CRITERIA FOR A RECOMMENDED STANDARD

OCCUPATIONAL EXPOSURE TO

DIISOCYANATES
criteria for a recommended standard....

OCCUPATIONAL EXPOSURE
TO
DIISOCYANATES

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service
Center for Disease Control
National Institute for Occupational Safety and Health
September 1978
DISCLAIMER

Mention of company name or product does not constitute endorsement by the National Institute for Occupational Safety and Health.

DHEW (NIOSH) Publication No. 78-215
PREFACE

The Occupational Safety and Health Act of 1970 emphasizes the need for standards to protect the health and provide for the safety of workers occupationally exposed to an ever-increasing number of potential hazards. The National Institute for Occupational Safety and Health (NIOSH) evaluates all available research data and criteria and recommends standards for occupational exposure. The Secretary of Labor will weigh these recommendations along with other considerations, such as feasibility and means of implementation, in promulgating regulatory standards.

NIOSH will periodically review the recommended standards to ensure continuing protection of workers and will make successive reports as new research and epidemiologic studies are completed and as sampling and analytical methods are developed.

The contributions to this document on diisocyanates by NIOSH staff, other Federal agencies or departments, the review consultants, the reviewers selected by the Society for Occupational and Environmental Health and the American Medical Association, and Robert B. O'Connor, M.D., NIOSH consultant in occupational medicine, are gratefully acknowledged.

The views and conclusions expressed in this document, together with the recommendations for a standard, are those of NIOSH. They are not necessarily those of the consultants, the reviewers selected by professional societies, or other Federal agencies. However, all comments, whether or not incorporated, have been sent with the criteria document to the Occupational Safety and Health Administration for consideration in setting the standard. The review consultants and the Federal agencies which received the document for review appear on pages v and vi.

J. Michael Lane, M.D.
Acting Director, National Institute for Occupational Safety and Health

iii
The Division of Criteria Documentation and Standards Development, National Institute for Occupational Safety and Health, had primary responsibility for the development of the criteria and recommended standard for diisocyanates. Stephanie Soucek of this Division served as criteria manager. SRI International developed the basic information for consideration by NIOSH staff and consultants under contract 210-77-0015.

The Division Review of this document was provided by Douglas L. Smith, Ph.D. (Chairman), Keith H. Jacobson, Ph.D., Howard L. McMartin, M.D., Geoffrey Taylor (Division of Respiratory Disease Studies), and Seymour D. Silver, Ph.D. (consultant).
REVIEW CONSULTANTS

N. Franklin Adkinson, Jr., M.D.
Assistant Professor of Medicine
The Johns Hopkins University
School of Medicine
Baltimore, Maryland 21205

Brian T. Butcher, Ph.D.
Assistant Professor of Medicine
Tulane University Medical Center
New Orleans, Louisiana 70112

George Ozga, Ph.D.
Division of Health Standards
Development
Occupational Safety and Health Administration
Washington, D.C. 20001

Lawrence Samlaska
President, Local 6-665
Oil, Chemical and Atomic Workers
International Union
Cumberland, Wisconsin 54829

Henry J. Surovic
Director
Erie County Health Department
Waterford, Pennsylvania 16441

David H. Wegman, M.D.
Associate Professor of Occupational Health
Harvard School of Public Health
Boston, Massachusetts 02115

Dietrich A. Weyel, Sc.D.
Manager, Corporate Industrial Hygiene Department
Mobay Chemical Corporation
Pittsburgh, Pennsylvania 15205
DEPARTMENT OF DEFENSE
Office of Assistant Secretary of Defense
for Energy, Environment, and Safety

DEPARTMENT OF THE ARMY
US Army Environmental Hygiene Agency

DEPARTMENT OF THE NAVY
Bureau of Medicine and Surgery
Navy Environmental Health Center

DEPARTMENT OF THE AIR FORCE
Office of the Surgeon General

CONSUMER PRODUCT SAFETY COMMISSION
Bureau of Biomedical Science

ENVIRONMENTAL PROTECTION AGENCY
Office of Assistant Administrator for
Research and Development
## CONTENTS

**PREFACE**  
Page iii

**REVIEW CONSULTANTS**  
Page v

**FEDERAL AGENCIES**  
Page vi

### I. RECOMMENDATIONS FOR A DIISOCYANATES STANDARD

- Section 1 - Environmental (Workplace Air)  
  Page 2
- Section 2 - Medical  
  Page 2
- Section 3 - Labeling and Posting  
  Page 4
- Section 4 - Personal Protective Equipment and Clothing  
  Page 5
- Section 5 - Informing Employees of Hazards from Diisocyanates  
  Page 8
- Section 6 - Work Practices  
  Page 9
- Section 7 - Sanitation  
  Page 12
- Section 8 - Monitoring and Recordkeeping  
  Page 13

### II. INTRODUCTION  
Page 15

### III. BIOLOGIC EFFECTS OF EXPOSURE  
Page 17
-Extent of Exposure  
  Page 17
-Historical Reports  
  Page 18
-Effects on Humans  
  Page 19
-Epidemiologic Studies  
  Page 39
-Animal Toxicity  
  Page 54
-Correlation of Exposure and Effect  
  Page 59
- Carcinogenicity, Mutagenicity, Teratogenicity, and Effects on Reproduction  
  Page 65

### IV. ENVIRONMENTAL DATA  
Page 69
- Environmental Concentrations  
  Page 69
- Engineering Controls  
  Page 72
- Sampling and Analysis  
  Page 73

### V. WORK PRACTICES  
Page 84

### VI. DEVELOPMENT OF STANDARD  
Page 90
- Basis for Previous Standards  
  Page 90
- Basis for the Recommended Standard  
  Page 91
CONTENTS (CONTINUED)

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>VII. RESEARCH NEEDS</td>
<td>102</td>
</tr>
<tr>
<td>VIII. REFERENCES</td>
<td>104</td>
</tr>
<tr>
<td>IX. APPENDIX I - Sampling and Analytical Method for Diisocyanates in Air</td>
<td>117</td>
</tr>
<tr>
<td>X. APPENDIX II - Material Safety Data Sheet</td>
<td>123</td>
</tr>
<tr>
<td>XI. TABLES AND FIGURE</td>
<td>131</td>
</tr>
</tbody>
</table>
I. RECOMMENDATIONS FOR A DIISOCYANATES STANDARD

NIOSH recommends that employee exposure to diisocyanates in the workplace be controlled by adherence to the following sections. The standard is designed to protect the health and provide for the safety of employees for up to a 10-hour workshift, 40-hour workweek, over a working lifetime. Compliance with all sections of the recommended standard should prevent adverse effects of diisocyanates on the health of unsensitized workers and provide for their safety. Sufficient technology exists to permit compliance with the recommended standard. Although NIOSH considers the workplace environmental limits to be safe levels based on current information, the employer should regard them as the upper boundaries of exposure and make every effort to keep the exposure as low as possible. The recommended standard will be reviewed and revised as necessary.

Diisocyanates irritate the respiratory tract and can act as respiratory sensitizers, producing asthma-like symptoms in sensitized individuals with exposure at very low concentrations. Exposure to diisocyanates may also result in chronic impairment of pulmonary function.

NIOSH published criteria for a recommended standard for toluene diisocyanate (TDI) in 1973. The present recommended standard is expanded to include all diisocyanates, but not their polymerized forms. It includes most of the provisions recommended in the TDI document but differs where appropriate to reflect newer information or special provisions for other diisocyanates. Most of the information currently available on effects of exposure to diisocyanates concerns TDI and, to a lesser extent, diphenylmethane diisocyanate (MDI). In addition to TDI and MDI, occupational exposure limits are recommended for other diisocyanates that have had widespread industrial application: hexamethylene diisocyanate (HDI), naphthalene diisocyanate (NDI), isophorone diisocyanate (IPDI), and dicyclohexyl methane diisocyanate (hydrogenated MDI).

"Occupational exposure to diisocyanates" is defined as exposure to airborne diisocyanates at concentrations above one-half the recommended time-weighted average (TWA) occupational exposure limit or above the recommended ceiling limit. Adherence to all provisions of the standard is required if employees are occupationally exposed to airborne diisocyanates. If employees are exposed to airborne diisocyanates at concentrations of one-half the recommended TWA workplace environmental limit or less, the employer shall comply with all sections of the recommended standard except Sections 2(b), 4(c), 8(b), and the monitoring provisions of 8(c).
Section 1 - Environmental (Workplace Air)

(a) Concentrations

Exposure to diisocyanates shall be controlled so that no employee is exposed at concentrations greater than the limits specified below. These limits expressed in µg/cu m are equivalent to a vapor concentration of 5 ppb as a TWA concentration for up to a 10-hour workshift, 40-hour workweek, and 20 ppb as a ceiling concentration for any 10-minute sampling period. The µg equivalents for selected diisocyanates are as follows:

<table>
<thead>
<tr>
<th>Compounds</th>
<th>TWA</th>
<th>Ceiling</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toluene diisocyanate (TDI)</td>
<td>35 µg/cu m</td>
<td>140 µg/cu m</td>
</tr>
<tr>
<td>Diphenylmethane diisocyanate (MDI)</td>
<td>50 µg/cu m</td>
<td>200 µg/cu m</td>
</tr>
<tr>
<td>Hexamethylene diisocyanate (HDI)</td>
<td>35 µg/cu m</td>
<td>140 µg/cu m</td>
</tr>
<tr>
<td>Napthalene diisocyanate (NDI)</td>
<td>40 µg/cu m</td>
<td>170 µg/cu m</td>
</tr>
<tr>
<td>Isophorone diisocyanate (IPDI)</td>
<td>45 µg/cu m</td>
<td>180 µg/cu m</td>
</tr>
<tr>
<td>Dicyclohexylmethane 4,4'-diisocyanate (hydrogenated MDI)</td>
<td>55 µg/cu m</td>
<td>210 µg/cu m</td>
</tr>
</tbody>
</table>

If other diisocyanates are used, employers should observe environmental limits equivalent to a ceiling concentration of 20 ppb and a TWA concentration of 5 ppb.

(b) Sampling and Analysis

Environmental samples shall be collected and analyzed by the methods described in Appendix I or by any other method at least equivalent in accuracy, precision, and sensitivity.

Section 2 - Medical

Medical surveillance shall be made available as outlined below to all workers exposed to diisocyanates in the workplace.
(a) Preplacement examinations shall include at least:

(1) Comprehensive medical and work histories, with special emphasis directed to evidence of preexisting respiratory conditions such as asthma. A smoking history should also be compiled.

(2) Physical examination giving particular attention to the respiratory tract.

(3) Specific clinical tests including a 14- x 17-inch posteroanterior chest roentgenogram and baseline measurements of forced vital capacity (FVC) and forced expiratory volume at 1 second (FEV 1).

(4) A judgment of the worker's ability to use negative and positive pressure respirators.

(b) Periodic examinations shall be made available at least annually, as determined by the responsible physician, and shall include:

(1) Interim medical and work histories.

(2) Physical examination giving particular attention to the respiratory tract and including measurements of FVC and FEV 1.

(c) During examinations, applicants or employees found to have medical conditions that could be directly or indirectly aggravated by exposure to diisocyanates, eg, respiratory allergy, chronic upper or lower respiratory irritation, chronic obstructive pulmonary disease, or evidence of sensitization to diisocyanates, shall be counseled on their increased risk from working with these substances. Chronic bronchitis, emphysema, disabling pneumoconiosis, or cardiopulmonary disease with significantly impaired ventilatory capacity similarly suggest an increased risk from exposure to diisocyanates. If a history of allergy other than respiratory allergy is elicited, applicants should be counseled that they may be at increased risk of adverse health effects from exposure to diisocyanates. Employees shall also be advised that exposure to diisocyanates may result in delayed effects, such as coughing or difficulty in breathing during the night.

(d) Pertinent medical records shall be maintained. Records of environmental exposures applicable to an employee shall be included in the employee's medical records. Such records shall be kept for at least 30 years after the last occupational exposure to diisocyanates. These records shall be made available to the designated medical representatives of the Secretary of Health, Education, and Welfare, of the Secretary of Labor, of the employer, and of the employee or former employee.
Section 3 - Labeling and Posting

(a) Warning signs shall be printed both in English and in the predominant language of non-English-reading workers. Workers unable to read labels and posted signs shall be instructed concerning hazardous areas and shall be orally informed of the instructions printed on labels and signs.

(b) Containers of diisocyanates shall carry a label that bears the chemical name of the compound contained therein and information on the compound's effects on human health and emergency measures. The name and pertinent information may be arranged as in the example below:

<table>
<thead>
<tr>
<th>COMPOUND NAME (Synonym or trade name)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HARMFUL IF INHALED</td>
</tr>
<tr>
<td>CAUSES BURNS</td>
</tr>
<tr>
<td>MAY CAUSE COUGH AND DIFFICULTY IN BREATHING DURING OR AFTER WORKSHIFT</td>
</tr>
</tbody>
</table>

Use with adequate ventilation.
Avoid breathing vapor, mist, or dust.
Do not get in eyes, on skin, or on clothing.
Wash thoroughly with water and alcohol after handling.

First Aid: In case of eye contact, flush eyes with copious amounts of water. If victim is overcome, remove to fresh air. If breathing stops, give artificial respiration. Call a physician immediately.

Firefighting: Use dry chemical powder, carbon dioxide, or foam extinguisher. Do not use water unless large quantities are available.

(c) In areas where diisocyanates are used, signs bearing information on the effects of the specific compound on human health and emergency measures shall be posted in readily visible locations. This information may be arranged as the example below:
COMPOUND NAME
(Synonym or trade name)

HARMFUL IF INHALED

CAUSES BURNS

MAY CAUSE COUGH OR DIFFICULTY IN BREATHING
DURING OR AFTER WORKSHIFT

First Aid: In case of eye contact, flush eyes with copious amounts of water. If victim is overcome, remove to fresh air. If breathing stops, give artificial respiration. Call a physician immediately.

Firefighting: Use dry chemical powder, carbon dioxide, or foam extinguisher. Do not use water unless large quantities are available.

(d) If respirators are required, the following statement shall be added in large letters to the sign required in Section 3(c):

RESPIRATORY PROTECTION REQUIRED IN THIS AREA

(e) In any area where there is a likelihood of emergency situations arising, signs required by Section 3(c) shall be supplemented with signs giving emergency and first-aid instructions and procedures, the location of first-aid supplies and emergency equipment, and the locations of emergency showers and eyewash fountains.

Section 4 - Personal Protective Equipment and Clothing

The employer shall use engineering controls where needed to keep the concentration of airborne diisocyanates at or below the limits specified in Section 1(a). The employer shall also provide employees with protective clothing and equipment of materials resistant to penetration by diisocyanates, such as rubber or polyvinyl chloride, when necessary to prevent skin and eye contact with diisocyanates. Protective equipment suitable for emergency use shall be located at clearly identified stations outside the work area.

(a) Eye Protection

The employer shall provide face shields (20-cm minimum) with goggles and shall ensure that employees wear the protective equipment during any operation in which
splashes of liquid diisocyanates are likely to occur. Protective devices for the eyes and face shall be selected, used, and maintained in accordance with 29 CFR 1910.133.

(b) Skin Protection

(1) The employer shall provide appropriate protective clothing and equipment that are resistant to penetration by diisocyanates, including gloves, aprons, suits, and boots, and shall ensure that employees wear these when needed to prevent skin contact with liquid diisocyanates. Workers within 10 feet of spraying operations, or at greater distance when there is a greater drift of spray, shall be protected with impervious clothing, gloves, and footwear in addition to required respiratory protection. Rubber shoes or rubbers over leather shoes shall be worn whenever there is a possibility that liquid diisocyanates may be present on floors.

(2) Protective clothing and equipment shall be cleaned inside and out after each use. Rubbers shall be decontaminated and ventilated if they have become contaminated with diisocyanates. Contaminated leather articles shall be decontaminated or discarded.

(c) Respiratory Protection

Engineering controls shall be used when needed to keep concentrations of airborne diisocyanates at or below the recommended environmental limits. Compliance with the permissible exposure limit by the use of respirators is permitted only during development, installation, and testing of engineering controls, during performance of nonroutine maintenance or repair, when working in confined spaces, during spraying operations in the field, or during emergencies. When use of a respirator is permitted, it shall be selected and used in accordance with the following requirements:

(1) To determine the type of respirator to be used, the employer shall measure the concentrations of airborne diisocyanates in the workplace initially and thereafter whenever control, process, operation, worksite, or climatic changes occur that are likely to increase the concentration of airborne diisocyanates.

(2) The employer shall provide respirators in accordance with Table I-1 and shall ensure that the employees use them properly when respirators are required. The respiratory protective devices provided in conformance with Table I-1 shall be those approved by NIOSH and the Mine Safety and Health Administration as specified in 30 CFR 11.
<table>
<thead>
<tr>
<th>Concentration</th>
<th>Respirator Type Approved under Provisions of 30 CFR 11*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than or equal to 1,000 ppb</td>
<td>Type C supplied-air respirator with full facepiece operated in pressure-demand or other positive pressure mode or with full facepiece, helmet, or hood operated in continuous-flow mode</td>
</tr>
<tr>
<td>Greater than 1,000 ppb</td>
<td>(1) Self-contained breathing apparatus with full facepiece operated in pressure-demand or other positive pressure mode</td>
</tr>
<tr>
<td></td>
<td>(2) Combination respirator including Type C supplied-air respirator with full facepiece operated in pressure-demand or other positive pressure mode with auxiliary self-contained breathing apparatus operated in pressure-demand or other positive pressure mode</td>
</tr>
<tr>
<td>Firefighting and Emergency</td>
<td>Self-contained breathing apparatus with full facepiece, operated in pressure-demand or other positive pressure mode</td>
</tr>
</tbody>
</table>

*Use of supplied-air suits may be necessary to prevent skin contact during exposure at high concentrations of airborne diisocyanates.
(3) Respirators specified for use at higher concentrations of airborne diisocyanates may be used in atmospheres with lower concentrations.

(4) The employer shall ensure that employees are properly instructed and drilled at least annually in the use of respirators assigned to them and on how to test for leakage, proper fit, and proper operation.

(5) The employer shall establish and conduct a program of cleaning, sanitizing, inspecting, maintaining, repairing, and storing respirators to ensure that employees are provided with clean respirators that are in good operating condition.

(6) Respirators shall be easily accessible, and employees shall be informed of their location.

(7) The employer shall ensure that no employee is exposed to diisocyanates above the recommended limits because of improper respirator selection, fit, use, or maintenance.


Section 5 - Informing Employees of Hazards from Diisocyanates

(a) All current and prospective employees working where occupational exposure to diisocyanates may occur shall be informed orally and in writing of the hazards, relevant signs and symptoms of exposure, appropriate emergency procedures, and proper conditions and precautions concerning safe use and handling of diisocyanates. The instructional program shall include a description of the general nature of the environmental and medical surveillance procedures and of the advantages to the employee of participating in these surveillance procedures. Employees exposed to diisocyanates should be warned that symptoms of exposure to diisocyanates, such as nocturnal dyspnea, may occur several hours after the end of the workshift. They should also be advised that improper home use of polyurethane products containing unpolymerized diisocyanates, such as foam kits and varnishes, may increase their risk of work-related health problems. Employees shall be instructed on their responsibilities for following work practices and sanitation procedures to help protect the health and provide for the safety of themselves and of fellow employees.

(b) The employer shall institute a continuing education program, conducted at least annually by persons qualified by experience or training, to ensure that all employees have current knowledge of job hazards, proper maintenance and cleanup methods, and proper respirator use. As a minimum, instruction shall include the information prescribed in paragraph 5(c) below. This information shall be readily
available to all employees involved in the manufacture, use, transport, or storage of diisocyanates and shall be posted in prominent positions within the workplace.

(c) Required information shall be recorded on the "Material Safety Data Sheet" shown in Appendix II or on a similar form approved by the Occupational Safety and Health Administration, US Department of Labor.

Section 6 - Work Practices

(a) Control of Airborne Diisocyanates

(1) Engineering controls, such as process enclosure or local exhaust ventilation, shall be used when needed to keep exposure to diisocyanates at or below the recommended environmental limit. Ventilation systems, if used, shall be designed to prevent accumulation or recirculation of diisocyanates in the workplace environment and to effectively remove diisocyanates from the breathing zone of employees.

(2) Exhaust ventilation systems discharging to outside air must conform to applicable local, state, and Federal air pollution regulations.

(3) Ventilation systems shall be regularly maintained and cleaned to ensure effectiveness, which shall be verified by semiannual airflow measurements. A log showing design airflow and the results of semiannual inspections shall be kept.

(4) Before maintenance work is undertaken, sources of diisocyanates shall be shut off and isolated. The need for and use of respiratory protective equipment shall be determined as outlined in Section 4.

(b) Confined Spaces

In confined areas where work is performed routinely, such as spray booths, exposure to diisocyanates shall be kept at or below the recommended limits by the use of engineering controls as described in Section 6(a). When nonroutine operations such as cleaning and maintenance must be performed in confined spaces not equipped with such engineering controls, the following requirements shall apply.

(1) Entry into confined spaces, eg, tanks, pits, or process vessels, that may contain diisocyanates shall be controlled by a permit system. Permits shall be signed by an authorized representative of the employer, certifying that preparation of the confined space, precautionary measures, and personal protective equipment are adequate and that prescribed procedures will be followed. Each work permit shall also be signed by the employee entering the confined space.
(2) Confined spaces that have contained diisocyanates shall be isolated by shutting off and sealing sources of diisocyanates.

(3) The confined space shall be cleaned with a solvent, flushed, washed with water, purged with air, and thoroughly ventilated. It shall then be inspected and tested for oxygen deficiency, diisocyanates, and the presence of combustible gases and other suspected contaminants before being entered and reinspected periodically at 1-hour intervals while occupied.

(4) Each employee entering the confined space shall be equipped with a self-contained breathing apparatus as specified in Section 4, a harness, and a lifeline. At least one other employee equipped for entry with the same type of protective equipment shall be stationed outside to monitor the operation. At least one additional person shall be available to assist in an emergency. All persons involved in the operation should be equipped with some mode of continuous communication. Mechanical ventilation shall be provided continuously when workers are inside the vessel.

(c) Storage and Handling

(1) Diisocyanates should be stored in closed containers and should be protected from heat and direct sunlight. They should not be stored near bases, primary or secondary amines, acids, or alcohols, since these chemicals may react violently with diisocyanates.

(2) Diisocyanate containers should be kept closed to prevent water from entering the containers, since water and diisocyanates react to produce a water-insoluble urea and carbon dioxide, which can generate enough pressure to rupture the containers. All containers of diisocyanates should be periodically inspected for signs of increased pressure within the containers and to ensure that the integrity of containers and seals are maintained. Leaking containers should be removed to the outdoors or to an isolated, well-ventilated area before the contents are transferred to other suitable containers, and leaks of diisocyanates should be cleaned up immediately.

(d) Control of Spills and Leaks

(1) Adequate facilities for handling spills of diisocyanates shall be provided and shall include suitable floor drainage and readily accessible hoses, mops, buckets, absorbent or decontaminating materials, and protective equipment and clothing.

(2) All spills or leaks of diisocyanates shall be given prompt attention by trained personnel, and all unessential personnel shall be evacuated from the area during cleanup.
(3) Waste material contaminated with diisocyanates shall be disposed of in a manner not hazardous to employees. Disposal methods must conform to applicable local, state, and Federal regulations and shall not constitute a hazard to the surrounding population or environment. Spills of diisocyanates shall not be allowed to enter public sewers or drains in amounts that could cause explosion or fire hazards.

(e) Emergency Procedures

Emergency plans and procedures shall be developed for all work areas where there is a potential for exposure to diisocyanates. The measures shall include those specified below and any others considered appropriate for a specific operation or process. Employees shall be trained to implement the plans and procedures effectively.

(1) Prearranged plans shall be instituted for obtaining emergency medical care and for the transportation of injured workers. A sufficient number of employees shall be trained in first aid so that assistance is available immediately when necessary.

(2) Employees who have significant skin contact with diisocyanates should wash with water or shower to remove the compound from the skin and should then wash the affected areas with alcohol. Contaminated clothing shall be removed and discarded or cleaned before reuse.

(3) In the event of a fire involving diisocyanates, all unessential personnel shall be evacuated from the area. The types of extinguishing media that should be used in fighting diisocyanate-supported fires are dry chemical powder, carbon dioxide, or foam. Water should be used only if large quantities are available. Firefighters should be cautioned of the possibility of exposure to other hazardous chemicals, such as hydrogen cyanide, phosgene, and carbon monoxide.

(4) After the fire has been extinguished, the area shall be inspected by properly protected personnel and shall be decontaminated to remove any suspected diisocyanate residues before unprotected workers are permitted to enter the area.

(f) Laundering

(1) Before being laundered, contaminated clothes shall be placed in a decontaminating solution of water containing 10% ammonia in a container that is impervious to diisocyanates.

(2) Personnel who clean contaminated clothing shall be informed of the hazards involved and shall be provided with guidelines on how to handle diisocyanates safely.
If an outside laundry facility is used, the launderers shall be advised of the hazards and proper procedures involved in handling contaminated work clothing. Contaminated clothing shall be transported to the outside laundry facility in sealed containers.

(g) Laboratory Activities

When diisocyanates are used in laboratory activities, the following provisions, in addition to other sections, shall be followed.

(1) Mechanical pipetting aids shall be used for all pipetting procedures.

(2) Experiments, procedures, and equipment that could produce aerosols or vapors of diisocyanates shall be confined to laboratory-type hoods, glove boxes, or other similar control apparatus. Exposure chambers and associated generation apparatus shall be separately ventilated.

(3) Surfaces on which diisocyanates are handled shall be impervious to absorption or penetration by these compounds.

(4) Laboratory vacuum systems, hoods, and exposure chambers shall be exhaust-ventilated in a manner consistent with Federal and local air pollution regulations.

(5) Airflow in the laboratory shall be established in a pattern flowing from the least to the most contaminated area. Contaminated exhaust air shall not be recirculated or discharged to other work areas.

Section 7 - Sanitation

(a) Preparing, storing, dispensing (including vending machines), and consuming food and smoking shall be prohibited in work areas where occupational exposure to diisocyanates may occur.

(b) Employees who handle diisocyanates or equipment contaminated with diisocyanates shall be advised to wash their hands thoroughly with soap or mild detergent and water before using toilet facilities, eating, or smoking.

(c) Plant facilities shall be maintained in a sanitary manner in accordance with sanitation requirements listed in 29 CFR 1910.141.

(d) The employer shall provide appropriate changing and shower rooms as required in 29 CFR 1910.141(d,e).
Section 8 - Monitoring and Recordkeeping

(a) Industrial Hygiene Surveys

Employers shall conduct an industrial hygiene survey at locations where diisocyanates are present in the workplace air to determine whether there is occupational exposure to airborne diisocyanates. Records of these surveys, including the basis for concluding that concentrations of airborne diisocyanates are at or below one-half the recommended limits, shall be maintained. Surveys shall be repeated at least annually and as soon as practicable after any change likely to result in increased concentrations of airborne diisocyanates.

(b) Personal Monitoring

If it has been determined that there is occupational exposure to diisocyanates, the employer shall fulfill the following requirements:

1) A program of personal monitoring shall be instituted to identify and measure, or permit calculation of, the exposure of each employee occupationally exposed to diisocyanates. Personal monitoring may be supplemented by source and area monitoring.

2) In all personal monitoring, samples representative of the exposure in the breathing zone of the employee shall be collected.

3) For each determination of the diisocyanate concentration, a sufficient number of samples shall be taken to characterize employee exposure. Variations in the employee's work schedule, location, or duties and changes in production schedules shall be considered in deciding when samples are to be collected.

4) Samples from each operation in each work area and each shift shall be taken at least once every 6 months or as otherwise indicated by a professional industrial hygienist. If monitoring shows that an employee is exposed to diisocyanates at concentrations above the environmental limits recommended in Section 1(a), additional monitoring shall be promptly initiated. If this confirms that exposure is excessive, control measures shall be initiated as soon as possible to reduce the concentration of diisocyanates in the employee's environment to less than or equal to the limits recommended in Section 1(a). The affected employee shall be notified of the excessive exposure and of the control measures being implemented. Monitoring of the employee's exposure shall be conducted at least every 30 days and shall continue until two consecutive determinations, at least 1 week apart, indicate that the employee's exposure no longer exceeds the recommended environmental limits. At that point, semiannual monitoring may be resumed.
(c) Recordkeeping

Environmental monitoring records and other pertinent records shall be kept for at least 30 years after the last occupational exposure to diisocyanates. The records shall include the dates and times of measurement, duties and job locations within the worksite, sampling and analytical methods used, the number, duration, and results of samples taken, concentrations of diisocyanates in air estimated from these samples, the type of personal protection in use at the time of sampling, and identification of the exposed employee. Employees shall be able to obtain information on their own environmental exposures. Environmental monitoring records shall be made available to designated representatives of the Secretary of Labor, the Secretary of Health, Education, and Welfare, and the employee or former employee.

Pertinent medical records shall be retained by the employer for 30 years after the last occupational exposure to diisocyanates. Records of environmental exposures applicable to an employee should be included in records. These medical records shall be made available to the designated representatives of the Secretary of Labor, of the Secretary of Health, Education, and Welfare, of the employer, and of the employee or former employee.
II. INTRODUCTION

This report presents the criteria and the recommended standard based thereon that were prepared to meet the need for preventing impairment of health arising from occupational exposure to diisocyanates. 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."

After reviewing data and consulting with others, NIOSH formalized a system for the development of criteria on which standards can be established to protect the health and to provide for the safety of employees exposed to hazardous chemical and physical agents. Criteria for a recommended standard should enable management and labor to develop better engineering controls resulting in more healthful work environments, and simply complying with the recommended standard should not be regarded as the final goal.

These criteria for a recommended standard for diisocyanates are part of a continuing series of documents published by NIOSH. The recommended standard applies to workplace exposure to diisocyanates arising from the processing, manufacture, and use of these compounds as applicable under the Occupational Safety and Health Act of 1970. The standard is not designed for the population-at-large, and any extrapolation beyond the occupational environment is not warranted. It is intended to: (1) protect against irritation of the skin, eyes, and respiratory tract by diisocyanates, reduce the likelihood of sensitization to these compounds, and minimize long-term effects on pulmonary function, (2) be measurable by techniques that are valid, reproducible, and available to industry and government agencies, and (3) be attainable with existing technology.

Criteria for a recommended standard for toluene diisocyanate (TDI) were published by NIOSH in 1973. The present document is intended to extend the coverage of the recommended standard to other diisocyanates and to take into account more recent data.

Occupational exposure to some of the diisocyanates has produced respiratory illness in workers. In addition to irritating the upper and lower respiratory tract, diisocyanates can cause sensitization, and sensitized individuals may develop asthma upon exposure to diisocyanates in very small amounts. Chronic impairment of pulmonary function has been reported in some workers exposed to diisocyanates. Diisocyanates are also irritating to the skin and eyes.
Further research is needed in a number of areas relevant to controlling occupational exposure to diisocyanates. The possibilities of carcinogenic, mutagenic, teratogenic, and reproductive effects from diisocyanates have not been adequately investigated. Studies in which effects on individuals are correlated with their actual exposures are also needed. Screening tests should be developed to permit early recognition of adverse respiratory effects resulting from sensitization to the diisocyanates. Animal experiments should be performed to determine how concentration and length of exposure affect the development of sensitization. Improved engineering controls should be developed to protect workers in certain diisocyanate applications, such as spraying.
III. BIOLOGIC EFFECTS OF EXPOSURE

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

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

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

Extent of Exposure

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

Diisocyanates are used to produce polyurethane foams, coatings, elastomers, and spandex fibers. Toluene diisocyanate (TDI), which is commercially available as standard mixtures of the 2,4- and 2,6-isomers, is generally used in producing flexible polyurethane foams. Methylene diphenyl diisocyanate (MDI), especially in partially polymerized forms, is used more frequently in rigid foams. A substantial amount of MDI (40-50% of the amount produced) is used in the manufacture of polyurethane systems, such as formulated packages of isocyanates, polyols, fluorocarbon blowing agents, fire retardants, surfactants, and catalysts. TDI and pure MDI, or special liquid MDI products, are used to make elastomers, which are used in manufacturing printing rolls, liners for mine chutes and grain elevator chutes, coated fabrics, shoe soles, and automobile bumpers [12,13]. MDI is also used in the foundry industry as part of a binding system for casting molds [14]. The total consumption of MDI and partially polymerized MDI in 1975 was about 300 million pounds. TDI consumption totaled about 400 million pounds, and only a few million pounds of other diisocyanates were used in 1975 [15].
Workers with potential occupational exposure to diisocyanates include adhesive workers, insulation workers, diisocyanate resin workers, lacquer workers, organic chemical synthesizers, paint sprayers, polyurethane makers, rubber workers, shipbuilders, textile processors, and wire-coating workers [16].

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

**Historical Reports**

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

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

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

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

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

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

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

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

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

Effects on Humans

Much of the investigation of the biologic effects of diisocyanates has been directed toward determining the extent and nature of sensitization to these compounds. In this document, sensitivity to diisocyanates denotes the tendency of
some individuals to have a respiratory response when they are exposed at concentrations much lower than those that irritate the respiratory tract in most people. Sensitization may develop gradually or suddenly after exposure to diisocyanates. The usual response is an asthmatic reaction, characterized by wheezing, dyspnea, and bronchial constriction. Use of these terms is not intended to implicate any particular mechanism as the cause of the reaction. The terms "allergy" and "allergic," on the other hand, are reserved for conditions in which an immunologic response is implied.

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

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

(a) Respiratory Effects

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

Pulmonary function testing has been used in many studies of workers exposed to TDI and other diisocyanates to evaluate changes in lung function. In 1964, seven furniture plant employees who sprayed, dipped, or painted with polyurethane varnish developed acute respiratory symptoms 0.5 hour to 3 weeks after their first known exposure [40]. Three measurements made after some improvements in ventilation showed TDI at 80, 100, and 120 ppb (570-850 μg/cu m). All seven men coughed and had difficulty in breathing and four had blood-stained sputum. Five of the seven were tested for forced vital capacity (FVC) and forced expiratory volume at 1 second (FEV1) 2-3.5 months after exposure and had higher values than they did shortly after exposure. The responses to a questionnaire given 22 months after
exposure after exposure suggested to the author that four of six who responded had become sensitized to TDI.

In 1965, Williamson [41] described six workers exposed to TDI in a polyurethane foam plant who developed symptoms that were considered suggestive of sensitization. Four of these, from a workforce of 99, had become sensitized during 18 months of exposure to TDI at concentrations usually below 20 ppb, apparently determined by area monitoring. The author believed that sensitization had resulted from exposure at higher concentrations caused by spills. Immediately after one spill, TDI at 200 ppb (1.4 mg/cu m) was found, but the concentration was less than 5 ppb (35 µg/cu m) 10 minutes later. All six affected workers had asthma or bronchitis with decreased ventilatory capacity (FVC and FEV1) during these incidents. Some of the subjects were also occasionally exposed to MDI, but always at concentrations below 20 ppb (204 µg/cu m).

In 1976, Charles et al [42] described a case of pneumonitis and three cases of chronic respiratory disease in workers exposed to TDI or HDI. Pneumonitis was diagnosed in a 50-year-old nonsmoker who had experienced difficulty in breathing, weight loss, and fever for 6 weeks at the time of examination. Prior to his 5 years of working in the polyurethane foam industry, he had been a coal miner for 11 years. Chest X-rays showed alveolar filling lesions in both the lungs. Two months later, pulmonary function tests showed reduced FEV1, vital capacity, total lung capacity, and residual volume of the lungs. A bronchogram showed peripheral cystic bronchiectasis in the right upper lobe. All immunologic tests for antibodies against TDI were negative. Microscopic examination of biopsy samples of lung tissue showed variations from normal architecture ranging from diffuse interstitial disease to acute inflammation and end-stage interstitial fibrosis. The authors stated that the areas of filled alveoli resembled desquamative interstitial pneumonitis and that the whole picture resembled that of a pulmonary hypersensitivity response to an inhaled allergen rather than coal-miners' pneumoconiosis, but they did not demonstrate that this was related to TDI exposure.

Two other workers developed severe dyspnea after exposure to spills of TDI [42]. Two to three years after exposure, both workers had moderate obstruction of the airways, as indicated by FEV1 measurements below predicted values; one also had a decreased vital capacity, and the other, although his vital capacity was normal, still experienced severe nonwheezing dyspnea after minimal exertion.

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

Pepys et al [43] tested four patients with occupational asthma for TDI sensitivity by simulating occupational exposures to a two-stage polyurethane varnish
with TDI activator. The subjects applied varnish with the TDI activator and, on a separate day, without the activator, to a surface in a small cubicle. When the activator was used, TDI concentrations in the air reached a maximum of almost 2 ppb (14 μg/cu m), as measured by the colorimetric method of Meddle et al [44]. No TDI was detected when the varnish alone was applied. All the subjects were essentially asymptomatic at the time of testing, and their FVC and FEV1 values were not more than 10% below predicted values. None showed positive responses in skin tests with common allergens, and none had a family or personal history of allergies.

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

The other two subjects were women who worked in a television factory department where coated wires were soldered [43]. The wire, coated with cured polyurethane and polyvinyl butyral, was dipped into a resin flux containing dimethylamine hydrochloride and then into multicore solder at 460 C. One woman, 44 years old, developed a chronic cough and, after 6 years, wheezing. The second woman, a 54-year-old supervisor in the same department, developed a productive cough, wheezing, and breathlessness, developing into severe bronchitis that kept her away from work for 5 weeks. Her symptoms recurred within 1 week of her return, and this pattern was repeated each time she attempted to return to work. Both women reacted to the varnish with TDI activator. The first woman had an immediate reaction that was resolved in 2 hours but was followed by a late reaction at 3-4 hours. The second woman had only a late reaction at 3-4 hours. She was also tested with various components used in the soldering operation. Positive results were obtained only with the simulation of the soldering operation using coated wire, but not with uncoated wire. This test produced a severe asthmatic reaction starting 30-60 minutes after exposure ended and continuing for 6 weeks before her FEV1 returned to pretest levels. Blood tests on these four patients showed no eosinophilia, but sputum collected from the 54-year-old woman contained eosinophils. This suggested to the authors a reagin-mediated reaction.

The sensitized individuals tested by Pepys and colleagues [43] had adverse reactions to TDI after exposures as brief as 10 minutes at reported concentrations of about 2 ppb (14 μg/cu m). The authors emphasized that none of these sensitized individuals had a known history of heavy TDI exposure, such as exposure
to spills. Thus, it appears that exposure to massive amounts of TDI, as from a spill, may not be necessary to produce sensitization.

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

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

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

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

All 63 workers were tested for respiratory responses when they painted a bench in a closed cubicle with varnish for 30 minutes [46]. After control values for pulmonary function were established, TDI was added to the varnish in increasing amounts on subsequent days until a reaction was elicited or until a maximum airborne TDI concentration of 20 ppb (140 μg/cu m) was reached. The test subject's FEV₁ and FVC were monitored before the exposure and for 8 hours afterwards. A subject was considered sensitive to TDI if his fall in FEV₁ after exposure was 15% more than on the control day. TDI concentrations in the cubicle were measured by a continuous monitor; in 23 cases, breathing-zone sampling was also performed, and the results of the two measurements were found to be closely correlated (r = 0.95).

Fifty-two of the workers were also tested by inhaling an aerosol of histamine acid phosphate at graded concentrations up to 32 mg/ml for 30-second periods [46]. A 20% fall in FEV₁ was considered evidence of bronchial hyperreactivity. Forty-six subjects participated in exercise testing, consisting of free running sufficient to increase the heart rate to 140 beats/minute. A fall in FEV₁ of more than 9% was regarded as indicative of an asthmatic reaction. All subjects were
prick tested with 23 common respiratory allergens, and those who reacted to 1 or more were considered atopic.

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

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

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

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

According to the authors, these two studies [46,47] suggested that both specific (probably immunologic) and nonspecific mechanisms contribute to
diisocyanate sensitivity. Among workers referred for respiratory symptoms, TDI-sensitive individuals were no more likely to have nonspecific asthmatic responses to histamine or exercise than were those who did not react to TDI. However, those who showed extreme sensitivity to TDI, reacting at concentrations of less than 1 ppb, did have an increased incidence of nonspecific asthmatic responses, suggesting to the authors that specific sensitivity to TDI might be exacerbated by irritative or pharmacologic hyperreactivity of the airways. The existence of such a dual mechanism in individuals extremely sensitive to diisocyanates was supported by the results of cross-challenging with TDI, MDI, and HDI [47]. The authors considered that immunologic cross-reactivity between these three compounds was unlikely because of their structural differences. They concluded that their results were consistent with the existence of a specific mechanism of TDI sensitivity coupled, in extremely sensitive individuals, with a pharmacologic mechanism that also caused increased reactivity to other diisocyanates.

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

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

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

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

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

Fifteen minutes after TDI inhalation, the values for FVC, FEV1, and forced expiratory flow between 25 and 75% of the FVC (FEF 25-75) in the worker who had previously been exposed to diisocyanates were 3.16, 2.79, and 3.62 liters, respectively, compared with corresponding preexposure values of 4.03, 3.68, and 5.92 liters. Airway resistance increased to 123% of the preexposure value at 15 minutes and 166% at 30 minutes. These changes were promptly reversed by a bronchodilator. In the other two subjects, there was no increase in airway resistance or decrease in FVC or FEV1, but one subject had a slight decrease in FEF 25-75 15 minutes after TDI inhalation.

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

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

(b) Immunologic Effects

The studies discussed in the preceding section indicate that some people are sensitive to diisocyanates, reacting to these substances in quantities much smaller than those that produce direct irritation of the lungs in most individuals. The mechanism of sensitization to the diisocyanates has been investigated in immunologic and pharmacodynamic studies on exposed workers.
Allergic responses that result from circulating antibodies can be either immediate or late, or a combination of the two. Immediate responses occur within minutes of exposure to the antigen, and late reactions appear a few hours after exposure. Immediate reactions to some substances are associated with atopy, an innate tendency to develop allergies, which may be related to high serum concentrations of reagin-type immunoglobulin (IgE). Atopy is often judged to be present if two or more skin tests with common inhalant allergens such as pollen and animal dander are positive.

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

In 1968, Bruckner et al [52] examined 26 workers exposed to unspecified isocyanates at reported concentrations of 0-240 ppb, with median values of 0-33 ppb. Air concentrations were determined by the Marcali method from samples taken near the workers' breathing zones. The workers, who had been exposed for 3 months to 11 years, were compared with 18 workers who had no known exposure to isocyanates. Blood from these workers was tested for reactivity by six immunologic assay techniques, using a conjugate of TDI with human serum albumin. Five of the 26 exposed workers were considered sensitized because they had asthmatic responses when exposed to small but unreported amounts of diisocyanates [52]. Four of these five, but only 1 of 21 unsensitized workers, had a history of allergies before working with diisocyanates. These four sensitized subjects also had clearly positive lymphocyte transformation tests, although all had been without exposure to diisocyanates for at least 6 months before testing. Neither unexposed nor unsensitized workers gave positive responses in this test. Passive cutaneous anaphylaxis (PCA), Prausnitz-Kuestner (P-K), leukocyte histamine release, passive hemagglutination, and gel diffusion precipitin tests were negative in all subjects and did not identify the sensitized workers. Subsequent studies by Nava et al [53] and Butcher et al [54] have not confirmed the diagnostic value of the lymphocyte transformation test for diisocyanate sensitivity.

Bruckner and coworkers [52] noted that all five sensitized workers had been exposed to diisocyanates at concentrations above 20 ppb. They also pointed out that the development of sensitization in these workers occurred only after 2 months to 5 years of repetitive exposures, concluding that overt clinical sensitization might be avoided if workers who showed increasingly severe signs of respiratory irritation were removed from further exposure to diisocyanates.
In 1970, Taylor [55] attempted to detect circulating antibodies to TDI in 55 workers with symptoms suggestive of TDI sensitivity. Their sera were compared with those from 40 unexposed textile workers for antibodies by tests for complement fixation, PCA, and red-cell-linked antiglobulin. None of the control sera, but 23 of the test sera, gave positive results in one or more tests. Five were positive in more than one test, but only one in all three tests. Six sera taken within a few months of an unusually high exposure to TDI that produced severe symptoms all showed positive test results. There was no correlation between positive antibody tests and eosinophilia as determined from blood or sputum samples. The author suggested that the lack of correlation between the tests indicated that they detect antibodies of slightly different specificity or of different immunoglobulin classes.

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

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

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

In 1975, Porter et al [56] published a retrospective study of sensitization in workers in a TDI manufacturing plant that had been in operation since 1956. The workforce exposed to TDI numbered about 200, remaining fairly constant throughout the study period, and the turnover during the 17 years of the study was about 100 workers. The investigators examined medical records of the workers to determine the relationship of clinical problems to TDI concentrations in the plant. Immunologic and lung function testing were performed on some workers.
Air samples analyzed by the Marcali method showed TDI concentrations of 50-100 ppb (350-700 μg/cu m), averaging 60 ppb (420 μg/cu m), prior to 1969; they were subsequently reduced by improved engineering controls to less than 50 ppb (350 μg/cu m) in 1970, 20 ppb (140 μg/cu m) in 1972, and 4 ppb (30 μg/cu m) in 1974 [56]. These values were not TWA concentrations, but averages of grab and continuous samples. Peak concentrations around 200 ppb (1,400 μg/cu m) resulting from leaks, spills, and loss of reaction control were measured on about 35 occasions; peak values were said to have decreased in the last 5 years of the study.

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

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

Porter et al [56] also presented case studies and results of immunologic and pulmonary function testing for 32 of the workers in this plant; some of these workers had signs of respiratory illness, according to medical diagnosis, while others were asymptomatic. Sera from these workers were tested for the presence of
### TABLE III-1

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

<table>
<thead>
<tr>
<th>Year</th>
<th>Sensitivity Cases</th>
<th>Average TDI Concentration (ppb)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1956*</td>
<td>1</td>
<td>60</td>
</tr>
<tr>
<td>1957</td>
<td>4</td>
<td>&quot;</td>
</tr>
<tr>
<td>1958</td>
<td>3</td>
<td>&quot;</td>
</tr>
<tr>
<td>1959</td>
<td>3</td>
<td>&quot;</td>
</tr>
<tr>
<td>1960</td>
<td>1</td>
<td>&quot;</td>
</tr>
<tr>
<td>1961</td>
<td>2</td>
<td>&quot;</td>
</tr>
<tr>
<td>1962</td>
<td>3</td>
<td>&quot;</td>
</tr>
<tr>
<td>1963</td>
<td>1</td>
<td>&quot;</td>
</tr>
<tr>
<td>1964</td>
<td>3</td>
<td>&quot;</td>
</tr>
<tr>
<td>1965</td>
<td>1</td>
<td>&quot;</td>
</tr>
<tr>
<td>1966</td>
<td>1</td>
<td>&quot;</td>
</tr>
<tr>
<td>1967</td>
<td>1</td>
<td>&quot;</td>
</tr>
<tr>
<td>1968</td>
<td>1</td>
<td>&quot;</td>
</tr>
<tr>
<td>1969</td>
<td>2</td>
<td>&quot;</td>
</tr>
<tr>
<td>1970</td>
<td>1</td>
<td>&lt;50</td>
</tr>
<tr>
<td>1971</td>
<td>2</td>
<td>&quot;</td>
</tr>
<tr>
<td>1972</td>
<td>0</td>
<td>&lt;20</td>
</tr>
<tr>
<td>1973</td>
<td>0</td>
<td>&quot;</td>
</tr>
<tr>
<td>1974</td>
<td>0</td>
<td>&lt;4</td>
</tr>
</tbody>
</table>

*Start-up

From Porter et al [56]
antibodies with the P-K test in monkeys and the PCA test in guinea pigs, by using a test antigen of TDI conjugated with serum protein from the same animal species; this is the only immunologic study found on TDI that used antigens made with homologous proteins in these tests. The P-K test was intended to identify IgE antibodies, which the authors expected to be associated with hypersensitivity reactions, and the PCA was to identify circulating IgG antibodies, which they assumed to confer immunologic protection. The workers' sera were similarly tested with a common pollen antigen.

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

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

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

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

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

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

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

In a subsequent report on the same study population, Butcher et al [58]
reported that PCA and P-K tests were negative throughout the 3 years of the
study. All radioimmunoassay tests were negative until March 1975, 2 years after
the study began. As of April 1976, weakly positive tests had been obtained on
eight men in the group with constant exposure, three in the intermittently exposed
group, and two in the unexposed group. By this time there had also been 10
positive skin tests; no group breakdown of these results was given. A later report
[59] indicated that skin testing had been discontinued because of its lack of
correlation with either clinical sensitivity, bronchial reactivity to challenge
exposures, or amount of exposure, and because it carried the risk of sensitizing the
subjects.
Immunologic studies on MDI have also produced ambiguous results, the immunologic findings showing little correlation with respiratory sensitivity. In 1966, Konzen et al. [60] described immune responses to MDI vapor and particulates in seven volunteers who sprayed polyurethane foam in an underground mine. Two of them had never been exposed to MDI, four had not been exposed during the last 6 months, and one worked with the substance daily. Concentrations of MDI were determined by the Marcali method; a comparison of prefiltred and unfiltered samples showed that, near the spraying operation, about 70-90% of the MDI detected was in the form of particles, mostly in the respirable range. During testing, the workers were intermittently exposed to MDI at reported concentrations of 13-244 ppb (130-2,500 µg/cu m) for 2.3-30 minutes. The workers' sera were tested for antibodies by the PCA test at 4 days, 14 days, 3 months, and 6 months after exposure. MDI conjugated to egg albumin was the test antigen.

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

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

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

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

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

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

Other studies, however, have indicated that a pharmacodynamic mechanism is also involved. Butcher et al [63] investigated the possible role of pharmacologic mediators in the bronchial response to TDI exposure. To determine whether TDI induced nonspecific histamine release, they measured spectrophotometrically the histamine released from leukocytes of 18 sensitive and 7 nonsensitive workers in response to TDI-HSA or HSA alone at 0.1-10 µg/ml for 40 minutes. The effect of TDI on beta-adrenergic receptors was examined by incubating lymphocytes from these workers with 10-150 µM TDI in the presence of isoproterenol, which stimulates the beta-adrenergic system, as indicated by an increase in cyclic 3',5'-adenosine monophosphate (AMP). Cyclic AMP levels were measured by a radioimmunoassay technique. The FEV 1's of 10 clinically sensitized workers and 10
workers without symptoms were also measured before and after exposure to mecholyl (acetyl-beta-methylcholine) at 25 mg/ml from a nebulizer to evaluate bronchial reactivity.

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

In the mecholyl challenge studies, 6 of the 10 clinically sensitive subjects showed a drop in FEV1 of more than 20% within 1.5 minutes after a single inhalation of mecholyl [63]. Only 1 of the 10 nonsensitized subjects gave such a response, and this occurred 5 minutes after inhaling mecholyl four times.

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

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

(c) Skin Effects

Some diisocyanates have been described as skin irritants [67,68], but there are few reports in the literature of skin effects from these compounds. Munn [35] has noted that, in several years of study, he has seen only two mild cases of skin irritation from diisocyanates and no cases of skin sensitization. Bruckner et al [52] reported that 6 of 44 workers in a chemical plant experienced skin irritation attributed to exposure to unspecified diisocyanates. These reactions consisted of erythema only on areas of skin that were in actual contact with the diisocyanates. One worker who often had diisocyanates on his hands noted that his skin had become hard and smooth, so that he had difficulty in turning pages.
Possible skin sensitization to TDI was described in two of the studies discussed in the previous section. Nava et al [53] reported that a worker with eczematous dermatitis was 1 of 3 workers who reacted positively to TDI in a patch test, out of 182 workers tested. Karol et al [62] found tolyl-specific IgE antibodies in two workers who displayed immediate skin reactions when exposed to TDI, apparently without a bronchial response. These skin reactions were extensive and not confined to areas where TDI had contacted the skin.

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

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

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

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

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

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

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

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

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

Le Quesne et al [73] and Axford et al [74] reported neurologic, respiratory, and gastrointestinal effects in men massively exposed to TDI while fighting a fire in a polyurethane foam factory. Two large tanks of TDI developed leaks during the
fire, and several men who attempted to close the leaking valves and fought the fire or who later removed the hoses and cleaned up the area were heavily exposed to TDI liquid and vapor, their clothing and shoes becoming soaked with it.

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

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

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

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

The effects of occupational exposure to HDI and several other chemicals were described in a 1968 report by Filatova et al [76] on 68 men and 14 women who manufactured the compound. Sixty-three of these workers (21-50 years old) had worked in the plant for 5 years or more. All the workers received a complete medical examination including several biochemical and clinical tests. Personal air
samples generally showed 100 µg/cu m (14 ppb) or less of HDI, 0.5 mg/cu m or less of phosgene, and 1.2-8 mg/cu m of chlorobenzene. Only the HDI concentrations were said to be in excess of the MAC.

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

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

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

Epidemiologic Studies

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

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

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

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

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

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

<table>
<thead>
<tr>
<th>Plant</th>
<th>Date</th>
<th>No. of Tests</th>
<th>Maximum</th>
<th>Average</th>
<th>Established Respiratory Cases</th>
<th>Questionable Respiratory Cases</th>
<th>Max. No. Workers at Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>1/58</td>
<td>8</td>
<td>10</td>
<td>8</td>
<td>3</td>
<td>0</td>
<td>50</td>
</tr>
<tr>
<td>2</td>
<td>12/58</td>
<td>6</td>
<td>&lt;10</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>50</td>
</tr>
<tr>
<td>2</td>
<td>12/60</td>
<td>6</td>
<td>50</td>
<td>40</td>
<td>14</td>
<td>25</td>
<td>100*</td>
</tr>
<tr>
<td>2</td>
<td>1/61</td>
<td>9</td>
<td>30</td>
<td>10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>6/61</td>
<td>6</td>
<td>20</td>
<td>8</td>
<td>3</td>
<td>2</td>
<td>50</td>
</tr>
<tr>
<td>2</td>
<td>1/62</td>
<td>6</td>
<td>14</td>
<td>8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>1958</td>
<td>4</td>
<td>20</td>
<td>10</td>
<td>0</td>
<td>0</td>
<td>25**</td>
</tr>
<tr>
<td>3</td>
<td>1961</td>
<td>8</td>
<td>15</td>
<td>7</td>
<td>0</td>
<td>0</td>
<td>25</td>
</tr>
<tr>
<td>4</td>
<td>1959</td>
<td>4</td>
<td>20</td>
<td>10</td>
<td>1</td>
<td>3</td>
<td>40</td>
</tr>
<tr>
<td>4</td>
<td>1961</td>
<td>5</td>
<td>1</td>
<td>0.6</td>
<td>0</td>
<td>0</td>
<td>40</td>
</tr>
<tr>
<td>4</td>
<td>1961</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>1959</td>
<td>4</td>
<td>20</td>
<td>15</td>
<td></td>
<td></td>
<td>6***</td>
</tr>
<tr>
<td>6</td>
<td>1961</td>
<td>28</td>
<td>70</td>
<td>15</td>
<td>3</td>
<td>0</td>
<td>40</td>
</tr>
<tr>
<td>9</td>
<td>1961</td>
<td>3</td>
<td>8</td>
<td>6</td>
<td>0</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>12</td>
<td>1962</td>
<td>6</td>
<td>-</td>
<td>9</td>
<td>0</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>13</td>
<td>1962</td>
<td>4</td>
<td>-</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>20</td>
</tr>
<tr>
<td>14</td>
<td>1962</td>
<td>6</td>
<td>-</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>20</td>
</tr>
</tbody>
</table>

*Additional company analyses verify that air levels were high*

**The workers wore respirators, which probably indicates acute irritation**

***Some workers had been transferred after complaints***

Adapted from reference 37
than the actual numbers exposed to TDI, which could not be determined from the paper.

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

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

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

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

All the workers tested were free of respiratory symptoms [17]. In four series of measurements of FVC and FEV1, the only significant change was a fall in FEV1 at the time of the second measurement (P<0.01), and subsequent tests showed no significant change from baseline FEV1 values. There was little difference between Monday and Friday values; daily changes were not measured. Williamson noted that an examination of the records of workers who had left the TDI operation uncovered no evidence that the study group had been self-selected for health reasons. A subsequent study of sensitized workers [41], including four from this group of employees who became sensitized during the 18 months following this investigation, has been described in Effects on Humans.

Adams [82,83] studied the long-term effects of TDI on the health of workers manufacturing it in England. A 1970 report [82] on pulmonary function testing of 175 men in a plant where TDI concentrations rarely exceeded 20 ppb (140 μg/cu m) indicated that decreases in the group mean FEV1 and FVC over 5 years significantly exceeded predicted values. However, new employees also had FVC and FEV1 measurements below predicted values, which were based on a North American survey. When the results from 114 men were examined individually, only 16 (11%) showed a decline in performance on pulmonary function tests significantly in excess of predicted values; 5 of these had decreases in both FVC and FEV1, 3 in FEV1 only, and 8 in FVC only. These results suggest that the decrease in group mean values was caused by 16 sensitized individuals. Adams pointed out that the validity of the data was questionable, since predicted values were based on a North American population and their relevance to English workers was unknown.

In a subsequent report, published in 1975, Adams [83] compared the TDI-exposed workers with unexposed control groups from the same geographic area. The workers included in this part of the study had been exposed to TDI for 1-11 years without adverse effects on their health. Records of pulmonary function tests
on 180 workers at two plants during 1964-1972 were compared with values for 608 control subjects living nearby who had no contact with TDI. Pulmonary function measurements were made on the same day each week between 2 and 3 in the afternoon. Results from the standard Medical Research Council (MRC) respiratory questionnaire given to 76 men still employed at the plants were compared with those from 76 controls who had no contact with TDI but who did similar work at a nearby chemical plant.

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

Comparison of the pulmonary function data from 180 workers with those from 608 control subjects revealed that exposure to TDI did not affect their FEV1 or FVC values [83]. No significant difference in respiratory symptoms was found between 76 currently employed men exposed to TDI and controls. Nine of 76 men in the control group had wheezing, compared with only 1 of 76 men exposed to TDI.

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

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

Pulmonary function data for 61 men who had had no contact with TDI for 2-11 years showed that their average FVC and FEV1 values were slightly lower than control values after adjustment for age and height [83]. Eleven of the 20 workers
who had been removed from the plants because of sensitization to TDI and whose preemployment lung function records were available were asymptomatic after 3-8 years without exposure, and 12 of these 20 had FEV₁ and FVC values unchanged from their preemployment levels. Six had FEV₁ and FVC values between 90 and 100% of their preemployment levels, and two had values of 80-90%. Those who had reduced pulmonary function complained of dyspnea on exertion, nocturnal dyspnea, and tightness in the chest.

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

Peters and his group [84-87] conducted a 2-year study of pulmonary function in workers in a polyurethane plant. They measured FVC, FEV₁, peak flowrate (PFR), and flowrates (FR) at 75, 50, 25, and 10% of vital capacity. Measurements were made at the beginning and end of work on Monday and later in the week; tests were repeated every 6 months. Detailed occupational and smoking histories were taken from the workers, and respiratory symptoms were evaluated by the MRC questionnaire. For environmental measurements, area samples, apparently collected at 6-month intervals, were analyzed by the Marcali method.

The initial study [84], made during December 1966, included 38 workers, 7 of them women, with an average age of 36.3 years (range 18-62 years), employed an average of 104.6 weeks (2-624 weeks). Environmental measurements taken during this period showed TDI concentrations ranging from 0.1 to 3.0 ppb (0.7-21 μg/cu m). Pulmonary function measurements on 34 workers showed a mean daily decrease in FEV₁ of 0.19 liter (P<0.001). Significant daily decreases were also noted in FVC (P<0.001), PFR (P<0.05), FR50% (P<0.01), and FR25% (P<0.05). From Monday morning to Friday morning, the mean FEV₁, FR50%, and FR25% all showed significant decreases (P<0.001). Responses for smokers and nonsmokers were similar, but workers with respiratory symptoms had a significantly greater decrease in FEV₁ than those without symptoms (P<0.05). The authors noted that there appeared to be no relationship between pulmonary function changes and amount of exposure, which they judged from the distance between work stations and sources of TDI.

At the 6-month followup [85], 28 of the 34 workers were still employed, and 6 new workers were added to the study group. Environmental concentrations at that time ranged from undetectable to a high of 12.0 ppb (85 μg/cu m) in the TDI pouring area. Monday preshift and postshift measurements of pulmonary function showed significant decreases (P<0.02) in both FVC and FEV₁; Tuesday morning tests showed essentially complete recovery in FVC, but FEV₁ values were still significantly lower than on the previous morning.

When pulmonary function test results were compared with those from tests done 6 months earlier, significant decreases were found in FEV₁, the ratio FEV
1/FVC, and FR values at 75, 50, 25, and 10% of vital capacity [86]. The authors noted that there was a high correlation (r=0.72) between the 1-day and 6-month decreases in FEV 1. The only other variable significantly correlated with pulmonary function test results was lifetime smoking history, and when this factor was held constant, the 6-month changes in FEV 1 were still significantly correlated with diurnal changes (r=0.60).

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

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

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

In another study from the same laboratory, Wegman et al [89,90] performed pulmonary function testing on 112 workers exposed to TDI in a factory manufacturing polyurethane cushions. Occupational and smoking histories and results from the MRC respiratory symptoms questionnaire were collected from each worker, and the FEV 1 was measured before and after work on a Monday following a 3-day weekend. Environmental concentrations of TDI were determined from breathing-zone samples analyzed by the Marcali method. The highest concentrations measured were 13 ppb [46] and 9 ppb [90] (90 and 60 µg/cu m). The workers were divided into groups of approximately equal size exposed at 1.5 ppb (12 µg/cu m) or less, 2.0-3.0 ppb (14-21 µg/cu m), and 3.5 ppb (25 µg/cu m) or more.
Initial measurements showed a dose-related diurnal decrease in FEV1 in the three groups [89]. At the 2-year followup [90], only 63 members of the original workforce were still employed. Examination of records showed that 40 of those no longer employed had resigned voluntarily and that these workers had shown a diurnal decrease in FEV1 of 0.126 liter at the earlier testing, compared with 0.096 liter in those who were still employed. While this difference was not significant, the authors noted that it reflected a trend for self-selection based on health among TDI workers.

In general, work assignments had been stable over the 2 years, with workers averaging 20 months at a work station; workers were therefore assigned to exposure groups on the basis of their usual work station [90]. Since 5 workers had variable exposures and could not be assigned to any group, final testing was performed on 57 workers; 20 of these in each of the high and low exposure groups and 17 were in the medium exposure group. The incidence of coughing and phlegm production increased with higher exposure; 15% of the 57-person study group had symptoms suggestive of chronic bronchitis, but these were not related to exposure level. The 2-year decrease in FEV1 averaged 0.102 liter (SD = 0.204 liter) in the exposed workers; the groups with low, medium, and high exposure had respective decreases of 0.012, 0.085, and 0.205 liter (SD = 0.204, 0.177, and 0.185 liter). The authors noted that the decrease in the high-exposure group was "clearly excessive," while that in the low-exposure group was "clearly within normal limits." The authors' analysis of variance showed the difference in 2-year decrement in FEV1 in the three groups to be significant at P<0.01. Age, length of employment, and smoking habits did not differ significantly in the three groups. Since several factors that affect lung size, including sex, height, and race, differed among the groups, the authors standardized for lung size by dividing the 2-year decrease by the initial FEV1 measurement; this standardized figure still showed a significant difference between exposure groups.

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

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

Detailed medical histories, clinical examinations, pulmonary function testing, and hematologic, chemical, and enzyme-diagnostic laboratory tests were made on the workers, who had been employed for up to 25 years. The time and frequency of these tests were not indicated. There was no significant difference in mean FEV1 between workers exposed for less than 3 years and those exposed 10-25 years, although the mean for smokers was significantly different from that for nonsmokers. Laboratory tests indicated there were no alterations of peripheral blood values, hematopoietic system, or kidney function.

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

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

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

Environmental concentrations of TDI were determined throughout the study by both area and personal monitoring [58]. Area monitoring was performed from August 1973 using Model 7000 TDI detectors from MDA scientific, calibrated with a gas diffusion cell and confirmed by the Marcali method. Personal monitoring with MCM monitors from the same supplier began in July 1975. All workers were
monitored continuously throughout a complete 22-day shift rotation. Area sampling showed frequent excursions above 20 ppb (140 μg/cu m) in TDI production and drumming areas, with weekly TWA concentrations as high as 40 ppb. However, the authors reported large discrepancies between area monitoring results and those of personal monitoring, which were generally lower.

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

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

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

Lung function test results were statistically correlated with these cumulative exposures in cross-sectional and longitudinal analyses [59]. Cross-sectional analysis of 139 men tested in December 1977 by step-up regression showed no significant association of pulmonary function test values with cumulative exposure.
Longitudinal analysis included all workers who had participated in pulmonary function testing a minimum of three times over at least 3 years and those who had been tested at least twice for lung volume and diffusing capacity over at least 2 years; the former group included 117 men, the latter 132 [59]. Correlation coefficients were calculated for cumulative exposure and annual rates of change in several pulmonary function variables, and mean values were compared by smoking and atopy categories. Step-up regression was used to regress annual rates of change in lung function onto cumulative exposure, smoking, atopy, and interactions between these variables.

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

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

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

In a 1973 NIOSH health hazard evaluation, Vandervort and Shama [93] investigated respiratory symptoms and acute lung function changes in workers exposed to TDI at low concentrations at a plant making polyurethane foam ice chests and picnic jugs. During a preliminary visit, air samples were collected and analyzed for TDI by the modified Marcali method of Grim and Linch [94].
questionnaire to identify histories of respiratory symptoms was administered to all 290 employees of the plant, about 200 of them exposed to TDI. The authors did not indicate the total number of workers with respiratory symptoms or describe their exposures to TDI. Twenty-nine of the 200 exposed workers were selected for further study; 13 of these were experiencing respiratory symptoms, as indicated in responses to the questionnaire, and 16 were asymptomatic. These workers were subdivided into moderate and low exposure groups on the basis of environmental measurements made at the time of the initial visit. The four workers making up the symptomatic low-exposure group were among 14 sensitized workers in the plant who had been transferred away from the immediate area of the foaming operation because of intolerance to TDI. Seven unexposed control employees, matched to the study group for age, sex, and smoking habits, were selected as controls.

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

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

Results of pulmonary function testing showed no significant difference between morning and evening testing except in the symptomatic low-exposure group of four sensitized workers who had been transferred out of the foaming area; this group also showed significantly greater decreases in FVC and FEV 1 than did the controls [93]. The individual with the greatest decrease, who had never smoked, was exposed at a concentration of only 0.2 μg/cu m and thus was highly sensitive to TDI.
In the asymptomatic groups with both moderate and low exposure, all but two of the workers reported mild irritation of the mucous membranes, and three had respiratory symptoms such as coughing or chest tightness [93]. All 13 workers in the symptomatic groups reported coughing, chest tightness, wheezing, or shortness of breath. There was a considerable increase over preshift findings in the number of symptoms reported at the end of the shift in both the moderate- and low-exposure symptomatic groups and some increase in the asymptomatic groups.

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

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

Although there have been several reports of respiratory effects in workers exposed to MDI, few studies have been found that indicate exposure concentrations associated with these effects. In a 1973 NIOSH health hazard evaluation, Vandervort and Lucas [61] investigated pulmonary function in workers in a plant manufacturing fibrous glass tanks. Concentrations of MDI were determined from both area and personal samples on 2 different days during MDI foaming operations and analyzed by the Marcali method as modified by Grim and Linch [94]. Breathing-zone concentrations of MDI reached 110 μg/cu m for some foam operators; other workers had average exposures of less than 50 μg/cu m. Workers in this process were also exposed to styrene at concentrations occasionally exceeding 100 ppm and to methylene chloride, toluene, and acetone at a few parts per million.
Preshift and postshift lung function testing was conducted on 29 exposed employees on a Monday when no MDI was used in the plant and on a Thursday when foaming operations took place; 12 of these employees worked in the immediate area of the foaming operation [61]. One worker had a preshift FEV1 less than 75% of his predicted value, and he and two other workers had abnormally low FEV1/FVC ratios; all three men were smokers, however, so the significance of these decrements is difficult to interpret. During the shift when foaming was carried out, none of the exposed workers showed a significant decrement in pulmonary function measurements compared with eight unexposed controls matched to them by age, sex, and smoking history.

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

Other studies found on populations of workers exposed to MDI have provided no quantitative information on exposure concentrations, but they do indicate that there is a relationship between adverse effects and exposure levels or duration of exposure. For example, in 1971, Tanser et al [97] examined the effects of MDI exposure on 57 employees in a factory producing rigid polyurethane foam moldings. Fourteen of the 57 workers reported that any contact with MDI vapor produced effects ranging from a sore throat and wheezing to severe asthma and tightness in the chest. Spirometric analysis showed that 8 of the 57 employees had an FVC of less than 90% of the predicted value or an FEV1/FVC ratio below 75%; only 2 of these 8 reported symptoms of sensitivity to MDI.

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

The 1976 studies of Saia et al [98] and Fabbri et al [99] explored the relationship between exposure to MDI and chronic nonspecific lung disease in workers in an Italian refrigerator factory. The total exposed workforce of 180 comprised 94 furnace workers (who removed polyurethane molds from the furnace and were estimated to have the highest exposures), 32 injectors, and 54 assembly line workers were also included. The groups were similar in average age and length of employment.
Responses to a questionnaire indicated that 85 of the workers in the plant had respiratory symptoms [98]. The prevalence of these symptoms was least in workers exposed less than 4 years and greatest in those exposed more than 8 years; the average age in all three groups was 37-38 years. Pulmonary function studies showed that about half of the 180 workers had vital capacity and FEV1 measurements below 90% of predicted values, and 15-20% had values below 80% of predicted [99]. The 85 workers with respiratory symptoms had pulmonary function measurements significantly lower than the average for the 180 employees. These measurements decreased with length of exposure even when adjusted for smoking.

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

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

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

Animal Toxicity

The acute toxicity of several diisocyanates, including TDI, MDI, HDI, NDI, and IPDI, has been studied in laboratory animals. Results of LD50 and LC50 determinations for diisocyanates are presented in Table XI-3 [2,5,36,91,101-104]. All the diisocyanates that have been studied caused irritation when applied directly to the skin of rabbits or instilled into their eyes. Their potentials as skin and eye irritants, determined from these studies, are summarized in Table XI-4 [2,104].
Several studies have also evaluated the effects of exposing animals to sublethal concentrations of diisocyanates. In 1962, Duncan et al [101] exposed mice, rats, guinea pigs, and rabbits to TDI at 2-10 ppm (14-70 mg/cu m) for 4 hours. Chamber concentrations were measured by the Marcali method. Microscopic examinations of tissue sections showed tracheitis and bronchitis with sloughing of the superficial epithelium in animals exposed to TDI at 2 ppm and killed by the 4th day after exposure. Lungs of animals killed 7 or more days after exposure did not differ significantly from those of controls, suggesting that the effects were reversible. In animals exposed at 5 or 10 ppm, damage was more severe and long-lasting. There were areas of coagulation necrosis of the superficial epithelium surrounded by inflammatory cells, and at points of deep ulceration, connective tissue had developed. Bronchopneumonia developed in all species except mice. Since the animals were exposed only once, this lung damage was the result of irritation rather than an allergic reaction.

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

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

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

Lung damage in these animals generally increased in severity for several days after exposure ended [106]. A rabbit examined immediately after exposure had essentially normal lungs, but animals killed 3-10 days later had bronchopneumonia, bronchitis, perivasculitis, and lung abscesses. A rabbit killed after 20 days had only
chronic bronchitis. Rats killed immediately had less inflammation than those killed later, but fibrous tissue had proliferated in the walls of the bronchioles in several rats. At 3–24 days after exposure, inflammation was marked, and animals had bronchopneumonia, extensive fibrous tissue proliferation, and polypoid hyperplasia of the epithelium. All control rats had bronchiectasis, which the authors attributed to chronic murine pneumonia. In guinea pigs, there were localized accumulations of lymphocytes, macrophages, and plasma cells throughout the lungs and varying degrees of pneumonitis and bronchopneumonia. No abnormalities of the heart, liver, kidneys, lymph nodes, or spleen were found in any of the animals.

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

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

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

Lomonova and Frolova [5] compared the toxic effects of inhalation of hexamethylene diisocyanate (HDI) with those of chlorhexyl isocyanate (CHI), a major
byproduct of HDI manufacture. Results of their 2-hour LC50 studies in mice showed that HDI was 2.3 times as toxic as CHI. The threshold concentration for influence on the CNS in mice was 1 mg/cu m for HDI and 10 mg/cu m for CHI, although the threshold concentrations for respiratory irritation were similar--2.9 mg/cu m for HDI and 4.5 mg/cu m for CHI.

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

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

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

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

Kondratyev and Mustayev [107] demonstrated skin sensitizing effects of HDI in experimental animals in 1974. Guinea pigs were sensitized by application of HDI in 50% solution in acetone to the skin for 2 days in a row. An initial irritant effect in the form of hyperemia, edema, and itching was observed at the sites of application. After 21 days, the degree of sensitization was determined by applying HDI in various concentrations to previously unexposed skin. A specific allergic reaction was seen in most animals at concentrations as much as 40 times less than the previously determined threshold dose of 50% for skin irritation. The epicutaneous sensitization observed was also accompanied by changes in the blood-serum protein fractions. This study suggests that skin contact with HDI in the workplace could lead to allergic dermatitis.
Kimmerle [104] found that IPDI produced moderate skin sensitization in guinea pigs. His experimental methods were not described but were said to follow the recommendations of the Food and Drug Administration. IPDI, administered intradermally, produced a larger area of swelling on reinjection than it had in an earlier injection in all 15 guinea pigs tested.

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

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

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

Guinea pigs previously exposed to TDI at 2-5 ppm showed changes in respiratory patterns when exposed at 20 ppb, but controls did not react to TDI at this concentration [109]. Patch tests showed skin sensitization to TDI, but serologic tests for sensitization were negative. Guinea pigs preexposed to TDI at 0.5 ppm did not show measurable respiratory changes, suggesting that a threshold for sensitization existed between 0.5 and 2.0 ppm. There was no evidence of sensitization in monkeys after reexposure, and there were no serologic changes indicative of sensitization. The authors concluded that exposure to large amounts
of TDI may produce sensitivity to TDI in lower concentrations, but that this sensitivity might not involve an allergic mechanism. However, they noted that the difficulty in preparing a suitable antigenic system made it impossible to determine whether an immunologic mechanism was involved.

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

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

Correlation of Exposure and Effect

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

The many reports of respiratory effects from exposure to TDI indicate a general correlation with exposure concentrations. The clearest evidence for such a relationship is that the number of affected workers decreases as concentrations are reduced. Elkins et al [32] determined average concentrations at 14 plants with a total workforce of 379 where 43 established cases of TDI intoxication had occurred. In the plant with the highest average concentration, 200 μg/cu m, 14 of 100
workers developed respiratory illnesses in 1 year. In all other plants with average TDI concentrations above 70 μg/cu m, there were cases of respiratory illness, but none occurred at plants where TDI concentrations averaged 30 μg/cu m or less.

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

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

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

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

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

A long-term study of workers in a TDI-manufacturing plant, conducted by Weill et al [57,59,92] and Butcher et al [54,58,62], showed no significant exposure-related changes in lung function. TDI concentrations in the plant generally ranged
from 14 to 50 µg/cu m during the 5.5-year study. The entire study population, which included controls from elsewhere in the chemical factory not exposed to TDI, had excessive declines in some pulmonary function measurements compared with predicted values, but there was no difference between groups with constant, intermittent, and no exposure, and decreases were not correlated with cumulative exposures. These findings are questionable on the basis that the control group may have been so affected by exposure to other chemicals that the study was insensitive to possible effects of TDI exposure.

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

Several studies have shown that sensitive persons react to TDI at very low concentrations and that their responses are dose-related. Butcher et al [54] reported that some sensitive individuals reacted at 70 µg/cu m but not at 35 µg/cu m, and two persons who reacted at the latter concentration were not affected by a challenge exposure at 20 µg/cu m [57]. Carroll et al [45] obtained asthmatic reactions in sensitized persons challenge-tested with TDI at about 7 µg/cu m. Some of these subjects reacted after a 15-minute exposure, while others reacted only if exposure lasted 30 or 60 minutes. O'Brien et al [46,47] found that about 25-50% of sensitized workers who reacted to TDI in challenge tests responded to even trace amounts of TDI (less than 1 ppb or 7 µg/cu m) with a decrease in pulmonary function; these extremely sensitive individuals also tended to have bronchial reactions to exercise, histamine inhalation, and other diisocyanates. In one plant, workers transferred away from foaming operations because they had become sensitive to TDI still experienced
respiratory symptoms in areas of the plant where concentrations were below 7 μg/cu m [93]. No one has demonstrated a concentration of TDI below which no sensitized individual will have a respiratory reaction.

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

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

The failure of these data to show a quantitative correlation of exposure and effect reflects the difficulty in evaluating and interpreting the "sensitized" state. There is evidence that a substantial proportion of the working population is potentially sensitizable to the effects of TDI. Williamson [41] reported symptoms of sensitization developing in 4-6 members of a workforce of 99, about a 5% sensitization rate. Other studies suggest that the rate of sensitization may be somewhat higher. Four of 47 workers (9%) in an office that received exhaust air from a nearby TDI plant became sensitized; in 3 of these, sensitization was confirmed by bronchial responses in challenge tests, and the 4th improved when he was removed from exposure [45]. Porter et al [56] reported that 30 of the 300 workers (10%) in a TDI plant were diagnosed as sensitive to TDI during 17 years of operation. Adams [83] found that 15% of the workforce in one plant left during their 1st year of employment because of effects on their health; 1-3.5% left for the same reason during subsequent years, for a total of about 20%. A similar rate
was suggested in a study by Bruckner et al [52], in which 5 of 26 workers exposed to unspecified isocyanates were considered sensitized because they had asthmatic reactions at low concentrations.

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

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

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

Far less information exists on exposure to the other diisocyanates, but their effects appear to be generally similar to those of TDI. Thirty-four of 35 workers, only 6 of whom were exposed to MDI at concentrations above 150 μg/cu m, experienced irritation of the eyes, nose, and throat, and half of them had bronchial symptoms [96]. Workers exposed to MDI at 50-110 μg/cu m did not have a significant decrease in FEV 1 during a workshift in which foaming was carried out, but 3 of 29 workers had respiratory symptoms [61]. Workers exposed to MDI at
unknown concentrations in an Italian refrigerator factory had reduced vital capacity and FEV 1, and 85 of 180 workers had respiratory symptoms [98,99]. This study indicated that the effects were dose-related, since furnace workers, who were exposed to MDI at the highest concentrations, had significantly lower pulmonary function values and a greater prevalence of respiratory symptoms than workers elsewhere in the plant. The incidence of respiratory symptoms also increased with years of employment at the plant.

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

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

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

In rabbits, the threshold concentration for irritative lung damage from HDI was 2,900 μg/cu m, and repeated exposures at 1,200 μg/cu m for 40 days caused significant decreases in weight gain and oxygen consumption in mice [5]. Rats exposed to IPDI at 1,370 μg/cu m repeatedly for 4 weeks had decreased in weight gain and liver and spleen weights, but these effects were not seen at 640 μg/cu m [104].
In addition to causing respiratory symptoms, the diisocyanates are skin irritants and skin sensitizers. TDI [62,69], MDI [69], and IPDI [69] have produced skin sensitization in humans, and skin sensitization by IPDI [104], and MDI [107] has been demonstrated in guinea pigs.

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

Carcinogenicity, Mutagenicity, Teratogenicity, and Effects on Reproduction

No reports were found to indicate that TDI, MDI, HDI, NDI, or other diisocyanates produce carcinogenic, teratogenic, or reproductive effects in humans or animals. MDI was mutagenic to Salmonella typhimurium in the presence of a mammalian liver activating system, but TDI and dicyclohexylmethane 4,4'-diisocyanate showed no mutagenic activity in the same system (J Foderaro, written communication, June 1978). In the absence of other data on mutagenicity, this single study is insufficient evidence that diisocyanates are likely to be mutagenic in humans.
TABLE III-3
EFFECTS OF EXPOSURE TO DIISOCYANATES ON HUMANS

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

[66]
TABLE III-3 (CONTINUED)

EFFECTS OF EXPOSURE TO DIISOCYANATES ON HUMANS

<table>
<thead>
<tr>
<th>Compound</th>
<th>Concentration*</th>
<th>Duration</th>
<th>No.</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ppb</td>
<td>µg/cu m</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TDI</td>
<td>2.8-10</td>
<td>20-70</td>
<td>15 min</td>
<td>-</td>
</tr>
<tr>
<td>&quot;</td>
<td>2-7</td>
<td>14-50</td>
<td>5.5 yr</td>
<td>166</td>
</tr>
<tr>
<td>&quot;</td>
<td>&lt;5</td>
<td>&lt;35</td>
<td>-</td>
<td>17</td>
</tr>
<tr>
<td>&quot;</td>
<td>&gt;3</td>
<td>&gt;20</td>
<td>2 yr</td>
<td>20</td>
</tr>
<tr>
<td>&quot;</td>
<td>0.1-3</td>
<td>0.7-20</td>
<td>-</td>
<td>38</td>
</tr>
<tr>
<td>&quot;</td>
<td>&lt;2</td>
<td>&lt;14</td>
<td>2 yr</td>
<td>20</td>
</tr>
<tr>
<td>&quot;</td>
<td>&lt;1</td>
<td>&lt;7</td>
<td>-</td>
<td>12</td>
</tr>
<tr>
<td>&quot;</td>
<td>&lt;1</td>
<td>&lt;7</td>
<td>-</td>
<td>9</td>
</tr>
</tbody>
</table>

References: 54, 57, 93, 90, 84, 95, 67
### TABLE III-3 (CONTINUED)

**EFFECTS OF EXPOSURE TO DIISOCYANATES ON HUMANS**

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

*Concentrations given are average or usual range of exposures and do not reflect excursions.

**Unidentified isocyanate, probably TDI

***Also exposed to other chemicals, including styrene, phosgene, or organic solvents
IV. ENVIRONMENTAL DATA

Environmental Concentrations

Area monitoring of the startup and on-line procedures for TDI synthesis during the 1st year of production in a new manufacturing plant was conducted by Weill et al [92]. TDI concentrations were determined using commercially available continuous-tape area monitors that had been calibrated against results obtained by the Marcali method [111]. During the startup procedures, the mean weekly TDI concentrations for the synthesis, finishing, and drumming areas were 5.6, 17.3, and 11 ppb (39, 122, and 78 μg/cu m), respectively. The respective maximum excursion concentrations were 7.1, 20.5, and 12.9 ppb (50, 146, and 92 μg/cu m). The initial on-line production concentrations for the three areas were 11.3, 16.4, and 7.5 ppb (80, 116, and 53 μg/cu m) with respective excursions to 13.8, 21.1, and 8.8 ppb (98, 150, and 62 μg/cu m). When 8-hour TWA concentrations for the entire plant were analyzed for the 11 months of monitoring, it was found that the 1973 NIOSH-recommended TWA concentration limit of 5 ppb (35 μg/cu m) was exceeded on approximately half of the days.

More recent studies of the same plant by Dharmarajan et al [112] compared the results of the area monitoring with values obtained by continuous-tape personal monitoring. Both monitoring methods were used simultaneously during some period each day for 22 months. When 8-hour TWA values were analyzed, no positive correlation could be found between personal and area sampling. Area monitoring, then, did not seem to accurately reflect actual individual exposures.

Hervin and Thoburn [100] reported that concentrations of airborne TDI were below the TLV of 20 ppb (140 μg/cu m) in an aircraft overhauling facility where the painters sprayed aircraft with polyurethane paints. Area and personal samples were analyzed by the thin-layer chromatographic method of Keller et al [113]. The concentrations of airborne TDI near the aircraft fin, near the wing, on the floor where mixing was done, and on the floor midway between the two bays were <30, <20-30, 20, and <20 μg/cu m (<4, <3-4, 3, and <3 ppb), respectively. The corresponding concentrations of HDI were 40-100, <30-60, <20-300, and <20 μg/cu m (6-15, <4-9, <3-45, and <3 ppb). Thirteen personal samples taken at various operations contained TDI at concentrations of 40 μg/cu m or less. Corresponding HDI concentrations ranged from less than 30 to 300 μg/cu m.

In an operation where polyurethane foam lines were used to make automobile seat cushions, Butler and Taylor [114] detected no TDI in the areas where TDI pouring, heat curing, molded product removal, mold cleaning, and molded product trimming took place. Vandervort and Shama [93] of NIOSH recorded TDI at 5-31 μg/cu m (0.7-4.3 ppb) during foaming operations in a plant manufacturing picnic jugs, ice chests, and metal vacuum bottles. Air collected from the breathing zones
of several foaming operators contained up to 40 μg/cu m of TDI, i.e., the concentrations were lower than the present Federal standard of 20 ppb (140 μg/cu m).

HDI concentrations measured by Filatova et al [76] were 0-100 μg/cu m (0-15 ppb) in all the departments of a plant manufacturing HDI. However, concentrations of 200-240 μg/cu m (30-35 ppb), which exceeded the USSR MAC of 50 μg/cu m (7 ppb), were recorded while spills were being cleaned up.

Konzen et al [60] measured concentrations of MDI while preexpanded polyurethane foam was applied for 2.3-10 minutes at four locations in an underground mine. Unfiltered air samples were collected 5, 25, 50, and 75 feet away from the spray operation, and prefiltered air samples were also collected 5 feet away. Air samples were collected for 2.2-30 minutes at a flowrate of 1.0 liter/minute. The air samples were analyzed by the Marcali method [111]. The data showed that the concentration of airborne MDI decreased with increasing distance from the spray. When the mine shaft air ventilation rate was 8 feet/minute, an MDI concentration of 1,360 μg/cu m (133 ppb) was found at 5 feet and 160 μg/cu m (16 ppm) was found at 75 feet from the source of the spray [60]. At an air ventilation rate of 100 feet/minute, the concentration of airborne MDI downstream was reduced from 2,290 μg/cu m (224 ppb) 8 feet from the spray to 1,320 μg/cu m (130 ppb) 50 feet away.

Collecting air through membrane filters with an average pore diameter of 0.8 μm removed approximately 80% of the reactive MDI found 5 feet from the spray [60]. Light and electron microscopic examination of polyurethane foam particles trapped on the membrane filters showed that over 98% of them were less than 3 μm in diameter and that about 85% were less than 1 μm.

Fitzpatrick et al [115] conducted a survey of workers applying polyurethane foam containing MDI to the walls of an underground mine. Unfiltered air samples were collected 5, 10, 25, 50, and 100 feet downstream from the spray operation, and a few prefiltered samples were also collected. Air samples were collected for up to 30 minutes with the ventilation velocity in the mine at 60 feet/minute, and the samples were analyzed by the Marcali method. The results showed that concentrations of airborne MDI decreased with increasing distance from the spray operation. A portable aerosol photometer and a cascade impactor were used to determine the concentration and size of particles produced during the generation of the polyurethane foam. About 73% of the particles were 1-2 μm in diameter.

Fitzpatrick et al [115] stated that most of the MDI detected in the air was carried by this particulate matter in the reactive form. The reaction of MDI with other components of the foam was complete within about a minute, or 60 feet downstream from the spraying operation.

Dharmarajan and Weill [116] found that approximately 90% of the MDI present in air during a foam spray operation was blocked by passage through glass fiber or
Teflon filters (0.5 μm pore diameter). The percentage blocked was independent of MDI concentration in the range 20-550 μg/cu m, a finding that supports the contention that most airborne MDI is present in particulate form. Furthermore, they found that approximately 50% of the particles were less than 10 μm in diameter. Assuming that all MDI in the air is in the form of aerosols and assuming an equal collection efficiency for simultaneous sampling of particulates on a filter and MDI in an absorber, the authors found that MDI constituted 3.03–20.34% of the mass of the airborne dust collected on a filter.

Vandervort and Lucas [61] measured concentrations of airborne MDI during foaming operations in a factory that manufactured fibrous glass tanks. One of four breathing-zone samples analyzed for MDI by a Marcali method [94] showed that a foam operator was exposed to MDI at 12 ppb (120 μg/cu m) for 30 minutes. Concentrations of airborne MDI in 16 of the 38 samples taken during foam application ranged from undetectable to 26 ppb (260 μg/cu m). The concentrations of airborne MDI were highest within 3 feet of the point of application. Two samples taken less than 3 feet from the operation 20 minutes after foaming stopped showed airborne MDI at 3 ppb (30 μg/cu m). Analysis of 71 air samples collected over an average of 6.5 hours from the breathing zones of 18 employees showed that workers were exposed to other contaminants, such as methylene chloride, toluene, and acetone, at concentrations of a few ppm and to airborne styrene at 18-130 ppm.

In the end-cap area, 13 samples taken during and directly after foaming showed MDI concentrations averaging 4 ppb [61]. One sample taken from the chemical assembly area during foaming showed that the foam operator was exposed for 8 minutes to MDI at 25 ppb (250 μg/cu m), and three samples collected within 3 feet of foaming showed MDI concentrations ranging from 0 to over 1,000 ppb, presumably the limit of the analytical procedures used. Two samples collected during the first 30 minutes after foaming showed only residual amounts of MDI. Eighteen more breathing-zone samples from 12 employees in the foaming, chemical assembly, and end-cap areas and the corresponding 18 area samples showed that MDI exposures ranged from 0 to 11 ppb (110 μg/cu m). The highest concentrations were found in samples from foam operators, and other employees were exposed to MDI at less than 5 ppb (50 μg/cu m). Area samples indicated that MDI concentrations ranged from 3 to 25 ppb (30-250 μg/cu m) within 3 feet of foaming operations and from 0 to 15 ppb beyond this area.

In another NIOSH health hazard evaluation, Bodner et al [96] measured the concentrations of airborne MDI in a fibrous glassing area where a foaming operator sprayed tubs and showers with a foaming agent. According to the supplier, the foaming agent contained no TDI. Analysis of area samples showed that the areas adjacent to the foam gunner and to the last roller in the assembly line had concentrations of airborne MDI of 150 and 10 μg/cu m (15 and 1 ppb), respectively. Analyses of breathing-zone air showed that the foam gunner in the area was exposed to MDI at an average of 230 μg/cu m (23 ppb), a concentration exceeding the present Federal standard of 20 ppb (200 μg/cu m).
Tubich [14] measured air concentrations of MDI generated in foundry operations, where it is present as a component of an oil-base no-bake binding system. The author did not describe the collection of samples or identify the analytical method used. No measurable MDI concentrations were found in 10 samples from the mixing operation and 12 from the molding operation; both operations are conducted at room temperature. Ten samples from the torching or oven-drying operation also showed no MDI, and 17 mold-pouring samples showed less than 7 ppb (70 μg/cu m); these operations involve elevated temperatures, and the author attributed the low concentrations to the brevity of the operations, which did not permit significant vapor concentrations to be generated. Mean concentrations of MDI exceeded the Federal limit of 20 ppb (200 μg/cu m) in shakeout and core knockout operations; MDI was present in 25 shakeout samples at 2-160 ppb (20-1,600 μg/cu m), and in 9 core knockout samples at 6-66 ppb (60-660 μg/cu m).

Engineering Controls

The engineering controls recommended for all diisocyanates in this chapter are similar to those described in the 1973 NIOSH recommendations for TDI [37]. These control measures are frequently applicable in the control of polymeric diisocyanates as well.

The primary objective of engineering controls for operations using diisocyanates must be to reduce the concentrations of airborne diisocyanates so that they are at or below the recommended environmental limits. Process equipment should be designed so that the system is totally enclosed and operates, if possible, under negative gage pressure [9]. When it is necessary to open a vessel or when leaks or spills are likely, local exhaust ventilation systems should be provided. Unless other means can be used to control the concentrations of diisocyanates, the source should be fitted with a local exhaust ventilation system [9]. If a process is too large for this type of enclosure, dilution ventilation may be necessary.

Numerous polyurethane products exist, and the polyurethane may sometimes be formed under circumstances that are not readily adaptable to conventional exhaust ventilation procedures, eg, application of polyurethane foam to storage tanks to prevent corrosion. Some operations, such as spraying, mixing, foaming, injecting, flushing, pouring in place, and painting, can occur either in fixed locations or in the field. Workers engaged in these operations may require additional protection, such as positive pressure supplied-air respirators [37] and additional protective clothing. Although many types of diisocyanates are used in urethane foam systems, many of these systems contain polymeric isocyanates, which usually have lower vapor pressures [117]. For work with these polymeric isocyanates in field operations, where aerosols are likely to be generated, the same protection recommended for TDI should be used; the rate of dilution ventilation should be varied according to the rate of release of airborne particulate [117]. When planning exhaust ventilation systems to control diisocyanates, designers should consult Fundamentals Governing the Design and Operation of Local Exhaust Systems.
The concentration of diisocyanates in the workplace may also be decreased by substituting a compound with a lower vapor pressure. For example, where formulation considerations permit, MDI might be substituted for TDI [120]. In spraying and certain foaming operations where the diisocyanate is present in aerosol form, this substitution may not be an effective means of controlling exposure.

When ventilation requirements for any diisocyanate work area are determined, and it is established that an exhaust ventilation system is necessary, care must be taken in the placement of intake and exhaust vents [121]. Carroll et al [45] described respiratory sensitization from TDI in office workers as a result of TDI-contaminated air being drawn into the ventilation system of an office building from the exhaust vents of a neighboring factory using TDI. This report emphasizes the importance of determining that intake air for the ventilation system is not drawn from areas in which other diisocyanates are handled, and that exhaust vents be positioned to avoid exposure of other persons to the diisocyanate-contaminated air.

Sampling and Analysis

(a) Interfering Reactions With Airborne Chemicals

Because of the chemical reactivity of the diisocyanates, exposure to and measurement of diisocyanate monomers, as well as the effects of exposure to diisocyanates, may be complicated by reactions with other airborne chemicals. Dyson and Herman [122] examined the effect of relative humidity on TDI concentration as determined by the Marcali method [111]. This method measures TDI and one possible TDI hydrolysis product, toluene diamine, but not the TDI urea, 3,3'-diisocyanato-4,4'-dimethylcarbanilide. Humidified air was added in increasing amounts to dynamically produced, steady-state atmospheres of TDI (80% 2,4-TDI, 20% 2,6-TDI) initially determined to be at 34 or 400 ppb (240 or 2,800 μg/cu m). The relative humidity at 75 °C achieved in the controlled reaction chamber by this procedure ranged from 0 to 80%. Increasing humidity was shown to cause linear decrease in the Marcali values, presumably reflecting increasing concentrations of TDI-urea. Regression analysis of the data determined that, independent of the TDI concentrations used, a decrease of 3.2% in the Marcali value would result with every increased unit of absolute humidity (in g water/kg dry air). The reaction of TDI with water was shown to be essentially complete within 75 seconds. For less chemically reactive diisocyanates such as HDI [123], hydrolysis would be expected to occur at considerably slower rates. The authors [122] concluded that increased humidity reduces the concentration of atmospheric TDI, but not to a degree that would prove useful as a routine control measure in the workplace. A decrease in apparent TDI concentrations due to humidity has also been observed by other investigators [44,111,124,125].
Volatilized amines may also be presented in workroom air where diisocyanates are being manufactured or used. Toluene diamine, a synthetic precursor to TDI and a possible hydrolysis product, is known to interfere positively in the Marcali determination of TDI [124,126,127]. Other primary aromatic amines would be expected to be positive interferences with any method in which diisocyanates are determined as secondary reaction products of their amine derivatives.

Meddle and Wood [126] developed a method for detecting aromatic isocyanates in air in the presence of primary aromatic amines. Individual air samples were bubbled through two different absorber solutions. A solution of dimethylformamide (DMF) and 1,6-diaminohexane (DH) was used to trap the primary aromatic amine and inactivate the isocyanate in one air sample. The second air sample was drawn through a solution of DMF, DH, and hydrochloric acid that traps the primary aromatic amine and hydrolyzes the isocyanate to its corresponding amine. The samples were then diazotized and coupled, and the amount of amine or isocyanate present was determined spectrophotometrically using standard calibration curves. The color in the DMF-DH absorbent solution is produced by the primary amine alone, and that in the DMF-DH-hydrochloric acid absorbent solution is produced by both the amine and the isocyanate. The amount of isocyanate present in the air sampled was determined by subtracting the former value from the latter.

Tertiary amines, such as triethylenediamine (TEDA), which are often used as catalysts in urethane polymerizations, have been shown to reduce the apparent concentration of airborne TDI [124,127]. Smith and Henderson [127] were the first to report the negative interference of TEDA vapors in the determination of gaseous TDI by the Marcali and Reilly tape methods. The fraction of apparent TDI loss, when analyzed by both methods, ranged from 49 to 88%. These results led the authors to question whether the tape and Marcali values were underestimating actual TDI exposure levels in polyurethane foaming operations. The reported degree of negative interference, however, appears independent of the TEDA concentrations. In addition, the ratios of TEDA to TDI examined, 17-262 [127], are 135-2,100 times those that might be expected during actual foaming or spraying operations [128,129].

In a later attempt to elucidate the mechanism of tertiary amine interference, Holland and Rooney [124] compared values obtained for TDI in mixed TDI-TEDA atmospheres by three analytical techniques: midget impinger sampling and analysis by the Marcali method, continuous-tape monitoring, and direct air-injection gas chromatography.

All methods gave similar values for TDI, and each showed similarly decreased values for the same TDI concentration in the presence of TEDA [124]. In contrast to the previous report [127], this study demonstrated that the reduction in measurable TDI exhibited some dependence on atmospheric amine concentration. A summary of the data shows that, at TEDA-to-TDI ratios of 9.6-25, about 90% of the input TDI could be measured; at a TEDA-to-TDI ratio of 105, only 21-25% could be measured. Six other catalysts used in polyurethane manufacturing were
said to give similar results. The effect of TEDA on measurable TDI was significantly reduced when glass components of the experimental apparatus were siliconized to decrease surface adsorption. The authors commented that gas chromatography did not detect any stable reaction intermediates, including toluene diamine, in the mixed gas stream. The only reaction product found proved to be the TDI urea that had formed as a white powder on the surface of the mixing system. The authors concluded that all three analytical methods gave accurate measurements of atmospheric TDI in the presence or absence of tertiary amine catalysts and that the observed negative interference reflected an actual reduction in TDI concentration. Furthermore, the mechanism by which this reduction occurred may have depended on surface effects, relative humidity, and constituent concentration and residence time.

The above reports [124,127] suggest that the presence of tertiary amine vapors may catalyze the hydrolysis of airborne TDI to its urea. The reaction appears to be facilitated by absorption of one or more of the reactants to a surface [124]. Whereas gas chromatography of the mixed gases failed to isolate any stable reaction intermediate, the existence of short-lived, potentially toxic, reactive complexes in minute amounts cannot be discounted. Both studies [124,127] used concentrations of TDI that may be representative of actual working environments, 18-400 ppm; however, since the relative concentrations of amine used far exceeded realistic levels, the relevance of these results to the workplace situation remains questionable.

(b) Colorimetric Methods

Two methods, those of Marcali and Ranta, and modifications of them are most commonly used to measure aromatic isocyanate concentrations in air. The Marcali method [111] for measuring TDI involves bubbling the air sample through an acid absorber medium in which TDI is collected and hydrolyzed to the corresponding toluene diamine derivative. The amine is diazotized and coupled with 1-naphthyl ethylenediamine to produce a reddish-blue color. The intensity of this color is measured spectrophotometrically at 550 nm to provide an indication of the amount of TDI present. Marcali [111] reported that the method was capable of detecting 10 ppb (70 μg/cu m) of toluene-2,4-diisocyanate. He also determined that recovery of total TDI was apparently reduced when 35% toluene-2,6-diisocyanate was present. A similar reduction was reported by Meddle et al [44] for TDI mixtures containing 20 or 40% of the 2,6-isomer. To increase the accuracy of measuring mixtures of TDI isomers, both Marcali [111] and Meddle et al [44] recommended that standard curves be constructed with the appropriate isomer ratios. A portable field kit employing stable color standards could easily detect TDI at 50 ppb (360 μg/cu m) and could be modified to detect TDI at 20 ppb (140 μg/cu m). The method does not detect the TDI urea, 3,3'-diisocyanato-4,4'-dimethylcarbanilide, a hydrolysis product that is formed on reaction of TDI with water.

When Grim and Linch [94] examined the Marcali method for use with MDI, they found that 2 hours were required for complete color development. By
increasing the concentration of coupling reagent and partially neutralizing the
absorber solution with sodium carbonate, the authors reduced the coupling time to 15
minutes. The 1974 NIOSH Manual of Recommended Analytical Methods [130] has
incorporated the modifications of Grim and Linch [94] for routine measurement of
MDI. The method as described can determine 7-73 ppb (70-750 µg/cu m) of MDI
in 20 liters of air.

The Ranta method, as described by Zapp [36] and Marcali [111] can measure
both TDI and TDI urea with equal efficiency and cannot distinguish between them.
The compounds are collected by bubbling the air sample through a reagent solution
of aqueous sodium nitrite, ethylene glycol monoethyl ether (Cellosolve), and boric
acid. The intensity of the resulting orange-yellow color, measured at 450 nm, is
proportional to the concentration of either compound.

On the basis of field and laboratory evaluations of these two methods,
Skonieczny [131] concluded that the Marcali method was more suitable for field
determination of peak concentrations and for detecting small amounts of TDI.
Because the Ranta method requires a sampling time of 10-30 minutes to collect
sufficient amounts of TDI under usual working conditions, Skonieczny noted that it
might not detect momentarily high concentrations.

In the 1973 criteria document, NIOSH [37] recommended a method for
sampling and analyzing TDI in air. Sampling was accomplished by drawing air
through an all-glass midget impinger containing 15 ml of absorbing solution for 20
minutes at a rate of 2 liters/minute. For analysis, NIOSH recommended the
Marcali method [111], incorporating modifications reported by Grim and Linch
[94] and Larkin and Kupel [132]. Toluene diamine was used in place of TDI for
standards, since it is less toxic and easier to work with at room temperature. The
range of standards used was 1.0-20.0 µg of TDI or 3.5-70 ppb (25-500 µg/cu m) in
a 40-liter air sample. The sensitivity of the method was said to be improved by
increasing the length of the light path in the spectrophotometric cells. If amounts
of TDI greater than 70 ppb must be measured, the final reagent solution can be
diluted with absorber solution or a smaller air sample can be taken. Although MDI
is detected by this method, the time required for complete color development under
the prescribed conditions is 1-2 hours, compared with 5 minutes for TDI [94]. It is
possible that TDI can be determined in the presence of MDI if the absorbance of
the test solution is measured within 10 minutes after adding the coupling agent.

Various field test kits using the principles of the Marcali or Ranta method
have been developed. These kits have simplified and standardized test procedures
for on-site measurement. Grim and Linch [94] described a field kit for
determining concentrations of TDI. Air was sampled through the standard midget
impinger using a self-powered, constant-rate air aspirator. The sensitivity of the
field kit employing the Marcali method was improved to allow detection of TDI at
10 ppb (70 µg/cu m) by collecting a larger volume of air and by reducing the
volume of the reagent used. By increasing the coupling reagent concentration and
adding sodium carbonate to the absorbing medium, the field kit could be used for
determinations of airborne MDI. The Ranta method was modified to allow measurement of TDI urea and TDI at concentrations as low as 10 ppb by increasing the volume of sample collected, reducing the volume of reagent used, and increasing the length of the light path in the colorimeter to 100 mm. To make the Ranta method suitable for field use, color standards that can be used with a portable visual comparator were developed and included in the kit.

Belisle [133,134] described a field kit suitable for measuring TDI in air. Air was sampled at a rate of 0.1 cu ft/minute through an acidified absorber solution in a modified midget impinger containing in situ-generated glutaric aldehyde and cation-exchange resin. This process converts TDI to its corresponding amine, which reacts with glutaric aldehyde to form an orange-red product. To measure the concentration of TDI, the orange-red color that appeared on the surface of the resin beads was matched against a set of color standards. Results reportedly agreed closely with those obtained by the Marcali method. A major advantage of this method is that the color develops while the air is being sampled. At a concentration of 10 ppb (70 µg/cu m) of TDI, sampling and analysis can be completed in 5 minutes. The method is capable of measuring TDI at 5 ppb (35 µg/cu m) in 0.5 cubic foot of air, and it may be modified to measure other aromatic isocyanates or aromatic amines by constructing appropriate calibration data.

Reilly [135] developed a field method for determining MDI in air. The sample was drawn through an acid absorber medium in which MDI was collected and hydrolyzed to the corresponding amine. The amine was diazotized and coupled with 3-hydroxy-2-naphthanilide to form a pinkish-orange azo compound. This was extracted into chloroform and compared visually with inorganic color standard solutions. The method was capable of measuring MDI at 10-40 ppb (100-400 µg/cu m) with a 5-liter sample of air. The equipment required is portable, and a complete determination can be accomplished in 12-15 minutes.

Meddle et al [44] extended the Grim and Linch adaptation [94] of the Marcali method to a general field-test procedure capable of detecting other aromatic diisocyanates in air. Procedures were described that established maximum sampling and analytical conditions for TDI, MDI, NDI, dianisidine disocyanate, and a polymeric form of MDI, polymethylene polyphenyl isocyanate. The authors noted that, with the exception of TDI, attempts to generate dynamic vapor atmospheres by bubbling dry nitrogen through liquified diisocyanates proved unsuccessful. Airborne concentrations produced by this method diminished rapidly indicating that these diisocyanates, where present in air, would be in aerosol form. Similar observations were made by Reilly [135] in his work with MDI. Analysis of all tested diisocyanates was subsequently performed on generated aerosol atmospheres [44]. A consequence of the aerosol nature of these test atmospheres was the adoption of a sintered dome bubbler for air sampling. To ensure complete recovery, aerosol particles trapped in the sintered dome during sampling were allowed time to dissolve in the absorber solution before coupling reagent was added. A 10-minute digestion time was judged sufficient under these conditions. Impinger
sampling at the same flowrate of 1 liter/minute was only 53% as efficient as sampling with the sintered dome bubbler. For use in the field, permanent color standards for MDI, NDI, TDI, and polymethylene polyphenyl isocyanate are available for concentrations of 10-40 ppb.

The aerosol nature of MDI in air was further supported by results of a recent study by Dharmarajan and Weill [116]. They found that MDI vapor generated by heating the diisocyanate to 110°C in a small enclosed room did not behave as a gas but rather as an aerosol. They compared the amount of MDI collected in absorbers according to the standard NIOSH-recommended method [130] with and without prefilters and found that 98% of the airborne MDI was collected on a Teflon filter backed with a cellulose pad and 87% was collected on the filter backed with a stainless-steel pad. Since the collection efficiency of the absorber for MDI aerosol was unknown in this study, it is likely that the actual amount of MDI in samples was higher than the amount detected. The percentage of the sample consisting of MDI aerosol could also have been underestimated. The authors also pointed out that since the major portion of MDI in air is present as an aerosol, concentrations of this compound should be reported in mg/cu m rather than ppm.

(c) Tape Methods

Reilly [136] developed a test-paper method to measure the concentration of TDI in air. A 5-liter air sample was drawn through a chemically treated filter paper at a rate of 1 liter/minute. After sampling was completed, stain was allowed to develop on the test paper for 15 minutes. The intensity of the stain was then compared with a set of color standards for TDI concentrations of 10, 20, 40, 60, and 100 ppb (70-700 μg/cu m). The method is specific for the aromatic diisocyanates, with no response obtained from the diamine derivatives. Several preparations of test paper, exposed to TDI at known concentrations, showed a variation in color development of about 20%. Qualitative tests indicate that the method may be adapted to detect MDI and NDI, and it is reported to require less analytical skill to perform than other methods.

Reilly's test-paper method was developed into a continuous monitor, the Dunlap/ICI Continuous TDI Monitor, which uses test-paper tape that moves continuously past a sampling port through which air is drawn by a vacuum pump. Fifteen minutes after it has been exposed to the air, the tape passes an optical readout head, and the intensity of the color produced by TDI on the tape is compared to an unexposed area of the tape and converted to concentrations. A strip-chart recorder connected to the instrument provides a permanent record of the measurements obtained. Miller and Mueller [137] evaluated the performance of this monitor by using the NIOSH-modified Marcali method [130] as a referent analytical procedure. When laboratory and field results were pooled and the data for the two methods compared by regression analysis, a correlation coefficient of 0.97 was found. It was suggested, however, that additional experimentation be done to determine the accuracy and precision of both methods for use in TDI
concentrations of 5 ppb (35 μg/cu m) or less. During the course of this study [137], the authors discovered that two midget impingers in series were necessary to trap airborne TDI adequately. Although the 1973 NIOSH criteria document [37] stated that a "single bubbler absorbs 95% of the diisocyanate if the concentration is below 2 ppm," Miller and Mueller determined that, at TDI concentrations ranging from 1 to 76 ppb (7-532 μg/cu m), the collection efficiency of the first bubbler was approximately 83%.

The Dunlap/ICI monitor has also been used to measure MDI under laboratory [116,138] and field [116,137] conditions. Development of tape color intensity in response to MDI, either as a vapor generated in toluene solution [138] or when spotted in known concentrations directly on the tape [116], was approximately 75% of the maximum when read at 15 minutes and the reaction was complete in 4 hours. Maximum color development with TDI, on the other hand, is complete at 15 minutes.

Where MDI may be found as a constituent of a reactive particulate, the accuracy of the monitor may be further reduced. In an initial test of the applicability of the Dunlap/ICI area monitor in MDI systems, results obtained by the monitor in foam and paint spraying operations were 36% and 35%, respectively [138], of those detected by the bubbler method of Meddle et al [44]. The author [138] explained that continued polymerization of MDI with other aerosol components would reduce the availability of reactive isocyanate functional groups for color formation.

Miller and Mueller [137] extended their evaluation of the TDI tape monitor for use in an MDI foaming operation. After applying the manufacturer's recommended correction factor, the authors found that the values obtained by the tape monitor at readings ranging from 1 to 5 ppb (10-50 μg/cu m) were in good agreement with those obtained by the spectrophotometric method.

Dharmarajan and Weill [116] assessed the performance of the TDI continuous tape monitor for analyzing both heat-generated and foam-spray-generated MDI aerosols. Eight-hour TWA concentrations of MDI in ppb determined by the monitors were compared with those obtained by the standard NIOSH-recommended method [130]. In the range of 5-8 ppb as determined by the NIOSH method, the tape monitors consistently gave readings indicating concentrations two to three times higher. The authors [116] explained this difference by pointing out that, whereas the filter tape medium of the monitors could be expected to collect 99.9% of the MDI aerosol, an impinger flowrate of 1 liter/minute would select against certain particle size populations. The absorber collection efficiency, however, was not determined in this study. Having emphasized the necessity for expressing MDI concentrations in units of mg/cu m, the authors devised a procedure for calibrating the TDI tape monitor for use in MDI aerosols. Known concentrations of MDI dissolved in toluene were spotted on the tape. After a time interval consistent with that used under workplace conditions, the tape was run through the photometric detector. Color intensity developed during this time could be
correlated with the known concentration of MDI in mg/cu m. However, the authors [116] did not test the validity of this calibration method in the workplace.

In view of these findings [116,138], it is important that calibration curves for continuous tape monitors used to detect MDI be constructed to simulate as closely as possible the actual conditions under which the monitor will be used.

The phenomenon described by a number of investigators [60,115,116,135,138], that MDI is rarely, if ever, found as a gas at ambient temperatures, has been shown to apply to NDI and dianisidine diisocyanate [44] and can be considered a general property of other diisocyanates that are solids or viscous liquids at room temperature.

(d) Chromatographic Methods

In 1974, Schanche and Hermann [125] described a paired sampling and analytical method that can reliably measure TDI concentrations in air in the ppb range. The sampling train consisted of three midget impingers connected in series, each containing 10 ml of chromatographic-grade toluene. To analyze TDI, the investigators used a gas chromatograph equipped with an electron-capture detector.

The impingers were connected by glass and Teflon connectors to prevent the surface absorption of TDI that would occur if synthetic or natural rubber connectors were used [125]. The sampling rate was limited to 1 liter/minute because at higher sampling rates the toluene in the impinger would bubble over into the next impinger in the series and because excessive evaporation of toluene could occur. The authors suggested that 0.1 ml should be the maximum allowable volume for evaporation for one impinger. This rate of evaporation would introduce an additional 1% error into the cumulative error for the resultant concentration. The total collection efficiency of this system was 98%, with the first impinger being 90% efficient.

The analytical system consisted of a Barber-Colman Series 5000 Selectra System gas chromatograph equipped with a tritium-source electron-capture detector [125]. A 4-foot Pyrex U-tube column (1/4-inch inner diameter) was packed with Chromosorb G (60/80 mesh) solid support coated with a mixture of Epon 1001 and Apiezon L. Oxygen-free nitrogen was used as the carrier gas at an optimum flow rate of 100 ml/minute at an inlet pressure of 15 psig. Operating temperatures were 150 C for the column and injection port and 170 C for the detector bath. The liquid sample size for injection was 5 μl [125]. Calibration curves were prepared by sequentially diluting TDI with chromatographic-grade toluene [125]. The calibration curves were then checked against a primary standard (TDI permeation tube). This paired system of sampling and analysis could accurately analyze TDI in a 10-liter sample of dry air at 1.4 ppb (10 μg/cu m). When the system was tested using air that had not been previously dried, readings were lower than expected. After appropriate corrections were made for the effects of humidity [122], the authors [125] obtained an overall efficiency of 97%.
A thin-layer chromatographic (TLC) method was developed by Keller et al [113] for isolation and quantitative determination of various isocyanate compounds. The method is based on the reaction of isocyanates with N-4-nitrobenzyl-N-n-propylamine (nitro reagent) to form the corresponding ureas. The concentration of the ureas are then determined. The method is said to be capable of isolating and measuring diisocyanate monomers in the presence of partially polymerized reaction products. Concentrations of both monomer and free isocyanate-containing polymer can be determined.

Air in the working environment is sampled with two impingers containing a solution of the nitro reagent [113]. The solutions in the impingers are then combined and evaporated to dryness, and the remaining residue is dissolved in benzene. The benzene solution is chromatographically analyzed on thin-layer silica-gel plates, and ureas are visualized by reducing the nitro groups to amines and by diazotizing the amines with nitrous fumes. After evaporation of the nitrous fumes, the thin-layer chromatographic plates are sprayed with N-1-naphthyl ethylenediamine and quantitative determinations are made by visual comparison of the samples with standards. Scanning densitometry can be used for more accurate determinations. The lower limit for the determinations was found to be 80 μg/cu m for MDI, HDI, and TDI. The method, however, is time consuming and requires skilled attention to detail during the reduction and coupling steps.

A high-performance liquid chromatographic (HPLC) method for detecting isocyanates was developed by Dunlap et al [139]. Concentrations in work environments were determined by collecting the isocyanates with an impinger at a flow rate of 2 liters/minute into nitro reagent dissolved in toluene. The reaction product ureas were analyzed using HPLC with ultraviolet detection. Chromatographic separation of the ureas was accomplished on a pellicular silica HPLC column. As with the TLC method [113], both aliphatic and aromatic isocyanates can be analyzed. The HPLC method, however, extended the detection limits to 5, 5, and 10 μg of TDI, MDI, and HDI, respectively. The values were based on a 20-liter air sample and a 90-μl injection volume. The method cannot be used to analyze atmospheres that can oxidize or reduce the nitro reagent used in the impingers during sampling.

A similar but independently derived HPLC method has been described and extensively characterized by Vogt et al [123]. The study examined a variety of column matrices, sizes, packing protocols and solvent programs for the determination of nitro-urea derivatives of MDI, 2,4-TDI, 2,6-TDI, HDI, and a polymeric form (primarily trimer) of HDI, 1,3,5-tris-(6-isocyanatohexyl) biuret. Similar to the results of Dunlap et al [139], excellent resolution of mixed ureas was obtained. Depending on the experimental conditions [123], minimal detectable limits were slightly variable; 1.2-2.0 ng for MDI and 2,4-TDI, 1.2-5.0 ng for 2,6-TDI, 5.0-6.2 ng for HDI, and 40-240 ng for the HDI biuret. The apparent reaction times of the diisocyanates with nitro reagent, judged to be pertinent in field applications, were also measured. Maximum urea formation for MDI, 2,4-TDI, 2,6-TDI, and HDI was complete in 10, 10, 20, and 60 minutes, respectively.
Reproducibility was well within experimental error, relative standard deviations being generally below 15%. Urea derivatives for all tested isocyanates were reportedly stable for about 10 days.

A preliminary NIOSH study [140] of the HPLC analytical technique failed in its attempts to reproduce the results obtained by the developers of the method [32,123]. The report [140] cited the following reasons for failure: deterioration of silica gel columns caused by excess nitro reagent in samples; oxidation of the nitro reagent after sampling; shipping and exposure problems posed by the use of toluene in the collection medium. The time allotted for the study precluded an attempt to resolve these problems.

Two of these difficulties have already been addressed by previous investigators [123,139]. To eliminate excess nitro reagent in samples, Vogt et al [123] added p-tolyl isocyanate to the absorbing solution after the collected diisocyanates were allowed time (about 1 hour) to react. The resulting monourea derivative was observed to run well ahead of the diureas. Alternatively, column life was preserved from the effects of excess nitro reagent by daily flushing of the column with solvent.

Decomposition of nitro reagent during sampling in oxidizing or reducing atmospheres remains a serious disadvantage of this method [123,139]. The decomposition reported [140], however, appeared to be a result of insufficient purification of the synthesized nitro reagent and of the grade of toluene used. Nitro reagent is now commercially available. When the nitro reagent is dissolved in chromatographic-grade toluene, absorber solution impurities should be minimal. Compounds that will interfere with this procedure are those that absorb in the ultraviolet range and also have the same column retention time as the diisocyanate being investigated.

Toluene remains the solvent of choice for this method [123,139,140]. Federal regulations (49 CFR 172) allow air transportation of toluene in quantities of up to 1 quart/package. Where personal sampling procedures may expose workers to toluene vapor for extended periods, air sampler outlets could be fitted with an appropriate scrubber.

After reviewing the currently available analytical methods, NIOSH recommends the HPLC procedure described above [123,139]. This method is described in detail in Appendix I. Although the method may necessitate some initial experimentation before routine measurements can be made, it is the most sensitive method. Because quantities of diisocyanates in the nanogram range may be determined, relatively short sampling times are allowed. Analysis of the primary reaction product of diisocyanate and absorber ensures direct measurement of available isocyanate functional groups and precludes interference by other diisocyanate reaction products. The relative chemical stability of the nitro-ureas [123,139] allows for possible elapsed time between air sampling and subsequent analysis. In addition, the procedure is capable of separating and identifying mixtures of
diisocyanate monomers as well as mixtures of monomer and partially polymerized products [123,139]. The procedure has not been tested with diisocyanates other than TDI, MDI, and HDI. It is reasonable to assume, however, that a method which can effectively separate the isomers of TDI, as does the HPLC method, [123,139] can be used successfully for measuring other diisocyanates. Where possible interference from reducing or oxidizing atmospheres may be encountered, alternate sampling and analytical methods should be calibrated with the HPLC procedure.

Numerous studies have shown that absorber collection efficiency may vary dramatically [44,111,116,125,137]. It is therefore recommended that two serially connected impingers be used for air sampling until a reproducible collection efficiency is established for any given operation, after which a single impinger may be used for routine monitoring. The recommended flowrate of 2 liters/minute for 10 minutes represents a compromise for efficient aerosol and vapor sampling [115,116].
V. WORK PRACTICES

Exposure to TDI has caused irritation of the respiratory tract and reduced pulmonary function; this can progress to a condition resembling asthma or chronic bronchitis [32,43], which in some cases has been fatal [22]. These effects have been observed in sensitized individuals exposed at concentrations as low as 7 μg/cu m [45], although respiratory effects have generally been reported in unsensitized workers only at concentrations of 140 μg/cu m or higher [90]. Irritation of the respiratory tract has also been observed in individuals exposed to MDI [61,97,98] and HDI [42]. Exposure to TDI and other diisocyanates at high concentrations, eg, during accidental spills, is a major cause of sensitization [31,41,42,52], and there is evidence that massive exposures may produce effects on the CNS [71,73]. Diisocyanates are also skin irritants and sensitizers [105,141]; however, effects on the skin from these compounds do not appear to have been a major problem in industry [35]. Eye contact with liquid TDI and TDI vapor has produced irritation and watering of the eyes [2,9,120], and it is likely that direct eye contact with other diisocyanates would produce similar effects.

Diisocyanates encompassing a wide range of molecular weights and physical properties (see Table XI-1) are available for use in industry. The potentials of these compounds to irritate the respiratory tract, mucous membranes, eyes, and skin vary depending on the particular diisocyanate being considered. The potential for skin irritation and eye injury is generally higher for the lower molecular weight diisocyanates and the severity of these irritant responses is reduced with increasing molecular weight [1,2,142,143].

The potential respiratory hazards encountered during the use of diisocyanates in the workplace are related to their vapor pressures [1,2,142]. The lower molecular weight diisocyanates tend to be more readily volatilized into the workplace atmosphere than the higher molecular weight diisocyanates [1,2]. Figure XI-1 presents graphically the decrease in vapor pressure with increasing molecular weight for several diisocyanates. The lower molecular weight diisocyanates, such as HDI and TDI, when handled without special precautions, can release amounts of vapor sufficient to be extremely irritating to the respiratory tract of workers [2,142]. Higher molecular weight compounds such as NDI, IPDI, and MDI present a lesser vapor hazard when handled in well-ventilated areas at normal room temperatures, ie, less than approximately 40 C (104 F) for MDI [1,2,6,104,121,142]. Although the vapor pressures of the higher molecular weight diisocyanates are relatively low, they may generate vapor concentrations sufficient to cause respiratory and mucous membrane irritation if they are handled in poorly ventilated areas. Air exhaust hoods may be necessary under such conditions [121]. High molecular weight diisocyanates like MDI may also present significant vapor hazards when heated or used in exothermic production processes [1,2,6,8].
The physical state of the diisocyanate being handled will also affect the potential hazards encountered during its use. MDI and NDI, which are normally solid materials at room temperature, present less vapor inhalation or skin contact hazard as a result of splashes or spills than the lower molecular weight liquid diisocyanates do [1,2]. However, workers should be aware of the possibility of respiratory and mucous membrane irritation from the dusts of such compounds, and of contamination of their clothing with the powdered diisocyanates. Operations involving the use of such compounds, such as weighing, should be performed with equipment incorporating a barrier between the worker and the diisocyanate. Local exhaust ventilation may also be necessary. Clothing contaminated with solid diisocyanate should be decontaminated and laundered as soon as possible to prevent further exposure of the worker and to avoid contamination of other work areas. Spills involving these compounds should also be decontaminated and cleaned up as soon as possible.

The processes and operations in which diisocyanates are used will affect the severity of the hazard. Industrial processes involving evaporation from large surface areas or spraying operations may result in a greater potential vapor hazard than operations involving pouring-in-place or frothing techniques [6,8,104,121]. Special hazards may arise in spraying operations since the diisocyanate-containing aerosol cloud may drift to areas beyond the immediate spraying area.

Diisocyanates react with water to form carbon dioxide and water-insoluble polyureas [11]. The rate of reaction is very slow for TDI and MDI at temperatures below 50 C. As the temperature increases, the reaction between these compounds and water becomes more vigorous. TDI and MDI will also react with bases, such as sodium hydroxide, ammonia, primary and secondary amines, acids, and alcohols. This reaction may be violent, producing enough heat to increase the evolution of diisocyanate vapor and the generation of carbon dioxide. These reactions, like the reactions with water, may lead to dangerously increased pressure in closed containers [144]. Thus, containers of diisocyanates should be kept closed as much as possible to prevent water, atmospheric moisture, or other reactive compounds from entering and vapors or solids from escaping.

Diisocyanates should be transported or stored in sealed, intact containers. A "sealed container" is one that has been closed and kept closed to the extent that there is no release of diisocyanates. An "intact container" is one that has not deteriorated or been damaged to the extent that diisocyanates are released. Diisocyanates in sealed, intact containers should pose no threat of exposure to employees; therefore, it is not necessary to comply with required monitoring and medical surveillance requirements in operations involving such containers. If, however, containers are opened or broken so that diisocyanates may be released, then all provisions of the recommended standard should apply. Indoor storage areas should be dry, fireproofed (automatic sprinkler systems should be considered), and well ventilated; temperature extremes in these areas should be avoided [9,121]. The storage area should have a firm floor made of some nonabsorbent material [6]. If diisocyanates are accidentally frozen during storage or while in transit,
they may be thawed by storage in a warm area [121]. Extreme caution must be used if heat is applied, and a flame or similar localized heat source should never be used.

Diisocyanates are transported in drums, tank trucks, or tank cars. Containers should be properly labeled and shippers should be aware of precautions to be taken for transporting, loading, and unloading the particular container and type of diisocyanate being transported. Emergency measures to be taken in the event of an accident or some type of damage to the container or tank en route should also be worked out in advance by the shipper and the supplier or producer [9]. The Hazardous Materials Regulations as promulgated by the US Department of Transportation in 49 CFR Subchapter C should be adhered to where applicable.

Where bulk quantities of diisocyanates are handled, adequate ventilation should be provided and respiratory protective equipment should be readily available. Workers should wear chemical safety goggles when handling solid diisocyanates and chemical safety goggles with face shields when using liquid diisocyanates. Local exhaust ventilation should be employed when opening containers of diisocyanates [9]. Local exhaust ventilation should also be used when performing laboratory operations involving diisocyanates.

Since the flashpoints of most diisocyanates are high, the compounds are not flammable under normal circumstances, although they can burn if they are heated sufficiently. Because of the wide range of physical and chemical properties of diisocyanates (see Table XI-1), it is important to be aware of the potential fire hazard that may be associated with a particular diisocyanate in the industrial setting in which it is used or stored. Any diisocyanate involved in a fire may produce high concentrations of toxic vapors, and only trained and properly equipped personnel should be involved in firefighting. All nonessential personnel should be evacuated from the area during a fire. Suitable extinguishing media for fighting diisocyanate-supported fires are dry chemical powder, carbon dioxide, or foam. Water should be used only if large quantities are available, since the reaction between water and a hot diisocyanate may be vigorous. After the fire is out, the area should be inspected by properly protected personnel, and any suspected residues should be decontaminated before other workers are permitted to return to the area.

Contact with diisocyanates will cause plastic and rubber materials to become brittle after a short time. This could result in leaks from plastic or rubber hoses. Where a particular machine requires high-pressure lines or hoses for diisocyanates, these lines should be made of polytetrafluorethylene or equivalent with metal braiding on the outside. Neither TDI nor MDI is corrosive to metals at temperatures normally encountered in industrial operations [144].

Under normal working conditions, where engineering controls and work practices are adequate to keep diisocyanate concentrations below the recommended environmental limits, employees should wear coveralls (heavy cotton material is
recommended) and gloves made of either rubber or polyvinyl chloride [144]. If liquid diisocyanates may be present on the floors of work areas, rubbers or shoe coverings made of materials resistant to the penetration of diisocyanates should be worn over leather safety shoes. Rubbers that become contaminated with diisocyanates should be decontaminated or cut up and discarded.

If splashes or contact with aerosols of diisocyanates are likely to occur, employees should wear rubber or polyvinyl chloride gloves and aprons and rubber boots; appropriate respiratory equipment, as described in Table I-1, should be readily available. Where supplied-air respirators are used, the air supply must come from a source not contaminated with diisocyanates [145]. For all workers near spray gun operations (within approximately 10 feet), an air-supplied hood, impervious gloves (rubber or polyvinyl chloride), tightly buttoned coveralls, and rubber galoshes or boots are needed [146]. Workers without this equipment should not be permitted close enough to spraying operations performed outdoors to be exposed to diisocyanate vapors or particulates. A minimum of 50 feet is recommended. For indoor spraying operations, the safe distance for unprotected workers will depend on the type and efficiency of the ventilation provided [147,60] while ambient conditions, such as wind direction and velocity, will be important in determining a safe distance for outdoor operations [146].

Cup-type chemical safety goggles with face shields should be worn wherever there is danger of liquid diisocyanate coming in contact with the eyes. For continuous eye protection under normal conditions, spectacle-type safety glasses with 48-wire mesh sideshields may be used. Equipment for eye protection must be in accordance with the American National Standard for Occupational and Educational Eye and Face Protection, Z87.1-1968 [148], as specified in 29 CFR 1910.133.

Protective clothing that has become contaminated with a diisocyanate to an extent that may result in an excessive respiratory or skin contact hazard should be promptly removed. Before being reused, the clothing should be soaked in a decontaminating solution (eg, 90% water, 2% liquid detergent, 8% concentrated ammonia solution) and then laundered normally. Employers are responsible for ensuring that employees who launder clothing contaminated with diisocyanates are provided with adequate protective equipment and are aware of the hazards of these compounds and appropriate methods for handling them safely. If an outside laundering facility is used, the laundry employer must be advised of the hazards involved in handling clothing contaminated with diisocyanates and of the requirements to ensure that the laundry employees are not exposed to diisocyanates.

When leaks or spills of diisocyanates occur, only properly trained and equipped personnel wearing appropriate protective clothing should be permitted to remain in the area [9]. If major spills occur, air-supplied masks or self-contained breathing apparatus as described in Table I-1 must be used by workers in the area. Leaking containers should be removed to the outdoors or to an isolated, well-ventilated area before the contents are transferred to other suitable containers. Adequate
facilities for handling spills should be provided, including suitable floor drainage and readily accessible hoses, mops, buckets, and absorbent materials. Spills should be cleaned up promptly. The effectiveness of water as a cleansing agent is considerably improved by adding 1-5% of ammonia, and adding 10% isopropyl alcohol further improves it. Oil-absorbent materials such as vermiculite are also useful in cleaning spills. After use, such material should be shovelled into an open steel container, and the container should then be covered and removed to a safe disposal area away from the operating area. The mixture should be soaked with water containing ammonia and should stand for 24 hours in an open or partially open container. The container can then be closed and discarded [67,68].

Liquid diisocyanates should never be washed directly down the drain with water, because the solids that result may plug the sewer line. Any existing regulations pertaining to the discharge of such materials into sewer lines should be strictly adhered to. Since spills of diisocyanates may freeze during cold weather, water and ammonia will merely coat the solid material with insoluble urea, stopping further reactions. In cold weather, cleanup should be performed with a mixture of equal parts of isopropyl alcohol and ethylene glycol [9,68]. A supply of this mixture should be on hand and ready for immediate use in cold weather.

If a worker's skin becomes contaminated to the extent that there is an increased inhalation hazard or the possibility of prolonged skin contact with liquid or solid diisocyanates, it should immediately be washed thoroughly with soap and water or isopropanol. If water is initially used to flush the skin, any remaining diisocyanate should be neutralized and removed with isopropanol [9]. If diisocyanates are splashed into the eyes, the eyes should be flushed with copious amounts of clean water for at least 15 minutes. The affected employee should then receive medical evaluation from a health professional and obtain further treatment if necessary [67].

Because of the potential hazards of exposure to diisocyanates, the importance of good housekeeping should also be emphasized. Spills should be cleaned up promptly, and all equipment used in the exposure areas, such as buckets, weighing containers, and funnels, should be decontaminated and cleaned immediately after use. Smoking and the carrying of smoking supplies should be prohibited in areas where exposure to diisocyanates may occur, as should preparing, storing, dispensing (including vending machines), and consuming food and beverages. Employees exposed to diisocyanates should be encouraged to wash their hands before eating, drinking, or smoking, and before and after using toilet facilities. The US Department of Labor regulations concerning general sanitation in the workplace as specified in 29 CFR 1910.141 should be adhered to.

Employees should be instructed on the health hazards of diisocyanates and the precautions to be followed in handling them. They should be trained to report promptly to their supervisors all leaks, suspected failures of equipment, exposures to diisocyanates, or symptoms of exposure. The location of safety showers and eyewash fountains should be clearly marked, and appropriate warning signs and
labels should be prominently displayed in exposure areas and on containers of diisocyanates. Emergency exits should be provided and be accessible at all times. All emergency shower, eyewash, protective, and firefighting equipment should be checked periodically to ensure its serviceability.
VI. DEVELOPMENT OF STANDARD

**Basis for Previous Standards**

In 1959, the American Conference of Governmental Industrial Hygienists (ACGIH) adopted a Threshold Limit Value (TLV) for TDI of 0.1 ppm (0.7 mg/cu m) as an 8-hour TWA concentration limit [149]. According to Elkins et al [32], this value was first proposed by Ayscue in 1954 and was based on the results of animal experiments conducted at Du Pont's Haskell Laboratory. In 1957, Zapp [36] also recommended that this limit not be exceeded because respiratory irritation occurred in animals exposed to TDI at concentrations of 1-2 ppm. He noted that TDI and similar diisocyanates are strong irritants to the skin, eyes, and gastrointestinal and respiratory tracts and that they may cause asthma-like symptoms in workers.

In 1962, the ACGIH reduced the TLV for TDI to 0.02 ppm (0.14 mg/cu m) [150]. The 1962 Documentation of Threshold Limit Values cited the study of Elkins et al [32], who reported respiratory irritation and asthma-like symptoms in workers in several plants where TDI concentrations were considerably below 0.1 ppm. The 1962 documentation [151] cited a Threshold Limits Committee Report by Elkins that presented similar information. A threshold limit of 0.01-0.03 ppm was suggested to minimize the respiratory effects of TDI. The 1962 documentation [151] concluded that a TLV of 0.02 ppm (0.14 mg/cu m) was necessary to protect against allergic sensitization.

In 1963, the ACGIH [152] noted that a TLV in the form of a TWA concentration limit might not provide a sufficient safety factor for fast-acting substances. Consequently, the TLV for TDI, which remained at 0.02 ppm (0.14 mg/cu m), was changed to a ceiling value that should not be exceeded.

Subsequent editions of the Documentation of Threshold Limit Values in 1966 [153] and 1971 [154] contained several additional reports of the effects of TDI on experimental animals. The 1971 documentation also cited studies by Williamson [41], which reported that workers were affected by TDI at concentrations normally below 0.02 ppm. The data of Peters et al [84,85], suggesting pulmonary function changes in workers exposed to concentrations of TDI below 0.01 ppm, were reported, but these changes were not considered of sufficient importance to invalidate the existing limit. A TLV of 0.02 ppm (0.14 mg/cu m) was considered "sufficiently low to prevent substantially all sensitization and to minimize allergic attacks."

For MDI, the ACGIH adopted a TLV of 0.02 ppm (0.2 mg/cu m) in 1965 [155]. This limit was intended as a ceiling value not to be exceeded. The 1971 Documentation of Threshold Limit Values [154] described the basis for this limit. Although the vapor pressure of MDI is relatively low, the 1971 documentation [154] noted that significant vapor concentrations occurred in the workplace.
Isocyanates in general were reported to irritate the skin, eyes, and respiratory tract and to cause respiratory sensitization when sufficient vapor concentrations were present even for a short time [120]. Konzen et al [60] observed an immunologic response in workers exposed to MDI at approximately 1.3 ppm-minute but not in workers exposed at 0.9 ppm-minute. Bruckner et al [52] noted that workers might become sensitized to isocyanates when exposed at concentrations above 0.02 ppm. According to the 1971 documentation [154], available data indicated that MDI was similar to TDI in its irritant and sensitizing properties, suggesting that a similar ceiling value of 0.02 ppm (0.2 mg/cu m) was warranted.

In the United States, occupational exposure standards for diisocyanates have been established only for TDI and MDI. According to the International Labour Office [156], occupational exposure limits for TDI, MDI, and several other diisocyanates have been set by foreign countries. These limits are summarized in Tables VI-1 and VI-2.

Current Federal standards (29 CFR 1910.1000) for the diisocyanates are ceiling limits of 0.02 ppm (0.14 mg/cu m) for TDI and 0.02 ppm (0.2 mg/cu m) for MDI.

In 1973, NIOSH [37] published criteria for a recommended standard for occupational exposure to TDI, recommending a TWA limit of 0.005 ppm (0.036 mg/cu m) and a ceiling limit of 0.02 ppm (0.14 mg/cu m). A careful review of the data of Elkins et al [32] revealed cases of respiratory illness in plants where average TDI concentrations were below 10 ppb (70 μg/cu m) but none in plants where concentrations were below 7 ppb (50 μg/cu m). A TWA limit of 5 ppb (36 μg/cu m) was therefore considered to provide some margin of safety. A ceiling limit of 20 ppb (140 mg/cu m) was based primarily on the findings of Hama [79], who reported that workers had no symptoms at concentrations below 10 ppb but developed respiratory illness within 1 week when concentrations rose to 30-70 ppb; when concentrations were reduced to 10-30 ppb, there were no further complaints. The recommended ceiling was intended to protect against irritative effects of TDI in nonsensitized workers, but evidence was insufficient to determine whether it would also protect against sensitization. The document noted that no evidence was available to point to a concentration of TDI that would be safe for workers already sensitized to TDI. The present document reexamines the earlier recommendations for a TDI standard, taking into account more recent information that has become available since 1973.

Basis for the Recommended Standard

(a) Permissible Exposure Limits

The available data indicate that at least three types of effects, direct irritation, sensitization, and chronic decrease in pulmonary function, should be
### TABLE VI-1

**OCCUPATIONAL EXPOSURE LIMITS (MG/CU M) FOR TDI AND MDI**

<table>
<thead>
<tr>
<th>Country</th>
<th>TDI</th>
<th>MDI</th>
</tr>
</thead>
<tbody>
<tr>
<td>United States</td>
<td>0.14*</td>
<td>0.2*</td>
</tr>
<tr>
<td>Australia</td>
<td>0.14*</td>
<td>0.2*</td>
</tr>
<tr>
<td>Belgium</td>
<td>0.12</td>
<td>0.2</td>
</tr>
<tr>
<td>Czechoslovakia</td>
<td>0.07**</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>0.14*</td>
<td>-</td>
</tr>
<tr>
<td>Federal Republic of Germany</td>
<td>0.14***</td>
<td>0.2***</td>
</tr>
<tr>
<td>Finland</td>
<td>0.14*</td>
<td>0.2*</td>
</tr>
<tr>
<td>German Democratic Republic</td>
<td>0.1**</td>
<td>0.15**</td>
</tr>
<tr>
<td></td>
<td>0.1 (STEL)*</td>
<td>0.15*</td>
</tr>
<tr>
<td>Hungary</td>
<td>0.5</td>
<td>-</td>
</tr>
<tr>
<td>Italy</td>
<td>0.5</td>
<td>0.7</td>
</tr>
<tr>
<td>Japan</td>
<td>0.14</td>
<td>-</td>
</tr>
<tr>
<td>Netherlands</td>
<td>0.14</td>
<td>0.2*</td>
</tr>
<tr>
<td>Poland</td>
<td>-</td>
<td>0.1*</td>
</tr>
<tr>
<td>Rumania</td>
<td>0.1**</td>
<td>0.15*</td>
</tr>
<tr>
<td></td>
<td>0.3</td>
<td>-</td>
</tr>
<tr>
<td>Sweden</td>
<td>0.07</td>
<td>0.1*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>***</td>
</tr>
<tr>
<td>Switzerland</td>
<td>0.14*</td>
<td>0.2*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>***</td>
</tr>
<tr>
<td>USSR</td>
<td>0.5*</td>
<td>-</td>
</tr>
<tr>
<td>Yugoslavia</td>
<td>0.14</td>
<td>0.2</td>
</tr>
</tbody>
</table>

*Ceiling limit
**TWA
***Designated as a sensitizer

Adapted from reference 156
## TABLE VI-2

**OCCUPATIONAL EXPOSURE LIMITS (MG/CU M) FOR OTHER DIISOCYANATES**

<table>
<thead>
<tr>
<th>Compound</th>
<th>Country</th>
<th>Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hexamethylene diisocyanate (HDI)</td>
<td>Bulgaria</td>
<td>0.05*</td>
</tr>
<tr>
<td></td>
<td>Federal Republic of Germany</td>
<td>0.14**</td>
</tr>
<tr>
<td></td>
<td>German Democratic Republic</td>
<td>0.05*</td>
</tr>
<tr>
<td></td>
<td>Poland</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td>Rumania</td>
<td>1***</td>
</tr>
<tr>
<td></td>
<td>Switzerland</td>
<td>0.14**</td>
</tr>
<tr>
<td></td>
<td>USSR</td>
<td>0.05***</td>
</tr>
<tr>
<td></td>
<td>Yugoslavia</td>
<td>0.05</td>
</tr>
<tr>
<td>Isophorone diisocyanate (IPDI)</td>
<td>Belgium</td>
<td>****</td>
</tr>
<tr>
<td></td>
<td>Federal Republic of Germany</td>
<td>0.18**</td>
</tr>
<tr>
<td></td>
<td>Netherlands</td>
<td>****</td>
</tr>
<tr>
<td></td>
<td>Switzerland</td>
<td>0.18***</td>
</tr>
<tr>
<td>Methylene-bis (4-cyclohexyl isocyanate)</td>
<td>Belgium</td>
<td>0.11*</td>
</tr>
<tr>
<td></td>
<td>Netherlands</td>
<td>0.11</td>
</tr>
<tr>
<td></td>
<td>Switzerland</td>
<td>0.22**</td>
</tr>
<tr>
<td>1,5-Naphthylene Diisocyanate (NDI)</td>
<td>Federal Republic of Germany</td>
<td>0.18**</td>
</tr>
</tbody>
</table>

*Ceiling limit  
**Designated as a sensitizer  
***TWA concentration  
****"Skin" notation  

Adapted from reference 156
considered in establishing an exposure limit for the diisocyanates. At relatively high concentrations, the diisocyanates produce direct irritation of the respiratory tract; such irritation has frequently been reported in workers exposed to spills or other sources of high concentrations [31,40,74,80,93], but there are few data to indicate a threshold concentration for this effect. In experimental 10-minute exposures, all of six volunteers experienced nose and throat irritation at 3,600 μg/cu m, one of six at 710 μg/cu m, and none at 360 μg/cu m; none of the volunteers reported chest symptoms from these brief exposures [38]. At an automobile plant, all 12 workers exposed to TDI developed severe respiratory symptoms during 1 week when concentrations rose to 210-500 μg/cu m, but they had no symptoms when concentrations remained below 210 μg/cu m [79]. The latter study was the primary basis for the ceiling limit of 20 ppb (140 μg/cu m) for TDI recommended by NIOSH in 1973 [37]. Since no reports have been found of irritative effects in workers exposed below this level, this appears to indicate that this ceiling limit provides adequate protection for unsensitized workers.

In individuals who are sensitized to diisocyanates, exposure at concentrations well below this limit can produce symptoms of asthma. Several reports [43,45-47,57] have described reactions in sensitized workers exposed to TDI at 35 μg/cu m or less. Sensitization to diisocyanates may involve an immunologic mechanism [62] and pharmacologic hyperreactivity to bronchoconstrictors [63,66]; either or both types of response may be present in an individual showing sensitivity to diisocyanates [46,47,56]. No threshold concentration for such reactions has been identified, but there is evidence that, for some individuals, it may be unmeasurably low [31,52,56]; thus, it is not possible at this time to establish a level below which sensitized workers will not experience adverse respiratory effects from exposure to diisocyanates.

Several studies have shown that 5-20% of the workforce may become sensitized to diisocyanates [32,52,56,83]. There is evidence, however, that the incidence of sensitization can be reduced by controlling exposures. The data of Elkins et al [32] on 15 TDI plants showed that all plants where average exposures exceeded 70 μg/cu m had workers with TDI-related respiratory illness, but no such illnesses were reported in plants where average exposures were 50 μg/cu m or lower. On the other hand, Weill [57] reported instances of sensitization developing in a plant where average TDI exposures ranged from 14 to 50 μg/cu m. These studies did not report the frequency or magnitude of excursions above these averages, so that the more precise estimates of exposure concentrations cannot be determined.

Several reports [31,41,42,52] have indicated that sensitization may follow exposure to spills or other unusually high concentrations. However, Pepys et al [43] described sensitization, verified by challenge testing with TDI, in four workers who had no known exposure to spills. Similar sensitization was reported by Carroll et al [45] in four office workers employed in building adjacent to a TDI factory. Two NIOSH health hazard evaluations [93,95] reported that, where TDI concentrations were 7 μg/cu m or below, only workers previously sensitized at
higher concentrations had respiratory symptoms. The indication of a dose-response effect in sensitized individuals [45,54,57] suggests that the number of already sensitized individuals who develop an overt asthmatic reaction can also be reduced by lowering exposure levels.

Exposure to diisocyanates may also cause chronic respiratory effects measurable as long-term decrement in pulmonary function, especially FEV\textsubscript{1}, in excess of that expected from aging. It is not clear from existing data whether this change occurs only in sensitized workers or whether it may also affect workers who show no clinical symptoms from diisocyanate exposure. The findings of Porter et al [56] indicate that some workers who are sensitive to TDI and who have anti-TDI antibodies may exhibit normal pulmonary function, while others with clinical symptoms of sensitization but negative results on immunologic tests may have severely impaired pulmonary function. In the study conducted by Wegman et al [90], in which workers exposed at concentrations above 20\,\mu g/cu m had a significantly greater decrease in FEV\textsubscript{1} than those exposed at lower concentrations, the workforce studied included both sensitized and unsensitized individuals. In the plant studied by Weill and colleagues [57-59], where workers who showed symptoms of clinical sensitization were not included in the study population, the investigators found no significant effects on lung function related to TDI exposures at average concentrations of 14-50\,\mu g/cu m. These findings indicate that the TWA limit of 5 ppb (35\,\mu g/cu m) for TDI recommended by NIOSH in 1973 [37], which was based on the findings of Elkins et al [32], provides adequate protection against chronic effects of TDI on pulmonary function of workers who are not sensitized.

Environmental data for the other diisocyanates are insufficient to establish a safe exposure limit. The diisocyanates commonly used in industry are respiratory irritants [2]. In a plant where area samples showed MDI concentrations of 10-150 \,\mu g/cu m and breathing zone concentrations for 6 sprayers were 120-270 \,\mu g/cu m, 34 of 35 workers had eye, nose, or throat irritation, and nearly half had wheezing, shortness of breath, and chest tightness [96]. In another plant, 3 of 29 workers exposed to MDI at 50-110 \,\mu g/cu m had respiratory symptoms [61]. Nine of 18 workers exposed to HDI at less than 300 \,\mu g/cu m and to an HDI trimer at less than 3,800 \,\mu g/cu m had irritation of the upper respiratory tract, cough, or chest tightness [100].

Like TDI, other diisocyanates are likely to be reactive with biologic macromolecules, such as proteins, and thus are potential sensitizers. Some authors [60,61] have reported that MDI produces respiratory sensitization, since affected workers gave positive results in immunologic tests. The assumption of a common mechanism of action suggests that structurally similar diisocyanates might produce cross-sensitization; there is one report [53] of positive tests for antibodies against MDI in workers sensitized to TDI, but the validity of these results is questionable because of the lack of characterization of the test antigen used. A study of skin sensitization [69] suggested that workers exposed to TDI and MDI were cross-sensitized to IPDI. In another study [47], some workers with previous exposure only to TDI had bronchial reactions to MDI and HDI as well. These workers were
significantly more hyperreactive to histamine than workers who reacted to TDI only, suggesting that cross-reactivity might involve a nonspecific pharmacologic mechanism.

The predicted reactivity of the diisocyanates with biologic macromolecules is the probable basis for their immunologic effects and perhaps for the respiratory symptoms and effects on pulmonary function produced at low concentrations. It is therefore reasonable to expect that other diisocyanates react similarly to TDI on a molar basis.

None of the studies completed since 1973 provides a clear indication that unsensitized workers suffer adverse effects from exposure to TDI at concentrations below the limits that were recommended by NIOSH, 20 ppb (140 μg/cu m) as a ceiling concentration and 5 ppb (35 μg/cu m) as a TWA concentration [37]. The report of Wegman et al [90] that workers exposed to TDI at concentrations above 25 μg/cu m showed an excessive long-term decrement in pulmonary function does not provide adequate justification to change these limits; it contains insufficient information on individual changes in pulmonary function, the effect of sensitization on these measurements, and the possible role of other chemicals. Another report [93] of respiratory effects in workers whose average exposure was reportedly below 35 μg/cu m did not provide sufficient information to indicate whether some of these workers might have been sensitive to TDI, and, if so, whether they might have become sensitized at concentrations in excess of the recommended ceiling limit.

In the absence of data indicating that any of the diisocyanates is substantially less toxic than TDI, the exposure concentrations recommended in 1973 should be extended to all diisocyanates. It is recommended that exposure to the diisocyanates be controlled so that no employee is exposed at concentrations in excess of the following environmental limits, equivalent, in the case of volatile diisocyanates that occur as vapors, to a TWA limit of 5 ppb for a 10-hour workshift, 40-hour workweek, and a ceiling limit of 20 ppb for a 10-minute sampling period:

<table>
<thead>
<tr>
<th>Substance</th>
<th>TWA</th>
<th>Ceiling</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toluene diisocyanate (TDI)</td>
<td>35 μg/cu m</td>
<td>140 μg/cu m</td>
</tr>
<tr>
<td>Diphenylmethane diisocyanate (MDI)</td>
<td>50 μg/cu m</td>
<td>200 μg/cu m</td>
</tr>
<tr>
<td>Hexamethylene diisocyanate (HDI)</td>
<td>35 μg/cu m</td>
<td>140 μg/cu m</td>
</tr>
<tr>
<td>Napthalene diisocyanate (NDI)</td>
<td>40 μg/cu m</td>
<td>170 μg/cu m</td>
</tr>
<tr>
<td>Isophorone diisocyanate (IPDI)</td>
<td>45 μg/cu m</td>
<td>180 μg/cu m</td>
</tr>
<tr>
<td>Dicyclohexylmethane 4,4'-diisocyanate (hydrogenated MDI)</td>
<td>55 μg/cu m</td>
<td>210 μg/cu m</td>
</tr>
</tbody>
</table>
If other diisocyanates are used, employers should observe environmental limits equivalent to a ceiling concentration of 20 ppb and a TWA concentration of 5 ppb.

(b) Sampling and Analysis

The method recommended for sampling and analysis of diisocyanates is capable of detecting TDI, MDI, and HDI at concentrations as low as 2-5 μg/cu m [123]. Because of this sensitivity, the recommended sampling time has been shortened to 10 minutes, rather than the 20-minute sampling period required for the Marcali method recommended in the 1973 TDI document [37]; this permits more accurate determinations of peak exposures.

The recommended method also permits separation of different diisocyanates in the same sample. It has not been tested with diisocyanates other than TDI, MDI, and HDI, but, with appropriate modifications and solvent systems, it should be capable of detecting these compounds in the same range.

The recommended method for sampling airborne diisocyanates consists of drawing air at a rate of 2 liters/minute for 10 minutes through two serially connected all-glass midget impingers, each containing 15 ml of absorbing solution. The use of two impingers in series is necessary until a reproducible collection efficiency is established for any given operation, since absorber collection efficiency is highly variable [44,111,116,125,137]. The diisocyanates react with the absorbing solution to form specific urea derivatives which are then injected into the high-speed liquid chromatograph for analysis. The method is described in detail in Appendix I.

(c) Medical Surveillance and Recordkeeping

Respiratory effects from exposure to diisocyanates have included chronic bronchitis [20,21], asthmatic reactions [43,45] and decreased pulmonary function [81,87]. To prevent development of serious respiratory symptoms, a medical surveillance program should provide for the timely detection of adverse health effects that develop from exposure to diisocyanates.

Employees with a history of respiratory illness, especially asthma, and those exposed to other respiratory irritants, eg, smokers, may be at increased risk of developing adverse health effects from exposure to diisocyanates, and they should be counseled on this risk. All employees should be monitored so that work-related symptoms or loss of pulmonary function can be detected early. Employees who develop symptoms of TDI sensitization should be counseled on the risks of continuing to work with TDI.

Each employee should receive a thorough preplacement medical examination, which includes a history of exposure to diisocyanates, a smoking history, and a history of respiratory illnesses. Each employee should receive pulmonary function tests, including FEV 1 and FVC, and a chest X-ray before beginning work in any
plant manufacturing or using diisocyanates. For employees with occupational exposure to diisocyanates, physical examinations should be repeated at least annually. Because of seasonal and diurnal variations in pulmonary function, the periodic examination of an individual employee should be performed at about the same time each year and at the same time of day, so that changes in respiratory function can be evaluated. Chest X-rays are not required at periodic examinations, and should be repeated at the discretion of the examining physician. Records of medical examinations should be kept for at least 30 years after the employee's last exposure to diisocyanates.

The previous NIOSH criteria document on TDI [37] recommended a leukocyte count with differential as part of the preplacement medical examination and suggested periodic eosinophil counts. However, there is no evidence at this time that blood findings are a significant indicator of adverse effects of TDI exposure. This change in the recommendations for the medical examination is consistent with the failure to find eosinophilia in TDI-sensitized individuals in recent studies [43,54,58].

(d) Personal Protective Equipment and Clothing

Where engineering controls are used to keep diisocyanate concentrations at or below the recommended exposure limits, minimal protective clothing is needed to safeguard workers. Under these conditions workers should wear coveralls and rubber or polyvinyl chloride gloves [144]. Where liquid diisocyanates may be present on floors, protective shoe coverings should be worn.

If the potential exists for splashes or contact with aerosols of diisocyanates, employees should be provided with face shields (20-cm minimum) with goggles, rubber or polyvinyl chloride gloves and aprons, rubber boots, and appropriate respiratory equipment as described in Table 1-1. Because diisocyanates have poor warning properties [36,39], the use of chemical cartridge respirators or gas masks is not recommended. At present, air-purifying respirators with an end-of-service-life indicator are not available for the diisocyanates. Demand-type (negative pressure) supplied-air respirators are not recommended because of the possibility of facepiece leakage. Workers within 10 feet of a unit spraying material containing diisocyanates should wear full-body protective clothing and appropriate respiratory protective devices [60,147].

All protective clothing that becomes contaminated with diisocyanates should be replaced or thoroughly decontaminated in a solution of 8% ammonia and 2% liquid detergent in water and cleaned before reuse. Lockers should be provided for workers so that work and street clothes can be stored separately. The employer should arrange for laundering of all work clothes and ensure that laundry workers are aware of the hazards of exposure and appropriate safety precautions.
(e) Informing Employees of Hazards

At the beginning of employment, all employees should be informed of the hazards from exposure to diisocyanates. Brochures and pamphlets may be effective aids in informing employees of hazards. In addition, signs warning of the danger of exposure to diisocyanates should be posted in any area where occupational exposure to the diisocyanates is likely. Access to areas of potential high exposure should be restricted to employees equipped with appropriate protective gear. A continuing education program, which includes training in the use of protective equipment such as respirators and information about the value of the periodic medical examinations, should be available to the employees. Employees exposed to diisocyanates should be informed that symptoms of exposure, such as nocturnal dyspnea, may occur several hours after the end of the workshift. Because of the possibility of sensitization to the diisocyanates, employees should be warned that the improper home use of polyurethane products, such as foam kits and varnishes, that contain diisocyanates may increase their risk of developing work-related health problems. Employees should be instructed in their own responsibility for following work practices and sanitation procedures to help protect the health and provide for the safety of themselves and their fellow employees.

(f) Engineering Controls and Work Practices

There is evidence that workers can become sensitized to diisocyanates during brief exposures at high concentrations [42,93]. Effective engineering controls and good work practices must be emphasized to minimize the possibility of such exposures.

Engineering controls, such as process enclosure or local exhaust ventilation, should be used where needed to maintain environmental concentrations of diisocyanates at or below the recommended limits. These systems should be designed to prevent the accumulation or recirculation of diisocyanates in the workplace environment and to effectively remove diisocyanate vapors or aerosols from the breathing zone of the employees. The ventilation systems should be periodically checked, including airflow measurements, to ensure that the systems are working properly. Exhaust ventilation systems discharging to outside air must conform to applicable local, state, and Federal air pollution regulations and must not constitute a hazard to employees or to the general public.

Diisocyanates should be protected from extreme heat or direct sunlight. Because of the reactivity of diisocyanates with water, caution should be taken to prevent moisture from entering containers. Diisocyanates should not be stored near acids, bases, alcohols, or amines. Containers of diisocyanates should be periodically inspected to assure that they are tightly sealed and that the integrity of the containers is maintained. Leaking containers should be removed to the outdoors or to an isolated, well-ventilated area before the contents are transferred to other suitable containers [144].
The flashpoints of most diisocyanates are high, and the compounds will not burn under normal circumstances, although they will burn if heated sufficiently. The combustion of diisocyanates produces high concentrations of toxic fumes, and appropriate protective equipment should be worn by firefighters. For fighting diisocyanate-supported fires, dry chemical powder, carbon dioxide, or foam extinguishing media should be used. Water should only be used if large quantities are available [144]. Only essential personnel should be permitted in the area during the actual firefighting, and unprotected workers should not be permitted back into the area until it has been thoroughly inspected and any suspected diisocyanate residues have been decontaminated.

Good housekeeping in the workplace is of prime importance in reducing exposure to diisocyanates. Adequate facilities for handling spills and leaks of diisocyanates should be provided, and workers should be thoroughly trained in cleanup procedures. Spills should be promptly cleaned up, and all equipment used in the exposure areas, such as buckets, weighing containers, and funnels, should be decontaminated and cleaned immediately after use. To reduce the possibility of leaks, plastic or rubber hoses, which become brittle from contact with diisocyanates, should be checked and replaced regularly.

Storing, handling, dispensing, and consuming food should be prohibited in work areas, regardless of the concentrations of diisocyanates. In addition, it is recommended that employees who work in areas that use diisocyanates wash their hands thoroughly before eating or using toilet facilities. Smoking should not be permitted in areas where diisocyanates are stored or used because of the possibility that smoking materials may become contaminated with diisocyanates.

(g) Monitoring and Recordkeeping Requirements

In addition to a program of regular personal monitoring of air concentrations, continuous area monitoring is strongly recommended where aliphatic diisocyanates such as TDI and MDI are present. This will permit engineering controls to be modified or improved to keep the concentrations of diisocyanates at or below the recommended limits. Monitoring should also be performed whenever there is a change in the process or materials used that could increase the exposure of employees.

Employers should monitor exposure of employees to diisocyanates by taking a sufficient number of breathing-zone samples to adequately characterize exposures for every operation. In determining the sampling strategy for a particular worker, the process and the job description of the worker should be considered, and those process cycles in which potential exposure is greatest should be given prime consideration.

Records should be kept for all sampling operations and should include the type of personal protective devices in use, if any, and the sampling and analytical methods used. Employees or their designated representatives should have access to
records of their own environmental exposures. These records should be kept at least 30 years after the employee's last exposure to diisocyanates.
VII. RESEARCH NEEDS

Information needed to develop a standard for occupational exposure to the diisocyanates is incomplete in many respects. It has been necessary to recommend a standard for the diisocyanates based on similarities to TDI and MDI, since adequate information is not available on other diisocyanates to demonstrate that they differ appreciably in their toxicity.

Detailed epidemiologic studies are needed to determine the long-term health effects of occupational exposure to diisocyanates and safe levels for such exposures. These studies should relate respiratory symptoms, pulmonary function data, and other health effects to actual individual exposures and should include long-term followup of persons leaving the workforce for health reasons.

Studies are required to ascertain whether all of the diisocyanates are sensitizing agents and whether they can produce cross-sensitization. Karol et al [62,110] have developed a test antigen by conjugating p-tolyl isocyanate with a protein carrier that has made it possible to demonstrate the existence of hapten-specific antibodies in workers exposed to TDI. Similar antigens would be useful for investigating the sensitizing properties of other diisocyanates, both in exposed workers and in animal studies.

Particularly needed are dose-response studies of sensitization to the diisocyanates to determine whether sensitization can result from long-term exposures at low concentrations and to investigate the relationship of length of exposure to the development of sensitization. These relationships could be studied in guinea pigs exposed to TDI, using the p-tolyl isocyanate antigen [110] to test for the induction of tolyl-specific antibodies. Sera from these animals should not be pooled, so that the standard deviation can be determined. Changes in respiratory response in exposed animals should also be evaluated to determine their correlation with the appearance of IgE or IgG antibodies. As a corollary experiment, animals should be exposed at the same total dose administered over varying time periods to simulate the effects of excursions while retaining the same 8-hour TWA exposure; e.g., groups of animals might be exposed at 5 ppb for 8 hours, 160 ppb for 15 minutes, and 2,400 ppb for 1 minute.

To improve protection of exposed workers, it is particularly desirable to determine whether there are intrinsic, predictable differences between sensitizable and nonsensitizable individuals. The studies of Butcher et al [63,65], showing that persons sensitized to TDI tend to be hyperreactive to bronchoconstrictors such as mechoyl, appear to offer promise in this regard. It is necessary to determine whether this hyperreactivity is a result of exposure or a preexisting factor that may indicate a predisposition to become sensitized to diisocyanates. Methods of identifying sensitized individuals before overt chronic symptoms develop should also be explored. The value of measurements of eosinophilia and cyclic AMP and of
pulmonary function studies and immunologic testing as diagnostic tools should be carefully evaluated, since existing reports of their usefulness are contradictory. The p-tolyl isocyanate test antigen developed by Karol and her colleagues [62] appears to be a particularly useful diagnostic tool for TDI sensitization, and analogous antigens should be developed for investigating sensitization to other diisocyanates.

Because the diisocyanates may be highly reactive biologically, it is important that their potential to cause carcinogenic and mutagenic effects be investigated. Mutagenicity screening in microbial tests should be carried out, using a test protocol that will decrease the likelihood of hydrolysis to possibly mutagenic amine intermediates. Diisocyanates, especially those that are positive in mutagenicity tests, should also be tested for carcinogenicity in animal experiments. Studies of absorption, distribution, metabolism, and excretion of diisocyanates are also needed to elucidate the mechanism of their action.

The consequences of exposure to the aerosols produced in many diisocyanate applications, such as spraying, should also be investigated. It has been assumed that reactive diisocyanates in aerosol form produce the same biologic consequences as diisocyanate vapors at equivalent concentrations. This assumption should be experimentally verified. Similarly, most applications of diisocyanates involve simultaneous exposure to other toxic chemicals, and inadequate information is available on the role of these chemicals in producing observed health effects in diisocyanate workers and their possible additive or synergistic nature.

Reliable, sensitive continuous monitoring methods should be developed for all the diisocyanates. The paper-tape method developed by Reilly [136] is a valuable method for continuous monitoring of the aromatic diisocyanates, particularly TDI. Comparable methods are needed for other diisocyanates to protect workers from dangerous excursions and to provide better information relating health effects to actual exposures.
VIII. REFERENCES


5. Lomonova GV, Frolova IN: [Comparative toxicity of hexamethylene diisocyanate and chlorohexyl isocyanate.] Gig Tr Prof Zabol 12:40-44, 1968 (Rus)

6. VEBA-IPDI--Unmatched for versatility, Data Sheet No. 22. Gelsenkirchen-Buer, West Germany, VEBA-CHEMIE AG, 1977, 79 pp


21. Fuchs S, Valade P: [Clinical and experimental study of several cases of intoxication by Desmodur T (toluene diisocyanate 1-2-4 and 1-2-6).] Arch Mal Prof 12:191-96, 1951 (Fre)

22. Reinal W: [Diseases in the manufacture of polyurethane-based plastics.] Zentralbl Arbeitsmed Arbeitsschutz 3:103-07, 1953 (Ger)


24. Schur E: [Injury from Desmodur lacquers--Irritating gas or allergy?] Med Klin 54:168-70, 1959 (Ger)

25. Reinal W: [Occupational asthma and similar illnesses and their insurance coverage.] Zentralbl Arbeitsmed Arbeitsschutz 5:33-37, 1955 (Ger)

27. Schuermann D: [Injuries to health caused by modern varnishes and foam materials.] Dtsch Med Wochenschr 80:1661-63, 1955 (Ger)


34. Gerritsen WB: [Allergic asthma caused by isocyanates.] Chem Weekbl 51:269-70, 1955 (Dut)


39. Ehrlicher H, Pilz W: [Preventive measures in industrial hygienics and occupational medicine when using isocyanates (Desmodur) and analytical determination of some aromatic isocyanates--Part II.] Arbeitsschutz (Cologne), 1957, pp 7-10 (Ger)


44. Meddle DW, Radford DW, Wood R: A field method for the determination of organic aromatic isocyanates in air. Analyst (London) 94:369-76, 1969


46. O'Brien IM, Newman-Taylor AJ, Burge PS, Harries MG, Fawcett IW, Pepys J: Toluene diisocyanate-induced asthma--Inhalation challenge tests and bronchial reactivity studies. Accepted for publication in Clin Allergy

47. O'Brien IM, Harries MG, Burge PS, Pepys J: Di-isocyanate induced asthma--Reactions to TDI, MDI, HDI and histamine. Accepted for publication in Clin Allergy


50. Lapp NL: Physiological changes as diagnostic aids in isocyanate exposure. Am Ind Hyg Assoc J 32:378-82, 1971


56. Porter CV, Higgins RL, Scheel LD: A retrospective study of clinical, physiologic and immunologic changes in workers exposed to toluene diisocyanate. Am Ind Hyg Assoc J 36:159-68, 1975


69. Rothe A: [Occupational skin diseases caused by polyurethane chemicals.] Berufs-Dermatosen 24:7-24, 1976 (Ger)

70. Chizikov VA: [The biological action and hygienic characteristics of small concentrations of stilbene diisocyanate.] Tr Tsentr Inst Usoversh Vrachei 76:324-26, 1964 (Rus)


75. Filatova VS, Babochkina MS, Kurando TB: [Problems of industrial hygiene and the state of health of workers in diisocyanate production plants.] Gig Tr Prof Zabol 6:25-31, 1962 (Rus)

76. Filatova VS, Kurando TB, Tubina AY: [Industrial hygiene and health status of workers engaged in production of hexamethylenediisocyanate.] Gig Tr Prof Zabol 12:3-7, 1968 (Rus)


79. Hama GM: Symptoms in workers exposed to isocyanates--Suggested exposure concentrations. AMA Arch Ind Health 16:232-33, 1957


120. Toxicity and Safe Handling of Isocyanates--A Review of the Literature (TDI) and Results of Toxicity Screening Studies on Additional Compounds. Pittsburgh, Pa, Mobay Chemical Co, 15 pp (undated)


129. Chemistry for Coatings. Pittsburgh, Pa, Mobay Chemical Corp, Plastics and Coatings Division, 1976, 16 pp


115

151. Documentation of Threshold Limit Values. Cincinnati, American Conference of Governmental Industrial Hygienists, Committee on Threshold Limit Values, 1962, p 104


IX. APPENDIX I

SAMPLING AND ANALYTICAL METHOD FOR DIISOCYANATES IN AIR

The following method for sampling and analysis of airborne diisocyanates is adapted from NIOSH Method No. MR 240 (Classification E) [123]. A Class E method is defined by NIOSH as "Proposed: A new, unproven, or suggested method not previously used by industrial hygiene analysts but which gives promise of being suitable for the determination of a given substance."

Principle of the Method

A known volume of air is drawn at a flowrate of 2 liters/minute through two midget gas impingers, connected in series, containing the nitro reagent absorber solution. The recommended airflow is 2 liters/minute, rather than 1 liter/minute as indicated in Method No. MR 240 [20], to ensure collection of particulate diisocyanates. At the time of analysis, the two impinger solutions are initially kept separate to allow determination of collection efficiency. The impinger solutions (separate or combined) are carefully rotary evaporated to dryness. The residue is then dissolved in 1.0 ml of methylene chloride, CH2Cl2, containing an internal standard. An aliquot of the solution is injected into a liquid chromatograph. The area of the resulting peak is determined and compared to areas obtained by injecting standard urea solutions of known concentration.

Range and Sensitivity

The upper limit of the range of the method depends on the concentration of the nitro reagent in the midget gas impingers. For a 10-liter air sample, the limit of diisocyanates that can be absorbed is 0.0015 millimole/cu m using 15 ml of 0.2 mM nitro reagent solution.

The minimum detectable limit is 2 ng/injection for TDI and MDI and 5 ng/injection for HDI. The advisable injection volume is 50 lli. Hence, for a 20-liter sample, the useful range is 2-300 μg/cu m of total diisocyanates. If a particular atmosphere is suspected of containing a large amount of isocyanate, a smaller sampling volume should be taken.

Interferences

Any compound that reacts with nitro reagent and has the same retention time as the analyte is an interference. Retention time alone cannot be considered proof of chemical identity. When the possibility of interference exists,
chromatographic conditions (e.g., modes of gradient, concentration of mobile phases, packings) have to be changed to circumvent the problem.

Precision and Accuracy

Precision and accuracy for the total analytical and sampling method have not been determined. However, the analytical method has been shown to have relative standard deviations within experimental error for peak areas and retention times of 2.8-16.5% and 0.6-4.1%, respectively, depending on the concentration of the analytes.

Advantages and Disadvantages of the Method

The sampling device is portable. The analytical method is specific for isocyanates, and interferences are minimal. Simultaneous analysis of five substances can be carried out routinely.

The nitro reagent must be prepared at rather frequent intervals. It is recommended that it not be stored for more than 3 weeks, and it should be kept in darkness. Commercially available nitro reagent may prove more stable. The ureas formed in solution are generally stable up to 7 days. Degradation or polymerization may occur after this period. Excess nitro reagent should be removed with p-tolyl isocyanate or by some other means before the solution is injected into the liquid chromatograph to maintain longer column life and precision.

Apparatus

(a) An approved and calibrated personal sampling pump whose flowrate can be determined within ±5% at the recommended flowrate.

(b) Two midget gas impingers connected in series, each containing 15 ml of 0.2 mM nitro reagent solution.

(c) A liquid chromatograph capable of gradient elution and equipped with a UV detector, 254 nm.

(d) A commercially available 25 cm Partisil 10, 4.4-mm inner diameter, stainless steel column. Other column packing material may prove to be less subject to the adverse effects of excess nitro reagent and provide equivalent or better urea separation.

(e) A recorder or computing integrator for measuring peak areas.

(f) Sample containers, 20-ml, with Teflon-lined caps.
Microliter syringes: 10-μl, 50-μl, and other convenient sizes.

Pipets: 1.0-ml graduated in 0.01-ml increments, 15.0-ml, and other convenient sizes for making standard solutions.

Volumetric flasks: convenient sizes for making standard solutions.

Reagents

(a) Isopropanol, certified grade or reagent grade.
(b) Methylene chloride, pesticide grade (certified by ACS).
(c) Toluene, chromatographic grade.
(d) 2,4-Toluene diisocyanate, 98% pure.
(e) 2,6-Toluene diisocyanate (not available in pure form commercially; found as mixture with 2,4-TDI).
(f) 4,4'-Methylene bisphenyl isocyanate, >98% pure.
(g) 1,6-Hexane diisocyanate, 99% pure.
(h) p-Tolylisocyanate as excess nitro reagent scrubber.
(i) N-4 nitrobenzyl-N-n-propylamine-HCl (nitro reagent).

Preparation of Nitro Reagent Solution: A typical procedure for the routine preparation of the nitro reagent solution is as follows. About 120 mg (0.52 millimole) of the commercially available hydrochloride of nitro reagent is dissolved in 25 ml of distilled water. Thirteen milliliters of 1 N NaOH is added to precipitate the free amine. The free amine is extracted with 50 ml of toluene. The toluene layer is dried over anhydrous CaSO4 (Drierite, WA Hammond Drierite Co, Xenia, Ohio), and the resulting solution is diluted to 250 ml to prepare a 2 mM solution and is stored in the refrigerator. The nitro reagent solution is further diluted 10-fold with toluene before it is added to the impinger collecting tubes. Prepared nitro reagent should be examined periodically by HPLC for the appearance of additional peaks that indicate reagent degradation.

Procedure

Until the collection efficiency of the impingers is determined adequately, the two impinger solutions for each sample must be prepared and analyzed separately. Once this information is accumulated and a consistent collection efficiency is
found, one impinger may be used and the collection-efficiency factor applied.

All glassware used should be washed with detergent and thoroughly washed with tapwater and distilled water.

(a) Collection and Shipping of Samples

The sample solution for each impinger should be transferred to a separate 20-
ml glass tube with a Teflon cap. Use 1 ml of toluene to wash each impinger, Repeat twice. Combine with the appropriate sample solution. Keep cap tight and wrap with paper tapes. Ship out to place of analysis immediately. All requirements for shipping toluene, as stated in CFR 49, Part 172.101, must be adhered to.

(b) Reaction to Nitro Reagent and Isocyanate

Samples containing any aliphatic diisocyanates, such as HDI, should be allowed to react for at least 1 hour with the nitro reagent before analysis is started.

(c) Preparation of Samples

Each sample solution is transferred to a round-bottom flask. The sample tube is washed twice with 1 ml toluene and combined with the sample. The round-bottom flask is attached to a rotary evaporator and the sample is evaporated to dryness at 50 C. It is then dried over dry N2 for 2 minutes before being redissolved into 1.0 ml of CH2Cl2 containing an internal standard. An aliquot is submitted to liquid chromatographic analysis.

(d) Liquid Chromatograph Conditions

Typical operating conditions for the chromatograph are:

(1) Flowrate: 2.0 ml/minute.

(2) Gradient elution: 10% B/A to 100% B in 10 minutes (B = 9.1% isopropanol/CH2Cl2; A = 100% CH2Cl2).

(3) Detector: uv at 254 nm.

(4) Temperature: ordinary room.

(5) Recorder chart speed: 0.5 inch/minute.

(6) Injection port: loop included.
(e) Injection

The syringe must be cleaned and dried thoroughly between injections. The syringe is then ready to take up sample for injection. A known amount of sample is injected into the liquid chromatograph. Size of injections may vary from 1 µl up to 50 µl.

(f) Measurement of Peak Area

The peak area is measured by peak height times peak width at half the height or by an electronic integrator such as a computing integrator. Preliminary results are read from a standard curve prepared as discussed below.

Calibration and Standards

(a) A series of standards varying in concentration over the range of interest are prepared. Calibration curves are established prior to sample analysis each day. When an internal standard is used, the analyte concentration is plotted against the area ratio of the analyte to that of the internal standard.

(b) Typical Preparation of Stock Standard Solutions.

(1) The following weights of the isocyanates are dissolved in 4.0-ml portions of CH₂Cl₂: 2.12 mg MDI; 29.60 mg of TDI (ie, 9.30 mg of 2,4-TDI and 10.30 mg of 2,6-TDI), 21.14 mg of HDI.

(2) Then 755 µl of MDI, 83.1 µl of TDI, and 75.5 µl of HDI are mixed and 1.017 ml CH₂Cl₂ is added to make a total of 2.00 ml (200 ng/liter of each). Then 1.0 ml nitro reagent (2.06 mg/ml in hexane) is added to 1.0 ml of the isocyanate mixture. The total isocyanate/nitro reagent mole ratio in this solution is 1:1. The reaction mixture is stored overnight. Dilutions are made from this solution. The solvent is evaporated in a rotary evaporator and the residue redissolved in 1 ml CH₂Cl₂. These solutions are used to establish the calibration curves, linear dynamic range, and minimum detectable amount in the 25-cm Partisil 10 column.

Calculations

Read the weight corresponding to each peak area from the standard calibration curve.

The concentration of the analyte in the air sampled can be expressed in µg/cu m:
\[
\mu g/cu \text{ m} = \frac{\text{Amount of analyte (\mu g)} \times 1,000 (\mu l) \times 1,000 (\text{liters/cu m})}{\text{Air volume sampled (liters) \times volume of injection (\mu l)}}
\]

If more than one diisocyanate is present in the sample, the concentrations of each compound expressed in \(\mu g/cu \text{ m}\) can be added together to get the total concentration of diisocyanates.

Another method of expressing vapor concentration is ppb (corrected to standard conditions of 25 °C and 760 mmHg):

\[
\text{ppb} = \frac{\mu g}{\text{cu m}} \times \frac{24.45 \times 760 \times (T + 273)}{\text{MW} \times P \times 298}
\]

where:

- \(P\) = pressure (mmHg) of air sampled
- \(T\) = temperature (°C) of air sampled
- 24.45 = molar volume (liter/mol)
- \(\text{MW}\) = molecular weight
- 760 = standard pressure (mmHg)
- 298 = standard temperature (K)

However, it must be noted that concentrations expressed in ppb must be converted to \(\mu g/cu \text{ m}\) before being added together to obtain the combined concentration of mixed diisocyanates.
The following items of information that are applicable to a specific product or material shall be provided in the appropriate block of the Material Safety Data Sheet (MSDS).

The product designation is inserted in the block in the upper left corner of the first page to facilitate filing and retrieval. Print in upper case letters as large as possible. It should be printed to read upright with the sheet turned sideways. The product designation is that name or code designation which appears on the label, or by which the product is sold or known by employees. The relative numerical hazard ratings and key statements are those determined by the rules in Chapter V, Part B, of the NIOSH publication, An Identification System for Occupationally Hazardous Materials. The company identification may be printed in the upper right corner if desired.

(a) Section I. Production Identification

The manufacturer's name, address, and regular and emergency telephone numbers (including area code) are inserted in the appropriate blocks of Section I. The company listed should be a source of detailed backup information on the hazards of the material(s) covered by the MSDS. The listing of suppliers or wholesale distributors is discouraged. The trade name should be the product designation or common name associated with the material. The synonyms are those commonly used for the product, especially formal chemical nomenclature. Every known chemical designation or competitor's trade name need not be listed.

(b) Section II. Hazardous Ingredients

The "materials" listed in Section II shall be those substances that are part of the hazardous product covered by the MSDS and individually meet any of the criteria defining a hazardous material. Thus, one component of a multicomponent product might be listed because of its toxicity, another component because of its flammability, while a third component could be included both for its toxicity and its reactivity. Note that a MSDS for a single component product must have the name of the material repeated in this section to avoid giving the impression that there are no hazardous ingredients.

Chemical substances should be listed according to their complete name derived from a recognized system of nomenclature. Where possible, avoid using common names and general class names such as "aromatic amine," "safety solvent," or "aliphatic hydrocarbon" when the specific name is known.
The "%" may be the approximate percentage by weight or volume (indicate basis) that each hazardous ingredient of the mixture bears to the whole mixture. This may be indicated as a range or maximum amount, ie, "10-40% vol" or "10% max wt" to avoid disclosure of trade secrets.

Toxic hazard data shall be stated in terms of concentration, mode of exposure or test, and animal used, eg, "100 ppm LC50-rat," "25 mg/kg LD50-skin-rabbit," "75 ppm LC-man," or "permissible exposure from 29 CFR 1910.1000," or, if not available, from other sources of publications such as the American Conference of Governmental Industrial Hygienists or the American National Standards Institute Inc. Flashpoint, shock sensitivity, or similar descriptive data may be used to indicate flammability, reactivity, or similar hazardous properties of the material.

(c) Section III. Physical Data

The data in Section III should be for the total mixture and should include the boiling point and melting point in degrees Fahrenheit (Celsius in parentheses); vapor pressure, in conventional millimeters of mercury (mmHg); vapor density of gas or vapor (air = 1); solubility in water, in parts/hundred parts of water by weight; specific gravity (water = 1); percent volatiles (indicated if by weight or volume) at 70 F (21.1 C); evaporation rate for liquids or sublimable solids, relative to butyl acetate; and appearance and odor. These data are useful for the control of toxic substances. Boiling point, vapor density, percent volatiles, vapor pressure, and evaporation are useful for designing proper ventilation equipment. This information is also useful for design and deployment of adequate fire and spill containment equipment. The appearance and odor may facilitate identification of substances stored in improperly marked containers, or when spilled.

(d) Section IV. Fire and Explosion Data

Section IV should contain complete fire and explosion data for the product, including flashpoint and autoignition temperature in degrees Fahrenheit (Celsius in parentheses); flammable limits, in percent by volume in air; suitable extinguishing media or materials; special firefighting procedures; and unusual fire and explosion hazard information. If the product presents no fire hazard, insert "NO FIRE HAZARD" on the line labeled "Extinguishing Media."

(e) Section V. Health Hazard Information

The "Health Hazard Data" should be a combined estimate of the hazard of the total product. This can be expressed as a TWA concentration, as a permissible exposure, or by some other indication of an acceptable standard. Other data are acceptable, such as lowest LD50 if multiple components are involved.

Under "Routes of Exposure," comments in each category should reflect the potential hazard from absorption by the route in question. Comments should indicate the severity of the effect and the basis for the statement if possible. The
basis might be animal studies, analogy with similar products, or human experiences. Comments such as "yes" or "possible" are not helpful. Typical comments might be:

Skin Contact--single short contact, no adverse effects likely; prolonged or repeated contact, possibly mild irritation.

Eye Contact--some pain and mild transient irritation; no corneal scarring.

"Emergency and First Aid Procedures" should be written in lay language and should primarily represent first-aid treatment that could be provided by paramedical personnel or individuals trained in first aid.

Information in the "Notes to Physician" section should include any special medical information which would be of assistance to an attending physician, including required or recommended preplacement and periodic medical examinations, diagnostic procedures, and medical management of overexposed employees.

(f) Section VI. Reactivity Data

The comments in Section VI relate to safe storage and handling of hazardous, unstable substances. It is particularly important to highlight instability or incompatibility to common substances or circumstances, such as water, direct sunlight, steel or copper piping, acids, alkalies, etc. "Hazardous Decomposition Products" shall include those products released under fire conditions. It must also include dangerous products produced by aging, such as peroxides in the case of some ethers. Where applicable, shelf life should also be indicated.

(g) Section VII. Spill or Leak Procedures

Detailed procedures for cleanup and disposal should be listed with emphasis on precautions to be taken to protect employees assigned to cleanup detail. Specific neutralizing chemicals or procedures should be described in detail. Disposal methods should be explicit including proper labeling of containers holding residues and ultimate disposal methods such as "sanitary landfill" or "incineration." Warnings such as "Comply with local, state, and Federal antipollution ordinances" are proper but not sufficient. Specific procedures shall be identified.

(h) Section VIII. Special Protection Information

Section VIII requires specific information. Statements such as "Yes," "No," or "If necessary" are not informative. Ventilation requirements should be specific as to type and preferred methods. Respirators shall be specified as to type and NIOSH or US Mine Safety and Health Administration approval class, ie, "Supplied air," "Organic vapor canister," etc. Protective equipment must be specified as to type and materials of construction.
(i) Section IX. Special Precautions

"Precautionary Statements" shall consist of the label statements selected for use on the container or placard. Additional information on any aspect of safety or health not covered in other sections should be inserted in Section IX. The lower block can contain references to published guides or in-house procedures for handling and storage. Department of Transportation markings and classifications and other freight, handling, or storage requirements and environmental controls can be noted.

(j) Signature and Filing

Finally, the name and address of the responsible person who completed the MSDS and the date of completion are entered. This will facilitate correction of errors and identify a source of additional information.

The MSDS shall be filed in a location readily accessible to employees exposed to the hazardous substance. The MSDS can be used as a training aid and basis for discussion during safety meetings and training of new employees. It should assist management by directing attention to the need for specific control engineering, work practices, and protective measures to ensure safe handling and use of the material. It will aid the safety and health staff in planning a safe and healthful work environment and in suggesting appropriate emergency procedures and sources of help in the event of harmful exposure of employees.
# MATERIAL SAFETY DATA SHEET

## I PRODUCT IDENTIFICATION

<table>
<thead>
<tr>
<th>MANUFACTURER'S NAME</th>
<th>REGULAR TELEPHONE NO</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ADDRESS</th>
<th>EMERGENCY TELEPHONE NO</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TRADE NAME</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SYNONYMS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
</tbody>
</table>

## II HAZARDOUS INGREDIENTS

<table>
<thead>
<tr>
<th>MATERIAL OR COMPONENT</th>
<th>%</th>
<th>HAZARD DATA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

## III PHYSICAL DATA

<table>
<thead>
<tr>
<th>BOILING POINT, 760 MM HG</th>
<th>MELTING POINT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SPECIFIC GRAVITY (H₂O: 1)</th>
<th>VAPOR PRESSURE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>VAPOR DENSITY (AIR: 1)</th>
<th>SOLUBILITY IN H₂O % BY WT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>% VOLATILES BY VOL</th>
<th>EVAPORATION RATE (BUTYL ACETATE: 1)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>APPEARANCE AND ODOR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
</tbody>
</table>
### IV Fire and Explosion Data

<table>
<thead>
<tr>
<th>Flash Point Test Method</th>
<th>Autoignition Temperature</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Flammable Limits in Air, % by Vol.</th>
<th>Lower</th>
<th>Upper</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Extinguishing Media</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Special Fire Fighting Procedures</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Unusual Fire and Explosion Hazard</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
</tbody>
</table>

### V Health Hazard Information

#### Health Hazard Data

#### Routes of Exposure

- Inhalation
- Skin Contact
- Skin Absorption
- Eye Contact
- Ingestion

#### Effects of Overexposure

- Acute Overexposure
- Chronic Overexposure

#### Emergency and First Aid Procedures

- Eyes
- Skin
- Inhalation
- Ingestion

#### Notes to Physician
<table>
<thead>
<tr>
<th>VI REACTIVITY DATA</th>
</tr>
</thead>
<tbody>
<tr>
<td>CONDITIONS CONTRIBUTING TO INSTABILITY</td>
</tr>
<tr>
<td>INCOMPATIBILITY</td>
</tr>
<tr>
<td>HAZARDOUS DECOMPOSITION PRODUCTS</td>
</tr>
<tr>
<td>CONDITIONS CONTRIBUTING TO HAZARDOUS POLYMERIZATION</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>VII SPILL OR LEAK PROCEDURES</th>
</tr>
</thead>
<tbody>
<tr>
<td>STEPS TO BE TAKEN IF MATERIAL IS RELEASED OR SPILLED</td>
</tr>
<tr>
<td>NEUTRALIZING CHEMICALS</td>
</tr>
<tr>
<td>WASTE DISPOSAL METHOD</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>VIII SPECIAL PROTECTION INFORMATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>VENTILATION REQUIREMENTS</td>
</tr>
<tr>
<td>SPECIFIC PERSONAL PROTECTIVE EQUIPMENT</td>
</tr>
<tr>
<td>RESPIRATORY (SPECIFY IN DETAIL)</td>
</tr>
<tr>
<td>EYE</td>
</tr>
<tr>
<td>GLOVES</td>
</tr>
<tr>
<td>OTHER CLOTHING AND EQUIPMENT</td>
</tr>
</tbody>
</table>
## IX SPECIAL PRECAUTIONS

<table>
<thead>
<tr>
<th>PRECAUTIONARY STATEMENTS</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>OTHER HANDLING AND STORAGE REQUIREMENTS</th>
</tr>
</thead>
</table>

**PREPARED BY**

---

**ADDRESS**

---

**DATE**

---

130
XI. TABLES AND FIGURE

TABLE XI-1

CHEMICAL AND PHYSICAL PROPERTIES OF SELECTED DIISOCYANATES

<table>
<thead>
<tr>
<th>Toluene diisocyanate (TDI)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Appearance</strong></td>
<td>Colorless to pale yellow liquid</td>
</tr>
<tr>
<td><strong>Formula</strong></td>
<td>C9H6N2O2</td>
</tr>
<tr>
<td><strong>Formula weight</strong></td>
<td>174.16</td>
</tr>
<tr>
<td><strong>Boiling point</strong></td>
<td>251 C (484 F) (all isomer ratios)</td>
</tr>
<tr>
<td></td>
<td>20-22 C (68-72 F)</td>
</tr>
<tr>
<td></td>
<td>(80/20% 2,4-/2,6-isomer mixture)</td>
</tr>
<tr>
<td><strong>Melting point</strong></td>
<td>20-22 C (68-72 F)</td>
</tr>
<tr>
<td></td>
<td>(80/20% mixture)</td>
</tr>
<tr>
<td><strong>Vapor pressure</strong></td>
<td>0.05 mmHg at 25 C (77 F)</td>
</tr>
<tr>
<td></td>
<td>(80/20% mixture)</td>
</tr>
<tr>
<td><strong>Specific gravity</strong></td>
<td>1.22 at 25 C (77 F)</td>
</tr>
<tr>
<td></td>
<td>(80/20% mixture)</td>
</tr>
<tr>
<td><strong>Vapor density (air = 1)</strong></td>
<td>6.0 (all isomer ratios)</td>
</tr>
<tr>
<td><strong>Flashpoint (open cup)</strong></td>
<td>135 C (275 F) (80/20% mixture)</td>
</tr>
<tr>
<td><strong>Autoignition temperature</strong></td>
<td>135 C (275 F) (80/20% mixture)</td>
</tr>
<tr>
<td><strong>Explosive limits (% volume in air)</strong></td>
<td>Soluble in aromatic hydrocarbons, nitrobenzene, acetone, ethers, esters (all isomer ratios)</td>
</tr>
<tr>
<td><strong>Solubility</strong></td>
<td></td>
</tr>
<tr>
<td>Conversion factors</td>
<td>1 µg/cu m = 0.1404 ppb</td>
</tr>
<tr>
<td></td>
<td>1 ppb = 7.123 µg/cu m</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Diphenylmethane diisocyanate (MDI)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Appearance</strong></td>
<td>White to pale yellow solid</td>
</tr>
<tr>
<td><strong>Formula</strong></td>
<td>C15H10N2O2</td>
</tr>
<tr>
<td><strong>Formula weight</strong></td>
<td>250.3</td>
</tr>
<tr>
<td><strong>Boiling point</strong></td>
<td>314 C (597 F)</td>
</tr>
<tr>
<td><strong>Melting point</strong></td>
<td>38 C (100.4 F)</td>
</tr>
<tr>
<td><strong>Vapor pressure</strong></td>
<td>0.00014 mmHg at 25 C (77 F)</td>
</tr>
<tr>
<td><strong>Specific gravity</strong></td>
<td>1.23</td>
</tr>
<tr>
<td><strong>Vapor density</strong></td>
<td>8.6</td>
</tr>
<tr>
<td><strong>Flashpoint (open cup)</strong></td>
<td>196 C (385 F)</td>
</tr>
<tr>
<td><strong>Autoignition temperature</strong></td>
<td>-</td>
</tr>
<tr>
<td><strong>Explosive limits</strong></td>
<td>-</td>
</tr>
<tr>
<td><strong>Solubility</strong></td>
<td>Soluble in aromatic hydrocarbons, nitrobenzene, acetone, ethers, esters</td>
</tr>
<tr>
<td>Conversion factors</td>
<td>1 µg/cu m = 0.098 ppb</td>
</tr>
<tr>
<td></td>
<td>1 ppb = 10.236 µg/cu m</td>
</tr>
<tr>
<td>CHEMICAL AND PHYSICAL PROPERTIES OF SELECTED DIISOCYANATES</td>
<td></td>
</tr>
<tr>
<td>----------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td><strong>Hexamethylene diisocyanate (HDI)</strong></td>
<td></td>
</tr>
<tr>
<td>Appearance: Liquid</td>
<td></td>
</tr>
<tr>
<td>Formula: C8H12N2O2</td>
<td></td>
</tr>
<tr>
<td>Formula weight: 168.0</td>
<td></td>
</tr>
<tr>
<td>Boiling point: 212.8 °C (415 °F) at 760 mmHg</td>
<td></td>
</tr>
<tr>
<td>Melting point:</td>
<td></td>
</tr>
<tr>
<td>Vapor pressure: 0.05 mmHg at 24 °C (75 °F)</td>
<td></td>
</tr>
<tr>
<td>Specific gravity: 1.04</td>
<td></td>
</tr>
<tr>
<td>Vapor density:</td>
<td></td>
</tr>
<tr>
<td>Flashpoint: 140 °C (284 °F)</td>
<td></td>
</tr>
<tr>
<td>Autoignition temperature:</td>
<td></td>
</tr>
<tr>
<td>Explosive limits:</td>
<td></td>
</tr>
<tr>
<td>Solubility: Poorly soluble in water, readily soluble in organic solvents</td>
<td></td>
</tr>
<tr>
<td>Conversion factors:</td>
<td></td>
</tr>
<tr>
<td>1 µg/cu m = 0.145 ppb</td>
<td></td>
</tr>
<tr>
<td>1 ppb = 6.879 µg/cu m</td>
<td></td>
</tr>
<tr>
<td><strong>Naphthalene diisocyanate (NDI)</strong></td>
<td></td>
</tr>
<tr>
<td>Appearance: White to yellow crystalline flakes</td>
<td></td>
</tr>
<tr>
<td>Formula: C12H6N2O2</td>
<td></td>
</tr>
<tr>
<td>Formula weight: 210</td>
<td></td>
</tr>
<tr>
<td>Boiling point: 263 °C (505 °F)</td>
<td></td>
</tr>
<tr>
<td>Melting point: 126.5-127 °C (259.7-260.6 °F)</td>
<td></td>
</tr>
<tr>
<td>Vapor pressure: 0.003 mmHg at 24 °C (75 °F)</td>
<td></td>
</tr>
<tr>
<td>Specific gravity:</td>
<td></td>
</tr>
<tr>
<td>Vapor density:</td>
<td></td>
</tr>
<tr>
<td>Flashpoint (open cup): 155 °C (311 °F)</td>
<td></td>
</tr>
<tr>
<td>Autoignition temperature:</td>
<td></td>
</tr>
<tr>
<td>Explosive limits:</td>
<td></td>
</tr>
<tr>
<td>Solubility:</td>
<td></td>
</tr>
<tr>
<td>Conversion factors:</td>
<td></td>
</tr>
<tr>
<td>1 µg/cu m = 0.116 ppb</td>
<td></td>
</tr>
<tr>
<td>1 ppb = 8.597 µg/cu m</td>
<td></td>
</tr>
<tr>
<td><strong>Isophorone diisocyanate (IPDI)</strong></td>
<td></td>
</tr>
<tr>
<td>Appearance: Colorless liquid</td>
<td></td>
</tr>
<tr>
<td>Formula: C12H18N2O2</td>
<td></td>
</tr>
<tr>
<td>Formula weight: 222.29</td>
<td></td>
</tr>
<tr>
<td>Boiling point: 158 °C (316 °F) at 10 mmHg</td>
<td></td>
</tr>
<tr>
<td>Melting point: Approximately -60 °C (-76 °F)</td>
<td></td>
</tr>
<tr>
<td>Vapor pressure: 0.0003 mmHg at 20 °C (68 °F)</td>
<td></td>
</tr>
</tbody>
</table>
TABLE XI-1 (CONTINUED)

CHEMICAL AND PHYSICAL PROPERTIES OF SELECTED DIISOCYANATES

<table>
<thead>
<tr>
<th>Isophorone diisocyanate (continued)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Specific gravity</td>
<td>1.062 g/ml at 20 C (68 F)</td>
</tr>
<tr>
<td>Vapor density</td>
<td>-</td>
</tr>
<tr>
<td>Flashpoint (closed cup)</td>
<td>155 C (311 F)</td>
</tr>
<tr>
<td>Autoignition temperature</td>
<td>430 C (806 F)</td>
</tr>
<tr>
<td>Explosive limits</td>
<td>-</td>
</tr>
<tr>
<td>Solubility</td>
<td>Miscible with esters, ketones, ethers, aromatic and aliphatic hydrocarbons</td>
</tr>
<tr>
<td>Conversion factors</td>
<td>1 µg/cu m = 0.110 ppb</td>
</tr>
<tr>
<td></td>
<td>1 ppb = 9.092 µg/cu m</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dicyclohexylmethane 4,4'-diisocyanate</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Appearance</td>
<td>Colorless to light yellow liquid</td>
</tr>
<tr>
<td>Formula</td>
<td>C15H22N2O2</td>
</tr>
<tr>
<td>Formula weight</td>
<td>262</td>
</tr>
<tr>
<td>Boiling point</td>
<td>-</td>
</tr>
<tr>
<td>Melting point</td>
<td>&lt;-10 C (&lt;-50 F)</td>
</tr>
<tr>
<td>Vapor pressure</td>
<td>0.4 mmHg at 150 C (238 F)</td>
</tr>
<tr>
<td></td>
<td>7.0 mmHg at 200 C (328 F)</td>
</tr>
<tr>
<td>Specific gravity</td>
<td>1.07</td>
</tr>
<tr>
<td>Vapor density</td>
<td>-</td>
</tr>
<tr>
<td>Flashpoint</td>
<td>-</td>
</tr>
<tr>
<td>Autoignition temperature</td>
<td>-</td>
</tr>
<tr>
<td>Explosive limits</td>
<td>-</td>
</tr>
<tr>
<td>Solubility</td>
<td>Reacts with water and ethanol; soluble in acetone</td>
</tr>
<tr>
<td>Conversion factors</td>
<td>1 µg/cu m = 0.093 ppb</td>
</tr>
<tr>
<td></td>
<td>1 ppb = 10.753 µg/cu m</td>
</tr>
</tbody>
</table>

Adapted from references 1-10
TABLE XI-2
SYNONYMS FOR DIISOCYANATE COMPOUNDS AND ISOMERS

<table>
<thead>
<tr>
<th>Compound</th>
<th>Synonyms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toluene diisocyanate</td>
<td>TDI</td>
</tr>
<tr>
<td></td>
<td>Tolylene diisocyanate</td>
</tr>
<tr>
<td></td>
<td>Methylphenylene isocyanate</td>
</tr>
<tr>
<td></td>
<td>Diisocyanatotoluene</td>
</tr>
<tr>
<td></td>
<td>Stilbene diisocyanate</td>
</tr>
<tr>
<td></td>
<td>2,4-Toluene diisocyanate</td>
</tr>
<tr>
<td></td>
<td>2,6-Toluene diisocyanate</td>
</tr>
<tr>
<td>Diphenylmethane diisocyanate</td>
<td>MDI</td>
</tr>
<tr>
<td></td>
<td>4,4'-Diisocyanatodiphenylmethane</td>
</tr>
<tr>
<td></td>
<td>Methylene bisphenyl isocyanate</td>
</tr>
<tr>
<td></td>
<td>Methylene isocyanate</td>
</tr>
<tr>
<td></td>
<td>Diphenyl methane 4,4'-diisocyanate</td>
</tr>
<tr>
<td></td>
<td>4,4'-Methylene diphenyl isocyanate</td>
</tr>
<tr>
<td>Hexamethylene diisocyanate</td>
<td>HDI</td>
</tr>
<tr>
<td></td>
<td>HMDI</td>
</tr>
<tr>
<td></td>
<td>1,6-Diisocyanatohexane</td>
</tr>
<tr>
<td>Naphthalene diisocyanate</td>
<td>NDI</td>
</tr>
<tr>
<td></td>
<td>1,5-Naphthalene diisocyanate</td>
</tr>
<tr>
<td></td>
<td>1,5-Diisocyanonaphthalene</td>
</tr>
<tr>
<td>Isophorone diisocyanate</td>
<td>IPDI</td>
</tr>
<tr>
<td></td>
<td>5-Isocyanato-1-(isocyanatomethyl)-1,3,3-trimethylcyclohexane</td>
</tr>
<tr>
<td>Dicyclohexylmethane 4,4'-diisocyanate</td>
<td>Hydrogenated MDI</td>
</tr>
<tr>
<td></td>
<td>4,4'-Diisocyanatodicyclohexylmethane</td>
</tr>
<tr>
<td></td>
<td>Methylene bis(4-cyclohexyl isocyanate)</td>
</tr>
</tbody>
</table>
## TABLE XI-3

**LC₅₀ AND LD₅₀ VALUES OF DIISOCYANATES IN ANIMALS**

<table>
<thead>
<tr>
<th>Compound</th>
<th>Species</th>
<th>LC₅₀</th>
<th>LD₅₀</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Concentration</td>
<td>Duration</td>
<td>Oral (mg/kg)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(mg/cu m)</td>
<td>(hr)</td>
<td></td>
</tr>
<tr>
<td>TDI</td>
<td>Rats</td>
<td>350 (M)</td>
<td>4</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>360 (F)</td>
<td>4</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>&quot;</td>
<td>98.7</td>
<td>4</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>&quot;</td>
<td>-</td>
<td>-</td>
<td>5,800</td>
</tr>
<tr>
<td></td>
<td>&quot;</td>
<td>57.7</td>
<td>1</td>
<td>3,060</td>
</tr>
<tr>
<td></td>
<td>Mice</td>
<td>68.9</td>
<td>4</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Guinea pigs</td>
<td>90.2</td>
<td>4</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Rabbits</td>
<td>-</td>
<td>-</td>
<td>10,000</td>
</tr>
<tr>
<td>MDI</td>
<td>Rats</td>
<td>369 (M)</td>
<td>4</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>380 (F)</td>
<td>4</td>
<td>-</td>
</tr>
<tr>
<td>HDI</td>
<td>&quot;</td>
<td>385</td>
<td>6</td>
<td>710</td>
</tr>
<tr>
<td></td>
<td>&quot;</td>
<td>310 (M)</td>
<td>4</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>350 (F)</td>
<td>4</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Mice</td>
<td>30</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Rabbits</td>
<td>-</td>
<td>-</td>
<td>570</td>
</tr>
<tr>
<td>NDI</td>
<td>Rats</td>
<td>-</td>
<td>-</td>
<td>&gt;10,000</td>
</tr>
<tr>
<td></td>
<td>Rabbits</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>IPDI</td>
<td>Rats</td>
<td>260</td>
<td>1</td>
<td>&gt;2,500</td>
</tr>
<tr>
<td></td>
<td>&quot;</td>
<td>160 (M)</td>
<td>4</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>&quot;</td>
<td>135 (F)</td>
<td>4</td>
<td>-</td>
</tr>
</tbody>
</table>

135
TABLE XI-3 (CONTINUED)

LC50 AND LD50 VALUES OF DIISOCYANATES IN ANIMALS

<table>
<thead>
<tr>
<th>Compound</th>
<th>Species</th>
<th>LC50</th>
<th>LD50*</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>IPDI</td>
<td>Rats</td>
<td>123</td>
<td>-</td>
<td>104</td>
</tr>
<tr>
<td>&quot;</td>
<td></td>
<td>33</td>
<td>-</td>
<td>104</td>
</tr>
<tr>
<td>&quot;</td>
<td>Mice</td>
<td>-</td>
<td>&gt;2,500</td>
<td>104</td>
</tr>
<tr>
<td>&quot;</td>
<td>Cats</td>
<td>-</td>
<td>&gt;1,000</td>
<td>104</td>
</tr>
<tr>
<td>Bitolylene diisocyanate</td>
<td>Rats</td>
<td>-</td>
<td>4,640</td>
<td>2</td>
</tr>
<tr>
<td>Dianisidine diisocyanate</td>
<td>&quot;</td>
<td>-</td>
<td>&gt;10,000</td>
<td>2</td>
</tr>
<tr>
<td>Diethylbenzene diisocyanate</td>
<td>&quot;</td>
<td>320</td>
<td>-</td>
<td>2</td>
</tr>
</tbody>
</table>

*Single dose
TABLE XI-4

SKIN AND EYE IRRITATION POTENTIAL OF DIISOCYANATES IN RABBITS

<table>
<thead>
<tr>
<th>Compound</th>
<th>Skin Irritation</th>
<th>Eye Injury</th>
</tr>
</thead>
<tbody>
<tr>
<td>TDI</td>
<td>Moderate</td>
<td>Severe</td>
</tr>
<tr>
<td>MDI</td>
<td>Slight</td>
<td>Moderate</td>
</tr>
<tr>
<td>HDI</td>
<td>Severe</td>
<td>Severe</td>
</tr>
<tr>
<td>NDI</td>
<td>&quot;</td>
<td>&quot;</td>
</tr>
<tr>
<td>IPDI*</td>
<td>Moderate</td>
<td>&quot;</td>
</tr>
<tr>
<td>Bitolylene diisocyanate</td>
<td>Slight</td>
<td>Slight</td>
</tr>
<tr>
<td>Dianisidene diisocyanate</td>
<td>None</td>
<td>&quot;</td>
</tr>
<tr>
<td>Diethylbenzene diisocyanate</td>
<td>Severe</td>
<td>Severe</td>
</tr>
</tbody>
</table>

*From reference 104

Adapted from Woolrich [2]
FIGURE XI-1

VAPOR PRESSURES OF DIISOCYANATES

Adapted from references 2,6,7