

**TOXICOLOGICAL PROFILE FOR  
HEXAMETHYLENE DIISOCYANATE**

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

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### **UPDATE STATEMENT**

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

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



## FOREWORD

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

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

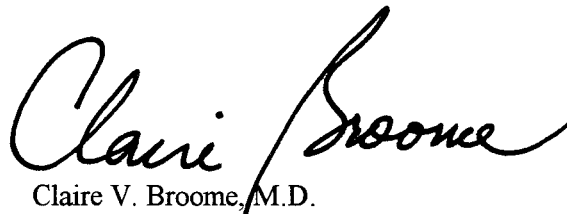
The focus of the profiles is on health and toxicologic information; therefore, each toxicological profile begins with a public health statement that describes, in nontechnical language, a substance's relevant toxicological properties. Following the public health statement is information concerning levels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

Each profile includes the following:

- (A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a hazardous substance to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects;
- (B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine levels of exposure that present a significant risk to human health of acute, subacute, and chronic health effects; and
- (C) Where appropriate, identification of toxicologic testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans.

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

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



Claire V. Broome, M.D.  
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Disease Registry

### \*Legislative Background

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

## CONTRIBUTORS

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### THE PROFILE HAS UNDERGONE THE FOLLOWING ATSDR INTERNAL REVIEWS:

1. Green Border Review. Green Border review assures consistency with ATSDR policy.
2. Health Effects Review. The Health Effects Review Committee examines the health effects chapter of each profile for consistency and accuracy in interpreting health effects and classifying end points.
3. Minimal Risk Level Review. The Minimal Risk Level Workgroup considers issues relevant to substance-specific minimal risk levels (MRLs), reviews the health effects database of each profile, and makes recommendations for derivation of MRLs.
4. Data Needs Review. The Research Implementation Branch reviews data needs sections to assure consistency across profiles and adherence to instructions in the Guidance.





## PEER REVIEW

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

1. Dr. Herbert Cornish, Private Consultant, Ypsilanti, MI;
2. Dr. Ernest McConnell, Private Consultant, Raleigh, NC; and
3. Mr. Lyman Skory, Private Consultant, Midland, MI.

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

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

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



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## 1. PUBLIC HEALTH STATEMENT

This public health statement tells you about hexamethylene diisocyanate (HDI) and the effects of exposure.

The Environmental Protection Agency (EPA) identifies the most serious hazardous waste sites in the nation. These sites make up the National Priorities List (NPL) and are the sites targeted for long-term federal clean-up activities. Hexamethylene diisocyanate has not been found in any of the 1,445 current or former NPL sites. However, the total number of NPL sites evaluated is not known. As more sites are evaluated, the number of sites at which HDI is found may increase. This is important because exposure to this substance may harm you and because these sites may be sources of exposure.

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

If you are exposed to hexamethylene diisocyanate, many factors determine whether you'll be harmed. These factors include the dose (how much), the duration (how long), and how you come in contact with it. You must also consider the other chemicals you're exposed to and your age, sex, diet, family traits, lifestyle, and state of health.

### 1.1 WHAT IS HEXAMETHYLENE DIISOCYANATE?

HDI is the common name for hexamethylene diisocyanate. It is also known as 1,6-hexamethylene diisocyanate, 1,6-diisocyanatohexane, Mondur HX, and Desmodur H. It is a pale yellow liquid with a strong odor. HDI is found in hardening agents for automobile paints.

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### 1.2 WHAT HAPPENS TO HDI WHEN IT ENTERS THE ENVIRONMENT?

HDI is most often found in air near locations where spray paints that contain it as a hardening agent are used, HDI in the air can enter the soil and water. HDI can also enter the soil if products containing it are dumped directly onto the soil. HDI can enter the water supply by washing out of soil that contains it or if products with HDI are dumped directly into water. Once it is in soil or water, HDI breaks down very quickly, so evaporation into the air is not expected. HDI also breaks down very quickly in the air, so it probably will not build up in the environment.

### 1.3 HOW MIGHT I BE EXPOSED TO HDI?

The most common products that contain HDI are called hardening agents and are used to spraypaint cars. The most common way a person can be exposed to HDI is by breathing air that contains it as a vapor or mist, like that made when spray-painting a car. Most of the people who are exposed to HDI work in the automotive painting industry or in areas where this is done. If you do this kind of work, you can be exposed to more HDI if you do not wear the right protective safety equipment such as a respirator or mask. If your safety equipment does not fit right or does not work properly when you are using products that contain HDI, you may be exposed to larger amounts. You can probably absorb some HDI through your skin. You could also accidentally swallow HDI if it is on your hands and you do not wash them before eating, drinking, or smoking.

Unless you have been employed in the automobile refinishing or other business where painters manually mix two-component polyurethane paint systems, it is unlikely that you will be exposed to large amounts of HDI.

## 1. PUBLIC HEALTH STATEMENT

### 1.4 HOW CAN HDI ENTER AND LEAVE MY BODY?

The most common way HDI enters your body is by breathing air that has it in it. You can probably absorb some HDI through your skin, and you can also accidentally swallow HDI if it is on your hands and you do not wash them before eating, drinking, or smoking. Once inside your body, HDI breaks down very quickly and is quickly excreted in the urine. Some HDI can attach itself to protein in your blood, but we do not know how long it takes for this form of HDI to break down and be excreted.

### 1.5 HOW CAN HDI AFFECT MY HEALTH?

To protect the public from the harmful effects of toxic chemicals and to find ways to treat people who have been harmed, scientists use many tests.

One way to see if a chemical will hurt people is to learn how the chemical is absorbed, used, and released by the body; for some chemicals, animal testing may be necessary. Animal testing may also be used to identify health effects such as cancer or birth defects. Without laboratory animals, scientists would lose a basic method to get information needed to make wise decisions to protect public health. Scientists have the responsibility to treat research animals with care and compassion. Laws today protect the welfare of research animals, and scientists must comply with strict animal care guidelines.

How HDI affects your health depends on how much is in the air you breathe. Tests using laboratory animals showed that breathing in high concentrations of HDI can irritate the nose, eyes, and throat. High concentrations have also caused pneumonia, difficulty in breathing, and death in some animals. Swallowing high concentrations of HDI also killed laboratory animals. When placed on the skin of these animals, HDI caused redness, irritation, and irreversible skin damage. People would probably be affected in many of the same ways if they were exposed to large amounts of HDI in air.

## 1. PUBLIC HEALTH STATEMENT

Many people who breathe in vapors from products with small amounts of HDI for many months or many years may develop an allergic, asthma-like reaction. Symptoms usually develop very slowly over a long time (months or years), but they can also develop within a couple of weeks after first breathing in HDI. At low concentrations, sensitized workers develop a burning sensation and a feeling of tightness in the chest, a cough (with and without phlegm), fever, and chills. They have a hard time breathing during their work day when using a product containing HDI. These signs usually are not seen on weekends, during vacations, or any time the person is not using a product that contains HDI. These reactions usually begin again soon after the person returns to work and begins to use the product with HDI.

Some studies in laboratory animals showed that, when breathed in over a long time, HDI did not produce cancer. No studies that show that HDI can cause cancer in people have been found.

### **1.6 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO HDI?**

Before you ask for special medical tests for HDI, you should talk with your doctor and tell him you work in a place that uses products that contain HDI. There are no good medical tests for finding out if you have been exposed to HDI. Some tests are available that measure the antibodies against HDI your body makes after you have been exposed to it. However, these blood tests are not very good because they can react with other substances that look like HDI in your blood. The test can show that you have been exposed to HDI when really you have not been exposed to it (false positives). Also, some people do not develop antibodies to HDI after they have been exposed. Another test looks for the breakdown products of HDI in the urine. This test is only good if you were exposed to HDI within the last 12-15 hours. It is not a good test to find out if you have been exposed to low amounts of HDI over many months or years. -

Unless you have been employed in the automobile refinishing or other business where painters manually mix two-component polyurethane paint systems, it is unlikely that you have been exposed to significant amounts of HDI. Your doctor can give you more information on medical tests that are available for determining if you have been exposed to HDI.

## 1. PUBLIC HEALTH STATEMENT

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

The federal government develops regulations and recommendations to protect public health. Regulations can be enforced by law. Federal agencies that develop regulations for toxic substances include the Environmental Protection Agency (EPA), the Occupational Safety and Health Administration (OSHA), and the Food and Drug Administration (FDA). Recommendations provide valuable guidelines to protect public health but cannot be enforced by law. Federal organizations that develop recommendations for toxic substances include the Agency for Toxic Substances and Disease Registry (ATSDR) and the National Institute for Occupational Safety and Health (NIOSH).

Regulations and recommendations can be expressed in not-to-exceed levels in air, water, soil, or food that are usually based on levels that affect animals, then they are adjusted to help protect people. Sometimes these not-to-exceed levels differ among federal organizations because of different exposure times (an 8-hour workday or a 24-hour day), the use of different animal studies, or other factors.

Recommendations and regulations are also periodically updated as more information becomes available. For the most current information, check with the federal agency or organization that provides it. Some regulations and recommendations for HDI include the following.

The EPA proposes to list HDI as a hazardous substance that will be required to be reported under the Emergency Planning and Community Right-to-Know Act for 1986 and the Pollution Prevention Act of 1990. Currently, some owners and operators using HDI are required to report every year how much HDI they release into the environment.

The NIOSH-recommended limit for occupational exposure is 0.035 milligrams of HDI per cubic meter of air (0.035 mg/m<sup>3</sup>), which is the same as 5 parts of HDI per billion parts of air (ppb). There is no established OSHA permissible exposure limit (PEL) for HDI at this time; however, a similar substance, toluene diisocyanate (TDI), has a PEL of 5 parts per billion (ppb).

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### 1.8 WHERE CAN I GET MORE INFORMATION?

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

Agency for Toxic Substances and Disease Registry  
Division of Toxicology  
1600 Clifton Road NE, Mailstop E-29  
Atlanta, GA 30333  
Internet address: <http://atsdrl.atsdr.cdc.gov>:8080

\* Information line and technical assistance  
Phone: (800) 447- 1544  
Fax: (404) 639-6315 or 6324

ATSDR can also tell you the location of occupational and environmental health clinics. These clinics specialize in recognizing, evaluating, and treating illnesses resulting from exposure to hazardous substances.

\* To order toxicological profiles, contact

National Technical Information Service  
5285 Port Royal Road  
Springfield, VA 22161  
Phone: (800) 553-6847 or (703) 487-4650



## 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 lowest observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELs have been classified into "less serious" or "serious" effects. "Serious" effects are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). "Less serious" effects are those that are not expected to cause significant dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether an end point should be classified as a NOAEL, "less serious" LOAEL, or "serious" LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify 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

## 2. HEALTH EFFECTS

is considered to be important because it helps the users of the profiles to identify levels of exposure at which major health effects start to appear. LOAELs or NOAELs should also help in determining whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

The significance of the exposure levels shown in the Levels of Significant Exposure (LSE) tables and figures may differ depending on the user's perspective. Public health officials and others concerned with appropriate actions to take at hazardous waste sites may want information on levels of exposure associated with more subtle effects in humans or animals (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.

## 2. HEALTH EFFECTS

### 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 known 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

## 2. HEALTH EFFECTS

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 trimer 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=10 males and 10 females per group) were exposed to 105, 143, 259, 341, 383, 443, 575, 589, or 719 mg HDI/m<sup>3</sup> (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<sup>3</sup> (15.3, 20.7 ppm) groups. Deaths occurred in 4 of 10 males and 1 of 10 females exposed to 259 mg HDI/m<sup>3</sup> (37.6 ppm); 9 of 10 males and 5 of 10 females exposed to 341 mg HDI/m<sup>3</sup> (49.4 ppm); 7 of 10 males and 6 of 10 females exposed to 383 mg HDI/m<sup>3</sup> (55.5 ppm); 8 of 10 males and 8 of 10 females exposed to 443 mg HDI/m<sup>3</sup> (64.2 ppm); 8 of 10 males and 9 of 10 females exposed to 575 mg

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HDI/m<sup>3</sup> (83.4 ppm); 9 of 10 males and 9 of 10 females exposed to 589 mg HDI/m<sup>3</sup> (85.4 ppm); and 10 of 10 males and 10 of 10 females exposed to 719 mg HDI/m<sup>3</sup> (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<sub>50</sub>) was calculated to be 310 mg/m<sup>3</sup> (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 chronic durations. 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

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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 2-1 and plotted in Figure 2-1.

### 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 2-1 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 confirm 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-1 second (FEV<sub>1</sub>), 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 <sup>a</sup>	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL		Reference Chemical Form
					Less serious (ppm)	Serious (ppm)	
<b>ACUTE EXPOSURE</b>							
<b>Death</b>							
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
<b>Systemic</b>							
6	Human	5 min	Resp  Hemato Metab		0.02 M (cough, inspiratory crackles, decreased FVC, PaO <sub>2</sub> , TLC, and VC)  0.02 M (elevated WBC count) 0.02 M (chills, increased body temperature)		Malo et al. 1983 polymeric HDI
7	Rat (Sprague-Dawley)	6 hr	Resp  Bd Wt		3 M (nasal irritation)	88 M (moderate to severe pulmonary edema and congestion)	Dow Chemical Co. 1964 HDI
				88 M			

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

Key to figure <sup>a</sup>	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL		Reference Chemical Form
					Less serious (ppm)	Serious (ppm)	
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 Bd Wt	27 M 27 M	72 M (cyanosis) 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 Bd Wt	30 M	30 M (corneal ulcer)		
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 <sub>50</sub> 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 <sup>a</sup>	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL		Reference Chemical Form
					Less serious (ppm)	Serious (ppm)	
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			
<b>Immunological/Lymphoreticular</b>							
16	Human	5 min			0.02 M (increased airway hyperexcitability and increased specific IgG against HDI-HSA)		Malo et al. 1983 polymeric HDI
<b>Neurological</b>							
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 figure <sup>a</sup>	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL		Reference Chemical Form
					Less serious (ppm)	Serious (ppm)	
<b>INTERMEDIATE EXPOSURE</b>							
<b>Systemic</b>							
19	Rat (Sprague-Dawley)	3 wk 5 d/wk 5 hr/d	Resp	0.005 <sup>b</sup>	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 <sup>a</sup>	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL		Reference Chemical Form
					Less serious (ppm)	Serious (ppm)	
<b>Immunological/Lymphoreticular</b>							
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
<b>Neurological</b>							
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
<b>Reproductive</b>							
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 figure <sup>a</sup>	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL		Reference Chemical Form
					Less serious (ppm)	Serious (ppm)	
<b>CHRONIC EXPOSURE</b>							
<b>Systemic</b>							
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 <sub>1</sub> , VC)		Tornling et al. 1990 HDI
31	Human	16.5 yrs	Resp		0.005 M (increase in wheezing; decrease in FVC, FEV <sub>1</sub> , VC)		Tornling et al. 1990 HDIt

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

Key to figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL		Reference Chemical Form
					Less serious (ppm)	Serious (ppm)	
32	Rat (Fischer- 344)	1 and 2 yrs 5 d/wk 6 hr/d	Resp		0.005 <sup>c</sup> 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			
<b>Immunological/Lymphoreticular</b>							
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 <sup>1</sup>		0.175			Mobay 1989 HDI
<b>Neurological</b>							
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 <sup>a</sup> figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL		Reference Chemical Form
					Less serious (ppm)	Serious (ppm)	
<b>Reproductive</b>							
38	Rat (Fischer- 344)	1 and 2 yrs 5 d/wk 6 hr/d		0.175			Mobay 1989 HDI

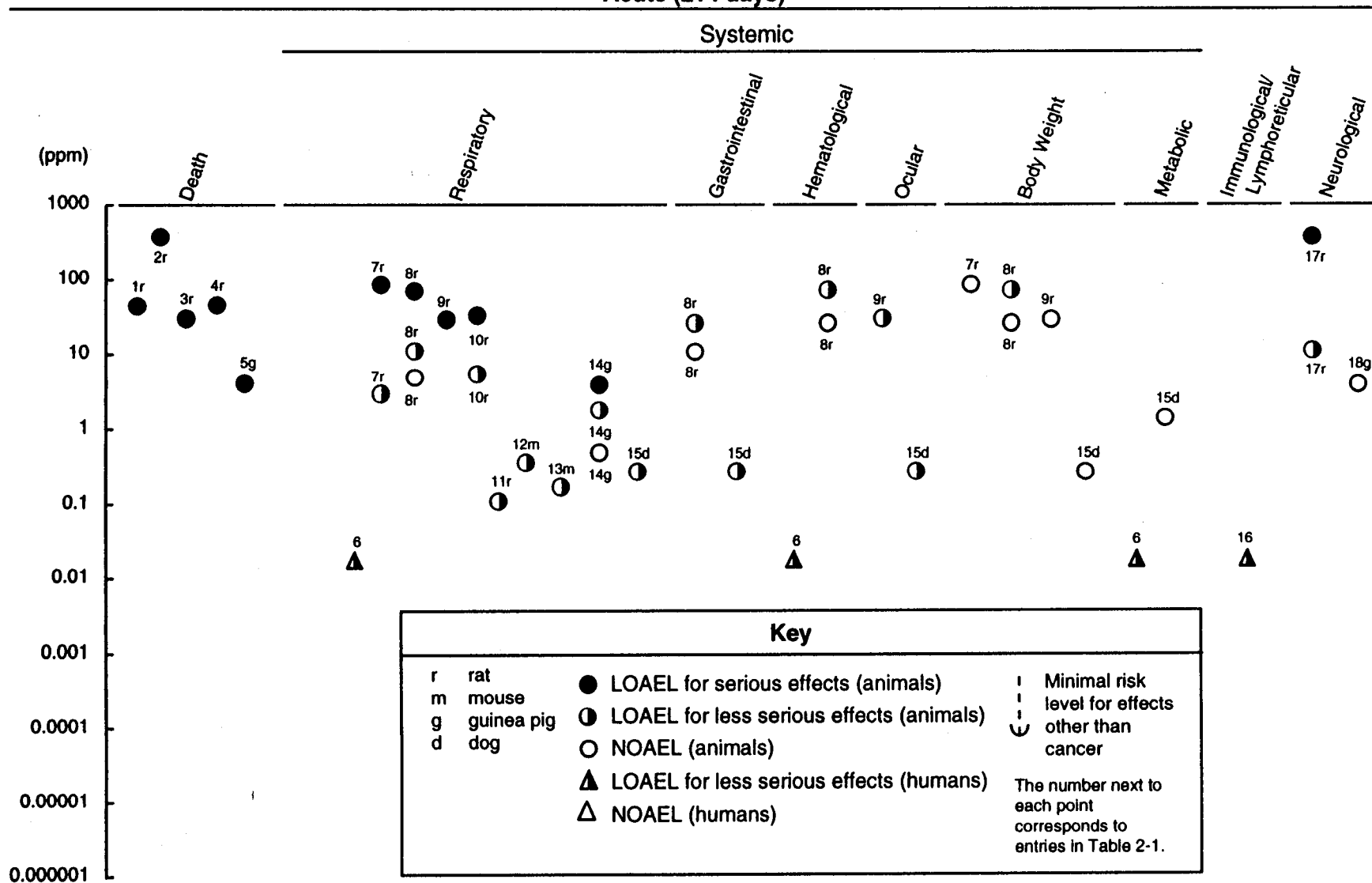
<sup>a</sup> The number corresponds to entries on Figure 2-1.

<sup>b</sup> Used to derive an intermediate inhalation minimal risk level (MRL) of 0.00003 ppm ( $3 \times 10^{-5}$ ) 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).

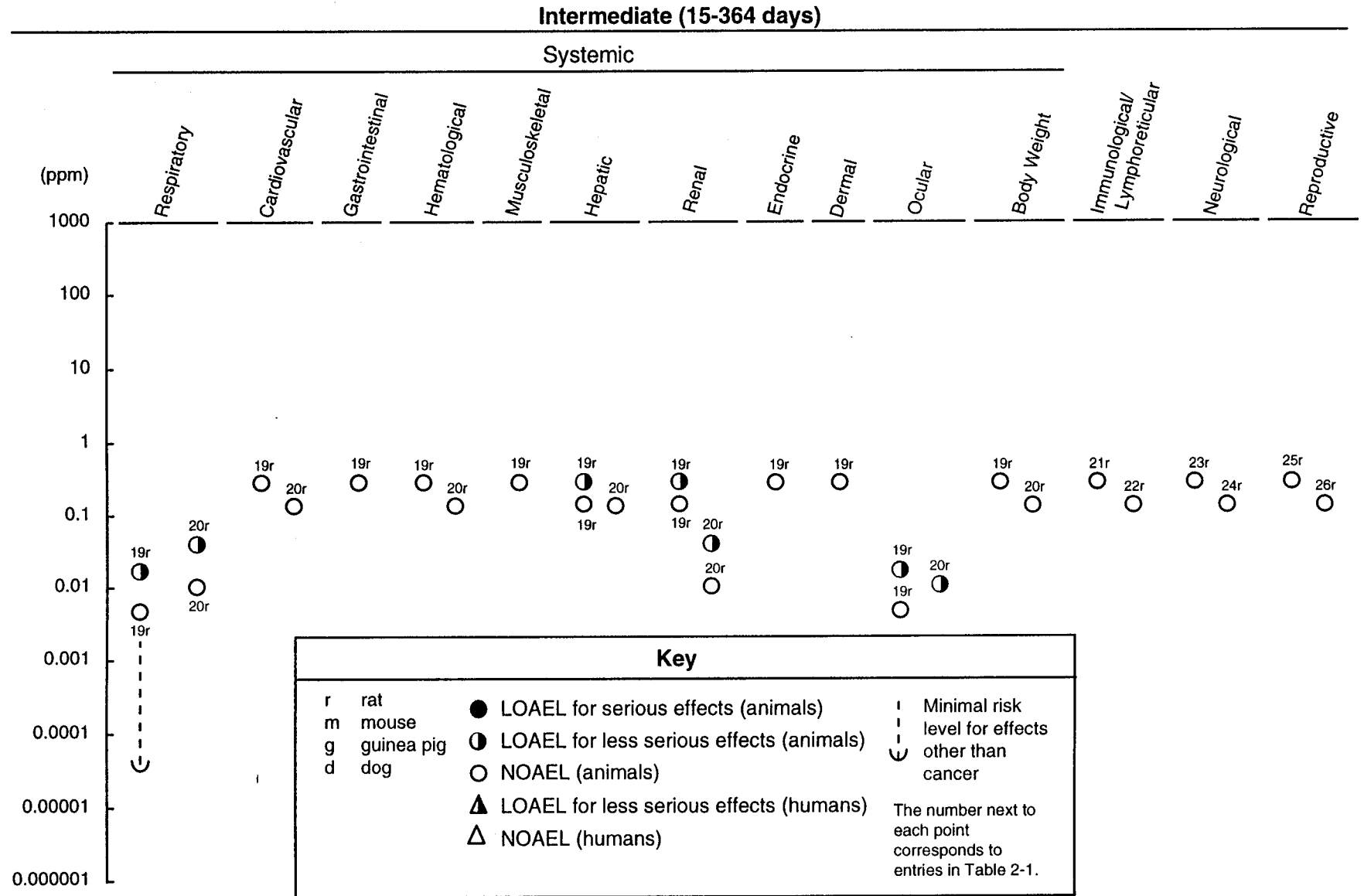
<sup>c</sup> Used to derive a chronic inhalation MRL of 0.00001 ppm ( $1 \times 10^{-5}$ ) using the regional gas dose ratio (ventilation to respiratory surface areas, animal:human); concentration divided by an uncertainty factor of 90 (3 for use of a minimal LOAEL, 3 for extrapolation from animals to 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<sub>2</sub> = 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 ( $\leq 14$  days)**



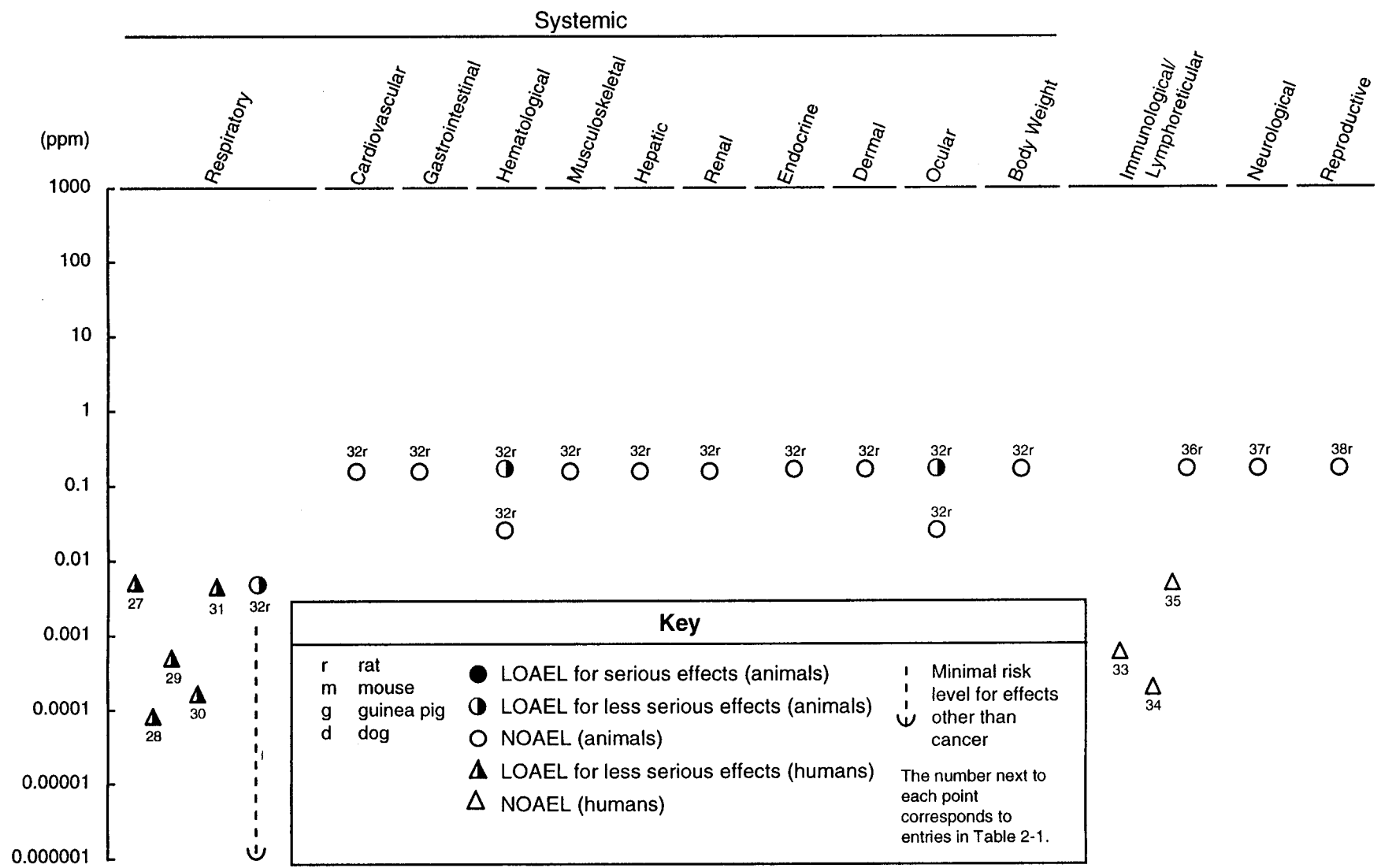
**Figure 2-1. Levels of Significant Exposure to Hexamethylene Diisocyanate - Inhalation (cont.)**





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

**Chronic ( $\geq 365$  days)**



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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<sub>1</sub>/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<sub>1</sub> also improved. This report suggested that the HDI 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<sub>2</sub>) and a bronchial reaction (characterized by drops in FEV<sub>1</sub>/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<sub>1</sub> 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<sub>1</sub> after 340 units; however, a subsequent challenge with methacholine following all of the HDI exposures gave a 20% decline in FEV<sub>1</sub> 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 known 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  $30 \pm 7$  years for the exposed workers and  $35 \pm 10$  years for controls; 47% of the exposed workers were smokers compared to 15% of the controls. Mean personal air samples indicated exposure to  $1.55 \pm 1.63$  ppb (approximately 0.002 ppm) HDI in exposed workers compared to  $0.67 \pm 0.25$  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 (FVC), 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 increase was not considered significant ( $p < 0.1$ ). 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  $FEV_1$  ( $p < 0.001$ ). Mean air samples indicated exposure to  $0.0010 \pm 0.0004$  ppm HDI,  $0.29 \pm 0.35$  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<sup>3</sup> (15.3,20.7,37.6,49.4,55.5,64.2, 83.4, 85.4, 104.3 ppm) in inhalation chambers 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 10-20 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<sub>50</sub>) were 0.96,0.35,0.35,0.22, and 0.17 ppm for the 10-, 30-, 60-, 120-, and 180 minute 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 2 minute 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 -1.95 ppm for IEP. The concentration that produced RD<sub>50</sub> was determined. HDI was determined to be approximately 3 times more irritating than TDI, IEM, and IEP, with an RD<sub>50</sub> 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<sub>50</sub> 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 (0.27-1.43 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<sup>3</sup> (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<sub>2</sub> in 20% O<sub>2</sub> and 70% N<sub>2</sub>, as indicators of ventilatory response. Particle sizes had a mass median diameter of 0.38 µm at low concentrations of HDI polymer and 0.73 µm at high exposures, with 98% of all particles (by weight) measuring <3 µm. Four animals were exposed to 22 mg/m<sup>3</sup> (1.1 ppm) and 84 mg/m<sup>3</sup> (4.3 ppm) HDI trimer for 3 hours per day for one exposure, challenged with CO<sub>2</sub> 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<sub>2</sub> as well as coughing and apnea. Their ventilatory response to 10% CO<sub>2</sub> 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<sub>2</sub> challenge. No

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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<sup>3</sup> (1.4 ppm-1.8 ppm) and during the 11-day exposure ranged from 65.1 to 74.4 mg/m<sup>3</sup> (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<sub>2</sub> in 20% O<sub>2</sub> and 70% N<sub>2</sub>, 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<sub>2</sub>. 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 1-month duration. Symptoms were reported to subside on weekends. He had used paint materials containing HDI 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  $3.0 \times 10^{-5}$  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



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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 case-control 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  $37.7 \pm 8.7$  years versus  $36.9 \pm 7.8$  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

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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 0.6-1.8 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 621 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 ( $p < 0.01$ ), urticaria/erythema, and hypersensitivity pneumonitis. Nonobstructive bronchitis was significantly more

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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 0.5-1% 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<sub>1</sub>), 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  $\mu\text{g}/\text{m}^3$  (0.006 ppm) (range, 10-385  $\mu\text{g}/\text{m}^3$  [0.0005-0.0197 ppm]). Nine of the 43 painters had exposures below 90  $\mu\text{g}/\text{m}^3$  (0.0046 ppm), 13 had exposure values between 90-180  $\mu\text{g}/\text{m}^3$  (0.0046-0.0092 ppm), and 9 had exposures between 180-360  $\mu\text{g}/\text{m}^3$  (0.0092-0.0184 ppm). Two workers had exposures in excess of 360  $\mu\text{g}/\text{m}^3$  (0.0184 ppm). High short-time exposure peaks of up to 13,500  $\mu\text{g}/\text{m}^3$  (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

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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 ( $FEV_1$ ),  $FEV_1\%$  ( $FEV_1/FVC \times 100$ ), 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  $0.0015 \text{ mg/m}^3$  (0.0002 ppm) HDI and  $0.09 \text{ mg/m}^3$  (0.005 ppm) HDI-BT. Painters reported a statistically significant higher frequency of wheezing than did controls for both the never-smoked 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  $p < 0.001$ , 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

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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 (ELISA) 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  $<0.08$ - $3.8 \mu\text{g}/\text{m}^3$  ( $0.00001$ - $0.0006$  ppm), while for HDI trimer the mean exposure levels were  $5.3$ - $75 \mu\text{g}/\text{m}^3$  ( $0.0003$ - $0.004$  ppm) among all classifications of work, with mean duration of exposure ranging from 24 to 51 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-to mild focal to multifocal lesions, classified as epithelialization (alveolar lining cell proliferation), interstitial pneumonia (septal thickening, alveolar cellular content, and increased alveolar lining 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 1-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 1-year exposure group at the same dose of HDI was also noted (Mobay Corporation 1989). A chronic inhalation MRL of  $1.0 \times 10^{-5}$  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

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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

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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 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. 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 unknown air concentration of HDI. The investigators estimated that 0.4% of the HDI in a bubbler was

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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 10-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,

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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 chronic duration 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, 0.27-1.43 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 1-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 3-11 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 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 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 exposure. 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 HDI 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  $3.8 \mu\text{g}/\text{m}^3$  (0.00001-0.0006 ppm), while for HDI trimer the mean exposure levels were  $5.3\text{-}75 \mu\text{g}/\text{m}^3$  (0.0003-0.0038 ppm) among all classifications of work, with mean duration of exposure ranging from 24 to 51 months. HDI 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 >1:1,000 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 were obtained from each person and analyzed via an ELISA using human serum albumin conjugates to each isocyanate for relative amounts of 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 symptomatology (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 ( $p < 0.01$ ), 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 1-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

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hours. Upon initial physical exam, no chest anomalies were found. To confirm that HDI was the compound responsible, the man was removed from the garage environment for several weeks and lung parameters were measured, including FEV<sub>1</sub>, 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 hours a day, 5 days 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 2-1 and plotted in Figure 2-1.

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### 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 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. 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 HDI 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 °C, 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 2-1.

### 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 2-1.

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### 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 HDI 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

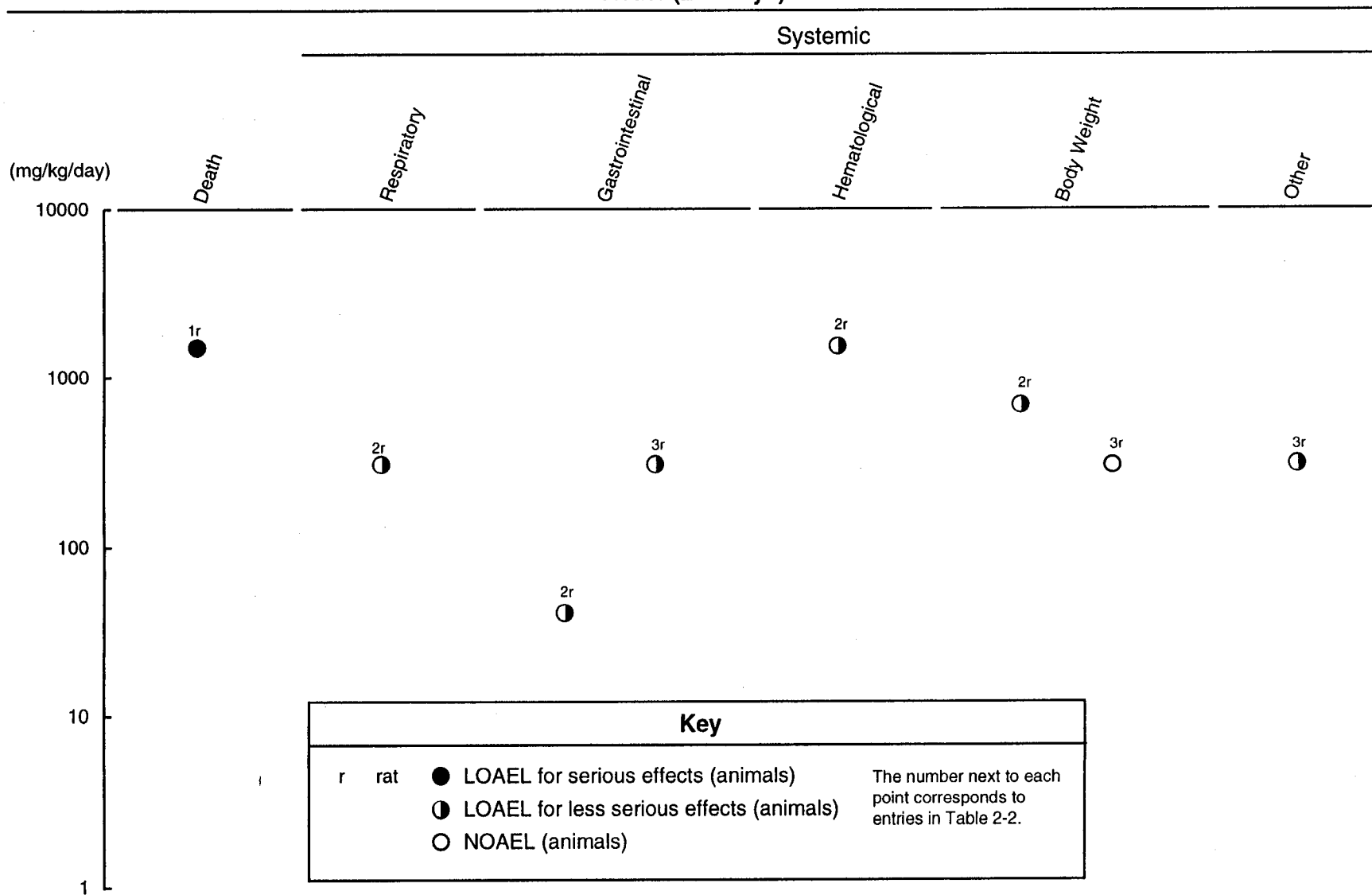
Key to <sup>a</sup> figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
<b>ACUTE EXPOSURE</b>							
<b>Death</b>							
1	Rat (CD)	once (G)				1500 M (approximate lethal dose)	Haskell Laboratory 1961
<b>Systemic</b>							
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)		

<sup>a</sup>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 ( $\leq 14$  days)**



## 2. HEALTH EFFECTS

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 chronic-duration 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 chronic-duration 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).

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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	
<b>ACUTE EXPOSURE</b>						
<b>Death</b>						
Mouse (BALB/c)	once				2800 M (5/5 died within 16 hrs of mg/kg exposure)	Thorne et al. 1987
<b>Systemic</b>						
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
<b>Immunological/Lymphoreticular</b>						
Mouse (BALB/c)	once			0.5 (dermal sensitization in 50% of animals)		Karol and Kramarik 1996
Mouse (BALB/c)	once			0.2 M (dermal sensitization in mg/kg 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		Reference
				Less Serious	Serious	
Mouse (BALB/c)	once			0.088 M (dermal sensitization in mg/kg 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
<b>INTERMEDIATE EXPOSURE</b>						
<b>Systemic</b>						
Gn Pig (albino)	3 wk 9 x	Dermal	0.05%	0.5% M (allergic contact dermatitis)		Haskell Laboratory 1961
<b>Immunological/Lymphoreticular</b>						
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

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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

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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) corneal 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 corneal lesions of both eyes and inflammation of the eyelids of the unwashed eye were also observed 8 days after treatment (Haskell Laboratory 1961).



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In a similar study, a single application of 100  $\mu$ L 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 corneal 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

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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  $\mu\text{g}$  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  $\mu\text{g}$  up to and including 100  $\mu\text{g}$  HDI, although not as clearly defined as with the companion guinea pig study. As the dose continued to increase above 100  $\mu\text{g}$ , the mean ear thickness began to decrease. Further analysis showed a clear dose-response relationship between the topical doses of 5 and 10  $\mu\text{g}$ . 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 homologous 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).

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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  $\mu$ L 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  $\mu$ L of the chemical was applied to each side of the right ear (40  $\mu$ L) total and an equal volume of acetone was applied to the left ear. The doses used for the challenge application, 40  $\mu$ g PI and 100  $\mu$ g 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  $\mu$ mol/Kg, compared with  $SD_{50}$  values of 0.5, 2.1, and 30.4  $\mu$ mol/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 10), moderate (1 of 10), and strong (2 of 10) erythema and erythema plus edema (6 of 10) was observed 24 hours after challenge and mild (1 of 10), moderate (2 of 10), 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

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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

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(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

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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 95-115 µg (0.01-0.02 ppm) of HDI in air (range, 25-29 µg/m<sup>3</sup> or approximately 0.004 ppm) for 7.5 hours. Blood

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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  $\mu\text{g/hr}$ , 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  $\mu\text{g}$ , which is about 11-21% 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; 1-6% 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

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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.



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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.

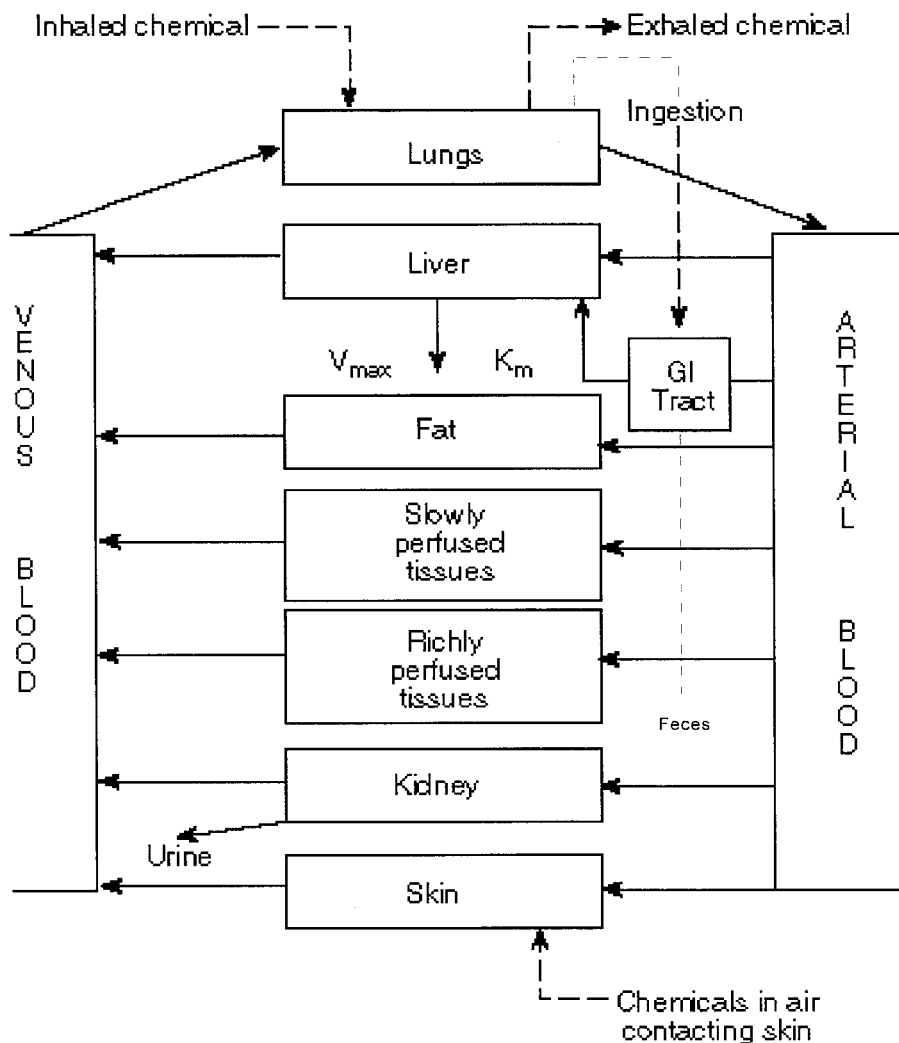
No PBPK/PD models were identified for HDI in the open literature.

### 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, pharyngeal 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 1961; Mobay Corp. 1981a; 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 macromolecules 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.

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**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.

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### 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.

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### **Minimal Risk Levels for Hexamethylene Diisocyanate.**

#### ***Inhalation MRLs.***

- An MRL of  $3.0 \times 10^{-5}$  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

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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 >1 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 attributed 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  $1.0 \times 10^{-5}$  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

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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  $1.0 \times 10^{-5}$  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,  $1.0 \times 10^{-5}$  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 is 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.

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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<sub>50</sub> values (lethal concentration, 50% kill) may be difficult to derive (Dow Chemical 1964, Haskell Laboratory 1961). Kimmerle (1976) reported an LC<sub>50</sub> of 45 ppm in male Wistar rats; however, this may be the LC<sub>50</sub> 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,

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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<sub>50</sub> 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 (<1-20 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<sub>2</sub> 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 >1 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

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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 < 1 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, 1961). 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 0.1%, 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  $\geq 0.164$  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

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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 serum 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  $\mu\text{mol}$  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

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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  $\mu\text{g}/\text{m}^3$  to 29  $\mu\text{g}/\text{m}^3$  (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.



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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

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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).

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### 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

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

	Death	Acute	Intermediate	Chronic	Systemic	Immunologic/Lymphoretic	Neurologic	Reproductive	Developmental	Genotoxic	Cancer
Inhalation		●	●	●	●						
Oral											
Dermal											

**Human**

	Death	Acute	Intermediate	Chronic	Systemic	Immunologic/Lymphoretic	Neurologic	Reproductive	Developmental	Genotoxic	Cancer
Inhalation	●	●	●	●	●	●	●		●	●	
Oral	●	●									
Dermal	●	●	●	●							

**Animal**

● Existing Studies

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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 Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (ATSDR 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

### 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.

## 2. HEALTH EFFECTS

**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 in males or females or on the developing fetus; 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. 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 in 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.

## 2. HEALTH EFFECTS

**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.



## 2. HEALTH EFFECTS

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 Medicin 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

## 2. HEALTH EFFECTS

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.

## 2. HEALTH EFFECTS

**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



### 3. CHEMICAL AND PHYSICAL INFORMATION

#### 3.1 CHEMICAL IDENTITY

Information regarding the chemical identity of HDI is located in Table 3-1. Most of the HDI manufactured in, or imported into, the United States is converted into HDI prepolymers (polyisocyanates). These prepolymers are biurets and trimers. Information for those prepolymers is shown in Table 3-2.

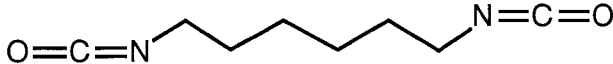
#### 3.2 PHYSICAL AND CHEMICAL PROPERTIES

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

HDI is a monomer used in the production of polyurethane foams and other related products, and is found in some industrial paints and spray painting operations. It is a compound which reacts readily with water and alcohols (Von Burg 1993). It has a vapor pressure of 0.05 mm Hg at room temperature, but can be present in aerosol form allowing a potentially higher exposure to individuals. The HDI-BT trimer is often present for similar industrial uses. It would be expected to have a lower vapor pressure; however, the aerosol form can also be present, allowing potentially higher exposure of HDI-BT to individuals. HDI reacts slowly with water to form carbon dioxide (HSDB 1996). The base-catalyzed reaction of HDI with alcohols should be carried out in inert solvents; the reaction may occur with explosive violence in the absence of solvents (NFPA 1994).

## 3. CHEMICAL AND PHYSICAL INFORMATION

**Table 3-1. Chemical Identity of Hexamethylene Diisocyanate**

Characteristic	Information	Reference
Chemical name	1,6-Hexamethylene diisocyanate	HSDB 1996
Synonym(s)	1,6-Diisocyanatohexane; HDI; HMDI	HSDB 1996
Registered trade name(s)	TL-78; Desmodur H; Mondur HX	HSDB 1996; Bagon et al. 1984; Dunlap 1976
Chemical formula	OCN-(CH <sub>2</sub> ) <sub>6</sub> -NCO	HSDB 1996
Chemical structure		
Identification numbers:		
CAS Registry	822-06-0	Lewis 1993
NIOSH RTECS	MO1740000	HSDB 1996
EPA Hazardous Waste	No data	
OHM/TADS	No data	
DOT/UN/NA/IMCO	UN2281; IMO 6.1	HSDB 1996
HSDB	6134	HSDB 1996
NCI	No data	

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

Table 3-2. Chemical Identity of Hexamethylene Diisocyanate Prepolymers

Characteristic	HDI biuret	HDI trimer
Chemical name	Hexamethylene diisocyanate biuret	Hexamethylene diisocyanate trimer
Synonym(s)	N,N',2-tris(6-isocyanatohexyl)-imidodicarbonic diamide; HDI-BT	1,3,5-Tris(6-isocyanatohexyl)-1,3,5-triazine-2,4,6(1H,3H,5H)-trione; HDI isocyanurate
Registered trade name(s)	Desmodur N-75; Desmodur N-100; Desmodur N-3200	Desmodur N-3300; Desmodur N3390
Chemical formula	$C_{23}H_{38}N_6O_5$	$C_{24}H_{36}N_6O_6$
Chemical structure		
Identification numbers:		
CAS registry	4035-89-6	3779-63-3
NIOSH RTECS	NR0195000	None
EPA hazardous waste	None	None
OHM/TADS	None	None
DOT/UN/NA/IMCO shipping	None	None
HSDB	None	None
NCI	None	None

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

## References:

CCOHS 1998  
 Janko et al. 1992  
 Maitre et al. 1996

Myer et al. 1993  
 RTECS 1998

## 3. CHEMICAL AND PHYSICAL INFORMATION

**Table 3-3. Physical and Chemical Properties of Hexamethylene Diisocyanate**

Property	Information	Reference
Molecular weight	168.22	HSDB 1996
Color	Pale yellow	Von Burg 1993
Physical state	Liquid	Lewis 1993
Melting point	-67 °C	ASTER 1995
Boiling point	255 °C 212.8 °C at 760 mm Hg	ASTER 1995 NIOSH 1978
Density at 25 °C	1.04 g/mL 1.0528 g/mL	HSDB 1996 Weast 1988
Odor	Pungent	Von Burg 1993
Odor threshold:		
Water	Not applicable, reacts with water	HSDB 1996
Air	0.001–0.02 ppm	HSDB 1996
Solubility:		
Fresh water at 20 °C	Poorly soluble; reacts	NIOSH 1978; Von Burg 1993
Salt water at 25 °C	No data	
Organic solvent(s)	Soluble in organic solvents Reacts with alcohols	NIOSH 1978 Von Burg 1993
Partition coefficients:		
Log K <sub>ow</sub>	3.1956 (estimated)	SRC 1995b
Log K <sub>oc</sub>	No data	
Vapor pressure at 20 °C	0.014 mbar; 0.05 mm Hg (24 °C)	Morel et al. 1981; NIOSH 1978
Henry's law constant: at 25 °C	4.8x10 <sup>-5</sup> atm-m <sup>3</sup> /mole	SRC 1994a
Autoignition temperature	454 °C	Morel et al. 1981
Flashpoint	140 °C; 135 °C (open cup)	NIOSH 1978; Morel et al. 1981
Flammability limits at 25 °C	No data	
Conversion factors (25 °C)	1 µg/m <sup>3</sup> = 0.145 ppb 1 ppb = 6.879 µg/m <sup>3</sup>	NIOSH 1978 NIOSH 1978
Explosive limits	1–24%	Von Burg 1993



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

### 4.1 PRODUCTION

Isocyanates are produced almost exclusively by the reaction of amines with phosgene ( $\text{COCl}_2$ ), with the specific reaction conditions varying particularly for aromatic and aliphatic isocyanates (Chadwick and Cleveland 1981; Codd et al. 1972; Ulrich 1989). Aliphatic diisocyanates are produced by reaction of phosgene with either a slurry of the carbamate salts obtained in the reaction of the aliphatic diamines with carbon dioxide, or with a slurry of the amine hydrochloride (Ulrich 1989). Hexamethylene diisocyanate (HDI) is produced by the reaction of phosgene with the amine salt (Chadwick and Cleveland 1981). The trimeric HDI biuret (HDI-BT), which has a low monomer content and is widely used in the formulation of exceptionally high quality polymer coatings, is produced by controlled reaction of HDI with water, a water generator, or an amine (Chadwick and Cleveland 1981).

Current U.S. producers of HDI are Arco Chemical Company, Lake Charles, Louisiana and Bayer Corporation, Baytown, Texas (formerly, Mobay Corporation and Miles Incorporated) (Chemical Manufacturers Association 1997). Data on U.S. production volumes of HDI could not be located in the available literature.

No information is available in the Toxics Release Inventory database for facilities that produce HDI because this compound is not included under SARA, Title III and, therefore, is not among the chemicals that facilities are required to report (EPA 1995).

### 4.2 IMPORT/EXPORT

Rhone-Poulenc, Inc. imports HDI (Chemical Manufacturers Association 1997); however, no information on import volume was found in the available literature. No information on export volumes of HDI was found in the available literature.

### 4.3 USE

HDI is one of the most commercially important isocyanate compounds currently used in the United States, HDI, toluene diisocyanate (TDI) and 4,4'-diphenylmethane diisocyanate (MDI) are widely used in the

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

production of polyurethane foams, elastomers, and coatings, which account for more than 90% of the commercial use of isocyanates (Kennedy and Brown 1992). Specific products include plastics, synthetic rubber, adhesives and glues, cable and wire insulations, anti-corrosive agents, varnishes, lacquers, and paints (Codd et al. 1972; Parmeggiani 1983; Plunkett 1987). One of the primary uses of HDI is as a polymerizing agent in polyurethane spray paint formulations (Butcher et al. 1993) and in other light-stable polyurethane coatings (Ulich 1989). Other uses of HDI are as solid rocket fuel binder or as paint thickener (Chemical Manufacturers Association 1997). Because of the potentially high exposures to HDI resulting from its high vapor pressure (see Table 3-3), a prepolymeric form of HDI, which has a much lower vapor pressure, is finding increasing use in industrial applications (Chadwick and Cleveland 1981; Dalene et al. 1994a). For example, HDI-biuret (HDI-BT), a trimeric condensation product of HDI, is widely used as a hardener in automobile and airplane paints. Automobile paint hardeners typically contain 0.5-1.0% monomeric HDI (Alexandersson et al. 1987). Consequently, use of these spray paints is one of the most significant sources of exposure to monomeric HDI and its prepolymers (e.g., HDI-BT) (Butcher et al. 1993).

#### 4.4 DISPOSAL

There are no regulations specifically governing the treatment and disposal of wastes containing HDI. Toluene diisocyanate is, however, regulated under the Resource Conservation and Recovery Act (RCRA) (EPA 1989). The recommended technology-based standards for treatment of waste containing TDI are carbon adsorption or incineration for waste waters, and fuel substitution or incineration for non-waste waters (EPA 1989). Toxic fumes of nitrogen oxides are emitted when HDI is heated to decomposition (Lewis 1992). Because oxides of nitrogen are criteria pollutants, the potential for their release to the atmosphere must be controlled during heating or incineration of HDI or waste containing HDI. Bicarbonate-catalyzed hydrolysis of HDI to 1,6-hexamethylene diamine (HDA) has been suggested as a possible treatment method in scrubbers used to purify HDI-contaminated atmospheres (Berode et al. 1991). No data were found in the available literature on the amount of HDI disposed of in the United States.

## 5. POTENTIAL FOR HUMAN EXPOSURE

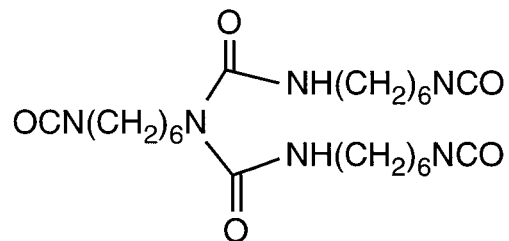
### 5.1 OVERVIEW

Hexamethylene diisocyanate is a highly reactive synthetic chemical that is widely used in the production of polyurethane materials. There is no natural source of HDI. All of the potential exposures to this compound are associated with the production, handling, use, and disposal of HDI and HDI-containing products or materials. Exposures to HDI are often associated with exposures to its prepolymers, especially to a trimeric biuretic prepolymer of HDI (HDI-BT) (see Figure 5-1a), which is widely used as a hardener in automobile and airplane paints, and which typically contains 0.5-1% unreacted HDI (Alexandersson et al. 1987; Hulse 1984; Karol and Hauth 1982). There is evidence that diisocyanate prepolymers may induce asthma at the same or greater frequency as the monomers (Seguin et al. 1987); therefore, there is a need to assess the potential for human exposure to prepolymeric HDI as well as monomeric HDI. Except for limited data on occupational exposures, no information was found in the available literature related to the potential for human exposure to prepolymers of HDI.

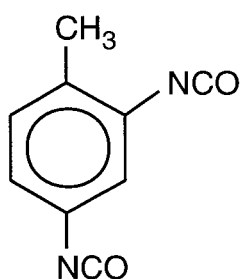
Little information is available about the potential for human exposure specifically to HDI. Some human exposure data have been published by Shepperly and Hathaway (1991) and DeWilde and Hathaway (1994); those study results and limitations have been discussed at length in Chapter 2. As a result, some of the information in this section has been extrapolated from the results of studies on the more widely used diisocyanates, particularly toluene diisocyanate (TDI) (see Figure 5-1b) and methylene bis(4-phenylisocyanate) (MDI) ( see Figure 5-1c). Information on the environmental fate of TDI and MDI is relevant to HDI because these diisocyanates undergo many of the same chemical reactions as HDI, particularly those such as hydrolysis, which involve reaction with active hydrogen compounds and addition to the carbon-nitrogen double bond of the highly reactive isocyanate group. In most of these reactions, the aromatic diisocyanates are more reactive than the aliphatic HDI (Chadwick and Cleveland 1981) so that direct quantitative extrapolations cannot be made.

No quantitative estimates of the volume of HDI or HDI prepolymers released to the environment were found in the available literature. HDI and HDI prepolymers may be released to the atmosphere during spray applications of polymer paints containing residual amounts ( $\leq 1\%$ ) of HDI (Alexandersson et al. 1987; Hulse 1984; Karol and Hauth 1982). Waste streams from HDI or HDI polymer production facilities may release HDI or HDI prepolymers to air, water, and soil. There is also a potential for release

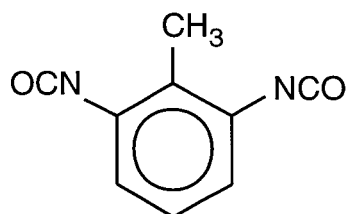
## 5. POTENTIAL FOR HUMAN EXPOSURE

**Figure 5-1. Selected Isocyanate Structures**

(a) Trimeric Biuret of Hexamethylene Diisocyanate (HDI-BT)

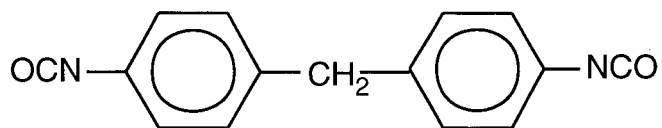


2,4-TDI



2,6-TDI

(b) Toluene Diisocyanate (TDI)



(c) Methylene Bis(4-phenylisocyanate) (MDI)

## 5. POTENTIAL FOR HUMAN EXPOSURE

of HDI to air, water, and soil at hazardous waste sites. HDI has not been found in any of the 1,445 current or former EPA National Priorities List (NPL) hazardous waste sites (HazDat 1996). However, the number of sites evaluated for HDI is not known.

In the atmosphere, HDI will exist entirely in the vapor phase (Bidleman 1988; Eisenreich et al. 1981). Partitioning to soil or water by wet or dry deposition are not expected to be significant fate processes for HDI. HDI degrades relatively rapidly in the atmosphere by reaction with hydroxyl radicals (half-life,  $\approx 2$  days), and may also undergo hydrolysis. Therefore, it is not expected that HDI will be transported long distances in the atmosphere. HDI is expected to hydrolyze rapidly (aqueous hydrolysis half-life,  $< 10$  minutes) in water and moist soil or sediment to form an amine (i.e., 1,6-hexamethylene diamine) and polyurea compounds. As a result, physical partitioning processes such as volatilization, leaching, and adsorption from water onto suspended particles or sediments will not be significant.

Except for occupational atmospheres, no information was found in the available literature on concentrations of HDI or HDI prepolymers in air, water, soil, or sediment. Because of the relatively rapid reaction of HDI with hydroxyl radicals in the atmosphere and its high reactivity with water, significant environmental concentrations of HDI are not expected to occur except near emission sources.

The general population may be exposed to HDI and HDI prepolymers during the nonoccupational use of polyurethane paints (Musk et al. 1988), primarily through inhalation of vapors and aerosols, and, to a much lesser extent, by dermal absorption. Occupational exposures to HDI and HDI prepolymers also occur via these routes. Estimates from the National Occupational Exposure Survey (NOES) conducted by the National Institute of Occupational Health (NIOSH) indicate that approximately 20,000 workers were potentially exposed to HDI in the United States from 1981 to 1983 (NIOSH 1989). This may be an underestimate because the numbers do not include workers potentially exposed to trade name compounds containing HDI. Professional painters and paint spraying-machine operators, aircraft engine and other mechanics, and aircraft machinists were among the occupations with the greatest potential for exposure to HDI. Similar data were not reported for HDI prepolymers; however, many of the potential HDI exposures may involve concurrent exposure to HDI prepolymers.

## 5. POTENTIAL FOR HUMAN EXPOSURE

### 5.2 RELEASES TO THE ENVIRONMENT

#### 5.2.1 Air

HDI and HDI prepolymers can be released to the atmosphere during spray applications of polymer paints containing residual amounts (0.5-1.%) of monomeric HDI (Alexandersson et al. 1987; Hulse 1984; Karol and Hauth 1982). These substances could also be released to the atmosphere from waste streams from sites of HDI or polymer production. No information is available in the Toxic Chemical Release Inventory database on the amount of HDI released to the atmosphere from facilities that produce or process HDI because this compound is not included under SARA, Title III, and therefore, is not among the chemicals that facilities are required to report (EPA 1995). There is also a potential for atmospheric release of HDI from hazardous waste sites; however, no information was found on detections of HDI in air at any NPL or other Superfund hazardous waste sites (1996). Because of the relatively rapid reaction of HDI with hydroxyl radicals in the atmosphere an possible hydrolysis (see Section 5.3.2.1), significant atmospheric concentrations are not expected to occur except near emission sources.

Releases of HDI and prepolymeric HDI to the atmosphere in occupational settings and available information on workplace exposure levels are discussed in Section 5.5.

#### 5.2.2 Water

Waste streams from sites of HDI or HDI polymer production may release HDI or HDI prepolymers to water. No information is available in the TRI database on the release of HDI to water from facilities that produce or process HDI because this compound is not included under SARA, Title III, and therefore, is not among the chemicals that facilities are required to report (EPA 1995). HDI and HDI prepolymers may also be released to water at hazardous waste sites; however, no information was found on detections of HDI in water at any NPL or other Superfund hazardous waste sites (HazDat 1996). Because of its reactivity with water to form amine or polyurea derivatives (Chadwick and Cleveland 1981; Hulse 1984; Kennedy and Brown 1992), monomeric HDI is not likely to be found in waste water streams or in other aquatic environments except near sources of release. Small amounts of HDI that have become encapsulated in water-insoluble polyurea agglomerates may persist in water (see Section 5.3.2.2).

## 5. POTENTIAL FOR HUMAN EXPOSURE

### 5.2.3 Soil

Waste streams from sites of HDI or HDI polymer production may release HDI and HDI prepolymers to soil. No information is available in the TRI database on the release of HDI to soil from facilities that produce or process HDI because this compound is not included under SARA, Title III, and therefore, is not among the chemicals that facilities are required to report (EPA 1995). HDI and HDI prepolymers may also be released to the soil at hazardous waste sites; however, no information was found on detections of HDI in soil at any NPL or other Superfund hazardous waste sites (HazDat 1996). Because of its expected reactivity with water in moist soil to form amine or polyurea derivatives, monomeric HDI is not likely to be found in soil in significant concentrations except near sources of release. Small amounts of HDI that have become encapsulated in water-insoluble polyurea agglomerates may persist in soils and sediments (see Section 5.3.2.3).

## 5.3 ENVIRONMENTAL FATE

### 5.3.1 Transport and Partitioning

No studies of the transport and partitioning of HDI in the environment were found in the available literature. Based on its vapor pressure of 0.05 mm Hg at 25 °C (see Table 3-3), HDI will exist entirely in the vapor phase in the atmosphere (Bidleman 1988; Eisenreich et al. 1981). Although the atmospheric hydrolysis of HDI with condensed water has not been investigated, wet deposition is probably not an important atmospheric removal process for HDI because of its reactivity with water (see Section 5.3.2.1). Because HDI exists as a vapor in the atmosphere, its removal from air by dry deposition is also likely to be negligible, although no estimates of the partition coefficient  $K_{oc}$ , for HDI are available to allow further evaluation of the potential for HDI to adsorb to airborne particles. Laboratory studies have shown that the highly adsorptive TDI vapor is not significantly removed from the atmosphere by dry deposition via adsorption on ammonium sulfate particles (reportedly the world predominant aerosol) (Duff 1985). Although TDI has a vapor pressure similar to that of HDI, the relevance of these results to the removal of HDI from the ambient atmosphere by dry deposition is not clear. Because of its relatively short atmospheric half-life of  $\approx 2$  days (SRC 1995a), and possible rapid hydrolysis (see Section 5.3.2), it is not expected that HDI will be transported long distances in air.

## 5. POTENTIAL FOR HUMAN EXPOSURE

Because of the rapid hydrolysis of HDI in water and moist soil or sediment (see Sections 5.3.2.2 and 5.3.2.3), neither volatilization from these media nor leaching from soil or sediment should be important partitioning processes. HDI would also not be expected to partition onto suspended solids and sediment in water. Henry's law constant(H) for HDI has been estimated to be  $4.80 \times 10^{-5}$  atm-m<sup>3</sup>/mol (SRC 1994a), which indicates a relatively slow rate of volatilization from water (Thomas 1990) and further suggests that with rapid hydrolysis occurring this would not be an important partitioning process. Estimates of  $K_{oc}$  (see Table 3-3) are not available to allow further evaluation of the possible importance of sorption partitioning processes. Also, because of the rapid hydrolysis of HDI in water and the ease with which this substance is metabolized in higher trophic animals (see Section 2.3), it is not expected that HDI will bioconcentrate in aquatic organisms or bioaccumulate in the food chain (Chadwick and Cleveland 1981; HSDB 1995; Hulse 1984). This conclusion is supported by the results of a study in which no accumulation of TDI, MDI, or their respective diamine hydrolysis products, TDA and MDA, was found in the whole bodies of carp (*Cyprinus carpio*) after 8 weeks of exposure in a river model system with initial TDI and MDI concentrations of 0.1 ppm (International Isocyanate Institute 1981). No bioconcentration factors (BCFs) for HDI in aquatic organisms were found in the available literature (ASTER 1995). A BCF of approximately 100 was calculated for HDI using the method of Veith et al. (1979), further indicating a very low bioaccumulation potential for HDI; however, the estimated  $\log K_{ow}$  value of 3.20 used for this calculation is questionable because of the rapid hydrolysis of isocyanates (SRC 1995b).

No information was found in the available literature on the transport and partitioning of HDI prepolymers. Because of their low vapor pressures (Rosenberg and Tuomi 1984), HDI prepolymers will exist in the atmosphere primarily as aerosols. Because of their reactive isocyanate groups, HDI prepolymers would not be expected to persist unchanged in the environment. Hydrolysis to form amines and higher molecular weight polyureas would be expected to be a controlling reaction in water and moist soil. However, additional studies are required to determine the environmental fate of HDI prepolymers.

### 5.3.2 Transformation and Degradation

#### 5.3.2.1 Air

No studies of the transformation and degradation of HDI in air were located in the available literature.



## 5. POTENTIAL FOR HUMAN EXPOSURE

Based on a vapor pressure of 0.05 mm Hg at 25 °C (see Table 3-3), HDI is expected to exist entirely in the vapor phase in the ambient atmosphere (Bidleman 1988; Eisenreich et al. 1981). The aliphatic isocyanates do not absorb light in the near ultraviolet region (Simons 1979); therefore, direct photolysis is not a probable atmospheric degradation mechanism for HDI. Based on a structure-reactivity relationship method (Atkinson 1987), the rate constant for the reaction of HDI with photochemically produced hydroxyl radicals in the atmosphere is estimated to be  $7.95 \times 10^{-12}$  cm<sup>3</sup>/molecule-sec at 25 °C, which corresponds to an estimated atmospheric half-life of approximately 2 days at 25 °C and an atmospheric concentration of hydroxyl radicals of  $5 \times 10^5$ /cm<sup>3</sup> (SRC 1995a). The products of the reaction of HDI with hydroxyl radicals have not been identified. The estimated rate constant for the reaction of HDI with hydroxyl radicals is in good agreement with the experimentally determined rate constant of  $7.4 \pm 0.2 \times 10^{-12}$  cm<sup>3</sup>/molecule-set for the reaction of TDI with hydroxyl radicals (International Isocyanate Institute 1987b).

Because isocyanates, including HDI, react readily with water to form amines and polyureas (Chadwick and Cleveland 1981; Hulse 1984; Kennedy and Brown 1992) (see Section 5.3.2.2) atmospheric hydrolysis of HDI may also occur. However, no estimates of the rate of atmospheric hydrolysis of HDI were found in the available literature. Laboratory studies indicate that reaction of TDI with water vapor in the atmosphere is not an important removal process (Duff 1983, 1985; Holdren et al. 1984); however, these studies did not investigate the condensed phase atmospheric hydrolysis of TDI (e.g., reaction with rain drops, fog, clouds). The typical half-life for aqueous hydrolysis of isocyanates, such as HDI, has been estimated to be less than 10 minutes (SRC 1994b), which suggests that the heterogeneous condensed phase atmospheric hydrolysis of HDI may proceed rapidly. Additional research is needed to determine the significance of atmospheric hydrolysis of HDI. No information was found in the available literature characterizing the atmospheric hydrolysis products of HDI. 1,6-Hexamethylene diamine (HDA) would be an expected atmospheric hydrolysis product, and this compound has been found in appreciable quantities in association with some HDI occupational exposures (Skarping et al. 1988). Results of laboratory studies indicate that the diamine (i.e., TDA) is not a significant product of gas phase hydrolysis of TDI (Duff 1983, 1985; Holdren et al. 1984). However, under simulated atmospheric conditions, the reactions of the diamine hydrolysis products of TDI and MDI with photochemically generated hydroxyl radicals have been found to proceed more rapidly than those of the parent compounds, suggesting that there would be no atmospheric accumulation of these diamines even if they were significant hydrolysis products (Gilbert 1988; International Isocyanate Institute 1987b). By

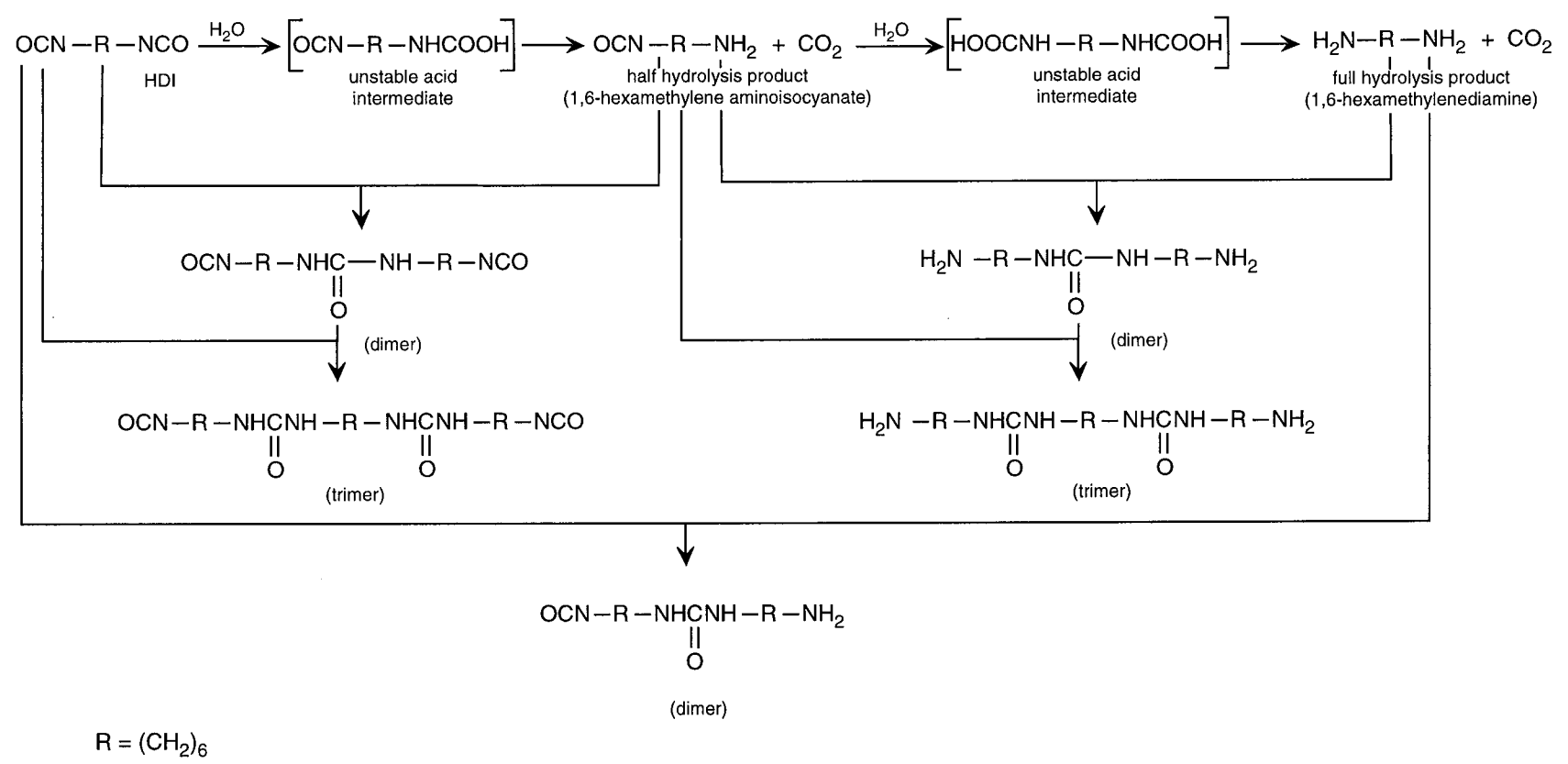
## 5. POTENTIAL FOR HUMAN EXPOSURE

analogy, significant atmospheric accumulation of HDA may not occur, except perhaps near sources of HDI emissions.

### 5.3.2.2 Water

Rapid hydrolysis is expected to be the only major transformation pathway for HDI in water. Typically, estimated aqueous hydrolysis half-lives of isocyanates such as HDI are less than 10 minutes (SRC 1994b). Although HDI is essentially insoluble in water (see Table 3-3), in the presence of excess water it can undergo competing two-phase reactions to form: (1) a complete hydrolysis product, HDA; (2) di-, tri-, or tetra-ureaisocyanates; and/or (3) higher molecular weight polyureas (Chadwick and Cleveland 1981; Hulse 1984; Kennedy and Brown 1992). The complex hydrolysis reactions of isocyanates usually involve a mechanism in which an unstable carbamic acid intermediate is initially formed, with subsequent decomposition to the amine and release of carbon dioxide; further reaction of the amine with isocyanate may occur to yield polyurea compounds (Chadwick and Cleveland 1981; Gilbert 1988; Kennedy and Brown 1992). A partial schematic of the possible hydrolysis reactions of HDI is shown in Figure 5-2. Studies on the environmental fate of TDI in water have shown that the polyurea hydrolysis products may form inert, water-insoluble agglomerates encapsulating small amounts of unreacted monomeric isocyanate (Brochagen and Grieveson 1984; Gilbert 1988) and it would be expected that this would also be the case for HDI. Laboratory studies of the hydrolysis of TDI in aqueous media have shown that the competing isocyanate hydrolysis reactions depend on several factors, including ionic strength, temperature, concentration of reactants, hydrophilic/hydrophobic nature of the reaction environment, mixing rate, and pH, with the formation of the diamine favored under basic or acidic conditions (Saunders and Frisch 1962). A single study of the hydrolysis of HDI (Berode et al. 1991) was found in the available literature, in which the reaction of HDI vapor with water in a dynamic system was found to be very slow without catalysts (<1% in 10 minutes at 30 °C; pH 7.4). However, under more typical physiologic conditions (i.e., in the presence of neutral buffers containing carboxylic acids), the hydrolysis of HDI vapor to HDA was markedly catalyzed, with a 20 mmol bicarbonate buffer being the optimum catalyst (95% in 10 minutes at 30 °C; pH 7.4). Results of experiments in a static system with liquid-phase HDI in water also indicated that the addition of simple carboxylic-acid-containing neutral buffers markedly increased the formation of HDA, with less acidic catalysts ( $pK_a > 6$ ), such as carbonic and citric acid, much more effective than those with higher acidity ( $pK_a < 5$ ), such as formic or oxalic acid. Because the experimental conditions of this study are not typical of those found in ambient or

Figure 5-2. Partial Scheme for Hydrolysis Reactions of Hexamethylene Diisocyanate



Source: Adapted from Kennedy and Brown 1992

Note: Top reaction sequence represents hydrolysis of isocyanate functions to corresponding amines. The remainder of the reaction scheme represents some of the potential side reactions of hexamethylene diisocyanate and the hydrolysis products of hexamethylene diisocyanate. Extended repetition of these reactions results in the formation of high molecular weight polyurea compounds.

## 5. POTENTIAL FOR HUMAN EXPOSURE

waste waters, it is not possible to draw any meaningful conclusions from the results regarding the rate of hydrolysis of HDI in these aquatic environments.

HDI is expected to be hydrolyzed much more quickly than it would undergo biodegradation in water, although the resulting amines should be subject to biodegradation (HSDB 1995). From initial concentrations of 50 ppm, both TDI and MDI (pure methylene bis[4-phenylisocyanate] and prepolymeric MDI consisting of short chain oligomers of MDI with reactive isocyanate terminal groups) were reported to be completely biodegraded (detection limits 0.02 ppm) within 15 days at 25 °C in a fresh water model river system with bottom sludge; whereas, in a similar salt water system, TDI could not be detected within 4 days and MDI disappeared after only one day (International Isocyanate Institute 1983, 1990). However, the role of hydrolysis in this process, which should be predominant, was not considered. The formation of TDA and MDA was observed, with maximum concentrations in fresh water of 0.3 and 0.1 ppm, respectively; and in marine water, of 4.0 and 0.02 ppm, respectively. TDA was not detected (detection limit 0.02 ppm) after 30 days in the fresh water system, and after 15 days in the marine water system; whereas MDA disappeared (detection limit 0.02 ppm) after only 4 days in both systems. In both systems, approximately 0.2% of the initial TDI was recovered as TDA from precipitation crusts after 30 days. Less than 0.02% of the initial MDI was recovered as MDA from precipitation crusts after 30 days in the fresh water system, and no MDA was detected in precipitation crusts in the marine water system after 30 days.

### 5.3.2.3 Sediment and Soil

No studies of the transformation and degradation of HDI in soil were located in the available literature. Isocyanates react readily with water to form amines and polyureas (Chadwick and Cleveland 1981; Hulse 1984; Kennedy and Brown 1992) and hydrolysis of HDI is expected to occur much more rapidly than biodegradation (HSDB 1995). Consequently, reaction with water is expected to be the only significant fate process of HDI in moist soil or sediment. The HDA resulting from hydrolysis, however, should be subject to various types of biodegradation (HSDB 1995). Gilbert (1988) has summarized the results of laboratory experiments on TDI in undisturbed moist sand, which indicate that TDI is converted to polyureas at a rapidly decreasing rate, with 5.5 and 3.5% of unreacted TDI remaining after 24 hours and 8 days, respectively. The toluene diamine hydrolysis product was not found above the detection limit of

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0.01 ppm. These results were interpreted as an indication of encapsulation of unreacted TDI within a rapidly forming water-insoluble polyurea crust. Similar results may be expected for HDI.

### 5.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

#### 5.4.1 Air

Except for occupational settings, no information was found in the available literature on concentrations of HDI or HDI prepolymers in air. Because of the relatively short atmospheric half-life (approximately 2 days) from reaction with hydroxyl radicals (see Section 5.3.2. 1), significant atmospheric concentrations of HDI would be expected to be found only near sources of this substance (e.g., waste streams from manufacturing or processing facilities, hazardous waste sites, occupational settings). Atmospheric concentrations of HDI and HDI-BT found in occupational settings are summarized in Section 5.5.

#### 5.4.2 Water

No information was found in the available literature on concentrations of HDI or HDI prepolymers in water. Because of the expected rapid hydrolysis of HDI, significant concentrations may not be found in water, except near sources of this substance (e.g., industrial waste streams, hazardous waste sites). Small amounts of unreacted HDI may persist in water if encapsulated in water-insoluble polyurea crusts formed during hydrolysis (Gilbert 1988).

#### 5.4.3 Sediment and Soil

No information was found in the available literature on concentrations of HDI or HDI prepolymers in sediment and soil. Because of the expected rapid hydrolysis of HDI in moist soil or sediment, significant concentrations may not be found in these media, except near sources of this substance (e.g., industrial waste streams, hazardous waste sites). Small amounts of unreacted HDI may persist in sediment and soil if encapsulated in water-insoluble polyurea crusts formed during hydrolysis (Gilbert 1988).

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### 5.4.4 Other Environmental Media

Biuret modified HDI (HDI-BT), a trimeric condensation product of HDI and water, which is commonly used as a hardener in 2-component coatings, typically contains unreacted HDI at concentrations below 1% (Alexandersson et al. 1987; Hulse 1984); however, after 3-6 months storage, the free monomer content may increase to approximately 1.6% (Hulse 1984). Polyurethane paints from 5 different manufacturers in Finland were found to contain HDI and HDI-BT at average concentrations of 0.24% (range, 0.19-0.32%) and 34% (range, 30-36%), respectively (Rosenberg and Tuomi 1984). Similar HDI concentrations (<1%) were found in a polyurethane varnish (Desmodur N<sup>®</sup>, Bayer AG) (Nielsen et al. 1985). HDI-BT (DES-N<sup>®</sup>, Mobay Corporation), which is commonly used in formulations of automobile and airplane coatings contains between 0.6 and 2.0% monomeric HDI (Karol and Hauth 1982). A polyisocyanate activator which was mixed 1:3 with an enamel contained 7% HDI-BT (Malo et al. 1983). In a Swedish study, the HDI-BT used in polyurethane paints contained 0.5-1.0% unreacted, monomeric HDI; the applied paint contained approximately 10% HDI-BT in the surface paint layer and varnish layer, compared to 3-6% HDI-BT in the primary paint layer (Alexandersson et al. 1987). No data on levels of HDI in other environmental media, including food, were found in the available literature. Because of the rapid hydrolysis of HDI (see Section 5.3.2) and the evidence against bioaccumulation of HDI in the food chain (see Section 2.3), it is not expected that HDI will be found in any significant concentrations in foods.

## 5.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

General population exposures to HDI may occur during the nonoccupational use of polyurethane coatings (Musk et al. 1988), primarily through inhalation of aerosols and vapors (Alexandersson et al. 1987; Grammar et al. 1988; Malo et al. 1983; Tulane Medican 1982a), and to a much lesser extent via dermal absorption (E.I. DuPont De Nemours 1977b; Haskell Laboratory 1961; Mobay Corporation 1981b; Stadler and Karol 1985). No information could be found in the available literature on levels of HDI in the environment, or of general population exposures; however, there were several reports of individuals with asthma-like hypersensitivities (see Chapter 2). Because of the expected rapid hydrolysis of HDI in the environment (see Section 5.3), significant general population exposures from air, water, or soil do not appear to be likely. Additionally, the rapid metabolism of HDI by higher trophic animals (see Section 2.3) indicates that this substance will not bioaccumulate in the food chain and, consequently, that general population exposures to HDI from foods will be insignificant.

## 5. POTENTIAL FOR HUMAN EXPOSURE

Occupational exposure to HDI occurs primarily through inhalation of aerosols and vapors and through dermal absorption (Alexandersson et al. 1987; Grammar et al. 1988; Hulse 1984; NIOSH 1992) with inhalation being the predominant route of exposure (Parmeggiani 1983). The NIOSH-recommended exposure limits (RELs) for HDI, expressed as a 0-hour time-weighted average (TWA) and 10-minute ceiling value, are 35 and 140  $\mu\text{g}/\text{m}^3$ , respectively (NIOSH 1992). The American Conference of Governmental Industrial Hygienists (ACGIH) has set an 8-hour TWA of 0.005 ppm as a threshold limit value (TLV) for HDI (ACGIH 1994).

Preliminary data from the NOES conducted by NIOSH from 1980 to 1983 indicates that an estimated 19,181 workers were potentially exposed to HDI in the United States from 1981 to 1983 (NIOSH 1989). These numbers do not include workers potentially exposed to trade name compounds that contain HDI, so that the actual number of exposed workers may be substantially higher than reported. Among the occupations with the greatest potential for exposure to HDI were painters and paint spraying-machine operators (6,139 potentially exposed workers), aircraft engine and other mechanics (7,516 potentially exposed workers), and aircraft machinists (3,317 potentially exposed workers) (NIOSH 1989). Other occupations with potential for exposure to HDI include construction laborers, chemical technicians, mixing and blending machine operators in the chemical industry, plumbers, pipefitters, steamfitters, metal plating machine operators, miscellaneous machine operators in the aircraft equipment industry, and production workers and supervisors in the fabricated structural metal industry (NIOSH 1989). Occupational exposures to HDI may also occur in the areas of spills; however, such exposures can be minimized by the rapid application of an aqueous surfactant solution, which has been shown to result in the complete mineralization of isocyanates such as TDI and MDI within minutes (Mobay Corporation 1980). The surfactant appears to act by solubilizing the isocyanate in an aqueous medium, thus facilitating the complete hydrolysis of the compound. The effectiveness of this treatment has been demonstrated in the laboratory and in soil under controlled conditions.

Prepolymeric HDI-BT paint formulations, which generally contain  $\leq 1\%$  monomeric HDI, are now widely used for coatings applications, particularly in the automobile and airplane industries (Alexandersson et al. 1987; Karol 1986; Key-Schwartz 1992; Nielson et al. 1985; Rosenberg and Savolainen 1986; Rosenberg and Tuomi 1984). Consequently, many reported occupational exposures to HDI are actually exposures predominantly to HDI-BT (Karol 1986; Karol and Hauth 1982). Although isocyanate prepolymers are safer to use than the free monomers, primarily because of their lower vapor pressures, they can still pose a health risk to workers when inhaled in the aerosol form (Karol and Hauth 1982;

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Rosenberg and Tuomi 1984). There is evidence that isocyanate prepolymers may induce asthma at the same or greater frequency as diisocyanate monomers (Seguin et al. 1987); therefore, characterization of both monomeric HDI and HDI-BT exposures is important to adequately assess the overall potential for health risk.

Most occupational isocyanate exposure studies have focused on toluene diisocyanate because of its widespread industrial use in the manufacture of flexible foam products (e.g., Alexandersson et al. 1985; Boeniger 1991; Dharmarajan et al. 1978; Diem et al. 1982; Huang et al. 1991a, 1991b; Jones et al. 1992; Maitre et al. 1993; Olsen et al. 1989; Omae 1984; Omae et al. 1992; Persson et al. 1993; Peters and Wegman 1975; Rando et al. 1987; Rosenberg 1984; Rosenberg and Savolainen 1986; Venables et al. 1985; Wegman et al. 1977; Weill et al. 1975). A more limited number of studies of occupational exposures to HDI and HDI-BT have been reported in the literature, some of which have found atmospheric HDI concentrations above the NIOSH TWA of  $35 \mu\text{g}/\text{m}^3$  (0.005 ppm) (NIOSH 1992). These are summarized below.

Hulse (1984) conducted a combined workplace and laboratory study to evaluate the exposure potential of HDI in vapor and aerosol states from HDI polyurethane spray paint aerosols. Sampling in 2 workplaces selected to represent worst-case exposures typical of spray painting in light aircraft maintenance facilities resulted in total personal and area HDI concentrations ranging from 13 to  $43 \mu\text{g}/\text{m}^3$  (0.002-0.006 ppm) and 39-63  $\mu\text{g}/\text{m}^3$  (0.006-0.009 ppm), respectively, with an average of 47% of the atmospheric HDI in the vapor phase. Results of the laboratory study suggested that for a given paint and process, a linear relationship exists between the aerosol mass concentration and the HDI concentration. Although this relationship was not found in workplace samples, the author concluded that the results of this study indicated that the NIOSH ceiling limit for HDI ( $140 \mu\text{g}/\text{m}^3$ ; 0.020 ppm) is unlikely to be exceeded at aerosol mass concentrations below  $20 \text{mg}/\text{m}^3$ . An average HDI concentration of 0.230 ppm ( $1,600 \mu\text{g}/\text{m}^3$ ) in curing oven exhaust was calculated from the results of a laboratory study using metal panels coated with a formulation (Desmodur LS-2800<sup>®</sup>) containing <0.3% HDI monomer and a blocking agent (Mobay Corporation 1986). A release profile indicated that once curing oven temperatures capable of releasing the HDI blocking agent in the formulation are reached (<400°C in this study), most of the HDI may be released over a relatively short time, which could result in momentary excursions of HDI concentrations above those calculated by a time average.



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In a study of U.S. workers involved in the mixing or application of HDI-BT spray paints, mean ambient air concentrations of HDI and HDI-BT ranged from  $<0.08$  to  $3.8 \mu\text{g}/\text{m}^3$  ( $<0.00001$ - $0.0006$  ppm) and  $5.3$ - $75 \mu\text{g}/\text{m}^3$  ( $0.0008$ - $0.011$  ppm), respectively (Grammar et al. 1988). Substantially higher ambient air concentrations of HDI were found at 4 different spray-painting operations at a U.S. Air Force base in Biloxi, Mississippi, ranging from  $12$  to  $59 \mu\text{g}/\text{m}^3$  ( $0.002$ - $0.009$  ppm); HDI-BT levels were not monitored (Rudzinski et al. 1994). Ambient air concentrations of HDI and HDI-BT in 3 automobile spray paint shops and one trade school for spray painters in Finland were found to range from  $6$  to  $120 \mu\text{g}/\text{m}^3$  ( $0.001$ - $0.018$  ppm) and  $280$ - $3,600 \mu\text{g}/\text{m}^3$  ( $0.043$ - $0.55$  ppm), respectively, with the concentration of HDI-BT 40 times that of HDI on average (Rosenberg and Tuomi 1984). In this same study, mean personal exposure concentrations (outside the respirator) of HDI and HDI-BT were  $490 \pm 220 \mu\text{g}/\text{m}^3$  ( $0.074 \pm 0.033$  ppm) and  $1,440 \pm 1,130 \mu\text{g}/\text{m}^3$  ( $0.219 \pm 0.172$  ppm) ( $\pm$ SD,  $n=10$ ), respectively. The use of respirators with combined charcoal and particle filters reduced mean personal exposure concentrations of HDI and HDI-BT to  $<1$  and  $<10 \mu\text{g}/\text{m}^3$  ( $<0.0002$  and  $<0.002$  ppm), respectively. In another study involving reconstruction of exposures of automobile painters in Sweden using HDI-BT spray paints, the mean exposure concentration of HDI was reported to be  $1.0 \mu\text{g}/\text{m}^3$  ( $0.0002$  ppm); whereas, the mean exposure concentration of HDI-BT was  $115 \mu\text{g}/\text{m}^3$  ( $0.017$  ppm) (range,  $10$ - $385 \mu\text{g}/\text{m}^3$ ;  $0.002$ - $0.058$  ppm), with short-term peak exposures up to  $13,500 \mu\text{g}/\text{m}^3$  ( $2.05$  ppm) (Alexandersson et al. 1987).

In some industrial processes, exposure to HDI may occur in the presence of its hydrolysis products, namely 1,6-hexamethyleneaminoisocyanate and HDA, both of which may also cause adverse respiratory effects (Beard and Noe 1981). In a study to evaluate isocyanate exposures of automobile repair workers involved in welding activities, which could lead to pyrolysis of HDI polymer-based paint, the atmospheric concentration ranges of HDI, 1,6-hexamethyleneaminoisocyanate, and HDA were found to be  $0.18$ - $1.3 \text{ mg}/\text{m}^3$  ( $0.027$ - $0.20$  ppm),  $<0.004$ - $0.24 \text{ mg}/\text{m}^3$  ( $<0.0006$ - $0.036$  ppm), and  $<0.004$ - $0.10 \text{ mg}/\text{m}^3$  ( $<0.0006$ - $0.015$  ppm), respectively, 25 cm from the source (Skarping et al. 1988). Concentrations of 1,6-hexamethyleneaminoisocyanate and HDA were on the order of 15% of the HDI concentrations.

Recent studies indicate that the toxic metabolite of HDI, HDA, may be monitored in urine hydrolytes as a biomarker of short-term exposure to HDI (Berode et al. 1991; Brorson et al. 1990a, 1990b; Dalene et al. 1990, 1994a; Rosenberg and Savolainen 1986). When exposure to HDI is on the order of the NIOSH REL of  $35 \mu\text{g}/\text{m}^3$  (NIOSH 1992), urinary HDA analyses are sensitive enough to monitor occupational

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HDI exposure (Brorson et al. 1990b; Dalene et al. 1990); however, the correlation between HDI exposure and urinary HDA levels requires further investigation. Because HDI exposures frequently involve exposure to prepolymeric HDI (e.g., HDI-BT), the uptake, metabolism, and excretion of HDI-BT must also be investigated (Brorson et al. 1990b). HDA is rapidly removed from the urine by N-acetylation (half-life,  $\approx 0.2$ -1.4 hours;  $>90\%$  urinary elimination of HDA within  $\approx 4$  hours of termination of inhalation exposure; therefore, HDA analysis must be performed on urine samples collected immediately after exposure (Brorson et al. 1990b; Dalene et al. 1990). Thus, HDA is not a suitable biomarker for assessing past exposures or other long-term exposures to HDI. No studies were found in the available literature reporting values of urinary HDA among occupationally exposed groups.

Workers in industries involved in the production or processing of HDI or prepolymeric HDI-BT, or who use products containing these materials (e.g., spray paints) also have potentially high exposures to HDI, HDI-BT, and HDI hydrolysis products (i.e., 1,6-hexamethyleneaminoisocyanate and HDA). The prevalence of respiratory symptoms among workers exposed to diisocyanate monomers has been estimated to range from 5 to 20%; although, in most studies, the occurrence of occupational asthma has not been confirmed through inhalation challenge tests (NIOSH 1978). Approximately 5% of workers in the isocyanate industry suffer from acute or chronic obstructive lung disease (Dewair et al. 1983).

Immunologic screening for IgE and IgG antibodies against HDI and HDI-BT conjugated to human serum albumin has also been used to identify occupational exposures to HDI and prepolymeric HDI-BT (Cvitanovic et al. 1989; Grammar et al. 1988, 1990; Karol and Hauth 1982; Malo et al. 1983; Welinder et al. 1988) (see Sections 2.2.1.3 and 2.6). However, because of the high amount of cross-reactivity between different isocyanates using HDI-human serum albumin (HSA) antibodies, this test is currently only reliable to detect exposures to diisocyanates in general, and not specifically to HDI or its prepolymers.

### 5.6 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Among the general population, subpopulations with potentially high HDI exposures include residents near industrial facilities releasing HDI into the environment and residents in the vicinity of HDI-containing hazardous waste sites. No data were found in the available literature, however, to characterize the extent of such exposures. The prevalence of asthma among residents in the vicinity of a factory in Finland producing TDI-based polyurethane was not found to be significantly different from controls,

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except for the middle-age (46-60 years old) group (Nuorteva et al. 1987). No additional information was found in the available literature to document exposures of these subpopulations. HDI has also not been detected in any media at any of the 1,445 current or former hazardous waste sites.

### 5.7 ADEQUACY OF THE DATABASE

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

#### 5.7.1 Identification of Data Needs

The following data needs are limited to HDI; however, these also apply to HDI prepolymers, which are often found in association with the monomer.

**Physical and Chemical Properties.** Although hydrolysis has been identified as a significant reaction in determining the fate of HDI (aqueous hydrolysis half-life, <10 minutes) (Chadwick and Cleveland 1981; Hulse 1984; Kennedy and Brown 1992; Saunders and Frisch 1962; SRC 1994b), this chemical is not well-defined in terms of its physical and chemical properties (see Table 3-3). Because of the rapid hydrolysis of the isocyanate functional group, available estimates of  $K_{ow}$  and Henry's law constant (H) are questionable (SRC 1994a, 1995b). No estimates of  $K_{oc}$  were found in the available literature. Further information on estimates of  $K_{ow}$ ,  $K_{oc}$ , and Henry's law constant (H) would be helpful in determining the environmental fate of this chemical and the rate at which it degrades in air, water, soil, and sediments.

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**Production, Import/Export, Use, Release, and Disposal.** The available production, use, and release information for HDI is insufficient to determine the amount of HDI that may be present in the environment. There is a need for data on HDI production and import/export volumes. The potential for exposure to HDI during production may be substantial; however, no information on past, present, or projected production volumes was found in the available literature. Descriptive information on the uses of HDI and HDI-based products is extensive and appears to be adequate; however, quantitative data on use patterns are needed. In addition, there is a lack of data on the amount of HDI that may be stored at waste sites. Little or no information was found in the available literature on current disposal methods for HDI, their efficiencies, the need for improvement, or the amount disposed of by each method. Additional information in this area is needed to assess the potential for human exposure to HDI from disposal activities.

According to the Emergency Planning and Community Right-to-Know Act of 1986, 42 U.S.C. Section 11023, industries are required to submit chemical release and off-site transfer information to the EPA. The Toxics Release Inventory (TRI), which contains this information for 1994, became available in May of 1996. This database will be updated yearly and should provide a list of industrial production facilities and emissions.

No information is available in the TRI database, however, because this substance is not included under SARA, Title III, and therefore, is not among the chemicals that facilities are required to report (EPA 1995). There is a need for such information in order to assess the potential for human exposure to this substance from their release from industrial production or processing facilities.

**Environmental Fate.** Extensive information is available on the general reactions of isocyanates that may pertain to the environmental fate of HDI (Chadwick and Cleveland 1981; Kennedy and Brown 1992). However, investigations of the environmental fate of isocyanates have focused primarily on TDI and MDI (Duff 1983, 1985; Gilbert 1988; Holdren et al. 1984). Only one laboratory study was located in the available literature specifically on the chemical reactions of HDI (i.e., bicarbonate buffer-catalyzed hydrolysis) that may be relevant to the environmental fate of HDI in water (Berode et al. 1991). HDI is expected to react relatively rapidly with hydroxyl radicals in the atmosphere and to be rapidly hydrolyzed in water and moist soils and sediment. The significance of atmospheric hydrolysis has not been evaluated. Additional field and laboratory studies are needed to adequately characterize the environmental fate of HDI in air, water, soil, and sediment.

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**Bioavailability.** HDI may be absorbed following inhalation (Alexandersson et al. 1987; Grammar et al. 1988; Malo et al. 1983; Tulane Medican 1982a), ingestion (Haskell Laboratory 1946, 1961), and dermal contact (Alexandersson et al. 1987; Grammar et al. 1988; Malo et al. 1983; Tulane Medican 1982a). The environmental factors that may influence the bioavailability of HDI from various environmental media have not been studied. The predicted rapid hydrolysis of HDI in water suggests that human exposure via contaminated drinking water or surface waters is unlikely, and no studies on the bioavailability of this compound from water are indicated at this time. No data were found in the available literature on the sorption of HDI to soil, sediments, or airborne particles; however, because of the rapid hydrolysis of HDI (see Section 5.3.2), sorption may not be a significant determinant in assessing the bioavailability of HDI from these media. There is a need for data characterizing the factors that affect the bioavailability of HDI from soils and sediments only if environmental fate or monitoring studies indicate that HDI persists in these media at significant concentrations.

**Food Chain Bioaccumulation.** Because of the rapid hydrolysis of HDI in water and the ease with which this substance is metabolized in higher trophic animals (see Section 2.3), it is not expected that this substance will bioconcentrate in aquatic organisms, or bioaccumulate in the food chain. Neither TDI and MDI, nor their diamine hydrolysis products, TDA and MDA, have been found to bioaccumulate in fish (*Cyprinus curpio*) in river model studies (International Isocyanate Institute 1990). No information on BCFs and food chain bioaccumulation could be found for HDI in the available literature; however, a BCF of approximately 100 was calculated using the method of Veith et al. (1979), which indicates a very low bioaccumulation potential for HDI. Further studies on the bioaccumulation of HDI do not appear to be warranted.

**Exposure Levels in Environmental Media.** No information was found in the available literature on concentrations of HDI in ambient air; surface, ground, and drinking water; sediment and soil; or other environmental media such as food. Because of the relatively rapid reaction of HDI with hydroxyl radicals in the atmosphere (SRC 1995a), and the rapid hydrolysis of HDI in other media (Chadwick and Cleveland 1981; Hulse 1984; Kennedy and Brown 1992; SRC 1994b), significant concentrations would not be expected to occur in air, water, or sediment and soil, except near potential emission sources of this substance (e.g., industrial waste streams, hazardous waste sites, occupational settings, environmental spills). Small amounts of unreacted HDI may persist in water, or sediment and soil, if encapsulated in water-insoluble polyurea crusts formed during hydrolysis (Brochagen and Grievesson 1984; Gilbert 1988). Data on concentrations in all environmental media (air, water, sediment and soil) near potential

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emission sources and at background sites are necessary to assess the potential for exposure to HDI of populations living near these potential sources. Only a small number of studies reporting concentrations of HDI in occupational settings in the United States were found in the available literature; additional data are needed to more fully characterize occupational exposures in this country. Because of the rapid hydrolysis of HDI in water and the ease with which this substance is metabolized in higher trophic animals (see Section 2.3), it is not expected that this substance will bioconcentrate in aquatic organisms, or bioaccumulate in the food chain. Consequently, concentrations of HDI in food should be insignificant and the need for data in this area is not pressing.

Reliable monitoring data for the levels of HDI in contaminated media at hazardous waste sites are needed so that the information obtained on levels of HDI in the environment can be used in combination with the known body burden of HDI to assess the potential risk of adverse health effects in populations living in the vicinity of hazardous waste sites.

No information was found in the available literature on estimates of human intake of HDI from the various environmental media. Because the potential for significant widespread environmental contamination is expected to be very low, such estimates would appear to be needed primarily for populations living or working near potential emission sources of HDI.

**Exposure Levels in Humans.** Recent studies indicate that the toxic metabolite of HDI, I-IDA, may be monitored in urine hydrolylates as a biomarker of short-term exposure to HDI (Berode et al. 1991; Brorson et al. 1990b; Dalene et al. 1990, 1994a; Rosenberg and Savolainen 1986). When exposure to HDI is on the order of the NIOSH TWA of 35  $\mu\text{g}/\text{m}^3$  (NIOSH 1992), urinary HDA analyses are sensitive enough to monitor occupational HDI exposure (Brorson et al. 1990b; Dalene et al. 1990); however, the correlation between HDI exposure and urinary HDA levels requires further investigation. Because HDA is rapidly removed from urine by N-acetylation (half-life,  $\approx 1.2$ -1.4 hours; >90% urinary elimination of HDA within 4 hours of termination of inhalation exposure), it is not a suitable biomarker for assessing past exposures or other long-term exposures to HDI and analyses must be performed on urine samples collected immediately after exposure (Brorson et al. 1990b; Dalene et al. 1990). The use of urinary HDA as a biomarker is still in the developmental stages and no data on concentrations of urinary HDA in occupationally exposed populations, populations living near hazardous waste sites, control groups, or the general population were found in the available literature. There is a need for further method

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development in this area, as well as for biomonitoring data in these populations. This information is necessary for assessing the need to conduct health studies on these populations.

Immunologic screening for IgE and IgG antibodies against HDI and HDI-BT conjugated to human serum albumin (HSA) has also been used to identify occupational exposures to HDI (Cvitanovic et al. 1989; Grammar et al. 1988, 1990; Karol and Hauth 1982; Malo et al. 1983; Welinder et al. 1988) (see Sections 2.2.1.3 and 2.6). However, because of the high amount of cross-reactivity between different isocyanates using HDI-HSA antibodies, this test is currently only reliable to detect exposures to diisocyanates in general, and not specifically to HDI or its prepolymers. Additional research is needed to develop bioassays that are specific for HDI and HDI prepolymers.

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

### 5.7.2 Ongoing Studies

A search of the Federal Research in Progress database (FEDRIP 1995) indicates that no research studies are in progress to fill the data gaps discussed in Section 5.7.1.





## 6. ANALYTICAL METHODS

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

### 6.1 BIOLOGICAL SAMPLES

Some of the methods used for determining HDI in biological media are reported in Table 6-1. Methods for the biological monitoring of exposures to HDI have been based on determination of the corresponding amine, hexamethylene diamine. Methods are available for determination of HDI in urine and plasma; however, no methods were found for mother's milk, or tissues.

The analysis methods use acid or base hydrolysis of the compound, extraction into solvent (usually toluene), derivatization, followed by chromatographic analysis. Determination is based on sensitive gas chromatography/mass spectrometry (GC/MS) techniques. Alternately, GC with specific detectors or high performance liquid chromatography (HPLC) may be used. The method based on hydrolysis and basic extraction of the liberated amine into toluene provides sensitive measurements, but the extraction recovery is low (Dalene et al. 1990). A method using hydrolysis followed by a two-phase derivatization procedure showed good recovery (above 90%) but less sensitivity (Dalene et al. 1994a). Very good sensitivity was reported for determination using HPLC-MS (Dalene et al. 1994b); however, this method requires state-of-the-art instrumentation.

Analysis of the degradation products of the oligomeric form of HDI, HDI-BT, may be possible by the above procedures; no experimental data are available.

**Table 6-1. Analytical Methods for Determining Biological Degradation Products of Hexamethylene Diisocyanate**

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Urine <sup>a</sup>	Heat with sulfuric acid; adjust pH to $\approx 9.2$ ; cleanup on SPE silica cartridge; solvent extraction (toluene); derivatization with heptafluorobutyric anhydride)	GC/MS	0.2 pmol per injection	No data	Rosenberg and Savolainen 1986
Urine <sup>a</sup>	Heat with aqueous hydrochloric acid; cool; pH adjustment; solvent extraction; derivatization with heptafluorobutyric anhydride	GC/MS (CI mode using ammonia)	>100 $\mu\text{g/L}$	34 $\pm$ 4%	Brorson et al. 1990; Dalene et al. 1990
Urine <sup>a</sup>	Alkaline hydrolysis; derivatization with trifluoroethyl chloroformate	GC/MS (CI mode using ammonia); GC/ TSD	0.5 $\mu\text{g/L}$ (GC/MS); 20 $\mu\text{g/L}$ (GC/TSD)	97 $\pm$ 5%	Dalene et al. 1994a
		HPLC-thermospray/ MS	1 $\mu\text{g/L}$	No data	Dalene et al. 1994b
Plasma, urine <sup>a</sup>	Acid hydrolysis; derivatization with pentafluoropropionic acid	GC/MS (CI-NI)	$\approx 0.04$ $\mu\text{g/L}$	No data	Skarping et al. 1996

<sup>a</sup> Analyte is hexamethylene diamine

CI = chemical ionization; CI-NI = monitoring negative ions in the chemical ionization mode; GC = gas chromatography; HPLC = high performance liquid chromatography; MS = mass spectrometry; pmol = picomole; SPE = solid-phase extraction; TSD = thermionic specific detection

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### 6.2 ENVIRONMENTAL SAMPLES

Methods are available for the determination of HDI in occupational and ambient air. A summary of representative methods is shown in Table 6-2. Much of the methodology involves drawing air through an impinger or sorbent-containing derivatizing reagent. The sample is then analyzed by HPLC with ultraviolet (UV) and/or electrochemical detection. A good review of these techniques is available. Two NIOSH methods (Methods 5505 and 5521) have been used to analyze for the isocyanates (NIOSH 1984). Both use HPLC with UV, or UV and electrochemical detection. Collection is carried out by passing sampled air through toluene containing 1-(2-methoxyphenyl)-piperazine to derivatize the HDI. They were specified for analysis of monomeric and oligomeric forms of isocyanates providing a total isocyanate concentration in air as well as some speciation. Method 5505 has been removed from the current NIOSH manual. Problems have been reported for Method 5521. The ratio criterion may not be suitable for qualitative identification of HDI oligomers (Key-Schwartz 1995).

There are also other techniques which use a similar sampling and analysis scheme. A number of methods used 9-(N-methylaminomethyl)anthracene as a reagent to derivatize the HDI allowing subsequent detection of a stable derivative by UV absorbance or fluorescence detection (Andersson et al. 1983; Gudehn 1984; Kormos et al. 1981; Sang and Zimerson 1980). The "nitro reagent" or N-4-nitrobenzyl-N-n-propylamine has also been used for derivatization prior to analysis by HPLC/UV or differential pulse polarography (Corbini et al. 1991; Dunlap et al. 1976; Graham 1980; Hakes et al. 1986). Various column types and eluent conditions were used in the HPLC separations cited above. The 1-(2-methoxyphenyl)-piperazine used as a derivatization reagent in the NIOSH methods was also used on a sorbent (Schmidtke and Seifert 1990) and inert supports (Huynh et al. 1992; Sesana et al. 1991) avoiding the use of toluene in the collection impinger. Another derivatization agent used was 1-(2-pyridyl)piperazine either in a toluene solution (Ellwood et al. 1981; Goldberg et al. 1981) or impregnated on glass fiber filters (Rudzinski et al. 1994). Samples were analyzed using TLC, capillary zone electrophoresis, or HPLC techniques. In addition to those listed in Table 6-2, there are methods which may be used for determination of the oligomeric form of HDI or HDI-BT (biuret trimer) (Bagon et al. 1984; Ellwood et al. 1981; Goldberg et al. 1981; Levine et al. 1979).

Additional novel analytical techniques include coating a polystyrene strip with cholinesterase, exposing the strip to an atmosphere (passive sampling), then immersing the strip in a cuvette with reagent for assay

**Table 6-2. Analytical Methods for Determining Hexamethylene Diisocyanate in Environmental Samples**

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Occupational air (total isocyanates)	Air collected/derivatized through 1-(2-methoxyphenyl)piperazine in toluene; acetylation; evaporation	HPLC with UV detection	≈0.2 μmol/sample	96% average	NIOSH 1984 NIOSH Method 5505
Occupational air (total isocyanates)	Air collected/derivatized through 1-(2-methoxyphenyl)piperazine in toluene; acetylation; evaporation	HPLC with electrochemical and UV detection	≈0.3 μg per sample	123% avg.	NIOSH 1984 NIOSH Method 5521
Occupational air	Air collected/derivatized through 9-( <i>N</i> -methylaminomethyl)anthracene in toluene; evaporation	HPLC with UV or fluorescence detection	0.1 μg/m <sup>3</sup>	No data	Sangö and Zimerson 1980
Occupational air	Air collected/derivatized through 9-( <i>N</i> -methylaminomethyl)anthracene impregnated XAD-2; desorption with <i>N,N</i> -dimethylformamide	HPLC with UV absorbance detection	25 ng/m <sup>3</sup> for 20 L air	81–91%	Andersson et al. 1983; Gudéhn 1984
Occupational air	air collected in mini-impinger containing "nitro reagent" in toluene; evaporation	HPLC with UV detection	1.5 ppb for 20 L air	No data	Dunlap et al. 1976
Occupational and indoor air (HDI and oligomers)	Collection/derivatization on 1-(2-methoxyphenyl)piperazine coated sorbent; desorption with methanol; concentration	HPLC with heart cutting with UV or electrochemical detection	60 ng/m <sup>3</sup> (UV); 1 ng/m <sup>3</sup> (electrochemical)	≤75–99%	Schmidtke and Seifert 1990
Occupational air (HDI and oligomers)	Air collected/derivatized through tubes with sintered glass (or GFFs) impregnated with 1-(2-methoxyphenyl)piperazine; solvent elution; reaction with acetic anhydride; evaporation	HPLC with UV detection	0.31 μg / sample; 3.4 μg/m <sup>3</sup> (lowest tested—GFFs)	95–107%	Sesana et al. 1991; Huynh et al. 1992
Air (HDI and oligomers)	Air collected/derivatized through 1-(2-pyridyl)-piperazine in toluene; evaporation;	HPLC with UV detection	0.7 μg/m <sup>3</sup> for 10 L air	No data	Goldberg et al. 1981
Air	Air collected/derivatized through sodium hydroxide in ethanol; neutralization; derivatization with heptafluorobutyric anhydride; solvent extraction	GC/thermionic specific detection	10 pg/μL injected	≈100% (simulated sample)	Skarping et al. 1988

**Table 6-2. Analytical Methods for Determining Hexamethylene Diisocyanate in Environmental Samples (continued)**

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Air (total isocyanate)	Air collected/ derivatized through tryptamine in 2,2,4-trimethylpentane; evaporation; derivatization with acetic anhydride	HPLC with fluorescence and electrochemical detection	1 ppb for 120 L air	90±5% (simulated sample)	Wu et al. 1990
Occupational air	Air exposed to polystyrene strip with adsorbed cholinesterase; assayed in cuvette with Ellman's reagent and acetylthiocholine	UV absorbance (412 nm)	≈20 ppb (1-min exposure)	No data	Brown et al. 1984
Air (total isocyanates)	None—direct air monitor	Proprietary paper tape chemistry	≈5 ppb (lowest reported); 50 ppb max.	No data	Dharmarajan and Rando 1980

ECD = electron capture detector; GC = gas chromatography; GFF = glass fiber filter(s); HPLC = high performance liquid chromatography; MS = mass spectrometry; NIOSH = National Institute of Occupational Safety and Health; nitro reagent = *N*-4-nitrobenzyl-*N*-*n*-propylamine; UV = ultraviolet

## 6. ANALYTICAL METHODS

by UV absorbance measurement (Brown et al. 1984). The disadvantage is that it does not differentiate between isocyanate species, but it is reasonably sensitive. Also available is a dedicated instrument, the Chemcasette<sup>®</sup> 7005, which uses proprietary paper tape chemistry and was reviewed for total isocyanates (Dharmarajan and Rando 1980). The only direct measurement technique for HDI using chromatography involved collection by impinger containing isooctane, then analysis by GC using the nitrogen sensitive thermionic specific detector (Skarping et al. 1985).

Methods for analysis of HDI in other media were not found. However, since HDI hydrolyzes rapidly in water, it is unlikely that significant amounts of HDI monomer would be found in water, soils, sediment, or food, except near sources of release.

### 6.3 ADEQUACY OF THE DATABASE

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

#### 6.3.1 Identification of Data Needs

**Methods for Determining Biomarkers of Exposure and Effect.** There is currently only one biomarker hexamethylene diamine, HDA, which is used for the monitoring exposure of individuals to HDI. This biomarker is convenient as it is readily excreted in urine and it can be detected at low concentration levels as indicated in Table 6-1. Additional recovery data are needed for HDA in order to

## 6. ANALYTICAL METHODS

improve exposure estimates, especially since the half-life of HDA in urine is difficult to determine for persons suspected of being exposed to HDI. No other biomarker has been cited as an alternative.

### **Methods for Determining Parent Compounds and Degradation Products in**

**Environmental Media.** Currently there is a fairly broad selection of analytical methods for the analysis of HDI in air. Since it degrades very quickly upon contact in water and soil, and degrades more slowly by reaction with hydroxyl radicals and water vapor in air, it is important for analyses to be focused on air as a medium. It is probably most important at this point to improve the speciation (chromatographic separations) of isocyanate forms including prepolymers which may provide toxic effects to individuals. This will allow more accurate measurement and control of hazards in the workplace and general environment. Better data on recovery would be useful for some air sampling techniques as air sampling is of greatest importance for exposure assessment. It is also important that more information is determined on chemical and physical properties for the biuret trimer form since little is currently available in the literature.

### **6.3.2 Ongoing Studies**

No ongoing studies related to methods for detection of HDI were found.





## 7. REGULATIONS AND ADVISORIES

The national and state regulations and guidelines regarding HDI in air, water, and other media are summarized in Table 7- 1. No international regulations were identified for HDI.

Diisocyanates such as HDI represent a group of chemicals that primarily target the upper and lower respiratory tract, resulting in chronic pulmonary irritation and asthmatic reaction in humans. HDI is also known to be a potent respiratory and dermal sensitizing agent. Because of its potential to cause adverse health effects in exposed people, a number of regulations and advisory values have been established for HDI.

ATSDR has derived an intermediate-duration inhalation MRL of  $3.0 \times 10^{-5}$  ppm for HDI, based on an NOAEL of 0.005 ppm for respiratory effects in rats in a study by Mobay Corporation (1984).

ATSDR has derived a chronic-duration inhalation MRL of  $1.0 \times 10^{-5}$  ppm for HDI, based on a LOAEL of 0.0001 ppm based on changes in percent closing volume (%CV) in a study of 3 groups of garage workers by Alexandersson et al. (1987).

HDI has not been evaluated by the EPA for evidence of human carcinogenic potential (IRIS 1997). However, the EPA has established an inhalation reference concentration (RfC) of  $1 \times 10^{-5}$  mg/m<sup>3</sup> for HDI (IRIS 1997).

An Occupational Safety and Health Administration (OSHA) permissible exposure limit (PEL) for HDI does not exist.

Hexamethylene- 1,6-diisocyanate is listed as a hazardous air pollutant (HAP) under to Section 112 (b) of the Clean Air Act (CAA) (U.S. Congress 1990). The national emission standards for hazardous air pollutants (NESHAP) which were established pursuant to Section 112 of the CAA (as amended November 15, 1990), regulate specific categories of stationary sources that emit or have the potential to emit one or more HAPS. HDI is listed as a volatile HAP for wood furniture manufacturing operations in Title 40 of the Code of Federal Regulations (CFR), Part 63, Subpart JJ (EPA 1995).

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On November 30, 1994, EPA added HDI and 285 other chemicals to the list of toxic chemicals that are subject to reporting under Section 313 of the Emergency Planning and Community Right-to-Know Act of 1986 (EPCRA) and Section 6607 of the Pollution Prevention Act of 1990 (EPA 1994). Section 313 of Title III of EPCRA requires owners and operators of certain facilities that manufacture, import, process, or otherwise use the chemicals on this list to report annually their release of those chemicals to any environmental media.

In 1989, the Interagency Testing Committee (ITC) designated HDI for health effects testing for chronic toxicity, oncogenicity, and reproductive and development effects. This decision was partially based on the potential for a substantial number of workers to be exposed to the chemical during its production and use in polyurethane paint systems (EPA 1997). EPA later responded to the ITC designation by issuing a proposed testing rule which also required testing for mutagenicity, neurotoxicity, pharmacokinetics, and hydrolysis. As the proposed rule was not finalized and EPA has reviewed new scientific data addressing chronic toxicity, subchronic toxicity, mutagenicity, and hydrolysis, the final scope of the testing requirements proposed earlier have changed. On September 30, 1997, EPA issued a testing consent order that incorporated an enforceable consent agreement with several companies to perform certain health effects tests on HDI (EPA 1997).

**Table 7-1. Regulations and Guidelines Applicable to Hexamethylene Diisocyanate**

Agency	Description	Information	References
<u>INTERNATIONAL</u>			
Guidelines:			
WHO	Guidelines for Drinking-water Quality	No information given	WHO 1984
<u>NATIONAL</u>			
Regulations:			
a. Air:			
	Listed as Hazardous Air Pollutant	Yes	U.S. Congress 1990
	National Emission Standards for Wood Furniture Manufacturing Operations—Table 2. List of Volatile Hazardous Air Pollutants	Yes	40 CFR 63, Subpart JJ EPA 1995
b. Other:			
DOT	Hazardous Materials and Special Provisions - Table 1	Yes	49 CFR 172.101 DOT 1976
EPA OERR	List of Hazardous Substances and Reportable Quantities	100 pounds (45.4 kg)	40 CFR 302.4 60 FR 30926 EPA 1995
	Toxic Chemical Release Reporting	Yes	40 CFR 372.65 59 FR 61432 EPA 1994
Guidelines:			
a: Air:			
ACGIH	Ceiling Limit for Occupational Exposure (TLV-TWA)	0.005 ppm	ACGIH 1994
NIOSH	Recommended Exposure Limit for Occupational Exposure (TWA)	0.005 ppm (35 µg/m <sup>3</sup> )	NIOSH 1997
	Recommended Exposure Limit for Occupational Exposure (Ceiling-10 min.)	0.020 ppm (140 µg/m <sup>3</sup> )	
b. Other:			
EPA	Reference Concentration (RfC)(inhalation)	1x10 <sup>-5</sup> mg/m <sup>3</sup> (1.45x10 <sup>-6</sup> ppm)	IRIS 1997
<u>STATE</u>			
Regulations and Guidelines:			
a. Air:			
	Average Acceptable Ambient Air Concentrations *		NATICH 1992
CT	8 hours	7x10 <sup>-1</sup> µg/m <sup>3</sup> (1.02x10 <sup>-4</sup> ppm)	
FL-Pinella	8 hours	3.50x10 <sup>-1</sup> µg/m <sup>3</sup> (5.09x10 <sup>-5</sup> ppm)	
	24 hours	8.40x10 <sup>-2</sup> µg/m <sup>3</sup> (1.22x10 <sup>-5</sup> ppm)	

**Table 7-1. Regulations and Guidelines Applicable to Hexamethylene Diisocyanate (continued)**

Agency	Description	Information	References
<u>STATE (cont.)</u>			
ND	8 hours	$3.40 \times 10^{-4}$ mg/m <sup>3</sup> ( $4.94 \times 10^{-5}$ ppm)	
OK	24 hours	$3.44 \times 10^{-1}$ µg/m <sup>3</sup> ( $5.00 \times 10^{-5}$ ppm)	
TX	30 minutes	$3.40 \times 10^{-1}$ µg/m <sup>3</sup> ( $4.94 \times 10^{-5}$ ppm)	
	Annual	$3.40 \times 10^{-2}$ µg/m <sup>3</sup> ( $4.94 \times 10^{-6}$ ppm)	
VA	24 hours	$5.7 \times 10^{-1}$ µg/m <sup>3</sup> ( $8.28 \times 10^{-5}$ ppm)	
WA-SWEST	24 hours	$1 \times 10^{-1}$ µg/m <sup>3</sup> ( $1.45 \times 10^{-5}$ ppm)	

<sup>a</sup> The values listed in NATICH 1992 as acceptable ambient concentrations may not be categorized as such by individual states and localities. Conversions in parenthesis are made using conversion factors in Chapter 3.

ACGIH = American Conference of Governmental Industrial Hygienists; DOT = Department of Transportation; EPA = Environmental Protection Agency; IRIS = Integrated Risk Information System; NATICH = National Air Toxics Information Clearinghouse; NESHAP = National Emission Standards for Hazardous Air Pollutants; NIOSH = National Institute for Occupational Safety and Health; OERR = Office of Emergency and Remedial Response; OSHA = Occupational Safety and Health Administration; OWRS = Office of Water Regulations and Standards; TLV = Threshold Limit Value; TWA = Time Weighted Average; WHO = World Health Organization

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## 9. GLOSSARY

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

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

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

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

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

**Carcinogen**-A chemical capable of inducing cancer.

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

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

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

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

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

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

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

## 9. GLOSSARY

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

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

***In Vivo***-Occurring within the living organism.

**Lethal Concentration<sub>(LO)</sub> (LC<sub>LO</sub>)**-The lowest concentration of a chemical in air which has been reported to have caused death in humans or animals.

**Lethal Concentration<sub>(50)</sub> (LC<sub>50</sub>)**-A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

**Lethal Dose<sub>(LO)</sub> (LD<sub>LO</sub>)**-The lowest dose of a chemical introduced by a route other than inhalation that is expected to have caused death in humans or animals.

**Lethal Dose<sub>(50)</sub> (LD<sub>50</sub>)**-The dose of a chemical which has been calculated to cause death in 50% of a defined experimental animal population.

**Lethal Time<sub>50</sub> (LT<sub>50</sub>)**-A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

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

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

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

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

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

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

**Octanol-Water Partition Coefficient (K<sub>ow</sub>)**-The equilibrium ratio of the concentrations of a chemical in n-octanol and water, in dilute solution.

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

## 9. GLOSSARY

**q<sub>1</sub>\***-The upper-bound estimate of the low-dose slope of the dose-response curve as determined by the multistage procedure. The q<sub>1</sub>\* can be used to calculate an estimate of carcinogenic potency, the incremental excess cancer risk per unit of exposure (usually µg/L for water, mg/kg/day for food, and µg/m<sup>3</sup> for air).

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

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

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

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

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

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

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

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

**Toxic Dose (TD<sub>50</sub>)**-A calculated dose of a chemical, introduced by a route other than inhalation, which is expected to cause a specific toxic effect in 50% of a defined experimental animal population.

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

**APPENDIX A****ATSDR MINIMAL RISK LEVEL**

The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) [42 U.S.C. 9601 et seq.], as amended by the Superfund Amendments and Reauthorization Act (SARA) [Pub. L. 99-4991, requires that the Agency for Toxic Substances and Disease Registry (ATSDR) develop jointly with the U.S. Environmental Protection Agency (EPA), in order of priority, a list of hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL); prepare toxicological profiles for each substance included on the priority list of hazardous substances; and assure the initiation of a research program to fill identified data needs associated with the substances.

The toxicological profiles include an examination, summary, and interpretation of available toxicological information and epidemiologic evaluations of a hazardous substance. During the development of toxicological profiles, Minimal Risk Levels (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 for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified duration of exposure. MRLs are based on noncancer health effects only and are not based on a consideration of cancer effects. These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.

MRLs are derived for hazardous substances using the no-observed-adverse-effect level/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived-for acute (1-14 days), intermediate (15-364 days), and chronic (365 days and longer) durations and for the oral and inhalation routes of exposure.

Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive chemical-induced end point considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.



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MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as a hundredfold below levels that have been shown to be nontoxic in laboratory animals.

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology, expert panel peer reviews, and agencywide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published levels. For additional information regarding MRLs, please contact the Division of Toxicology, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road, Mailstop E-29, Atlanta, Georgia 30333.

## APPENDIX A

**MINIMAL RISK LEVEL (MRL) WORKSHEETS**

Chemical name: 1,6-Hexamethylene Diisocyanate  
CAS number: 822-06-0  
Date: February 25, 1998  
Profile status: Second Draft  
Route:  Inhalation  Oral  
Duration:  Acute  Intermediate  Chronic  
Key to figure: 19  
Species: Sprague-Dawley rat

MRL:  $3.0 \times 10^{-5}$   mg/kg/day  ppm  mg/m<sup>3</sup>

Reference: Mobay Corporation 1984

Experimental design: The purpose of this study was to determine the toxicity of HDI via inhalation exposures over a 3-week period in Sprague-Dawley rats. Groups of 10 male and 10 female rats were exposed (head-only) to vapors of HDI at average concentrations of 0, 0.005, 0.0175, 0.15, or 0.3 ppm for 5 hours/day, 5 days/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. Hematology, blood chemistry, gross necropsy, and histopathology were conducted on all animals, as well as urinalysis (UA), body weight measurements and feed consumption.

Effects noted in study and corresponding doses: All animals exposed to all concentrations of HDI exhibited varying degrees of irritation of eyes and/or noses during exposure and at 1 hour postexposure, with all animals appearing normal the following morning. No clinical signs of toxicity were observed during the non-exposure days (i.e., 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. Sneezing was attributed to irritation of the nasal cavity. All animals in the control group showed slightly irritated eyes and/or noses at 1 hour postexposure and appeared normal at all other times. The severity of the irritation in the animals exposed to the 0.005 ppm level was mild and appeared to be slightly above that of controls. No significant differences in body weights, feed consumption, blood chemistry, UA and hematology were observed compared to control animals for both male and female rats. At an HDI exposure concentration of 0.3 ppm, a statistically significant decrease in liver and kidney absolute and relative weights of 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 showed a significant decrease in the relative and absolute kidney weights, but not for liver weights. No other statistically significant changes in organ weights were observed at any of the lower inhalation doses of HDI. No significant changes in gross pathology of any of the other body organs were found. Microscopic 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 to a more flattened squamous type 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 as described above, while at 0.15 ppm, 50–70% were affected with a slightly milder severity. At 0.005 ppm and

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0.0175 ppm, the changes were minimal to mild in severity and were 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 were not dose related.

The dose response effects reported in this study are summarized below:

0.3 ppm: Nasal epithelial changes in 80–90% of animals; moderate severity. No observed effects were noted for the following systems: cardiac, gastrointestinal, hematological, musculoskeletal, hepatic (males only), endocrine, dermal, immunological/lymphoreticular, neurological, reproductive and body weight (NOAELs). Decreased kidney weights (males and females) and decreased liver weights (females only) were also noted (both are less serious LOAELs).

0.15 ppm: Nasal epithelial changes in 50–70% of animals at slightly milder severity. No observed adverse hepatic effects (females only) and no observed adverse renal effects (males and females).

0.0175 ppm: Minimal LOAEL. Hemorrhage, inflammatory exudate, epithelial changes in nasal cavity.

0.005 ppm: NOAEL.

Dose end point used for MRL derivation:

NOAEL  LOAEL

Uncertainty factors used in MRL derivation:

1  3  10 (for use of a NOAEL)  
 1  3  10 (for extrapolation from animals to humans)  
 1  3  10 (for human variability)

Was a conversion factor used from ppm in food or water to a mg/body weight dose?

If so, explain:

No.

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

The NOAEL Human Equivalent Dose (NOAEL<sub>HEC</sub>) was calculated using Equation 4-16 from EPA (1994):

$$\text{NOAEL}_{\text{HEC}} = \text{NOAEL} \times \text{RGDR}_r$$

where  $\text{RGDR}_r$  is the Regional Gas Dose Ratio for the region of interest. For HDI, the region of interest for this exposure route and duration for the rat is the nasal cavity. Again using EPA (1994) guidance and the dose-response relationships observed in rats outlined above, HDI effects would be classified as extrathoracic. HDI is also classified as a Category 1 gas (see pages 3–38 and 3–39 of EPA 1994), hence, Equation 4-18 of EPA (1994) was used to calculate the  $\text{RGDR}_{\text{ET}}$ .

$$\text{NOAEL}_{[\text{HEC}]} = \text{NOAEL} \times \text{RGDR}_{\text{ET}}$$

$$\text{NOAEL}_{[\text{HEC}]} = (0.005 \text{ ppm}) \times (V_E / \text{SA}_{\text{ET}})_A / (V_E / \text{SA}_{\text{ET}})_H$$

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$$\text{NOAEL}_{[\text{HEC}]} = 0.005 \text{ ppm} \times (0.24 \text{ m}^3/\text{day} / 11.6 \text{ cm}^2) / 20 \text{ m}^3/\text{day} / 177 \text{ cm}^2)$$

$$\text{NOAEL}_{[\text{HEC}]} = 0.005 \text{ ppm} \times 0.183$$

$$\text{NOAEL}_{[\text{HEC}]} = 0.0009 \text{ ppm}$$

*Therefore:*

$$\text{MRL} = \text{NOAEL}_{[\text{HEC}]} / \text{UF}$$

$$\text{MRL} = 0.0009 \text{ ppm} / 30$$

$$\text{MRL} = 3.0 \times 10^{-5} \text{ ppm}$$

where the  $\text{NOAEL}_{[\text{HEC}]}$  is the Human Equivalent Concentration for the no-observed-adverse-effect level, the RGDR is the Regional Gas Dose Ratio (animal (A): human (H)),  $V_E$  is the ventilation volume (tidal volume in  $\text{m}^3/\text{day}$ ), SA is the regional surface area of the toxic effect observed (in  $\text{cm}^2$ ), and UF are the uncertainty factors.

Was a conversion used from intermittent to continuous exposure?

If so, explain:

No.

Other additional studies or pertinent information that lend support to this MRL:

Similar nasal lesions were reported in another study of intermediate duration (Mobay Corporation 1988); however the lowest air concentration found that induced a LOAEL (ocular irritation and lacrimation) was twice the LOAEL for the Mobay Corporation study. In support of the 0.005 ppm NOAEL in rats, 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 >1 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 the 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 attributed to human error. These study limitations precluded either of these reports from being used to derive an intermediate-duration MRL based on human exposures, but they do lend some support to the MRL based on results found using the rat model.

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**MINIMAL RISK LEVEL WORKSHEET**

Chemical name: 1,6-Hexamethylene Diisocyanate  
CAS number: 822-06-0  
Date: February 25, 1998  
Profile status: Second Draft  
Route:  Inhalation  Oral  
Duration:  Acute  Intermediate  Chronic  
Key to figure: 32  
Species: Fischer 344 rat

MRL:  $1.0 \times 10^{-5}$   mg/kg/day  ppm  mg/m<sup>3</sup>

Reference: Mobay Corporation 1989

Experimental design: The purpose of this study was to provide information on the NOAEL/LOAEL and the toxic and oncogenic effects associated with exposure of rats to HDI by the inhalation route over a period of 2 years. Groups of 60 male and 60 female Fischer 344 rats were exposed to 0, 0.005, 0.025, or 0.175 ppm HDI for 5 days/week, 6 hours/day for 2 years. Control rats were sham exposed rats (conditioned air exposure). HDI vapor concentrations were generated by passing filtered, dry air through liquid HDI in a glass bubbler immersed in a heated water bath, with the temperature of the bath altered to affect the concentration of HDI needed for exposure. Animals were monitored for clinical signs of toxicity, ophthalmological examinations, body weight changes, organ weight changes (at gross necropsy), and changes in hematologic, urine and blood chemistry parameters during the course of the study.

Effects noted in study and corresponding doses: HDI caused eye irritation in males exposed to the 0.175 ppm dose only during the first year of the study and not during the second year. No other HDI-related eye lesions were detected during ophthalmologic examinations performed during the 2-year study. 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. Hematologically, the only effect that HDI may have had was an increase in the number of reticulocytes at different intervals during the study in both males and females exposed to the 0.175 ppm concentration of HDI, suggesting anemia. No statistically significant HDI exposure-related changes in serum chemistry and urinalysis were noted. At gross necropsy, many non-HDI body organ changes were noted; however, there were increases in the relative brain, heart, lung, and spleen weights in the 0.175 ppm HDI-treated females, with an increase in absolute spleen weight in this group as well. 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. HDI-related histopathological changes were limited to the nasal cavity and lungs. Lung lesions included epithelialization, interstitial pneumonia or alveolar macrophage accumulation in both sexes in the 0.025 and 0.175 ppm exposure groups, but not at the 0.005 ppm dose level. Histopathological lesions within the nasal cavity were numerous; however, only a few were considered to be a direct effect of HDI inhalation exposure. The 0.175 ppm exposure group lesions included degeneration of the olfactory epithelium, hyperkeratosis, occasional atrophy, and focal erosion or ulceration of the olfactory epithelium, with these lesions not present in the lowest (0.005 ppm) exposure group. Other lesions in the nasal cavity that occurred due to HDI exposure in the 0.025 and 0.005 ppm exposure groups include hyperplasia/metaplasia, mucus hyperplasia, and inflammation. Combining information obtained from a satellite group of rats exposed to HDI at identical

## APPENDIX A

concentrations, it was found that after 1 year of exposure, an adaptive nasal epithelial response (mucus secretory cell and epithelial hyperplasia) was observed at the lowest dose (0.005 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 of exposure, 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 the 1-year exposure group (at the same dose of HDI) was also noted.

The dose response effects noted in this study are summarized below:

0.175 ppm: Reticulocytosis (less serious LOAEL). Eye irritation observed in males only, first year only (less serious LOAEL). No observed effects (NOAEL) on the following systems: cardiac, gastrointestinal, musculoskeletal, hepatic, renal, endocrine, dermal, ocular (females only), body weight, immunologic/lymphoreticular, neurological, reproductive.

0.025 ppm: Nasal cavity hyperplasia/metaplasia, lung epithelialization, alveolar macrophage accumulation (less serious LOAEL). No observed effects in hematological parameters (NOAEL).

0.005 ppm: Nasal cavity epithelial hyperplasia (minimal LOAEL).

Dose end point used for MRL derivation:

NOAEL  LOAEL

Uncertainty factors used in MRL derivation:

1  3  10 (for use of a minimal LOAEL)

1  3  10 (extrapolation from humans to animals)

1  3  10 (for human variability)

Was a conversion factor used from ppm in food or water to a mg/body weight dose?

If so, explain:

No.

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

The LOAEL Human Equivalent Dose (LOAEL<sub>HEC</sub>) was calculated using Equation 4-16 from EPA (1994):

$$\text{LOAEL}_{\text{HEC}} = \text{LOAEL} \times \text{RGDR}_r$$

where RGDR<sub>r</sub> is the Regional Gas Dose Ratio for the region of interest. For HDI, the region of interest for this exposure route and duration for the rat is the nasal cavity. Again using EPA (1994) guidance and the dose-response relationships observed in rats outlined above, HDI effects would be classified as extrathoracic. HDI is also classified as a Category 1 gas (see pages 3–38 and 3–39 of EPA 1994), hence, Equation 4-18 of EPA (1994) was used to calculate the RGDR<sub>ET</sub>.

$$\text{LOAEL}_{[\text{HEC}]} = \text{LOAEL} \times \text{RGDR}_{\text{ET}}$$

$$\text{LOAEL}_{[\text{HEC}]} = (0.005 \text{ ppm}) \times (V_E/\text{SA}_{\text{ET}})_A / (V_E/\text{SA}_{\text{ET}})_H$$

$$\text{LOAEL}_{[\text{HEC}]} = 0.005 \text{ ppm} \times ([0.24 \text{ m}^3/\text{day} / 11.6 \text{ cm}^2]) / [20 \text{ m}^3 / 177 \text{ cm}^2]$$

$$\text{LOAEL}_{[\text{HEC}]} = 0.005 \text{ ppm} \times 0.183$$

$$\text{LOAEL}_{[\text{HEC}]} = 0.0009 \text{ ppm}$$

*Therefore:*

$$\text{MRL} = \text{LOAEL}_{[\text{HEC}]} / \text{UF}$$

$$\text{MRL} = 0.0009 \text{ ppm} / 90$$

$$\text{MRL} = 1.0 \times 10^{-5} \text{ ppm}$$

where the LOAEL<sub>HEC</sub> is the Human Equivalent Concentration for the lowest-observed-adverse-effect level, the RGDR is the Regional Gas Dose Ratio (animal (A): human (H)), V<sub>E</sub> is the ventilation volume (tidal volume in m<sup>3</sup>/day), SA is the regional surface area of the toxic effect observed (in cm<sup>2</sup>), and UF are the uncertainty factors.

Was a conversion used from intermittent to continuous exposure?

If so, explain:

No.

Other additional studies or pertinent information that lend support to this MRL:

The only other study considered for deriving a chronic inhalation MRL was the epidemiological study by Alexandersson et al. (1987). Although the study showed promise as a human epidemiology study, these workers were exposed to the HDI monomer as well as to the HDI pre-polymers (biuret trimer). The study did not distinguish between the effects produced by the monomer versus the polymer; therefore, since this was a combination/mixture exposure, it was not considered appropriate for use in determining a chronic MRL. 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. A later study by

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DeWilde and Hathaway (1994), again using chronically exposed workers at the plant in Freeport, Texas, 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 to which the workers were exposed, 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 they do lend some support to the MRL based on results found using the rat model.

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  $1.0 \times 10^{-5}$  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, and therefore should be classified as a NOAEL. Foureman et al. (1994) conclude that the olfactory degenerative response should be considered the significant effect in these rats, and not the hyperplastic response, supported by the fact that the degeneration of the olfactory epithelium did follow 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 degeneration of the olfactory epithelium was an adverse (toxic) response 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,  $1.0 \times 10^{-5}$  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 is not always clearly defined, and it may be a matter of opinion as to whether the effects are true adverse toxic responses.

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## APPENDIX B

### USER'S GUIDE

#### Chapter 1

##### Public Health Statement

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

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

#### Chapter 2

##### Tables and Figures for Levels of Significant Exposure (LSE)

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

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE Table 2-1 and Figure 2-1 are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

#### LEGEND

##### See LSE Table 2-1

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

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- (2) Exposure Period Three exposure periods - acute (less than 15 days), intermediate (15-364 days), and chronic (365 days or more) are presented within each relevant route of exposure. In this example, an inhalation study of intermediate exposure duration is reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.
- (3) Health Effect The major categories of health effects included in LSE tables and figures are death, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the "System" column of the LSE table (see key number 18).
- (4) Key to Figure Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 18 has been used to derive a NOAEL and a Less Serious LOAEL (also see the 2 "1 Sr" data points in Figure 2- 1).
- (5) Species The test species, whether animal or human, are identified in this column. Section 2.5, "Relevance to Public Health," covers the relevance of animal data to human toxicity and Section 2.3, "Toxicokinetics," contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.
- (6) Exposure Frequency/Duration The duration of the study and the weekly and daily exposure regimen are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 1 S), rats were exposed to 1,1,2,2-tetrachloroethane via inhalation for 6 hours per day, 5 days per week, for 3 weeks. For a more complete review of the dosing regimen refer to the appropriate sections of the text or the original reference paper, i.e., Nitschke et al. 198 1.
- (7) System This column further defines the systemic effects. These systems include: respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. "Other" refers to any systemic effect (e.g., a decrease in body weight) not covered in these systems. In the example of key number 18, 1 systemic effect (respiratory) was investigated.
- (8) NOAEL A No-Observed-Adverse-Effect Level (NOAEL) is the highest exposure level at which no harmful effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system which was used to derive an intermediate exposure, inhalation MRL of 0.005 ppm (see footnote "b").
- (9) LOAEL A Lowest-Observed-Adverse-Effect Level (LOAEL) is the lowest dose used in the study that caused a harmful health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific end point used to quantify the adverse effect accompanies the LOAEL. The respiratory effect reported in key number 18 (hyperplasia) is a Less serious LOAEL of 10 ppm. MRLs are not derived from Serious LOAELs.
- (10) Reference The complete reference citation is given in chapter 8 of the profile.

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- (11) CEL A Cancer Effect Level (CEL) is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases.
- (12) Footnotes Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. Footnote “b” indicates the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

**LEGEND****See Figure 2-1**

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

- (13) Exposure Period The same exposure periods appear as in the LSE table. In this example, health effects observed within the intermediate and chronic exposure periods are illustrated.
- (14) Health Effect These are the categories of health effects for which reliable quantitative data exists. The same health effects appear in the LSE table.
- (15) Levels of Exposure concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale “y” axis. Inhalation exposure is reported in mg/m<sup>3</sup> or ppm and oral exposure is reported in mg/kg/day.
- (16) NOAEL In this example, 18r NOAEL is the critical end point for which an intermediate inhalation exposure MRL is based. As you can see from the LSE figure key, the open-circle symbol indicates to a NOAEL for the test species-rat. The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the Table) to the MRL of 0.005 ppm (see footnote “b” in the LSE table).
- (17) CEL Key number 38r is 1 of 3 studies for which Cancer Effect Levels were derived. The diamond symbol refers to a Cancer Effect Level for the test species-mouse. The number 38 corresponds to the entry in the LSE table.
- (18) Estimated Upper-Bound Human Cancer Risk Levels This is the range associated with the upper-bound for lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. These risk levels are derived from the EPA’s Human Health Assessment Group’s upper-bound estimates of the slope of the cancer dose response curve at low dose levels (qi\*).
- (19) Key to LSE Figure The Key explains the abbreviations and symbols used in the figure.

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**Chapter 2 (Section 2.5)****Relevance to Public Health**

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

1. What effects are known to occur in humans?
2. What effects observed in animals are likely to be of concern to humans?
3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

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

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

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

**Interpretation of Minimal Risk Levels**

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

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

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

**SAMPLE**

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

1 →

Key to figure <sup>a</sup>	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect)		Reference
					Less serious (ppm)	Serious (ppm)	
<b>INTERMEDIATE EXPOSURE</b>							
2 →	5	6	7	8	9		10
3 →	Systemic	↓	↓	↓	↓		↓
4 →	18	Rat	13 wk 5d/wk 6hr/d	Resp	3 <sup>b</sup>	10 (hyperplasia)	Nitschke et al. 1981
<hr style="border-top: 1px dashed black;"/>							
<b>CHRONIC EXPOSURE</b>							
						11	
	Cancer					↓	
	38	Rat	18 mo 5d/wk 7hr/d			20	(CEL, multiple organs) Wong et al. 1982
	39	Rat	89–104 wk 5d/wk 6hr/d			10	(CEL, lung tumors, nasal tumors) NTP 1982
	40	Mouse	79–103 wk 5d/wk 6hr/d			10	(CEL, lung tumors, hemangiosarcomas) NTP 1982

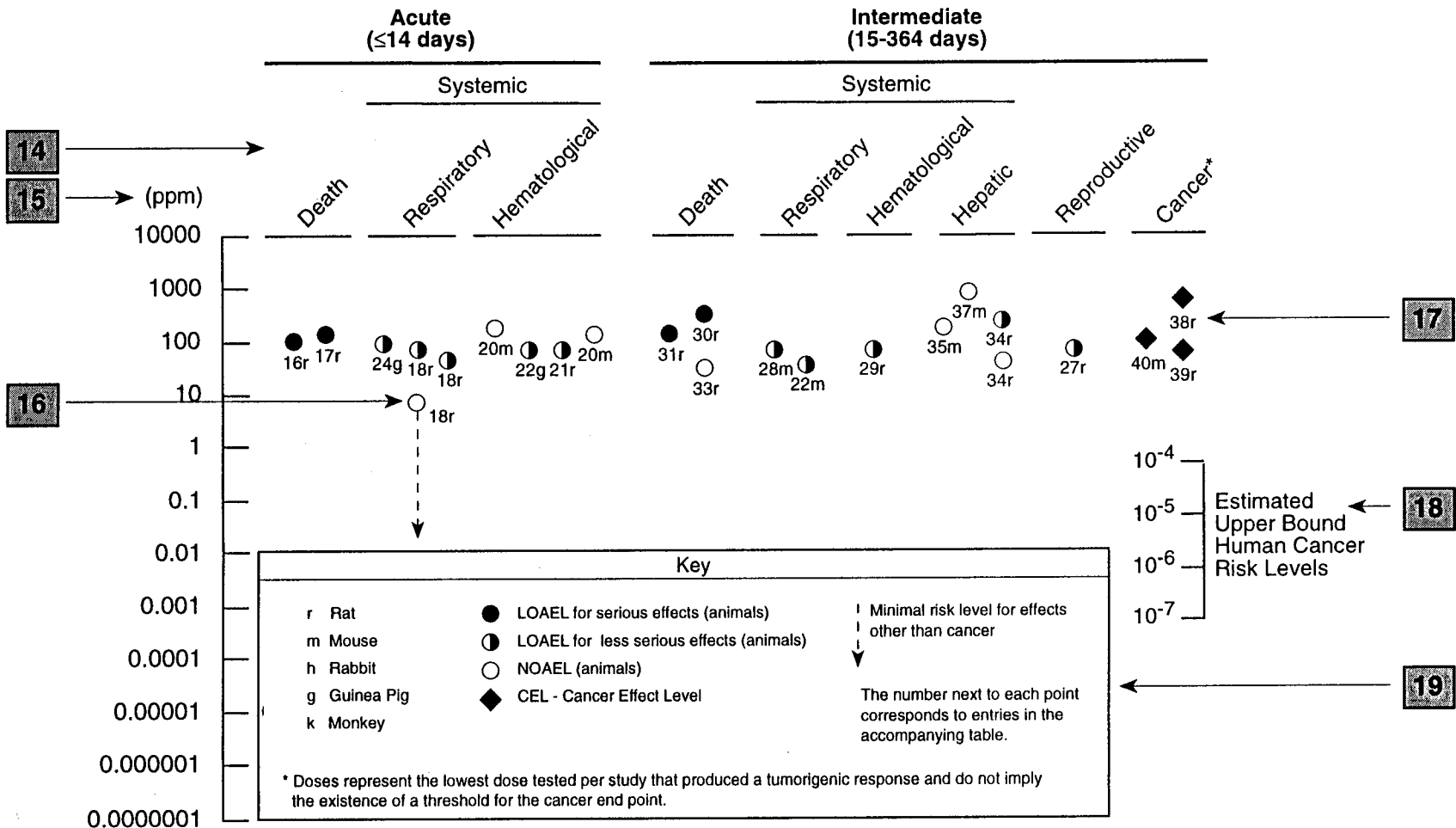
12 →

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

<sup>b</sup> Used to derive an intermediate inhalation Minimal Risk Level (MRL) of  $5 \times 10^{-3}$  ppm<sup>3</sup> dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

**SAMPLE**

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



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

## APPENDIX C

## ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ADME	Absorption, Distribution, Metabolism, and Excretion
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
BCF	bioconcentration factor
BSC	Board of Scientific Counselors
C	Centigrade
CDC	Centers for Disease Control
CEL	Cancer Effect Level
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
CLP	Contract Laboratory Program
cm	centimeter
CNS	central nervous system
d	day
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DOL	Department of Labor
ECG	electrocardiogram
EEG	electroencephalogram
EPA	Environmental Protection Agency
EKG	see ECG
F	Fahrenheit
F <sub>1</sub>	first filial generation
FAO	Food and Agricultural Organization of the United Nations
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
fpm	feet per minute
ft	foot
FR	<i>Federal Register</i>
g	gram
GC	gas chromatography
gen	generation
HPLC	high-performance liquid chromatography
hr	hour
IDLH	Immediately Dangerous to Life and Health
IARC	International Agency for Research on Cancer
ILO	International Labor Organization
in	inch
K <sub>d</sub>	adsorption ratio
kg	kilogram
kkg	metric ton
K <sub>oc</sub>	organic carbon partition coefficient
K <sub>ow</sub>	octanol-water partition coefficient



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

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