the only lesions attributable to HDI toxicity (at 0.143 and 0.041 ppm

doses only) were hyperplasia and/or squamous metaplasia, mucous cell hyperplasia and inflammation in the anterior nasal cavity of both sexes of rats. The author determined that the health effects of HDI at an inhaled concentration of 0.011 ppm in rats were very mild, and that this concentration could be considered to be a threshold level (Mobay Corporation 1988).

Chronic-duration inhalation exposures to HDI in humans are a more frequently reported phenomenon, exhibiting mixed results on health effects. Exposure to low doses of HDI over long periods of time have shown no changes in respiratory function. In one study at a plant in Freeport, Texas, a matched casecontrol epidemiologic study was undertaken to determine if chronic exposure to HDI resulted in an added decline in respiratory function above what is expected from aging alone. Workers were identified as having a potential for HDI exposure (n=30) or not (controls, n=30) and then matched according to age, height, smoking history, sex and race. All subjects were male. The average age for HDI-exposed workers was 37.7 ± 8.7 years versus 36.9 ±7.8 years for controls. One-third of all HDI-exposed and control workers fell into the categories of current smokers, previous smokers, or having never smoked. The mean annual change on pulmonary function tests results, including forced vital capacity (FVC), forced expiratory volume in 1 second (FEV_1), and mean forced expiratory flow during the middle half of FVC ($FEF_{25-75\%}$) were compared statistically. No estimation of an average exposure for workers potentially exposed to HDI was reported. However, the authors speculated that the actual average exposures, when considering the protection from respirators, was below 5 ppb. No statistically significant differences in pulmonary function tests were observed among the workers with potential HDI exposure and controls. The authors noted a number of study design flaws, including a small sample, a large variance in pulmonary function test values, inability to define an exposure dose, and malfunctioning of the industrial hygiene monitoring devices (interference from high humidity and NO_x from welding fumes). Also, radio frequency emissions from portable radios adversely affected personal dosimetry measuring devices, which also gave falsely high readings (Shepperly and Hathaway 1991).

In a related study, a matched case-control epidemiologic study to determine if chronic exposure to HDI resulted in an added decline in respiratory function above what is expected from aging alone was undertaken again at a plant in Freeport, Texas from 1988 to 1991 (see Shepperly and Hathaway 1991). This report added data from additional pulmonary function tests obtained in 1991, 1992, and 1993. Workers were again identified as having a potential for HDI exposure (n=41) or not (controls, n=43) and were matched according to age and smoking history. All subjects were male. The average age for HDI-exposed workers was 42.6 years versus 35 years for controls. The smoking history of HDI-exposed

was 34% current smokers, 37% previous smokers, and 29% never smoked. The smoking history of control was 40% current smokers, 26% previous smokers, and 35% never smoked. Area monitoring estimated HDI levels of 7, 5.4, 3.4, 2.3, 4.7, and 0.5 ppb for 1988, 1989, 1990, 1991, 1992, and 1993, respectively. Personal monitoring of HDI levels ranged from 0.7 to 3.9 ppb in HDI-exposed workers in 1992 and 0.6-l .8 ppb in 1993. Again, no statistically significant differences in incidence of respiratory complaints or in pulmonary function tests were observed among the workers with potential HDI exposure and controls. As in the Shepperly and Hathaway (1991) study, a major limitation of this study was the inability of the authors to define a dose for the HDI-exposed workers during this 5-year period. According to the authors, workers may have been exposed to air concentrations of HDI ranging from 7 ppb in 1988 to 0.5 ppb in 1993. A number of air samples were taken each year; however, no data were provided as to the variance between air samples taken each year in the areas where the HDI workers were exposed; only mean values were supplied. Respirators worn by some of the exposed workers may have further decreased the actual amounts of HDI breathed in. No estimates of dose was provided by the authors for the workers using the respirators (DeWilde and Hathaway 1994).

Other studies have indicated respiratory effects from chronic exposure to HDI. The radioallergosorbent test (RAST) method and skin tests were used to evaluate the significance of type I sensitization, its incidence, and relationship to respiratory dysfunctions in a large population of isocyanate-exposed workers. A group of 62 1 workers engaged in isocyanate processing for a period of 2 weeks to 40 years were studied. Sex of the workers was not reported. Of these workers, 183 had contact with TDI; 66 with diphenylmethane diisocyanate (MDI); 82 with HDI; 220 with a combination exposure of TDI, MDI, and "other aromatic isocyanates;" 30 with a combination of TDI, MDI, and HDI; and 32 with other isocyanates. Air concentration data (where available) tended to range from 0.02 to <0.005 ppm, indicating very low exposures to these isocyanates. Of the 621 workers in this study, 247 were considered symptomatic for isocyanate exposure, exhibiting clinical signs such as bronchial asthma, chronic obstructive pulmonary decrease (COPD), nonobstructive bronchitis, rhinitis, conjunctivitis, urticaria/erythema, eczema, pyrexia, and hypersensitivity pneumonitis. Most workers had more than one of these symptoms simultaneously. Of these 247 workers, 212 were RAST negative (i.e., no detectable levels of IgE antibodies to any of the isocyanates tested). The remaining 35 workers (14% of symptomatic workers) were symptomatic for isocyanate exposure and were RAST-positive; only 1 worker was RAST-positive and asymptomatic. These 35 workers suffered more frequently than RAST negative symptomatic workers from bronchial asthma, rhinitis, conjunctivitis ($p<0.0l$), urticaria/ erythema, and hypersensitivity pneumonitis. Nonobstructive bronchitis was significantly more

frequently associated with negative RAST results. Frequencies of COPD, eczema, and fever were not remarkably different in positive and negative RAST groups (Baur et al. 1984).

Alexandersson et al. (1987) studied the clinical signs and changes in lung function parameters of 3 groups of garage workers to HDI and HDI-BT (HDI-biuret trimer). Average duration of employment was 7 years. Group 1 consisted of 41 male car painters exposed to several diisocyanates, but mostly to HDI and HDI-BT. The hardener sprayed onto surfaces and containing the HDI compounds contained 40-50% HDI-BT and 0.5-l% unreacted HDI. Car platers were the second group, consisting of 48 males exposed to high amounts of dust (but not isocyanates) but usually equipped with masks. The third group was the control group composed of car mechanics (70 males) who were not considered to be exposed to HDI or other related diisocyanate compounds. All groups were subjected to lung function testing parameters periodically, including forced vital capacity (FVC), forced expiratory volume after 1 second ($FEV_{,,,}$ maximum mean expiratory flow (MMV), and nitrogen washout with subsequent calculations of phase III and closing volume (volume expired after the onset of phase IV, the departure of the nitrogen level from the alveolar plateau). The mean exposure to HDI-BT through car painting was 115 $\mu g/m^3$ (0.006 ppm) (range, l0-385 $\mu g/m^3$ [0.0005-0.0197 ppm]). Nine ofthe 43 painters had exposures below 90 $\mu g/m^3$ (0.0046 ppm), 13 had exposure values between 90-180 $\mu g/m^3$ (0.0046-0.0092 ppm), and 9 had exposures between 180-360 $\mu g/m^3$ (0.0092-0.0184 ppm). Two workers had exposures in excess of 360 $\mu g/m^3$ (0.0184 ppm). High short-time exposure peaks of up to 13,500 $\mu g/m^3$ (0.6897 ppm) were also noted in this study. Results of a questionnaire indicated that eye, nose, and throat irritation occurred more frequently in car painter and car platers than in controls, but the difference was significant for car platers only. Although many lung parameters were measured, the only significant difference in values was found in the percentage of closing volume (%CV) for car painters compared to controls the Monday before the work week began, where %CV was significantly higher ($p<0.003$) for car painters than in controls. This difference was attributed to an effect on the small airways and could fit with the small airways disease associated with other diisocyanate exposures. The %CV increased as the work week progressed (2.6%), lending more validity to this observation.

A follow-up study of these garage workers was performed by Tornling et al. (1990). At the time of this study, the mean duration of employment was 16.5 years. Group 1 consisted of 36 of the 46 male car painters examined in 1978. These workers had been exposed to several diisocyanates, but predominately to HDI and HDI-BT. Within this group, 28 worked as painters during the entire 6-year period between studies. The second group consisted of 115 of the 142 male controls examined in 1987; these workers

were mainly car platers and mechanics and may have been exposed to high amounts of dust (but usually while equipped with masks), but not to HDI or to other related diisocyanate compounds. These groups were further divided based upon smoking history (current and ex-smokers versus those who never smoked). Among those who never smoked, 9 were car painters and 27 were controls; among current or former smokers, 27 were car painters and 115 were controls. Exposure was assessed for the 28 who worked as painters for the entire 6-year period. Both groups were again subjected to lung function tests, performed during the first 3 hours of a working day, which included forced vital capacity (FVC), forced expiratory volume after 1 second (FEV_1), FEV% ($FEV_{1/}$FVC x l00), maximum mean expiratory flow (MMF), and nitrogen breath washouts with subsequent calculations of phase III and closing volume (volume expired after the onset of phase IV, the departure of the nitrogen level from the alveolar plateau). IgG and IgE levels were also analyzed in all workers, with IgE antibodies specific to isocyanates analyzed only in the group of painters. Exposure calculations indicated that the painters had a mean exposure of 0.0015 mg/m^3 (0.0002 ppm) HDI and 0.09 mg/m^3 (0.005 ppm) HDI-BT. Painters reported a statistically significant higher frequency of wheezing than did controls for both the neversmoked category ($p<0.01$) and the current or ex-smoker category ($p<0.05$). Other airway and eye symptoms were reported more frequently among car painters than among controls; however, the differences were not statistically significant. Among the current and former smokers, decreases in $FEV_{1,}$ VC, and FVC over the 6-year period were significantly greater in the painter groups versus controls ($p<0.05$,$p<0.01$, and $p<0.00$l, respectively). Among those who never smoked, the decrease in lung function over the 6-year period was similar for painters and controls. Among those workers continuously employed as painters during the 6-year period, the number of yearly peak exposures was significantly correlated with decrease in FVC ($p<0.05$); however, the decrease in FVC was correlated with main exposure levels. None of the painters had IgE specific to isocyanates. Six painters and 20 controls had IgE levels above reference (122 kilo units/litre), while none of the painters and 10 of the controls had IgG levels exceeding reference values (19.9 g/L). However, the workers studied were exposed to a combination of diisocyanates, particularly HDI and HDI-BT, so it was not possible to determine which chemical form was responsible for the symptomatology and clinical signs.

Another study (Grammar et al. 1988) evaluated (using a questionnaire) a group of 149 men and 1 woman who worked with HDI to determine any clinical illness associated with HDI exposure and via blood antibody production to both HDI and the HDI trimer. This population worked in a factory that spraypainted trucks with paint containing HDI and HDI trimer. The authors classified each person as to a particular task (laborer, plumber, paint mixer, spray painter, etc.), had each fill out questionnaires about

clinical symptomology, took blood samples periodically for antibody determination, and sampled the ambient air in their work environment for HDI and HDI trimer concentrations over an IS-month period. Serum samples were analyzed via an enzyme-linked immunosorbent assay (ELBA) for antibodies to HDI and/or HDI trimer. Mean levels of exposure for both HDI and HDI trimer seemed to be extremely variable. For the HDI, the levels were <0.08-3.8 μg/m^3 (0.00001-0.0006 ppm), while for HDI trimer the mean exposure levels were 5.3-75 μg/m^3 (0.0003-0.004 ppm) among all classifications of work, with mean duration of exposure ranging from 24 to 5 1 months. HDI trimer seemed to be the main exposure concern for this group of workers. Eighteen workers reported at least one respiratory system symptom on their questionnaire; however, only one person developed symptoms that were compatible with work-related respiratory disease; that worker also had no antibody response to either HDI or HDI trimer, with the symptoms clearing after relocating to another area of the plant.

Only one chronic-duration inhalation study was identified in laboratory animals exposed to HDI. In that study, male and female Fischer 344 rats were exposed to 0,0.005, 0.025, or 0.175 ppm HDI. HDI-related histopathological changes were limited to the nasal cavity and lungs. Lung lesions included minimal-tomild focal to multifocal lesions, classified as epithelialization (alveolar lining cell proliferation), interstitial pneumonia (septal thickening, alveolar cellular content, and increased alveolar ling cell prominence), and alveolar macrophage accumulation (histiocyte cells in alveolar space). The authors considered there to be an exposure-related incidence of these lesions in the rats (both sexes) exposed to 0.025 and 0.175 ppm of HDI. Histopathological lesions within the nasal cavity were numerous; however, only a few were considered to be a direct effect of HDI inhalation exposure. Lesions observed in the 0.175 ppm exposure group included degeneration of the olfactory epithelium, characterized by hyperkeratosis, occasional atrophy, and focal erosion or ulceration; these lesions were not present at lower exposure concentrations. Other lesions in the nasal cavity that occurred due to HDI exposure in the 0.025 and 0.005 ppm exposure groups included hyperplasia/metaplasia, mucus hyperplasia, and inflammation. Combining information obtained from a satellite group of rats exposed to HDI at identical concentrations but for a l-year duration instead of 2 years. After 1 year of exposure, an adaptive nasal epithelial response (mucus secretory cell and epithelial hyperplasia) was observed in females at the lowest dose (0.005 ppm) and males at the highest dose (0.175 ppm). At the 0.025 and 0.175 ppm concentrations, a progression from this response occurred, exhibited as hyaline droplet degeneration, hyperkeratosis, chronic inflammation, and olfactory epithelial damage. After 2 years, an adaptive response at the lowest concentration occurred, characterized by hyperplasia/metaplasia and hyaline droplet degeneration. At the 0.025 and 0.175 ppm concentrations, a progression of the lesions noted in

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the l-year exposure group at the same dose of HDI was also noted (Mobay Corporation 1989). A chronic inhalation MRL of $1.0x10^{-5}$ ppm was derived, based on nasal cavity epithelial hyperplasia in female rats (minimal LOAEL) .

Cardiovascular Effects. No studies were located regarding cardiovascular effects in humans after inhalation exposure to HDI.

Based on the few laboratory animal studies available, the cardiovascular system does not appear to be a target organ system for HDI toxicity. No studies were located regarding cardiovascular effects in animals following acute-duration inhalation exposure. Groups of 10 male and 10 female rats were exposed (head-only) to HDI vapors at average concentrations of 0.005, 0.0175, 0.15, or 0.3 ppm for 5 hours a day, 5 days a week for 3 weeks. Five animals per sex per exposure concentration were sacrificed at the end of the exposure period; the balance of the animals were allowed a 2-week recovery period and then sacrificed. No significant changes in heart weights or histopathology were observed at any dose of HDI (Mobay Corporation 1984).

In another study of intermediate-duration, Fischer 344 rats were exposed to 0, 0.011, 0.041, or 0.143 ppm HDI in air for 66-69 days for 6 hours per day over a period of approximately 13 weeks. Animals were exposed to HDI in 2-cubic-meter chambers (whole body). All rats were sacrificed during week 14. No compound-related toxic effects were noted by changes in heart weights or heart weight to body weight ratios at gross necropsy. Histopathologic evaluation of the cardiovascular tissue was also conducted, and no compound-related effects were found (Mobay Corporation 1988).

In a chronic-duration study, groups of 60 male and 60 female Fischer 344 rats were exposed to 0, 0.005, 0.025, or 0.175 ppm HDI over a 2-year period. At gross necropsy at the end of the study, many non-HDI body organ weight changes were noted; however, there were increases in the relative heart weights in the 0.175 ppm HDI treated females. Although these organs had increased weight compared to controls, the values were still within accepted control range values and not considered an effect of HDI inhalation exposure. Histopathologic evaluation of the cardiovascular tissue was also conducted and no-compoundrelated effects were found (Mobay Corporation 1989).

Gastrointestinal Effects. No studies were located regarding gastrointestinal effects in humans after inhalation exposure to HDI.

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Based on the few laboratory animal studies available, the gastrointestinal tract does not appear to be a target organ system for HDI toxicity. Two female Beagle dogs were exposed to <2 ppm of HDI 6 times (2 hours each) over a 10-day period. The length of time between exposures was not reported. Average HDI concentrations were 0.28, 0.32, 0.39, 0.55, 0.89, and 1.07 ppm for each trial. These dogs were reported to cough up foamy material (not specified if this material was from the lung or stomach), and vomiting was observed. Generally, the severity of these signs of toxicity correlated with the inhaled HDI concentration. Recovery was complete by the end of each exposure day, and no other clinical effects were observed, based on rectal temperature, weight, or general condition (Haskell Laboratory 1961).

In another acute-duration exposure using higher concentrations of HDI, groups of 4 male albino ChR-CD rats were exposed to 5, 11, 26, 27, 72, or 370 ppm HDI for 4 or 8 hours. The only pathology attributed to HDI toxicity observed at sacrifice was chronic gastritis in 2 rats exposed for 4 hours to 26 ppm HDI. Rats exposed to 11 ppm for 4 hours showed clinical signs of toxicity seen at higher concentrations, but no tissue changes were noted in the gastrointestinal tract. No histopathological effects were observed in rats exposed to 5 ppm for 4 hours (Haskell Laboratory 1961).

In an intermediate-duration study, groups of 10 male and 10 female Sprague-Dawley rats were exposed (head-only) of HDI vapors at average concentrations of 0.005, 0.0175, 0.15, or 0.3 ppm for 5 hours a day, 5 days a week for 3 weeks. Five animals per sex per exposure concentration were sacrificed at the end of the exposure period; the remaining animals were allowed a 2-week recovery period and then sacrificed. No clinical signs of toxicity were observed during the non-exposure days (i.e., weekends). No statistically significant changes in gross pathology or in the gastrointestinal organ weights were observed at any of the inhalation doses of HDI (Mobay Corporation 1984).

In a chronic-duration study, groups of 60 male and 60 female Fischer 344 rats were exposed to 0, 0.005, 0.025, or 0.175 ppm HDI over a 2-year period. Control rats were sham-exposed rats (conditioned air exposure). No significant changes in absolute or relative gastrointestinal tract organ weights were found (Mobay Corporation 1989).

Hematological Effects. No studies were located regarding hematological effects in humans following intermediate- or chronic-duration inhalation exposure to HDI. Several case reports were available that described some hematological effects of HDI after acute-duration inhalation exposures. In one report, a 35-year-old male who sprayed his car with a polyurethane paint containing prepolymerized

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HDI and also 1.6% or less of a monomer of HDI in a poorly ventilated workshop on 3 separate occasions over the span of about a year, experienced several adverse clinical signs. Within 15 minutes after beginning one painting, a cough, tight chest, and chills occurred and progressed into a serious asthmatic reaction, for which he was admitted into an intensive care unit the following day. Respiratory signs, such as dyspnea, prolonged expirations, and crepitating rales, were observed. Blood gases showed hypoxia; however, no fever, leucocytosis, or eosinophilia was observed, indicating no hematological effects due to HDI exposure were detected (Belin et al. 1981).

In another report, the occurrence of respiratory effects in a 34-year-old male working as a spray painter was investigated. He had no previous history of lung disease and was otherwise in good health. After ruling out a possible immunologic trimellitic anhydride (TMA) hemorrhagic pneumonitis, the possibility of HDI-induced asthma was considered. After the paint (containing the monomer HDI, as presumably the biuret form as well) was sprayed on a warm metal surface, the worker subsequently developed an acute illness, including hemoptysis, dyspnea, bilateral pleuritic chest pain, and bilateral pulmonary opacities, which then progressed to respiratory failure. White blood cells were elevated at 14,500, with the cell differential showing 8 lymphocytes, and 1 mono and 91 segmented neutrophils. Recovery occurred with the assistance of corticosteroid therapy, suggesting an allergic reaction had occurred (Patterson et al. 1990).

Another case involved a 56-year-old male who worked as a foreman in a garage where painting was performed. One of the paints used contained 7% polymeric HDI to which he was exposed intermittently for 5-6 years. During that time, episodes of shortness of breath, wheezing, malaise, and chills were reported. Symptoms tended to occur in the late afternoons of working days and lasted for several hours. An inhalation challenge to the paint the worker was using was performed; HDI concentration was measured in the room during exposure at 0.02 ppm (polymeric forms of HDI were not measured in this study). In addition to respiratory signs of an asthmatic reaction beginning to occur 1 hour after exposure began, an elevated WBC count from a blood sample taken 3 hours after exposure began was noted (WBC count = 18,700, 60% segs, 1% eosinophils); however, a chest radiograph at that time was normal (Malo et al. 1983).

Based on these few human case reports, it appears that the major hematological effect, if present, incurred by inhalation of HDI (either monomer or monomer and polymeric forms) is a mild leucocytosis without eosinophilia.

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In an acute-duration inhalation exposure study, groups of 4 male albino ChR-CD rats were exposed to 5, 11, 26, 27, 72, or 370 ppm HDI for 4 or 8 hours. Rats survived a 4-hour exposure to 72 ppm but showed severe respiratory impairment and cyanosis during exposure. No other hematologic pathology was described (Haskell Laboratory 1961).

In studies of intermediate-duration, groups of 10 male and 10 female rats were exposed (head-only) to HDI vapors at average concentrations of 0.005, 0.0175, 0.15, or 0.3 ppm for 5 hours a day, 5 days a week for 3 weeks. Five animals per sex per exposure concentration were sacrificed at the end of the exposure period; the remaining animals were allowed a 2-week recovery period and then sacrificed. No significant differences in blood chemistry and hematology were observed compared to control animals for both male and female rats (Mobay Corporation 1984). Similarly, Fischer 344 rats were exposed to 0, 0.011, 0.041, or 0.143 ppm HDI in air for 6 hours per day for 66-69 days over a period of approximately 13 weeks. Animals were exposed to HDI in 2-cubic-meter chambers (whole body). All rats were sacrificed at week 14. Hematology and blood chemistry were performed to determine the lesions that might be associated with HDI inhalation exposure at these doses. No compound-related changes in blood chemistry and hematology were found (Mobay Corporation 1988).

In a chronic-duration study, groups of 60 male and 60 female Fischer 344 rats were exposed to 0, 0.005, 0.025, or 0.175 ppm HDI over a 2-year period. Control rats were sham exposed rats (conditioned air exposure). Hematologically, the only effect that HDI may have had was an increase in the number of reticulocytes at sporadic intervals during the study in both males and females exposed to the 0.164 ppm concentration of HDI, suggesting anemia. No statistically significant HDI exposure-related changes in serum chemistry were noted (Mobay Corporation 1989).

Based on the data found in all of these laboratory animals studies, the bone marrow appears not to be a system significantly affected by inhalation exposure at the low concentrations of HDI tested.

Musculoskeletal Effects. No studies were located regarding musculoskeletal effects in humans after inhalation exposure to HDI.

No studies were located regarding musculoskeletal effects in animals after acute-duration inhalation exposure to HDI. A study by Mobay Corporation (1984), using male and female Sprague-Dawley rats exposed to 0.005-0.3 ppm HDI for 5 hours a day, 5 days a week for 3 weeks, failed to produce

musculoskeletal lesions at the highest dose tested. Similarly, Mobay Corporation (1989) found that in male and female Fischer 344 rats exposed to HDI concentrations ranging from 0.005 to 0.175 for 6 hours a day, 5 days a week over a 2-year period, no musculoskeletal lesions could be found at gross necropsy or during histopathologic examinations at the end of the study period.

Hepatic Effects. No studies were located regarding hepatic effects in humans after inhalation exposure to HDI.

No studies were located regarding hepatic effects in animals following acute-duration inhalation exposure to HDI. The only notable change in laboratory animals was decreased liver weights at 0.3 ppm in female rats. In that study, groups of male and female rats were exposed (head-only) to HDI vapors at average concentrations of 0.005, 0.0175, 0.15, and 0.3 ppm for 5 hours a day, 5 days a week for 3 weeks. At an HDI exposure concentration of 0.3 ppm, a statistically significant decrease in liver absolute and relative weights in female rats only was observed in those animals sacrificed immediately after the 3-week exposure was completed. Male rats exposed to 0.3 ppm HDI failed to show a significant decrease in the relative and absolute liver weights. No significant changes in gross pathology or histopathology of the liver were found in either sex (Mobay Corporation 1984).

In another study of intermediate-duration, Fischer 344 rats were exposed to 0, 0.011, 0.041, or 0.143 ppm HDI in air 6 hours per day for 66-69 days over a period of approximately 13 weeks. Animals were exposed to HDI in 2-cubic-meter chambers (whole body). All rats were sacrificed during week 14. No compound related toxic effects were noted by changes in liver weights or liver weight to body weight ratios at gross necropsy (Mobay Corporation 1988).

In a chronic-duration study, groups of 60 male and 60 female Fischer 344 rats were exposed to 0,0.005, 0.025, or 0.175 ppm HDI over a 2-year period. At gross necropsy at the end of the study, many non-HDI related body organ changes were noted; however, there were no increases in the relative liver weights in the 0.175 ppm HDI treated females (Mobay Corporation 1989).

Renal Effects. No studies were located regarding renal effects in humans after inhalation exposure to HDI.

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No studies were located regarding renal effects in animals following acute-duration inhalation exposure to HDI. The only notable changes in the kidneys of laboratory animals were in decreased organ weights at 0.3 ppm in both male and female rats and increased urinary ketone concentrations in male rats at a lower dose of HDI. Groups of male and female Sprague-Dawley rats were exposed (head-only) to HDI vapors at average concentrations of 0.005, 0.0175, 0.15, or 0.3 ppm for 5 hours a day, 5 days a week for 3 weeks. Five animals per sex per exposure concentration were sacrificed at the end of the exposure period; the remaining animals were allowed a 2-week period recovery period and then sacrificed. At an HDI exposure concentration of 0.3 ppm, a statistically significant decrease in absolute and relative kidney weights in male and female rats was observed in those animals sacrificed immediately after the 3-week exposure was completed. No other statistically significant changes in kidney weights were observed at any of the lower inhalation doses of HDI. No significant changes in the gross pathology or histopathology of the kidney were found (Mobay Corporation 1984).

Fischer 344 rats were exposed to 0, 0.011, 0.041, or 0.143 ppm HDI in air for 6 hours per day for 66-69 days over a period of approximately 13 weeks. Animals were exposed to HDI in 2-cubic-meter chambers (whole body). All rats were sacrificed at week 14. After exposures ended, urine analysis in male rats exposed to 0.041 ppm HDI showed a statistically significant increase in urinary ketone concentration. No other compound-related induced urine changes were noted. No compound-related toxic effects were noted by changes in kidney weights or kidney weight to body weight ratios at gross necropsy. No HDI-related histopathologic lesions were noted in the kidney of the treated rats (Mobay Corporation 1988).

Groups of 60 male and 60 female Fischer 344 rats were exposed to 0, 0.005, 0.025, or 0.175 ppm HDI over a 2-year period. Control rats were sham-exposed rats (conditioned air exposure). No HDI-related lesions were found at gross necropsy or during histopathologic examination (Mobay Corporation 1989).

Endocrine Effects. No studies were located regarding endocrine effects in humans after inhalation exposure to HDI.

No studies were located regarding endocrine effects in animals following acute-duration inhalation exposure to HDI. A study by Mobay Corporation (1984), using male and female Sprague Dawley rats exposed to exposed to 0.005-0.3 ppm HDI for 5 hours a day, 5 days a week for 3 weeks, failed to reduce endocrine organ lesions at the highest dose tested. Similarly, Mobay Corporation (1989) found

that in male and female Fischer 344 rats exposed to HDI concentrations ranging from 0.005 to 0.175 for 6 hours a day, 5 days a week over a 2-year period, no endocrine organ lesions could be found at gross necropsy or during histopathologic examinations at the end of the study period.

Dermal Effects. No studies were located regarding dermal effects in humans after inhalation exposure to HDI.

No studies were located regarding dermal effects in animals following acute-duration inhalation exposure to HDI. A study by Mobay Corporation (1984), using male and female Sprague Dawley rats exposed to 0.005-0.3 ppm HDI for 5 hours a day, 5 days a week for 3 weeks, failed to produce dermal lesions at the highest dose tested. Similarly, Mobay Corporation (1989) found that in male and female Fischer 344 rats exposed to HDI concentrations ranging from 0.005 to 0.175 for 6 hours a day, 5 days a week over a 2-year period, no dermal lesions could be found at gross necropsy or during histopathologic examinations at the end of the study period.

Ocular Effects. No studies were located regarding ocular effects in humans after inhalation exposure to HDI.

Ocular toxicity via vapor exposure to HDI has been reported and is somewhat milder than when HDI is placed directly into the eyes (see Section 2.2.3). Two female Beagle dogs were exposed to <2 ppm of HDI 6 times (2 hours each) over a lo-day period. The length of time between exposures was not reported. Average HDI concentrations were 0.28,0.32,0.39,0.55,0.89, and 1.07 ppm for each exposure. Severe nose, throat, and eye irritation (including lacrimation) was observed in both dogs at all concentrations of HDI tested (0.27-1.43 ppm) with the severity of these signs of irritation generally correlated to the inhaled HDI concentration. Recovery was complete by the end of each exposure day, and no effects were observed based on rectal temperature, weight, or general condition (Haskell Laboratory 1961).

In other acute-duration studies, groups of 4 male albino ChR-CD rats were exposed to 30 ppm HDI for 4 hours daily for 10 days over a 2-week period. A slit-shaped opacity of the cornea (clinically interpreted to be a comeal ulcer) of one eye was reported in one rat that died after exposure had ended (Haskell Laboratory 1961). In another study, male rats (strain not specified) were exposed for 6 hours to an unlmown air concentration of HDI. The investigators estimated that 0.4% of the HDI in a bubbler was

potentially evaporated, but total air flow through the chamber was not measured, so that it is not possible to precisely calculate the air concentration of HDI inhaled by the test animals. Animals were observed for behavioral changes for 10 days after exposure. All animals survived exposure and the lo-day observation period. The authors concluded that HDI was mildly toxic. The fumes were moderately irritating to the conjunctiva of the eye soon after the start of exposure (Mobay Corporation 1966).

For intermediate-duration studies, Fischer 344 rats were exposed to 0, 0.011, 0.041, or 0.143 ppm HDI in air for 6 hours per day for 66-69 days over a period of approximately 13 weeks. Animals were exposed to HDI in 2-cubic-meter chambers (whole body). All rats were sacrificed at week 14. Ocular opacity was observed in all groups of rats tested, including control animals, and did not exhibit a concentration-dependent response; the only compound-related clinical sign was ocular irritation with subsequent lacrimation (Mobay Corporation 1988).

Male and female Sprague-Dawley rats were exposed (head-only) to HDI vapors at average concentrations of 0.005,0.0175,0.15, or 0.3 ppm for 5 hours a day, 5 days a week for 3 weeks. Five animals of each sex per exposure concentration were sacrificed at the end of the exposure period; the remaining animals were allowed a 2-week recovery period and then sacrificed. All animals exposed to all concentrations of HDI exhibited varying degrees of irritation of eyes and/or noses during exposure and at 1 hour post-exposure, with all animals appearing normal the following morning (Mobay Corporation 1984).

In a chronic-duration study, groups of 60 male and 60 female Fischer 344 rats were exposed to 0,0.005, 0.025, or 0.175 ppm HDI over a 2-year period. Control rats were sham-exposed rats (conditioned air exposure). HDI caused eye irritation in males exposed to the 0.175 ppm dose only during the first year of the study but not during the second year. No other HDI-related eye lesions were detected during ophthalmologic examinations performed during the 2-year study (Mobay Corporation 1989).

Metabolic Effects. No studies were located regarding metabolic effects in humans following intermediate or chronic-duration inhalation exposure to HDI.

One report described a case of a 56-year-old man who worked as a foreman in a garage where automobile painting was performed and consequently was exposed intermittently to paints containing HDI for 5-6 years. He reported having developed respiratory and systemic reactions after exposure to paints (which contained 7% polymeric HDI) used in the garage. Episodes of shortness of breath, wheezing,

malaise, and chills were reported, with symptoms occurring in the late afternoons of working days and lasting for several hours thereafter. In an attempt to confirm that HDI was the compound responsible, the man was removed from the garage environment for several weeks and then exposed to an inhalation test exposure to one of the spray paints in which the HDI concentration was measured to be 0.02 ppm (polymeric forms of HDI were not measured. No abnormalities in clinical signs were noted during the first hour after exposure. During the third hour of exposure, chills, headache, and malaise were noted, with the man prostrate at 6 hours after exposure (Malo et al. 1983).

No studies were located regarding metabolic effects in animals following intermediate- or chronicduration inhalation exposure to HDI. No effect on rectal temperature was observed in 2 female Beagle dogs exposed to <2 ppm of HDI 6 times (2 hours each) over a 10-day period. The length of time between exposures was not reported. Average HDI concentrations were 0.28, 0.32, 0.39, 0.55, 0.89, and 1.07 ppm for each exposure (range, 0.27-l .43 ppm) (Haskell Laboratory 1961).

Body Weight Effects. No studies were located regarding body weight effects in humans after inhalation exposure to HDI.

The body of information available suggests that HDI does little to affect body weight at the concentrations of 0.3 ppm or less, while changes in body weight are marginal at inhaled concentrations of 3 ppm or higher for l-time exposures. To demonstrate this, male albino Sprague-Dawley rats were exposed to HDI air concentrations of 3,4, 6, 11, 22, 44, or 88 ppm for 6 hours. Surviving animals were kept as long as 15 days after the single exposure, with some animals sacrificed between 0 and 15 days after exposure to determine lung damage. Animals exposed to 3 and 4 ppm had an initial weight loss of 10 g when sacrificed at 24 hours after exposure. After exposure to 3-l 1 ppm of HDI, rats showed a slight weight gain of approximately 10 g (about 3%) during the first week after exposure. Rats exposed to 22 and 44 ppm showed a 15-20 g loss of weight (about 6%) during the first week, followed by a recovery to more than their original weight when sacrificed 2 weeks after exposure (Dow Chemical Co. 1964). No effect on body weight was observed in male albino Chrl-CD rats exposed to 300 ppm HDI 4 hours per day for 10 days over a 2-week period (Haskell Laboratory 1961). Similarly, no body weight effects were observed in female Beagle dogs exposed to 0.27 ppm HDI via whole-body inhalation 2 hours per day for 6 days over a 10-day period (Haskell Laboratory 1961). However, severe body weight loss was observed in male albino Chrl-CD rats exposed to 72 ppm HDI after a single 4-hour exposure (Haskell Laboratory 1961).

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Male and female Sprague-Dawley rats were exposed (head-only) to HDI vapors at average concentrations of 0.005, 0.0175, 0.15, or 0.3 ppm for 5 hours a day, 5 day a week for 3 weeks. Five animals of each sex per exposure concentration were sacrificed at the end of the exposure period; the remaining animals were allowed a 2-week period recovery period and then sacrificed. No significant differences in body weights were observed compared to control animals for both male and female rats (Mobay Corporation 1984).

Fischer 344 rats were exposed to 0, 0.011, 0.041, or 0.143 ppm HDI in air for 6 hours per day for 66-69 days over a period of approximately 13 weeks. Animals were exposed to HDI in 2-cubic-meter chambers (whole body). All rats were sacrificed during week 14. Statistically significant increases in body weight were noted after exposure ended in female rats dosed at all 3 concentrations of HDI and in male rats dosed at 0.143 ppm HDI. During the exposure period, no statistically significant weight differences were noted. Since similar findings were noted for control rats, these findings were not considered to be related to HDI treatment (Mobay Corporation 1988).

Male and female Fischer 344 rats were exposed to 0, 0.005, 0.025, or 0.175 ppm HDI over a 2-year period. Decreases in body weight (compared to control animals) were small (only a 5% decrease) but consistent, and were considered to be related to the toxicity of HDI in female rats exposed to the 0.175 ppm dose during the second year of the study only. There were also no statistically significant differences in terminal body weight between controls and exposed male rats at the end of the study (Mobay Corporation 1989).

2.2.1.3 Immunological and Lymphoreticular Effects

In addition to their local irritant effects on the respiratory tract, the diisocyanates also have a propensity to induce an immunological response in some individuals, which is characterized by an asthma-like respiratory reaction, and will induce the formation of antibodies to both the monomeric and polymer forms of HDI. A few studies have examined the immunological effects of HDI toxicity in humans, with some data available from laboratory animal studies as well.

Several studies have reported antibodies being produced in response to an HDI inhalation exposures. In one study, 149 men and 1 woman were selected to prospectively evaluate any clinical signs of illness associated with HDI exposure and, by blood antibody production, to both HDI and HDI trimer. These workers were employed in a factory that spray-painted trucks with paint containing HDI and HDI trimer.

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Questionnaires were distributed that asked about clinical symptomology, blood samples were taken periodically for antibody determination, and the ambient air in their work environment was sampled for HDI and HDI trimer concentrations over an 18-month period. Serum samples were analyzed via an ELISA for antibodies to HDI and/or HD1 trimer. Mean levels of exposure for both HDI and HDI trimer were found to be extremely variable. For the HDI monomer, the levels were between <0.08 and 3.8 $\mu g/m^3$ (0.00001-0.0006 ppm), while for HDI trimer the mean exposure levels were 5.3-75 $\mu g/m^3$ (0.0003-0.0038 ppm) among all classifications of work, with mean duration of exposure ranging from 24 to 51 months. HD1 trimer seemed to be the main exposure concern for this group of workers. The mean indices of IgG and IgE to HDI-human serum albumin (HSA) antibodies were 1.65 and 1.22, respectively; the mean indices of IgG and IgE to HDI trimer-HSA antibodies were 1.63 and 1.19, respectively. Approximately 21% of all workers had a positive antibody response to either of these 2 antigens. There was no significant correlation between any mean antibody levels and mean duration of isocyanate exposure; however, among the plumber/painter exposure group, there were significant positive correlations between exposure duration and IgG antibody to HDI-HSA and HDI trimer-HSA. Eighteen workers reported at least one respiratory system symptom on their questionnaire; however, only one person developed symptoms that were compatible with work-related respiratory disease; that worker also had no antibody response to either HDI or HDI trimer, with the symptoms clearing after relocating to another area of the plant (Grammar et al. 1988).

Another report described a 35-year-old male who used a polyurethane paint containing prepolymerized HDI and 1.6% or less of the monomer of HDI in a poorly ventilated workshop on 3 separate occasions over the span of about 1 year. Cough, dyspnea, prolonged expirium and crepitating rales, and chest tightness, progressing into a serious asthmatic reaction (after the third exposure), were observed. No fever, leucocytosis, eosinophilia, or wheezing was observed. The patient's serum was analyzed with the radioallergosorbent test (RAST) method, and IgE antibodies, particularly to HDI-HSA and to MDI-HSA and, to a lesser extent, TDI-HSA were found. The authors stated that the positive result with MDI and TDI was probably due to cross-reactivity. Six months later, the patient was skin-tested with the prick test method. Common allergens gave negative results. Conjugates of HDI-HSA and MDI-HSA elicited significant wheal and flare reactions (Belin et al. 1981).

High levels of IgG and IgE antibodies were detected against HDI-HSA and TDI-HSA in a 34-year-old male working as a spray painter. Exposure to spray paint that containing HDI and an aliphatic polyisocyanate 1 week prior to the onset of respiratory symptoms was noted, so immunoassays for MDI,

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HDI, and toluene diisocyanate (TDI) conjugated to human serum albumin (HSA) were carried out. Radioimmunoassay RIA) results for IgG and IgE against HDI-HSA were noted: IgG titres were >l:1,000 for HDI-HSA; IgE antibodies against HDI-HSA were also present at a 1:1,000 dilution; results for IgG and IgE against MDI-HSA were negative. Based on the blood antibody data collected, the authors proposed that the pathogenesis of this case of hemorrhagic pneumonitis this man experienced was immunologic in nature because of uncontrolled exposures to HDI and TDI (Patterson et al. 1990).

Relative amounts of specific IgE and IgG in challenge-positive and challenge-negative were determined in workers in another study to determine the specificity of the isocyanate antibodies for hapten-protein conjugates. The study examined 55 workers (sex not specified) who had respiratory symptoms while working with TDI, MDI, or HDI. Sera was obtained from each person and analyzed via an ELISA using human serum albumin conjugates to each isocyanate for relative amounts IgG and IgE antibodies to the above isocyanates using an IgG or IgE index. Each isocyanate was tested against human serum albumin conjugate carrier molecules. Index values of >2 were considered positive to that antibody. Crossreactivity with other isocyanate-protein conjugates (dog serum albumin, ovalbumin, etc.) was also demonstrated and the degree of cross-reactivity varied with the individual. None of the TDI workers were found to have a positive IgE index for TDI-HSA, and only two of the six workers were found to have positive IgG indices for TDI-HSA. None of the 11 MDI workers had a positive IgE index, but 4 of the 11 workers had positive IgG indices. Eight of the 38 HDI workers had a positive IgE index, and 21 of 38 workers had positive IgG indices to HDI-HSA (Grammar et al. 1990). These results suggest that the antibody formed is directed against the combined complex formed by HDI and tissue protein, rather than against either fraction alone.

RAST and skin tests were used to evaluate the significance of type I sensitization, its incidence, and its relationship to respiratory dysfunctions in a large population of isocyanate-exposed workers. A group of 621 workers (sex not specified) engaged in isocyanate processing for a period of 2 weeks to 40 years was studied. Of these workers, 183 had contact with TDI; 66 with MDI; 82 with HDI; 220 with a combination exposure of TDI, MDI, and “other aromatic isocyanates;” 30 with a combination of TDI, MDI and HDI; and 32 with other isocyanates. Air concentration data (where available) tended to range from <0.005 to 0.02 ppm, indicating very low exposures to these isocyanates. Of the 247 workers with clinical symptomology (symptomatic workers) related to HDI toxicity, 212 were RAST negative (i.e., no detectable levels of IgE antibodies to any of the isocyanates tested); the remaining 35 workers (14% of symptomatic workers) were symptomatic for isocyanate exposure and were RAST-positive (only

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1 worker was RAST-positive and asymptomatic). The 35 RAST-positive workers suffered more frequently than RAST negative symptomatic workers from bronchial asthma, rhinitis, conjunctivitis ($p<0.0l$), urticaria/erythema, and hypersensitivity pneumonitis. Nonobstructive bronchitis was significantly more frequently associated with negative RAST results. Frequencies of chronic obstructive pulmonary disease (COPD), eczema, and fever were not remarkably different in positive and negative RAST groups. Of the 35 RAST-positive workers, 27 cases were positive for HDI; all but one worker (worker #12) showed positive RAST results to other isocyanates in addition to HDI. Fifty-three symptomatic workers underwent skin testing for specific isocyanate testing; five workers gave positive skin test results (wheal-and-flare reaction) for the HDI-HSA conjugate. The authors concluded that: (1) the existence of an immunologically mediated type 1 sensitization to isocyanate components is supported by the observed clinical symptomatology after inhalation challenge and RAST results, and (2) for routine investigations and for follow-up studies, RAST and skin testing with isocyanate-HSA conjugates appear to be suitable methods for detecting immunologically sensitized workers. The failure to detect isocyanate antibodies in the sera of symptomatic workers may indicate the involvement of other non-immunologic mechanisms, such as a local effect of the isocyanate on the lung tissue (binding to certain proteins and enzymes) that alters lung function and may induce the clinical symptoms associated with isocyanate-induced lung disease (Baur et al. 1984).

A 60-year-old male automobile paint sprayer was examined following health complaints of shortness of breath, productive cough, and intermittent fever of l-month duration, about when he began using paint containing HDI. Increased number of activated cytotoxic T lymphocytes in the bronchoalveolar lavage fluid (BALF) and an increased percentage and absolute number of non-major histocompatibility complex-restricted natural killer cells in the peripheral blood during the recovery phase of hypersensitivity pneumonitis were discovered. The total number of cells was markedly elevated and the differential counts of lymphocytes and neutrophils were increased. ELISA revealed that IgG and IgA antigen-specific antibodies to TDI and HDI were present in BALF and the serum (Usui et al. 1992).

Increased levels of specific IgG antibodies against HDI-HSA and MDI-HSA were demonstrated in a 56-year-old male, who worked as a foreman in a garage where one or more of several paints containing 7% polymeric HDI were used. The man reported that he had developed respiratory and systemic reactions after exposure to HDI after a history of being intermittently exposed to paint containing HDI for 5-6 years. During that period of time, episodes of shortness of breath, wheezing, malaise, and chills were reported. Symptoms tended to occur in the late afternoons of working days and lasted for several

hours. Upon initial physical exam, no chest anomalies were found. To confirm that HDI was the compound responsible, the man was removed horn the garage environment for several weeks and lung parameters were measured, including FEV_1, FVC, VC, FRC, and TLC. Body temperature and blood samples were also collected. Inhalation HDI challenge was performed. No reactions were noted when the man was challenged with enamel or air. After being challenged with HDI for 5 minutes (air concentrations measured to be 0.02 ppm), he developed general malaise, cough, fever, and leukocytosis beginning 3 hours after exposure, together with a mixed restrictive and obstructive breathing defect (Malo et al. 1983).

No studies were located regarding immunological and lymphoreticular effects in animals following acute-duration inhalation exposure to HDI. For laboratory animal studies, the data is mainly limited to the investigation of changes in lymphoreticular organs. Male and female Sprague-Dawley rats were exposed (head-only) to HDI vapors at average concentrations of 0.005, 0.0175, 0.15, or 0.3 ppm for 5 hour a day, 5 day a week for 3 weeks. No statistically significant difference in the weight or gross pathology of the spleen was observed, when compared to control animals, for both male and female rats (Mobay Corporation 1984). Similarly, male and female Fischer 344 rats were exposed to 0, 0.011, 0.041, or 0.143 ppm HDI in air for 6 hours per day for 66-69 days over a period of approximately 13 weeks. All rats were sacrificed at week 14. There were no changes in the relative or absolute weight of spleen at gross necropsy (Mobay Corporation 1988).

In a chronic-duration study, male and female Fischer 344 rats were exposed to 0, 0.005, 0.025, or 0.175 ppm HDI for a 2-year period. At gross necropsy, many non-HDI-related body organ changes were noted; however, there were increases in the relative weight of the spleen in the 0.175 ppm HDI treated females, with an increase in absolute spleen weight as well. Although the spleen had an increased weight compared to controls, the values were still within the accepted control range and not considered an effect of HDI inhalation exposure (Mobay Corporation 1989).

The highest NOAEL values and all LOAEL values from each reliable study for immunological and lymphoreticular effects in each species and duration category are recorded in Table 2-l and plotted in Figure 2-1.

2.2.1.4 Neurological Effects

No studies were located regarding neurological effects in humans after intermediate-duration inhalation exposure to HDI. One report described a case of a 56-year-old man who worked as a foreman in a garage where automobile painting was performed and consequently was exposed intermittently to paints containing HD1 for 5-6 years. He reported having developed respiratory and systemic reactions after exposure to paints (which contained 7% polymeric HDI) used in the garage. Episodes of shortness of breath, wheezing, malaise, and chills were reported, with symptoms occurring in the late afternoons of working days and lasting for several hours. In an attempt to confirm that HDI was the compound responsible, the man was removed from the garage environment for several weeks. The man was then exposed to an inhalation test exposure to one of the spray paints in which the HDI concentration was measured to be 0.02 ppm (polymeric forms of HDI were not measured). No abnormalities in clinical signs were noted during the first hour after exposure. At three hours, a productive cough with headache and malaise was reported. The man was prostrate at six hours after exposure (Malo et al. 1983).

Few neurological toxicities after inhalation exposures to HD1 could be identified in laboratory animals. In an acute-duration study, groups of 4 male albino ChR-CD rats were exposed to various concentrations of HDI for 4 or 8 hours. When rats were exposed to 370 ppm from a bubbler of HDI warmed to 40-50 ºC, they died after 2-3 hours of exposure, with irritation and convulsions observed prior to death. However, mechanical difficulties with the exposure apparatus may have contributed other factors that might have been responsible for the convulsions and eventual death of these animals (Haskell Laboratory 1961).

Other neurological aberrations have been reported in laboratory animals. Groups of 4-6 male English smooth-haired guinea pigs were exposed to 0.5 ppm HDI for 6 hours, 1.8 ppm for 2 hours, or 4 ppm for 3 hours. Erythrocyte acetylcholinesterase and plasma cholinesterase were determined prior to and during HDI exposures. Pulmonary cholinesterase was determined from bronchial lavage fluid after animals were sacrificed. Enzyme levels were not significantly different ($P<0.05$) from controls. Although some of the animals exposed to HDI displayed severe respiratory irritation, slowed respiratory rate and labored breathing, and 50% of the animals died at the 4 ppm dose level, no inhibition of serum cholinesterase or erythrocyte acetylcholinesterase activity was detected following any of the exposures (Karol et al. 1984).

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A study by Mobay Corporation (1984), using male and female Sprague Dawley rats exposed to 0.005-0.3 ppm HDI for 5 hour a day, 5 day a week for 3 weeks, failed to produce any neurological lesions at the highest dose tested. In a study by Mobay Corporation (1988), male and female Fischer 344 rats dosed with HDI in concentrations ranging from 0.011 to 0.143 ppm for 6 hour a day, 5 day a week for 66-69 days showed no clinical neurological effects or neurological lesions at gross necropsy or during histopathological examinations. In a later study by Mobay Corporation (1989), male and female Fischer 344 rats were exposed to HDI concentrations ranging from 0.005 to 0.164 ppm for 6 hour a day, 5 day a week over a 2-year period. Again, no clinical neurological effects or neurological lesions could be found at gross necropsy or during histopathologic examinations at the end of the study period.

The highest NOAEL values and all LOAEL values from each reliable study for neurological effects in each species and duration category are recorded in Table 2- 1 and plotted in Figure 2-l.

2.2.1.5 Reproductive Effects

No studies were located regarding reproductive effects in humans after inhalation exposure to HDI.
No studies were located regarding reproductive effects in animals after acute-duration inhalation exposure to HDI. No reproductive tract effects could be identified in laboratory animals exposed to inhalation doses of HDI. A study by Mobay Corporation (1984), using male and female Sprague Dawley rats exposed to 0.005-0.3 ppm HDI for 5 hour a day, 5 day a week for 3 weeks, failed to produce lesions in any of the male or female reproductive organs at the highest dose tested. In a study by Mobay Corporation (1988), male and female Fischer 344 rats dosed with HDI in concentrations ranging from 0.011 to 0.143 ppm for 6 hour a day, 5 day a week for 66-69 days showed no reproductive organ lesions at gross necropsy or during histopathological examinations. In a later study by Mobay Corporation (1989), male and female Fischer 344 rats were exposed to HDI concentrations ranging from 0.005 to 0.175 ppm for 6 hour a day, 5 day a week over a 2-year period. Again, no reproductive organ lesions could be found at gross necropsy or during histopathologic examinations at the end of the study period.

All LOAEL values from each reliable study for reproductive effects in each species and duration category are recorded in Table 2-1 and plotted in Figure 2-l.

2. HEALTH EFFECTS

2.2.1.6 Developmental Effects

No studies were located regarding developmental effects in humans or animals after inhalation exposure to HDI.

2.2.1.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans or animals after inhalation exposure to HDI.

2.2.1.8 Cancer

No studies were located regarding cancer in humans after inhalation exposure to HDI.

Only one study was identified that described the potential carcinogenic activity in laboratory animals. In that study, groups of 60 male and 60 female Fischer 344 rats were exposed 6 hour a day, 5 day a week for 2 years to 0, 0.005, 0.025, or 0.175 ppm HDI via inhalation. Control rats were sham-exposed (conditioned air exposure). At the end of the 2-year study period, none of the 3 inhaled concentrations of HDI was shown to have an effect on the incidence of cancer in treated rats when compared to control animal populations (Mobay Corporation 1989).

2.2.2 Oral Exposure

There is considerably less information available on the toxicology of HDI after oral exposure compared to the data available on the inhalation toxicology of HD1 discussed in the previous section of this profile. Clearly, inhalation is the major route of occupational exposure to HDI; however, given exposure routes such as the lung mucocilliary clearance pathways, a very small amount of HDI could eventually enter the gastrointestinal tract and be presented for absorption, with possible systemic effects. Most of the information available on the oral absorption of HDI is about relatively large doses of HDI administered to laboratory animals, with no information located on the health effects of HDI in humans after oral exposure.

2. HEALTH EFFECTS

2.2.2.1 Death

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

Death in laboratory animals has been reported in studies of acute-duration; however, no studies were located for oral exposures of an intermediate and chronic-duration to HDI. Based on the information available, large, single megadoses of HDI (i.e., >940 mg/kg) administered to rats orally were associated with increased mortality, while lower single doses (<620 mg/kg) or lower multiple doses were associated with little or no mortality in rats.

Reports of death after an acute oral exposure to HDI in laboratory animals appear in some older toxicological studies on HDI. Rats (sex and strain not specified) received a single oral dose of 280, 420, 620, 940, 1,400, or 2,100 mg/kg of HDI. A single rat was used for each dose level. Rats at the 3 highest doses died within 24 hours of exposure; however, rats at the 3 lower doses survived and were sacrificed 10 days after exposure and examined for lesions. The estimated minimum lethal dose in these rats was calculated to be 940 mg/kg (Haskell Laboratory 1946).

In a later study by the same laboratory, HDI, undiluted or as a 5% solution in peanut oil, was administered via gavage to male albino ChR-CD rats, in single doses from 12 to 3,400 mg/kg. Animals receiving 3,400,2,250, and 1,500 mg/kg died within 2-21 hours. Prior to death, these animals developed pallor, cyanosis, slow and deep breathing, and diarrhea. The approximate lethal dose (ALD) in that study was determined to be 1,500 mg/kg (Haskell Laboratory 1961).

Male albino ChR-CD rats were administered 300 mg/kg HDI in peanut oil (as a 5% solution) via gavage for 10 days over a 2-week period. All rats survived the treatments (Haskell Laboratory 1961).

The LOAEL values resulting in mortality in all species are recorded in Table 2-2 and plotted in Figure 2-2.

2.2.2.2 Systemic Effects

No studies were located regarding cardiovascular, musculoskeletal, hepatic, renal, endocrine, dermal, ocular, or metabolic effects in humans or animals after oral exposure to HDI. The LOAEL values from

Table 2-2. Levels of Significant Exposure to Hexamethylene Diisocyanate - Oral

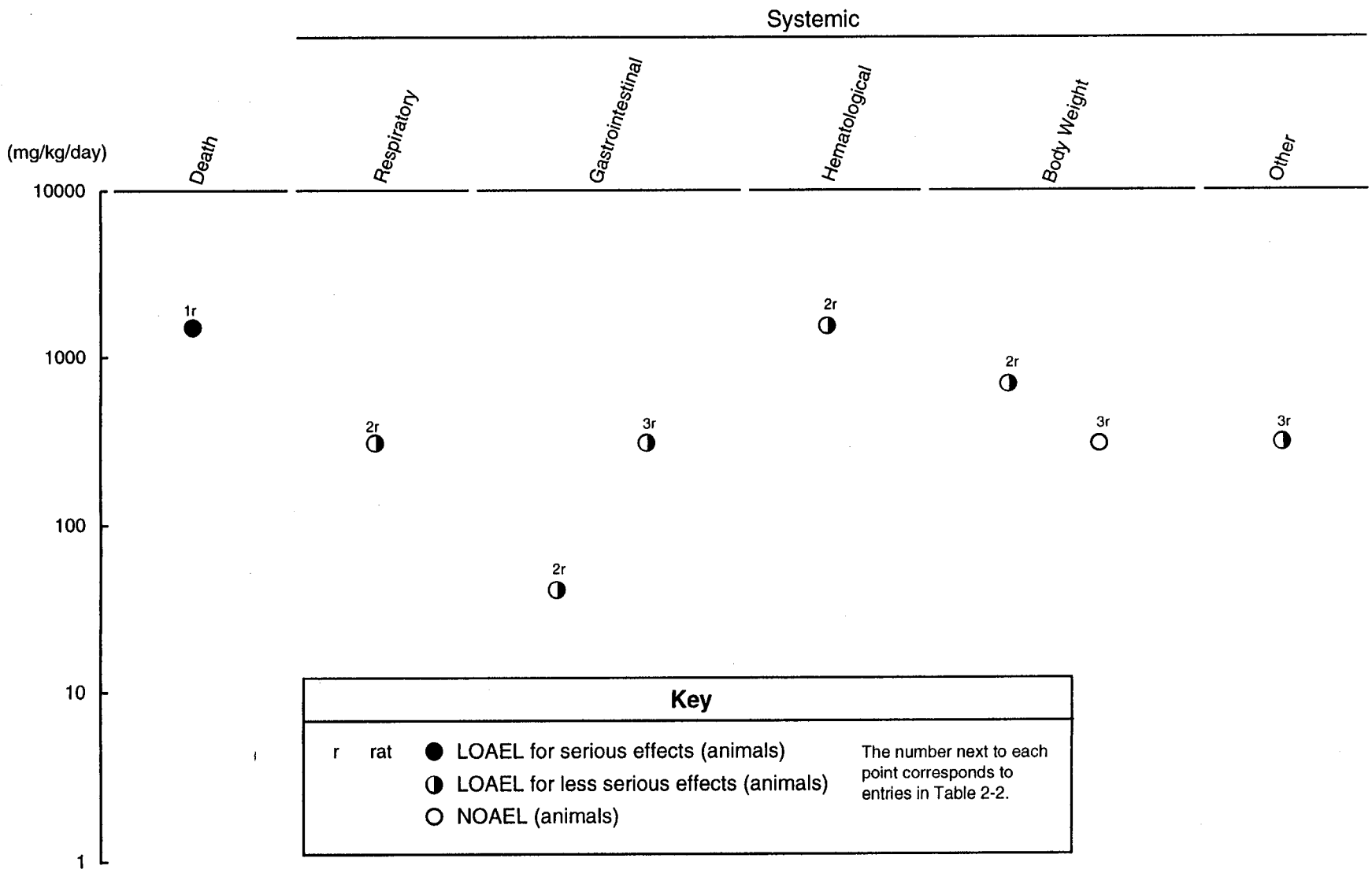
Key to[a] figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
	ACUTE EXPOSURE						
	Death						
1	Rat (CD)	once (G)				1500 M (approximate lethal dose)	Haskell Laboratory 1961
	Systemic						
2	Rat (CD)	once (G)	Resp		300M (slowed respiration)		Haskell Laboratory 1961
			Gastro		40M (diarrhea)		
			Hemato		1500M (cyanosis)		
			Bd Wt		670M (unspecified decreased body weight)		
3	Rat (CD)	2 wk 5 d/wk (GO)	Gastro		300M (ulcerative gastritis, salivation, and diarrhea)		Haskell Laboratory 1961
			Bd Wt	300 M			
			Other		300M (increased water consumption)		

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

Bd Wt = body weight; d = day(s); Gastro = gastrointestinal; (G) = gavage; (GO) = gavage with oil; Hemato = hematological; LOAEL = lowest-observed-adverse-effect level; M = male; NOAEL = no-observed-adverse-effect level; Resp = respiratory; wk = week(s)

Figure 2-2. Levels of Significant Exposure to Hexamethylene Diisocyanate - Oral

Acute (≤14 days)



each reliable study for each systemic effect in each species in the acute-duration category are recorded in Table 2-2 and plotted in Figure 2-2.

Respiratory Effects. No studies were located regarding respiratory effects in humans after oral exposure to HDI.

No studies were located regarding respiratory effects in animals following intermediate- or chronicduration oral exposure to HDI. Based on the available information at hand, the respiratory tract seems to be a target organ of HDI toxicity after oral exposure. Rats (sex and strain not specified) received a single oral dose of HDI, at a dose of 280, 420, 620, 940, 1,400, or 2,100 mg/kg of HDI, with one rat dosed at each dose level. Rats at the 3 highest doses died within 24 hours of exposure; however, the rats at the 3 lower doses survived and were sacrificed 10 days after exposure. The rats that died showed congestion of the lungs and spleen. Rats given the 420 and 620 mg/kg doses showed slight peribronchial edema, but the authors doubted the significance of this finding (Haskell Laboratory 1946).

In another study of acute-duration, HDI, undiluted or as a solution with peanut oil, was administered via gavage to male albino ChR-CD rats, in single doses from 12 to 3,400 mg/kg, one rat per dose level. Rats receiving high sublethal doses of 1,000 and 670, as well as those receiving 450 and 300 mg/kg, were observed to have slowed respiration after dosing (Haskell Laboratory 1961).

Gastrointestinal Effects. No studies were located regarding gastrointestinal effects in humans after oral exposure to HDI.

No studies were located regarding gastrointestinal effects in animals following intermediate- or chronicduration oral exposure to HDI. Male albino ChR-CD rats were administered 300 mg/kg HDI in peanut oil via gavage for 10 days over a 2-week period. Half the animals were sacrificed after the final exposure and half were sacrificed 10 days later. All rats survived treatment; however, some rats showed signs of diarrhea and salivation during treatment. No clinical signs of toxicity were observed during the 10-day post-treatment observation period. Ulcerative gastritis was observed in rats sacrificed immediately after treatment, and healing gastritis was observed in rats sacrificed after the 10-day observation period (Haskell Laboratory 1961). Rats administered a single dose of HDI in peanut oil also showed inflammation of the stomach mucosa and diarrhea at the 60 and 40 mg/kg doses, respectively (Haskell Laboratory 1961).

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Hematological Effects. No studies were located regarding hematological effects in humans after oral exposure to HDI.

No studies were located regarding hematological effects in animals following intermediate- or chronic-duration oral exposure to HDI. Pallor, cyanosis, slow and deep breathing, and diarrhea were observed prior to death in male albino CD rats that were administered a single gavage dose of 1,500, 2,250, or 3,400 mg/kg HDI in peanut oil. These animals died within 2-21 hours of dosing (Haskell Laboratory 1961).

Body Weight Effects. No studies were located regarding body weight effects in humans after oral exposure to HDI.

No studies were located regarding body weight effects in animals following intermediate- or chronicduration oral exposure to HDI. An unspecified decrease in body weight was observed in male albino CD rats that were administered a single gavage dose of 670 mg/kg HDI in peanut oil (Haskell Laboratory 1961). However, no body weight effects were observed in male albino CD rats administered 300 mg/kg HDI in peanut oil by gavage for 10 days over a 2-week period (Haskell Laboratory 1961).

Other Systemic Effects. No studies were located regarding other systemic effects in humans after oral exposure to HDI.

An unspecified increase in water consumption during the second week of exposure was observed in male albino CD rats administered 300 mg/kg HDI in peanut oil by gavage for 10 days over a 2-week period (Haskell Laboratory 1961).

2. HEALTH EFFECTS

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

2.2.2.3 Immunological and Lymphoreticular Effects

2.2.2.4 Neurological Effects

2.2.2.5 Reproductive Effects

2.2.2.6 Developmental Effects

2.2.2.7 Genotoxic Effects

2.2.2.8 Cancer

2.2.3 Dermal Exposure

Dermal exposure to HDI, like oral exposure, is considered to be a secondary route of exposure in humans. Little information is available on the toxicity of HDI applied to skin in either humans or in animals.

2.2.3.1 Death

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

A study by Thorne et al. (1987) described the effects of diisocyanates after topical exposure. The dermal sensitization capabilities HDI and several other isocyanates (TDI, MDI, HDI) in BALB/cBy mice exposed to a variety of topical doses of each isocyanate was performed. Groups of 4-32 male mice were exposed to dermal doses of HDI in acetone. A topical dose of HDI at 2,800 mg/kg was shown to be lethal to 100% of the mice within 16 hours of exposure. No other reports of death after topical exposure to HDI were located.

The LOAEL values resulting in mortality in all species are recorded in Table 2-3.

2.2.3.2 Systemic Effects

No studies were located regarding respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, endocrine, metabolic, or body weight effects in humans or animals after

Table 2-3. Levels of Significant Exposure to Hexamethylene Diisocyanate - Dermal

Species/ (Strain)	Exposure/ Duration/ Frequency	System	NOAEL	LOAEL		Reference
				Less Serious	Serious	
ACUTE EXPOSURE						
Death						
Mouse (BALB/c)	once				2800 M mg/kg (5/5 died within 16 hrs of exposure)	Thorne et al. 1987
Systemic						
Gn Pig (albino)	once	Dermal	0.1% M			E.I. Dupont de Nemours 1977a
Gn Pig (albino)	once	Dermal	0.01% M	0.1% M (slight irritation)		E.I. Dupont de Nemours 1977b
Gn Pig (English)	once	Dermal	0.01 M mg	0.1 mg M (erythema)		Stadler and Karol 1985
Rabbit (albino)	once	Ocular			0.1 mL (severe conjunctival inflammation with serous and hemorrhagic exudates; severe/ moderate corneal injury)	Haskell Laboratory 1961
Rabbit (New Zealand)	once ≥30 sec	Ocular		100 µL M (irritation and damage to the cornea, iris, and conjunctiva)		Mobay Corp. 1981a
Rabbit (New Zealand)	4 hr	Dermal		500 µL M (severe irritation; moderate severe to severe erythema with severe edema)		Mobay Corp. 1981b
Immunological/Lymphoreticular						
Mouse (BALB/c)	once			0.5 (dermal sensitization in 50% of animals)		Karol and Kramarik 1996
Mouse (BALB/c)	once			0.2 M mg/kg (dermal sensitization in 50% of animals)		Stadler and Karol 1985

Table 2-3. Levels of Significant Exposure to Hexamethylene Diisocyanate - Dermal (continued)

Species/ (Strain)	Exposure/ Duration/ Frequency	System	NOAEL	LOAEL Less Serious	LOAEL Serious	Reference
Mouse (BALB/c)	once			0.088 M mg/kg (dermal sensitization in 50% of animals)		Thorne et al. 1987
Gn Pig (English)	once		0.01 M mg	0.1 mg M (skin sensitization)		Stadler and Karol 1985
INTERMEDIATE EXPOSURE						
Systemic						
Gn Pig (albino)	3 wk 9 x	Dermal	0.05%	0.5% M (allergic contact dermatitis)		Haskell Laboratory 1961
Immunological/Lymphoreticular						
Gn Pig (albino)	3 wk 1 x/wk + 3 x/6 wk		0.01% M	0.05% M (dermal sensitization in 4/10 after challenge with HDI; mild and moderate erythema)		E.I. Dupont de Nemours 1977a
Gn Pig (albino)	3 wk 1 x/wk + 2 x/ 4 wk		0.05% M	0.1% M (dermal sensitization in 5/10 after first challenge; mild and moderate erythema)		E.I. Dupont de Nemours 1977b

Gn Pig = guinea pig; hr = hour(s); LOAEL = lowest-observed-adverse-effect level; M = male; NOAEL = no-observed-adverse-effect level; sec = second(s); wk = week(s); x = times

dermal exposure to HDI. The highest NOAEL values and all LOAEL values from each reliable study for each systemic effect in each species and duration category are recorded in Table 2-3.

Dermal Effects. No studies were located regarding dermal effects in humans after dermal exposure to HDI.

The bulk of the studies identified described the acute toxicological effects of HDI topically applied to the skin of animals. Many of these studies described the ability of HDI to be a direct irritant to the skin of laboratory animals at concentrations as low as 0.1%, while fewer studies described HDI's ability to be a dermal sensitizer. No studies were located regarding dermal effects in animals following chronic-duration dermal exposure to HDI.

To demonstrate the ability of HDI to be a direct irritant to the skin, HDI was applied to the non-occluded intact skin of adult male albino guinea pigs either undiluted (100%) or in solutions of 0.05, 0.5, 5, or 25% in 1:1 acetone-dioxane containing 13% guinea pig fat. HDI was demonstrated to produce severe-erythema and edema when applied to the skin at concentrations of 5, 25, and 100%. Application of undiluted material resulted in frank skin necrosis. Moderate irritation to intact skin was noted at the 0.5% HDI dose, while a 0.05% solution failed to produce any perceptible cutaneous irritation response (Haskell Laboratory 1961).

Similar effects were observed by Stadler and Karol (1985). Male guinea pigs were first exposed to a topical sensitizing dose of HDI (total dose approximately 105 mg). Seven days after the initial dose, another topical dose of either 0, 0.01, 0.1, 1, or 10 mg was placed on the skin and examined for erythema for up to 48 hours after this second challenge. Erythema was noted by 8 hours following challenge and reached a maximum intensity at 24 hours after topical exposure. It was found that as the topical dose of HDI increased, the intensity of the erythema scores also increased in a dose-responsive manner. Erythema scores were lowest in the 0.1 mg treatment group and highest in 10 mg treatment group. Erythema ranged from a pale pink color to a bright red cutaneous reaction. The relationship between dose and response was found to be statistically significant ($p<0.05$). No erythema response was noted in the lowest dose treatment group, 0.01 mg.

Another test for primary irritation was conducted by applying and lightly rubbing in 1 drop (approximately 0.05 mL) each of a 0.1% and 0.01% solution (vol/vol) of hexamethylene ester isocyanic

acid (HDI) in acetone on the shaved, intact and non-occluded shoulder skin of 10 male albino guinea pigs. HDI caused slight to no irritation at 24 hours as a 0.1% acetone solution and no irritation at 48 hours. As a 0.01% solution, no irritation was observed (E.I. DuPont de Nemours 1977a, 1977b).

Toxic cutaneous reactions also have been demonstrated in rabbits. Male New Zealand albino rabbits were topically exposed to HDI by covering shaved skin with 2.5x2.5 cm cloths saturated with 500 µL of undiluted HDI and covered with an inert PVC film (i.e., occluded dermal exposure). Duration of exposure was for 4 hours. The skin under the patch was observed immediately following exposure and 24, 48, and 72 hours and 8 days later. HDI was found to be a direct irritant and severely irritating to the skin of rabbits. Moderate to severe erythema and slight scabbing or corrosion was observed in all animals 4 hours after exposure. Severe cutaneous edema was also observed in all but one animal 4 hours after exposure. The application area showed severe congestion and severe skin thickening within 4 hours after topical exposure. The epidermis subsequently underwent a parchment-like change (dry surface necrosis). No gross cutaneous changes were reported 8 days after exposure (Mobay Corporation 1981b).

In an intermediate-duration study, HDI was applied 9 times over a period of 3 weeks to abraded skin of adult male albino guinea pigs in solutions of 0.05-0.5% in 1:1 acetone-dioxane containing 13% guinea pig fat. After a 3-week rest period, a repeat topical challenge test showed that 8 of 9 guinea pigs tested had developed an allergic contact dermatitis to HDI at these concentrations (Haskell Laboratory 1961).

Ocular Effects. No studies were located regarding ocular effects in humans after topical exposure to HDI.

HDI has been demonstrated to be an ocular irritant in laboratory animals in several studies. HDI (0.1 mL, undiluted) was instilled into both eyes of a male albino rabbit. One eye was washed 20 seconds later with large amounts of water, whereas the other eye was not washed. The animal was sacrificed 8 days after treatment. Initially, the exposure caused severe conjunctival inflammation accompanied by serous and hemorrhagic exudates of both eyes, with severe (unwashed eye) or moderate (washed eye) cornea1 injury. When the rabbit was sacrificed 8 days after treatment, the corneas of both eyes appeared dull and the eyelids were inflamed and still showed the hemorrhagic and serous exudates. Healed cornea1 lesions of both eyes and inflammation of the eyelids of the unwashed eye were also observed 8 days after treatment (Haskell Laboratory 1961).

In a similar study, a single application of 100 µL of HDI was placed into the conjunctival sac of the lower lid of both eyes in 6 male New Zealand albino rabbits. The lids were then held together for 1 second after application. The right eye was flushed 30 seconds after the application with saline and the left eye was left unflushed. Eyes were examined for irritation with an ophthalmoscope and fluorescein test (after 1 hour for the right eye and after 24 hours for the left eye). A high level of damage occurred to the cornea, iris, and conjunctiva of both eyes. Detectable gross damage was caused to the eye after only 30 seconds of material contact. Damage to the cornea and iris of both the right and left eyes became more severe as time since exposure increased. Seventy-two hours after exposure, no reflex reaction of the eye to light stimulation was noted, with hemorrhaging, and/or gross destruction of the iris also observed. The conjunctiva of the right and left eyes was inflamed and swollen, and discharge was observed with damage becoming most severe by 24-48 hours and remaining severe throughout the remainder of the study; inflammation was less severe in the left eye than in the right eye. Eight days after exposure, complete cornea1 opacity was observed, with the iris not visible. As in the previous study, HDI as a neat solution was confirmed to be corrosive to the eye when applied directly to the eye and conjunctiva (Mobay Corporation 1981a).

2.2.3.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological and lymphoreticular effects in humans after topical exposure to HDI.

In addition to its toxicity to the respiratory tract in both humans and animals, HDI has also been demonstrated to be a contact skin sensitizer after dermal exposure in laboratory animals. Having seen that other chemicals produce a dose-response relationship to dermal sensitization, Stadler and Karol (1985) determined that such an approach could also be used to observe sensitizing potencies of HDI for simulation of human occupational exposures. Male guinea pigs were first exposed to a topical sensitizing dose of HDI (total dose approximately 105 mg). Seven days after the initial dose, another topical dose of either 0, 0.01, 0.1, 1, or 10 mg was placed on the skin and examined for erythema for up to 48 hours after this second challenge. Erythema was noted by 8 hours following challenge and reached a maximum intensity at 24 hours after topical exposure. It was found that as the topical dose of HDI increased, the intensity of the erythema scores also increased in a dose-responsive manner. Erythema scores were lowest in the 0.1 mg treatment group and highest in 10 mg treatment group. Erythema ranged from a pale pink color to a bright red cutaneous reaction. The relationship between dose and

response was found to be statistically significant ($p<0.05$). No erythema response was noted in the lowest dose treatment group, 0.01 mg.

A similar study also conducted by Stadler and Karol (1985) was performed in mice. Groups of BALB/cBy mice were again exposed to a sensitizing dose of HDI placed on the skin (total dose approximately 105 mg). Five days after the initial topical dose, another dose of 1, 10, 100, or 1,000 µg was placed on the ear, followed by examination for an increase in ear thickness (i.e., swelling) 24 hours later. A general dose-response curve was found for topical doses of HDI from 1 pg up to and including 100 µg HDI, although not as clearly defined as with the companion guinea pig study. As the dose continued to increase above 100 µg, the mean ear thickness began to decrease. Further analysis showed a clear dose-response relationship between the topical doses of 5 and 10 pg. The dose of chemical required to sensitize 50% of the mice (SD_{50}) was calculated to be approximately 0.20 mg/kg.

The dermal sensitization capabilities of HDI and several other isocyanates (MDI, HMDI, and TDI) were determined using BALB/cBy mice exposed to a variety of topical doses of each isocyanate. The study also attempted to determine if one isocyanate would confer dermal reactivity to another isocyanate (i.e., cross-reactivity). Groups of male mice were exposed to dermal doses of HDI and other diisocyanates (separately) in acetone. Animals exposed only to topical doses of acetone served as controls and no dermal reactions were noted in these animals. Dermal reactivity of each dose of HDI was determined by using the Mouse Ear Skin Test (MEST). A dose-dependent increase in ear swelling was observed for mice as the dose of HDI increased. The SD_{50} was calculated to be 0.088 mg/kg (60 times more potent than TDI). The maximum sensitization dose of HDI was 2.80 mg/kg. Exposure of mice to 28 mg/kg gave a comparable dermal response. This study also found that the order of potency for dermal sensitization of the isocyanates tested was: HDI>HMDI>MDI>TDI. With respect to the cross-sensitization potential of HDI with other isocyanates, mice sensitized to a specific isocyanate demonstrated cross-reactions with all dermally applied aromatic or aliphatic isocyanates (including HDI). For all isocyanates tested in this study, the severity of the dermal reactions was greatest when rechallenged with the same isocyanate used for sensitization. Heterologous isocyanate challenges elicited significantly smaller responses than homologus challenges. TDI was the least potent sensitizer, and was the compound least able to evoke a dermal response in mice sensitized to other isocyanates. This study also noted that the aromatic isocyanates (associated most frequently with respiratory sensitization) induced less severe dermal reactions when compared to the aliphatic isocyanates, which are most frequently associated with dermal sensitization (Thorne et al. 1987).

2. HEALTH EFFECTS

The immunologic activity of phenyl isocyanate (PI) was investigated in Balb/c (6-8 weeks old) mice and compared with responses to TDI, MDI, and HDI. The MEST was determined by adding 100 pL containing 0.03-250 pg of the chemical diluted in acetone to the shaven abdomen of mice (n=6/group; sex not specified). Doses of 0.001, 0.004, and 0.024 mmol/kg HDI were used. Four days later, 20 uL of the chemical was applied to each side of the right ear (40 μL) total and an equal volume of acetone was applied to the left ear. The doses used for the challenge application, 40 μg PI and 100 μg HDI, were determined to be nonirritant in pilot studies. Ear thickness was measured at 24 hours following the challenge. A significant response was defined as an increase in ear thickness >2 standard deviations (SD) above the mean response of control animals which had received acetone on the abdomen and were challenged on the ear with isocyanate. Serum IgE was assessed in mice exposed to PI and to TDI, and the specific antibody response to PI was evaluated using ELISA. PI was found to be the most potent isocyanate tested yielding an SD_{50} of 0.04 μmol/Kg, compared with SD_{50} values of 0.5, 2.1, and 30.4 μmol/kg for HDI, MDI, and TDI, respectively. PI was 12 times more potent than HDI (the second most potent chemical), and 760 times more potent than TDI. Antibody titers to PI were more than 10-fold greater than those induced by TDI. The results suggest that PI is a potent inducer of both cellular and humoral immune responses (Karol and Kramarik 1996).

HDI has also been identified as a skin sensitizer in studies of intermediate-duration. To test for sensitization potential, a series of 4 four intradermal injections, once each week over a 3-week period, were administered over the sacral skin area of male guinea pigs. Injection consisted of 0.1 mL of a 1% solution (vol/vol) of HDI in dimethyl phthalate. Following a 2-week rest period, the test animals were challenged for sensitization by applying and lightly rubbing in 1 drop each of a 0.1, 0.05, 0.01, and 0.005% solution (vol/vol) of HDI in acetone on non-occluded, shaved, intact shoulder skin. A group of 10 previously unexposed guinea pigs received similar applications at the time of challenge to provide a direct comparison of the challenge reactions on skin of similar age. After a 2-week rest period, these test animals were rechallenged for sensitization by applying and lightly rubbing in 1 drop of a 0.5 and 0.1% solution of HDI in acetone. Of the animals tested, 50% showed sensitization responses when challenged with a 0.1% acetone solution; mild (5 of 10) and moderate (5 of 10) erythema was observed. Challenge with 0.05, 0.01, and 0.005% did not elicit a sensitization response. A rechallenge with the 0.5% HDI solution showed sensitization in 8 of 10 animals; mild (1 of l0), moderate (1 of l0), and strong (2 of 10) erythema and erythema plus edema (6 of 10) was observed 24 hours after challenge and mild (1 of l0), moderate (2 of l0), and strong (3 of 10) erythema and erythema plus edema (4 of 10) was observed 48 hours after challenge. Rechallenge with 0.1% HDI did not elicit a sensitization response; mild

erythema (5 of 10) was observed at 24 and 48 hours post-challenge. The author concluded that HDI is both a strong skin irritant and sensitizer (E.I. DuPont de Nemours 1977b).

Skin sensitization reactions can also occur with polymers of HDI. To test for HDI's sensitization potential to polymers, a series of 4 intradermal injections was given over the sacral area of the back of male guinea pigs, one each week over a 3-week period. Each injection consisted of 0.1 mL of a 1% solution (vol/vol) of the HDI monomer in dimethyl phthalate. Following a 2-week rest period, the test animals were challenged for sensitization by applying and lightly rubbing in 1 drop each of a 0.1, 0.05, 0.01, and 0.005% solution (vol/vol) of HDI in acetone on the shaved intact shoulder skin. A group of 10 previously unexposed guinea pigs received similar applications at the time of challenge to provide a direct comparison of the challenge reactions on skin of similar age. After a rest period of 1 week, the animals were treated with the HDI polymer, Desmodur N-75, which contained 74% 1,3,5-tris (normal-hexylisocyanate)-biuret and 0.45% free HDI monomer. The polymer had been diluted with acetone to contain 0.1, 0.05, and 0.01% residual monomer. A rechallenge was done after an additional 3-week rest period, and an additional group of previously untreated control animals were added for comparison with previously treated control animals to determine if their previous exposures had caused sensitization. When the polymer containing 0.45% residual monomer (HDI) was diluted with acetone to contain 0.1, 0.05, and 0.01% residual monomer, sensitization responses were elicited in 8 of 9 test animals; 0.01% appeared to be a marginal "no response" level. Mild (4 of 9), moderate (2 of 9), and strong (3 of 9) erythema was observed 24 hours after challenge; and mild (4 of 9), moderate (4 of 9), and strong (1 of 9) erythema was observed 48 hours after challenge with 0.1%. Mild (6 of 9) and strong (1 of 9) erythema was observed 24 hours after challenge and mild (8 of 9) erythema was observed 48 hours after challenge with 0.05%. At this time, 4 of 10 control animals had become sensitized by the single topical exposure to the monomer during the first challenge; mild, moderate, or strong erythema was observed. When rechallenged and compared to previously untreated controls, the sensitization response ratio had increased to at least 6 of 10 of the original controls, with questionable reactions observed in the remaining 4 animals; mild or moderate erythema or erythema plus edema was observed in affected animals.

In rechallenged test animals, mild (3 of 9), moderate (2 of 9) and strong (3 of 9) erythema and erythema plus edema (1 of 9) was observed 24 hours after rechallenge and mild (3 of 9), moderate (5 of 9), and strong (1 of 9) erythema was observed 48 hours after rechallenge with 0.1%. Mild (5 of 9) and moderate (2 of 9) erythema and erythema plus edema (1 of 9) was observed 24 hours after rechallenge and mild

(5 of 9) and moderate (2 of 9) erythema was observed 48 hours after rechallenge with 0.05%. Mild (2 of 9) and moderate (1 of 9) erythema was observed 24 hours after rechallenge and mild (3 of 9) erythema was observed 48 hours after rechallenge with 0.01% (E.I. DuPont de Nemours 1977a). This study demonstrated that HDI monomer may not be the only component in a Desmodur N-75 that can elicit cutaneous sensitization reactions in laboratory animals.

The highest NOAEL values and all LOAEL values from each reliable study for immunological and lymphoreticular effects in each species in the acute-duration category are recorded in Table 2-3.
No studies were located regarding the following effects in humans or animals after dermal exposure to HDI:

2.2.3.4 Neurological Effects

2.2.3.5 Reproductive Effects

2.2.3.6 Developmental Effects

2.2.3.7 Genotoxic Effects

2.2.3.8 Cancer

2. 3 TOXICOKINETICS

Very little information exists on the toxicokinetics of HDI in animals. More information is available on the toxicokinetic and pharmacokinetics of aromatic diisocyanates. Since HDI is an aliphatic diisocyanate, no useful toxicokinetic extrapolations can be applied to derive information about the absorption, distribution, metabolism, and excretion behavior of HDI in animals.

Based on some known properties of HDI in some *in vitro* studies, HDI can be expected to hydrolyze in aqueous media. This hydrolysis process is fairly slow, but is accelerated in the presence of carboxylic acid-containing neutral buffers (Berode et al. 1991), such as are present in biological matrices. Hydrolysis probably begins in the aqueous media lining the trachea and bronchi (inhalation route) or by water and acid hydrolysis (oral route) and continues at an accelerated rate. Because of this hydrolytic action, the toxic potential of HDI (particularly in acute exposures) is directly applicable to its concentration and direct interaction with cellular components at the site of exposure. Absorption of significant amounts of HDI into the general circulation would, therefore, not be expected. Any free HDI

that may reach the blood may bind to serum proteins and not be available as a free form in the blood (Tse and Pesce 1979). No reports were found in the literature that reported detecting blood levels of HDI in humans or animals. The major urinary metabolite of HDI reported in the literature is 1,6-hexamethylene diamine (HDA) (Brorson et al. 1990a, 1990b), with several reported methods for its detection available (Dalene et al. 1990, 1994; Rosenberg and Savolainen 1986). Since little HDI is absorbed, the only toxicokinetic parameters that are readily available in the literature are the absorption and excretion data. No reports on the absorption or metabolism of HDI after topical exposure were available in the literature.

2.3.1 Absorption

Little information was located in the available literature on the absorption of HDI after inhalation, oral, or dermal exposure. Information is limited to one report of oral administration to men (Brorson et al. 1990a). The metabolite of HDI (1,6-hexamethylene diamine, HDA) was not detected in the serum of these men after a 7.5-hour inhalation exposure to HDI (Brorson et al. 1990b).

2.3.2 Distribution

No information was located in the available literature on the distribution of HDI after inhalation, oral, or dermal exposure.

2.3.3 Metabolism

As stated earlier, the major metabolite of HDI in humans appears to be 1,6-hexamethylene diamine (HDA). No information was located in the available literature that specifically addressed the metabolism of HDI after inhalation, oral or dermal exposures.

2.3.4 Elimination and Excretion

2.3.4.1 Inhalation Exposure

Only one study was located in the literature that described the elimination and excretion of HDI after an inhalation exposure. In that study, 5 men (age, 36-50 years; mean age, 42 years) inhaled 95-l 15 µg (0.01-0.02 ppm) of HDI in air (range, 25-29 µg/m^3 or approximately 0.004 ppm) for 7.5 hours. Blood

and urine samples were taken at 2-hour intervals. Beginning almost immediately after exposure, urinary levels of 1,6-hexamethylene diamine (HDA) began to accumulate in the urine. The urinary elimination rates for all men ranged from 1.1 to 1.7 μg/hr, with the average urinary level of I-IDA ranging from 0.01-0.03 mmol/mol creatinine for the S-hour sample and 0.006 mmol/mol creatinine for the 10-hour sample. HDA levels were undetectable by 15 hours after exposure began (or 7.5 hours after exposure ended). The cumulative excretion of HDA over a 28hour period was 8.0-14 μg, which is about 1l-21% of the inhaled dose of HDI. The half-life of HDA in the urine in these men ranged from 1.1 to 1.4 hours (mean = 1.2 hours) (Brorson et al. 1990b).

2.3.4.2 Oral Exposure

Little information was located in the available literature on the elimination of HDI after oral exposure.

One study by Brorson et al. (1990a) was located that described the elimination and excretion of HDA in the urine of men after oral dosing with HDA. Six males were administered an oral dose of 0.1 mg/kg HDA on 2 occasions 3 months apart, and urine was collected for several hours after dosing. Peak amounts of free HDA in single urine samples ranged from 0.080 to 0.19 mg 2-5 hours after dosing. Four of the 6 men tested had no detectable levels of HDA in their urine 10 hours after dosing; however, 2 subjects had detectable levels of HDA in the urine 15 hours after dosing. The elimination half-life was calculated to be approximately 1.5 hours; l-6% of the total HDA dose was recovered in the urine. The authors also noted two pathways by which HDA could be metabolized: (1) to N-acetyl-1,6-hexamethylene diamine, via N-acetyl transferase, and (2) 6-aminohexanoic acid, via diamine oxidase. Both HDA metabolites may appear in the urine.

2.3.4.3 Dermal Exposure

No information was located in the available literature on the elimination of HDI after dermal exposure.

2.3.5 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models

Physiologically based pharmacokinetic (PBPK) models use mathematical descriptions of the uptake and disposition of chemical substances to quantitatively describe the relationships among critical biological processes (Krishnan et al. 1994). PBPK models are also called biologically based tissue dosimetry

models. PBPK models are increasingly used in risk assessments, primarily to predict the concentration of potentially toxic moieties of a chemical that will be delivered to any given target tissue following various combinations of route, dose level, and test species (Clewell and Andersen 1985). Physiologically based pharmacodynamic (PBPD) models use mathematical descriptions of the dose-response function to quantitatively describe the relationship between target tissue dose and toxic end points.

PBPK/PD models refine our understanding of complex quantitative dose behaviors by helping to delineate and characterize the relationships between: (1) the external/exposure concentration and target tissue dose of the toxic moiety, and (2) the target tissue dose and observed responses (Andersen and Krishnan 1994; Andersen et al. 1987). These models are biologically and mechanistically based and can be used to extrapolate the pharmacokinetic behavior of chemical substances from high to low dose, from route to route, between species, and between subpopulations within a species. The biological basis of PBPK models results in more meaningful extrapolations than those generated with the more conventional use of uncertainty factors.

The PBPK model for a chemical substance is developed in four interconnected steps: (1) model representation, (2) model parametrization, (3) model simulation, and (4) model validation (Krishnan and Andersen 1994). In the early 1990s, validated PBPK models were developed for a number of toxicologically important chemical substances, both volatile and nonvolatile (Krishnan and Andersen 1994; Leung 1993). PBPK models for a particular substance require estimates of the chemical substancespecific physicochemical parameters, and species-specific physiological and biological parameters. The numerical estimates of these model parameters are incorporated within a set of differential and algebraic equations that describe the pharmacokinetic processes. Solving these differential and algebraic equations provides the predictions of tissue dose. Computers then provide process simulations based on these solutions.

The structure and mathematical expressions used in PBPK models significantly simplify the true complexities of biological systems. If the uptake and disposition of the chemical substance(s) is adequately described, however, this simplification is desirable because data are often unavailable for many biological processes. A simplified scheme reduces the magnitude of cumulative uncertainty. The adequacy of the model is, therefore, of great importance, and model validation is essential to the use of PBPK models in risk assessment.

PBPK models improve the pharmacokinetic extrapolations used in risk assessments that identify the maximal (i.e., the safe) levels for human exposure to chemical substances (Andersen and Krishnan 1994). PBPK models provide a scientifically sound means to predict the target tissue dose of chemicals in humans who are exposed to environmental levels (for example, levels that might occur at hazardous waste sites) based on the results of studies where doses were higher or were administered in different species. Figure 2-3 shows a conceptualized representation of a PBPK model.

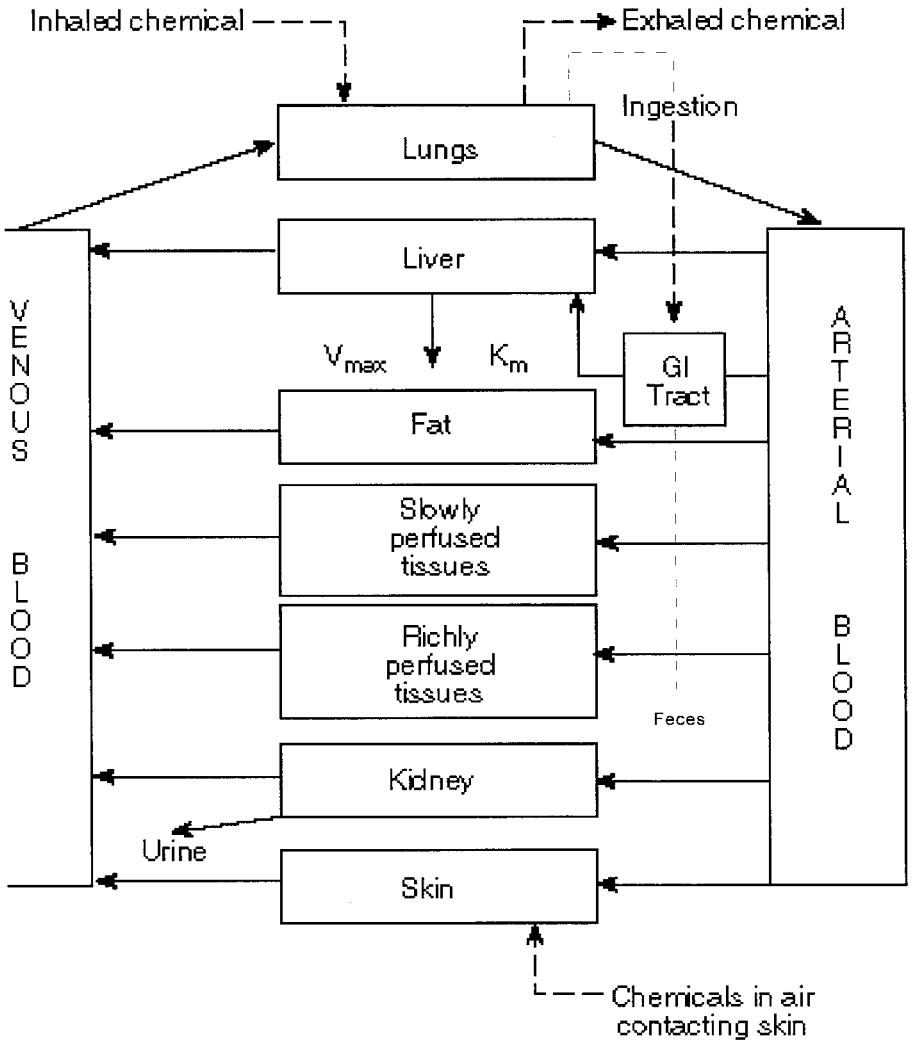
If PBPK models for HDI exist, the overall results and individual models are discussed in this section in terms of their use in risk assessment, tissue dosimetry, and dose, route, and species extrapolations.

No PBPK/PD models were identified for HDI in the open literature.

2.4 MECHANISMS OF ACTION

No specific information on the pharmacokinetic mechanisms, mechanisms of toxicity, or animal-to-Human extrapolations of these parameters for HDI were located in the available literature. In general, both aliphatic and aromatic isocyanates are considered to be pulmonary, oral, and dermal irritants. Several studies discussed earlier have reported respiratory irritation, which included burning and irritation to the nasal tract, throat, and the chest after inhalation exposure (Baur et al. 1984; Cockcroft and Mink 1979; Grammer et al. 1988; Patterson et al. 1990; Tornling et al. 1990; Usui et al. 1992). Oral exposure can also produce irritation of the mouth, pharangeal region, and the gastrointestinal tract. Eye contact produced severe eye irritation, resulting in moderate-to-severe lacrimation, photophobia, and edema, as well as severe dermatitis after topical skin exposure (Patterson et al. 1990; Haskell Laboratory 196 1; Mobay Corp. 198la; Von Burg 1993). The exact mechanism of action for producing irritation by all of these routes are unknown, but it is likely related to their high reactivity with biological macro-molecules and various body proteins (Karol 1986; Von Burg 1993). Most isocyanates are also considered to be potential respiratory tract sensitizers (E.I. DuPont de Nemours 1977b; Malo et al. 1983; Tornling et al. 1990) and, although many investigators have attempted to elucidate the immunological mechanisms behind this response, the mechanism(s) involving sensitization are likely quite complex and are still unknown.

Figure 2-3. Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance



Source: adapted from Krishnan et al. 1994

Note: This is a conceptual representation of a physiologically based pharmacokinetic (PBPK) model for a hypothetical chemical substance. The chemical substance is shown to be absorbed via the skin, by inhalation, or by ingestion, metabolized in the liver, and excreted in the urine or by exhalation.

2. HEALTH EFFECTS

2.5 RELEVANCE TO PUBLIC HEALTH

Overview

There is a large body of information available in the open literature on the toxicological and occupational hazards of diisocyanate compounds (particularly on toluene diisocyanate); however, relatively little information is available specifically for HDI or HDI polymers. It would be convenient to be able to use the available data on other diisocyanates, such as toluene diisocyanate, to extrapolate any missing information on HDI toxicity; however, fundamental differences in chemical properties and metabolism have precluded that possibility.

Based on the limited human and animal data at hand, it is possible to draw a few conclusions about the toxicity of HDI in both humans and animals. HDI is an occupational health hazard to some individuals, especially people employed in the automotive paint industry who come in contact with paint hardeners containing HDI monomers and polymers (Belin et al. 1981; Grammar et al. 1988; Patterson et al. 1990; Tornling et al. 1990). The target organ of HDI toxicity in humans is the respiratory tract, with most exposures resulting from inhaling vapors from HDI or its prepolymers (Alexandersson et al. 1987; Malo et al. 1983; Tornling et al. 1990; Tulane Medican 1982a, 1982b). All the data suggest that HDI is a direct irritant to the respiratory tract. A significant immune component is also present in HDI-induced respiratory toxicity, resulting in asthma-like symptoms (Belin et al. 1981; Grammar et al. 1988; Patterson et al. 1990). Other organs may also be affected in humans; however, the only supporting data available for this conclusion comes from laboratory animals exposed to HDI or its prepolymers (Haskell Laboratory 1961; Mobay Corporation 1984, 1989). Toxic effects of HDI exposure via the oral and dermal routes of exposures have been demonstrated in laboratory animals as well; however, this does not seem to be a major route of exposure for humans (Haskell Laboratory 1961). HDI has been demonstrated to be a strong dermal sensitizer in mice, with dermal cross-reactivity demonstrated with other aliphatic and aromatic isocyanates as well (Thorne et al. 1987). If unreacted HDI were present at hazardous waste sites, the major concern would be exposure via the inhalation route; thus, respiratory protection would be required in those situations. HDI has not been detected at any hazardous waste site. It is unlikely that unreacted HDI would be present at any such site, due to HDI's propensity to react quickly to form other compounds. Those persons involved in the clean-up at the site should also be aware of the skin irritant potential of this compound.

2. HEALTH EFFECTS

Minimal Risk Levels for Hexamethylene Diisocyanate.

Inhalation MRLs.

- An MRL of 3.0x 10^{-5} ppm has been derived for intermediate-duration inhalation exposure (15-364 days) to hexamethylene diisocyanate.

The intermediate-duration inhalation MRL was based on a NOAEL of 0.005 ppm administered to rats for 5 hours a day, 5 days a week for 3 weeks (doses were 0.005 ppm, 0.0175 ppm, 0.15 ppm, 0.3 ppm) (Mobay Corporation 1984). At 0.3 ppm, decreased kidney weights were observed in both male and female rats, with decreased liver weights observed in females only. Hepatic and renal effects were not seen at an inhaled dose of 0.15 ppm and lower. Nasal lesions occurred in 80-90% of the animals exposed at the 0.3 ppm level, while only 50-70% of the animals were affected at the 0.15 ppm concentration. No significant lower respiratory tract alterations were noted at the 0.0175 ppm inhalation dose; however, hemorrhage, inflammatory exudate, and epithelial changes were observed in the nasal cavity. Subsequently, these effects at the 0.0175 ppm dose were classified as minimal and used to base the inhalation intermediate-duration MRL. The NOAEL was placed at 0.005 ppm. For purposes of calculating human equivalency concentrations, these effects were also classified as extra-thoracic respiratory tract effects (EPA 1994b). Since there is no reported threshold for HDI immunological hypersensitivity in humans, this MRL may not be protective for persons with hypersensitivities to HDI. Respiratory tract lesions in laboratory animals have been described in other studies (Dow Chemical 1964; E.I. DuPont de Nemours 1978; Haskell Laboratory 1961; Karol et al. 1984); however, the doses tested were much higher than those tested in the Mobay Corporation (1984) study. More information on the Mobay Corporation (1984) study and the calculations used to derive this MRL are available in Appendix A.

No human studies were located that described any of the nasal tract lesions which occurred in the HDI-exposed rats. However, the available studies did not specifically examine this particular endpoint in HDI-exposed human populations. In addition, anatomical differences exist between rodents and humans (e.g. complex nasal turbinates and close apposition of the epiglottis and soft palate in rodents). It has been suggested that because of these differences, nasal epithelial changes observed in rats may roughly translate into effects in the more distal sections of the human respiratory tract (Haschek and Witschi 1991). This may be a significant point that may require further investigation. Several human studies indicated other toxicological properties that can be attributed to either HDI, HDI polymers, or a combination of both of these chemical forms functioning in tandem to produce the reported health effects in humans. It is clearly preferable to utilize human exposure studies when

deriving MRLs; however, given the typical exposure scenarios reported in Section 2.2 of this profile, the human data suggest that auto painters (the population most likely to be exposed to HDI) are exposed to mixtures of both HDI and HDI polymers, making it difficult to definitively state that effects (LOAELs) such as coughing, alterations in pulmonary function parameters, chills, chest tightness; alterations in immune function, or any number of other health effects, are due exclusively to exposure to HDI and not its polymers, and vice-versa (Alexandersson et al. 1987; Grammar et al. 1988; Malo et al. 1983; Tornling et al. 1990). This mixture exposure (HDI, HDI polymers, volatile organics, etc.) disqualified many of the human studies reported in this profile that could otherwise have been used for MRL derivation. A study by Shepperly and Hathaway (1991) reported a NOAEL for workers exposed to HDI at concentrations of 5 ppb (0.005 ppm) or less at a plant in Freeport, Texas. These workers had been chronically exposed to HDI for >l year with no statistically significant differences in pulmonary function test data, nor any significant increase in the frequency of respiratory complaints observed in these exposed workers versus the control (unexposed) population. A later study by DeWilde and Hathaway (1994), again using chronically exposed workers at the Freeport, Texas plant, found no statistically significant differences in pulmonary function data among HDI-exposed individuals and the control group. The dose in that study was estimated to be between 0.5 and 7 ppb (0.0005-0.007 ppm). Both the Shepperly and Hathaway (1991) and the DeWilde and Hathaway (1994) studies provided estimates of HDI doses to which workers were exposed, but neither study could provide definitive exposure doses to the worker populations. Both studies also had difficulties with some of the industrial hygiene monitoring devices and personal dosimetry devices, which may have provided inaccurate exposure data. In addition to occasional high short-term exposures (10-20 ppb), there were also some large variations in pulmonary function test results, which varied markedly from year to year and were attrihuted to human error. Again, these study limitations precluded either of these reports from being used to derive an intermediate-duration MRL based on human exposures, but do lend some support to the MRL based on results found using the rat model.

- An MRL of $1.0x10^{-5}$ ppm has been derived for chronic-duration inhalation exposure (365 days or more) to hexamethylene diisocyanate.

The chronic-duration inhalation MRL was based on the study by Mobay Corporation (1989). Fischer 344 rats were exposed to 0, 0.005, 0.025, or 0.175 ppm HDI for 5 day a week, 6 hour a day for 2 years. A satellite group was also exposed for 1 year. Reticulocytosis (less serious LOAEL), as well as eye irritation (observed in males only, first year only), were noted at the 0.175 ppm dose. At the

0.025 ppm dose, nasal cavity hyperplasia/metaplasia, lung epithelialization, alveolar macrophage accumulation (less serious LOAEL) were observed. Nasal cavity epithelial hyperplasia (minimal LOAEL) was also reported at the 0.005 ppm dose level in female rats and was used to derive the chronic inhalation MRL for HDI.

It should be noted that the EPA Reference Concentration (RfC) for HDI was based on the same study as this chronic-duration inhalation MRL (Mobay 1989) and was also calculated to be 1.0×10^{-5} ppm. A report by Foureman et al. (1994) described how this RfC was derived using the 0.005 ppm as the NOAEL dose end point; for purposes of chronic-duration inhalation MRL derivation, the MRL was based on the same dose end point, but was classified as a minimal LOAEL. Foureman et al. (1994) argue that although an effect was seen at the 0.005 ppm dose (nasal epithelial hyperplasia), this response should be classified as an adaptive response (as noted with many types of other irritants) and not a true toxic response. They concluded that the olfactory degenerative response should be considered the significant effect in these rats, because it followed a concentration-response relationship for both incidence and severity. In contrast, the hyperplastic and inflammatory responses followed the traditional dose-response for incidence, but not for severity of the lesions. The ATSDR Minimal Risk Level Workgroup carefully reviewed this data and the arguments presented by the Foureman et al. (1994) report and concluded that the hyperplasia and hyperkeratosis were, indeed, adverse (toxic) effects and warranted a classification as a minimal LOAEL. After uncertainty factors were applied, the RfC and the MRL concentration values resulted in the same value, $1.0x10^{-5}$ ppm, despite the differences in end point classification. This study involving the exposure of rats to HDI demonstrates that the line between an adaptive and toxic response in not always clearly defined, and it may be a matter of scientific judgement as to whether the effects are true adverse toxic responses.

A few human studies (Alexandersson et al. 1987; Cockcroft and Mink 1979; Grammar et al. 1988) were identified that described the respiratory toxicity associated with the inhalation of HDI and, as such, were considered for use in deriving the chronic-duration inhalation MRL. The human studies had many limitations and generally did not adequately define concentrations and chemical compositions of the inhaled vapor. The Alexandersson et al. (1987) study was determined not to be suitable for use in deriving an MRL, due to the fact that workers were simultaneously exposed to both the monomeric as well as the trimer forms of HDI, as discussed earlier. The authors of that study were unable to determine if the toxicological effects described were solely due to the monomeric or trimer form of HDI, or if the combination of the two chemicals were responsible for the observed changes in respiratory function.

2. HEALTH EFFECTS

As discussed earlier, a study by Shepperly and Hathaway (1991) reported a NOAHL for workers exposed to HDI at concentrations of 5 ppb (0.005 ppm) or less at a plant in Freeport, Texas. A later study by DeWilde and Hathaway (1994), again using chronically exposed workers at the Freeport, Texas plant, found no statistically significant differences in pulmonary function data among HDI-exposed individuals and the control group. The dose in that study was estimated to be between 0.5 and 7 ppb (0.0005- 0.007 ppm). Both the Shepperly and Hathaway (1991) and the DeWilde and Hathaway (1994) studies provided estimates of doses that the workers were exposed to, but could not provide definitive exposure doses to the worker populations. Both studies also had a number of difficulties (discussed above), which precluded their use in deriving a chronic-duration MRL based on human exposures, but do lend some support to the chronic-duration MRL based on results found using the rat model.

The Mobay Corporation (1989) study was the only animal study identified that defined the chronic toxicity of inhaled monomeric HDI in laboratory animals. More information on the Mobay Corporation (1989) study and the calculations used to derive this MRL are available in Appendix A.

Oral MRLs.

MRLs for oral exposure to HDI were not derived for any duration category because the available data in the open literature were considered to be insufficient. No reports of humans orally exposed to HDI were found in the open literature; very few reports of oral exposure in laboratory animals exist (Haskell Laboratory 1946, 1961).

Death. No reports of death were found in humans exposed to HDI by any route of exposure; however, several dated reports of death occurring in laboratory animals were found for all three primary routes of exposure. When inhaled, HDI causes death in animals at doses as low as 4 ppm when exposed for 4 hours (Karol et al. 1984). Death was related to respiratory impairment. Higher inhaled doses resulted in death as well (Dow Chemical Co. 1964; Haskell Laboratory 1961). Some of the studies that described exposure to HDI for acute durations used small numbers of animals for each exposure concentration, so firm LC_{50}, values (lethal concentration, 50% kill) may be difficult to derive (Dow Chemical 1964, Haskell Laboratory 1961). Kimmerle (1976) reported an LC_{50}, of 45 ppm in male Wistar rats; however, this may be the LC,, for the mixture (HDI + solvent) and not for the HDI itself. Animals exposed via inhalation to lower concentrations of HDI (<1 ppm) for intermediate and chronic durations had high survival rates,

indicating that HDI seems to be tolerated at low doses for long periods of time with no outward adverse effects (Mobay Corporation 1984, 1988, 1989).

Deaths due to oral exposures were reported to occur at very high doses in laboratory animals (>940 mg/kg). The cause of death in many cases was not reported; however, respiratory impairment may have been responsible (Haskell Laboratory 1961). Due to the limited data available, it is not known if the vehicle plays a role in oral HDI toxicity in laboratory animals. As with the inhalation studies described above, using small numbers of animals in testing lethal oral concentrations makes deriving a firm LD_{50} difficult. Larger doses of HDI placed topically also resulted in death (Thorne et al. 1987).

Systemic Effects.

Respiratory Effects. Several studies have described the respiratory toxicity of HDI monomer and HDI polymers after inhalation exposures in both humans and laboratory animals. A few reports indicated that no respiratory effects after prolonged exposure to HDI at concentrations as low as 0.5 ppb (0.0005 ppm) and as high as 7 ppb (0.007 ppm) could be found (DeWilde and Hathaway 1994; Shepperly and Hathaway 1991). Unfortunately, these studies suffered from small sample sizes and a number of difficulties in determining an accurate exposure dose. Conversely, in the majority of the reports in which humans were exposed to either the same or similar range of doses as those in the Shepperly and Hathaway (1991) and DeWilde and Hathaway (1994) studies (<l-20 ppb), the predominant clinical sign is an asthma-like syndrome, appearing soon after an exposure to a commercial product containing HDI and its polymers. Clinical signs indicate respiratory compromise, including shortness of breath, wheezing, tightness of the chest, bronchitis, and coughing (non-productive and productive). When individuals with these clinical signs were subjected to respiratory function tests, total lung capacity, vital capacity, forced expiratory volume (1 set), and PaO_2 were noted to markedly decrease, with an increase in residual lung capacity (Akbar-Khanzadeh and Rivas 1996; Bauer et al. 1984; Cockcroft and Mink 1979; Malo et al. 1983; Tulane Medican 1982a). A bronchoconstrictive response may or may not be demonstrated with the use of bronchoconstrictive agents (acetylcholine, histamine, etc.) (Alexandersson et al. 1987; Malo et al. 1983; Tulane Medican 1982a). These studies clearly indicate that HDI (either in the monomeric or polymeric form), either through some local, direct effect or via immune system modulation, adversely affects the ability of the lungs to function during and after HDI exposure (Alexandersson et al. 1987; Tornling et al. 1990).

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Many of these reports imply that monomeric HDI is the causative principal agent responsible for these respiratory and immunologic reactions; however, other HDI prepolymers (dimeric, biuret, or trimer) and other diisocyanates may also be responsible for inducing an asthmatic reaction in sensitized individuals (Vandenplas et al. 1993), but this possibility was overlooked in those studies. It seems likely that HDI prepolymers are also responsible for these reactions because most commercial products containing HDI (i.e., paint hardeners) contain as little as 0.2% monomeric HDI and up to 50-70% (estimates vary) of the prepolymer forms, as well as other organics (xylene, etc.) (Alexandersson et al. 1987). Most of these human reports are based on cases in which a worker who is suspected of having HDI intolerance (usually with a history of being an automobile painter or similar factory worker) is subjected to a controlled exposure to the paint vapor for a small amount of time, and the elicited response (clinical signs, blood gas, respiratory parameters, etc.) is recorded. Although a significant number of responses are incurred in these studies in this way, it is obvious that some component(s) of the paint induce an asthmatic reaction in these individuals. However, it is by no means clear that the HDI monomer is the specific chemical responsible for these reactions (Alexandersson et al. 1987; Tomling et al. 1990; Tulane Medican 1982a). Only one study (Vandenplas et al. 1993) has demonstrated that some individuals do have asthmatic reactions to only the HDI monomer, some to only the prepolymer form, and others to both monomer and prepolymer. It has also been demonstrated that there is significant cross-reactivity among aromatic diisocyanates (TDI, MDI) in their ability to induce asthmatic reactions in humans. This may occur through IgE-hapten formation, a local effect of the isocyanates on the lung tissue (due to irritant or pharmacological actions on the airways), or a combination of specific hypersensitivity to diisocyanates with an increase in non-specific bronchial airway reactivity (International Isocyanate Institute 1987a). The conclusion to be drawn from all of these studies is that the HDI monomer may be responsible for eliciting the asthmatic reactions observed in sensitized individuals; however, other compounds aerosolized with the monomer (in particular the HDI polymers) may also elicit these reactions by themselves or in concert with the HDI monomer.

While the human studies describe the allergic component of HDI toxicity, most of the animal studies describe the direct irritant effects of HDI and HDI prepolymers after inhalation. Laboratory animals exposed to HDI via inhalation showed such adverse signs as respiratory irritation, tracheitis, pleural effusion, pulmonary hemorrhage, bronchitis, and bronchopneumonia, mostly at concentrations >l ppm (Dow Chemical 1964; E.I. DuPont de Nemours 1978; Haskell Laboratory 1961; Karol et al. 1984). These studies clearly demonstrated that HDI is irritating to the respiratory tract and may be responsible for the decreased respiratory rates noted in two studies (E.I. DuPont de Nemours 1978; Mobay

Corporation 1982). The RD_{50} was calculated in mice to be 0.36 ppm during a 3-minute exposure and 1.42 ppm for a 30-minute exposure, with evidence to suggest that rats develop tolerance to HDI after short periods of exposure (Mobay Corporation 1982). HDI was also demonstrated to be much more of a respiratory irritant than other more commonly used diisocyanates (e.g., TDI and MDI) (E.I. DuPont de Nemours 1978).

When tested in laboratory animals at < l ppm concentrations, the animals exhibited varying degrees of respiratory tract irritation and degenerative nasal responses. Nasal lesions tended to occur in a dose- related manner, which included varying degrees of hemorrhage, inflammatory exudate, epithelial changes, loss of cilia, and changes in cell type, which strongly indicate cellular damage induced by HDI vapor in rats over a 3-week exposure period (Mobay Corporation 1984). The lungs of rats exposed for a 2-year period also sustained histologic damage. Lung anomalies induced over a 2-year period in rats included epithelialization and interstitial pneumonia with macrophage accumulation in the lung; however, the nasal lesions, which included hyperplasia/metaplasia, atrophy, ulceration of the olfactory epithelium, hyaline droplet degeneration, hyperkeratosis and chronic inflammation, were still the most outstanding lesions found, with an adaptive nasal response occurring in the lowest dose group (0.005 ppm) after 1 year (Mobay Corporation 1989). These studies indicate that, at least in laboratory animals, HDI induces a highly toxic response in the nasal cavity and in the lungs when inhaled at very low (0.005-0.175 ppm) concentrations over a long period of time (2 years). The exact mechanisms responsible for these nasal lesions are unknown, but may be related to the nose's ability to remove a large percentage of some organic compounds for metabolism or for temporary storage and removal into the exhaled air-stream (Dahl and Hadley 1991; Dahl and Lewis 1993; Dahl et al. 1991; Gerde and Dahl 1991; Lewis et al. 1992; Snipes et al. 1990). Increasing the interaction time of HDI with the nasal mucosal tissue possibly resulted in the gross and histological lesions observed in these animals. Although these reports find compelling evidence for the induction of nasal lesions due to long-term HDI exposure in laboratory animals, there have been no reports of similar nasal lesions found in humans exposed to HDI.

It is unclear what the precise effects of HDI are on the respiratory tract after oral exposure. In the studies that were examined, any effects on the respiratory tract were a result of megadoses of HDI. In many cases, these doses resulted in death, with congestion of the lungs, peribronchial edema, altered respiration, and other non-specific respiratory symptoms (Haskell Laboratory 1946,196l). No histopathology was performed on the lungs in these studies, so it is not possible to speculate about what was occurring at the cellular and molecular level in these tissues.

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Cardiovascular Effects. Limited information on the cardiovascular toxicity of HDI was available. Three inhalation studies conducted in large numbers of rats exposed to doses ranging from 0.005 to 0.3 ppm for intermediate- and chronic-durations did examine the heart tissue post-mortem and failed to produce any biologically significant gross anatomical or histopathological evidence of HDI-induced toxicity (Mobay Corporation 1984, 1988, 1989). It is not known if there are significant changes in heart function parameters (ECG, heart rate, stroke volume, etc.) during HDI exposures. No oral or dermal exposure studies were located that described the cardiac toxicity of HDI in either humans or laboratory animals.

Gastrointestinal Effects. Reports of gastrointestinal effects of HDI toxicity have been found in laboratory animals only. Ulcerative gastritis was reported in male rats after they received HDI in peanut oil via gavage; however, it is not known whether this was a side-effect of gavage administration technique (Haskell Laboratory 1946, 1961) or if the data were skewed by the small numbers of animals used during that study. One inhalation study did report chronic gastritis in male rats exposed to 72 ppm HDI (Haskell Laboratory 1961), but 2 other studies using much lower exposure concentrations (<1 ppm) failed to produce any gastrointestinal tract lesions. Based on this limited data, it is unclear whether HDI has ulcerogenic properties at higher doses in laboratory animals.

Hematological Effects. HDI appears to produce some mild hematological effects in both humans and laboratory animals. If an allergic component was producing adverse effects, elevations in circulating IgE (as well as other immunoglobulins) and increased numbers of eosinophils can reasonably be expected in peripheral blood. Following inhalation of HDI-containing vapors in humans, mild leucocytosis but no eosinophilia were noted in two cases that occurred after an asthmatic reaction began to occur (Malo et al. 1983; Patterson et al. 1990). In both cases, the workers were not exposed to the pure form of HDI, but rather to a vapor and particulates produced by paints containing HDI, HDI prepolymers, and other organics normally found in automotive paints. Allergic reactions to either of these forms of HDI, in addition to any of the other myriad of organics found in these paints, may have elicited this mild elevation of leukocytes. No data were available on changes in hematology after oral or dermal exposure routes.

Decreased acetylcholinesterase activity has been reported with other diisocyanates (Manno and Lotti 1976; Trevisan and Moro 1981). However, no significant changes in plasma cholinesterase have been noted in laboratory animals exposed to HDI via inhalation (Karol et al. 1984).

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Hepatic Effects. No information is available on the hepatic effects of HDI in humans. Limited information exists on these effects in laboratory animals and is confined to inhalation studies. One study of intermediate-duration showed decreased liver weights in female rats dosed at 0.3 ppm (Mobay Corporation 1984); however, 2 studies of longer durations and slightly lower inhaled doses showed no changes in liver weights attributable to HDI toxicity (Mobay Corporation 1988, 1989). It appears that the changes in liver weights are a transitory phenomenon in laboratory animals.

Renal Effects. No information is available on the renal effects of HDI in humans. Renal changes appeared to be mild when rats were exposed to HDI. Decreased kidney weights were noted in one study of intermediate-duration in both male and female rats (Mobay Corporation 1984), while two other studies of longer duration noted no significant changes in kidney weights (Mobay Corporation 1988, 1989). The changes in kidney weights, like the changes in liver weights, appear to be a transient phenomenon. Male rats experienced an increase in urinary ketone concentration in two separate studies (Mobay Corporation 1984, 1988). No changes in urine ketones were noted in one study of chronic-duration (Mobay Corporation 1989). Anorexia, resulting in decreasing body weight and mobilization of fat stores, may be a reasonable cause for observing increased ketone bodies in the urine. However, both of the studies that noted ketonuria also reported no significant changes in body weight throughout the study. It is unclear why urinary ketone bodies increased in HDI-exposed rats.

Dermal Effects. Dermal effects of HDI are limited to those cases of topical exposure. HDI has been demonstrated to be a topical irritant in several studies in laboratory animals at topical (non-occluded) doses as low as 0.l%, resulting in erythema, edema, and, in some cases, frank skin necrosis (Haskell Laboratory 1961). Studies that dosed HDI on the skin of rabbits, with the dosing site occluded, resulted in more severe cutaneous reactions (Mobay Corporation 1981a). In addition to its local irritation effect, HDI also induces an allergic contact dermatitis in guinea pigs (Haskell Laboratory 1961). Neither direct irritant or allergic contact dermatitis effects of HDI have been documented in humans.

Ocular Effects. No ocular effects due to HDI toxicity have been reported in humans. Ocular effects due to HDI toxicity have been documented in dogs, rats, and rabbits (Haskell Laboratory 1961; Mobay Corporation 1966, 1988, 1989). When HDI was placed directly into the eyes of laboratory animals, direct irritation resulted in the form of severe conjunctivitis, damage to the cornea and iris, and an inflammatory reaction (Haskell Laboratory 1961; Mobay Corporation, 1981a). Clinical signs of ocular irritation have been observed when animals were exposed to vapor concentrations as low as 0.01 ppm

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(Mobay Corporation 1988), but reactions were limited to lacrimation and conjunctivitis. The severity of signs was generally proportional to the air concentration (Haskell Laboratory 1961). At air concentrations ≥ 0.164 ppm, the clinical signs were observed during and shortly after the HDI exposure, with a full recovery observed by the following day (Mobay Corporation 1989). Ophthalmologic or histopathological examination after two years of exposure revealed no compound-related ocular effects (Mobay Corporation 1989). These studies demonstrate the HDI, even at very low concentrations, functions as a direct irritant to the eye and surrounding structures, and as a result are considered to be transient physiological responses.

Body Weight Effects. HDI does not appear to have an appreciable effect on the body weights of animals, based on inhalation dosing. Only one study showed a mild drop in body weight within 1 day or 1 week after exposure began (Dow Chemical 1964); however, the effect appeared transient, was accompanied by a rebound weight gain, and was probably related to the relatively high concentrations of HDI used in that study. Other studies using doses of HDI at <0.3 ppm for intermediate- and chronic-durations failed to elicit a significant change in body weights (Mobay Corporation 1984, 1988, 1989).

Neurological Effects. Little information was available to determine the neurotoxicity or the mechanism of neurotoxicity of HDI after inhalation, oral, or dermal exposure. Headache was reported in only one human exposure case (Malo et al. 1983). Neurotoxic effects (convulsions) may occur in laboratory animals if concentrations reach high levels in the air (Haskell Laboratory 1961); however, since HDI is metabolized quickly in a biological matrix (Berode et al. 1991), little intact HDI is expected to reach the nervous tissue to elicit a toxic response, except possibly at very high concentrations. No neurological effects have reported in laboratory animals, or in humans exposed chronically to low concentrations of HDI (Mobay Corporation 1989). HDI, in addition to other isocyanates, have been shown to inhibit acetylcholinesterase in human erythrocytes (Dewair et al. 1983), human serum acetylcholinesterase (Brown et al. 1982), as well as equine serum, bovine erythrocyte, and eel acetylcholinesterase (Brown et al. 1982).

Immunological and Lymphoreticular Effects. Many reports confirmed that both HDI monomer and prepolymers can elicit an immunological reaction in both humans and laboratory animals after inhalation and dermal exposures. There is clear evidence that in mice and guinea pigs, HDI and HDI prepolymers can induce sensitization reactions after one sensitizing dermal exposure (E.I. DuPont de Nemours 1977b, 1977a; Stadler and Karol 1985; Thorne et al. 1987), although there have been no reports

of human dermal sensitization. The information on the immunological reactions in humans is limited to inhalation data; however, these reports indicate that the immune system responds to HDI exposure by producing IgG, IgE (Belin et al. 1981; Grammar et al. 1988, 1990; Patterson et al. 1990), and IgA antibodies (Usui et al. 1992) after inhalation exposure to very small doses (<0.2 ppm) in some individuals. IgG is the prevalent antibody produced in humans exposed to HDI (Grammar et al. 1990). Antibody detection in the serum and BALF is usually performed using an RIA or ELISA utilizing the diisocyanate conjugated to human senm albumin (HSA).

Presently, there is no one specific test to detect antibodies produced exclusively in response to HDI exposure, although HDI-HSA antigens are available to detect immunoglobulins produced in response to HDI exposure. It has been demonstrated that some cross-reactivity does occur with the HDI-HSA antigen and other aromatic isocyanates, such as TDI and MDI (Belin et al. 1981), making serum or skin antibody measurements of limited value as a biomarker of HDI exposure. In addition, most reports indicate that both presence and quantity of antibodies found in the serum or after RAST and skin prick tests do not always correlate to the occurrence of respiratory symptoms experienced in many exposed workers (Baur et al. 1984; Grammar et al. 1988, 1990). In other words, the presence of respiratory symptoms attributed to HDI exposure does not always produce a detectable antibody response to HDI, and *vice versa.* Although current data are admittedly scant in this area, it appears that in addition to a pharmacologic mechanism(s) of pulmonary toxicity to HDI, there is an immunologic component involved in inducing HDI respiratory toxicity. The immune system's specific role in HDI-induced pulmonary toxicity is unclear and requires further study to properly elucidate these immunologic and pharmacologic mechanisms.

Genotoxic Effects. HDI was demonstrated to be non-mutagenic against some *Salmonella typhimurium* strains with or without metabolic activation (Anderson et al. 1980). HDI also inhibited the growth of Ehrlich ascites tumor cells in female mice (Moos et al. 1971) and decreased the mutation frequency in *Escherichia coli* (Kawazoe et al. 1981). Calf thymus DNA incubated in vitro with 10.4 or 52 μmol of HDI for 10 or 20 minutes produced no evidence of intrastrand cross-links or DNA strand breaks (Peel et al. 1997). No studies were located that studied the genotoxic effects of HDI on human cells or that described the ability of prepolymer forms of HDI to induce genotoxicity."

Cancer. No reports of HDI-induced cancer in humans were retrieved. One study in rats showed no increase in the incidence of cancer at the concentrations tested (Mobay Corporation 1989).

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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 (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 hexamethylene diisocyanate are discussed in Section 2.6.1.

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

Few biomarkers are available for determining exposure to HDI. Detection of HDI in the blood, serum, urine and other body fluids would be difficult, given the accelerated rate at which hydrolysis of HDI probably occurs in biological matrices (see Figure 5-1) (Berode et al. 1991; Brorson et al. 1990b). According to surveyed literature, parent HDI has not been detected following exposure in humans or animals. The hydrolysis product of HDI, 1,6-hexamethylene diamine (HDA) has also not been detected in the blood after HDI exposure; however, it has been detected in the urine of humans exposed by the inhalation route (Brorson et al. 1990b) and via the oral route several hours after ingestion of HDA (Brorson et al. 1990a). The average half-life of HDA in the urine after inhalation exposure to HDI for 8 hours at concentration levels ranging from 25 μg/m^3 to 29 μg/m^3 (63% to 73% of the Swedish TLV) was reported to be 1.2 hours. The half-life after oral ingestion of 0.1 mg/kg of I-IDA was 1.5 hours. Urine levels of HDA (after oral ingestion or after inhalation of HDI) were generally undetectable after 13-15 hours, indicating that HDA may be a suitable biomarker for determining acute exposure to HDI when air concentrations are near TLV. Urinary HDA assessment would be of little value in determining exposures occurring at air concentrations far below the TLV, or >12-15 hours post exposure. The use of two known urinary metabolites of HDA (N-acetyl-1,6-hexamethylene diamine and 6-aminohexanoic acid) as biomarkers is unclear; however, given their probable shorter half-lives (compared to HDA), these metabolites would probably be of little value.

The study by Brorson et al. (1990b) suggests an additional feature that may be important in biological monitoring. On the basis of the ability to acetylate an oral dose of HDA, Brorson determined the phenotypes of 6 individuals as either rapid or slow acetylators. The rapid acetylators excreted approximately twice as much acetylated HDA over the subsequent 15 hours as did the slow acetylators. The potential importance of this difference in excretory rates with respect to toxicity has not been investigated. However, the author suggests that after measurements of urinary metabolites have been made in conjunction with determinations of acetylation phenotypes, it would be worth considering the possibility of biological monitoring of occupation exposure to HDA and HDI.

HDI exposure has also been reported to induce the production of immunoglobulins, mainly IgG and IgE (Belin et al. 1981; Grammar et al. 1988, 1990; Patterson et al. 1990), making this response a potential for use as a biomarker of exposure. Several difficulties arise when attempting to use blood immunoglobulin levels specifically as an HDI biomarker of exposure. As discussed earlier, there is no one specific test to detect the antibodies produced exclusively in response to HDI exposure. Cross-reactivity does occur with the HDI-HSA antigen and other aromatic isocyanates, such as TDI and MDI (Belin et al. 1981), making serum or skin antibody measurements of limited value as a biomarker of HDI exposure when workers may have been exposed to more than one diisocyanate. The presence and quantity of antibodies found in the serum or after RAST and skin prick tests do not always correlate to the occurrence of ocular, nasal, and respiratory tract symptoms experienced in many exposed workers (Baur et al. 1984; Grammar et al. 1988, 1990). Furthermore, it has been documented that many exposed workers will not mount an immune response (i.e., IgG, IgE, or IgA production) after exposure to HDI, yielding false negatives for exposure (Baur et al. 1984; Grammar et al. 1988, 1990). Given these difficulties, the use of blood immunoglobulins as a biomarker of exposure to HDI may be of limited use. With the current tests available, immunoglobulin levels may be of more use in determining an individual's exposure to diisocyanates in general, although a positive titre to the HDI antigen may indicate exposure to HDI itself. Exposure history to diisocyanates would be a useful tool for assessing the validity of the test data. Immunoglobulins may also be more useful than urinary HDA levels because the immunoglobulins will persist in the blood for an extended length of time after an exposure has occurred.

2.62 Biomarkers Used to Characterize Effects Caused by Hexamethylene Diisocyanate.

The primary target organ for HDI toxicity is the respiratory tract. The signs and symptoms of exposure to HDI (burning and irritation of the respiratory tract, headache, bronchitis, asthmatic reactions, obstructive breathing defects, tightness of the chest, pulmonary edema, etc.) are easily recognizable; however, none are specific for exposure to HDI. No specific biomarkers used to characterize effects caused by HDI were located in the literature.

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

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2.7 INTERACTIONS WITH OTHER CHEMICALS

There were no reliable reports available in the surveyed literature that described the interaction of HDI with other chemicals.

2.8 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to hexamethylene diisocyanate than will most persons exposed to the same level of hexamethylene diisocyanate in the environment. Reasons may include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters may result in reduced detoxification or excretion of hexamethylene diisocyanate, or compromised function of target organs affected by hexamethylene diisocyanate. Populations who are at greater risk due to their unusually high exposure to hexamethylene diisocyanate are discussed in Section 5.6, Populations With Potentially High Exposure.

People who have developed hypersensitization to HDI are likely to be most susceptible to the toxic effects of HDI. People may develop a hypersensitization to HDI after only one exposure, either at a very low concentration for many hours or to a high concentration for just a few seconds. The first exposure may induce only the local irritant effects of HDI, depending on the exposure concentration and duration of exposure. However, upon re-exposure at very low concentrations (TLV or lower), sensitized persons may exhibit respiratory symptoms resembling an asthma attack (e.g., shortness of breath, difficulty in breathing, burning sensation in the chest, bronchoconstriction). Individuals with pre-existing lung disease who are also sensitized to HDI (or other diisocyanates) are another population unusually susceptible to the effects of HDI. HDA, the metabolite of HDI, is known to be excreted in the urine of humans after inhalation exposure (Brorson et al. 1990b) and is moderately toxic in fasted rats (Dashiell and Kennedy 1984). It is not known whether severely impaired renal functions in humans exposed to HDI has an impact on HDA-induced toxicity.

2.9 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to hexamethylene diisocyanate. 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

hexamethylene diisocyanate. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice. The following texts provide specific information about treatment following exposures to hexamethylene diisocyanate:

- Ellenhom, MJ and Barceloux, DG. 1988. Medical Toxicology: Diagnosis and Treatment of Human Poisoning. Elsevier Publishing, New York, NY.
- Dreisback, RH. Handbook of Poisoning 1987. Appleton and Lange., Norwalk, CT.
- Haddad, LM and Winchester, JF (ed.) 1990. Clinical Management of Poisoning and Drug Overdose. 2nd edition, WB Saunders, Philadelphia, PA.
- Aaron, CK and Howland, MA (ed.) 1994. Goldfrank's Toxicologic Emergencies. Appleton and Lange, Norwalk, CT.

2.9.1 Reducing Peak Absorption Following Exposure

Few specific recommendations can be made for reducing the absorption of HDI after exposure. To avoid exposure, persons handling or transporting products containing it should ensure that all devices containing the HDI are sealed and intact. HDI should be used in a well ventilated area at normal room temperatures. Owing to the low molecular weight of HDI, increased room temperatures may increase the vaporization of HDI into the room air, increasing the risk of human exposure. Adequate ventilation should always be provided when using products containing HDI; respiratory equipment may also be necessary, depending on working conditions. If splashes or contact with aerosols are likely to occur in the working environment, workers should protect themselves by wearing rubber or polyvinyl chloride gloves, aprons, rubber boots, goggles, and respiratory equipment as needed to prevent exposure (NIOSH 1978).

If the skin comes into contact with HDI or products containing HDI, workers should flush their skin with water to remove the agent and wash the contaminated area with soap and water. Isopropyl alcohol can also be used to neutralize any remaining HDI after washing with soap and water, provided the skin barrier is intact. If HDI comes into contact with the eyes or conjunctiva, copious amounts of water should be used to gently flush the eyes for at least 15-20 minutes. To avoid oral exposure to HDI, persons should thoroughly wash their hands after handling products containing HDI prior to eating, drinking, or smoking (NIOSH 1978).

2.9.2 Reducing Body Burden

No reports were found in the open literature on methods to reduce the body burden of HDI after inhalation, oral or dermal exposures. No blood, tissue or urine concentrations of HDI have been reported in the surveyed literature. Since HDI is easily hydrolyzed in biological media (Berode et al. 1991; Brorson et al. 1990b), little if any HDI is expected to accumulate in the tissues of humans after acute or chronic exposures.

2.9.3 Interfering with the Mechanism of Action for Toxic Effects

The mechanism of action of HDI has not been elucidated to any great extent in the surveyed literature. No information is available to determine what action, if any, can be taken to interfere with the mechanism of action of HDI toxicity.

2.10 ADEQUACY OF THE DATABASE

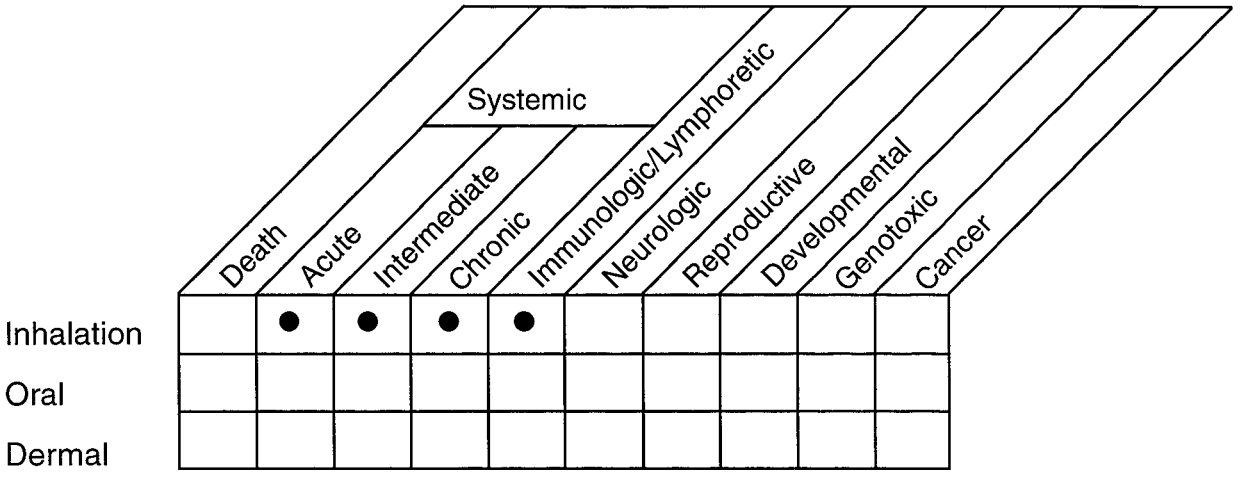
Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of hexamethylene diisocyanate is available. Where adequate information 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 hexamethylene diisocyanate.

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.

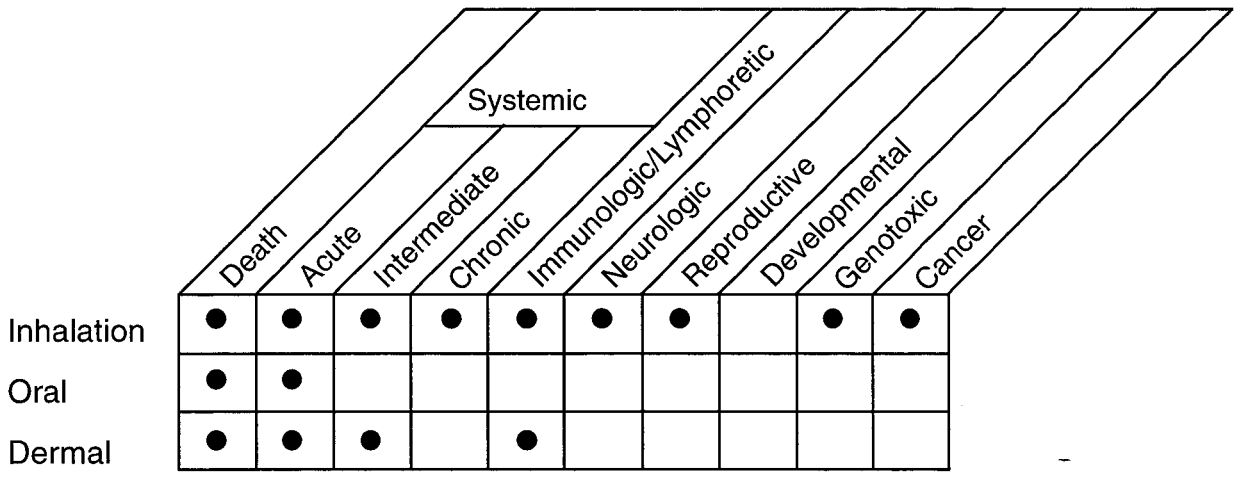
2.10.1 Existing Information on Health Effects of Hexamethylene Diisocyanate

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to hexamethylene diisocyanate are summarized in Figure 2-4. The purpose of this figure is to illustrate the

Figure 2-4. Existing Information on Health Effects of Hexamethylene Diisocyanate



Human



Animal

● Existing Studies

existing information concerning the health effects of hexamethylene diisocyanate. 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 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 Identifyng 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.

2.10.2 Identification of Data Needs

Acute, Intermediate and Chronic-Duration Exposures. Inhalation exposures in both humans and laboratory animals predominate in the available information on acute, intermediate, and chronic effects of HDI, and will be considered here as a group. Information on laboratory animals describes the direct irritant effects of HDI, which was usually inhaled in large doses (>4 ppm); however, no information on the allergic component of HDI toxicity at low doses, the type of dose most commonly encountered in humans, was provided. Information on acute inhalation exposure of humans may be misleading. In most cases of acute exposure, the workers had been exposed to HDI and HDI prepolymers in their workplace for several months or several years (doses often not available). These workers were then tested with a small dose of either HDI or a product containing HDI with the HDI prepolymers and other organics. Workers were tested for an acute duration (<1 hour) (Belin et al. 1981; Cockcroft and Mink 1979; Malo et al. 1983; Patterson et al. 1990; Tulane Medican 1982a, 1982b) and a chronic duration (Alexandersson et al. 1987). Allergic reactions in these workers were often reported. From these data, it is unclear whether it is the HDI component or the HDI prepolymers of these products that are responsible for eliciting the observed allergic reactions (Malo et al. 1983; Tulane Medican 1982a). Better designed studies are needed to determine if humans never exposed to HDI and then given small doses of HDI (<0.02 ppm) or HDI prepolymers for an acute duration, can develop these hypersensitivities, as well as at what inhaled concentrations these sensitivities can be expected to occur or not occur. It is also important to determine if it is the HDI component, the HDI prepolymers, or an additive and synergistic effect of these components that elicit the allergic reactions observed in those individuals exposed chronically to products containing these components. Finally, studies are also necessary to determine if respiratory and dermal allergic reactions can be induced in humans after dermal exposure only, as was observed in laboratory animals.

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Genotoxicity. HDI was demonstrated to be non-mutagenic against some *S. typhimurium* strains with or without metabolic activation (Anderson et al. 1980). HDI also inhibited the growth of Ehrlich ascites tumor cells in female mice (Moos et al. 1971) and decreased the mutation frequency in *E. coli* (Kawazoe et al. 1981). No studies were located that studied the genotoxic effects of HDI on human cells or that described the ability of the prepolymer forms of HDI to induce genotoxicity. Although the limited data suggest that HDI is not genotoxic, a data need exists here to confirm that both HDI and the prepolymer of HDI are not capable of inducing genotoxic effects in human cell lines.

Reproductive Toxicity. No reproductive toxicological studies were located in the surveyed literature for HDI. Only a few animal studies examined the reproductive organs of both male and female animals, with no gross or histological results evident (Mobay Corporation 1984, 1988,1989); none of the human studies of acute, intermediate, or chronic durations directly addressed the issue of reproductive toxicity. The majority of studies used male humans and animals, presumably because human males are presently the predominant sex in the automotive painting industry and, therefore, more likely to be exposed to HDI. It is not known if HDI affects reproductive tissues in males or females; however, given its short half-life in biological fluid, this seems unlikely. HDI has been reported to bind to biological tissues (protein) (Ted and Pesce 1979); however, the relevance of this observation to reproductive toxicity is not known. The toxicity of the HDI metabolite HDA) is not known. Toxicological studies should be designed to answer questions about the potential reproductive toxicity of HDI or its prepolymers in both male and female humans and laboratory animals.

Developmental Toxicity. No developmental toxicological studies were located in the surveyed literature for HDI. It is not known if HDI exerts an effect on reproductive tissues iu males or females or on the developing fetus; however, given its short half-life in biological fluid, this seems unlikely0 HDI has been reported to bind to biological tissues (protein) (Ted and Pesce 1979); however, the relevance of this observation to reproductive toxicity is not known. The toxicity of the HDI metabolite (HDA) is not known. Toxicologic studies should be devised to answer questions about HDI's potential developmental toxicity or its prepolymers in the developing human or laboratory animal.

Immunotoxicity. No immunotoxicity induced by HDI was observed in the studies found in the open literature. HDI can, however, elicit immunological reactions iu both humans and animals. There appears to be an immunological component involved in HDI respiratory toxicity. The immune system's specific role in HDI-induced pulmonary toxicity may be useful.

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Neurotoxicity. Little information was available to determine the neurotoxicity of HDI after inhalation, oral or dermal exposure. Neurotoxic effects may occur if concentrations reach high levels in the air (Haskell Laboratory 1961); however, since HDI is metabolized quickly in a biological matrix (Berode et al. 1991), little intact HDI is expected to reach the nervous tissue to elicit a toxic response, except possibly at very high concentrations. No neurological effects have reported in laboratory animals, or in humans exposed chronically to low concentrations of HDI (Mobay Corporation 1989); therefore the data need for determining the neurotoxicity of HDI is a low priority.

Epidemiological and Human Dosimetry Studies. The target population for HDI toxicosis is the worker using products that contain both HDI and/or HDI in combination with the HDI prepolymers, usually in the form of automobile paint hardeners. One flaw in these reports is that the dosimetry data were not well described in many cases (Baur et al. 1984; Grammar et al. 1990; Malo et al. 1983; Patterson et al. 1990; Usui et al. 1992); often concentrations were not stated or a wide-range of exposure concentrations reported. The usual scenario noted from the majority of these reports was that a worker was exposed to products containing both HDI and HDI prepolymers for a period of several weeks or several years with accompanying allergic (asthmatic) symptoms. The worker was administered an inhalation challenge to the paint he was using and subsequently developed the clinical symptomatology, with HDI assumed to be the causative agent, although there was no conclusive proof that it was the chemical responsible for eliciting the reaction. In some of these reports, the possibility of the prepolymeric form inducing an allergic reaction was not considered (Bauer et al. 1984; Belin et al. 1981; Grammar et al. 1988; Patterson et al. 1990; Tulane Medican 1982a; Usui et al. 1992), while in other reports this was addressed to some extent (Alexandersson et al. 1987; Grammar et al. 1988; Malo et al. 1983). A strong data need in this area is to determine definitively if it is the HDI, the HDI prepolymer, a combination of the HDI and HDI prepolymer, or (less likely) other organic components in these products that are eliciting the allergic and irritant reactions observed in these chronically exposed workers.

Biomarkers of Exposure and Effect.

Exposure. Only one biomarker of exposure, HDA, was located in the surveyed literature (Brorson et al. 1990a,b). This biomarker may be some use for acute-duration exposures, but only if urine is collected from the exposed person within 6-12 hours after exposure. No reliable biomarkers of exposure are available for chronic, low-level exposures in humans, although blood immunoglobulins (in particular IgG) may be useful in determining exposures to the diisocyanates as a group, and not a specific exposure to HDI.

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Studies to determine other biomarkers that would be sensitive enough to detect chronic, low-level exposures to HD/HDI prepolymers and be specific to HDI only, with low cross-reactivity to other diisocyanates, would be extremely useful, and would enhance the database.

Effect. No studies were found in the open literature that used a biomarker of effect to HDI toxicity. The target organ of HDI toxicity is the respiratory system, with significant effects on the eyes if present in high concentrations (Haskell Laboratory 1961; Mobay Corporation 1981 a). More effort to identify subtle biochemical changes to serve as biomarkers of effects of HDI would be useful in detecting early, subtle signs of HDI-induced toxicity.

Absorption, Distribution, Metabolism, and Excretion. There is an obvious data need to determine the pharmacokinetic and toxicokinetic behavior of HDI in both humans and laboratory animals. Determination of blood levels of inhaled, ingested and dermally absorbed HDI would be difficult, given the very short half-life in biological matrices (Berode et al. 1991) and the rate at which HDI binds to proteins in the blood. Although some information is known about the metabolism of HDI in humans inhaling a known quantity of HDI (Brorson et al. 1990), the rate at which absorption occurs, where the majority of the metabolism of HDI occurs (in the water in the mucous layer of the bronchi as opposed to the blood or the kidney), and the distribution patterns and toxic effects of the metabolite (if any) are not well described. Information in these areas of toxicokinetics and toxicodynamics could also be useful in developing a PBPK/PD model for HDI. Research should focus on the respiratory and dermal routes of exposure.

Comparative Toxicokinetics. Little information is present on the comparative toxicokinetics of HDI, both between laboratory animal species and between humans and laboratory animals. As discussed earlier in this chapter, the majority of the laboratory animal studies have focused on the direct irritant effects of HDI after inhalation exposure (E.I. DuPont de Nemours 1978; Haskell Laboratory 1961; Karol et al. 1984; Mobay Corporation 1982, 1989), while the human studies have described the allergic components of HDI exposure (Alexandersson et al. 1987; Bauer et al. 1984; Grammar et al. 1988; Malo et al. 1983; Tulane Medican 1982a; Usui et al. 1992). The allergic component of HDI toxicity has been described in laboratory animals after dermal exposure (E.I. DuPont de Nemours 1977a, 1977b; Haskell Laboratory 1961; Stadler and Karol 1985; Thorne et al. 1987), but no reports of such reactions have been located for humans. Efforts should focus on finding a laboratory animal that would serve as a suitable

model for studying the allergic respiratory system reactions seen in humans and in *in vitro* studies that would outline the mechanism of action of the toxic effects of HDI on a cellular and molecular level.

Methods for Reducing Toxic Effects. No studies were located that described methods for reducing the toxic effects of HDI after exposure has occurred. A data need exists here to determine the mechanistic pathways of HDI toxicity, followed by research that determines the best way to reduce these toxic effects (i.e., the allergic reactions) observed.

2.10.3 Ongoing Studies

A few research projects are in progress that investigate the health effects of HDI. The projects relevant to HDI are summarized in Table 2-4.

Table 2-4. Research in Progress Relevant to Hexamethylene Diisocyanate

Investigator	Affiliation	Research description	Sponsor
Rochester, Carolyn L.	Yale University, New Haven, Connecticut	Induction of lung DTH and airway hyperreactivity by TDI	National Heart, Lung, and Blood Institute
Lee, Lu-Yuan	University of Kentucky, Lexington, Kentucky	Airway responses mediated by nociceptive afferents	National Heart, Lung, and Blood Institute
Stetter, Joseph R.	Transducer Research Inc.	Portable liquid chromatograph to monitor isocyanates in air	Small Business Innovative Research Program