III. BIOLOGIC EFFECTS OF EXPOSURE

Toluene diisocyanate (TDI) is manufactured from toluene diamine by reaction with carbonyl chloride (phosgene). Isocyanates are chemical compounds containing the N=C=O group. TDI has the formula CH3C6H3 (NCO)2. Two isomers are commonly used. These are 2,4-toluene diisocyanate and 2,6-toluene diisocyanate. It is commercially available in three isomer ratios:

(a) 100% 2,4

(b) 80% 2,4:20% 2,6

(c) 65% 2,4:35% 2,6

The two isomers are believed to have similar physiological properties. [1] Their physical and chemical properties are very similar except that the 2,6 isomer has a lower freezing point. [2] The 80% 2,4:20% 2,6 mixture represents better than 95% of industrial usage. [3] Properties of commercial samples of this mixture are listed in Table XIII-1.

Extent of Exposure

TDI is the principal isocyanate of industry and may be employed in almost all the applications in which isocyanates are used as precursors in the production of polyurethanes, polyureas, polyamides, allophanates, biurets, and simple polymers of the isocyanates themselves. All these compounds, in industry, are collectively referred to as "polyurethanes" or "polyurethane plastics".

Isocyanates react with a wide variety of compounds containing active hydrogen atoms to produce such products as rigid or flexible foams, surface coatings, adhesives, rubbers, and fibers. Wide application of the products ranges from packaging to insulation materials to upholstery in automobiles and furniture to shoe soles. Production of polyurethane products began to reach an important scale in the 1950's and has grown rapidly during the past two decades. Most of the flexible foams are produced in large-scale specialized operations in the form of slabs, blocks or sheets, which after curing should contain no free TDI. Such operations are generally quite amenable to engineering controls.

A significant proportion of the rigid polyurethane foams, however, are generated with portable equipment, or virtually no equipment at all, by mixing the TDI and other polymerizing ingredients, resins, polyols, polyethers, emulsifiers, catalysts, water, and sometimes "frothing" or "blowing" agents on site and pouring them into the mold or structural cavity which is to be filled with the rigid foam. Another method of application of rigid foam is by spraying the polymerizing ingredients immediately after mixing onto a surface which is to be coated with a layer of foam. In such situations the problems of limiting TDI concentration in the breathing zone are difficult.

Among occupations with potential exposures are the following [4]:

abrasion resistant rubber makers	polyurethane sprayers
adhesive workers	polyurethane foam makers
aircraft builders	ship burners
insulation workers	ship welders
lacquer workers	spray painters
mine tunnel coaters	textile processors
organic chemical synthesizers	TDI workers
plastic foam makers	upholstery makers
plasticizer workers	wire coating workers

The number of workers with potential exposure to TDI has been estimated by NIOSH to be approximately 40,000. Small numbers of workers in a large number of workplaces probably represents the rule, with some exceptions.

Historical Reports

The Germans, making extensive use of TDI in their war industries in World War II, apparently encountered human toxicity problems according to Brugsch and Elkins [5] but the first report in the medical literature occurred in 1951 in France, by Fuchs and Valade. [6] These authors reported 9 cases of progressive bronchial irritation, of which 7 went on to develop an asthma-like syndrome on continued exposure to a 60:40 mixture of the 2,4 and 2,6 isomers of TDI (Desmodure T). The latter phenomenon was identified as allergic. No environmental data are available, but some of the affected workers

had no direct contact with TDI and were in the vicinity only sporadically.

From Germany in 1953, 17 similar cases were reported, 13 of them severe and one ultimately fatal. [7] Pulmonary emphysema was attributed to the isocyanate exposure in two cases, one of which progressed to fatal cor pulmonale. This case was also reported to show an eosinophilia of 7%. Environmental measurements were not reported but exposure in all cases was to TDI or other isocyanates.

Two years later the same author [8] reported two further cases of occupational illness associated with isocyanates. One was a woman who developed bronchial asthma following exposure to a polyurethane-based glue. The other was a man who was initially affected by paroxysmal cough, rhinitis and conjuctivitis and on reexposure to TDI became severely asthmatic.

Eight further cases of severe respiratory illness featuring constriction of the chest, asthma-like bronchospasms, bronchitis, and bronchopneumonia, associated with exposure to TDI in the production of a polyurethane foam "Moltopren" were reported from Germany around this time. [9]

Three cases of bronchial asthma or chronic bronchitis attributed to TDI in the production of foam and nine similar cases associated with the use of TDI lacquer (Desmodur-Desmophen), one of them fatal, were described by Schurmann. [10]

Fifteen cases of respiratory toxicity from TDI in Sweden were reported in 1955. [11] The three cases described in detail involved

polyisocyanate lacquer spraying and all were manifested as bronchial asthma with evidence of sensitization.

The first report, by Woodbury, [12] of occupational poisoning by TDI in the United States appeared in 1956. He reported 8 cases from a work force of 25 men involved in the manufacture of polyurethane foam. One case of primary irritation following acute accidental exposure, one case of acquired hypersensitivity to TDI, and one case of sensitization in a subject of known allergic predisposition to "atopy" were described in detail.

In 1957, a further 17 U. S. cases of irritation of the mucous membranes and respiratory tract by TDI were reported by Johnstone [13] from two plants producing polyurethane foam. Five cases were briefly described, of varying severity, but the author eschewed classifying any of the reaction as bronchial asthma.

The same year 42 cases of respiratory irritation ascribed to TDI exposure, of which 9 required hospitalization, were reported by Sands et al [14] from a plant manufacturing polyurethane foam.

Also in 1957 in the U. S. it was reported [15] that the entire work force of 12 handling TDI in a small plant was affected to some degree by the vapor, 3 of them severely. The report referred to "organic isocyanates", but the author (GM Hama, written communication, June 1973) has confirmed that the isocyanate studied was TDI.

In 1959, 3 cases of severe respiratory illness with features of bronchitis and bronchial asthma were reported in painters using TDI (Desmodure-T)-based lacquers by Schur. [16] This author discussed at

some length the issue of direct irritation vs. sensitization or allergy.

The same year a total of 99 cases of respiratory illness, of which 9 were classified as bronchial asthma, were attributed to TDI in a single U. S. plant producing polyurethane foam. [17]

In 1960 a further report [18] came from Germany. Eleven respiratory cases were reported, 4 of these in women employed in the tinning of electrical wire coated with a polyisocyanate lacquer. The authors assumed that the women were exposed to TDI in the pyrolysis fumes from the cured lacquer.

In another German paper in the same year, [19] a single severe case of bronchial asthma attributed to TDI in a painter employing TDI-based lacquers, progressing within four years after the exposure to chronic asthma with bronchitis, emphysema, and secondary bronchiectasis was described.

The first reports of TDI toxicity from England appeared in the same year. [20] One case of recurrent bronchitis in a young female laboratory assistant was attributed to traces of vapor of methylene di-(4-phenylisocyanate) (MDI) containing about 10% TDI from a closed bottle in her laboratory. In contrast, one case of acute accidental exposure from TDI that was spilled over the person resulted in mild bronchitic symptoms and keratoconjuctivitis. A third case of acute attacks of bronchial asthma occurred in a maintenance worker in a TDI pilot plant at what was probably a low concentration.

Also in 1960 five additional cases were reported by Johnstone and Miller [21] from the same U.S. plants from which Johnstone had reported 17 cases in 1957. [13]

Finally in 1960 there was one further report [22] from the U. S. of a single severe case of respiratory illness in a worker exposed on only four occasions to TDI in the small-scale production of a polyurethane foam.

Since 1960, cases of occupational poisoning by TDI have continued to occur but the hazard has become well recognized and simple reports of such cases are no longer newsworthy as such. The focus of interest of the occupational medical literature in more recent years has been on the validation of the Threshold Limit Value, currently 0.02 ppm, pulmonary function testing of workers exposed to low levels of TDI, and the nature of the sensitization to TDI to which a certain proportion of workers seem to be susceptible.

Effects on Humans

(a) Theoretical

Lowe [23] has discussed chemical reactions of isocyanates in terms of their use; these reactions also have biological implications. TDI in common with other organic isocyanates is a highly reactive compound. It reacts vigorously and exothermically with water with the formation of an unstable carbamic acid which immediately dissociates to form a primary amine with the evolution of CO2. (For simplicity TDI may be represented as having only one isocyanate group and may thus be represented generically as R-NCO):

R-NCO + H20 yields RNH-COOH which yields R-NH2 + CO2

The primary amine so produced will react further with excess TDI with the formation of a urea derivative:

R-NH2 + RNCO yields RHN-CO-NHR

TDI also reacts vigorously with all organic compounds containing reactive hydrogen atoms, especially where the hydrogen atom is attached to oxygen, nitrogen or sulfur. -OH, -NH and -SH groups all occur abundantly in protein so that TDI will react and combine with a variety of sites on the living protein molecule to form addition compounds, which are themselves reactive, with a tendency to form further addition compounds and to polymerize. Such addition reactions can denature protein, form abnormal cross-linkages, and generally disorganize the protein so that it will lose its normal function, be it structural or enzymatic. Its reactivity with protein can account for its potency as a sensitizing agent in man in the immunologic sense, for the TDI-conjugated or TDI-modified protein can act as an antigen. [24]

Thus in the human toxicology of TDI one is concerned with two classes of reaction: that of primary irritation, toxicity or "pharmacodynamic action" [24] to which all exposed persons are susceptible to some degree, and that of the sensitization reaction, "hypersensitivity response" or "allergic response" to TDI, at much

lower exposure levels than those necessary to evoke the primary reaction, in those persons who have become sensitized or "allergic" to TDI during earlier exposure. Some believe [24,25] that certain persons in any population, those with atopy or an innate predisposition to allergy in general, are more susceptible to sensitization to TDI. The prevalence of this phenomenon of atopy is variously estimated as between 1.5 and 5% [25] to as high as 15% [26] in various populations studied.

(b) Observed Effects

TDI is a powerful irritant to all living tissues with which it comes into contact, and especially to the mucous membranes of the eyes, the gastrointestinal and the respiratory tracts. [3,6,7,11] Probably because it reacts avidly with all proteins, its direct effects are, in accidental or occupational exposure of man, virtually confined to its reaction upon the surface membranes of the body. Systemic absorption of TDI, with toxic effects upon internal organs, has not been reported in man, except in the special sense of the hypothetical immunologic involvement of the reticuloendothelial system in those subjects who become sensitized to TDI.

In the occupational exposure of man to TDI in the vapor or aerosol phase, its impact upon the respiratory tract is overwhelmingly the most important. Its topical effects upon other tissues will be briefly considered first.

(1) Skin: Liquid TDI produces a marked inflammatory reaction on direct skin contact. [27] However, perhaps because of TDI's known irritant properties with resultant caution in handling, chemical dermatitis has not presented much of a problem to industry. [20] Although sensitization of the skin to TDI undoubtedly does occur, [28] it also is uncommon and rarely produces an industrial problem. [20] There seems to be little relation in individuals between skin sensitivity and bronchial or respiratory sensitivity to TDI. [29]

TDI vapor and aerosol may also cause skin irritation. [27] It appears that this occurs only at higher levels than those causing respiratory effects.

(2) Conjunctiva: Splashes of liquid TDI into the eye will cause severe conjunctival irritation and lacrimation. No reports have appeared in the industrial medical literature of permanent corneal or ocular damage resulting from such incidents however.

In chronic exposure to low concentrations of TDI vapor or aerosol smarting, burning or pricking sensations in the eyes are a common symptomatic feature. [30] In some of the earlier clinical reports [6] of TDI toxicity such eye symptoms were reported as preceding respiratory symptoms by some weeks, but in other cases the upper respiratory symptoms were the first to appear and eye irritation only occurred on heavier exposure. [13]

(3) Gastrointestinal Effects: According to Wolf, [31] accidental ingestion of liquid TDI has not been reported in the industrial medical literature. However, nausea, vomiting, and

abdominal pain have frequently been described as part of the symptom complex following inhalation of TDI vapor or aerosol, especially in the early European reports. [6,10] Epigastric and hypochondriac pain may be secondary to the paroxysmal or persistent cough associated with inhalation. [6]

(4) Respiratory Tract Effect: Inhaled TDI vapor or aerosol in sufficient concentration has a primary irritant effect upon all parts of the respiratory tract with which it comes into contact: nose, nasopharynx, larynx, trachea, bronchial tree, and bronchiolar system. [6,9,10] Subjects exposed enough to develop symptoms complain of burning or irritation of the nose and throat, of a choking sensation, and of cough which may be paroxysmal and may or may not be productive of sputum. This may be associated with retrosternal soreness and general chest pain.

All exposed persons are susceptible to the foregoing effects, with the usual individual variations in degree. These effects are variously referred to as "primary irritation", "pharmaco-dynamic effects", [24] or "overdose response" or minimal response. [32] They have been likened to and sometimes mistaken for the effects of a coryza or upper respiratory tract infection. [6]

If the concentration of TDI vapor or aerosol is high enough the effects may progress to a chemical bronchitis with severe bronchospasm associated with a sensation of oppression or constriction of the chest and with auscultatory rales and rhonchi. [33] This type of response, described as "asthma" [34] or as an "asthmatic syndrome", [17] has

been termed the "pharmacologic overdose response" according to Dinman in a review by Wolf [31] and the contention of most recent authors is that all persons are susceptible to it, even on first exposure to TDI [28], if the inhaled dose is sufficiently high. [26] Some cases have been classified as a chemical pneumonitis [28] and have followed a clinical course similar to that of bronchopneumonia from bacterial infection. In such cases secondary bacterial invasion of the inflamed bronchial tree and lungs is very likely to occur. Pulmonary edema may complicate the picture. The early German literature contains many descriptions of individual cases with the above features. [7,9,10] However, it is not always clear whether these cases were of the "pharmacologic overdose" category or involved "hypersensitivity reactions" (see below). Additional symptoms reported [35] in these acute cases include headache, insomnia, and in one outbreak the acute neurological symptoms of euphoria and ataxia. In one other incident of acute over-exposure [36] 4 out of 24 workers developed anxiety neurosis with depression and even paranoid tendencies in addition to the characteristic respiratory symptoms.

(5) Sensitization: From the earliest reports of respiratory toxicity of TDI [6] a picture began to emerge, in contrast to the above acute symptoms, of respiratory problems of insidious onset, becoming progressively more pronounced with continued occupational exposure, over a period of days to months. A part of this insidious symptomatology observed by Munn [20] and by Peters and Wegman [JM Peters and DH Wegman, written communications, April 1973] is nocturnal

dyspnea and/or nocturnal cough. The ultimate clinical picture was that of asthmatic bronchitis. There was strong clinical and circumstantial evidence that this gradual process reflected progressive sensitization of the subject to TDI. Often, when the respiratory illness had become incapacitating and the worker had been hospitalized or otherwise removed from exposure, on return to work and renewed exposure to TDI, sometimes at a much lower level than previously, an acute and severe asthmatic attack would ensue almost immediately or within a few hours. [20] Another pattern is that of the worker who had only minimal upper respiratory symptoms or no apparent effects at all from several weeks of low level exposure, but then suddenly developed an acute asthmatic reaction to the same or slightly higher level.

The asthmatic reaction to TDI of the sensitized individual can be very severe indeed and may result in status asthmaticus, which has been fatal in a few cases. [16] In one German case, [10] the autopsy findings were severe bronchitis with marked tissue eosinophilia and acute pneumonitis with inflammatory edema of the lungs.

The nature of this sensitization process is still controversial. Many authors [17,20,26,29,34] have referred to it as allergy and to the respiratory response in sensitized subjects as true asthma, comparable to the allergic asthma excited by pollens and other exo-allergens. [25,26,34] Sweet [29] has suggested an idiosyncratic type of reaction on the grounds that many apparently TDI-sensitized persons give no history of collateral allergic disease.

The question of mechanism is undoubtedly complicated by the fact that TDI itself can cause histamine release in the bronchial tissue as part of its irritant effect and that there are a few cases on record of asthmatic response on first exposure to relatively high doses of inhaled TDI. [26,28,33]

Support is lent to the allergic nature of the phenomenon by the observation [7,11,16,17] of significant eosinophilia in many cases of hypersensitivity reaction and the demonstration [37] of circulating antibodies to TDI or to TDI-animal protein conjugate in TDI workers with symptoms suggestive of TDI sensitivity. Further evidence is the demonstration [32] of lymphocyte transformation in TDI-sensitized workers induced by TDI-conjugated proteins.

The question of whether all persons are potentially sensitizable to TDI, or only those with atopy, is a point not yet resolved.

There is a third type of respiratory system response to inhaled TDI which is currently under active investigation, that of both an acute and chronic diminution of ventilatory capacity, commonly measured by a decrease in FEV 1.0 (the volume of air expelled in the first second of forced expiration) in most or all workers exposed to TDI at very low levels in the absence, in many cases, of overt symptoms of respiratory difficulty. [38-44]

This type of effect was first described in an Australian study [38] of 14 employees in a small polyurethane foam producing plant employing TDI, in which there had been an outbreak of respiratory complaints. In this study half the subjects, who were all cigarette

smokers, also showed bronchial hyperreactivity to histamine aerosol. This may be a manifestation of an asthmatic tendency.

More extensive and prolonged studies [39-45] have been conducted since in the U.S. and in England. These researchers have been able to demonstrate not only an acute diminution in FEV 1.0 in TDI workers over the course of a working day, but some cumulative decrease over the course of a working week (ie Monday to Friday); a further decrease of FEV 1.0 over a follow-up period of more than 2 years, in excess of the predicted decrement due to aging alone, has been shown by Peters and his group. [39-44]

(6) Other Chronic Respiratory Effects: The acute respiratory effects of TDI have often been completely reversible, [15] that is the subjects have made a complete recovery on removal from further exposure and with appropriate medical treatment. However, some cases in the earlier German literature continued in TDI employment, suffered recurrent acute attacks of asthmatic bronchitis or bronchopneumonia, and were finally totally incapacitated or died with chronic bronchitis, emphysema and cor pulmonale, attributed to the prolonged effects of TDI. [7,8,10]

An implication of the work of Peters and associates and of Adams [39-45] is of cumulative impairment of lung function as long as TDI exposure continues. Whether this impairment would be reversible on reduction or cessation of exposure is not yet known. [45]

Twenty-two workers who had been employed in industrial processes using TDI were studied on the average 2 1/2 years after cessation of

exposure and almost half had developed simple or mucopurulent bronchitis within six months of the incident and three simple bronchitics claimed that their bronchitic symptoms had been made worse. [35]

(7) Carcinogenesis, Teratogenesis, and Mutagenesis: No evidence that TDI or other isocyanates have any carcinogenic, teratogenic or mutagenic effects in man has been found.

(8) Radiological Manifestations: In most of the clinical reports in the literature where chest X-rays have been taken of acute or subacute cases of TDI poisoning, the results have been described as either negative or nonspecific. [46,47] Where the cases have been of a severity amounting to bronchopneumonia or pulmonary edema corresponding radiological changes have been reported.

One paper addressed specifically to pulmonary opacities resulting from diisocyanate exposure [47] describes evidence of consolidation in the chest radiographs of 4 out of 7 cases examined, which cleared moderately quickly on removal from exposure and appropriate medical treatment.

Epidemiologic Studies

There are several reports on groups of cases of TDI toxicity for which at least some environmental data, that is estimates or measurements of TDI levels in the work atmosphere, are available.

Twelve workers in an automobile plant were engaged in making crashpads of polyurethane foam, prepared in situ from liquid TDI and other ingredients. [15] During an initial period of about three weeks

the men were exposed to air levels of TDI not exceeding 0.01 ppm estimated by the "du Pont method"; this method was the Ranta method, later described by Zapp. [48] During this time there were no complaints or symptoms of illness in the work force. For the next week the air level of TDI rose to 0.03 - 0.07 ppm because of an increase in the volume of the manual mixing operations, and during this period the entire work force of 12 complained of mild to severe respiratory symptoms including coryzal symptoms, continuous coughing, sore throat, dyspnea, fatigue, and night sweats. As a result the operations were once more reduced to the original scale and the TDI levels, measured from time to time, fell to the 0.01 to 0.03 ppm range. During the ensuing 3-1/2 months there were no further respiratory symptoms or complaints from the same work force. None appeared to have suffered any persistent or permanent effects from the intervening week of higher exposure, and none appeared to have become sensitized to TDI during that period.

In a plant producing slabs of polyurethane foam by a continuous process air levels of TDI and the workers' health were studied for a period of 2-1/2 years. [17] More than 1,000 air samples were analyzed. The extreme range of air level values at various sites and times was a reported 0.00 to 3.0 ppm. The range of average values for the various sites was given as 0.00 to 2.6 ppm. It is impossible to determine a time-weighted average level from the data published, but monthly average levels throughout the plant were reported to be in the 0.00 to 0.15 ppm range. During the study period a total of 83

illnesses attributed to TDI required medical attention. These cases were broken down as follows: upper respiratory infection 54; tracheitis 11; bronchitis 9; and bronchial asthma 9. The total work force at risk was not given. Of the 83 cases, 7 were hospitalized for from 1 to 49 days. A large number of minor cases, in addition to the 83, also arose. Most cases of illness appeared in workers between the third and fourth week from commencement of exposure. There was abundant evidence of sensitization of workers. [17]

In 1962 Elkins and his co-workers published a report [49] on experiences with TDI in 15 plants in Massachusetts from 1957 through 1962. The authors' tabulation of their results is reproduced in Table XIII-2. In conclusion they suggested 0.01 ppm as "a not unreasonable limit" for TDI.

In 1963, from Australia, Gandevia published a study [38] of respiratory ventilation measurements (FEV 1.0) in a group of 15 out of 20 men exposed to approximately 0.9 ppm TDI (estimate). The results on individual men were pooled and decreases in mean FEV 1.0 of the order of 0.18 liter were detected during the course of a single working day, with some cumulative deficit from Monday to Friday and possible further cumulative deficit over a period of two working weeks. In individual cases such daily decrease in FEV 1.0 was prevented by the prophylactic administration of theophylline, a bronchodilator drug, tending to confirm that the acute ventilatory change was due to bronchoconstriction. In addition to these changes

in spirometric measurements, several of the work force reported mild "bronchitis and asthma" and there were two severe cases.

In 1964 from New Zealand environmental measurements and cases of toxicity were reported from 3 plants. [50] In one plant where polyurethane foam was produced in a batch molding process and the atmosphere TDI levels ranged from 0.003 to 0.0123 ppm, three cases of respiratory sensitization occurred during one year. In another similar plant the TDI air levels ranged from 0.005 to 0.100 ppm; two mild cases of coryzal symptoms, one case of possible sensitization, and one case of an acute asthmatic attack on heavy exposure with no evidence of sensitization arose. In a third plant where polyurethane foam was produced by a continuous slab process, atmospheric TDI levels ranged from a reported 0.000 to 0.018 ppm and two cases of very mild coryzal symptoms without evidence of sensitization occurred in men who wore canister-type masks on the job. The total work-force at risk in any of these plants were not reported.

In England in 1962 Williamson [51] studied 18 workers exposed to levels of TDI generally below 0.02 ppm, apart from one brief excursion to at least 0.2 ppm for not more than 10 minutes following an accidental spill. The workers were studied over a period of 14 months and were interviewed, examined, and their FEV 1.0 or FVC (forced vital capacity) measured in four series of tests at roughly 6-month intervals. On each occasion the spirometry was performed on each subject twice daily, early and late in the work-shift, for a full working week. No significant differences in ventilatory measurements were

detected, within a work-shift, from Monday to Friday, or over the 14-month duration of the study. During the study period none of the men suffered illness attributed to TDI and none developed symptoms suggestive of TDI sensitization.

In a further part of the same study six subjects who had become sensitized to TDI were described. [33] Four of these came from a work force of 99 and became sensitized over a period of 18 months in an atmosphere in which the TDI level was not observed to have risen above 0.02 ppm. The author suggested that these subjects were sensitized by exposure to the occasional short periods of higher TDI concentration occurring after spillages. During one such accident a level of 0.2 ppm was measured but fell to less than 0.005 ppm after ten minutes. All six sensitized subjects displayed symptoms of asthma or bronchitis and all demonstrated marked decrease of ventilatory capacity (FVC and FEV 1.0) during and for a while after such episodes. Some of these workers were also exposed occasionally to similarly acting methylene di-(4-phenylisocyanate) (MDI) but the atmospheric level of this isocyanate never reached 0.02 ppm.

Also in 1964 a study of 7 men in the U.S. who developed acute respiratory symptoms after exposure to TDI in a plastic varnish was published. [52] Only three measurements of TDI in air were made and these showed 0.08, 0.10, and 0.12 ppm. In all cases, symptoms developed within half an hour to 3 weeks following first known exposure. All 7 men had cough and dyspnea and 4 had hemoptysis. Vital capacity and FEV 1.0 determinations were made in all 7 men shortly

after the symptomatic exposure, and again after 2 to 3 1/2 months. All but 2 gave higher values on the second occasion of measurement than during the immediate post-exposure period. Four had a third measurement of FVC and FEV 1.0 at 22 months. Two of these showed a decrease in ventilation, one of whom had radiological evidence of emphysema, not necessarily related to TDI. At the 22-month examination there was evidence from responses to a questionnaire that 4 of the 6 had become sensitized to TDI. [52]

From Canada in 1965 came a report [36] that 12 out of 24 maintenance workers employed in cleaning up a TDI plant had developed symptoms of TDI toxicity. From 3 to 7 days after commencement of exposure these men experienced symptoms including coryzal symptoms, laryngitis, sore throat, tracheitis, bronchitis, and pneumonitis. Six required hospitalization. Four patients developed anxiety neuroses, psychosomatic complaints, depression, and even paranoid tendencies. One year following the incident these men had not returned to full-time employment. One additional case exhibited a delusional psychosis during the period of acute dyspnea, but this was ascribed to the corticosteroid therapy he was receiving. No measurements of TDI in the environment were made, but this series is cited because of the unusual psychological symptoms reported. In addition, there were 5 workers who experienced respiratory irritation from inhaling pyrolysis fumes from cured polyurethane foam during a hot lamination operation. One of these workers appeared to have developed hypersensitivity. Air

samples were found to contain 3 ppm TDI prior to the installation of local exhaust ventilation. [36]

In 1968 a U.S. study was published [32] of 26 workers exposed to a range described as 0.0 to 0.24 ppm isocyanates and a range of median values reported as 0.0 to 0.033 ppm, over an 11-year period, in research, development, and production of isocyanates, presumably including TDI. A further 18 workers with no known exposure were studied as controls. The exposed workers were classified in three clinical groups: "minimal response" (5), "overdose response" (16), and "sensitized" (5). Minimal response refers to minimal symptoms of mucous membrane irritation, and overdose response to moderate to marked signs of chemical irritation of the respiratory tract. The figures imply a sensitization rate of almost 20%.

Four of the 5 sensitized subjects showed a clearly positive lymphocyte transformation test (an indication of an immunologic allergic sensitization) using TDI-human serum albumin conjugate as the antigen. The remaining sensitized worker who failed to give this lymphocyte response had not been exposed to isocyanates for the 5 years preceding the test. [32]

Peters and his group have been involved in a long-term study of ventilatory measurements on workers repeatedly exposed to TDI at levels well below the current TLV of 0.02 ppm. [39,41,44] In the first study published [39] 38 workers were examined, 7 of them female, before beginning work on Monday mornings, on Monday afternoons, and on Friday afternoons. The TDI levels in the plant atmosphere were

reported in the range 0.0001 to 0.0030 ppm. The air data were summarized very briefly and only one pair of values for each of two sites was given for each of two months during 1966, the first year of the study. The possibility that there may have been brief excursions above these low levels during accidental spills or plant maintenance was not mentioned by these authors. Several indices of pulmonary function were recorded including Forced Vital Capacity (FVC), FEV 1.0, Peak Flow Rate (PFR), and Flow Rates (FR), at 75, 50, 25 and 10% of vital capacity (FR 75%, etc). In summary, they found significant decreases in the means of all 38 workers' FVC, FEV 1.0, PFR, FR 50%, and FR 25% during the course of the first working day of the week. Thirty-four of the same workers were reexamined on the following Friday also and it was found that their mean FVC had returned to baseline (Monday morning level), the mean FEV 1.0 was still depressed, and the mean of their expiratory flow rates was more depressed. The few workers with respiratory symptoms showed greater decrease in FEV 1.0 than the workers without symptoms.

A follow-up study of 28 of the above 34 workers still accessible was performed six months later. [41] A comparison of the Monday morning spirometric values of December 1966 with Monday morning of May 1967 was made. The TDI levels recorded for the Monday in May 1967 ranged from a reported 0.0000 to 0.0120 ppm, in contrast to 0.0001 to 0.0030 ppm found in 1966. [39] Only 2 samples were taken from each of four working sites.

As a group the 28 workers showed a significant decrease in mean FEV 1.0 (0.14 liter), a 4.5% decline in the ratio FEV 1.0/FVC, and a significant decline in flow rates, over the six-months interval. This decline in group mean FEV 1.0 was much greater than the predicted decline due to aging alone, taking smoking habits, height, sex, and age into consideration, and suggests a cumulative effect of exposure to TDI. [41]

Eight of the workers had cough and phlegm as determined by a respiratory symptoms questionnaire, and these 8 showed a greater mean decline of FEV 1.0 during the course of a single working day and over the six-month interval than the whole group. The effect of smoking was also investigated, but no significant differences in the decrease of FEV 1.0 over the six months between current smokers and nonsmokers was found. [41]

A group of 18 welders not exposed to TDI was studied by the same methods as controls and no significant changes in ventilation were detected over a working day. The investigators themselves underwent spirometry and showed no changes in FEV 1.0 over the course of a day spent in their lab but on days spent at the TDI plant they showed a decline in FEV 1.0 similar to that of the workers. [41]

Twenty-five of the 28 workers studied in the preceding two surveys have been examined a third time, about one year after the first. [44] There was no further decline in group mean FEV 1.0 during the second 6-month interval.

Twenty of the original cohort of workers had by 1969 been followed at 6-monthly intervals for a total of two years (five series of examinations). [42] During the second year of follow-up the decline of FEV 1.0 had continued at a mean annual rate of 0.11 liters, which exceeds the predicted rate of decline due to aging alone. It is confirmed in this report [42] that acute daily changes in ventilatory capacity continued to occur in workers after two years and more continued exposure to TDI at low levels, that workers with respiratory symptoms showed a greater acute and cumulative response to TDI than asymptomatic workers, that there was a strong correlation between one-day change and cumulative effect, and that the effect of smoking does not seem important.

In England 175 process and maintenance workers in two TDI plants have been studied spirometrically, annually, for five years. [45] The TDI levels in the plant atmosphere were monitored frequently throughout the 24 hours and rarely exceeded 0.02 ppm. The group mean annual deterioration of FEV 1.0 and FVC over the five years has significantly exceeded the predicted rate of decline, suggesting cumulative diminution of lung function. However, when the readings of 114 men were examined individually it was found that only 5 showed deterioration in FEV 1.0 and FVC, 3 showed decline of FEV 1.0 only, and 8 in FVC only. Presumably, therefore, 98, or 86% of the workers studied individually were not significantly affected in ventilatory capacity. This suggests that changes in the group mean values may have been largely influenced by a hypersusceptible (sensitized)

minority of the work force. Another qualification of Adams' results which he made [45] is that they are based upon comparisons with predicted values from a North American population and such comparison may not be valid in northwest England. He is seeking to eliminate this possible bias by performing a comparison study on men in a nearby plant where there is no TDI.

The results obtained by Peters and his group [39,41,44] are at variance with those reported earlier by Williamson, [51] who found no significant change in FEV 1.0 in 18 workers examined spirometrically on a similar basis to Peters' subjects. The discrepancy may be explained by possible differences in the levels of exposure to TDI. Judging from the published reports, it would appear that measurements of TDI in the air were made more regularly and frequently in Williamson's study [51] than in Peters'. [39-44] The figures that Peters and associates gave are all very low, well below the current standard of 0.02 ppm, but it is possible that at various times there may have been much higher excursions [53] so that overall exposure of Peters' workers may have been higher than that of Williamson's. Another distinction between the two studies is that Williamson treated 6 subjects who were definitely sensitized to TDI separately. [33] It is not clear whether at least four of these became sensitized in the same plant where the 18 with negative results were exposed. As Peters and co-workers [39-44] reported no individual readings, it is possible that the changes in group mean values were largely or entirely brought about by major changes in a sensitized subgroup. They did report that

those workers with respiratory symptoms had greater daily and longitudinal declines in FEV 1.0 than the asymptomatic workers. This second possibility is supported by Adams' results. [45]

Animal Studies

The first animal studies with TDI are attributed to Gross and Hellrung in Germany in 1941. Their research was not published but they are cited by Friebel & Luchtrath [54] as having exposed dogs, cats, rabbits, and guinea pigs to high concentrations of Desmodur-T (a commercial mixture of the 2,4 and 2,6 isomers of TDI) ranging from 14 to 1400 ppm. The lower concentrations rapidly caused respiratory tract irritation indicated by catarrh, cough, and increased rate of respiration; at the higher concentrations there were bronchitis, pneumonia, and pulmonary edema.

Fuchs and Valade [6] supplemented their report on cases of human occupational poisoning with an account of some animal experiments. They found that subcutaneous injections of Desmodur-T at 10-500 mg/kg had no apparent systemic toxic effect in guinea pigs. They found that 5 cu mm of Desmodur applied on the normal or on the abraded skin of rabbits' ears caused no local lesions or systemic toxicity. Dogs, rabbits, and guinea pigs were exposed by inhalation for an unstated period of time to concentrations equivalent to 140 to 280 ppm TDI. The reactions were surprisingly mild in view of the high concentrations of TDI claimed: sneezing, lacrimation, and increased respiratory rate. All signs rapidly disappeared on cessation of exposure and all the animals survived. On necropsy they were found to

have patchy pulmonary congestion and edema, and in one guinea pig, bronchopneumonia.

In 1955 Friebel and Luchtrath reported [54] experiments on guinea pigs which were exposed to TDI by intratracheal injection, and by inhalation of both aerosol (120 ppm) and vapor (50-80 ppm) of TDI. Some of the guinea pigs had been deliberately sensitized to egg albumin a year before and had been subjected to several asthmatic attacks by challenge with egg albumin aerosol. Despite this added experimental stress, these investigators were unable to reproduce in these animals the respiratory sensitization to TDI and the allergic asthmatic response which was already a well-recognized feature of human occupational cases. They concluded that the effect of TDI on the respiratory tract of the guinea pig was purely one of primary toxic irritation. In addition to the lung changes reported by earlier workers they described a bronchiolitis obliterans after repeated exposures.

The first animal studies in the U.S. are those reported by Zapp in 1957. [48] He employed rats, guinea pigs, dogs, and rabbits and exposed them to much lower concentrations of TDI by inhalation, for longer periods of intermittent exposure, ie 1-5 ppm for 10-79 six-hour exposure. In most cases the exposure levels were measured by analysis of air samples from the exposure chambers, whereas the earlier workers had all calculated their exposure levels and probably estimated them far too high.

The microscopic changes in Zapp's experiments [48] were those of tracheobronchitis, bronchitis, emphysema, and bronchopneumonia, according to the exposure level and number of exposures. None of the animals showed an asthmatic response or evidence of sensitization.

Despite this negative finding, the author predicted that asthmatic attacks would result in a significant proportion of men exposed to inhalation of the vapors and that skin sensitization might occur in a few exposed to vapor or liquid. These statements are probably based upon the clinical experiences of others and on theoretical considerations. Zapp [48] patch-tested 209 volunteers and was unable to produce any significant dermatitis or evidence of skin sensitization.

On the basis of the positive respiratory tract response of animals exposed to 1 to 2 ppm TDI, Zapp recommended a TLV of 0.1 ppm. [48] He also pointed out that, as the least detectable odor of TDI by 12 out of 24 men was 0.4 ppm, analytical monitoring of the workplace is essential.

Zapp also determined the oral LD50 for the rat, employing 60 animals by administering graded doses of the undiluted material by stomach tube. His estimate of the LD50 was 5800 mg/kg. Necropsy revealed a corrosive action on the stomach as well as possible toxic effects on the liver. [48]

Some five years later the quantitative aspects of Zapp's inhalation studies were challenged in a German paper by Henschler and co-workers. [55] These authors performed similar inhalation

experiments on rats and guinea pigs, exposed to 10, 5, 1, 0.5, and 0.1 ppm of a 65/35 technical mixture of the 2,4 and 2,6 isomers of TDI. Their results were qualitatively similar to Zapp's except that they observed approximately the same pathological and lethal effects at one tenth the exposure levels reported by Zapp.[48] They also conducted experiments on human volunteers and estimated the odor threshold of TDI at 0.05 ppm in contrast to Zapp's much-quoted figure of 0.4 ppm. Henschler and his co-workers [55] attributed this apparent discrepancy entirely to differences in the method used for analyzing the TDI content of the air. The method used by Zapp, that of Ranta, is not specific for TDI but also measures its breakdown products. Henschler et al used the method of Ehrlicher & Pilz [56] which they claimed is more specific and accurate for TDI. They implied that all Zapp's quantitative conclusions were wrong by a factor of 10, and used this argument to vindicate the then newly reduced Threshold Limit Value of 0.02 ppm. They also failed to produce any evidence of respiratory sensitization or other allergic reaction in guinea pigs on prolonged intermittent exposure to TDI.

The same year additional acute inhalation studies on mice, rats, guinea pigs, and rabbits were published. [57] These animals were given a single 4-hour exposure to TDI at 0.1, 1.0, 2, 5, 10, 20 or 34 ppm. The surviving animals were killed at 28 days. The Marcali method [58] was used for measuring the TDI in the chamber air. The results were entirely consistent with those of earlier studies, ie TDI acts as a corrosive agent with irritant manifestations proportional to

the exposure level, and the effect is primarily on the trachea and larger intrapulmonary air passages. These authors estimated the 14-day LC50 (the concentration which would kill half the test animals within 14 days, following a single 4-hour inhalation exposure) of TDI for several species. Their results were: mouse 9.7 ppm, guinea pig 12.7 ppm, and rat 13.9 ppm.

In 1965 a study of the toxicity of chronic intermittent low level exposure to TDI in rats, rabbits, and guinea pigs was published. [59] The TDI level was 0.1 ppm in all experiments. Rabbits and rats received 38 six-hour weekly exposures and rabbits, rats, and guinea pigs received 58 six-hour daily exposures. The chamber air was analyzed for TDI by the Marcali method. [58] The results were again consistent with those of earlier studies, described above, ie, changes indicative of respiratory irritation were found.

In recent years a totally different aspect of the effects of TDI in animals, the immunochemical or immunological aspect, has been studied, in the hopes of elucidating the nature and mechanisms of sensitization in man. In one such study, [24] TDI antigens were produced by conjugating TDI with egg albumin and the immunochemistry of these antigenic conjugates was studied. In animals exposed to TDI by inhalation, TDI-specific antibodies were demonstrable in the blood.

In later research [60] the effects of prior administration of alloxan, which generally depresses immunologic reactivity, and of insulin and pertussis vaccine, which both enhance it, upon rats exposed to 1 ppm of TDI for 10 hours were studied. The results as

reported appear to be equivocal but in the opinion of the authors, Thompson and Scheel, [60] militate against an immunologic basis for the lung damage caused by inhaled TDI in these animals, and support a chemical damage mechanism.

More recently respiration studies [61] to elicit any evidence of sensitization were conducted on guinea pigs and rhesus monkeys, both species being chosen because of their immunological similarities to man. These animals were exposed to levels of TDI ranging from 0.01 to 5 ppm for three six-hourly periods, and then reexposed three weeks later, together with previously unexposed animals as controls, to 0.02 ppm TDI, and their respiratory patterns recorded by plethysmography on a telemetric strain-gauge device. Animals previously exposed to high levels (2 - 5 ppm) of TDI did show increased reactivity on reexposure to TDI at levels as low as 0.02 ppm, to which the control animals did not respond. They also showed evidence of skin sensitization to TDI by patch testing. Serological tests for sensitization were, however, negative. Guinea pigs preexposed to only 0.5 ppm TDI showed no greater sensitivity on reexposure at 0.02 ppm, suggesting that there is a sensitization threshold for these animals, somewhere between 0.5 and 2.0 ppm TDI. The monkeys, which showed great sensitivity to TDI at levels as low as 0.4 ppm, gave however no evidence of sensitization on reexposure, or of serological changes indicative of sensitization. The authors concluded [61] that although gross exposure to TDI may cause greater sensitivity of the respiratory system of these animals to subsequent exposure to lower levels of TDI, this may not involve

sensitization by an allergic mechanism, but by some other mechanism such as chemical damage.

Correlation of Exposure and Effect

There is little doubt that the primary irritant or pharmacodynamic effects of TDI in man are dose-dependent, both in the proportion of exposed subjects who will be affected and in the severity of those effects.

In the early years of industrial use of TDI, when its hazards were not fully appreciated, relatively high environmental levels of TDI were encountered and very high proportions of the exposed workers were affected. Many individuals, on first exposure, developed severe asthmatic bronchitis or bronchopneumonia. [7,9,10,28,36] Although few environmental measurements of TDI were recorded in these earlier incidents, from the descriptions of working conditions and of the physical plant it may be calculated that levels were high and much in excess of the current standard of 0.02 ppm.

With the development in the TDI industry of mechanization, automation, and deliberate hygiene controls, ambient TDI levels have been significantly reduced and both the incidence and the severity of primary respiratory irritation of workers have declined. [15,17,49,62]

Once individuals are sensitized to TDI, however, it is generally agreed that for them there is little or no dose-response relationship, or at least no measurable dose-response relationship. Sensitization in many cases appears to be progressive with each reexposure until ultimately the individual may respond severely to the minutest trace

of TDI, below the limit of measurability. For the highly sensitized individual it is doubtful whether there is a measurable safe level for TDI below which that individual is completely safe from response. Whether there is a measurable level below which no one will become sensitized de novo is not completely clear from the available evidence to date, although this is the intended basis for the TLV of 0.02 ppm adopted by the ACGIH in 1961. [49] Lack of clarity on this crucial point arises from the fact that in none of the relevant investigations have continuous recordings of TDI air levels been made. Williamson [33] evidently believes that new sensitization does not actually occur below 0.02 ppm and explains sensitization that does appear as due to brief and unrecorded excursions above that level during accidental spills, etc. If the results of Peters' [39-44] and Adams' [45] studies are interpreted as implying sensitization of a proportion of their subjects, and full reliance is placed on their environmental data as published, then it must be inferred that sensitization can occur at levels well below 0.02 ppm. The issue is further complicated by the still unresolved question as to whether only persons with a constitutional allergic diathesis or atopy are potentially sensitizable to TDI (as believed by Rye [25] and Wolf, [31] among others), or whether TDI is a universal sensitizer at some level of exposure (Skonieczny reported on a U.S. plant which had to shut down in 1958 because the entire work force had become sensitized [63]). For some years persons with a known personal or family history of allergy have been deliberately excluded from certain TDI work-forces

as a matter of precautionary policy, so that different work populations studied may not all be the same in this respect. The weight of opinion of industrial physicians with experience with TDI is that atopic individuals are much more, if not exclusively, prone to sensitization to TDI. [25,31-33,62]