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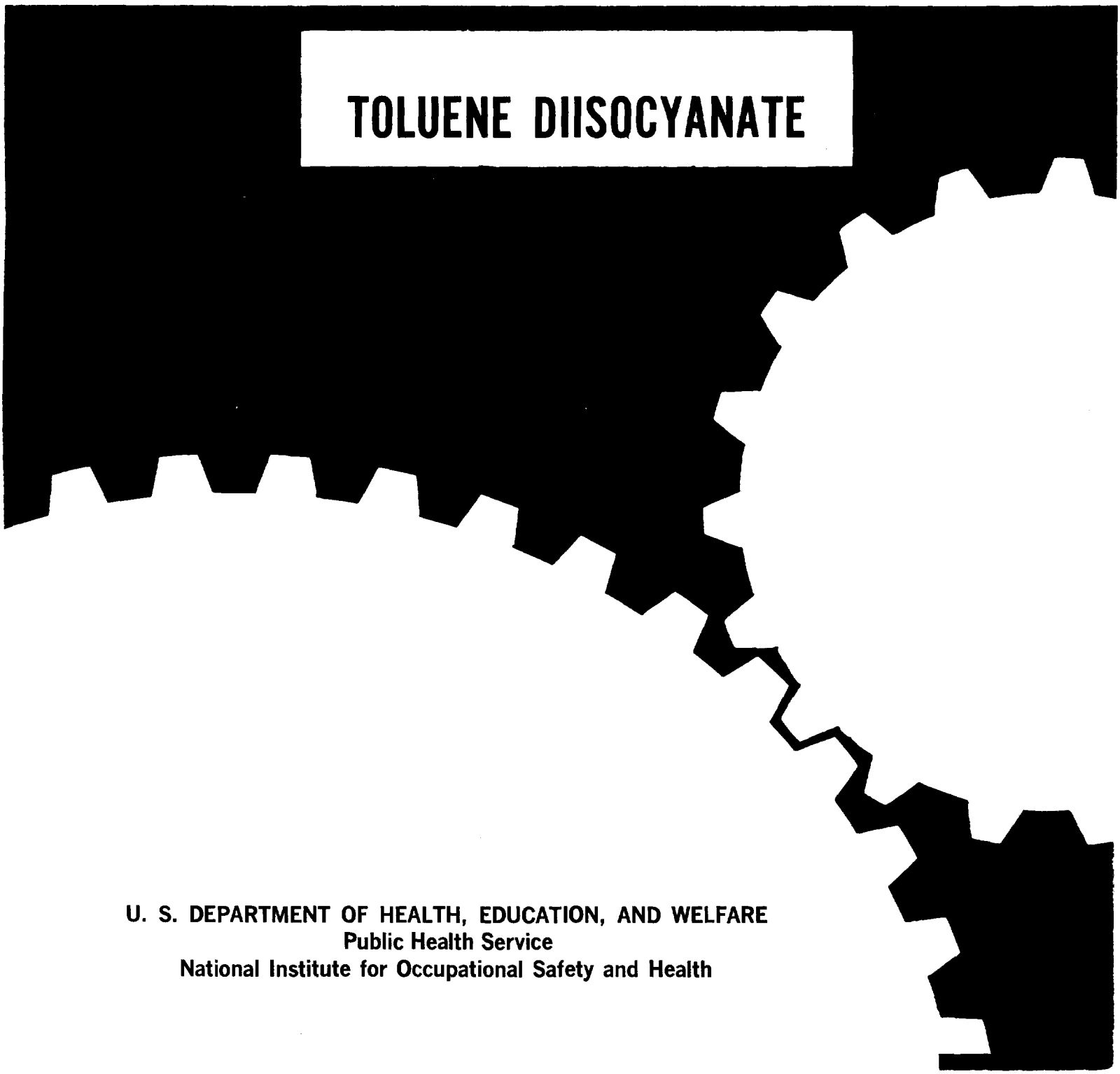
OCCUPATIONAL EXPOSURE TO

TOLUENE DIISOCYANATE



U. S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service
National Institute for Occupational Safety and Health

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OCCUPATIONAL EXPOSURE TO TOLUENE DIISOCYANATE

U. S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
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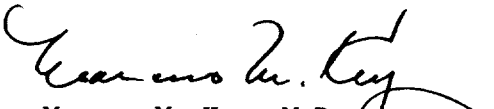
PREFACE

The Occupational Safety and Health Act of 1970 emphasizes the need for standards to protect the health and safety of workers exposed to an ever-increasing number of potential hazards at their workplace. To provide relevant data from which valid criteria and effective standards can be deduced, the National Institute for Occupational Safety and Health has projected a formal system of research, with priorities determined on the basis of specified indices.

It is intended to present successive reports as research and epidemiologic studies are completed and sampling and analytical methods are developed. Criteria and standards will be reviewed periodically to ensure continuing protection of the worker.

I am pleased to acknowledge the contributions to this report on toluene diisocyanate by members of my staff and the valuable constructive comments by the Review Consultants on Toluene Diisocyanate, by the ad hoc committee of the American Industrial Hygiene Association, by Robert B. O'Connor, M.D., NIOSH consultant in occupational medicine, and by Edwin C. Hyatt on respiratory protection. The NIOSH recommendations for standards are not necessarily a consensus of all of the consultants and professional societies that reviewed this criteria document on toluene diisocyanate. Lists of the NIOSH Review Committee members and of the Review Consultants appear on the following pages.



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The Office of Research and Standards Development, National Institute for Occupational Safety and Health, had primary responsibility for development of the criteria and recommended standard for toluene diisocyanate. Tabershaw-Cooper Associates, Inc. developed the basic information for consideration by NIOSH staff and consultants under contract No. HSM-99-72-128. Keith H. Jacobson, Ph.D., served as criteria manager and had NIOSH program responsibility.

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CRITERIA DOCUMENT: RECOMMENDATIONS FOR AN
OCCUPATIONAL EXPOSURE STANDARD FOR TOLUENE DIISOCYANATE

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I. RECOMMENDATIONS FOR A TOLUENE DIISOCYANATE STANDARD

The National Institute for Occupational Safety and Health (NIOSH) recommends that worker exposure to toluene diisocyanate (also called tolylene diisocyanate or TDI) in the workplace be controlled by requiring compliance with the following sections. The standard is designed to protect the health and safety of workers for an 8-hour day, 40-hour week over a working lifetime. Compliance with the standard should therefore prevent adverse effects of TDI on the health and safety of workers except in those workers already sensitized to TDI; they should not be exposed to any amount at all. The standard is measurable by techniques that are valid, reproducible, and available to industry and governmental agencies. Sufficient technology exists to permit compliance with the standard. The standard will be subject to review and will be revised as necessary.

"Exposure to toluene diisocyanate" includes work in any area where toluene diisocyanate is stored, transported, or used.

Section 1 - Environmental (Workplace air)

(a) Concentration

Occupational exposure to toluene diisocyanate (TDI) shall be controlled so that no worker shall be exposed to a time-weighted average (TWA) of more than 0.005 ppm (0.036 mg/cu m) for any 8-hour workday or for any 20-minute period to more than 0.02 ppm (0.14 mg/cu m).

(b) Sampling and Analysis

Procedures for sampling, calibration of equipment, and analysis of TDI samples shall be as provided in Appendices I and II, or by methods shown to be equivalent or better in sensitivity, precision, and accuracy.

Section 2 - Medical

(a) Medical Examinations

(1) Preplacement: A comprehensive physical examination for all workers shall be made available to include as a minimum: medical history, a 14" by 17" chest roentgenogram, total white blood cell count with differential, baseline forced vital capacity (FVC) and forced expiratory volume at one second (FEV 1.0). An absolute eosinophil count on capillary blood is recommended as an additional useful baseline measurement. The history should pay particular attention to the presence and degree of any respiratory symptoms, ie breathlessness, cough, sputum production, wheezing, and tightness in the chest. Smoking history should also be elicited.

If a positive personal history of respiratory allergy, previous sensitization to TDI, or chronic obstructive pulmonary disease is elicited, the applicant shall be counseled on his increased risk from occupational exposure to TDI. Chronic bronchitis, emphysema, disabling pneumoconiosis, or cardiopulmonary disease with significantly impaired ventilatory capacity similarly suggest an increased risk from exposure to TDI. If a history of allergy other than respiratory or of other chronic respiratory disease is elicited,

the applicant should be counseled by the physician that he may be at increased risk of adverse health effects from industrial exposure to isocyanates. At the time of this examination, the advisability of the worker's using negative or positive pressure respirators shall be evaluated.

(2) Periodic: The above examinations (with interim history), with the exception of the chest roentgenogram, shall be provided annually, or as otherwise indicated by professional medical judgment, so long as occupational exposure to TDI continues. Repeat white cell counts with differential and absolute eosinophil counts on peripheral blood may also be useful. An estimation of FVC and FEV 1.0 at the beginning and the end of a work shift within the first six months of employment with TDI is recommended as a useful means of surveillance for TDI reaction. Diagnosis of sensitization to isocyanates, for example from the occurrence of acute asthma, nocturnal dyspnea, nocturnal cough, or eosinophilia, at any time including annual periodic evaluations should exclude the worker from further exposure to isocyanates.

Because of seasonal variations in pulmonary function, it is desirable, for comparison of changes in respiratory function, that the periodic examination of an individual worker be performed about the same time each year.

(3) The periodic medical program required in (2) above should be considered a minimal program. In addition, changes in processes or the occurrence of spills or other emergencies that may

cause changes in normal exposure levels, such as brief, high, excursions, should be reported to the responsible physician, who may require additional medical examinations or other medical procedures. A decrement in FEV 1.0 as measured before commencement of the work-shift and again after completion of the work-shift is a valuable indication of specific reaction to TDI at the operational exposure level. A rise in eosinophil count may also provide evidence of a sensitization phenomenon.

(b) Medical Records

Medical representatives of the Secretaries of Health, Education and Welfare and of Labor, and of the employer, and those physicians designated and authorized by the employee shall have access to medical records, which shall include records of all required examinations. These records shall be kept for 20 years, or, if the employee dies sooner, one year after his death.

Section 3 - Labeling (Posting)

Containers of toluene diisocyanate shall carry a label stating:

TOLUENE DIISOCYANATE

DANGER! HARMFUL IF INHALED

CAUSES BURNS

MAY CAUSE SKIN OR

RESPIRATORY REACTION

Do not breathe vapor.

Do not get in eyes, on skin, on clothing.

Keep container closed.

Use with adequate ventilation.

Wash thoroughly after handling.

First Aid: In case of contact immediately flush eyes or skin with plenty of water for at least 15 minutes while removing contaminated clothing and shoes. Call a physician immediately. If TDI is inhaled, remove the victim to fresh air. If not breathing give artificial respiration; if breathing is difficult, give oxygen. Call a physician immediately.

Work areas where exposure to toluene diisocyanate is likely to occur shall be posted with signs stating:

TOLUENE DIISOCYANATE

(TDI)

DANGER

UNAUTHORIZED PERSONS KEEP OUT

HARMFUL IF INHALED

CAUSES BURNS

MAY CAUSE SKIN

OR RESPIRATORY REACTION

Also, the sign shall give information on the location of respirators.

Section 4 - Personal Protective Equipment and Work Clothing

Subsection (a) shall apply whenever a variance from the standards recommended in Section 1 is granted under the provisions of the Occupational Safety and Health Act or in the interim period during the application for a variance. Until the limits of exposure to TDI

in paragraph (a) of Section 1 are met by limiting the concentration of TDI in the work environment, an employer must utilize, as provided in subsection (a) of this Section, a program of respiratory protection to effect the required protection of every worker exposed.

(a) Respiratory protection

Engineering controls shall be used wherever feasible to maintain TDI vapor or particulate concentrations below the prescribed limits. Appropriate respirators shall be provided and used when a variance has been granted to allow respirators as a means of control of exposure to routine operations and while the application is pending. Administrative controls can also be used to reduce exposure to TDI. Respirators shall be provided and used for nonroutine operations (occasional brief exposures above the limits and for emergencies); however, for these instances a variance is not required but the requirements set forth below continue to apply. In addition, appropriate respirators and protective work clothing shall be provided to and used by employees involved in spray operations, as specified below. Appropriate respirators as described in Table I-1 shall only be used pursuant to the following requirements:

(1) To determine the class of respirator to be used, the employer shall measure the atmospheric concentration of TDI in the workplace when the initial application for variance is made and thereafter whenever process, worksite, climate or control changes occur which are likely to increase the TDI concentration; this requirement shall not apply when only positive pressure respirators

will be used. The employer shall ensure that no worker is being exposed to TDI in excess of the standard either because of improper respirator selection or improper respirator fit.

(2) A respiratory protective program meeting the general requirements outlined in Section 3.5 of the American National Standard for Respiratory Protection, ANSI Z88.2-1969, shall be established and enforced by the employer.

(3) Respiratory protective devices described in Table I-1 shall be either those approved under the following listed regulations or those approved under 30 CFR 11, published March 25, 1972:

Gas mask--30 CFR 13 (Bureau of Mines Schedule 14F)

Type C continuous-flow, supplied air respirator--30 CFR 12 (Bureau of Mines Schedule 19B)

Self-contained breathing apparatus--30 CFR 11 (Bureau of Mines Schedule 13E)

(4) Workers engaged in spraying material containing TDI and others within 10 feet of the spray unit shall wear Type C continuous-flow, supplied air, positive-pressure, impervious hoods. These shall also be worn in field and construction work where TDI is being used in pour, froth, or insulation operations. Use of such respiratory protective equipment does not eliminate the need for adequate ventilation for vapor control, but is additional protection from mist. Gas masks may be used at distances greater than 10 feet from the spray operations if it is shown that the concentration of TDI

Table I-1

Respirator Selection Guide for Protection Against TDI

Multiple of TWA Limit	Respirator Type
Less than 100 X	Gas mask, industrial size combination canister for organic vapors and with high efficiency filter.
Less than 100 X	Type C demand type (negative pressure) supplied air respirator with full face-piece.
Less than 1000 X	For routine (nonemergency) use: Type C continuous-flow (positive pressure) supplied air respirator with full face-piece
Greater than 1000 X (and at lower concentrations)	For emergency use: Self-contained breathing apparatus, in pressure demand mode (positive pressure).

does not exceed 100 times the time-weighted average for continuous work, or 100 times the ceiling for work of short duration, eg 20 minutes or less.

(5) The employer shall provide respirators in accordance with Table I-1 and shall assure that the employee uses them when required. Employees shall be instructed on the use and cleaning of respirators assigned to them, and how to test for leakage.

(b) Protective Work Clothing

(1) Where there is likelihood of skin contact with liquid TDI the employer shall provide employees with impervious clothing. These garments shall be cleaned inside and out each time they are used. Rubber shoes or rubbers over leather shoes shall be worn where there is possibility of foot contact with liquid TDI. Rubbers shall be decontaminated and ventilated after contamination. Leather shoes which have been contaminated with TDI shall be decontaminated or disposed of.

Workers within 10 feet of spray operations, or at greater distances when there is a greater drift of spray, shall be protected with impervious clothing, gloves, and footwear in addition to a supplied air impervious hood.

(2) Chemical workers' goggles shall be worn where splashes are likely to occur.

Section 5 - Apprisal of Employees of Hazards from Toluene Diisocyanate

Each employee exposed to TDI shall be apprised of the hazards, relevant symptoms, and proper conditions and precautions concerning use or exposure. In addition to the better known symptoms, nocturnal dyspnea or nocturnal cough should be mentioned as less obvious symptoms of TDI reaction. The information shall be kept on file and readily accessible to the worker at all places of employment where TDI is manufactured or used. Information as specified in Appendix III shall be recorded on U. S. Department of Labor Form OSHA-20, "Material Safety Data Sheet", or on a similar form approved by the Occupational Safety and Health Administration, U. S. Department of Labor.

Section 6 - Work Practices and Control Procedures

(a) Containers of toluene diisocyanate shall be examined for leaks upon arrival. The containers shall be properly closed at all times when not in actual use. Workers shall wear chemical safety goggles while handling liquid toluene diisocyanate, and protective clothing where contact is likely.

(b) All spills shall be cleaned up promptly in accordance with the procedures described in Part VI. A supply of materials to facilitate clean-up operations shall be kept on hand in all areas where toluene diisocyanate is regularly used.

(c) Waste materials containing toluene diisocyanate can be removed to an isolated area in the open air or with exhaust ventilation and soaked with 10% ammonia-in-water mixture for 24 hours

before discarding. (Caution: Do not tightly close containers used for decontamination, because of a possible increase in gas pressure.)

(d) All employees working in areas where toluene diisocyanate is regularly used shall be instructed in procedures to be used in the event of spills, and shall be instructed in the types of protective equipment to be used during both normal and emergency conditions.

(e) Individuals not having legitimate reasons to be in the TDI work area shall not be allowed access.

(f) Local exhaust ventilation shall be employed wherever possible in indoor operations where toluene diisocyanate is used. Such ventilation shall be designed to prevent the vapor from reaching the breathing zone of workers and shall be maintained in proper working order.

(g) Procedures including fire-fighting procedures shall be established and implemented to meet foreseeable emergency events. Fire fighters shall be cautioned that toxic products, such as hydrogen cyanide, phosgene, and carbon monoxide can be formed from the pyrolysis of polyurethane products, and be prepared to avoid exposure to such products, as well as to TDI. Respirators shall be available for wearing during evacuation if long distances need to be traversed; supplied air respirators shall be available for use where equipment or operations cannot be abandoned.

Section 7 - Sanitation Practices

(a) Washing Facilities

Emergency showers and eye fountains shall be provided in areas

where there is a potential exposure to toluene diisocyanate. They shall be inspected frequently to make sure that they are in proper working condition.

(b) Food Facilities

Food preparation and eating should be prohibited in toluene diisocyanate areas. Smoking in such areas should also be prohibited.

(c) Clothing

Workers should change into work clothing at the start of work, and remove it at the end of the workday.

Clothing on which toluene diisocyanate has been spilled shall be placed in a tightly sealed container until removal for laundering. The employer shall provide for laundering such clothing. If commercial laundering facilities are used, the employer shall inform the launderer of the precautions required in handling such clothing.

Section 8 - Monitoring and Recordkeeping Requirements

(a) Employers shall monitor environmental exposures to TDI based upon the following sampling schedule:

(1) Monthly requirements: Except as otherwise indicated by a professional industrial hygiene survey, breathing zone samples shall be collected at least monthly to permit construction of a time-weighted average exposure for every operation in which there is a potential for exposure to airborne TDI, so that each employee or employee location is sampled at least once every 6 months.

(2) Weekly requirements: If monthly sampling shows the time-weighted average (0.005 ppm) or ceiling (0.02 ppm) values to

be exceeded at any employee station, immediate steps shall be taken to reduce the exposure. Weekly sampling of that station shall be instituted and continued until all samples for two consecutive weeks meet the standard.

Monitoring shall also be performed weekly whenever there is a change in process or in materials used that could result in increased exposure of workers. Such weekly sampling shall be performed until all samples for two consecutive weeks meet the standard.

(b) Records shall be maintained for all sampling schedules and shall include the type of personal protective devices in use, if any, and the sampling and analytical methods in use. Records shall be classified or readily classifiable by employee, so that each employee has reasonable access to records of his own environmental exposure.

These records (and records of all required medical examinations) shall be maintained for 20 years, or, if the employee dies sooner, one year after his death.

II. INTRODUCTION

This report presents the criteria and the recommended standard based thereon which were prepared to meet the need for preventing occupational diseases arising from exposure to toluene diisocyanate (TDI). The criteria document fulfills the responsibility of the Secretary of Health, Education, and Welfare, under Section 20(a)(3) of the Occupational Safety and Health Act of 1970 to "...develop criteria dealing with toxic materials and harmful physical agents and substances which will describe...exposure levels at which no employee will suffer impaired health or functional capacities or diminished life expectancy as a result of his work experience."

The National Institute for Occupational Safety and Health (NIOSH), after a review of data and consultation with others, formalized a system for the development of criteria upon which standards can be established to protect the health of workers from exposure to hazardous chemical and physical agents. It should be pointed out that any recommended criteria for a standard should enable management and labor to develop better engineering controls resulting in more healthful work practices and should not be used as a final goal.

These criteria and recommended standard for TDI are in a continuing series of criteria developed by NIOSH. The proposed standard applies only to the processing, manufacture, and use of TDI products as applicable under the Occupational Safety and Health Act of 1970.

TDI is an irritating material, both in its liquid and airborne forms. It can produce skin and respiratory tract irritation, and can cause sensitization, so that sensitized workers are subject to asthmatic attacks on reexposure to extremely low concentrations of TDI in air.

Environmental limits are recommended to prevent acute and chronic irritation and sensitization of workers but not to prevent a response in already sensitized workers, because available knowledge does not indicate any safe concentration for such persons.

There are conflicts in available epidemiological data. In addition, methods for sampling and analysis of airborne TDI are inadequately sensitive. Thus, further research in these areas is needed in order to demonstrate means by which these recommended standards can be refined.

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 + C02

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]

IV. ENVIRONMENTAL DATA

Sampling and Analytical Methods

Several methods have been developed for determination of isocyanates in air. In the Ranta method described by Zapp, [48] the sample is collected by passing air through a bubbler containing aqueous sodium nitrite and ethylene glycol monoethyl ether (cellosolve). TDI that is present results in the formation of a yellow-orange color, the density of which is read in a photoelectric colorimeter, using a 450 nm filter, and comparing against standards containing known amounts of TDI. This method measures both TDI and TDI urea, the latter being formed in moist air. In the Marcali method, [58] TDI is hydrolyzed to an amine by bubbling the sampled air through a dilute mixture of acetic and hydrochloric acids. The amine is diazotized and coupled with N-1-naphthylethylenediamine. The reddish-blue color produced is measured spectrophotometrically at 550 nm.

There are commercially available field kits employing modifications [64] of the Marcali method. While very useful for routine monitoring, the lowest concentration measurable with their present color standards is 0.01 ppm. If the kits can be improved to accurately measure 0.005 ppm, they should be acceptable to meet the monitoring requirements of the standard.

In England, Reilly [65] developed a test paper method reported to require less analytical skill than the Marcali method. The intensity of a stain produced by TDI on a treated paper is compared

with artificial standards. A continuous monitoring unit has since been developed [66] in which a tape of the treated test paper, through which the sampled air is drawn, is monitored by a lamp and photocell. The signal from the photocell is amplified and used to drive a readout meter and an alarm system operating at a preset level, usually 0.02 ppm. A recorder can also be connected to the monitor. The sensitivity of this continuous monitor was not reported, [66] but the lowest readout point (above zero) is 0.01 ppm.

Belisle [67] has described a field kit employing another method which involves drawing the air sample through an acidified absorber solution in a modified midget impinger containing beads of an ion-exchange resin and glutaconic aldehyde. The color which develops on the resin beads is matched against color standards. Results are reported to check closely with those obtained by the Marcali method.

Other methods or modifications of the Marcali method have been developed. [64,68,70,71] However, the Marcali method, [58] with some modifications, is presently the recommended method, because of its demonstrated reliability and wide use. Most of the information about the health effects of TDI, as well as its environmental control, is related to data obtained by the Marcali method.

The value of a reliable recording continuous monitoring system for TDI is self-evident. If the tests under in-plant situations show good correlations between the new continuous tape monitor [66] and the Marcali method, and adequate sensitivity, use of the monitor should be encouraged.

A gas chromatographic method has recently been developed [72] that is claimed to give much greater sensitivity than existing methods (ER Hermann, written communication, April 1973). If subsequent evaluation bears this out, this method, or a modification thereof, may prove to be a much better method for analyzing airborne TDI, and may resolve the present difficulties in detecting brief excursions of TDI, believed to be of toxicological importance, and still allow sensitive detection of TDI concentrations below the recommended time-weighted average.

Control of Exposures

The engineering control of TDI vapors is, in theory, clear-cut, since the application of established principles of exhaust ventilation will remove them from the work environment. However, although the techniques have been known for a number of years, they are not as widely used as they should be. [73] In practice, these principles are feasible to apply in many, but not all situations in which TDI exposures occur. The data shown in Table XIII-2 testify to the feasibility of controlling levels within the recommended limits. [49] In fixed locations most operations may be successfully enclosed or hooded, with ventilation face velocities of the order of 200 feet per minute being adequate to control vapor concentrations. [14]

There are a vast number of polyurethane products, and there are a great many uses for polyurethanes, some of which require that they be formed in the field under circumstances where the use of conventional exhaust ventilation procedures is difficult. A variety

of operations may be involved, in the field as well as in fixed locations. These include spraying, mixing, foaming, injection, flushing, pouring-in-place, and painting. Many operations require few people; some involve teams consisting of only two or three workers, some possibly even one. Even where exhaust ventilation is feasible for vapor control, operations such as spraying produce high concentrations of isocyanate mist. [74] Adequate protection in such cases requires exposed workers to have the supplementary protection of positive pressure supplied air respirators. [1]

In employing exhaust ventilation for the control of TDI, the design principles presented in Industrial Ventilation - Manual of Recommended Practice, [75] published by the American Conference of Governmental Industrial Hygienists, and Fundamentals Governing the Design and Operation of Local Exhaust Systems, Z9.2-1971, [76] published by the American National Standards Institute, should be followed. Recirculation of exhaust air within the workplace should be prohibited. The exhaust air should be scrubbed before discharge.

Scrupulous housekeeping, with immediate cleanup of spills, removal of all scrap, and proper closure and storage of containers of TDI is of paramount importance. Any large quantity of TDI that is to be disposed of should first be transformed into a urea, by reacting with water, to which a small amount of isopropyl alcohol and ammonia may be added. [2,14] Poor maintenance of equipment and facilities can negate the usefulness of expensive exhaust and general ventilation.

If a satisfactory product can be made, the degree of isocyanate exposure can be markedly reduced by substitution of a less volatile isocyanate compound, such as diphenylmethane diisocyanate (MDI) or a polymeric isocyanate. [77] Because of its lower vapor pressure, MDI concentrations in air will not normally be high enough to cause marked toxic effects, unless the temperatures are significantly raised. However, reactions involved in producing urethanes are exothermic. [17] Thus, elevated temperatures may cause an increase in airborne diisocyanate.

V. DEVELOPMENT OF STANDARD

Basis for Previous Standards

An environmental limit of 0.1 ppm was first proposed as a tentative value, according to Elkins, [49] by Ascue in 1954 on the basis of animal experiments at the Haskell Laboratory and later published by Zapp. [48] The same figure was endorsed by Zapp, in his 1957 paper, [48] and based on the respiratory tract irritation of animals at concentrations of 1 to 2 ppm TDI, employing an arbitrary safety margin of 10- to 20-fold. The analytical method employed in the studies on which these recommendations were based was that of Ranta as described by Zapp. [48]

According to Elkins et al [49], the Threshold Limits Committee of the American Conference of Governmental Industrial Hygienists (ACGIH) adopted 0.1 ppm as a tentative Threshold Limit Value (TLV) in 1956 and as a recommended value in 1959 largely on the basis of Zapp's animal work.

However, reports of adverse effects (respiratory sensitization and asthma-like phenomena) found in a number of work populations in different countries continued even though a TLV of 0.1 ppm had been observed. This and the work of Elkins and co-workers [49] influenced the Threshold Limits Committee of the ACGIH to reduce the TLV to 0.02 ppm in 1961. [78] Elkins et al [49] in fact had recommended a reduction to 0.01 ppm which has been followed as the standard in Massachusetts. In 1962 the reduction to 0.02 ppm was endorsed by Henschler et al [55] who had repeated Zapp's original animal studies

and found very similar results but at 1/10 of the exposure levels published by Zapp. [48] The discrepancy was attributed to the different analytical methods used for TDI.

The ACGIH still recommends a TLV of 0.02 [78] which is a "ceiling" value, not to be exceeded. Although the Committee acknowledged the reports of Peters and his group [39-44] on acute and chronic effects observed in workers apparently not exposed to levels as high as 0.02 ppm, they did not consider these changes to be of sufficient importance to invalidate this TLV.

In 1959 Smelyanskiy and Ulanova [79] of the U.S.S.R. published the maximum permissible level (ie a ceiling value) of TDI as 0.07 ppm. This is noteworthy because Soviet MAC's tend to be very much lower than ACGIH recommendations. This figure was only slightly lower than the ACGIH TLV for the same year, and is three and a half times higher than the ACGIH limits from 1961 to the present time. Their report [79] listed permissible levels of many substances and did not report the basis for the TDI level.

The current Federal Standard (see 29CFR 1910.93), a ceiling value of 0.02 ppm, is based on the ACGIH recommendation. It is published in the Federal Register,Volume 37, Number 202, page 22141, dated October 18, 1972.

Basis for Recommended Environmental Standard

There is reason to believe from the recent studies of Scheel [80] that cases of sensitization continue to occur. Whether such sensitization takes place at levels of exposure to TDI at or below a

time-weighted average of 0.02 ppm or during brief excursions to higher levels following accidental spillage [51] cannot be determined from the available data because in no case has continuous monitoring of TDI air levels been reported. Some authors [20,25] believe that preplacement screening and exclusion of employees with a personal or family history of clinical allergy or atopy largely eliminates the problem of sensitization to TDI in industry. Even if this were the case, such an approach is not consistent with the current objective of a standard to protect all workers. Moreover there is at least some suggestion that TDI may be a universal sensitizer. [63]

A different kind of problem is raised by the findings of Peters and his co-workers [39,41,44] in New England which are to some extent corroborated by Adams [45] in Britain. (These studies are discussed in some detail under the heading of Epidemiologic Studies in Section III.) Peters has been studying a dwindling cohort of workers, originally 38 in number but reduced by loss to follow-up to 13, since 1966. Working in a plant producing polyurethane foam by a continuous process, in which air levels of TDI had never been found to exceed 0.014 ppm, Peters and his coileagues have found acute reductions of ventilatory capacity (FEV 1.0) in workers at the afternoon (end-of-shift) measurement compared to the morning (pre-shift) measurement. These acute changes were not completely reversed overnight; cumulative changes exceeding by 3- to 4-fold those associated with age alone have occurred over periods of 6, 12, 18, and 24 months; symptomatic workers showed a greater response to TDI than asymptomatic ones; and a

substantial positive correlation existed between the acute and cumulative changes in FEV 1.0. In the published papers cited, [39-44] all the physiological data from individual workers have been pooled and expressed as group mean values. Moreover, the published environmental data in these studies are sparse. However, the nature of the continuous pouring process and of the plant is such that spillages and their attendant excursions are less likely than in some other operations. The only level of TDI at which Peters [42] recorded a minimal diurnal decrement in FEV 1.0 (a mean decrease of only 0.05 liters in 43 workers) was very low, with a maximum concentration of only 0.0015 ppm. The findings of Peters and his colleagues can be challenged on the grounds that they failed to detect significant excursions that might have occurred; thus, the implications of Peters' findings in the development of a standard are difficult to interpret except as probably indicative that the standard of 0.02 ppm is too high, and that the limit recommended in the 1962 report of Elkins et al [49] of 0.01 ppm may also be too high.

Peters' results, although inconsistent with the negative findings of insignificant diurnal changes in FEV 1.0 in 18 TDI workers exposed to higher levels, [51] were presaged by those of Gandevia [38] who found a group mean diurnal decrease of FEV 1.0 of 0.18 liters in 15 workers exposed to substantially higher levels of TDI (estimated at 0.9 ppm), and are corroborated by more recent studies by Adams [45] who has been following, spirometrically, more than 100 TDI workers in Britain for five years. In this last study TDI air levels appear to

have exceeded those which Peters found but "rarely exceed 0.02 ppm." [45]

It appears therefore that a time-weighted average standard of 0.02 ppm TDI is too high to prevent the acute and cumulative decreases in ventilatory capacity, measured by FEV 1.0, as reported by Peters and Adams.

At the same time, a reduction of the standard to the level at which Peters reported only minimal effects, ie 0.0015 ppm, does not seem to have sufficient justification. The majority of the workers in Peters' [39-44] and Adams' [45] studies appeared to be asymptomatic and it is possible that the effects were caused by brief, unrecorded excursions, or that insufficient samples were collected to define the environmental exposures. The long-term health effects of the observed accelerated decrement in ventilatory capacity, as reflected by the FEV 1.0, are not known, nor is it known whether these effects may be reversible on removal from exposure. [45]

With consideration to the limitations imposed by data both conflicting and lacking in important detail, it is concluded that protection of the worker not yet sensitized to TDI can best be achieved by adherence to both a ceiling limit and a time-weighted average limit. The data on which the ACGIH TLV, and thus the Federal Standard, of 0.02 ppm was based were from the report of Elkins and co-workers. [49] They had recommended a lower value, 0.01 ppm, to the ACGIH in 1961, and their subsequently published data [49] justified a value lower than 0.02 ppm.

After a review of these and other quantitative data relating exposure to effect, it is concluded that these data still offer the best basis for recommending a time-weighted average limit, and give some, but limited, support for the recommended ceiling limit. The summary table from the report of Elkins et al, [49] shown in Table XIII-2 primarily because of its information on average environmental levels, can be misleading in trying to relate TDI effects with environmental levels, because the concentrations listed are often averages over a long period, up to several years, whereas the effects noted occurred over a small part of that period at a different exposure level, described in the text of the report and in other tables. Data relevant to the present discussion have been taken from that report after careful study of all tables and textual discussion, and are summarized in Table V-1. In the early phases of this study, the Ranta method [48] was used for analysis, but later the Marcali method [58] was adopted in its place. The authors compared the two methods, and reported that they gave reasonable agreement, but preferred the Marcali method because of its greater sensitivity.

Data from the report that the authors felt to be of doubtful validity were excluded from Table V-1, as were some data which do not allow comparison of concentration and response. It was not possible in most cases to glean from this report an accurate estimate of the number of workers exposed, and the number in the column listing the maximum number of workers at risk is probably higher than the true number at risk in most cases.

From these data, it can be seen that at all exposure levels of 0.01 ppm or higher, some cases of TDI toxicity occurred, but there were no cases at 0.007 or lower. At 0.009 ppm, there were no established cases, but one questionable one; there were several established cases at 0.008 ppm. It is concluded that the time-weighted average environmental limit should be below 0.01 ppm, and should be 0.005 ppm to ensure some margin of safety.

A ceiling of 0.02 ppm is interpretable from several studies, such as that of Williamson, [33] who believed cases of sensitization occurred only when spills resulted in excursions over 0.02 ppm. Some of the data of Elkins and co-workers [49] could be interpreted to support such a ceiling, if, as seems likely, the workers in plant 3 in the 1958 survey (see Table V-1) who wore respirators did so because of the acute response to levels around 0.02 ppm. But the data which better support a ceiling are those of Hama, [15] who found no evidence of toxic effects by TDI when the environmental level was under 0.03 ppm. The airborne TDI level had been about 0.01 ppm, with no complaints, when an operational change resulted in an increase in TDI levels, to a range of 0.03 to 0.07 ppm; all 12 workers were then adversely affected. When hygiene was improved, airborne TDI was reduced to between 0.01 and 0.03 ppm. Over a period of several months at this level, no worker suffered from TDI effects. From this a ceiling limit of 0.03 can be interpreted. A limit of 0.02 ppm is nevertheless recommended, in part because of the long sampling time (20 minutes) dictated by the lack of sensitivity of the Marcali

Table V-1

Summary of Dose-Response Data of Elkins et al [49]

Plant	Date	No. of Tests	Concentration, ppm Max.	Concentration, ppm Av.	No. of workers affected: Estab-lished	No. of workers affected: Question-able	Max. No. at risk	Notes
2	1/58	8	0.01	0.008	3		50	
2	12/58	6	<0.01	0.005	0	0	50	
2	12/60	6	0.05	0.04	14	25	100	(1)
2	1/61	9	0.03	0.01				
2	6/61	6	0.02	0.008	3	2	50	
2	1/62	6	0.014	0.008				
3	1958	4	0.02	0.01	0	0	25	(2)
3	1961	8	0.015	0.007	0	0	25	
4	1959	4	0.02	0.01	1	3	40	
4	1961	5	0.001	0.0006	0	0	40	
4	1961	0			4			
5	1959	4	0.02	0.015	?	?	6	(3)
6	1961	28	0.07	0.015	3	0	40	
9	1961	3	0.008	0.006	0	0	4	
12	1962	6		0.009	0	1	6	
13	1962	4		Nil	0	1	20	
14	1962	6		0.000	0	0	20	

Notes:

(1) Additional company analyses verify that air levels were high.

(2) The workers wore respirators, which probably indicates acute irritation.

(3) Some workers had been transferred after complaints.

method. [58] A 20-minute sampling time is barely adequate for adherence to the recommended TWA, and any reduction for testing compliance with ceiling values will preclude checking compliance with TWA's. Thus, the limits and many of the data from which they are derived represent a compromise resulting in part from the lack of optimal sensitivity of the analytical method.

If only a small part of the working population is sensitizable to TDI, as believed by some investigators, [25,31] it could be inferred that the ceiling that protects against acute irritation in most workers also protects against sensitization in a few. But the available data do not allow such precision of interpretation.

The use of parts per million (ppm) throughout this document follows convention in treating TDI as a vapor. However, it is possible that TDI may exist in particulate form in some operations. Data on relative toxicities of particulate and vapor-phase TDI are lacking, but it is believed there would be no significant difference in toxicity of the two forms. Large-size particulates may be removed in the upper respiratory tract, and thus not reach the bronchioles, but they are doubtlessly irritating to the upper respiratory tract, so sampling for selected particle sizes is not proposed. Additionally, the reaction of TDI with upper respiratory tract tissue cannot be ruled out as an initiator of the sensitization reaction. Partially polymerized particles of TDI will probably be less toxic than the monomer, but such particles will be sampled and analyzed as TDI to a lesser degree. From a theoretical point of view, the decrease in

toxicity of TDI with degree of polymerization should parallel the decrease in sensitivity to polymerization of the sampling and analysis. Thus, it is proposed that the environmental limits of 0.005 ppm TWA and 0.02 ppm ceiling also apply to particulate TDI, expressed as 0.036 mg/cu m TWA and 0.14 mg/cu m ceiling.

Available evidence does not point to a level of airborne TDI that is safe for workers already sensitized to TDI. While it can be speculated that there is a dose-response relationship for sensitized individuals, from theoretical considerations and from interpretation of some unpublished observations, there is no substantial evidence either that such a dose-response relationship exists or that points to what a safe concentration for sensitized people is. Thus, the common warning that those sensitized to TDI should not be exposed to the compound at any concentration, and should be removed from work involving possible exposure to TDI, seems sound from present information.

The decrement in respiratory function seen in the studies of Peters et al and of Adams seems consistent with a prediction of the development of obstructive lung disease if such a decrement progresses for a long time. Similarly, repeated asthmatic-like incidents among workers exposed to TDI might be followed by the development of obstructive lung disease. Thus, the medical recommendations include X-rays and pulmonary function tests to try to detect both acute and chronic effects on the respiratory system. It is desirable to perform occasional "before and after" tests of pulmonary function, ie, tests

of function at the beginning of the workday and at the end, to see if there are small but significant changes in an otherwise apparently safe work environment.

A questionnaire to elicit any history of relevant respiratory problems has been found useful in some industries, and may be of value to others. An example of a useful questionnaire, given in Appendix V, is that published by the Health Advisory Committee of the British Rubber Manufacturers' Association [81] for TDI workers.

VI. WORK PRACTICES

Toluene diisocyanate containers should be kept closed as much as possible to prevent the escape of vapors and to prevent water from getting in. When it is necessary to open a container, adequate ventilation should be provided and, in addition, workmen should wear chemical safety goggles and respiratory protective equipment. When it is necessary to pour TDI from a container, a flexible hose leading to the exhaust system should be placed in the container. [2]

When TDI leaks or spills occur only properly protected personnel should remain in the area. Leaking containers should be removed to the outdoors or to an isolated, well-ventilated area, and the contents transferred to other suitable containers. Adequate preparation and facilities for handling spills should be provided. These include suitable floor drainage and ready accessibility of hoses, mops, buckets, and absorbent materials. Spills should be cleaned up promptly. The effectiveness of water is considerably improved by the addition of 1 to 5% of ammonia. This solution is further improved by the addition of up to 10 % of isopropyl alcohol. Oil absorbent materials such as sawdust or vermiculite are also useful in facilitating clean-up of spills. Such material, after use, should be shovelled into an open top steel container, the container then covered and removed to a safe disposal area away from the operating area. The mixture should be soaked with water containing ammonia and allowed to stand for 24 hours in an open or partially open container, after which the container can be closed and discarded. [3,82]

Liquid TDI should never be washed directly down the drain with water, because the solids that result may plug the sewer line. Spills of TDI will freeze during cold weather. In such cases the use of water and ammonia will merely coat the solid material with insoluble urea stopping further reaction. In cold weather clean-up should be performed with a mixture of equal parts of isopropyl alcohol and perchloroethylene. It is advisable to have a supply of this mixture on hand and ready for immediate use for cold weather.

If major spills occur, air-supplied masks or self-contained breathing apparatus must be used by workers in the area.

Unprotected workers should not be permitted within 50 feet of spraying operations performed outdoors. A greater distance is required to protect against drift during indoor spraying operations, the distance being dependent upon the ventilation provided. An air-supplied hood, impervious gloves, tightly buttoned coveralls, and impervious foot covering are needed by all workers within 10 feet of a spray gun in operation, according to Peterson et al. [74]

Employees shall be instructed concerning TDI hazards and the precautions to be followed. They must be trained to report promptly to their supervisors all leaks, suspected failures, exposures to TDI, or symptoms of exposure. The location of safety showers, fountains, and eye baths must be made known to all employees. The importance of good housekeeping should be emphasized and the need for immediate removal of TDI or reacting foams spilled on the skin, by thorough washing with soap and water, should be impressed upon all workers.

The necessity for prompt and thorough flushing of the eyes with water for 15 minutes in the event of contact should also be stressed. If TDI gets into the eyes a physician should also be called. [3]

Cup-type chemical safety goggles should be worn wherever there is danger of liquid TDI coming in contact with the eyes. For normal continuous eye protection, spectacle-type safety glasses with 48-wire mesh side shields may be used. Eye protection equipment should meet the specifications of the Z87.1-1968 standard of the American National Standards Institute. [83] Only respiratory protective equipment specified in Section 4 of this recommended standard should be used. Where supplied air equipment is used, the air supply must be from a source not subject to contamination with TDI. [84] Safety shoes are recommended for workers handling drums of TDI. Rubbers may be worn over leather safety shoes. Rubbers should be thoroughly cleaned and ventilated after contamination. Shoes which have become contaminated with TDI should be decontaminated or cut up and disposed of. [2]

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VIII. APPENDIX I - Sampling and Calibration Methods

(a) Sampling

The sample is drawn through an all-glass midget impinger containing 15 ml of absorbing solution (Appendix II). Sampling is performed for 20 minutes at a rate of 2 liters per minute, using a personal sampling pump or other satisfactory source of suction. The flow rate, with an impinger on line, should be checked before and after the sample is taken.

Care should be taken to prevent any loss of the sample due to spillage, leakage or evaporation during transfer or shipment to the laboratory. If the impingers are to be shipped intact, then the tips of the stem should be securely capped with parafilm or a polytetrafluoroethylene sleeve. If the stem is to be removed, be sure to allow all of the absorbing solution to run out of the tube before removing; complete drainage must be provided by touching the tip against the inner surface of the cylinder, by careful blowout into the cylinder or by gently tapping the tube against the inside cylinder wall. After the stem has been removed, stopper the cylinder with a clean polyethylene stopper. Do not use rubber stoppers. The cylinders should be shipped in an upright position in a hand-carrying case after careful and secure packing with cushioning materials. The TDI reaction product in the absorbing solution is stable for at least 2 weeks.

(b) Calibration

Since the accuracy of an analysis can be no greater than the accuracy of the volume of air which is measured, the accurate calibration of a sampling device is essential to the correct interpretation of an instrument's indication. The frequency of calibration is dependent on the use, care, and handling to which the pump is subjected. Pumps should be calibrated if they have been subjected to misuse or if they have just been repaired or received from a manufacturer. If the instrument receives hard usage, more frequent calibration may be necessary.

Ordinarily, pumps should be calibrated in the laboratory both before they are used in the field and after they have been used to collect a large number of field samples. The accuracy of calibration is dependent on the type of instrument used as a reference. The choice of calibration instrument will depend largely upon where the calibration is to be performed. For laboratory testing, a 1-liter burette or wet-test meter is recommended, although other standard calibrating instruments such as spirometer, Marriott's bottle, or dry-gas meter can be used. The actual set-up will be the same for either instrument. The calibration instrument will be connected in sequence to the impinger unit which will be followed by the sampler pump. In this way, the calibration instrument will be at atmospheric pressure. If the personal sampler pump is used, each pump must be calibrated separately. If the burette is used, it should be set up so that the flow is toward the narrow end of the unit.

Care must be exercised in the assembly procedure to ensure that seals at the joints are airtight and that the length of connecting tubing is kept at a minimum. Calibration should be performed under the same conditions of pressure and temperature as those encountered in use. The calibrated pump rotameter should be used to set the flow rate in the field.

The microimpinger tip inside diameter tolerance must be maintained at 1.000 ±0.025 mm, and a calibration must be provided with each impinger used to maintain volumetric accuracy within 5% to compensate for differences in pressure drop caused by orifice diameters outside this tolerance range. Calibration should be performed under the same conditions of pressure and temperature as will be encountered in use.

IX. APPENDIX II - Analytical Methods

Toluene diisocyanate in air: The Marcali method [58], incorporating modifications by Grim and Linch [64] and Larkin and Kupel, [71] is recommended.

Principle

TDI is hydrolyzed by the absorbing solution to the corresponding toluene diamine derivative.

The diamine is diazotized by the sodium nitrite-sodium bromide solution.

The diazo compound is coupled with N-(1-Naphthyl)ethylene-diamine to form a colored complex.

The amount of colored complex formed is in direct proportion to the amount of TDI present. The amount of colored complex is determined by reading the absorbance of the solution at 550 nm.

Toluene diamine is formed on a mole for mole basis from TDI. This amine is used in place of TDI for standards. This accomplishes two things. First, the amine is not as toxic as TDI. Second, TDI is semi-solid at room temperature. Weighing the semi-solid is more difficult than weighing the dry amine. Both compounds have been tested by this method and the results compare favorably.

Range and Sensitivity

The range of the standards used is equivalent to 1.0 - 20.0 µg TDI. In a 40-liter air sample, this range converts to 0.0035 - 0.070 ppm. The sensitivity can be increased by using longer path length spectrophotometer cells.

If the sample is so concentrated its absorbance is greater than the limits of the standard curve, it can be diluted with absorber solution and the absorbance reread. This extends the upper limit of the range. The upper limit can also be extended by taking a smaller air sample.

A single bubbler absorbs 95% of the diisocyanate if the concentration is below 2 ppm. Above 2 ppm, about 90% is recovered.

Interferences

Any free organic amine will interfere, including any that may be present in detergents.

Methylene-di-(4-phenylisocyanate) (MDI) will form a colored complex in this reaction. However, its color development time is about 1 - 2 hours compared with 5 minutes for TDI. Therefore MDI is not a serious problem, if color density is determined within 10 minutes of the addition of coupling reagent.

Apparatus

Beckman Model B spectrophotometer or equivalent

Cells, 1-cm, 4-cm,5-cm,or 10-cm matched cells

Several (each) volumetric flasks: 50 ml, 100 ml, 1-liter, glass-stoppered

Balance capable of weighing to at least three decimal places

Pipettes: 0.5 ml, 1 ml, 15 ml

Graduated cylinders: 25 ml, 50 ml

Reagents

All reagents must be ACS reagent grade or better

Double distilled water

2, 4-diaminotoluene

Hydrochloric acid, concentrated, 11.7 N

Glacial acetic acid, concentrated, 17.6 N

Sodium bromide

Sodium nitrite solution: Dissolve 3.0 g sodium nitrite and 5.0 g sodium bromide in about 80 ml double distilled water. Adjust volume to 100 ml with double distilled water.

Sulfamic acid

Sulfamic acid solution, 10% w/v: dissolve 10 g sulfamic acid in 100 ml double distilled water.

N-(1-Naphthyl)ethylenediamine dihydrochloride

N-(1-Naphthyl)ethylenediamine solution: Dissolve 50 mg in about 25 ml double distilled water. Add 1 ml concentrated hydrochloric acid and dilute to 50 ml with double distilled water. Solution should be clear; any coloring is due to contamination by free amines, and if the solution is colored it should not be used.

Absorber solution: Add 35 ml concentrated hydrochloric acid and 22 ml glacial acetic acid to approximately 600 ml double distilled water. Dilute the solution to 1 liter with double distilled water. Use 15 ml in each sample-collecting impinger.

Standard solution A: Weigh out 140 mg of 2,4-toluenediamine (equivalent to 200 mg of 2,4-toluene diisocyanate). Dissolve in 660 ml of glacial acetic acid, transfer to a 1-liter glass-stoppered volumetric flask, and make up to volume with double distilled water.

Standard solution B: Transfer 10 ml of standard solution A to a glass-stoppered 1-liter volumetric flask. Add 27.8 ml of glacial acetic acid so that when solution B is diluted to 1 liter with double distilled water, it will be 0.6N with respect to acetic acid.

Procedure

Cleaning Equipment:

Wash all glassware in a hot amine-free detergent solution, or soak in a 1% aqueous trisodium phosphate (analytical reagent) solution at room temperature, preferably overnight, to remove any oil.

Rinse well with hot tap water.

Rinse well with double distilled water. Repeat this rinse several times. Any amines from organic detergents must be removed to prevent interferences.

Analysis of Samples:

Remove impinger tube taking care not to lose any absorber solution.

Start blank at this point by adding 15 ml fresh absorber solution to a clean impinger cylinder. To each bubbler add 0.5ml of 3% sodium nitrite solution, gently agitate, and allow solution to stand for 2 minutes.

Add 1 ml of 10% sulfamic acid solution, agitate and allow solution to stand about 2 minutes to destroy all the excess nitrous acid present.

Add 1 ml of 0.1% N-(1-Naphthyl)ethylenediamine solution. Agitate and allow color to develop. Color will be developed in 5 minutes. A reddish-blue color indicates the presence of TDI.

Add double distilled water to adjust the final volume to 20 ml in the cylinder. Mix.

Transfer each sample and blank to 1-cm or longer spectrophotometer cell.

Using the blank, adjust the spectrophotometer to 0 absorbance

Determine the absorbance of each sample at 550 nm.

From the previously prepared calibration curve (see below) read the micrograms TDI corresponding to the absorbance of the sample and calculate the parts per million TDI.

Calibration and Standards

To each of a series of eight 25-ml graduated cylinders add 5 ml of 1.2N hydrochloric acid.

To these cylinders add the following amounts of 0.6N acetic acid: 10.0, 9.5, 9.0, 8.0, 7.0, 6.0, 5.0, and 0.0 ml, respectively.

To these cylinders add standard solution B in the same order as the acetic acid is added: 0.0, 0.5, 1.0, 2.0, 3.0, 4.0, 5.0, and 10.0 ml, so that the final volume is 10 ml. None (0.0 ml) of the standard is added to the 10 ml acetic acid; 0.5 ml of the standard is added to the 9.5 ml acid; and so on. The cylinders now contain the equivalent of 0.0, 1.0, 2.0, 4.0, 6.0, 8.0, 10.0, and 20.0 µg TDI, respectively. The standard containing none of the standard solution is the blank.

Add 0.5 ml of the 3.0% sodium nitrite reagent to each cylinder. Mix. Allow to stand 2 minutes.

Add 1 ml of the 10% sulfamic acid solution. Mix. Allow to stand for 2 minutes.

Add 1 ml of the N-(1-Naphthyl)ethylenediamine solution. Mix. Let stand for 15 minutes.

Make up to exactly 20 ml with double distilled water.

Transfer each solution to 1-cm or longer spectrophotometer cell. (At the lower end of the calibration curve, 5-cm cells give an 11% relative instrumental error for the 1.0 μg TDI standard. For smaller path lengths, the error is greater.)

Using the blank, adjust the spectrophotometer to 0 absorbance at 550 nm.

Determine the absorbance of each standard at 550 nm.

A standard curve is constructed by plotting the absorbance against micrograms TDI.

Calculations

$$ppm = \frac{micrograms \times 24.45}{174.15 \times 40} = micrograms \times 0.00351$$

micrograms - micrograms TDI taken from standard curve

mol wt = wt TDI = 174.15

V = volume of air sample in liters (40 liters)

X. APPENDIX III - MATERIAL SAFETY DATA SHEET

The following items of information which are applicable to any specific product or material containing toluene diisocyanate shall be provided in the appropriate section of the Material Safety Data Sheet or approved form. If a specific item of information is inapplicable (ie, flash point) initials "n.a." (not applicable) should be inserted.

(i) The product designation in the upper left hand corner of both front and back to facilitate filing and retrieval. Print in upper case letters in as large print as possible.

(ii) Section I. Name and Source.

(A) The name, address, and telephone number of the manufacturer or supplier of the product.

(B) The trade name and synonyms for a mixture of chemicals, a basic structural material, or for a process material; and the trade name and synonyms, chemical name and synonyms, chemical family, and formula for a single chemical.

(iii) Section II. Hazardous Ingredients.

(A) Chemical or widely recognized common name of all hazardous ingredients.

(B) The approximate percentage by weight or volume (indicate basis) which each hazardous ingredient of the mixture bears to the whole mixture. This may be indicated as a range of maximum amount, ie, 10-20% V; 10% max. W.

(C) Basis for toxicity of each hazardous material such as established OSHA standard in appropriate units and/or LD50 showing

amount and mode of exposure and species, or LC50 showing concentration, duration of exposure, and species.

(iv) Section III. Physical Data.

(A) Physical properties of the total product including boiling point and melting point in degrees Fahrenheit; vapor pressure, in millimeters of mercury; vapor density of gas or vapor (air = 1); solubility in water, in parts per hundred parts of water by weight; specific gravity (water = 1); percentage volatile (indicate if by weight or volume) at 70 Fahrenheit; evaporation rate for liquids (indicate whether butyl acetate or ether = 1); and appearance and odor.

(v) Section IV. Fire and Explosion Hazard Data.

(A) Fire and explosion hazard data about a single chemical or a mixture of chemicals, including flash point, in degrees Fahrenheit; flammable limits, in percent by volume in air; suitable extinguishing media or agents; special fire-fighting procedures; and unusual fire and explosion hazard information.

(vi) Section V. Health Hazard Data.

(A) Toxic level for total compound or mixture, relevant symptoms of exposure, skin and eye irritation properties, principal routes of absorption, effects of chronic (long-term) exposure and emergency and first-aid procedures.

(vii) Section VI. Reactivity Data.

(A) Chemical stability, incompatibility, hazardous decomposition products, and hazardous polymerization.

(viii) Section VII. Spill or Leak Procedures.

(A) Detailed procedures to be followed with emphasis on precautions to be taken in cleaning up and safe disposal of materials leaked or spilled. This includes proper labeling and disposal of containers containing residues, contaminated absorbants, etc.

(ix) Section VIII. Special Protection Information.

(A) Requirements for personal protective equipment, such as respirators, eye protection and protective clothing, and ventilation, such as local exhaust (at site of product use or application), general, or other special types.

(x) Section IX. Special Precautions.

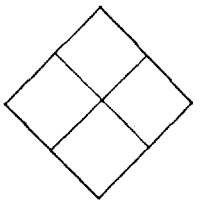
(A) Any other general precautionary information, such as personal protective equipment for exposure to the thermal decomposition products listed in Section VI, and to particulates formed by abrading a dry coating, such as by a power sanding disc.

(xi) The signature of the responsible person filling out the data sheet, his address, and the date on which it is filled out.

PRODUCT DESIGNATION

MATERIAL SAFETY DATA SHEET

Form Approved
Budget Bureau No.
Approval Expires
Form No. OSHA



SECTION I SOURCE AND NOMENCLATURE

MANUFACTURER'S NAME	EMERGENCY TELEPHONE NO.
ADDRESS (Number, Street, City, State, ZIP Code)	
TRADE NAME AND SYNONYMS	CHEMICAL FAMILY
CHEMICAL NAME AND SYNONYMS	FORMULA

SECTION II HAZARDOUS INGREDIENTS

BASIC MATERIAL	APPROXIMATE OR MAXIMUM % WT. OR VOL.	ESTABLISHED OSHA STANDARD	LD 50		LC 50	
			ORAL	PERCUT.	SPECIES	CONC.

SECTION III PHYSICAL DATA

BOILING POINT °F.	VAPOR PRESSURE mm Hg.
MELTING POINT °F.	VAPOR DENSITY (Air=1)
SPECIFIC GRAVITY (H_2O=1)	EVAPORATION RATE (=1)
SOLUBILITY IN WATER Pts/100 pts H_2O	VOLATILE % Vol. % Wt.
APPEARANCE AND ODOR	

SECTION IV FIRE AND EXPLOSION HAZARD DATA

FLASH POINT	FLAMMABLE (EXPLOSIVE) LIMITS	UPPER
METHOD USED		LOWER
EXTINGUISHING MEDIA		
SPECIAL FIRE FIGHTING PROCEDURES		
UNUSUAL FIRE AND EXPLOSION HAZARDS		

PRODUCT DESIGNATION

SECTION V HEALTH HAZARD DATA	
TOXIC LEVEL	CARCINOGENIC
PRINCIPAL ROUTES OF ABSORPTION	SKIN AND EYE IRRITATION
RELEVANT SYMPTOMS OF EXPOSURE	
EFFECTS OF CHRONIC EXPOSURE	
EMERGENCY AND FIRST AID PROCEDURES	

SECTION VI REACTIVITY DATA
CONDITIONS CONTRIBUTING TO INSTABILITY
CONDITIONS CONTRIBUTING TO HAZARDOUS POLYMERIZATION
INCOMPATIBILITY (Materials to Avoid)
HAZARDOUS DECOMPOSITION PRODUCTS

SECTION VII SPILL OR LEAK PROCEDURES
STEPS TO BE TAKEN IN CASE MATERIAL IS RELEASED OR SPILLED
WASTE DISPOSAL METHOD

SECTION VIII SPECIAL PROTECTION INFORMATION	
VENTILATION REQUIREMENTS LOCAL EXHAUST	PROTECTIVE EQUIPMENT (Specify Types) EYE
MECHANICAL (General)	GLOVES
SPECIAL	RESPIRATOR
OTHER PROTECTIVE EQUIPMENT	

SECTION IX SPECIAL PRECAUTIONS
PRECAUTIONS TO BE TAKEN IN HANDLING AND STORAGE
OTHER PRECAUTIONS

Signature _____ Address

Date

XI. APPENDIX IV - DEFINITION OF TERMS AND ABBREVIATIONS

FEV 1.0 - Forced expiratory volume in 1 second. (The volume of air expired during the first one second of a maximally forced expiration.)

FR 75% - Flow rate at 75% (etc.) of vital capacity.

FVC - Forced vital capacity.

PFR - Peak Flow rate.

TLV - Threshold Limit Value, an occupational health guide recommended by the American Conference of Governmental Industrial Hygienists (ACGIH) as a safe limit for long-term exposures of workers for an 8-hour day, 40-hour week work schedule.

XII. APPENDIX V

British Rubber Manufacturers' Association Questionnaire

Use the actual wording of each question. Put x in the appropriate space after each question. When in doubt record 'NO'.

PREAMBLE I am going to ask you some questions mainly about your chest. I should like you to answer 'YES' or 'NO' whenever possible.

		YES	NO	N/A
1.	Do you usually cough first thing in the morning or on getting up?	___	___	
	(Count a cough with first smoke or on first going out of doors. Exclude throat clearing or a single cough.			
2.	Do you cough like this on most days for as much as three months each year?	___	___	___
3.	Do you cough at work?	___	___	
4.	Do you usually bring up any phlegm from your chest first thing in the morning or on getting up?	___	___	
	(Count phlegm with the first smoke or on first going out of doors. Exclude phlegm from the nose. Count swallowed phlegm.			
5.	Do you bring up phlegm like this on most days for as much as three months each year?	___	___	___
6.	In the past three years, have you had a period of (increased) cough and phlegm lasting 3 weeks or more?	___	___	
7.	Have you had more than one such period?	___	___	
8.	Does your chest ever feel tight or your breathing become difficult?	___	___	
9.	Do you get this apart from colds?	___	___	
	If YES: specify.....(Interviewer to code:)			
	(a) With exercise	___	___	
	(b) At work	___	___	

(c) Any other time ___ ___

If disabled from walking by skeletal or other physical disability put 'X' here. ___

10. Are you troubled by shortness of breath, when hurrying on the level or walking up a slight hill? ___ ___

(If 'No' omit questions 11 and 12)

11. Do you get short of breath walking with other people of your own age on level ground? ___ ___

(If 'No' omit question 12)

12. Do you have to stop for breath when walking at your own pace on level ground? ___ ___

13. Do you usually have a stuffy nose or catarrh at the back of your nose in the winter? ___ ___

14. Do you have this in the summer? ___ ___

(If 'No' to both questions 13 and 14, go to question 16)

15. Do you have this on most days for as much as three months each year? ___ ___

16. During the past 3 years have you had any chest illness which has kept you off work or from your usual activities for as much as a week? ___ ___

17. Did you bring up more phlegm than usual in any of these illnesses? ___ ___

18. Have you had more than one illness with phlegm like this in the last 3 years? ___ ___

HAVE YOU EVER HAD:

19. An injury or operation affecting your chest? ___ ___

_____

20. Heart trouble? _____ ___ ___

_____

21. Bronchitis? _____ ___ ___

_____

22. Pneumonia? _____ ___ ___

23. Pleurisy? _____ ___ ___

24. Pulmonary tuberculosis? _____ ___ ___

25. Bronchial asthma? _____ ___ ___

26. Eczema? _____ ___ ___

27. Dermatitis? _____ ___ ___

28. Pneumoconiosis? _____ ___ ___

29. Byssinosis? _____ ___ ___

30. Other chest trouble? _____ ___ ___

Give relevant details after each positive answer.

31. Do you smoke? ___ ___

(Record 'Yes' if regular smoker up to one month ago)
If 'No' to 31:

32. Have you ever smoked? ___ ___

(Record 'No' if subject has never smoked as much as one cigarette a day, or 1 oz. tobacco a month, for as long as one year)

33. Age when stopped _____ years. Was this in last month? ___ ___

If 'Yes" to 31 or 32: Fill in figures below:

	Amount smoked	
	Now	Before stopping
Cigarettes/day (Average including weekends)	...	.....
Oz. tobacco/week (handrolled) ..	...	.....
Oz. tobacco/week (pipe)	...	.....
Cigars/week (large)	...	.....
Cigars/week (small)	...	.....

OCCUPATION (1st interview only)

(Record on dotted lines the years in which subject has worked in any of these industries, e.g. 1960-63)

		YES	NO
34.	Have you ever worked in a dusty job? _____	___	___
35.	In a coal mine? _____	___	___
36.	In any other mine? _____	___	___
37.	In a quarry? _____	___	___
38.	In a foundry? _____	___	___
39.	In a pottery? _____	___	___
40.	In a cotton, flax or hemp mill? _____	___	___
41.	With asbestos? _____	___	___
42.	In any other dusty job? _____	___	___
	If 'Yes', specify _____		
	_____		
43.	Have you been exposed regularly to irritating gas or chemical fumes? _____	___	___

If 'Yes' give details of nature and duration _____

_____

OCCUPATION (Follow-up only)

44. What is your present job? _____

45. How long have you been doing it? _____

46. What was your previous job in the factory? _____

Taken with minor changes from Operating and Medical Codes of Practice for Safe Working with Toluene Di-isocyanate, Health Advisory Committee, British Rubber Manufacturers' Association Ltd. [81]

Table XIII-1

Properties of Commercial Samples of 80% 2,4:20% 2,6 Toluene Diisocyanate*

Molecular Weight		174.16	
Flash Point		275 F	(135 C)
Specific Gravity of Liquid		1.22 at 77 F	(25 C)
Boiling Point		482 F	(250 C)
Freezing Point		68-72 F	(20-22C)
Vapor Pressure	Temp. F	Temp. C	mm Hg
	50	10	.02
	77	20	.05
	100	38	.10
	150	66	.43
	200	93	1.90
	250	121	10.0
	300	149	36.0

*Taken from Upjohn Technical Bulletin 105. [3]

Table XIII-2

Summary of TDI Concentrations in Air and Cases of TDI Intoxication at 14 Plants

		Air Analyses			Number of Cases	
Plant	Year(s)	Number of Tests	Av. TDI Conc. ppm	Workers Exposed	Accepted or Established	Questionable or Disputed
1	1957	--	---	2	1	1
2	1957-58	14	0.005	50	3	28
	1960	33	0.028	100	14	25
	1961-62	55	0.015	50	3	2
3	1958-60	12	0.009	25	0	0
4	1958-62	21	0.004	40	5	15
5	1958-61	11	0.008	6	1	?
6	1958-61	28	0.015	40	8	0
7	1961	4	<0.001	4	0	0
8	1961	5	<0.001*	5	1	0
9	1961	3	0.006	4	0	0
10	1961	14	0.002**	3	2	0
11	1961	14	0.54**	4	4	0
12	1962	6	0.009	6	0	1
13	1962	4	Nil	20	0	1
14	1962	6	0.000	20	0	0
Total		230		379	42	73

*Probably not representative of exposure.
**Not representative of exposure.
From Elkins et al. [49]

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