III. BIOLOGIC EFFECTS OF EXPOSURE

The diisocyanates are chemical compounds in which two isocyanate groups, -NCO, are attached to carbon atoms of an organic radical. The chemical and physical properties of various diisocyanates are listed in Table XI-1 [1-10]. Synonyms for these compounds are listed in Table XI-2.

Many diisocyanates exhibit high chemical reactivity [11]. In the presence of water they react exothermically to produce an unstable carbamic acid that rapidly dissociates to form a primary amine and carbon dioxide. The primary amine can react further with excess isocyanate to form a urea derivative.

Isocyanates also react vigorously with organic compounds containing reactive hydrogens, especially where the hydrogen atom is attached to oxygen, nitrogen, or sulfur [11]. In biologic macromolecules, these groups occur abundantly, and the isocyanates will therefore react and combine with a variety of sites on these molecules. Polyfunctional isocyanates, such as the diisocyanates, can act as cross-linking agents with biologic macromolecules.

Extent of Exposure

The most common method of synthesis of the diisocyanates is the reaction of primary amines with phosgene [12]. In this process, a primary aliphatic or aromatic amine, dissolved in a solvent such as xylene, monochlorobenzene, or dichlorobenzene, is mixed with phosgene dissolved in the same solvent and allowed to react for several hours at temperatures of about 200 C. More phosgene is added during the process, and the final reaction mixture is fractionated to recover the isocyanate product, as well as hydrochloric acid, unreacted phosgene, the solvent for recycling, and the distillation residue for incineration.

Diisocyanates are used to produce polyurethane foams, coatings, elastomers, and spandex fibers. Toluene diisocyanate (TDI), which is commercially available as standard mixtures of the 2,4- and 2,6-isomers, is generally used in producing flexible polyurethane foams. Methylene diphenyl diisocyanate (MDI), especially in partially polymerized forms, is used more frequently in rigid foams. A substantial amount of MDI (40-50% of the amount produced) is used in the manufacture of polyurethane systems, such as formulated packages of isocyanates, polyols, fluorocarbon blowing agents, fire retardants, surfactants, and catalysts. TDI and pure MDI, or special liquid MDI products, are used to make elastomers, which are used in manufacturing printing rolls, liners for mine chutes and grain elevator chutes, coated fabrics, shoe soles, and automobile bumpers [12,13]. MDI is also used in the foundry industry as part of a binding system for casting molds [14]. The total consumption of MDI and partially polymerized MDI in 1975 was about 300 million pounds. TDI consumption totaled about 400 million pounds, and only a few million pounds of other diisocyanates were used in 1975 [15].

Workers with potential occupational exposure to diisocyanates include adhesive workers, insulation workers, diisocyanate resin workers, lacquer workers, organic chemical synthesizers, paint sprayers, polyurethane makers, rubber workers, shipbuilders, textile processors, and wire-coating workers [16].

A NIOSH survey conducted in 1972-1974 estimated that 50,000-100,000 employees in the United States were potentially exposed to diisocyanates. This number does not include occasional users of isocyanate preparations such as polyurethane varnish and may therefore underestimate the number of workers exposed.

Historical Reports

Toluene diisocyanate and hexamethylene diisocyanate (HDI) were the most widely used diisocyanates in the early stages of the industry, according to Williamson [17] and Munn [18]. Consequently, the earliest reports of hazards from exposure to isocyanates usually involved these compounds. Both of these compounds are among the more volatile diisocyanates, and respiratory and other health problems associated with these compounds prompted the development of less volatile diisocyanates and derivatives, as well as improved handling techniques. As a result, although many new diisocyanate products have been used in industrial applications more recently, the number of reports of toxic effects from exposure to diisocyanates has decreased.

In Germany in 1941, Gross and Hellrung, according to Friebel and Luchtrath [19], investigated the toxicity of TDI in animal experiments. They exposed dogs, cats, rabbits, and guinea pigs to a commercial TDI preparation at 14-1,400 ppm and reported that, at the lower concentrations studied, irritation of the respiratory tract occurred, and, at the higher concentrations, bronchitis, pneumonia, and pulmonary edema resulted.

According to Brugsch and Elkins [20], toxic effects of TDI had been observed in German workers handling the substance in war-related industries during World War II. However, the first published account of TDI toxicity in humans was a 1951 report by Fuchs and Valade [21]. They described nine cases of progressive bronchial irritation in French workers exposed to TDI. On continued exposure, seven of the affected workers developed an asthma-like condition, which the authors suggested was allergic.

In 1953, Reinl [22] reported a human fatality attributed to organoisocyanate exposure. This was 1 of 17 cases of respiratory illness in German workers exposed to TDI or other isocyanates. Thirteen of these illnesses were severe. Two workers developed pulmonary edema, which in one case was fatal, terminating in cor pulmonale. In the same year, in Sweden, Swensson et al [23] described three cases

of respiratory illness in painters who used lacquer containing isocyanates. Two of these workers had spirometric pulmonary function measurements suggestive of emphysema.

In the 1950's many similar cases of isocyanate toxicity were reported in Europe [24-26], including another fatality [27], and in the United States [25,28-31]. These occurred in workers exposed to TDI in manufacturing polyurethane foam or using TDI- or polyisocyanate-based lacquers and glues. As many as 99 cases of respiratory illness were reported from a single US plant manufacturing polyurethane foam [31]. A 1962 review by Elkins et al [32] reported a total of 222 cases of respiratory illness attributed to TDI exposure in the literature through 1960.

Goldblatt and Goldblatt [33], in a 1956 report, described a case of a chemist exposed to the vapor of heated 1,5-naphthalene diisocyanate (NDI). The chemist developed a severe cough that recurred each time he returned to the laboratory. Gerritsen [34] suggested in 1955 that an asthmatic condition in workers exposed to HDI was the result of an allergic mechanism.

Most of the early reports of respiratory illness in workers exposed to diisocyanates described bronchial asthma or chronic bronchitis, often considered by the authors to involve evidence of sensitization [23-25,28]. However, some respiratory illnesses were attributed to direct irritation from TDI, usually as a result of acute accidental exposures [28-30,35].

Friebel and Luchtrath [19], in 1955, attempted to demonstrate sensitization to TDI in guinea pigs. They were not able to produce allergic asthmatic responses in animals exposed to TDI aerosol at 120 ppm or TDI vapor at 50-80 ppm. Effects on the animals' lungs were attributed to primary toxic action by TDI. Zapp [36], in 1957, also reported only direct effects on the respiratory tract in rats, guinea pigs, dogs, and rabbits exposed to TDI at 1.5 ppm for about 80 exposures of 6 hours each.

Since 1960, additional cases of occupational illness attributed to exposure to diisocyanates have been reported, but these have been less frequent and less severe as recognition of the hazard has increased. In 1973, NIOSH published criteria for a recommended standard for occupational exposure to TDI [37]. The studies of TDI toxicity on which NIOSH based its 1973 recommendations are discussed in the following sections, as is information on TDI that has appeared in the literature more recently and data on other diisocyanates. Most studies on TDI in this chapter that are dated prior to 1973 were discussed in the earlier document.

Effects on Humans

Much of the investigation of the biologic effects of diisocyanates has been directed toward determining the extent and nature of sensitization to these compounds. In this document, sensitivity to diisocyanates denotes the tendency of

some individuals to have a respiratory response when they are exposed at concentrations much lower than those that irritate the respiratory tract in most people. Sensitization may develop gradually or suddenly after exposure to diisocyanates. The usual response is an asthmatic reaction, characterized by wheezing, dyspnea, and bronchial constriction. Use of these terms is not intended to implicate any particular mechanism as the cause of the reaction. The terms "allergy" and "allergic," on the other hand, are reserved for conditions in which an immunologic response is implied.

Workers occupationally exposed to the diisocyanates in various industries have developed adverse respiratory effects; reports of skin disease and evidence suggesting systemic toxicity from such exposures have been far less numerous. Most of the affected workers have been exposed in manufacturing diisocyanates, in using these compounds to manufacture polyurethane products such as foam, and in painting or spraying polyurethane varnishes and paints. These activities also involve possible exposure to other potentially harmful chemicals, including chlorobenzene, phosgene, styrene, and amines, and little is known of how such mixed exposures may affect the toxicity of the diisocyanates.

Most of the data available on exposure to diisocyanates are on TDI. Several reports on MDI and a smaller number on other diisocyantes, including HDI and NDI, have also been published. In the following subsections, information on the biologic effects of TDI is discussed first, followed by data on MDI and other diisocyanates.

(a) Respiratory Effects

The odor threshold for TDI estimated by Zapp [36] in 1957 was 400 ppb (2.8 mg/cu m) in 12 of 24 men tested. Five years later, Henschler et al [38] estimated an odor threshold of 50 ppb (360 µg/cu m), using the analytical method of Erlicher and Pilz [39], which they found was more accurate and sensitive than the Ranta method used by Zapp. Eye irritation was experienced by three of six volunteers exposed at this concentration for 10 minutes and five of six exposed for 15 minutes; one also had nasal irritation [38]. At 100 ppb (700 µg/cu m), two of six complained of throat irritation, and exposure at 500 ppb (3,600 µg/cu m) produced eye, nose, and throat irritation in all volunteers.

Pulmonary function testing has been used in many studies of workers exposed to TDI and other diisocyanates to evaluate changes in lung function. In 1964, seven furniture plant employees who sprayed, dipped, or painted with polyurethane varnish developed acute respiratory symptoms 0.5 hour to 3 weeks after their first known exposure [40]. Three measurements made after some improvements in ventilation showed TDI at 80, 100, and 120 ppb (570-850 µg/cu m). All seven men coughed and had difficulty in breathing and four had blood-stained sputum. Five of the seven were tested for forced vital capacity (FVC) and forced expiratory volume at 1 second (FEV 1) 2-3.5 months after exposure and had higher values than they did shortly after exposure. The responses to a questionnaire given 22 months after

exposure after exposure suggested to the author that four of six who responded had become sensitized to TDI.

In 1965, Williamson [41] described six workers exposed to TDI in a polyurethane foam plant who developed symptoms that were considered suggestive of sensitization. Four of these, from a workforce of 99, had become sensitized during 18 months of exposure to TDI at concentrations usually below 20 ppb, apparently determined by area monitoring. The author believed that sensitization had resulted from exposure at higher concentrations caused by spills. Immediately after one spill, TDI at 200 ppb (1.4 mg/cu m) was found, but the concentration was less than 5 ppb (35 µg/cu m) 10 minutes later. All six affected workers had asthma or bronchitis with decreased ventilatory capacity (FVC and FEV 1) during these incidents. Some of the subjects were also occasionally exposed to MDI, but always at concentrations below 20 ppb (204 µg/cu m).

In 1976, Charles et al [42] described a case of pneumonitis and three cases of chronic respiratory disease in workers exposed to TDI or HDI. Pneumonitis was diagnosed in a 50-year-old nonsmoker who had experienced difficulty in breathing, weight loss, and fever for 6 weeks at the time of examination. Prior to his 5 years of working in the polyurethane foam industry, he had been a coal miner for 11 years. Chest X-rays showed alveolar filling lesions in both the lungs. Two months later, pulmonary function tests showed reduced FEV 1, vital capacity, total lung capacity, and residual volume of the lungs. A bronchogram showed peripheral cystic bronchiectasis in the right upper lobe. All immunologic tests for antibodies against TDI were negative. Microscopic examination of biopsy samples of lung tissue showed variations from normal architecture ranging from diffuse interstitial disease to acute inflammation and end-stage interstitial fibrosis. The authors stated that the areas of filled alveoli resembled desquamative interstitial pneumonitis and that the whole picture resembled that of a pulmonary hypersensitivity response to an inhaled allergen rather than coal-miners' pneumoconiosis, but they did not demonstrate that this was related to TDI exposure.

Two other workers developed severe dyspnea after exposure to spills of TDI [42]. Two to three years after exposure, both workers had moderate obstruction of the airways, as indicated by FEV 1 measurements below predicted values; one also had a decreased vital capacity, and the other, although his vital capacity was normal, still experienced severe nonwheezing dyspnea after minimal exertion.

Similar symptoms occurred in a 61-year-old man who had been a paint sprayer for 43 years with no previous history of respiratory illness; he developed wheezing, dyspnea, and sweating within hours when he first used a polyurethane paint containing HDI [42]. Whenever he was reexposed to the paint by casual contact with fumes from other spraying operations, he again developed symptoms. Testing 1 year after exposure showed moderate obstruction of airways, and he complained of nonwheezing dyspnea after exertion.

Pepys et al [43] tested four patients with occupational asthma for TDI sensitivity by simulating occupational exposures to a two-stage polyurethane varnish

with TDI activator. The subjects applied varnish with the TDI activator and, on a separate day, without the activator, to a surface in a small cubicle. When the activator was used, TDI concentrations in the air reached a maximum of almost 2 ppb (14 µg/cu m), as measured by the colorimetric method of Meddle et al [44]. No TDI was detected when the varnish alone was applied. All the subjects were essentially asymptomatic at the time of testing, and their FVC and FEV 1 values were not more than 10% below predicted values. None showed positive responses in skin tests with common allergens, and none had a family or personal history of allergies.

A 26-year-old boatbuilder, who had been using a two-stage polyurethane varnish system for 8 years, had cough and dyspnea at night [43]. The attacks gradually became more severe and occurred earlier in the day, appearing only when the two-stage varnish was used. Another man, 46 years old, had worked for 8 years as a maintenance engineer whose duties included maintenance of a polyurethane foam machine. He had chest tightness and shortness of breath, which disappeared within 20 minutes after he left work. His symptoms also became progressively worse, developing into severe asthma. Neither man had any known exposure to spills of TDI. In challenge testing, both reacted to the varnish only when the TDI activator was added. The boatbuilder developed a late asthmatic reaction that appeared at 1-2 hours and reached a maximum at 3-4 hours, while the maintenance engineer showed an immediate reaction.

The other two subjects were women who worked in a television factory department where coated wires were soldered [43]. The wire, coated with cured polyurethane and polyvinyl butyral, was dipped into a resin flux containing dimethylamine hydrochloride and then into multicore solder at 460 C. One woman, 44 years old, developed a chronic cough and, after 6 years, wheezing. The second woman, a 54-year-old supervisor in the same department, developed a productive cough, wheezing, and breathlessness, developing into severe bronchitis that kept her away from work for 5 weeks. Her symptoms recurred within 1 week of her return, and this pattern was repeated each time she attempted to return to work. Both women reacted to the varnish with TDI activator. The first woman had an immediate reaction that was resolved in 2 hours but was followed by a late reaction at 3-4 hours. The second woman had only a late reaction at 3-4 hours. She was also tested with various components used in the soldering operation. Positive results were obtained only with the simulation of the soldering operation using coated wire, but not with uncoated wire. This test produced a severe asthmatic reaction starting 30-60 minutes after exposure ended and continuing for 6 weeks before her FEV 1 returned to pretest levels. Blood tests on these four patients showed no eosinophilia, but sputum collected from the 54-year-old woman contained eosinophils. This suggested to the authors a reagin-mediated reaction.

The sensitized individuals tested by Pepys and colleagues [43] had adverse reactions to TDI after exposures as brief as 10 minutes at reported concentrations of about 2 ppb (14 µg/cu m). The authors emphasized that none of these sensitized individuals had a known history of heavy TDI exposure, such as exposure

to spills. Thus, it appears that exposure to massive amounts of TDI, as from a spill, may not be necessary to produce sensitization.

The same technique of challenge exposure to polyurethane varnish was used by Carroll and coworkers [45] to test four employees who worked in an office adjacent to a factory that used TDI. Three clerical workers and a security guard, among 47 workers in the office block, had histories of asthma-like symptoms, and in two cases these were clearly alleviated during periods away from work. It was discovered that the air inlet for the office building was located only 23 feet from the ventilation outflow of the factory that used TDI, but actual air concentrations in the offices were not determined.

The polyurethane varnish mixture used in the challenge testing was one-third TDI, and the authors [45] stated that the atmospheric concentration of TDI created by painting it on a surface in the test chamber was about 1 ppb (7 µg/cu m), but the method of determination was not described. Three of the patients reacted to TDI, one after a 15-minute exposure, one after 30 minutes, and one only after a 60-minute exposure. Exposures to the varnish without the TDI activator produced no reactions.

The authors [45] also mentioned that one additional office worker had asthmatic symptoms that were relieved by removal from the environment. This suggests that 4 of the 47 workers were sensitized to TDI, a sensitization rate of about 9%.

To evaluate the specificity of TDI sensitivity, O'Brien et al [46] tested the responses of TDI workers to TDI, histamine, and exercise. The 63 men studied had been referred for investigation of possible work-related respiratory symptoms.

All 63 workers were tested for respiratory responses when they painted a bench in a closed cubicle with varnish for 30 minutes [46]. After control values for pulmonary function were established, TDI was added to the varnish in increasing amounts on subsequent days until a reaction was elicited or until a maximum airborne TDI concentration of 20 ppb (140 µg/cu m) was reached. The test subject's FEV 1 and FVC were monitored before the exposure and for 8 hours afterwards. A subject was considered sensitive to TDI if his fall in FEV 1 after exposure was 15% more than on the control day. TDI concentrations in the cubicle were measured by a continuous monitor; in 23 cases, breathing-zone sampling was also performed, and the results of the two measurements were found to be closely correlated ($r = 0.95$).

Fifty-two of the workers were also tested by inhaling an aerosol of histamine acid phosphate at graded concentrations up to 32 mg/ml for 30-second periods [46]. A 20% fall in FEV 1 was considered evidence of bronchial hyperreactivity. Forty-six subjects participated in exercise testing, consisting of free running sufficient to increase the heart rate to 140 beats/minute. A fall in FEV 1 of more than 9% was regarded as indicative of an asthmatic reaction. All subjects were

prick tested with 23 common respiratory allergens, and those who reacted to 1 or more were considered atopic.

Thirty-seven of the 63 workers were sensitive to TDI as indicated by respiratory responses to challenge testing, which included 2 immediate, 17 late, and 18 dual reactions [46]. Nine of these workers reacted to TDI at concentrations of less than 1 ppb (7 µg/cu m). When challenged with histamine, 17 of 31 TDI-sensitive and 8 of 21 nonsensitive workers tested showed bronchial hyperreactivity. Exercise-induced asthma was detected in 18 of 29 sensitive and 9 of 17 nonsensitive workers. Differences between the TDI-sensitive and nonsensitive groups were not significant (at $P=0.05$) by Wilcoxon's nonparametric test for unpaired samples. However, in the subgroup of sensitive workers who responded to TDI at less than 1 ppb, there were significantly more reactions to both histamine ($P<0.005$) and exercise ($P<0.01$) than in those who reacted only at higher TDI concentrations; this extremely sensitive group also had a singificantly higher incidence of exercise-induced asthma than the group that did not react to TDI ($P<0.025$). Age, atopic status, and history of rhinitis were similar in the TDI sensitive and nonsensitive groups, but there was a higher incidence of asthma prior to work with TDI and of a family history of allergy in the nonsensitive group. There was no significant differences between smokers, exsmokers, and nonsmokers on the TDI, histamine, or exercise tests.

In a further study, O'Brien et al [47] investigated cross-reactivity to TDI, MDI, and HDI in 24 diisocyanate workers referred for investigation of respiratory symptoms. All 24 men had been exposed to TDI, 14 to MDI, and 6 to HDI; 5 of the latter group had been exposed to all 3 diisocyanates.

All subjects were challenged with TDI by the procedure previously described and with MDI over the same range of concentrations (<1-20 ppb) by heating the material in a closed cubicle [47]. Nine, including the six with previous exposure to HDI, were also challenged by painting with an HDI varnish, but air concentrations of HDI were not measured. All subjects were tested by histamine inhalation.

Sixteen of the subjects were sensitive to TDI, and eight of these also reacted to MDI, including four who had no known previous exposure to MDI [47]. Three of the nine workers tested with HDI showed positive responses; all three had also reacted to both TDI and MDI, and two of them had no previous exposure to HDI. Histamine inhalation produced a positive reaction in five of the eight subjects who did not respond to challenge with diisocyanates, one of the eight who reacted only to TDI, and six of the eight who reacted to both TDI and MDI (including all three who also reacted to HDI). The authors reported that subjects who reacted to more than one diisocyanate had a greater degree of histamine reactivity and reacted to TDI at lower concentrations than did those who reacted only to TDI.

According to the authors, these two studies [46,47] suggested that both specific (probably immunologic) and nonspecific mechanisms contribute to

diisocyanate sensitivity. Among workers referred for respiratory symptoms, TDI-sensitive individuals were no more likely to have nonspecific asthmatic responses to histamine or exercise than were those who did not react to TDI. However, those who showed extreme sensitivity to TDI, reacting at concentrations of less than 1 ppb, did have an increased incidence of nonspecific asthmatic responses, suggesting to the authors that specific sensitivity to TDI might be exacerbated by irritative or pharmacologic hyperreactivity of the airways. The existence of such a dual mechanism in individuals extremely sensitive to diisocyanates was supported by the results of cross-challenging with TDI, MDI, and HDI [47]. The authors considered that immunologic cross-reactivity between these three compounds was unlikely because of their structural differences. They concluded that their results were consistent with the existence of a specific mechanism of TDI sensitivity coupled, in extremely sensitive individuals, with a pharmacologic mechanism that also caused increased reactivity to other diisocyanates.

Occupational exposure to MDI has produced respiratory effects similar to those reported from TDI exposure. Longley [48], in 1964, described an incident in which 12 men who worked 60-120 feet from an MDI foam-spraying operation developed symptoms, including asthmatic breathing, retrosternal soreness, constriction of the chest, cough, retrobulbar pain, depression, headache, nasal discharge, and insomnia. All 12 workers developed symptoms within several hours after exposure to the mist. The workers actually spraying the MDI foam, who wore full protective clothing and air-supplied respirators, were unaffected.

Munn [18], in 1965, described two cases of apparent sensitivity to MDI. A worker who used MDI mixed with resin to manufacture television scenery experienced several asthma attacks. A technical service representative who demonstrated MDI spraying and dispensing techniques developed tightness of the chest when performing or watching these demonstrations. He noticed these symptoms under conditions in which others were not affected and which had not initially affected him. Munn concluded that MDI was a potential respiratory irritant and that in rare instances it could cause sensitization.

In 1972, Lob [49] described a reaction to MDI in a 50-year-old worker in a polyurethane factory who had no history of allergies, bronchitis, or asthma. He intermittently experienced malaise accompanied by fever, nausea, and coughing, usually at the end of the day. After one such attack, a thorough examination showed that he had a slightly decreased vital capacity. After another attack, he had an increased white blood cell count (WBC) of 12,650/cu mm.

To determine the factors producing these symptoms, Lob [49] exposed the worker for 3-4 minutes in a simulated operation where plastic belts were welded by heat. The author stated that MDI was detected in the whitish fumes given off during the welding process, but the concentration was not given; no TDI was detected. The worker's body temperature increased to 39 C within 4-5 hours after he was exposed, and he had nausea and a severe cough. Vital capacity decreased slightly, WBC increased, and he had congested conjunctiva, increased pulse, and

decreased blood pressure. All these signs were normal the next day. Lob concluded that the onset, severity, persistence, and recurrence of the symptoms were suggestive of an allergic reaction to MDI.

In 1971, Lapp [50] described the effects of brief exposures to TDI and MDI on three men. One was a 38-year-old worker in a chemical plant who had worked with diisocyanates for 13 years. The other two were 25- and 23-year-old medical officers with no previous exposure to diisocyanates. Each subject slowly inhaled TDI from a sniff bottle. After at least 1 day without exposure, each subject was challenged with MDI in the same manner. Pulmonary function of each subject was determined before and after each exposure.

Fifteen minutes after TDI inhalation, the values for FVC, FEV 1, and forced expiratory flow between 25 and 75% of the FVC (FEF 25-75) in the worker who had previously been exposed to diisocyanates were 3.16, 2.79, and 3.62 liters, respectively, compared with corresponding preexposure values of 4.03, 3.68, and 5.92 liters. Airway resistance increased to 123% of the preexposure value at 15 minutes and 166% at 30 minutes. These changes were promptly reversed by a bronchodilator. In the other two subjects, there was no increase in airway resistance or decrease in FVC or FEV 1, but one subject had a slight decrease in FEF 25-75 15 minutes after TDI inhalation.

After the challenge with MDI, the worker occupationally exposed to diisocyanates again showed an increase in airway resistance at 15 and 30 minutes [50]. He was unable to perform the FVC tests because of recurring cough spasms at the 15-minute test period. The effects of MDI were reversed following administration of a bronchodilator. Approximately 4-6 hours later, the man again experienced chest tightness and wheezing and his temperature increased to 100 F. All these symptoms had disappeared by the next morning. The other two subjects showed no loss of pulmonary function after exposure to MDI. Minor changes in their airway resistance and thoracic volume were probably due to chance, according to the author, though he noted that these might have been caused by irritation.

Lapp [50] concluded that the changes observed in the previously exposed individual who was exposed to TDI and MDI at levels that did not cause such reactions in the other subjects confirmed his respiratory sensitivity to these compounds. Since the isocyanates to which this worker had previously been exposed were not identified, this study does not provide evidence on the potential of diisocyanates to produce cross-sensitization.

(b) Immunologic Effects

The studies discussed in the preceding section indicate that some people are sensitive to diisocyanates, reacting to these substances in quantities much smaller than those that produce direct irritation of the lungs in most individuals. The mechanism of sensitization to the diisocyanates has been investigated in immunologic and pharmacodynamic studies on exposed workers.

Allergic responses that result from circulating antibodies can be either immediate or late, or a combination of the two. Immediate responses occur within minutes of exposure to the antigen, and late reactions appear a few hours after exposure. Immediate reactions to some substances are associated with atopy, an innate tendency to develop allergies, which may be related to high serum concentrations of reagin-type immunoglobulin (IgE). Atopy is often judged to be present if two or more skin tests with common inhalant allergens such as pollen and animal dander are positive.

Molecules with molecular weights of less than 10,000 are rarely antigenic; thus, immunologic activity of the diisocyanates probably results from a reaction with a hapten complex formed from a diisocyanate and a naturally occurring antigenic substance such as protein or polysaccharide. Because isocyanates react with hydroxyl, amino, sulfhydryl, or similar groups, it is likely that hapten complexes may be formed. Most investigators who have studied the immune response to diisocyanates have attempted to duplicate this hapten complex by conjugating the isocyanate with a protein such as egg albumin or human serum albumin for use as an antigen in immunologic tests, using a modification of the method described in 1964 by Scheel et al [51].

In 1968, Bruckner et al [52] examined 26 workers exposed to unspecified isocyanates at reported concentrations of 0-240 ppb, with median values of 0-33 ppb. Air concentrations were determined by the Marcali method from samples taken near the workers' breathing zones. The workers, who had been exposed for 3 months to 11 years, were compared with 18 workers who had no known exposure to isocyanates. Blood from these workers was tested for reactivity by six immunologic assay techniques, using a conjugate of TDI with human serum albumin.

Five of the 26 exposed workers were considered sensitized because they had asthmatic responses when exposed to small but unreported amounts of diisocyanates [52]. Four of these five, but only 1 of 21 unsensitized workers, had a history of allergies before working with diisocyanates. These four sensitized subjects also had clearly positive lymphocyte transformation tests, although all had been without exposure to diisocyanates for at least 6 months before testing. Neither unexposed nor unsensitized exposed workers gave positive responses in this test. Passive cutaneous anaphylaxis (PCA), Prausnitz-Kuestner (P-K), leukocyte histamine release, passive hemagglutination, and gel diffusion precipitin tests were negative in all subjects and did not identify the sensitized workers. Subsequent studies by Nava et al [53] and Butcher et al [54] have not confirmed the diagnostic value of the lymphocyte transformation test for diisocyanate sensitivity.

Bruckner and coworkers [52] noted that all five sensitized workers had been exposed to diisocyanates at concentrations above 20 ppb. They also pointed out that the development of sensitization in these workers occurred only after 2 months to 5 years of repetitive exposures, concluding that overt clinical sensitization might be avoided if workers who showed increasingly severe signs of respiratory irritation were removed from further exposure to diisocyanates.

In 1970, Taylor [55] attempted to detect circulating antibodies to TDI in 55 workers with symptoms suggestive of TDI sensitivity. Their sera were compared with those from 40 unexposed textile workers for antibodies by tests for complement fixation, PCA, and red-cell-linked antiglobulin. None of the control sera, but 23 of the test sera, gave positive results in one or more tests. Five were positive in more than one test, but only one in all three tests. Six sera taken within a few months of an unusually high exposure to TDI that produced severe symptoms all showed positive test results. There was no correlation between positive antibody tests and eosinophilia as determined from blood or sputum samples. The author suggested that the lack of correlation between the tests indicated that they detect antibodies of slightly different specificity or of different immunoglobulin classes.

In 1975, Nava et al [53] described immunologic research on 182 clinical patients, all but one of whom had respiratory symptoms, who had been exposed to diisocyanates in the workplace. Ninety-six of these patients reacted positively to intradermal testing with TDI-protein conjugates. Thirty-seven of the 96 workers with positive tests and 6 of 86 with negative ones were atopic. However, in the 45 patients with immediate reactions, 60% were atopic. The authors concluded that atopy was not a factor in TDI sensitization, since most patients with positive reactions to TDI in intradermal tests were not atopic. However, their data suggest that atopy may be a predisposing factor.

Intradermal tests with an MDI-protein conjugate were performed on 61 subjects who had been exposed to TDI but not to MDI and who had clearly positive responses in intradermal tests with TDI [53]. Eleven of these reacted to MDI, suggesting cross-sensitization between the two diisocyanates. However, the authors did not report the results of control testing with the protein component alone. Results of other immunologic tests with TDI and MDI conjugates correlated poorly with those of intradermal tests.

Nava and associates [53] also performed pulmonary function testing on 45 of these patients who were exposed to TDI at 100-130 µg/cu m (14-18 ppb) in challenge tests. Thirty-five patients showed decreased pulmonary function after TDI challenge. An immediate or dual response occurred in 25, whereas 10 had only a late response; in contrast, over half the positive reactions in intradermal tests consisted of a late response only. Tests with acetylcholine on 18 subjects showed that those who were hyperreactive to this bronchoconstrictor tended to have immediate bronchial reactions to TDI. This suggests that a pharmacologic mechanism, as well as an immunologic one, is involved in diisocyanate sensitivity.

In 1975, Porter et al [56] published a retrospective study of sensitization in workers in a TDI manufacturing plant that had been in operation since 1956. The workforce exposed to TDI numbered about 200, remaining fairly constant throughout the study period, and the turnover during the 17 years of the study was about 100 workers. The investigators examined medical records of the workers to determine the relationship of clinical problems to TDI concentrations in the plant. Immunologic and lung function testing were performed on some workers.

Air samples analyzed by the Marcali method showed TDI concentrations of 50-100 ppb (350-700 µg/cu m), averaging 60 ppb (420 µg/cu m), prior to 1969; they were subsequently reduced by improved engineering controls to less than 50 ppb (350 µg/cu m) in 1970, 20 ppb (140 µg/cu m) in 1972, and 4 ppb (30 µg/cu m) in 1974 [56]. These values were not TWA concentrations, but averages of grab and continuous samples. Peak concentrations around 200 ppb (1,400 µg/cu m) resulting from leaks, spills, and loss of reaction control were measured on about 35 occasions; peak values were said to have decreased in the last 5 years of the study.

From 1956 to 1974, 30 of 300 workers at risk in the plant were judged on the basis of medical examinations to have become sensitized to TDI [56]. At least six workers were hypersensitive to TDI on first exposure, reacting at concentrations below 5 ppb (35 µg/cu m); in other workers, sensitization developed as late as 14 years after initial exposure. The authors noted that, as individuals became more sensitized, they responded more quickly to TDI exposures and recovered more slowly after removal from exposure. Table III-1 shows the number of new cases of sensitization diagnosed each year in relation to the average air concentration of TDI. The data indicate that a dose-response relationship for sensitization may exist. It is also clear, however, that the incidence of sensitization decreased with time during the years before 1970 when there were no significant changes in average TDI concentrations. The authors attributed this not only to improved control of peak concentrations and increased employee understanding of TDI effects, but also to possible "hardening" of exposed workers.

It appears more likely that most potentially sensitizable workers became sensitized during their earlier years at the higher exposures. The authors [56] noted that sensitized workers were relocated out of the TDI handling area to other parts of the plant. These considerations preclude the assumption that 20 ppb can be regarded as a no-effect level for sensitization on the basis of this study. The low turnover rate implies that only an average of 5-6 workers each year were newly exposed to TDI, so that most of the workers exposed during the last 3 years of the study already had several years of exposure at higher average concentrations. Some workers became sensitized after 14 years of exposure, indicating that some of the sensitivity cases reported in about 1970 developed when the average TDI concentrations were about 60 ppb. It is unclear whether the authors used a weighting procedure in calculating the average concentrations, or perhaps, averaged all results. For this reason it is impossible to conclude what the TWA concentrations were in the plant, and thus impossible to ascertain a concentration sufficiently low to prevent sensitization.

Porter et al [56] also presented case studies and results of immunologic and pulmonary function testing for 32 of the workers in this plant; some of these workers had signs of respiratory illness, according to medical diagnosis, while others were asymptomatic. Sera from these workers were tested for the presence of

TABLE III-1

TDI CONCENTRATIONS AND CASES OF SENSITIZATION IN A TDI-MANUFACTURING PLANT

Year	Sensitivity Cases	Average TDI Concentration (ppb)
1956*	1	60
1957	4	"
1958	3	"
1959	3	"
1960	1	"
1961	2	"
1962	3	"
1963	1	"
1964	3	"
1965	1	"
1966	1	"
1967	1	"
1968	1	"
1969	2	"
1970	1	<50
1971	2	"
1972	0	<20
1973	0	"
1974	0	<4

*Start-up

From Porter et al [56]

antibodies with the P-K test in monkeys and the PCA test in guinea pigs, by using a test antigen of TDI conjugated with serum protein from the same animal species; this is the only immunologic study found on TDI that used antigens made with homologous proteins in these tests. The P-K test was intended to identify IgE antibodies, which the authors expected to be associated with hypersensitivity reactions, and the PCA was to identify circulating IgG antibodies, which they assumed to confer immunologic protection. The workers' sera were similarly tested with a common pollen antigen.

In the cases described, there was no correlation between the presence of IgE or IgG antibodies against TDI and either clinical symptoms, lung function, or reactivity to pollen antigens. For example, apparent sensitivity to TDI accompanied by loss of lung function was reported in a worker who had a positive PCA test with TDI antigen but not with pollen antigen and in one who gave a positive P-K test with pollen but showed no antibodies against TDI; another sensitized worker had positive PCA to both TDI and pollen but refused pulmonary function testing. Two workers with sensitization reactions to TDI had positive results with TDI antigen in the P-K test, but no loss of lung function. Workers who showed no signs of sensitization to TDI included some who gave negative results in all immunologic tests and others with positive reactions to TDI in the PCA, P-K test, or both.

These results do not support the authors' hypothesis regarding the roles of IgE and IgG antibodies in TDI sensitization. The authors attributed the loss of lung function, which was apparently independent of the presence of antibodies, to bronchoconstriction; the reactions of these individuals occurred almost immediately upon exposure and were relieved by treatment with a bronchodilator. In contrast, clinical reactions in the two workers with positive immunologic tests but no loss of lung function had developed gradually after several years of exposure. The findings of this study indicate that an immunologic mechanism may be involved in diisocyanate sensitivity but that sensitivity in some individuals may also result from a nonimmunologic mechanism.

As part of a long-term study of workers exposed to TDI, described in detail in Epidemiologic Studies, Butcher and associates [54] reported in 1976 the results of immunologic and inhalation challenge studies of 167 employees who worked in a factory producing TDI. Before TDI production began and at 6 and 18 months afterward, employees were prick-tested to determine their reactivity to a conjugate of TDI with human serum albumin (HSA) and to HSA alone. They were also prick-tested with 15 common inhalant allergens. Using blood taken from the workers at the same test intervals, the investigators determined eosinophil counts and immunoglobulin levels. To identify TDI-specific antibodies, sera were tested with the TDI-HSA antigen by radioimmunoassay tests, the PCA test on guinea pigs, and the P-K test on monkeys. Employees who developed symptoms of airway obstruction on minimal exposure to TDI were challenge-tested by exposure to TDI vapor at concentrations of 5-20 ppb (35-140 µg/cu m) for 15 minutes. TDI concentrations were measured by a continuous monitoring method and verified by

the Marcali method. Pulmonary function of each individual was measured before and after challenge exposures. Five of the TDI-sensitive individuals were also evaluated by lymphocyte transformation tests.

Workers were subdivided into groups with constant, intermittent, or no exposure [54]. On initial testing, four workers had positive skin reactions to both TDI-HSA and HSA alone; however, during the third plant visit 6 months later, three individuals reacted positively to TDI-HSA but not to HSA. The authors did not indicate the exposure groups of these persons, but they noted that none of the three showed clinical respiratory responses to TDI.

Both before and after TDI production began, PCA, P-K, and radioimmunoassay tests for TDI antibodies were negative in all subjects [54]. Eosinophil counts did not differ in exposed and unexposed groups. Immunoglobin levels were similar in all three exposure groups. Six months after production began, both IgG and IgE had increased significantly over preexposure values; however, this increase was apparent in all groups, and the IgE increase was greatest in the unexposed group. The authors therefore concluded that the increase was not related to TDI exposure but probably reflected seasonal variation.

TDI challenge exposures of 11 individuals showed that 5 had a significantly decreased FEF 25-75 immediately following challenge [54]. Two of these five had dual responses, and two others also had late responses, with FEF 25-75 showing a decrease that began within 1 hour after an exposure and lasted for at least 6 hours. In some workers, a dose-related response could be demonstrated, since a reduction in lung function occurred at 10 ppb (70 µg/cu m) but not at 5 ppb (35 µg/cu m). In a followup study [57], at least two individuals did respond to TDI at 5 ppb but not at 2.8 ppb (20 µg/cu m).

There was no pattern of hay fever or asthma or of atopy (indicated by skin testing) in the clinically sensitized individuals or in those reacting to the bronchial inhalation challenge [54]. Leukocyte transformation tests performed on five of the clinically sensitive subjects were negative. The authors concluded that positive bronchial responses to TDI challenge were not related to either skin-sensitizing or precipitating antibodies in workers with TDI-induced asthma.

In a subsequent report on the same study population, Butcher et al [58] reported that PCA and P-K tests were negative throughout the 3 years of the study. All radioimmunoassay tests were negative until March 1975, 2 years after the study began. As of April 1976, weakly positive tests had been obtained on eight men in the group with constant exposure, three in the intermittently exposed group, and two in the unexposed group. By this time there had also been 10 positive skin tests; no group breakdown of these results was given. A later report [59] indicated that skin testing had been discontinued because of its lack of correlation with either clinical sensitivity, bronchial reactivity to challenge exposures, or amount of exposure, and because it carried the risk of sensitizing the subjects.

Immunologic studies on MDI have also produced ambiguous results, the immunologic findings showing little correlation with respiratory sensitivity. In 1966, Konzen et al [60] described immune responses to MDI vapor and particulates in seven volunteers who sprayed polyurethane foam in an underground mine. Two of them had never been exposed to MDI, four had not been exposed during the last 6 months, and one worked with the substance daily. Concentrations of MDI were determined by the Marcali method; a comparison of prefiltered and unfiltered samples showed that, near the spraying operation, about 70-90% of the MDI detected was in the form of particles, mostly in the respirable range. During testing, the workers were intermittently exposed to MDI at reported concentrations of 13-244 ppb (130-2,500 µg/cu m) for 2.3-30 minutes. The workers' sera were tested for antibodies by the PCA test at 4 days, 14 days, 3 months, and 6 months after exposure. MDI conjugated to egg albumin was the test antigen.

None of the workers developed respiratory symptoms after exposure, but one developed a temperature of 101 F about 6 hours after an initial exposure at about 130 ppb (1,330 µg/cu m) for 30 minutes [60]. One subject, who had had no previous exposure to MDI and who had the lowest exposure during testing, showed no antibodies to MDI at any test interval. The others showed positive or strongly positive PCA tests at the 14-day interval, declining at 3 months and disappearing by 6 months. The individual who received the greatest exposure was the one who had been exposed daily to MDI, but he gave a weaker positive response than most other exposed subjects. Thus, there may be little relationship between an individual's immunologic reactivity to MDI and the amount of exposure he has received.

Relating antibody responses to cumulative exposures during the test (concentration x length of exposure), Konzen et al [60] found that the six individuals who had positive PCA tests had cumulative exposures ranging from 1,300 to 9,400 ppb-minutes, while the subject who did not develop antibodies had a total exposure of 900 ppb-minutes. However, the authors noted that the number of individuals tested was too small to indicate that antibody titer was proportional to exposure.

In a 1973 NIOSH health hazard evaluation, Vandervort and Lucas [61] investigated immunologic responses of 90 workers exposed to MDI at average concentrations of up to 11 ppb (110 µg/cu m) in a plant manufacturing fibrous glass tanks. PCA, P-K, and agglutination tests were carried out with a "specially prepared isocyanate antigen," not otherwise characterized. Of 12 men with positive P-K tests, 2 showed respiratory responses to MDI, and 1 had decreased pulmonary function; pulmonary function testing was recommended for 2 others to evaluate their status. The other seven showed no evidence of adverse reactions to MDI, and the authors considered them "hardened" to its effects. Forty workers who gave positive results only in the PCA or agglutination tests were also asymptomatic. It is possible, as the authors suggested, that certain workers giving positive tests for antibodies were immunologically "hardened" to the effects of MDI and that the circulating IgG antibodies that might be indicated by positive PCA tests were

involved in conferring such immunologic protection. However, the inadequate characterization of the antigen used in testing makes it difficult to determine the validity of these results.

To evaluate whether the difficulty in detecting diisocyanate antibodies might be due to nonavailability of exposed hapten groups in the antigen, Karol et al [62], in a 1978 study, used a conjugate of p-tolyl isocyanate with human serum albumin (TMI-HSA) as a test antigen. Because it contained only one isocyanate group on each molecule, this monoisocyanate would not cross-link the protein component of the antigen, increasing the probability that the tolyl portion of the molecule would be sterically exposed. The authors tested 23 employees of a large TDI production facility, 4 of whom were considered sensitized to TDI. Three of these had had a sensitivity response, either bronchial or skin reaction, within 1 year before the study; the fourth had avoided exposure to TDI for at least 2 years. The remaining 19 workers were considered unsensitized because they showed no adverse effects when exposed to TDI; in some cases, this judgment was confirmed by negative results in challenge tests with TDI at 20 ppb (140 µg/cu m).

A radioimmunoassay for IgE bound to TMI-HSA showed that the 19 unsensitized workers had antibody titers similar to those of 10 blood-blank donors [62]. However, the sensitized group showed a significantly elevated titer of anti-tolyl antibodies ($P<0.01$). The three workers who had had TDI reactions within the last year had antibody titers higher than any of the unsensitized or control individuals. Serum-binding to the antigen was inhibited in the presence of nonisocyanate tolyl compounds, suggesting to the authors that the antibodies were tolyl-specific. There was no correlation between the tolyl-specific IgE antibodies and the levels of total IgE in the sera.

The highest titer of tolyl-specific IgE antibodies was found in a worker with acute pulmonary sensitivity to TDI [62]. He responded to a bronchial challenge with TDI at 6 ppb (40 µg/cu m). The other two workers with high antibody titers reacted to TDI exposure with immediate skin reactions, not confined to the area of contact with TDI. The authors concluded that their findings supported the hypothesis that an IgE-mediated immunologic mechanism is responsible for hypersensitivity to TDI.

Other studies, however, have indicated that a pharmacodynamic mechanism is also involved. Butcher et al [63] investigated the possible role of pharmacologic mediators in the bronchial response to TDI exposure. To determine whether TDI induced nonspecific histamine release, they measured spectrophotometrically the histamine released from leukocytes of 18 sensitive and 7 nonsensitive workers in response to TDI-HSA or HSA alone at 0.1-10 µg/ml for 40 minutes. The effect of TDI on beta-adrenergic receptors was examined by incubating lymphocytes from these workers with 10-150 µM TDI in the presence of isoproterenol, which stimulates the beta-adrenergic system, as indicated by an increase in cyclic 3,5-adenosine monophosphate (AMP). Cyclic AMP levels were measured by a radioimmunoassay technique. The FEV 1's of 10 clinically sensitized workers and 10

workers without symptoms were also measured before and after exposure to mecholyl (acetyl-beta-methylcholine) at 25 mg/ml from a nebulizer to evaluate bronchial reactivity.

Incubation with TDI-HSA conjugate did not cause histamine release from leukocytes obtained from sensitive or nonsensitive subjects [63]. Incubating lymphocytes from sensitive and nonsensitive workers with TDI in the absence of isoproterenol did not affect cyclic AMP levels. There was a dose-dependent inhibition of isoproterenol-stimulated cyclic AMP levels in lymphocytes from both sensitive and nonsensitive subjects; there was no significant difference in the ability of cells from these two groups to exhibit cyclic AMP stimulation.

In the mecholyl challenge studies, 6 of the 10 clinically sensitive subjects showed a drop in FEV 1 of more than 20% within 1.5 minutes after a single inhalation of mecholyl [63]. Only 1 of the 10 nonsensitized subjects gave such a response, and this occurred 5 minutes after inhaling mecholyl four times.

This study [63] indicates that TDI is not a histamine releaser per se but that it does suppress stimulation of the beta-adrenergic system by isoproterenol. These results agree with those of a similar study by Van Ert and Battigelli [64] on the effects of TDI on histamine release in vitro. Butcher et al [63] concluded that their findings suggested that TDI may act as a beta-receptor blocking agent. This would produce increased reactivity to agents capable of causing bronchoconstriction, such as mecholyl. In a followup reported in two 1978 abstracts [65,66], blood testing after challenge exposures to TDI showed that histamine levels increased after a bronchial reaction, while complement components were not affected. In this study, all TDI reactors reacted positively to mecholyl challenge, and the authors [65] noted that kinetic studies had revealed a strong indication that cells from TDI reactors respond differently than those of nonreactors to the beta-adrenergic agonists isoproterenol and prostaglandin E, and to TDI added alone.

These studies [63-66] suggest that a pharmacologic mechanism is involved in respiratory sensitivity to TDI, but there is no indication whether mecholyl hyperreactivity is a preexisting factor or a result of TDI exposure.

(c) Skin Effects

Some diisocyanates have been described as skin irritants [67,68], but there are few reports in the literature of skin effects from these compounds. Munn [35] has noted that, in several years of study, he has seen only two mild cases of skin irritation from diisocyanates and no cases of skin sensitization. Bruckner et al [52] reported that 6 of 44 workers in a chemical plant experienced skin irritation attributed to exposure to unspecified diisocyanates. These reactions consisted of erythema only on areas of skin that were in actual contact with the diisocyanates. One worker who often had diisocyanates on his hands noted that his skin had become hard and smooth, so that he had difficulty in turning pages.

Possible skin sensitization to TDI was described in two of the studies discussed in the previous section. Nava et al [53] reported that a worker with eczematous dermatitis was 1 of 3 workers who reacted positively to TDI in a patch test, out of 182 workers tested. Karol et al [62] found tolyl-specific IgE antibodies in two workers who displayed immediate skin reactions when exposed to TDI, apparently without a bronchial response. These skin reactions were extensive and not confined to areas where TDI had contacted the skin.

Rothe [69], in 1976, described 20 cases of occupational skin disease in workers exposed to polyurethanes. Clinical examinations, observation of the course of the disease, reexposure tests, and skin tests were carried out. Standard and special tests using a variety of isocyanates, amines, and additives were used to determine the specific sensitivity of the workers.

Rothe [69] found 12 cases of contact eczema characterized by follicular papules in workers exposed to MDI or partially polymerized MDI. Ten of these constituted more than half the total number of workers who had come into contact with a polyurethane sealing compound at one plant, and two were from another plant. Several inspections showed that there was very close contact between the workers' skin and the sealing compound. Work clothes were often soaked with resin. The workers had positive skin test reactions to the isocyanate component of the sealing compound. Twenty-five unexposed persons with eczema had negative results. Five of seven workers with MDI allergies exhibited typical eczema reactions to diaminodiphenyl methane (MDA). Only one of these had had previous contact with the MDA, which was not used at the plant.

Four similar cases of eczema were seen in workers exposed to isophorone diisocyanate (IPDI) [69]. A 1-hour exposure caused eczema in three of them. One worker had had previous contact with IPDI, but the other three had had contact only with TDI and MDI, suggesting cross-sensitization. Skin disease disappeared in all four persons sensitized to IPDI after exposure was stopped. Three of the investigators tested themselves with undiluted IPDI and no reactions occurred within 4 days [69]. However, two of the three investigators developed follicular papules 10 days after testing. Sensitization in these investigators was confirmed in a later test with a 1% IPDI solution, which produced no reactions in six nonexposed subjects.

The other four patients with skin disease included two cases of eczema from TDI exposure, one case with exposure mainly to TDI but also to MDI, and one case of eczema probably related to exposure to triphenylmethane triisocyanate [69]. In all 20 cases there was a pattern of brief exposure to the isocyanate, often caused by spills, with subsequent development of eczema. In most cases, sensitization was confirmed by skin-testing with a dilute solution of the isocyanate suspected to be the agent.

(d) Other Effects

Although most reports of diisocyanate toxicity have described effects on the respiratory tract or skin, some have noted other effects. These have included eye irritation, psychologic symptoms and CNS effects, and hematologic changes. Most of these effects have occurred following mixed exposures to diisocyanates and other chemicals, and such effects cannot be clearly ascribed to the diisocyanate exposures.

Several studies have suggested that TDI, especially at very high exposure levels, may cause neurologic or CNS effects. In the first published report of occupational illness from TDI exposure, Fuchs and Valade [21] noted that insomnia was often the first complaint of affected workers, preceding any respiratory symptoms. They also mentioned that three patients had a decrease of the knee-jerk and Achilles reflexes. In one patient, who completely lacked these reflexes, the condition persisted for 2 months after he stopped working with TDI and then abruptly returned to normal. In the absence of other signs of exposure-related nervous disorders, the authors did not specifically implicate TDI as the cause of this condition.

A 1964 USSR study [70] investigated the effects of TDI on electrical activity in the human cerebral cortex. No experimental details were reported, but TDI was said to affect electroencephalographic (EEG) rhythms at a threshold concentration of 100 µg/cu m (14 ppb). This study was not included in the 1973 criteria document on TDI [37]. Little can be made of these results in the absence of any information on experimental methods, but the implication of CNS effects at a such a low concentration suggests that such effects should be more carefully evaluated.

In 1965, a Canadian report [71] indicated that 12 of 24 maintenance workers developed respiratory symptoms after they had cleaned pipes and vessels contaminated with TDI. In addition, four of the workers developed psychologic problems, including anxiety neuroses, psychosomatic complaints, depression, and even paranoid tendencies. A year after exposure, they had not returned to work; some still complained of cough and difficulty in breathing, although their pulmonary function tests were normal. This report suggests the possibility that TDI produces CNS effects; cleaning processes, however, involve the use of solvents to which these CNS effects might be attributed. This report did not detail the procedures or solvents used in cleaning the TDI-contaminated vessels.

Burton [72], reviewing Ontario workmen's compensation claims in 1972, mentioned an incident of TDI exposure in a rubber plant. One of three women employees who developed chronic obstructive lung disease after an acute exposure to TDI also had a "psychogenic problem," not otherwise described.

Le Quesne et al [73] and Axford et al [74] reported neurologic, respiratory, and gastrointestinal effects in men massively exposed to TDI while fighting a fire in a polyurethane foam factory. Two large tanks of TDI developed leaks during the

fire, and several men who attempted to close the leaking valves and fought the fire or who later removed the hoses and cleaned up the area were heavily exposed to TDI liquid and vapor, their clothing and shoes becoming soaked with it.

Of 35 men interviewed after the fire, 25 had experienced irritation of the eyes and upper respiratory tract during the fire and 14 of these also coughed or had difficulty in breathing [74]. Seventeen others reported similar symptoms that developed only 8 hours or more after the fire. After 4 years, according to the authors, 15 men showed some evidence of long-term respiratory damage. Fifteen of the 35 men also experienced nausea or vomiting during or after the fire.

A total of 23 of the 35 men complained of neurologic symptoms, including a feeling of drunkenness, numbness, or loss of balance during the fire and subsequent inability to concentrate, loss of memory, headache, irritability, confusion, depression, temporary impotence, difficulty with balance, and tingling, burning, or numbness of the skin [73]. Neurologic examination showed slight ataxia in six, and EEG's were essentially normal. Some of the complaints, especially loss of memory, persisted up to 4 years after the fire. Thirteen of the men who were considered still clinically affected at this time had a significantly lower memory quotient ($P<0.02$) than did a control group of 15 firemen who had not been exposed to TDI.

Le Quesne et al [73] were convinced that the complaints of the men were real and the result of exposure to TDI. Other chemicals in the plant were present in much smaller quantities, and the authors noted that none of them was known to produce the observed symptoms. They pointed out that toxic combinations or breakdown products might have developed during the fire but added that some of the affected men were involved only in cleanup operations the morning after the fire. Nevertheless, it is not unequivocal that the effects reported were caused by TDI.

In a 1962 report, Filatova et al [75] described the effects of mixed exposures to TDI, chlorobenzene, phosgene, toluene diamine, and HDI on 63 men and 17 women who had manufactured diisocyanates for 1-2 years. These effects included irritation of the eyes, nose, and skin, coughing, difficulty in breathing, headaches, insomnia, weakness, tremors, reflex changes, and chest and abdominal pain. Hematologic tests showed decreases in eosinophils and neutrophils, and some workers had slightly enlarged livers with no functional impairment. The authors concluded that the substances produced during diisocyanate production were toxic, but they could not attribute the symptoms to TDI alone, since other compounds that were present could have produced similar effects.

The effects of occupational exposure to HDI and several other chemicals were described in a 1968 report by Filatova et al [76] on 68 men and 14 women who manufactured the compound. Sixty-three of these workers (21-50 years old) had worked in the plant for 5 years or more. All the workers received a complete medical examination including several biochemical and clinical tests. Personal air

samples generally showed 100 µg/cu m (14 ppb) or less of HDI, 0.5 mg/cu m or less of phosgene, and 1.2-8 mg/cu m of chlorobenzene. Only the HDI concentrations were said to be in excess of the MAC.

Thirty-two workers complained of headaches, 36 of increased perspiration, 20 of aches in the area of the heart and under the right ribs, 13 of dream disturbances, 12 of difficulty in breathing, 19 of general weakness, and 6 of coughing [76]. All workers reported that HDI vapor irritated their eyes and upper respiratory tract. Nineteen workers, who had worked in the plant for 7-13 years, had developed slightly enlarged livers that were painful upon palpation. Duodenal sampling and blood bilirubin and cholesterol analyses revealed no hepatic lesions. Most of the 55 workers examined for liver abnormalities showed hypocholesteremia, indicating to the authors an early stage of disturbance of liver function. Most workers also showed abnormalities in blood proteins and serum cholinesterase activity.

Approximately 50% of the examined workers had developed chronic subatrophic pharyngitis without any pathologic changes in the lungs [76]. Effects on the cardiovascular system were seen in 47 workers, 27-40 years old, more than half of whom had sinus arhythmia, bradycardia, extrasystole, and slowing of endoatrial conductivity indicative of toxic myocardiodystrophy. Some workers had tremors of the fingers and eyelids and increased muscular excitability.

Filatova et al [76] concluded that the adverse effects on workers' health were produced by a mixture of toxic compounds whose main component was HDI. No other reports of hepatotoxicity or cardiovascular effects in diisocyanate workers have been found. It should be noted that chlorobenzene is a hepatotoxin that has reportedly caused hepatic necrosis in animals at high doses [77] and produced an increase in liver weight in rats inhaling 1,150 mg/cu m for 6 months [78].

Epidemiologic Studies

Studies of worker populations exposed to TDI have related environmental exposure levels to the incidence and severity of respiratory symptoms, changes in pulmonary function, and immunologic reactivity. Investigations of workers exposed to MDI and HDI have generally provided less useful data because they involved mixed exposures to several other toxic chemicals.

In 1957, Hama et al [79] reported that 12 workers exposed to isocyanates (TDI) at 30-70 ppb (210-500 µg/cu m) for 1 week in an automobile plant had mild to severe respiratory symptoms including cold symptoms, continuous coughing, sore throat, dyspnea, fatigue, and nocturnal sweating. No symptoms had developed during the previous month when isocyanate concentrations were below 10 ppb (70 µg/cu m), and when concentrations were subsequently reduced to the 10-30 ppb range (70-210 µg/cu m), no further complaints occurred in over 3 months. A written communication from Hama (June 1973) confirmed that the isocyanate was TDI and indicated that exposure concentration measurements were based on breathing-zone

samples analyzed by the Ranta method. This method is unable to distinguish between TDI and the TDI urea formed in the presence of water. Thus, the concentrations of TDI in the area were probably less than the reported values.

A detailed 2.5-year study by Walworth and Virchow [31] of a polyurethane foam plant was published in 1959. TDI concentrations ranged as high as 300 ppb (2,200 µg/cu m), but monthly averages were generally below 150 ppb (1,100 µg/cu m). Eighty-three cases of respiratory illness that required medical attention were attributed to TDI exposure; most of them occurred after 3-4 weeks of exposure. The total number of workers at risk was not reported. The authors noted that there was little correlation between measured TDI concentrations and the appearance of respiratory symptoms. They attributed this largely to short exposures at high concentrations not reflected in the measurements of average exposures. They added that once workers experienced adverse effects from TDI they could not tolerate even minute exposures.

In 1964, toxic effects from TDI in workers in three New Zealand plants were reported [80]. At one plant, where usual TDI concentrations ranged from 3 to 120 ppb (20-850 µg/cu m), three cases of respiratory sensitization occurred in 1 year. In two of these workers, symptoms first appeared after 2-3 hours of pouring TDI inside a refrigerated van, where unusually high concentrations were likely. The third worker, whose symptoms developed gradually, could work 50-60 feet away from the foaming operation, where TDI concentrations were about 5 ppb (35 µg/cu m), but he had a respiratory reaction when he worked within the foaming area. In a similar plant, where TDI concentrations were usually below 20 ppb (140 µg/cu m), there were two cases of mild cold symptoms and one case of possible sensitization, all associated with a foaming operation in which concentrations reached 100 ppb (700 µg/cu m). This plant also reported one case of a severe asthmatic attack and collapse in a worker exposed at a very high concentration. He subsequently returned to work with no evidence of sensitization. In the third plant, two workers exposed to TDI at 18 ppb (130 µg/cu m) wearing canister-type masks experienced very mild cold symptoms at the end of the day when a double run was carried out. The total workforce at risk in these plants was not reported.

In 1962, Elkins et al [32] described experiences with TDI in 15 Massachusetts plants over a 5-year period. They evaluated the cases of respiratory illness occurring in each of the plants and made environmental measurements, apparently from area samples. Most of the samples were analyzed by the Marcali method. The Ranta method was used for some of the early measurements and found to be less accurate, but the authors did not indicate which measurements were made by this method. Other methods used in a few plants reportedly gave results comparable to the Marcali method. The findings of Elkins and coworkers, as adapted by NIOSH to present what were considered to be relevant dose-response data, were summarized in the 1973 TDI criteria document [37], and are shown in Table III-2. This table omits data from plants where environmental levels were not determined or where the authors considered that these measurements were not representative of exposure. The numbers given for workers at risk are probably somewhat higher

TABLE III-2

SUMMARY OF DOSE-RESPONSE DATA OF ELKINS ET AL [32]

Plant	Date	No. of Tests	Concentration (ppb) Maximum	Average	Established Respiratory Cases	Questionable Respiratory Cases	Max. No. Workers at Risk
2	1/58	8	10	8	3		50
2	12/58	6	<10	5	0	0	50
2	12/60	6	50	40	14	25	100*
2	1/61	9	30	10			
2	6/61	6	20	8	3	2	50
2	1/62	6	14	8			
3	1958	4	20	10	0	0	25**
3	1961	8	15	7	0	0	25
4	1959	4	20	10	1	3	40
4	1961	5	1	0.6	0	0	40
4	1961	0			4		
5	1959	4	20	15			6***
6	1961	28	70	15	3	0	40
9	1961	3	8	6	0	0	4
12	1962	6	-	9	0	1	6
13	1962	4	-	0	0	1	20
14	1962	6	-	0	0	0	20

*Additional company analyses verify that air levels were high
**The workers wore respirators, which probably indicates acute irritation
***Some workers had been transferred after complaints

Adapted from reference 37

than the actual numbers exposed to TDI, which could not be determined from the paper.

Elkins et al [32] found a total of 42 established cases and 73 questionable cases of respiratory illness associated with TDI exposure. Concentrations higher than 20 ppb (140 µg/cu m) were measured in only three plants. From the data in Table III-2, it can be seen that cases of respiratory illness were associated with all exposure concentrations above 10 ppb (70 µg/cu m), but there were no cases at 7 ppb (50 µg/cu m) or lower. At 9 ppb there were no established cases but one questionable one; there were several established cases at 8 ppb. The authors concluded that the environmental limit for TDI should be considerably less than 100 ppb (700 µg/cu m), and they suggested that 10 ppb (70 µg/cu m) was "not an unreasonable limit."

While the data of Elkins et al [32] appear to indicate that average TDI concentrations above 10 ppb are associated with respiratory illness, there are several problems in interpreting these findings. Almost no information is available on extremes of exposure, since the maximum concentrations given are based on intermittent and infrequent sampling. The low values measured in each plant are not given, nor are there any data indicating the actual exposures of affected workers. In addition, there are a number of uncertainties about the validity of the measurements. The authors did not indicate which values were based on the Ranta method, which they conceded to be less sensitive than the other methods used. Data in the paper indicated that some of the measurements in Plant 2 were based on very short sampling times, 3-10 minutes. These sampling times were very short for the low values reported, considering the sensitivity of both the Ranta and Marcali methods.

Several investigators have attempted to correlate exposure to TDI with changes in lung function, often with contradictory results. In 1963, Gandevia [81] reported the results of pulmonary function testing on employees of a factory producing rigid polyurethane foam. Concentrations of airborne TDI were not determined at the time of the study, but 2 weeks later the TDI concentration in the spraying areas was measured at 900 ppb. Fifteen of 20 men employed in the TDI area were available for pulmonary function testing. Over a 3-week period, these workers had a significant decrease in FEV 1 of 0.227 liter ($P<0.02$); the mean diurnal decrease of 0.18 liter during a normal working day was also significant ($P<0.05$). The author noted that values determined on Friday morning were significantly lower than those on Monday ($P<0.01$), indicating that the effects were cumulative and complete recovery did not occur overnight. Administration of a bronchodilator on Tuesday of the 2nd week prevented the daily decrease in FEV 1 but did not affect the cumulative decrease. Eight men who had a positive reaction to histamine had a larger daily decrease in FEV 1 than did nonreactors (0.310 vs 0.115 liter). Smoking status was not significantly related to the changes in FEV 1.

Gandevia's findings [81] showed a decrease of pulmonary function, not fully reversible overnight, in workers exposed to TDI. The limited environmental data suggest that some of the workers may have been exposed at very high concentrations. In addition, preexposure baseline values for lung function were not determined and the measured changes were not compared with predicted changes due to aging. It is therefore difficult to evaluate the significance of the changes reported.

The following year, Williamson [17] reported the results of pulmonary function testing over a 14-month period on 15 workers in an operation where TDI was separated from a solvent by distillation. Frequent environmental measurements were made and these never showed TDI concentrations above 20 ppb (140 µg/cu m), but average concentrations were not given. One major spill occurred during the study, causing concentrations high enough to permit detection of odor, from which the author inferred that the concentration was at least 200 ppb, and the room was immediately cleared.

All the workers tested were free of respiratory symptoms [17]. In four series of measurements of FVC and FEV 1, the only significant change was a fall in FEV 1 at the time of the second measurement ($P<0.01$), and subsequent tests showed no significant change from baseline FEV 1 values. There was little difference between Monday and Friday values; daily changes were not measured. Williamson noted that an examination of the records of workers who had left the TDI operation uncovered no evidence that the study group had been self-selected for health reasons. A subsequent study of sensitized workers [41], including four from this group of employees who became sensitized during the 18 months following this investigation, has been described in Effects on Humans.

Adams [82,83] studied the long-term effects of TDI on the health of workers manufacturing it in England. A 1970 report [82] on pulmonary function testing of 175 men in a plant where TDI concentrations rarely exceeded 20 ppb (140 µg/cu m) indicated that decreases in the group mean FEV 1 and FVC over 5 years significantly exceeded predicted values. However, new employees also had FVC and FEV 1 measurements below predicted values, which were based on a North American survey. When the results from 114 men were examined individually, only 16 (11%) showed a decline in performance on pulmonary function tests significantly in excess of predicted values; 5 of these had decreases in both FVC and FEV 1, 3 in FEV 1 only, and 8 in FVC only. These results suggest that the decrease in group mean values was caused by 16 sensitized individuals. Adams pointed out that the validity of the data was questionable, since predicted values were based on a North American population and their relevance to English workers was unknown.

In a subsequent report, published in 1975, Adams [83] compared the TDI-exposed workers with unexposed control groups from the same geographic area. The workers included in this part of the study had been exposed to TDI for 1-11 years without adverse effects on their health. Records of pulmonary function tests

on 180 workers at two plants during 1964-1972 were compared with values for 608 control subjects living nearby who had no contact with TDI. Pulmonary function measurements were made on the same day each week between 2 and 3 in the afternoon. Results from the standard Medical Research Council (MRC) respiratory questionnaire given to 76 men still employed at the plants were compared with those from 76 controls who had no contact with TDI but who did similar work at a nearby chemical plant.

Area concentrations of TDI, analyzed by the Marcali method, were measured about 250 times a week at each plant [83]. From 1962 to 1965, 21-72% of the tests for airborne TDI in one plant showed concentrations above 50 ppb (360 µg/cu m). During 1966-1970, concentrations of TDI exceeded 20 ppb (140 µg/cu m) in 1-4% of the tests. In the second plant, concentrations in 1-8% of the samples were above 20 ppb from 1966 to 1970.

Comparison of the pulmonary function data from 180 workers with those from 608 control subjects revealed that exposure to TDI did not affect their FEV 1 or FVC values [83]. No significant difference in respiratory symptoms was found between 76 currently employed men exposed to TDI and controls. Nine of 76 men in the control group had wheezing, compared with only 1 of 76 men exposed to TDI.

In the second part of the study, Adams [83] examined men who had been removed from the TDI plants because of respiratory symptoms such as mild to severe bronchospasm and dyspnea. About 15% of the men employed in the TDI plant were removed from the plants in their 1st year because they developed respiratory symptoms. In the 2nd year of employment, only 3.5% of the remaining workers developed respiratory symptoms, and the rate gradually dropped to less than 2%/year after the 5th year, totaling about 20% of the original workforce over the 9 years of the study. Information on symptoms in 46 men removed from the plant, who had not been exposed to TDI for 2-11 years, was collected annually by respiratory questionnaire and compared with responses from 46 age-matched workers not exposed to TDI. These results were correlated with the results of pulmonary function tests. The data were analyzed for statistical significance by chi-square test.

Data from 46 controls and 46 men previously exposed to TDI showed no differences in their smoking habits [83]. However, 17 of the 46 workers previously exposed to TDI developed breathlessness after exertion, significantly more than the 5 men in the control group with this symptom ($P<0.01$). Wheezing occurred in 17 workers but only in 7 controls ($P<0.05$). These findings indicated that respiratory symptoms persisted in some subjects after exposure to TDI had ceased.

Pulmonary function data for 61 men who had had no contact with TDI for 2-11 years showed that their average FVC and FEV 1 values were slightly lower than control values after adjustment for age and height [83]. Eleven of the 20 workers

who had been removed from the plants because of sensitization to TDI and whose preemployment lung function records were available were asymptomatic after 3-8 years without exposure, and 12 of these 20 had FEV 1 and FVC values unchanged from their preemployment levels. Six had FEV 1 and FVC values between 90 and 100% of their preemployment levels, and two had values of 80-90%. Those who had reduced pulmonary function complained of dyspnea on exertion, nocturnal dyspnea, and tightness in the chest.

Adams [83] concluded that exposure to TDI at about 20 ppb (140 µg/cu m) for 5 years did not increase respiratory symptoms or affect the lung function of workers who were not sensitized to the compound. However, sensitized workers, even when no longer exposed to TDI, had more respiratory symptoms than did unexposed controls, suggesting that effects of TDI are, to some extent, irreversible.

Peters and his group [84-87] conducted a 2-year study of pulmonary function in workers in a polyurethane plant. They measured FVC, FEV 1, peak flowrate (PFR), and flowrates (FR) at 75, 50, 25, and 10% of vital capacity. Measurements were made at the beginning and end of work on Monday and later in the week; tests were repeated every 6 months. Detailed occupational and smoking histories were taken from the workers, and respiratory symptoms were evaluated by the MRC questionnaire. For environmental measurements, area samples, apparently collected at 6-month intervals, were analyzed by the Marcali method.

The initial study [84], made during December 1966, included 38 workers, 7 of them women, with an average age of 36.3 years (range 18-62 years), employed an average of 104.6 weeks (2-624 weeks). Environmental measurements taken during this period showed TDI concentrations ranging from 0.1 to 3.0 ppb (0.7-21 µg/cu m). Pulmonary function measurements on 34 workers showed a mean daily decrease in FEV 1 of 0.19 liter ($P<0.001$). Significant daily decreases were also noted in FVC ($P<0.001$), PFR ($P<0.05$), FR50% ($P<0.01$), and FR25% ($P<0.05$). From Monday morning to Friday morning, the mean FEV 1, FR50%, and FR25% all showed significant decreases ($P<0.001$). Responses for smokers and nonsmokers were similar, but workers with respiratory symptoms had a significantly greater decrease in FEV 1 than those without symptoms ($P<0.05$). The authors noted that there appeared to be no relationship between pulmonary function changes and amount of exposure, which they judged from the distance between work stations and sources of TDI.

At the 6-month followup [85], 28 of the 34 workers were still employed, and 6 new workers were added to the study group. Environmental concentrations at that time ranged from undetectable to a high of 12.0 ppb (85 µg/cu m) in the TDI pouring area. Monday preshift and postshift measurements of pulmonary function showed significant decreases ($P<0.02$) in both FVC and FEV 1; Tuesday morning tests showed essentially complete recovery in FVC, but FEV 1 values were still significantly lower than on the previous morning.

When pulmonary function test results were compared with those from tests done 6 months earlier, significant decreases were found in FEV 1, the ratio FEV

1/FVC, and FR values at 75, 50, 25, and 10% of vital capacity [86]. The authors noted that there was a high correlation (r=0.72) between the 1-day and 6-month decreases in FEV 1. The only other variable significantly correlated with pulmonary function test results was lifetime smoking history, and when this factor was held constant, the 6-month changes in FEV 1 were still significantly correlated with diurnal changes (r=0.60).

The 12-month followup, made in December 1967, showed a much lower diurnal decrease in FEV 1, 0.05 liter [87]. In the 25 workers still available from the original 34, the decrease in FEV 1 over 1 year was still significant, but the entire decrease was accounted for by changes during the first 6 months. The authors noted that TDI concentrations measured at this time were very low; the maximum concentration detected was only 1.5 ppb (11 µg/cu m).

Subsequent environmental measurements showed maximum TDI concentrations of 14.5 ppb (103 µg/cu m) at the time of the 18-month followup [86] and 12.5 ppb (89 µg/cu m) at the 2-year followup [87]. In December 1968, when final pulmonary function tests were made, 18 of the original 34 workers were still included [87]. The average FEV 1 had decreased 0.22 liter in these workers over the 2 years, a mean annual decrement of 0.11 liter/year. The authors noted that this difference could not be accounted for by normal aging, citing several reports in their paper that showed annual decreases of 0.025-0.047 liter/year in normal working and general populations and 0.08 liter/year in patients with chronic, nonspecific lung disease. The decrease in 2 years was twice as great in workers reporting symptoms as in those that did not.

In a 1978 abstract, Musk et al [88] described a 5-year investigation that was apparently a followup of the study by Peters and coworkers [84-87]. Musk et al reported on findings in 107 subjects, presumably the entire population at risk over the 5 years, and did not provide specific data on the dwindling cohort (34 workers) for which the Peters group obtained initial pulmonary function measurements. Diisocyanate (TDI and MDI) concentrations were said to be "well below" 20 ppb. The authors reported that there was no signficant decrease in FEV 1 compared with predicted values. In addition, no acute decrease was observed in preshift and postshift values on a Monday either before or after a 2-week vacation, and there was no increase in FEV 1 over the vacation period.

In another study from the same laboratory, Wegman et al [89,90] performed pulmonary function testing on 112 workers exposed to TDI in a factory manufacturing polyurethane cushions. Occupational and smoking histories and results from the MRC respiratory symptoms questionnaire were collected from each worker, and the FEV 1 was measured before and after work on a Monday following a 3-day weekend. Environmental concentrations of TDI were determined from breathing-zone samples analyzed by the Marcali method. The highest concentrations measured were 13 ppb [46] and 9 ppb [90] (90 and 60 µg/cu m). The workers were divided into groups of approximately equal size exposed at 1.5 ppb (12 µg/cu m) or less, 2.0-3.0 ppb (14-21 µg/cu m), and 3.5 ppb (25 µg/cu m) or more.

Initial measurements showed a dose-related diurnal decrease in FEV 1 in the three groups [89]. At the 2-year followup [90], only 63 members of the original workforce were still employed. Examination of records showed that 40 of those no longer employed had resigned voluntarily and that these workers had shown a diurnal decrease in FEV 1 of 0.126 liter at the earlier testing, compared with 0.096 liter in those who were still employed. While this difference was not significant, the authors noted that it reflected a trend for self-selection based on health among TDI workers.

In general, work assignments had been stable over the 2 years, with workers averaging 20 months at a work station; workers were therefore assigned to exposure groups on the basis of their usual work station [90]. Since 5 workers had variable exposures and could not be assigned to any group, final testing was performed on 57 workers; 20 of these in each of the high and low exposure groups and 17 were in the medium exposure group. The incidence of coughing and phlegm production increased with higher exposure; 15% of the 57-person study group had symptoms suggestive of chronic bronchitis, but these were not related to exposure level. The 2-year decrease in FEV 1 averaged 0.102 liter (SD = 0.204 liter) in the exposed workers; the groups with low, medium, and high exposure had respective decreases of 0.012, 0.085, and 0.205 liter (SD = 0.204, 0.177, and 0.185 liter). The authors noted that the decrease in the high-exposure group was "clearly excessive," while that in the low-exposure group was "clearly within normal limits." The authors' analysis of variance showed the difference in 2-year decrement in FEV 1 in the three groups to be significant at $P<0.01$. Age, length of employment, and smoking habits did not differ significantly in the three groups. Since several factors that affect lung size, including sex, height, and race, differed among the groups, the authors standardized for lung size by dividing the 2-year decrease by the initial FEV 1 measurement; this standardized figure still showed a significant difference between exposure groups.

Wegman and colleagues [90] concluded that an excessive loss of lung function resulted from exposure to TDI at concentrations at least as low as 3.5 ppb (25 µg/cu m) and possibly as low as 2.0 ppb (14 µg/cu m). They suggested several reasons for the difference between their findings and those of Adams [83], who concluded that exposure at 20 ppb (140 µg/cu m) did not affect lung function. Adams determined TDI concentrations by area monitoring rather than personal sampling, so that results may have had little relationship to actual exposures of the workers; he did not group workers by exposure level, possibly obscuring significant effects at higher concentrations; lung function testing was done in the afternoon, following a day of exposure, so that no baseline measurements were available; and changes in lung function were evaluated by regression analysis, a less sensitive indicator of changes over time than the method of paired differences used by Wegman et al [90]. An additional consideration is that Adams [83] studied workers in TDI-manufacturing plants, whereas the studies of Peters et al [84-87] and of Wegman et al [90] involved polyurethane foam plants. Exposure to other chemicals is likely in both situations, and it is possible that chemicals other than TDI may have affected the results of lung function studies. Workers involved in the

manufacture of TDI may be exposed to toluene diamine, phosgene, hydrogen chloride, and chlorine. Workers in foaming processes, on the other hand, are invariably exposed to TDI in the presence of other formula components such as volatile amine catalysts and fluorocarbon blowing agents.

A 2-year study by Erlicher, summarized by Bunge, Erlicher, and Kimmerle [91] in 1977, evaluated the health of 341 men exposed to TDI, MDI, and NDI in plants processing raw materials for polyurethane. A total of 159 air samples showed a mean diisocyanate concentration of 19.7 ppb (about 140 µg/cu m). This was not a TWA concentration but was based on samples taken only from selected work processes. Peak concentrations of up to 1,300 ppb (9,200 µg/cu m) were recorded.

Detailed medical histories, clinical examinations, pulmonary function testing, and hematologic, chemical, and enzyme-diagnostic laboratory tests were made on the workers, who had been employed for up to 25 years. The time and frequency of these tests were not indicated. There was no significant difference in mean FEV 1 between workers exposed for less than 3 years and those exposed 10-25 years, although the mean for smokers was significantly different from that for nonsmokers. Laboratory tests indicated there were no alterations of peripheral blood values, hematopoietic system, or kidney function.

Weill et al [57,59,92] and Butcher et al [54,58,63] have reported on the first 5 years of a longitudinal study of respiratory symptoms, pulmonary function, and immune responses in workers at a TDI-manufacturing plant. The study was initiated in April 1973, before TDI production began at the plant, and is planned to extend through 1978.

The original group of workers in the study consisted of 166 men subdivided into three exposure groups [58]. The 77 men in group 1 were assigned to areas in which they had daily contact with TDI; group 2 consisted of 36 men with intermittent contact with TDI, such as maintenance workers; group 3 included 53 workers from other areas of the plant who had no known exposure to TDI.

Before TDI production began and at 6-month intervals thereafter, the workers were admininstered a modified MRC questionnaire to determine their smoking habits and the existence of respiratory symptoms [58]. Pulmonary function testing and determinations of lung volume and diffusion capacity were made. Workers were skin-tested for sensitivity to TDI and to several common inhalant allergens, and those showing positive results with two or more allergens were classified as atopic. Blood samples were taken for immunoglobulin determination, eosinophil counts, and antibody detection.

Environmental concentrations of TDI were determined throughout the study by both area and personal monitoring [58]. Area monitoring was performed from August 1973 using Model 7000 TDI detectors from MDA scientific, calibrated with a gas diffusion cell and confirmed by the Marcali method. Personal monitoring with MCM monitors from the same supplier began in July 1975. All workers were

monitored continuously throughout a complete 22-day shift rotation. Area sampling showed frequent excursions above 20 ppb (140 µg/cu m) in TDI production and drumming areas, with weekly TWA concentrations as high as 40 ppb. However, the authors reported large discrepancies between area monitoring results and those of personal monitoring, which were generally lower.

By October 1975, 30 of the workers originally included in the study had left and several had failed to participate in one or more sets of measurements [58]. In addition, several of the original control subjects had been transferred to the exposed group because of job changes. Longitudinal data on respiratory symptoms was available on 103 of the original study group, and only 14 of these had not been exposed to TDI. A significant proportion of exposed workers had an increase in lower respiratory symptoms ($P<0.01$), while unexposed workers did not. This difference was accounted for by a significant excess of new symptoms in exposed workers who had never smoked ($P<0.05$).

Pulmonary function data during the first 2 years of exposure showed an increase in FVC and FEV 1 in both exposed and unexposed groups [58]. There were slight declines in FEF 25-75, in FEV 1/FVC, and in instantaneous flowrates at 50 and 25% of FVC (Vmax 50 and Vmax 25), but these did not differ significantly from zero or from expected effects due to aging, nor were there significant differences between exposed and unexposed groups. There were significant differences between groups in measurements of lung volumes and diffusing capacities, but these were paradoxical, with greater declines in groups having less exposure. The authors concluded that there was no exposure-related decline in pulmonary function.

In the 1978 annual report on this study, Weill et al [59] noted that only 88 of the original 166 workers were still participating. To offset attrition, workers had been added during the first 3 years of the study, so that some data were available on a total of 277 workers. The original exposure groups were no longer considered valid because of workers transferring from one exposure category to another. Personal monitoring data collected since 1975 were therefore used to estimate cumulative exposures in ppm-months for each worker. Mean TWA exposures were calculated for each of six job categories, ranging from 2 to 6 ppb (14-40 µg/cu m). TDI concentrations for jobs assigned to the control group were found to be below the limit of detectability of the method (reported as 1.5 ppb) more than 99% of the time, and the author assigned these jobs a mean TWA concentration of 0 ppb. For each worker, time spent in each job category was multiplied by the mean TWA concentration for that job and results were summed to determine cumulative exposures.

Lung function test results were statistically correlated with these cumulative exposures in cross-sectional and longitudinal analyses [59]. Cross-sectional analysis of 139 men tested in December 1977 by step-up regression showed no significant association of pulmonary function test values with cumulative exposure.

Longitudinal analysis included all workers who had participated in pulmonary function testing a minimum of three times over at least 3 years and those who had been tested at least twice for lung volume and diffusing capacity over at least 2 years; the former group included 117 men, the latter 132 [59]. Correlation coefficients were calculated for cumulative exposure and annual rates of change in several pulmonary function variables, and mean values were compared by smoking and atopy categories. Step-up regression was used to regress annual rates of change in lung function onto cumulative exposure, smoking, atopy, and interactions between these variables.

The results of this analysis did not show significant adverse effects of TDI exposure on pulmonary function at $P<0.05$; effects that were marginally significant ($0.05<P<0.10$) did not fit recognized patterns of airways dysfunction and were often paradoxical, with higher TDI exposures associated with less decrement in lung function [59]. There were "clearly excessive" annual declines in FEV 25-75, Vmax 25, Vmax 50, and diffusing capacity, but this was true for the entire test population and the declines did not differ significantly between exposure groups or show a positive correlation with cumulative exposure. The only annual change that was significantly correlated with cumulative exposure was an abnormally small increment in residual volume associated with higher TDI exposure. The authors were unable to interpret the biologic significance of this finding in the absence of other dose-related changes in lung volume.

Exposed subjects again showed a greater increase than controls in respiratory symptoms [59]. The difference was significant ($P=0.008$) only for bronchitis (defined as cough and phlegm for at least 3 months of the year), but increases also occurred in both upper and lower respiratory symptoms. When results were analyzed by smoking and atopy categories, most of the increase in bronchitis was accounted for by nonatopic smokers in the exposed group. There was no significant difference between continuously and intermittently exposed groups, but correlations with cumulative exposures were not made.

This study [54,57-59,63,92] is the only study available on TDI workers that provides preexposure data for all workers. In addition, because of the use of continuous personal monitoring, it provides realistic information on actual exposures. Findings in this TDI manufacturing plant indicate that exposure to TDI at TWA concentrations of 2-6 ppb (14-40 µg/cu m) can produce an increase in respiratory symptoms, apparently without any exposure-related decrement in pulmonary function. However, pulmonary function test results in this study are ambiguous, possibly because of exposure of the participants, including controls, to chemicals other than TDI.

In a 1973 NIOSH health hazard evaluation, Vandervort and Shama [93] investigated respiratory symptoms and acute lung function changes in workers exposed to TDI at low concentrations at a plant making polyurethane foam ice chests and picnic jugs. During a preliminary visit, air samples were collected and analyzed for TDI by the modified Marcali method of Grim and Linch [94]. A

questionnaire to identify histories of respiratory symptoms was administered to all 290 employees of the plant, about 200 of them exposed to TDI. The authors did not indicate the total number of workers with respiratory symptoms or describe their exposures to TDI. Twenty-nine of the 200 exposed workers were selected for further study; 13 of these were experiencing respiratory symptoms, as indicated in responses to the questionnaire, and 16 were asymptomatic. These workers were subdivided into moderate and low exposure groups on the basis of environmental measurements made at the time of the initial visit. The four workers making up the symptomatic low-exposure group were among 14 sensitized workers in the plant who had been transferred away from the immediate area of the foaming operation because of intolerance to TDI. Seven unexposed control employees, matched to the study group for age, sex, and smoking habits, were selected as controls.

Two weeks after the initial visit, the investigators [93] performed preshift and postshift pulmonary function testing on the exposed and control workers selected for the study. The TWA exposure concentration of each employee was determined for the shift from breathing-zone samples. Short questionnaires were administered before and after the monitored shift and again the next morning to determine whether the employees were experiencing symptoms.

Thirty-four environmental samples taken on the day of the first visit, mostly in the breathing zones of employees, all indicated TDI concentrations under 35 µg/cu m (5 ppb) [93]. Only seven were above 7 µg/cu m (1 ppb), and five of these were from workers operating foaming machines, whose exposures ranged from 10.1 to 25.9 µg/cu m (1.42-3.64 ppb). On the second visit, 88 samples were taken, 2-4 for each employee in the study. The maximum concentration measured was 39.9 µg/cu m (5.60 ppb); only four samples showed concentrations above 35 µg/cu m. TWA exposure concentrations for the 17 workers in the moderate exposure group ranged from 0.6 to 30.0 µg/cu m (0.1-4.2 ppb) with 4 workers exposed above 20 µg/cu m (2.8 ppb). Twelve of the 13 asymptomatic workers, who did not work in TDI areas and were presumably exposed only incidentally, had exposures of 0.2-3.4 µg/cu m (less than 0.5 ppb), but 1 worker in this group was exposed at 27.9 µg/cu m (3.9 ppb). The investigators noted that the operations involved are highly repetitive and the concentrations measured should therefore be representative of the usual exposure of these employees. However, spills of TDI had occurred in the plant, undoubtedly producing transient TDI concentrations much higher than those measured.

Results of pulmonary function testing showed no significant difference between morning and evening testing except in the symptomatic low-exposure group of four sensitized workers who had been transferred out of the foaming area; this group also showed significantly greater decreases in FVC and FEV 1 than did the controls [93]. The individual with the greatest decrease, who had never smoked, was exposed at a concentration of only 0.2 µg/cu m and thus was highly sensitive to TDI.

In the asymptomatic groups with both moderate and low exposure, all but two of the workers reported mild irritation of the mucous membranes, and three had respiratory symptoms such as coughing or chest tightness [93]. All 13 workers in the symptomatic groups reported coughing, chest tightness, wheezing, or shortness of breath. There was a considerable increase over preshift findings in the number of symptoms reported at the end of the shift in both the moderate- and low-exposure symptomatic groups and some increase in the asymptomatic groups.

This study [93] indicates that workers usually exposed to TDI at concentrations less than 35 µg/cu m (5 ppb) may experience respiratory symptoms related to their exposure. However, the investigators noted that it could not be assumed that workers had become sensitized at these low levels. Nine of the 13 symptomatic employees had been exposed to spills of TDI in the past, and 8 of these 9 developed symptoms at the time of the spill, so sensitization may have developed as a result of these exposures. The authors could not determine whether this was the first occasion on which they showed symptoms. Because only one set of personal monitoring measurements was obtained, this study does not indicate whether chronic exposure at these low concentrations can produce sensitization to TDI or a long-term decrease in lung function. However, at still lower concentrations of 7 µg/cu m (1 ppb) or less, only individuals previously sensitized to TDI at higher concentrations had respiratory symptoms or a decrement in lung function.

Roper and Cormer [95], in another NIOSH health hazard evaluation, performed a similar study in 1975 on nine employees who poured and molded polyurethane foam at another plant. Breathing-zone samples for these workers showed TDI concentrations of 0.1-2.2 ppb (0.7-16 µg/cu m). Only 2 of 21 samples showed concentrations above 1 ppb (7 µg/cu m), and most were well below this level. None of the workers in this study showed either acute changes in pulmonary function or respiratory symptoms, although some reported that they had experienced symptoms in the past when spills of TDI occurred. The absence of repeated sampling data and the small number of workers limit the significance of this study.

Although there have been several reports of respiratory effects in workers exposed to MDI, few studies have been found that indicate exposure concentrations associated with these effects. In a 1973 NIOSH health hazard evaluation, Vandervort and Lucas [61] investigated pulmonary function in workers in a plant manufacturing fibrous glass tanks. Concentrations of MDI were determined from both area and personal samples on 2 different days during MDI foaming operations and analyzed by the Marcali method as modified by Grim and Linch [94]. Breathing-zone concentrations of MDI reached 110 µg/cu m for some foam operators; other workers had average exposures of less than 50 µg/cu m. Workers in this process were also exposed to styrene at concentrations occasionally exceeding 100 ppm and to methylene chloride, toluene, and acetone at a few parts per million.

Preshift and postshift lung function testing was conducted on 29 exposed employees on a Monday when no MDI was used in the plant and on a Thursday when foaming operations took place; 12 of these employees worked in the immediate area of the foaming operation [61]. One worker had a preshift FEV 1 less than 75% of his predicted value, and he and two other workers had abnormally low FEV 1/FVC ratios; all three men were smokers, however, so the significance of these decrements is difficult to interpret. During the shift when foaming was carried out, none of the exposed workers showed a significant decrement in pulmonary function measurements compared with eight unexposed controls matched to them by age, sex, and smoking history.

In 1974, Bodner et al [96] conducted another NIOSH health hazard evaluation in a plant manufacturing fibrous glass products. Thirty-five workers, six of whom were sprayers, were employed in areas where exposure to MDI was likely. Breathing-zone samples for the sprayers showed MDI concentrations of 120-270 µg/cu m (12-26 ppb if the MDI was present as vapor), and area samples gave concentrations of 10-150 µg/cu m (1-15 ppb). Thirty-four of the employees (97%) experienced some form of eye, nose, or throat irritation, and 49% had wheezing, shortness of breath, or chest tightness. These workers were also exposed to styrene at concentrations greater than 200 ppm, making it unlikely that the symptoms resulted solely from MDI.

Other studies found on populations of workers exposed to MDI have provided no quantitative information on exposure concentrations, but they do indicate that there is a relationship between adverse effects and exposure levels or duration of exposure. For example, in 1971, Tanser et al [97] examined the effects of MDI exposure on 57 employees in a factory producing rigid polyurethane foam moldings. Fourteen of the 57 workers reported that any contact with MDI vapor produced effects ranging from a sore throat and wheezing to severe asthma and tightness in the chest. Spirometric analysis showed that 8 of the 57 employees had an FVC of less than 90% of the predicted value or an FEV 1/FVC ratio below 75%; only 2 of these 8 reported symptoms of sensitivity to MDI.

The authors [97] reported that most of the symptoms appeared to be those of direct irritation and not of an allergic reaction. However, four workers who had contact with MDI were diagnosed as having possible hypersensitivity; three of these had severe asthma, and the fourth developed fever, headaches, aching limbs, and cough following exposure.

The 1976 studies of Saia et al [98] and Fabbri et al [99] explored the relationship between exposure to MDI and chronic nonspecific lung disease in workers in an Italian refrigerator factory. The total exposed workforce of 180 comprised 94 furnace workers (who removed polyurethane molds from the furnace and were estimated to have the highest exposures), 32 injectors, and 54 assembly line workers were also included. The groups were similar in average age and length of employment.

Responses to a questionnaire indicated that 85 of the workers in the plant had respiratory symptoms [98]. The prevalence of these symptoms was least in workers exposed less than 4 years and greatest in those exposed more than 8 years; the average age in all three groups was 37-38 years. Pulmonary function studies showed that about half of the 180 workers had vital capacity and FEV 1 measurements below 90% of predicted values, and 15-20% had values below 80% of predicted [99]. The 85 workers with respiratory symptoms had pulmonary function measurements significantly lower than the average for the 180 employees. These measurements decreased with length of exposure even when adjusted for smoking.

Results were also analyzed by job function in 160 workers who had no history of previous occupational exposure to respiratory irritants [98,99]. Furnace workers had significantly lower pulmonary function values and a greater prevalence of respiratory symptoms than workers in other jobs.

Exposure data were not reported and control groups were not used in these studies [98,99], severely limiting their usefulness. The authors did not reveal the source of data on predicted pulmonary function values, so it is impossible to determine the relevance of these data to the worker population studied.

Only one study, a 1975 NIOSH health hazard evaluation by Hervin and Thoburn [100], has been found on workers exposed to HDI. These workers, 18 spray painters in an airplane repair facility, were exposed to HDI at up to 300 µg/cu m (40 ppb); they were also exposed to trimeric biuret compounds of HDI at up to 3,800 µg/cu m and to a variety of organic solvents at concentrations above the Federal standards. Pulmonary function measurements in spray painters and the decrements in these measurements over the workshift did not differ significantly from values in 40 controls who worked during shifts when spray painting was never performed. All the spray painters, who wore respirators but no eye protective devices, complained of eye irritation while painting, and about half complained of nose and throat irritation, cough, and chest discomfort. The authors mentioned that the respirator program was deficient in many respects. This report suggests that MDI produces symptoms similar to those from TDI and MDI. However, it does not provide any indication of the concentrations of HDI that produce irritation, since there was simultaneous exposure to organic solvents and to trimeric HDI at relatively high concentrations.

Animal Toxicity

The acute toxicity of several diisocyanates, including TDI, MDI, HDI, NDI, and IPDI, has been studied in laboratory animals. Results of LD50 and LC50 determinations for diisocyanates are presented in Table XI-3 [2,5,36,91,101-104]. All the diisocyanates that have been studied caused irritation when applied directly to the skin of rabbits or instilled into their eyes. Their potentials as skin and eye irritants, determined from these studies, are summarized in Table XI-4 [2,104].

Several studies have also evaluated the effects of exposing animals to sublethal concentrations of diisocyanates. In 1962, Duncan et al [101] exposed mice, rats, guinea pigs, and rabbits to TDI at 2-10 ppm (14-70 mg/cu m) for 4 hours. Chamber concentrations were measured by the Marcali method. Microscopic examinations of tissue sections showed tracheitis and bronchitis with sloughing of the superficial epithelium in animals exposed to TDI at 2 ppm and killed by the 4th day after exposure. Lungs of animals killed 7 or more days after exposure did not differ significantly from those of controls, suggesting that the effects were reversible. In animals exposed at 5 or 10 ppm, damage was more severe and long-lasting. There were areas of coagulation necrosis of the superficial epithelium surrounded by inflammatory cells, and at points of deep ulceration, connective tissue had developed. Bronchopneumonia developed in all species except mice. Since the animals were exposed only once, this lung damage was the result of irritation rather than an allergic reaction.

In another 1962 study, Henschler et al [38] exposed rats and guinea pigs to TDI repeatedly at concentrations of 0.1-10 ppm (0.7-70 mg/cu m). In rats, three 4-hour exposures at 10 ppm were lethal for all animals; four exposures at 5 ppm or 10 exposures at 1 ppm were lethal for most rats. At 0.5 ppm, adult rats could withstand 24 exposures, but this exposure regimen killed about half the young rats exposed. Most deaths were due to severe peribronchitis and bronchial pneumonia. In surviving animals, lung changes were reversible within several months. Rats exposed at 0.1 ppm for 40 exposures had no changes in the lungs that were attributable to TDI exposure, but they did gain less weight than controls. In guinea pigs, these authors were unable to find any evidence of sensitization to TDI after 48 exposures at 0.5 ppm, which was lethal to most of the animals.

These results were qualitatively similar to those reported by Zapp [36] 5 years earlier, but Henschler et al [38] obtained these results at about one-tenth the exposure levels that Zapp reported. Henschler and coworkers suggested that the discrepancy might have resulted from the difference in methods used to analyze chamber concentrations of TDI. Zapp had used the method of Ranta, which also measures decomposition products of TDI. In the later study, the authors used the method described by Ehrlicher and Pilz [39], which is based on the same principle as the Marcali method [105]; these two methods were said to give identical results [38].

In 1965, Niewenhuis et al [106] described the effects on animals of repeated exposure to TDI at a low concentration. They exposed rats, rabbits, and guinea pigs to TDI at 0.1 ppm (0.7 mg/cu m), 6 hours/day for either 38 consecutive days or 5 days/week for 58 exposures. Chamber concentrations were measured by the Marcali method.

Lung damage in these animals generally increased in severity for several days after exposure ended [106]. A rabbit examined immediately after exposure had essentially normal lungs, but animals killed 3-10 days later had bronchopneumonia, bronchitis, perivasculitis, and lung abscesses. A rabbit killed after 20 days had only

chronic bronchitis. Rats killed immediately had less inflammation than those killed later, but fibrous tissue had proliferated in the walls of the bronchioles in several rats. At 3-24 days after exposure, inflammation was marked, and animals had bronchopneumonia, extensive fibrous tissue proliferation, and polypoid hyperplasia of the epithelium. All control rats had bronchiectasis, which the authors attributed to chronic murine pneumonia. In guinea pigs, there were localized accumulations of lymphocytes, macrophages, and plasma cells throughout the lungs and varying degrees of pneumonitis and bronchopneumonia. No abnormalities of the heart, liver, kidneys, lymph nodes, or spleen were found in any of the animals.

The authors [106] suggested that the absence of inflammation in animals examined immediately after exposure indicated that later damage was caused by a secondary infection. They interpreted their results as indicating that TDI exposure inhibits the action of destructive organisms but also breaks down the normal protective mechanisms of the body, thus making the exposed animal vulnerable to later infections. Their findings of lung damage in animals exposed at 0.1 ppm do not agree with the essentially negative results of Henschler et al [38] in rats receiving similar exposures. The difference may be attributable to secondary infection, especially since bronchiectasis was observed in control animals in this study [106].

In a 1964 report from the USSR, Chizikov [70] attempted to determine the effects of exposure at very low concentrations of TDI. Groups of 15 white rats were exposed continuously to TDI for 84 days at 2,000, 200, and 20 µg/cu m (280, 28, and 2.8 ppb). Exposure at 2,000 µg/cu m caused retarded weight gain, a 35-50% increase in cholinesterase activity, a decrease in the albumin-to-globulin ratio, and porphyrinuria. Effects of exposure at 200 µg/cu m were similar but less severe. Effects on the CNS were indicated by inverse flexor and extensor muscle chronaxy ratios in animals exposed at 2,000 or 200 µg/cu m. Microscopic examination showed degeneration in the parenchymatous organs and inflammation of the respiratory tract. Results of tests on animals exposed at 20 µg/cu m did not differ from those of controls.

The toxicity of isophorone diisocyanate (IPDI) was investigated by Kimmerle [104]. He exposed groups of 20 male rats 4 hours/day, 5 days/week, for 4 weeks to IPDI at 250, 640, and 1,370 µg/cu m. No obvious signs of toxicity were observed during the test. Rats exposed at the highest concentration gained significantly less weight than those at the lowest concentration ($P<0.05$). No significant differences between exposure groups were found in blood composition, liver function, urinalysis, or kidney function, and no damage to any organ was observed in macroscopic examinations. However, there was an increased lung-to-body weight ratio in the high-exposure group. Animals exposed at 1,370 µg/cu m had significantly lower liver and spleen weights than those exposed at 250 µg/cu m. The author did not suggest an interpretation of these differences.

Lomonova and Frolova [5] compared the toxic effects of inhalation of hexamethylene diisocyanate (HDI) with those of chlorhexyl isocyanate (CHI), a major

byproduct of HDI manufacture. Results of their 2-hour LC50 studies in mice showed that HDI was 2.3 times as toxic as CHI. The threshold concentration for influence on the CNS in mice was 1 mg/cu m for HDI and 10 mg/cu m for CHI, although the threshold concentrations for respiratory irritation were similar--2.9 mg/cu m for HDI and 4.5 mg/cu m for CHI.

In albino rats exposed to each substance at 60 mg/cu m for 4 hours, maximum weight loss occurred 7 days after exposure to HDI, but not until 15 days after exposure to CHI [5]. Greater hypothermia, eosinopenia, and lymphopenia were found in HDI-exposed animals, suggesting that this compound caused a generalized stress reaction. Most deaths in HDI-exposed rats occurred 5-7 days after exposure, while most deaths in CHI-exposed rats occurred 17-19 days later. Microscopic examination of lung tissue from both groups of animals showed mild edema, bronchitis, emphysema, peribronchitis, and pneumonia.

The authors [5] also exposed mice to both compounds at fractions of the LC50 for longer periods of time. Doubling the duration of exposure to CHI at half the LC50 produced no deaths, but mice died from HDI exposure at less than one-fourth the LC50 when exposure time was increased proportionately, indicating a dose-dependent toxicity.

Mice and rats were also exposed 4 hours/day for 40 days to HDI at about 1.2 mg/cu m and to CHI at about 2.9 mg/cu m [5]. Repeated exposure to HDI caused statistically significant decreases in body weight gain and oxygen consumption in both species. Forced swimming time also decreased in mice, but CNS capacity to assimilate subthreshold impulses increased. Exposure to CHI caused only a nonsignificant decrease in weight gain.

According to the authors [5], adding chlorine to the molecule of an organic compound would be expected to increase the toxicity of the compound. Yet the results of this series of experiments showed that HDI was substantially more toxic than CHI. The fact that the lethality of HDI was dose dependent may indicate that the compound is absorbed systemically, while the effects of CHI appear to result only from local irritation of the respiratory tract.

Kondratyev and Mustayev [107] demonstrated skin sensitizing effects of HDI in experimental animals in 1974. Guinea pigs were sensitized by application of HDI in 50% solution in acetone to the skin for 2 days in a row. An initial irritant effect in the form of hyperemia, edema, and itching was observed at the sites of application. After 21 days, the degree of sensitization was determined by applying HDI in various concentrations to previously unexposed skin. A specific allergic reaction was seen in most animals at concentrations as much as 40 times less than the previously determined threshold dose of 50% for skin irritation. The epicutaneous sensitization observed was also accompanied by changes in the blood-serum protein fractions. This study suggests that skin contact with HDI in the workplace could lead to allergic dermatitis.

Kimmerle [104] found that IPDI produced moderate skin sensitization in guinea pigs. His experimental methods were not described but were said to follow the recommendations of the Food and Drug Administration. IPDI, administered intradermally, produced a larger area of swelling on reinjection than it had in an earlier injection in all 15 guinea pigs tested.

Animal experimentation has been used in several studies to investigate the mechanism of sensitization to diisocyanates. In 1964, Scheel et al [51] investigated the immunologic aspects of TDI sensitization. The authors produced TDI antigens by conjugating TDI with egg albumin; they attempted to characterize the antigen, and their method of preparation, with modifications, became the standard for many subsequent immunologic studies on TDI. TDI-specific antibodies were demonstrated in rabbits exposed to TDI by inhalation at 100 ppb (700 µg/cu m) 6 days/week for 2-4 weeks. When a purified protein derivative of the tubercule bacillus was injected during TDI inhalation, a skin sensitivity response to TDI could also be demonstrated; animals so treated reacted to 0.001 mg of TDI applied to the skin, while unsensitized animals reacted only to 0.2 mg. When the proportion of TDI in the antigen was increased, the antigenicity of the protein was masked so that it would not react with antibodies to egg albumin. This demonstrated that the circulating antibodies contained a reacting group specific for the TDI hapten.

Thompson and Scheel [108], in 1968, investigated the effects of TDI on rats pretreated with alloxan to suppress anaphylaxis or with insulin and pertussis vaccine to enhance the responses. Rats were exposed to TDI at 1 ppm (7 mg/cu m) for 10 hours. Although the authors found that pretreatment altered the effects of TDI exposure on the lungs in the predicted direction, they concluded that the mechanism of lung damage was not immunologic. This interpretation was based on their inability to elicit a reaction to cutaneous or intravenous challenge and the fact that reexposure to TDI produced less response than the original exposure. In addition, microscopic findings indicated that the lung effects produced were consistent with chemical damage rather than an immunologic process and that they occurred primarily in the first few days after exposure.

In 1970, Stevens and Palmer [109] studied sensitization in guinea pigs and rhesus monkeys exposed to TDI at 0.01-5 ppm for three 6-hour periods. Three weeks later, these animals and previously unexposed animals were exposed to TDI at 20 ppb (140 µg/cu m). Breathing patterns of the animals were measured by plethysmography to detect changes indicative of respiratory sensitivity.

Guinea pigs previously exposed to TDI at 2-5 ppm showed changes in respiratory patterns when exposed at 20 ppb, but controls did not react to TDI at this concentration [109]. Patch tests showed skin sensitization to TDI, but serologic tests for sensitization were negative. Guinea pigs preexposed to TDI at 0.5 ppm did not show measurable respiratory changes, suggesting that a threshold for sensitization existed between 0.5 and 2.0 ppm. There was no evidence of sensitization in monkeys after reexposure, and there were no serologic changes indicative of sensitization. The authors concluded that exposure to large amounts

of TDI may produce sensitivity to TDI in lower concentrations, but that this sensitivity might not involve an allergic mechanism. However, they noted that the difficulty in preparing a suitable antigenic system made it impossible to determine whether an immunologic mechanism was involved.

Karol et al [110], in 1978, were able to demonstrate the production of serum antibodies specific for the tolyl portion of an isocyanate molecule. They exposed guinea pigs by inhalation to a conjugate of the monofunctional p-tolyl isocyanate with egg albumin (EA). This antigen induced a respiratory response in the animals beginning about the 8th day of exposure, and serum antibodies were detectable by gel diffusion and immunoelectrophoresis by the 14th day. The authors concluded that the antibodies were hapten-specific, since p-tolyl isocyanate that was bound to another protein carrier, such as bovine serum albumin, elicited both respiratory reactions and serum antibody responses in animals previously sensitized to the isocyanate-EA antigen. In addition, sensitivity to the EA carrier in the conjugate was not produced, suggesting to the authors that the conjugate contained sufficient isocyanate molecules to effectively shield antigenic determinants in the protein molecule. In a subsequent study, which has been described in Effects on Humans, Karol and her colleagues [62] used this antigen to demonstrate IgE antibodies in the sera of workers who had sensitivity reactions to TDI.

Mutagenicity testing on TDI, MDI, and dicyclohexylmethane 4,4'-diisocyanate has been performed in Du Pont's Haskell Laboratory (J Foderaro, written communication, June 1978). The compounds were tested on Salmonella typhimurium strains TA1535, TA1537, TA1538, TA98, and TA100, with and without a mammalian liver microsome activating system. MDI was mutagenic in strains TA98 and TA100 in the presence of the liver activating system. The other diisocyanates tested did not show mutagenic activity. Details of the experimental procedure and quantitative results were not provided.

Correlation of Exposure and Effect

In the early days of the industry, a large proportion of the workforce exposed to TDI developed respiratory illnesses [29-31]. Concentrations in these studies were seldom reported but were probably very high. These studies indicated that exposure to TDI caused respiratory irritation, progressing in some workers to asthma [20,21,32]. Continued exposure at high concentrations has produced pulmonary edema, occasionally resulting in fatalities [22,27]. One case of interstitial pneumonitis has been attributed to TDI [42].

The many reports of respiratory effects from exposure to TDI indicate a general correlation with exposure concentrations. The clearest evidence for such a relationship is that the number of affected workers decreases as concentrations are reduced. Elkins et al [32] determined average concentrations at 14 plants with a total workforce of 379 where 43 established cases of TDI intoxication had occurred. In the plant with the highest average concentration, 200 µg/cu m, 14 of 100

workers developed respiratory illnesses in 1 year. In all other plants with average TDI concentrations above 70 µg/cu m, there were cases of respiratory illness, but none occurred at plants where TDI concentrations averaged 30 µg/cu m or less.

The adverse effects of TDI on the lungs may result from direct irritation caused by exposure at relatively high concentrations. An experiment on volunteers [38] showed that one of six subjects experienced irritation of the nose and throat during a 10-minute exposure at 710 µg/cu m and that all experienced it at 3,600 µg/cu m; however, these subjects did not report chest symptoms. In an automobile plant, all 12 workers exposed to TDI developed severe respiratory symptoms when TDI concentrations were 30-70 ppb (210-500 µg/cu m) [79]. Their symptoms disappeared when concentrations remained below 30 ppb.

Acute and chronic respiratory effects caused by exposure to TDI have been reported, but the results of such studies have been inconsistent. Results appear to differ substantially depending on the type of operation or process in which TDI exposure occurs. In a spraying operation, where TDI concentrations reached 6,400 µg/cu m, Gandevia [81] found a significant decrease in FEV 1 during the course of a workday in 20 exposed men. This decrease was not fully reversed overnight or on the weekend and the cumulative decrease over 3 weeks was also significant.

In a TDI distilling operation where concentrations were generally less than 140 µg/cu m, Williamson [17] found no significant changes, compared with preexposure baseline values, in the pulmonary function of 21 men over 14 months. He also reported little difference between Monday and Friday values.

In another type of exposure situation, a polyurethane foam plant, Peters et al [84-87] found significant daily, weekly, and cumulative decreases over a 2-year period in workers exposed at concentrations below about 100 µg/cu m. This study did not include preexposure measurements, but the mean annual decrement in FEV 1 of 0.11 liter/year was considerably higher than those the authors found in the literature for normal working and general populations, which ranged from 0.025 to 0.047 liter/year. FEV 1 was measured every 6 months and showed a significant decrement each time except during one 6-month period when the maximum TDI concentration detected was only 11 µg/cu m [87]. The authors also found that the daily decrement during the workshift was closely correlated with the annual decrement for each individual.

At another polyurethane foam plant, Wegman et al [89,90] reported finding a significant dose-related loss of lung function in a 2-year study. Workers exposed at 14-21 µg/cu m had a decrease in FEV 1 of 0.085 liter/year (SD = 0.177), while the annual decrement was 0.205 liter (SD = 0.185) in those exposed at concentrations above this range and 0.012 liter (SD = 0.204) at lower concentrations.

A long-term study of workers in a TDI-manufacturing plant, conducted by Weill et al [57,59,92] and Butcher et al [54,58,62], showed no significant exposure-related changes in lung function. TDI concentrations in the plant generally ranged

from 14 to 50 µg/cu m during the 5.5-year study. The entire study population, which included controls from elsewhere in the chemical factory not exposed to TDI, had excessive declines in some pulmonary function measurements compared with predicted values, but there was no difference between groups with constant, intermittent, and no exposure, and decreases were not correlated with cumulative exposures. These findings are questionable on the basis that the control group may have been so affected by exposure to other chemicals that the study was insensitive to possible effects of TDI exposure.

The disagreement of these findings with those obtained in polyurethane foam plants [87,90] may also reflect differences in exposure to other chemicals and failure to detect occasional excursions to much higher exposure concentrations than those usually prevailing. Both TDI manufacturing and polyurethane foam production involve mixed exposures, but in the latter process, exposures to other chemicals are likely to be much more closely correlated with exposures to TDI. Thus, the apparent dose-response relationship to TDI exposure in the polyurethane foam plant [90] may be misleading. In the absence of confirmation by other investigators, the findings of these studies [87,90] cannot be regarded as conclusive evidence of adverse effects by TDI at concentrations below 140 (ug/cu m). In both of the polyurethane foam plants studied, the study populations were small and there was considerable turnover during the period of the investigations. The populations evaluated included both sensitized and unsensitized workers. Peters et al [87] indicated that 2-year decreases in FEV 1 were twice as great in workers reporting symptoms as in those that did not. The large standard deviations that Wegman et al [90] obtained for 2-year decrements in pulmonary function also suggest a population that may not have been normally distributed and may have contained separate subgroups of sensitized and unsensitized individuals. Only summarized data were presented in these studies. Since experimental values obtained for individual subjects were not reported, evaluation of the study population is limited and the significance of the reported findings remains equivocal.

Several studies have shown that sensitive persons react to TDI at very low concentrations and that their responses are dose-related. Butcher et al [54] reported that some sensitive individuals reacted at 70 µg/cu m but not at 35 µg/cu m, and two persons who reacted at the latter concentration were not affected by a challenge exposure at 20 µg/cu m [57]. Carroll et al [45] obtained asthmatic reactions in sensitized persons challenge-tested with TDI at about 7 µg/cu m. Some of these subjects reacted after a 15-minute exposure, while others reacted only if exposure lasted 30 or 60 minutes. O'Brien et al [46,47] found that about 25-50% of sensitized workers who reacted to TDI in challenge tests responded to even trace amounts of TDI (less than 1 ppb or 7 µg/cu m) with a decrease in pulmonary function; these extremely sensitive individuals also tended to be have bronchial reactions to exercise, histamine inhalation, and other diisocyanates. In one plant, workers transferred away from foaming operations because they had become sensitive to TDI still experienced

respiratory symptoms in areas of the plant where concentrations were below 7 µg/cu m [93]. No one has demonstrated a concentration of TDI below which no sensitized individual will have a respiratory reaction.

Attempts to determine the concentrations of TDI necessary to produce sensitization have not been fruitful. Porter et al [56] reported that there were no new cases of sensitization in a TDI plant in 2 years when average TDI concentrations were below 140 µg/cu m; during the previous 16 years of operation, when TDI concentrations had averaged 350-420 µg/cu m, from one to four cases of sensitization had been diagnosed each year, the number gradually decreasing with increasing length of operation. Superficially, these data suggest an average TDI exposure, 140 µg/cu m, below which sensitization does not occur. However, examination of the data reveals that, even during the years when the average TDI concentration remained constant at 420 µg/cu m (1956-1969), there was a general decline in the number of cases of sensitization, suggesting that potentially sensitive individuals may have become sensitized and left the workforce during their early years of employment. Thus, these findings do not rule out the possibility that sensitization might develop in newly hired workers exposed at less than 140 µg/cu m for longer periods of time.

Several authors have noted that workers often become sensitized during brief exposures at high concentrations resulting from spills, leaks, or spraying [31,41,42,52]. However, sensitivity to TDI has been observed in workers with no known exposure to spills or spraying operations [43,45]. A NIOSH health hazard survey of a plant making polyurethane foam found respiratory symptoms in workers at a foaming operation where no TDI concentrations of more than 35 µg/cu m were measured [93]. However, 9 of 13 workers who had been transferred away from the foaming operation because of severe symptoms were known to have been exposed previously to spills of TDI. In another NIOSH survey, none of the nine employees of a polyurethane foam plant where TDI concentrations averaged less than 7 µg/cu m and did not exceed 16 µg/cu m had respiratory symptoms [95], indicating that sensitization may be rare or nonexistent at such low concentrations.

The failure of these data to show a quantitative correlation of exposure and effect reflects the difficulty in evaluating and interpreting the "sensitized" state. There is evidence that a substantial proportion of the working population is potentially sensitizable to the effects of TDI. Williamson [41] reported symptoms of sensitization developing in 4-6 members of a workforce of 99, about a 5% sensitization rate. Other studies suggest that the rate of sensitization may be somewhat higher. Four of 47 workers (9%) in an office that received exhaust air from a nearby TDI plant became sensitized; in 3 of these, sensitization was confirmed by bronchial responses in challenge tests, and the 4th improved when he was removed from exposure [45]. Porter et al [56] reported that 30 of the 300 workers (10%) in a TDI plant were diagnosed as sensitive to TDI during 17 years of operation. Adams [83] found that 15% of the workforce in one plant left during their 1st year of employment because of effects on their health; 1-3.5% left for the same reason during subsequent years, for a total of about 20%. A similar rate

was suggested in a study by Bruckner et al [52], in which 5 of 26 workers exposed to unspecified isocyanates were considered sensitized because they had asthmatic reactions at low concentrations.

Some reports have suggested that sensitization to TDI is related to a personal history of allergy [52] or to atopy, as indicated by reactivity to prick tests with common inhalant allergens [53]. However, most investigators report that there is no pattern of allergies or atopy in sensitized workers [43,46,49,54,56].

Several investigators have attempted to demonstrate an immunologic mechanism for TDI sensitivity. In 1964, Scheel et al [51] demonstrated circulating antibodies and positive skin reactions in guinea pigs sensitized to TDI by inhalation, but later workers were unable to confirm these results in guinea pigs, rats, and monkeys [108,109]. In humans, immunologic testing has indicated the existence of both reagin-type antibodies and circulating IgG antibodies in some workers exposed to TDI [53-57]. However, these test results have generally correlated poorly with symptoms suggestive of TDI sensitivity or with respiratory responses to challenges with TDI at low concentrations. Since the TDI molecule has been thought to be too small to be antigenic in itself, a central problem in immunologic testing has been the development of an appropriate test antigen (a conjugate of TDI with a carrier protein). A recent study by Karol et al [62], using a test antigen of p-tolyl (mono)isocyanate, demonstrated the presence of tolyl-specific antibodies in the sera of three of four TDI workers who had sensitivity reactions to TDI; the fourth worker had not been exposed to TDI for 5 years. This study showed that an immunologic mechanism may be involved in TDI sensitization.

Studies by Butcher et al [63,66] and Van Ert and Battigelli [64] have suggested that a pharmacologic mechanism is also involved in respiratory sensitivity to TDI. These investigators showed that TDI inhibited the isoproterenol-stimulated cyclic AMP levels in human lymphocytes. The effect was greater in lymphocytes from individuals who were sensitive to TDI [65]. These and other investigators have reported that many TDI reactors were hyperreactive to cholinergic agents (bronchoconstrictors) [46,53,56,63,67]. Porter et al [56] found that persons hyperreactive to bronchoconstrictors exhibited TDI sensitivity even though they could not be shown by immunologic testing to have antibodies against TDI. These results suggest that TDI may block the beta-adrenergic system, making the cholinergic effect more intense in some individuals. It has not been determined whether hyperreactivity to bronchoconstrictors is a result of TDI exposure or a predisposing factor for sensitization to TDI.

Far less information exists on exposure to the other diisocyanates, but their effects appear to be generally similar to those of TDI. Thirty-four of 35 workers, only 6 of whom were exposed to MDI at concentrations above 150 µg/cu m, experienced irritation of the eyes, nose, and throat, and half of them had bronchial symptoms [96]. Workers exposed to MDI at 50-110 µg/cu m did not have a significant decrease in FEV 1 during a workshift in which foaming was carried out, but 3 of 29 workers had respiratory symptoms [61]. Workers exposed to MDI at

unknown concentrations in an Italian refrigerator factory had reduced vital capacity and FEV 1, and 85 of 180 workers had respiratory symptoms [98,99]. This study indicated that the effects were dose-related, since furnace workers, who were exposed to MDI at the highest concentrations, had significantly lower pulmonary function values and a greater prevalence of respiratory symptoms than workers elsewhere in the plant. The incidence of respiratory symptoms also increased with years of employment at the plant.

MDI-specific antibodies have been reported in the sera of exposed workers [60,61], but immunologic test results have shown little correlation with respiratory sensitivity to MDI. Workers with respiratory sensitivity to TDI who have not been previously exposed to MDI have had positive skin tests to MDI, suggesting that cross-sensitization may occur.

O'Brien et al [47] reported bronchial reactions to MDI in four TDI-sensitive workers with no known previous exposure to MDI; two of these also reacted to HDI without any previous exposure. These authors considered immunologic cross-sensitivity unlikely because of the differences in structure between the compounds. The subjects who cross-reacted to other diisocyanates tended to react to extremely low concentrations of TDI (less than 1 ppb) and to be hyperreactive to histamine. The authors suggested that extreme sensitivity to TDI might be the result of both an immunologic mechanism and a nonspecific pharmacologic or irritative mechanism, with the latter mechanism accounting for the cross-reactions to MDI and HDI. This is compatible with the reports of Butcher et al [63,66] that TDI may block the beta-adrenergic system and with the suggestive evidence obtained by Porter et al [56] that TDI sensitivity does not necessarily require the presence of anti-TDI antibodies. However, the possibility of immunologic cross-sensitivity between diisocyanates remains to be tested with a specific antigen system like that of Karol et al [62,110] and is at present only speculative.

Irritation of the respiratory tract has also been reported in workers exposed to HDI [42,76,100]. The limited environmental data and the high levels of other toxic chemicals in these studies preclude any estimate of dose-response relationships. In a factory where HDI levels were generally less than 30 µg/cu m and TDI was present at less than 40 µg/cu m, 9 of 18 workers experienced irritation of the upper respiratory tract, cough, or chest tightness, although lung function values did not differ significantly from those of controls or show a significant daily decrease [100]. Since symptoms of respiratory irritation are not experienced by most workers exposed to TDI alone at comparable concentrations, this study suggests a possible additive or synergistic effect of HDI.

In rabbits, the threshold concentration for irritative lung damage from HDI was 2,900 µg/cu m, and repeated exposures at 1,200 µg/cu m for 40 days caused significant decreases in weight gain and oxygen consumption in mice [5]. Rats exposed to IPDI at 1,370 µg/cu m repeatedly for 4 weeks had decreased in weight gain and liver and spleen weights, but these effects were not seen at 640 µg/cu m [104].

In addition to causing respiratory symptoms, the diisocyanates are skin irritants and skin sensitizers. TDI [62,69], MDI [69], and IPDI [69] have produced skin sensitization in humans, and skin sensitization by IPDI [104], and MDI [107] has been demonstrated in guinea pigs.

Reports of systemic effects of the diisocyanates are rare. A few studies have suggested that massive exposures to TDI may produce neurologic or psychologic symptoms [21,71,72]. Five of 35 firefighters who were exposed to large quantities of TDI liquid and vapor experienced a feeling of drunkenness, nonsensical behavior, loss of balance, or tremors and numbness of the extremities during the fire, and 23 subsequently developed symptoms such as loss of memory or personality changes [73]. Similar symptoms have been reported in workers exposed to HDI [75,76], but these workers were also exposed to other toxic chemicals. A USSR study has reported EEG changes in volunteers exposed to TDI at 100 µg/cu m and reflex changes in rats exposed at 200 µg/cu m for 84 days [70].

Carcinogenicity, Mutagenicity, Teratogenicity, and Effects on Reproduction

No reports were found to indicate that TDI, MDI, HDI, NDI, or other diisocyanates produce carcinogenic, teratogenic, or reproductive effects in humans or animals. MDI was mutagenic to Salmonella typhimurium in the presence of a mammalian liver activating system, but TDI and dicyclohexylmethane 4,4'-diisocyanate showed no mutagenic activity in the same system (J Foderaro, written communication, June 1978). In the absence of other data on mutagenicity, this single study is insufficient evidence that diisocyanates are likely to be mutagenic in humans.

TABLE III-3

EFFECTS OF EXPOSURE TO DIISOCYANATES ON HUMANS

Compound	Concentration*		Duration	No.	Effects	Reference
	ppb	µg/cu m				
TDI	900	6,400	3 wk	15	Significant daily and cumulative decrease in lung function	81
"	500	3,600	10 min	6	Eye, nose, throat irritation in all	38
"	100	710	10 min	6	Nasal irritation in 1	38
"**	30-70	210-500	1 wk	12	Mild to severe respiratory symptoms in all, disappearing at lower concentrations	79
"	50	360	10 min	6	Eye irritation in 3	38
"	20-50	140-360	5 yr	180	No significant change in lung function compared to controls; sensitization of about 20%	83
"	<20	<140	18 mo	99	Respiratory sensitization in 4	41
"	"	"	5 yr	114	Significant decrease in lung function accounted for by decrease in only 16 individuals	82
"	"	"	1 yr	15	No significant change in lung function	17
"	14	100	-	-	Changes in EEG rhythms	70
"	1.5-14.5	10-103	2 yr	34	Significant daily and cumulative decrease in lung function	87

TABLE III-3 (CONTINUED)

EFFECTS OF EXPOSURE TO DIISOCYANATES ON HUMANS

Compound	Concentration*		Duration	No.	Effects	Reference
	ppb	µg/cu m				
TDI	2.8-10	20-70	15 min	-	Asthmatic reactions at 5 but not 2.8 ppb in 2, at 10 but not 5 ppb in other sensitized persons	54, 57
"	2-7	14-50	5.5 yr	166	No significant effects on lung function related to exposure levels	57
"	<5	<35	-	17	Respiratory symptoms in some; no significant daily decrease in lung function	93
"	>3	>20	2 yr	20	Significant decrease in lung function compared to normal populations	90
"	0.1-3	0.7-20	-	38	Significant daily decrease in lung function	84
"	<2	<14	2 yr	20	No significant decrease in lung function compared to normal population	90
"	<1	<7	-	12	Respiratory symptoms and significant daily decrease in lung function only in sensitized persons	93
"	<1	<7	-	9	No respiratory symptoms or daily decrease in lung function	95

TABLE III-3 (CONTINUED)

EFFECTS OF EXPOSURE TO DIISOCYANATES ON HUMANS

Compound	Concentration*		Duration	No.	Effects	Reference
	ppb	µg/cu m				
MDI	130	1,300	30 min-3 hr	7	Slight febrile reaction in 1	60
"***	12-26	120-270	-	6	Eye, nose, or throat irritation in 35; wheezing, shortness of breath, or chest tightness in 17	96
	1-15	10-150	-	29		
"	5-11	50-110	-	29	No significant daily decrease in lung function; values below predicted in 3; respiratory symptoms in 6	61
HDI***	14	100	up to 13 yr	82	Respiratory tract irritation, dyspnea, coughing, headaches, chest pains, enlarged livers	76
HDI***	<5	<30	-	18	No significant daily decrease or difference from controls in lung function; eye irritation in all; nose or throat irritation, cough, or chest tightness in half	100
TDI	<5.6	<40				

*Concentrations given are average or usual range of exposures and do not reflect excursions.
**Unidentified isocyanate, probably TDI
***Also exposed to other chemicals, including styrene, phosgene, or organic solvents