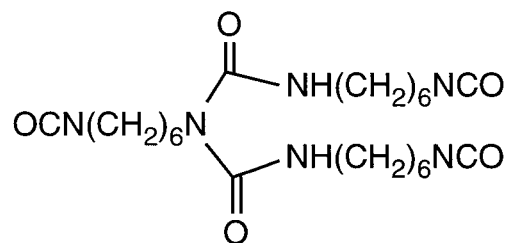## 5. POTENTIAL FOR HUMAN EXPOSURE

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-l% 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-lb) 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 (≤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
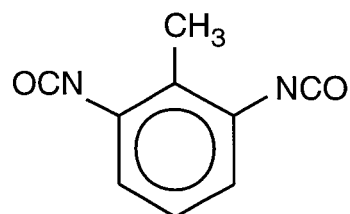
5. POTENTIAL FOR HUMAN EXPOSURE

Figure 5-1. Selected Isocyanate Structures

(a) Trimeric Biuret of Hexamethylene Diisocyanate (HDI-BT)
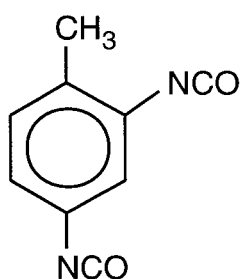
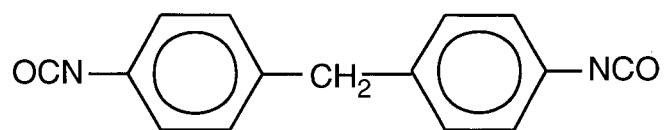2,4-TDI   2,6-TDI

(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.

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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-l.%) 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).

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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

53.1   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 ºC (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 tcrthe removal of HDI from the ambient atmosphere by dry deposition is not clear. Because of its relatively short atmospheric half-life of ≈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.

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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 4.80×10^{-5} atm-m^3/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 198 1). 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.

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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 7.95×10^{-12} cm^3/molecule-see 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 5×10^5/cm^3 (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^3/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
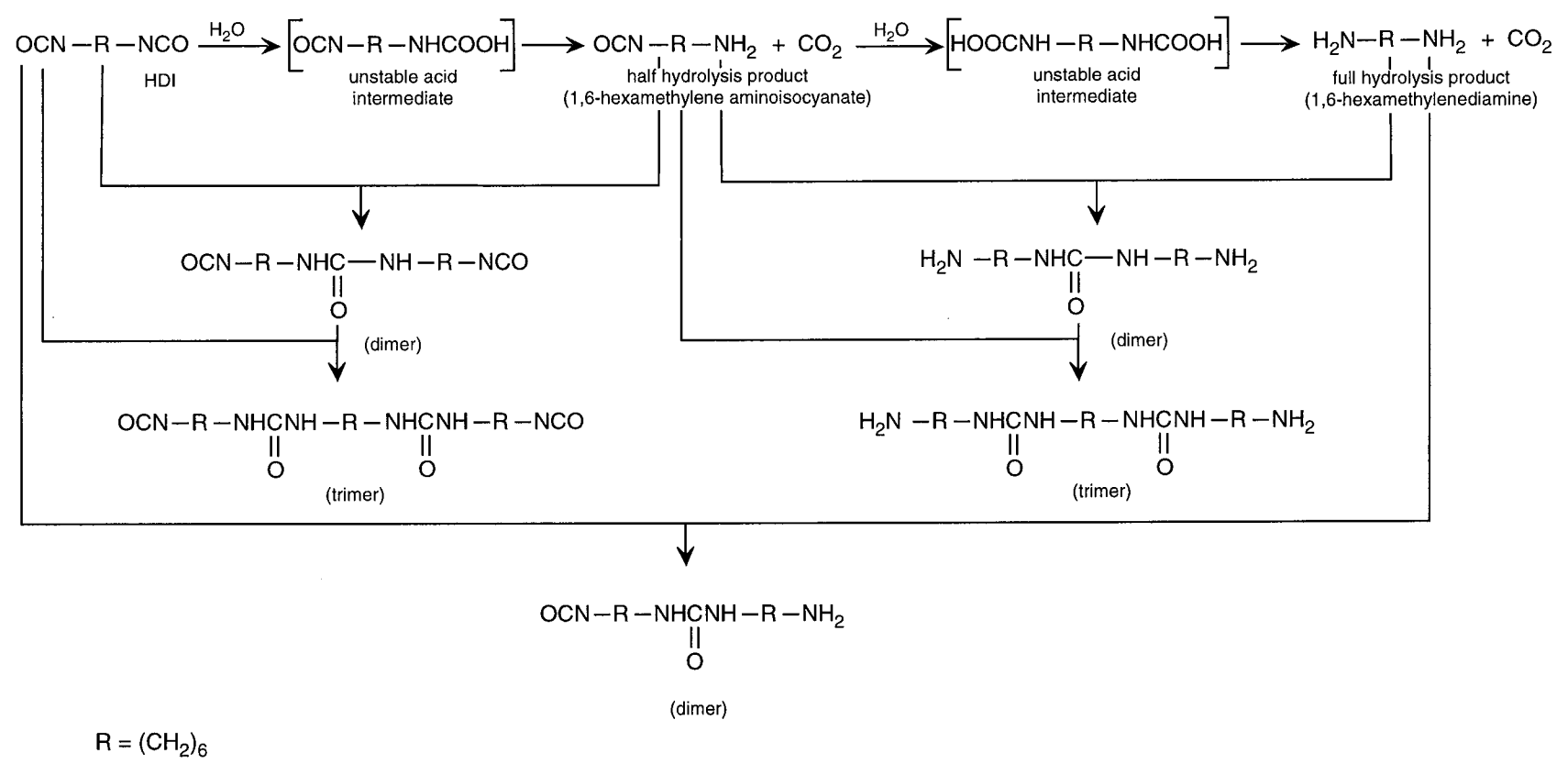
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analogy, significant atmospheric accumulation of HDA may not occur, except perhaps near sources of HDI emissions.

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 198 1; 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 ºC; 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 ºC; pH 7.4). Results of experiments in a staticsystem 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

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

$$OCN-R-NCO \xrightarrow{H_2O} \left[OCN-R-NHCOOH\right] \longrightarrow OCN-R-NH_2 + CO_2 \xrightarrow{H_2O} \left[HOOCNH-R-NHCOOH\right] \longrightarrow H_2N-R-NH_2 + CO_2$$

HDI   unstable acid intermediate   half hydrolysis product (1,6-hexamethylene aminoisocyanate)   unstable acid intermediate   full hydrolysis product (1,6-hexamethylenediamine)

$$OCN-R-NHC-NH-R-NCO$$
$$\parallel$$
$$O$$
(dimer)

$$H_2N-R-NHC-NH-R-NH_2$$
$$\parallel$$
$$O$$
(dimer)

$$OCN-R-NHCNH-R-NHCNH-R-NCO$$
$$\parallel \qquad\qquad \parallel$$
$$O \qquad\qquad O$$
(trimer)

$$H_2N-R-NHCNH-R-NHCNH-R-NH_2$$
$$\parallel \qquad\qquad \parallel$$
$$O \qquad\qquad O$$
(trimer)

$$OCN-R-NHCNH-R-NH_2$$
$$\parallel$$
$$O$$
(dimer)

$$R = (CH_2)_6$$

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.

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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-phenylisocyante] 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

54.1   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. l), 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[®], Bayer AG) (Nielsen et al. 1985). HDI-BT (DES-N[®], 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-l.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 uf 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.

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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 $\mu g/m^3$, respectively (NIOSH 1992). The American Conference of Governmental Industrial Hygienists (ACGIH) has set an S-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, steamtitters, 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 ≤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 $\mu g/m^3$ (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 $\mu g/m^3$ (0.002-0.006 ppm) and 39-63 $\mu g/m^3$ (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 $\mu g/m^3$; 0.020 ppm) is unlikely to be exceeded at aerosol mass concentrations below 20 mg/m^3. An average HDI concentration of 0.230 ppm (1,600 $\mu g/m^3$) in curing oven exhaust was calculated from the results of a laboratory study using metal panels coated with a formulation (Desmodur LS-2800[®]) 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 $\mu g/m^3$ (<0.0000l-0.0006 ppm) and 5.3-75 $\mu g/m^3$ (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 $\mu g/m^3$ (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 $\mu g/m^3$ (0.001-0.018 ppm) and 280-3,600 μ/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±220 $\mu g/m^3$ (0.074±0.033 ppm) and 1,440±1,130 $\mu g/m^3$ (0.219±0.172 ppm) (±SD, n=l0), 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 $\mu g/m^3$ (<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 $\mu g/m^3$ (0.0002 ppm); whereas, the mean exposure concentration of HDI-BT was 115 $\mu g/m^3$ (0.017 ppm) (range, 10-385 $\mu g/m^3$; 0.002-0.058 ppm), with short-term peak exposures up to 13,500 $\mu g/m^3$ (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-l .3 mg/m^3 (0.027-0.20 ppm), <0.004-0.24 mg/m^3 (<0.0006-0.036 ppm), and <0.004-0.10 mg/m^3 (<0.0006-0.0 15 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 hydrosylates 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 $\mu g/m^3$ (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, ≈01.2-l .4 hours; >90% urinary elimination of HDA within ≈ 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 Grieveson 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 hydrosylates as a biomarker of short-term exposure to HDI (Berode et al. 199 1; 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 $\mu g/m^3$ (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-l .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.