IPCS International Programme on Chemical Safety

Environmental Health Criteria 75

Toluene Diisocyanates

Published under the joint sponsorship of the United Nations Environment Programme, the International Labour Organisation, and the World Health Organization

WORLD HEALTH ORGANIZATION GENEVA 1987

Other titles available in the ENVIRONMENTAL HEALTH CRITERIA series include:

1. Mercury
2. Polychlorinated Biphenyls and Terphenyls
3. Lead
4. Oxides of Nitrogen
5. Nitrates, Nitrites, and *N*-Nitroso Compounds
6. Principles and Methods for Evaluating the Toxicity of Chemicals, Part 1
7. Photochemical Oxidants
8. Sulfur Oxides and Suspended Particulate Matter
9. DDT and its Derivatives
10. Carbon Disulfide
11. Mycotoxins
12. Noise
13. Carbon Monoxide
14. Ultraviolet Radiation
15. Tin and Organotin Compounds
16. Radiofrequency and Microwaves
17. Manganese
18. Arsenic
19. Hydrogen Sulfide
20. Selected Petroleum Products
21. Chlorine and Hydrogen Chloride
22. Ultrasound
23. Lasers and Optical Radiation
24. Titanium
25. Selected Radionuclides
26. Styrene
27. Guidelines on Studies in Environmental Epidemiology
28. Acrylonitrile
29. 2,4-Dichlorophenoxyacetic Acid (2,4-D)
30. Principles for Evaluating Health Risks to Progeny Associated with Exposure to Chemicals during Pregnancy
31. Tetrachloroethylene
32. Methylene Chloride
33. Epichlorohydrin
34. Chlordane
35. Extremely Low Frequency (ELF) Fields
36. Fluorine and Fluorides
37. Aquatic (Marine and Freshwater) Biotoxins
38. Heptachlor
39. Paraquat and Diquat
40. Endosulfan
41. Quintozene
42. Tecnazene
43. Chlordecone
44. Mirex
45. Camphechlor
46. Guidelines for the Study of Genetic Effects in Human Populations
47. Summary Report on the Evaluation of Short-Term Tests for Carcinogens (Collaborative Study on *In Vitro* Tests)
48. Dimethyl Sulfate
49. Acrylamide
50. Trichloroethylene
51. Guide to Short-Term Tests for Detecting Mutagenic and Carcinogenic Chemicals
52. Toluene
53. Asbestos and Other Natural Mineral Fibres
54. Ammonia
55. Ethylene Oxide
56. Propylene Oxide
57. Principles of Toxicokinetic Studies
58. Selenium
59. Principles for Evaluating Health Risks from Chemicals During Infancy and Early Childhood: The Need for a Special Approach
60. Principles for the Assessment of Neurobehavioural Toxicology
61. Chromium (in preparation)
62. 1,2-Dichloroethane
63. Organophosphorus Insecticides — A General Introduction
64. Carbamate Pesticides — A General Introduction
65. Butanols — Four Isomers
66. Kelevan
67. Tetradifon
68. Hydrazine

Environmental Health Criteria 75

TOLUENE DIISOCYANATES

Published under the joint sponsorship of
the United Nations Environment Programme,
the International Labour Organisation,
and the World Health Organization

World Health Organization
Geneva, 1987

The **International Programme on Chemical Safety (IPCS)** is a joint venture of the United Nations Environment Programme, the International Labour Organisation, and the World Health Organization. The main objective of the IPCS is to carry out and disseminate evaluations of the effects of chemicals on human health and the quality of the environment. Supporting activities include the development of epidemiological, experimental laboratory, and risk-assessment methods that could produce internationally comparable results, and the development of manpower in the field of toxicology. Other activities carried out by IPCS include the development of know-how for coping with chemical accidents, coordination of laboratory testing and epidemiological studies, and promotion of research on the mechanisms of the biological action of chemicals.

ISBN 92 4 154275 6

ISSN 0250-863X
PRINTED IN FINLAND
DHSS — VAMMALA — 5500

WORLD HEALTH ORGANIZATION

CORRIGENDA

ENVIRONMENTAL HEALTH CRITERIA
No. 75

TOLUENE DIISOCYANATES

Page 6, line 7:

Delete: Blaska

Insert: Blaschka

Page 8, line 10:

Delete: diaminotoluenes

Insert: toluene diisocyanates. It stressed that this document pertains only to TDI and not to other isocyanates, polyurethanes derived from TDI, or pyrolysis products from TDI or polyurethanes.

Page 11, line 9:

Delete: *in vivo* system

Insert: *in vivo* micronucleus system

Page 16, line 27:

Delete: carbanic

Insert: carbonic

Page 52, line 12:

Delete: dhallenge

Insert: challenge

CONTENTS

Page

Page

WHO TASK GROUP ON TOLUENE DIISOCYANATES (TDIs)

Members

Dr X. Baur, Pulmonary Section, Klinikum Grosshaden, University of Munich, Munich, Federal Republic of Germany

Dr L. Belin, Department of Medicine, Sahlgren's Hospital, Goteborg, Sweden

Ms Andrea Blaska, Office of Toxic Substances, US Environmental Protection Agency, Washington DC, USA (Co-Rapporteur)

Dr M. Dieter, US National Institute for Environmental Health Sciences, Research Triangle Park, North Carolina, USA (Co-Rapporteur)

Dr M. Greenberg, Department of Health and Social Security, London, United Kingdom.

Dr I. Gut, Institute of Hygiene and Epidemiology, Prague, Czechoslovakia (Chairman)

Dr M. Mann, Bayer AG, Leverkusen, Bayerwerk, Federal Republic of Germany

Dr C. Rosenburg, Institute of Occupational Health, Department of Industrial Hygiene and Toxicology, Helsinki, Finland

Professor H. Sakurai, School of Medicine, Keio University, Tokyo, Japan

Secretariat

Dr G.C. Becking, International Programme on Chemical Safety, Interregional Research Unit, World Health Organization, Research Triangle Park, North Carolina, USA (Secretary)

Mr A.C. Fletcher, International Agency for Research on Cancer, Lyons, France

NOTE TO READERS OF THE CRITERIA DOCUMENTS

Every effort has been made to present information in the criteria documents as accurately as possible without unduly delaying their publication. In the interest of all users of the environmental health criteria documents, readers are kindly requested to communicate any errors that may have occurred to the Manager of the International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland, in order that they may be included in corrigenda, which will appear in subsequent volumes.

* * *

A detailed data profile and a legal file can be obtained from the International Register of Potentially Toxic Chemicals, Palais des Nations, 1211 Geneva 10, Switzerland (Telephone no. 988400 - 985850).

ENVIRONMENTAL HEALTH CRITERIA FOR TOLUENE DIISOCYANATES

A WHO Task Group on Environmental Health Criteria for Diaminotoluenes met at the Monitoring and Assessment Research Centre, London, United Kingdom, from 20 to 25 October 1986. Professor P.J. Petersen welcomed the participants on behalf of the host Institution, and Dr G.C. Becking opened the meeting on behalf of the three co-sponsoring organizations of the IPCS (ILO/UNEP/WHO). The Task Group reviewed and revised the draft criteria document and made an evaluation of the health risks of exposure to diaminotoluenes.

The efforts of DR M. DIETER, US NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH SCIENCES, Research Triangle Park, North Carolina, USA, in the preparation of the draft, and of all others who helped in the preparation and finalization of the document are gratefully acknowledged.

* * *

Partial financial support for the publication of this criteria document was kindly provided by the United States Department of Health and Human Services, through a contract from the National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina, USA — a WHO Collaborating Centre for Environmental Health Effects. The United Kingdom Department of Health and Social Security generously supported the cost of printing.

1. SUMMARY AND CONCLUSIONS

1.1 Summary

1.1.1 Identity, properties, analytical methods

Toluene diisocyanates (TDIs) are synthetic organic chemicals of low relative molecular mass (174.17). They are colourless to pale yellow liquids, at room temperature, with a distinct pungent odour detectable around 0.7 mg/m^3, which is well above current exposure limits. The different commercial grades solidify at between 4.7 °C and 22 °C and boil at 251 °C at 760 mmHg. Toluene diisocyanates react with water to form polyureas, carbon dioxide gas, and small amounts of diaminotoluenes, depending on the amount of water present. They also react with basic chemicals, including proteins.

Adequate analytical methods have been developed to measure air levels of toluene diisocyanates in the work-place, for both area and personal monitoring. The methods include: (a) high-pressure liquid chromatography; (b) photometric methods; and (c) the use of direct-reading instruments in which a chemically impregnated paper tape changes colour on exposure to toluene diisocyanates. The detection limits, ranging from 0.0001 to 0.07 mg/m^3, depend on the sampling and analytical procedure.

Analytical methods have also been developed to measure toluene diisocyanates levels in environmental media and consumer products.

1.1.2 Production, uses, and sources of exposure

Toluene diisocyanates are commercially available as $\geq$ 99.5% pure 2,4-toluene diisocyanate (2,4-TDI), and 80:20 or 65:35 mixtures of the 2,4- and 2,6-isomers. "Crude"-TDI, with an unidentified isomer ratio, is also commercially available, but not widely used. By far the most widely used compound is the 80:20 isomer mixture.

Toluene diisocyanates are important industrial intermediates used in conjunction with polyether and polyester polyols as co-reactants in the manufacture of polyurethane foams, paints, varnishes, elastomers, and coatings. TDI-based polyurethane foams are widely used in the automotive and furniture industries, and in packaging and insulation.

Toluene diisocyanates released into the environment, will tend to partition into water and undergo rapid hydrolysis (half-life of 0.5 seconds - 3 days in water, depending on pH and water turbidity) leading predominantly to the formation of relatively inert polymeric ureas. Toluene diisocyanates would

also be expected to undergo photolysis and hydroxy radical oxidation. Therefore, transport and occurrence would be limited to the immediate vicinity of effluents or spills, and the resulting polyureas would probably be resistant to further biodegradation.

Consumer products, including single-pack paints and lacquers, may include traces of free toluene diisocyanates.

Exposure may occur in a wide variety of occupations, including the manufacture and use of chemicals, and work with polyurethane-coating products. It may also occur during transport, as a result of spills or leaks. Excursions above safety limits are of particular concern for sprayers and their co-workers.

1.1.3 Kinetics, biotransformation, and elimination

Toluene diisocyanates are highly reactive in body fluids with a reported half-life of less than 30 seconds in serum and < 20 min in stomach contents. However, in oral administration studies using high doses, TDI forms insoluble polyurea-coated globules and persists much longer. It is believed that TDIs react with the tissues they contact rather than being absorbed and distributed in the body in free form. Isocyanates react with hydroxyl, amino, carboxyl, and sulfhydryl groups and can inactivate proteins by covalent bonding. Animals, treated orally with 2,6-TDI, excreted mono- and di-acetylated diaminotoluene, indicating that diaminotoluene may be formed as a TDI metabolite. Its immunogenic action may derive from relations with proteins or polyaccharides to form a hapten complex and new antigenic determinants.

1.1.4 Effects on experimental animals

When inhaled, toluene diisocyanates are very toxic for animals. The 4-h LC_{50} ranges from 70 to 356 mg/m^3. Animals die of pulmonary oedema and haemorrhage. TDIs, ingested orally or in contact with the skin, are relatively less toxic in terms of lethal dose. The oral LD_{50} ranges from 3.06 to 4.13 g/kg body weight, and the dermal LD_{50} in rabbits is 10 g/kg body weight. Liver, kidney, gastro-intestinal, and skin damage occur via these routes.

Toluene diisocyanates are irritants for the mucous membranes of the respiratory tract, eyes, and skin and are sensitizers of the respiratory tract and skin.

Dermal application of toluene diisocyanates in one animal model resulted in sensitization, and subsequent bronchial challenge produced a hypersensitive response.

The mechanism of the sensitization reaction has been the subject of extensive research and is still under debate. It

has been suggested that sensitization, which may develop gradually or suddenly after exposure to toluene diisocyanates, may be due both to immunological factors, as evidenced by the production of TDI-specific antibodies, and to non-immunological factors, as evidenced by increased carbachol-induced contractibility.

TDI was positive in two bacterial mutagenicity tests. Toluene diisocyanates were negative for cell transformation in two mammalian *in vitro* systems and one *in vivo* system.

The results of 2-year, inhalation studies on mice and rats, using commercial grade 80:20 TDI at doses of 0.356 and 1.068 mg/m^3, administered for 6 h/day, 5 days per week, for periods ranging from 104 to 108 weeks, were negative for carcinogenicity. In 2-year oral gavage studies with an 80:20 commercial grade mixture of TDI in corn oil (30 - 240 mg/kg), the incidences of a variety of tumours increased in both male and female rats and in female mice. The tumours consisted of subcutaneous fibromas/fibrosarcomas and pancreatic acinar cell adenomas in male rats, subcutaneous fibromas/fibrosarcomas, pancreatic islet cell adenomas, neoplastic nodules of the liver, and mammary gland fibroadenomas in female rats, and haemangiomas/haemangiosarcomas and hepatocullular adenomas in female, but not male, mice.

1.1.5 Effects on human beings

Exposure to toluene diisocyanates can lead to adverse effects on the respiratory tract, skin, eyes, and gastrointestinal tract. A variety of respiratory illnesses have been induced in workers exposed occupationally to toluene diisocyanates, including irritation of the upper and lower respiratory tract, an asthma-like sensitization response, and individual and group mean decreases in lung function. These decreases have been noted, in some cases, after exposure to an estimated average TDI concentration of $\geq$ 0.014 mg/m^3 (for short-term as well as long-term occupational exposure).

Irritation of the eye, nose, and respiratory tract has been reported at levels of $\geq$ 0.35 mg/m^3. The respiratory tract sensitization response, producing bronchial asthma in up to 10% of previously exposed individuals, may occur at a level of 0.036 mg/m^3.

1.1.6 Effects on organisms in the environment

TDIs have been lethal for certain aquatic organisms at concentrations of between 10.5 and 508.3 mg/litre; the LD_{50} for two avian species was about 100 mg/kg body weight.

1.2 Evaluation of Hazards from Long-Term Exposure to Toluene Diisocyanates

The risk of respiratory toxicity from repeated exposure can be summarized as follows:

(a) chronic loss of ventilatory capacity, as measured by forced expiratory volume and forced vital capacity; and

(b) immediate and/or delayed asthmatic responses.

Estimates of past mean exposures to TDI have been made in many epidemiological studies in attempts to quantify dose-response relationships for respiratory ill-health. Because of inconsistencies in the hygiene sampling and measurements used in the past, it is difficult to be confident about the exact levels at which TDI causes the above-mentioned health effects. It should be remembered that fluctuations in true individual exposure occur and, as the size and extent of the intermittent peaks is not known, their biological significance cannot be evaluated.

Once individuals are sensitized to toluene diisocyanates, low concentrations, much below current occupational exposure limits, can induce asthma. Studies on experimental animals have shown that skin application of TDI can lead to pulmonary sensitization; thus, it is prudent to avoid repeated skin contact.

No data were available on the carcinogenic effects of toluene diisocyanates in human beings.

No carcinogenic effects of TDI were noted in an inhalation study on rats and mice. However, gavage of the 80:20 mixture in corn oil produced dose-related carcinogenic effects in male and female rats and female mice. It is considered that there is sufficient evidence for the carcinogenicity of TDI for experimental animals.

There is evidence of mutagenicity in two bacterial tests.

It is not possible, on the basis of available data, to evaluate the hazards for non-human targets from environmental levels of TDI.

1.2.1 Conclusions and recommendations

1. There is sufficient knowledge about TDI to classify it as a very toxic compound, when inhaled, and it should be treated as a potential human carcinogen and as a known animal carcinogen. Consequently, the greatest priority should be given to safe methods of use, and the education, training, and supervision of operatives, together with state enforcement of

legislation by an effective inspectorate. Special attention should be paid to the prevention and adequate treatment of unscheduled releases and spills.

2. Additional animal carcinogenicity testing using the inhalation route should be carried out.

3. Morbidity and mortality studies are required on occupational groups, for whom reliable exposure levels are available, to address the question of cancer, and to evaluate potential long-term human hazards under current standards of good working practice.

4. Because it is not possible to reach confident conclusions from data on the neurotoxicity of TDI, neurophysiological and behavioural studies should be carried out on asymptomatic workers exposed at current hygiene standards.

5. For the foreseeable future, exposed workers require health monitoring by systematic symptom enquiry and by standardized measurement of ventilatory function, with subsequent analysis of trends in individual, and group mean, values.

6. Appropriate sampling strategies, together with existing analytical methods, have to be developed and used to obtain better information about exposure. Special attention should be given to the detection and characterization of peak values. The results of these analyses should be evaluated in parallel with careful health studies.

7. Further metabolic studies of a qualitative and quantitative nature are required with a view to developing methods of measuring TDI uptake and monitoring exposure.

8. Whether TDI produces sensitization in human beings by pharmacological or immune mechanisms needs to be elucidated with a view to determining whether restrictions placed on the employment of atopic subjects, in areas where TDI is produced or used, are justified.

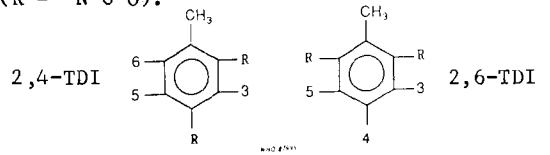
9. Studies are required to determine whether TDI has embryotoxic and teratogenic properties or induces adverse reproductive effects at current exposure levels.

10. Further environmental studies are required to monitor general environmental levels of TDI in the neignborhood of sources and to collect ecotoxicity data.

2. IDENTITY, PHYSICAL AND CHEMICAL PROPERTIES, ANALYTICAL METHODS

2.1 Identity

Toluene diisocyanates (TDIs) are synthetic organic chemicals with a molecular formula of $C_9H_6N_2O_2$; a relative molecular mass of 174.17; and the following chemical structure (R = -N=C=O):



Toluene diisocyanates are produced as 2 isomers (2,4-toluene diisocyanate (2,4-TDI) and 2,6-toluene diisocyanate (2,6-TDI)) and are commercially available in 3 isomer ratios: (a) $\geq$ 99.5% 2,4-TDI; (b) 80% 2,4-TDI/20% 2,6-TDI, which is the most common and referred to in this document as 80:20 mixture; and (c) 65% 2,4-TDI/35% 2,6-TDI. "Crude" toluene diisocyanate (Crude-TDI), with an unidentified isomer ratio, is also commercially available, but not widely used. Various identification codes for the most commonly marketed toluene diisocyanates are listed in Table 1.

Table 1. Identification codes of commercial toluene diisocyanates[a]

Numeric index	2,4-TDI	2,6-TDI	Commercial (80:20) mixture
CAS register number	584-84-9	91-08-7	26471-62-5
RTECS access number	CZ6300000	CZ6310000	CZ6200000
Wiswesser line notation	OCNR B1 ENCO	OCNR B1 CNCO	-
Shipping ID number	UN 2078	-	UN 2078
OHM TADS number	-	1-	7217313
Hazard substances data bank number	0874	5272	6003

[a] "Crude" toluene diisocyanate (unidentified isomers). CAS No. 1321-38-6 and chemical abstracts name benzene, diisocyanatomethyl-.

The chemical, common, and trade names for toluene diisocyanates are listed in Table 2.

Table 2. Toluene diisocyanates: Synonymous and Trade Names

I. Commercial mixtures: 2,4-, 2,6-isomers	
Chemical abstracts name	benzene, 1,3-diisocyanatomethyl-
Other chemical names	diisocyanatotoluene; isocyanic acid; methyl-m-phenylene ester; methyl-m-phenylene isocyanate; methylphenylene isocyanate; toluene diisocyanate; tolylene diisocyanate
Common name	TDI
Trade names	Desmodur T65 (also-T80); Hylene T (also, -TCPA, -TLC, -TM, -TM65, -TRF); Isocyanic acid; Lupranat T80; Mondur TD (also, -TD80, -TDS); Nacconate 100; NCI-C50533; Niax TDI; Niax TDI-P; Rubinate TDI 80/20; TDI 80
II. 2,4-TDI	
Chemical abstracts name	benzene, 2,4-diisocyanato-1-methyl-
Other chemical names	di-iso-cyanatoluene; di-isocyanate de toluylene; diisocyanat-toluol; isocyanic acid; 4-methyl-m-phenylene ester; tolueen-diisocyanaat; toluen-disocianato; toluene diisocyanate; toluene-2,4-diisocyanate; toluene, 2,4-diisocyanato-; toluilenodwuizocyjanian; toluylene-2,4-diisocyanate; tolylene-2,4-diisocyanate; tolylene diisocyanate; tuluylendiisocyanat; 2,4-Dicyanato-1-methylphenylene; 2,4-diisocyanato-1-methylbenzene; 2,4-diisocyanatotoluene; 2,4-toluene diisocyanate; 2,4-toluene diisocyanate; 4-methyl-m-phenylene diisocyanate; 4-methyl-m-phenylene isocyanate; 4-methyl-phenylene diisocyanate; 4-methyl-phenylene isocyanate
Common names	TDI, 2,4-TDI
Trade names	Desmodur T65 (also-T80); Hylene T (also, -TCPA, -TLC, -TM, -TM65, -TRF); Isocyanic acid; Lupranat T80; Mondur TD (also, -TD80, -TDS); Nacconate 100; NCI-C50533; Niax TDI; Niax TDI-P; Rubinate TDI 80/20; TDI 80
III. 2,6-TDI	
Chemical abstracts name	benzene, 2,6-diisocyanato-1-methy-
Other chemical names	benzene, 1,3-diisocyanato-2-methyl-; isocyanic acid; meta-tolylene diisocyanate; 2-methyl-m-phenylene isocyanate; 2,6-toluene diisocyanates
Common name	2,6-TDI
Trade names	not commercially available

The isomer or mixture studied is often not reported in the literature. For the purposes of this document, in such cases, the chemical will be referred to as toluene diisocyanates. When identified, the name of the particular isomer or mixture will be used.

2.2 Physical and Chemical Properties

Toluene diisocyanates are colourless liquids or crystals, turning pale yellow on standing, and having a characteristic sharp pungent, sweet, fruity odour. Some of the physical and chemical properties of toluene diisocyanates are listed in Table 3.

No properties of 2,6-TDI were found in the published literature, except for a boiling point of 129 - 133 °C at 18 mmHg, and a specific gravity similar to that of 2,4-TDI (Pollock & Stevens, 1974).

Toluene diisocyanates are soluble in acetone, ethyl acetate, ether, benzene, carbon tetrachloride, chlorobenzene, kerosene, and various oils, e.g., corn oil. They may react violently with compounds containing active hydrogen, such as alcohols, with the generation of enough heat to lead to self-ignition and subsequent release of toxic combustion products. Other such solvents that must not be mixed with toluene diisocyanates include water, acids, bases, and strong alkaline materials, such as sodium hydroxide and tertiary amines, etc.

Toluene diisocyanates react with water and most acids to produce unstable carbanic acids, which subsequently decarboxylate (raising the pressure in closed containers) to yield relatively chemically inert and insoluble polymeric urea (Hardy & Purnell, 1978). According to Holdren et al. (1984), reaction of TDI-vapour with water vapour does not take place in the gaseous phase. They concluded that loss due to surface adsorption takes place first, since no diaminotoluenes or TDI-ureas could be detected in an environmental chamber. Toluene diisocyanates also react with (-NH-)-containing compounds to form ureides or ureas. Each reaction pathway is important in terms of the health hazard potential associated with toluene diisocyanates, since both pathways are biologically, as well as commercially, significant, and occur at room temperature (Chadwick & Cleveland, 1981).

Toluene diisocyanates dimerize slowly at ambient temperatures and more rapidly at elevated temperatures. Trimerization occurs at 100 - 200 °C and, above 175 °C, carbodiimides form with the release of carbon dioxide (CO_2) (Chadwick & Cleveland, 1981; Ulrich, 1983).

Table 3. Physical and chemical properties of toluene diisocyanates

Properties	2,4-TDI	Commercial mixture (2,4-, 2,6-isomers)
Freezing point (°C)	14 - 20[a] 15[c]	11.5 - 13.5 (80:20 mix) 11 - 14 (80:20 mix) 3 - 5 (65:35 mix)[b] T80 = 12.5 - 13.5° T65 = 4.7 - 6
Melting point (°C)	22[b]	12.5 - 13.5 (80:20 mix) 4.7 - 6 (65.35 mix)
Boiling Point (°C)		
at 10 mmHg	120[b]	121[c]
at 760 mmHg	251[c]	251 (both mixes)
Flash point (°C)		
open cup	135[a]	132 (both mixes)
closed cup	127[b]	-
Explosive limits: Concentration (% v/v)		
lower	0.9	0.9
upper	9.5	9.5
Temperature (°C)		
lower	-	118
upper	-	150
Fire temperature (°C)	-	142
Autoignition temperature (°C)	620	620
Volatility; vapour pressure	1 mmHg (80 °C)[d]	1.9 mmHg (94 °C)[a] 0.01 mmHg (20 °C)
Vapour density (air = 1)	6[d]	6[e]
Density (g/cm^3)[b,c]	1.22 25/15 1.2244 20/4[c]	1.22 25/15 (both mixes) -
Odour threshold	0.36 - 0.92 mg/m^3	

[a] From: Woolrich & Rye (1969).
[b] From: Chadwick & Cleveland (1981).
[c] From: Windholz (1983).
[d] From: Hartung (1982).
[e] From: NIOSH (1978).
[f] From: Olin product literature.

2.3 Conversion Factors

At 25 °C and 760 mmHg:

1 mg/m³ = 0.14 ppm in air

1 mg/litre = 140.5 ppm.

2.4 Analytical Methods

The sampling and determination of toluene diisocyanates in air has been the subject of several studies. The method originally published by Marcali (1957) has been modified by several investigators (Grim & Linch, 1964; Meddle & Wood, 1970). Photometric methods are non-specific and most of them pool all the isocyanates. Also, most procedures are severely hampered because other agents, particularly aromatic amines, interfere in a way that may result in falsely high readings. In contrast, chromatographic techniques are specific and measure individual isocyanate species (Table 4).

Most recent analytical methods involve high-performance liquid chromatography (HPLC) using ultra-violet, fluorescence, or electrochemical detection (Dunlap et al., 1976; Sango & Zimerson, 1980; Warwick et al., 1981). Improved sampling techniques include the use of solid adsorbents (Tucker & Arnold, 1982). The Marcali method has been evaluated for its response for the two isomers of toluene diisocyanate. The simple modification involving changes in diazotization time and temperature eliminates the isomeric effect (Rando & Hammad, 1985). An extension of the spectrophotometric method is the development of a tape method involving a chemically impregnated paper tape that changes colour on exposure to toluene diisocyanates (Reilly, 1968). However, the presence of diaminotoluenes at concentrations similar to that of the toluene diisocyanates leads to significant negative interference with the colour-forming reaction (Walker & Pinches, 1981). Also, at low humidity, the tape monitor tends to give falsely low readings (Mazur et al., 1986).

Levels of toluene diisocyanates in consumer products (lacquers) are usually determined, after appropriate extraction techniques, by gas chromatography and high-performance liquid chromatographic methods (McFadyen, 1976; Conte & Cossi, 1981).

In general, it should be understood that, with all analytical methods, reliable figures for isocyanate concentrations in air can be obtained only in the range of at least 5 - 10 times the detection limit.

Table 4. Analytical methods for the determination of toluene diisocyanates

Purpose/method	Detection limit	Reference
I. Detection of TDIs in work-place air		
1. Spectrophotometry TDIs hydrolysed to the corresponding diamines, diazotized, coupled to N-1-naphthyethylene-diamine, and final colour measured at 550 nm; Note: as the concentration of 2,6-TDI increases in the mixture, the total recovery of TDIs is reduced	0.07 mg 2,4-TDI/m³; field kit, 0.14 mg/m³	Marcali (1957)
a modification of the Marcali method, in an attempt to circumvent interference by primary aromatic amines		Meddle & Wood (1970)
a further modification to eliminate the difference in response for the two isomers		Rando & Hammad (1985)
2. Gas chromatography 2,4-TDI hydrolysed in dilute hydrochloric acid and subsequent determination by gas-liquid chromatography/mass fragmentography 2,4-DAT; instrument detection limit is 500 pg	0.06 - 0.23 mg/m³	De Pascale et al. (1983)
gas liquid chromatography: TDIs hydrolysed to the corresponding amines in dilute sulfuric acid; 2,4- and 2,6-TDI detection limit depends on sample volume	0.004 mg/m³	Audunsson & Mathiasson (1983)
3. High-performance liquid chromatography TDI sampled in derivatizing absorber (N-(4-nitro benzyl)propylamine) and subsequent determination of the urea derivative formed by UV detection; sample volume 20 litre at 1 - 2 litre/min	14 µg/m³	Dunlap et al. (1976)

Table 4 (contd).

I. Detection of TDIs in work-place air (contd).		
3. High-performance liquid chromatography (contd).		
TDI derivatized during sampling with γ-(N-methylaminomethyl)anthracene and analysis by fluorescence or UV detection; sample volume 15 litre at 1 litre/min	0.0001 mg/m³	Sangö & Zimerson (1980)
TDI sampled in absorbed solution containing 1-(2-methoxyphenyl) piperazine; the derivative formed is detected by electrochemical or UV detection; instrument detection limit 200 pg; sampling time 10 min at 1 litre/min	0.0002 mg/m³	Warwick et al. (1981)
TDI detected with electrochemical detection of the derivative formed after treatment with p-aminophenol, instrument detection limit 100 pg; flow rate of 1 litre/min, for 10 min Note: formation of multiple derivatives might lead to somewhat complex chromatograms	5 µg/m³	Meyer & Tallman (1983)
TDIs determined as N-(4-nitrobenzyl)propylamine derivatives with UV detection using a 10-litre sample	1 µg/m³	Rosenberg (1984)
4. Direct read-out		
Tape-monitor using impregnated paper that yields colour stain on exposure to isocyanate vapour	0.07 mg/m³	Reilly (1968)

Table 4 (contd).

Purpose/method	Detection limit	Reference
I. Detection of TDIs in work-place air (contd).		
4. Direct read-out (contd).		
TDIs absorbed on a piezoelectric quartz crystal coated with polyethylene glycol (PEG 400); resulting change in weight of crystal is monitored by the associated change in the oscillation frequency; PEG 400 minimizes the effect of water vapour	0.14 mg/m³ (portable kit); 0.043 mg/m³	Alder & Isaac (1981a,b)
detection of TDIs with a coated quartz piezoelectric crystal	0.07 mg/m³ 76 Hz cps SI	Fielden et al. (1984)
II. Determination of free TDIs in flexible foam		
1. Infrared spectroscopy		
based on the N=C=O stretching vibration; detects the presence of N=C=O groups independently of the molecular structure; extraction of unreacted TDIs in the foam with o-dichlorobenzene and gas chromatographic determination using a flame ionization detector; free TDIs present at levels of about w/w foam in fresh foam (1 h after production) disappear after 24 h, under all storage conditions (both ambient and dry air)		Conte & Cossi (1981)

3. SOURCES OF HUMAN AND ENVIRONMENTAL EXPOSURE

3.1 Natural Occurrence

Toluene diisocyanates are not known to occur as natural products.

3.2 Man-Made Sources

3.2.1 Production levels and processes

Toluene diisocyanates are manufactured by the reaction of diaminotoluenes with phosgene. The reaction temperature increases from ambient in the first reactor to about 200 °C in the last reactor. The isomer mixture is stripped of solvent and separated by distillation (NIOSH, 1978; IARC, 1979; Chadwick & Cleveland, 1981).

The most widely marketed grade of toluene diisocyanate is the 80:20 mixture of the 2,4- and 2,6-isomers. A mixture of 65:35 of 2,4-; 2,6-isomers is also available. "Pure" 2,4-TDI is manufactured in small quantities and used for special applications. The residue product (i.e., "crude" -TDI) is sold as a speciality isocyanate (Chadwick & Cleveland, 1981; Ulrich, 1983).

3.2.1.1 World production figures

The production of 80:20 mixture accounts for > 90% of the total toluene diisocyanates produced in USA. In 1983, approximately 300 x 10^6 kg were produced in the USA; 29% of the 1983 production was exported to Belgium, Canada, the Federal Republic of Germany, Japan, Korea, the Netherlands, and other countries (US ITC, 1985). In the USA, it has been projected that the domestic demand for toluene diisocyanates will increase at the rate of 1 - 3% annually, until the year 1990 (Anon., 1983).

Production of toluene diisocyanates in Canada in 1975 amounted to 9 x 10^6 kg. In 1982, the annual production capacity for toluene diisocyanates was 20 x 10^6 kg for Brazil and 12 x 10^6 kg for Mexico. Western European nations (mainly Belgium, France, the Federal Republic of Germany, Italy, and Spain) reported a combined annual capacity for the production of toluene diisocyanates in 1982 of > 326 x 10^6 kg. Production capacity during 1982 within the Netherlands, Portugal, and the United Kingdom was not reported; however, production in 1976 in the United Kingdom was 25 x 10^6 kg. Seventy percent of the western European production was consumed nationally and 30% was exported,

primarily to eastern Europe, the Middle East, and North Africa. In eastern Europe, the German Democratic Republic and Yugoslavia had a combined production capacity of 47 x 10^6 kg toluene diisocyanates in 1982. No figures were available for production within the USSR. Japan reported an effective annual production capacity of 78 x 10^6 kg in 1982, and actual production reached 67 x 10^6 kg. The global capacity for the production of toluene diisocyanates in 1982 was reported to be > 817 x 10^6 kg (Ulrich, 1983).

3.2.1.2 Manufacturing processes: release into the environment

Toluene diisocyanates are manufactured in a closed system, and air emission is minimal. However, toluene diisocyanates may be emitted into the atmosphere during the removal of phosgene and hydrogen chloride from the first fractionating column. It is the belief of the Task Group that few of these products are emitted, because of improved manufacturing facilities. After gas scrubbing, they may be discharged into the waste effluent (Dyson & Hermann, 1971; Bagon & Hardy, 1978; Dharmarajan et al., 1978).

Levels of toluene diisocyanates ranging from 0.1 to 17.7 mg/m^3 have been monitored in stack gases from 3 plants manufacturing polyurethane foams (Grieveson & Reeve, 1983). It was estimated that approximately 50 ± 5 g toluene diisocyanates/tonne of TDI processed within the plant was emitted during the manufacture of soft-block foams (Grieveson & Reeve, 1983).

3.2.2 Uses

Toluene diisocyanates are reactive intermediates that are used in combination with polyether and polyester polyols to produce polyurethane products. The production of flexible polyurethane foams represents the primary use of toluene diisocyanates (≈ 90% of the total supply). The 80:20 mixture is used in their production at an average of 30% by weight. Domestic consumption of flexible polyurethane foam in the USA in 1981, estimated at 499 x 10^6 kg, can be broken down into the following uses (in million kg): furniture (208.7); transportation (99.8); bedding (63.5); carpet underlay (72.6); and other uses (11.3). An estimated 27 x 10^6 kg of rigid polyurethane foams, used in refrigeration equipment, was produced with "crude"-TDI in the USA in 1982 (US EPA, 1984).

Polyurethane coatings represent the second largest market for toluene diisocyanates. Toluene diisocyanates are also used in the production of polyurethane elastomeric casting systems, adhesives, sealants, and other limited uses (Brandt, 1972; Granatek et al., 1975; Aragon et al., 1980).

4. ENVIRONMENTAL TRANSPORT, DISTRIBUTION, AND TRANSFORMATION

There are very few studies on the overall environmental fate of toluene diisocyanates in the published literature. Available studies have been summarized by Duff (1983). On the basis of this review and available information on the physical and chemical properties, the following statements can be supported.

4.1 Air

It has been demonstrated in environmental chambers that, in the gaseous phase, TDI vapour and water vapour do not react to form diaminotoluenes, since not even trace amounts of these compounds were detected (Holdren et al., 1984). A rate of loss of about 20% of TDI-vapour per hour could be explained by surface adsorption. This rate of loss was much higher and more rapid when comparable concentrations of an aliphatic amine were simultaneously present in the chamber. Again, no hydrolysis products of TDI could be detected.

4.2 Water

In most industrial situations, toluene diisocyanates are hydrolysed by water to give the corresponding polymeric ureas and carbon dioxide (Chadwick & Cleveland, 1981). However, when toluene diisocyanates come into contact with water without agitation, as in spills, a hard crystalline crust of polymeric ureas forms slowing down further degradation of the toluene diisocyanates, unless the crust is mechanically broken. The solid reaction products are insoluble and biologically inert (Brochhagen & Grieveson, 1984).

4.3 Soil

A computerized partitioning model proposed by Mackay (1979) indicated that toluene diisocyanates released into the environment will tend to partition into water. However, in making this prediction, the reactivity of the compounds was not taken into consideration.

4.4 Biotransformation

Studies were conducted under laboratory or environmental conditions to evaluate the potential degradation of soft

polyurethane foams, with either a polyester or a polyether base, both prepared with an isomeric mixture of 2,4 and 2,6-diisocyanates (Martens & Domsch, 1981). Polyurethane-ether foams were highly resistant to chemical and microbial degradation. Polyurethane-ester foams were quite susceptible to degradation, especially at elevated temperatures (50 °C), yielding 0.25% 2,4-toluenediamine and 0.38% 2,6-toluenediamine in acidic (pH 1) water extracts of leachate after 3 months incubation in the laboratory. The incubation mixture contained 1 g of finely chopped soft polyurethane foam of a polyester base prepared with the isomeric mixture of 2,4- and 2,6-diisocyanates, in 100 ml of leachate (pH 7.5) from a refuse tip near Braunschweig, Federal Republic of Germany. An experimental study conducted near this site corroborated the laboratory results. Soft polyurethane foam cubes were checked for weight loss after 13 months incubation in the refuse tip, where they were found in the refuse layer of a 25:10:1 (weight) mixture of municipal refuse, sewage sludge, and caustic lime. The polyurethane-ester foam cubes lost 17 - 31% of their initial weight in the stratified filling, and, if the layers of fill were mixed, weight loss ranged between 35 and 86%. The polyurethane-ether foam cubes did not degrade under these conditions. It was concluded that soft polyurethane foams prepared with toluene diisocyanate isomers are susceptible to chemical hydrolysis under extreme environmental conditions, and that under these circumstances, an accumulation of aromatic amines can occur, if their microbial degradation is impeded.

4.5 Bioaccumulation

There are no data on the bioaccumulation of TDIs.

5. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

No data were found on levels of toluene diisocyanates in the general environment.

5.1 General Population Exposure

Human beings and animals would be exposed to toluene diisocyanates in environmental media only in the immediate vicinity of effluents, factories, or areas of spillage (sections 3.2.1.2 and 4). Consumers may also be exposed to toluene diisocyanates through the indiscriminate use of several commercially available household products, such as polyurethane foam kits (US EPA, 1984). For example, Peters & Murphy (1971) tested 5 "instant" polyurethane foam products and found that concentrations of toluene diisocyanates in the air ranged from 0 to 0.15 mg/m^3 during applications. They also noted that labels on the cans were inadequate regarding contents, precautions, and toxicity warnings. Consumers may also be exposed to toluene diisocyanates during the application of polyurethane varnishes (US EPA, 1984).

Beall & Ulsamer (1981) suggested that toluene diisocyanates might be an indoor air pollutant. During pyrolysis of polyurethanes, the general public could be exposed to the pyrolytic products of toluene diisocyanates. No monitoring levels were given.

5.2 Occupational Exposure

Because of the volatility of toluene diisocyanates, exposure can occur in all phases of their manufacture and use (Sittig, 1979). Monitoring data for toluene diisocyanates in the work-place is extensive with levels found between 0.014 and 1.050 mg/m^3 (NIOSH, 1978; Hosein & Farkas, 1981; Belin et al., 1983). During the production of polyurethane-coated wire, toluene diisocyanates may be found in the work-place, during the different stages of the coating process, at concentrations ranging between < 0.001 and 0.11 mg/m^3 (Rosenberg, 1984). The highest levels have occurred during spraying with polyurethane foam, a procedure that is usually conducted in confined spaces (Hosein & Farkas, 1981). Isocyanate lacquers contain 0.2 - 1% monomeric toluene diisocyanates (Tu & Fetsch, 1980), and short-term excursions above safe limits are of a particular concern for spray workers and their assistants.

Sittig (1979) estimated that approximately 40 000 workers in the USA were potentially exposed to toluene diisocyanates in such jobs as adhesive production, insulation, application

and production of toluene diisocyanate resins and lacquers; organic chemical synthesis, paint spraying, polyurethane foam production, working with rubber, shipbuilding, textile processing, and wire-coating. Consumer use of products containing TDI could result in many more cases of exposure.

6. KINETICS AND METABOLISM

6.1 Absorption

Absorption of toluene diisocyanates through the respiratory tract is suggested by: (a) their high acute toxicity for animals via inhalation (section 8.1); and (b) reports on systemic effects and antibody formation in individuals exposed to toluene diisocyanates primarily via inhalation (Sharonova & Kryzhanovskya, 1976; Steinmetz et al., 1976; White et al., 1980; Sharonova *et* al., 1982).

6.2 Distribution

No information was found regarding the distribution of toluene diisocyanates in mammalian systems. Because of the wide distribution of water and other nucleophiles in tissues, it is likely that toluene diisocyanates will react with the tissues they initially contact and be transformed into various products, rather than that they will be absorbed and distributed throughout the body as toluene diisocyanates.

6.3 Metabolic Transformation and Elimination

No published studies on the biotransformation of toluene diisocyanates were found. However, one report (NTP, 1985) on the disposition of 2,6-TDI in Fischer 344 rats was available to the Task Group. The apparent half-life of 2,6-TDI was dependent on the vehicle in which it was administered, its concentration in the solvent, and the rate of mixing as the compound was added. In an aqueous suspension of stomach contents, the half-life of 2,6-TDI was < 2 min, whereas in serum, the half-life was < 30 seconds.

When [C^{14}]-2,6-TDI was given orally to rats in corn oil, most of the compound formed polymers in the gastrointestinal tract. At doses of 900 mg/kg body weight, the insoluble polyureas usually lined the stomach, slowing down or preventing the migration of stomach contents into the intestine. At a 60 mg/kg dose level, these results were not observed (NTP, 1985). Most 2,6-TDI-derived materials were eliminated in the faeces or were found in the gastrointestinal tract 72 h after dosing. Approximately 12% of the low dose (60 mg/kg body weight) and only 5% of the high dose (900 mg/kg) were excreted in the urine (24-h after treatment), mainly in the form of 2,6-bis(acetylamino) toluene (54%). Increased urinary excretion of 2,6-TDI metabolites with decreasing dosage was consistent with the lower concentration of the compound in the stomach permitting increasing amounts

of the 2,6-TDI to be hydrolysed completely to monomeric 2,6-diaminotoluene rather than forming polymers. The 2,6-diaminotoluene could then be absorbed, acetylated, and excreted in the urine. Materials derived from 2,6-TDI were not concentrated in any tissue (NTP, 1985). In rats exposed dermally to 2,4-TDI, no unreacted isocyanate was detected in the urine, but 2,4-TDA was detected after hydrolysis of the urine (Rosenberg & Savolainen, 1985). The same authors studied workers occupationally exposed to the 80:20 TDI isomer mixture, and reported that concentrations of TDA in the urine after hydrolytic treatment were linearly related to the estimated TDI dose (Rosenberg & Savolainen, 1986). A possible biochemical pathway would involve the formation of TDA, its conjugation and excretion, but it was not known if this had taken place.

6.4 Reaction with Body Components

Toluene diisocyanates are highly reactive towards a large number of active hydrogen and basic nitrogen compounds (Ozawa, 1967; Alarie, 1973; Brown & Wold, 1973; Brown et al., 1982). Thus, more than one reaction may occur in a system at a given time. The results of an in vitro study reported by the NTP (1985) showed that 2,6-TDI would react with both rat serum and stomach contents at 37 °C. The 2,6-TDI appeared to form a polymeric film, which encapsulated globules of 2,6-TDI, thus limiting the availability of the compound in the interior of the globules for further reaction.

Mixtures of TDI isomers, such as 80:20, may behave in a different manner to single 2,6- or 2,4-TDI isomers.

Isocyanates react with carboxyl groups and form amines, acid anhydrides, and ureas (Fry, 1953). Ozawa (1967) and Brown & Wold (1973) demonstrated that diisocyanates were active-site-specific reagents towards the hydroxyl groups of serine in proteases. Such reactions can result in the irreversible inactivation of enzymes, such as adenylate cyclase, serine proteases, alcohol dehydrogenase, and cholinestrase (Brown & Wold, 1973; Twe & Wold, 1973; Butcher et al., 1979; Dewair et al., 1983). Isocyanates react with amino groups to form ureas, which are also highly stable and unlikely to dissociate under biological conditions.

Isocyanates form thiolic acid and esters when reacting with sulfhydryl groups in proteins. However, this reaction takes place at low pH only, whereas the products are unstable at pH 7 or higher (Twe & Wold, 1973).

Toluene diisocyanates may react with naturally occurring proteins or polysaccharides and form immuno hapten complexes. The results of an in vitro study by Ted Tse & Pesce (1979) showed that toluene diisocyanates will react with human

serum-albumin via one, or both, of the isocyanate groups to form mono- or bisureido protein derivatives. Such derivatives may be immunogenic and may possibly lead to allergenic responses, as well as new antigenic determinants (Baur, 1983).

7. EFFECTS ON ORGANISMS IN THE ENVIRONMENT

Lethality data for some avian and aquatic species are listed in Table 5.

Although practically insoluble in water, dispersed TDI can form droplets and cause toxicity in aquatic systems.

Curtis et al. (1979) reported that 2,4-toluene diisocyanates appeared to be toxic for fathead minnows only in the unreacted form, and most lethality occurred during the first 12 h of the test. The LC_{50} for aquatic species ranged from 10.5 to 508.3 mg/litre in static tests. The oral LD_{50} for avian species was $\geq$ 100 mg/kg body weight (Schafer et al., 1983).

Table 5. Lethality of toluene diisocyanates for aquatic and avian species

Species	Dose/concentration (mg/litre)	Condition	Lethality	Reference
Freshwater				
Fathead Minnow (Pimephales promelas)	194[a] 172.1 164.5	static static static reconstituted softwater (20 °C)	24-h LC_{50} 48-h LC_{50} 96-h LC_{50}	Curtis et al. (1979)
Saltwater				
Grass shrimp (Palaemonetes pugio)	508.3[a]	salinity 25 parts/ thousand; 22 °C; static	mortality less than 65% below this level within 96 h	Curtis et al. (1979)
Harpacticoid copepod (Nitocra spinipes Boeck) Crustacea	11.8[b] (10.5 - 13.2)	salinity 7 parts/ thousand; static	96-h LC_{50}	Bengtsson & Tarkpea (1983)
Avian				
Redwinged blackbird (Agelaius phoeniceus)	100 mg/kg[c]	oral	LD_{50}	Schafer et al. (1983)
Starling (Sturnus vulgaris)	> 100 mg/kg[c]	oral	LD_{50}	Schafer et al. (1983)

[a] 2,4-isomer.
[b] Authors did not state the units; mg/litre were assumed on the basis of previous publication of Lindén et al. (1979).
[c] 2,6-isomer.

8. EFFECTS ON EXPERIMENTAL ANIMALS AND IN VITRO TEST SYSTEMS

8.1 Single Exposures

Application of drops of toluene diisocyanates in the eyes of rabbits caused immediate reaction suggestive of pain, lachrymation, swelling of the eyelids, a conjunctival reaction, and mild damage to the cornea (Zapp, 1957; Grant, 1974; Duprat et al., 1976; Woolrich, 1982).

Intratracheal administration of 0.3 ml toluene diisocyanates in guinea-pigs resulted in coagulation of proteins in the respiratory tract and rapid death from respiratory distress (Friebel & Lüchtralh, 1955). The acute toxicity of toluene diisocyanates via various routes of exposure is summarized in Table 6.

Table 6. Lethality of toluene diisocyanates

Route/species	Concentration	Duration (h)	Lethality	Reference
Inhalation				
Rat	56.96 mg/m³	1	LC_{50}	Harton & Rawl (1976)
Rat	98.96 ± 8.6 mg/m³	4	LC_{50}	Duncan et al. (1962)
Rat (male)	348.88 mg/m³	4	LC_{50}	Bunge et al. (1977)
(female)	356 mg/m³	4	LC_{50}	
Mouse	69.1 ± 9.96 mg/m³	4	LC_{50}	Duncan et al. (1962)
Rabbit	78.32 mg/m³	4	LC_{50}	Duncan et al. (1962)
Guinea-pig	90.4 ± 19.2 mg/m³	4	LC_{50}	Duncan et al. (1962)
Oral				
Rat	3060 mg/kg body weight	-	LD_{50}	Harton & Rawl (1976)
Mouse (male)	4130 mg/kg body weight	-	LD_{50}	Woolrich (1982)
Dermal				
Rabbit	10 000 mg/kg	-	LD_{50}	Harton & Rawl (1976)

The toxicity of toluene diisocyanates, administered orally, is low, but they are very toxic after inhalation exposure. Animals reportedly died of acute pulmonary congestion, oedema, and haemorrhage. Duncan et al. (1962) reported that during inhalation exposures, all animals (Table 6) exhibited irritation. Tracheitis and bronchitis, with sloughing of superficial epithelium, occurred after exposure to 14.2 mg/m^3 for 4 h. Rapid coagulation and necrosis of the epithelium was evident following exposure to 35.8 mg/m^3, suggesting direct chemical injury.

8.2 Short-Term Exposures

8.2.1 Inhalation

8.2.1.1 Guinea-pig

Exposure of guinea-pigs to 1200 mg toluene diisocyanates/m^3, as an aerosol, or 250 - 550 mg/m^3, as a vapour, for 10 - 20 min at irregular intervals, for one month, caused asthmatic reactions after the first few inhalations, changing into continuous dyspnoea in the course of the study (Friebel & Lüchtralh, 1955). Attainment of these concentrations could only be achieved with both aerosol and vapours. Bronchiolitis obliterans, pneumonia, and emphysema occurred with little healing. Guinea-pigs sensitized to chicken albumin responded in the same manner as untreated animals, indicating the predominance of a primary toxic effect. However, a possible role of allergic type reactions could not be excluded completely.

Immunological sensitization and pulmonary hypersensitivity to an 80:20 mixture were evaluated in the guinea-pig. Five days after exposure to 1.78 mg/m^3 (3 h/day for 5 days), 3 out of 16 exposed guinea-pigs had developed antibody against TDI-guinea-pig serum-albumin antigen, as demonstrated by immuno-diffusion, compared with 0/16 before exposure (Karol et al., 1980). Three additional animals showed antibody responses with the more sensitive passive cutaneous anaphylaxis assay (PCA). That is, a total of 6/16 exposed animals were antibody positive. No consistent increases indicative of a pulmonary hypersensitive reaction were observed.

Concentration-dependent immunological responses to toluene diisocyanates were measured following exposures that mimicked industrial exposures and might lead to allergic reactions in exposed workers (Karol, 1983). Guinea-pigs were exposed to 0.85 - 71.2 mg 80:20 mixture/m^3, 3 h/day, for 5 days. On day 22, assays for TDI-specific antibody, skin sensitivity, and pulmonary sensitivity to toluene diisocyanates were performed.

No antibody to toluene diisocyanates was detected in animals exposed to a concentration of 0.85 mg/m³, whereas 55% of the animals exposed to ≥ 2.56 mg 80:20 mixture/m³ displayed TDI-specific antibody in a dose-related fashion. Pulmonary sensitivity to TDI-protein antigen was observed at concentrations exceeding 2.6 mg/m³. Doses higher than 14.2 mg/m³ resulted in pneumotoxicity and fewer pulmonary hypersensitivity reactions. Exposure of a group of 24 guinea-pigs to 0.14 mg 80:20 mixture /m³ (6 h/day, 5 days/week, for 70 days) in whole-body exposure chambers, did not elicit these reactions (Karol, 1983).

8.2.1.2 Mouse

The effects of single and repeated exposures to 2,4-TDI (99.7% pure) vapour at concentrations ranging from 0.05 to 14.2 mg/m³ were investigated in male Swiss-Webster mice, to detect the level of sensory irritation caused by this chemical (Sangha & Alarie, 1979). The results obtained demonstrated that the level of response not only depended on the concentration, but also on the duration of exposure; recovery rates also depended on the duration of exposure. The RD_{50} (respiratory rate decrease of 50%) values decreased significantly between 10 and 180 min and the levels of response were exactly the same at 180 and 240 min of exposure. The RD_{50} found at 180 or 240 min of exposure was 1.42 mg/m³. Repeated exposures to 2,4-TDI concentrations of or above 0.14 mg/m³ resulted in cummulative effects, because of incomplete recovery prior to a repeat exposure.

Weyel et al. (1982) measured the sensory irritation of 2,6-TDI vapour at 0.37 - 7.6 mg/m³ in male Swiss-Webster mice. After a 3-h exposure, a decrease in respiratory rate occurred with a pattern indicative of sensory irritation of the upper respiratory tract, which was similar to that noted by Sangha & Alarie (1979) with exposure to 2,4-TDI at levels of > 0.14 mg/m³. An inverse linear relationship (respiratory rate decrease versus log concentration of 2,6-TDI) was obtained that was identical to the slope and relationship obtained in the earlier study on 2,4-TDI. From the concentration-response (sensory irritation) relationship for 2,6-TDI, the RD_{50} was determined to be 1.85 mg/m³.

Lesions in the nasal cavity with a distinct anterior-posterior severity gradient developed in mice after exposure to toluene diisocyanates at 2.84 mg/m³, for 6 h/day, over 5 days (Buckley et al., 1984). The lesions ranged from slight epithelial hypertrophy or hyperplasia to epithelial erosion, ulceration, and necrosis with variable inflamation of the subepithelial tissues. There was also an associated loss of the olfactory nerves in the lamina prioria in exposed animals.

8.2.1.3 Rat

Studies by Henschler et al. (1962) on the inhalation toxicity of toluene diisocyanates are summarized in Table 7.

Table 7. Inhalation toxicity of toluene diisocyanates[a]

Number of exposures (schedule)	Concentration (mg/m^3)	Lethality
24 (6 h/day, 6 days/week, twice, miss 4 weeks, repeat second 12 exposures)	3.56	45% fatality of animals with initial body weight of 91 - 124 g; 0% fatality of animals with initial body weight of 140 - 180 g
10	7.12	75% fatality
4	35.6	65% fatality
2	71.2	lethal for most animals; 2,4-isomer more toxic than 2,6-isomer
3 or 5	71.2	lethal for all exposed animals

[a] The 71.2 level mg/m^3 was for 2,4- or 2,6-isomer or a 65:35 mixture of isomers. The 35.6, 7.12, and 3.56 mg/m^3 levels were for the 80:20 mixture. From: Henschler et al. (1962).

At exposure levels of 35.6 and 71.2 mg toluene diisocyanates/m^3, death was due to mechanical blocking of the respiratory passages by mucosal tissue detached from bronchi and trachea. At lower exposure levels, the fatal sequelae also included heavy peribronchitis and spreading bronchopneumonia. After cessation of exposure, partial reversal of pulmonary changes occurred after several months in the 7.12 mg/m^3 exposure group, and complete remission occurred in the 3.56 mg/m^3 exposure group. After 40 exposures at 0.712 mg/m^3, there were no definitive changes in the respiratory tract, the only toxicological response being a depression in body weight (Henschler et al., 1962).

8.2.1.4 Dog

Four male dogs were exposed to concentrations of toluene diisocyanates averaging 10.68 mg/m^3, 35 - 37 times, for various lengths of exposure (30 - 120 min), over a period of

4 months. The dogs showed lachrymation, coughing, restlessness, and expectoration of white frothy material. When killed after the last exposure, all dogs showed mild congestion and inflammation of the trachea and large bronchi. A conspicuous feature was the presence of thick mucous plugs in some of the bronchial branches (Zapp, 1957).

8.2.2 Dermal

Toluene diisocyanates were described as a "medium" irritant for rabbits and guinea-pigs, capable of producing cutaneous sensitivity similar to contact allergy. The allergenic capacity was long-lasting and depended on the allergen concentration (Zapp, 1957; Duprat et al., 1976).

8.2.2.1 Guinea-pig

Dermal contact with toluene diisocyanates in the animal model resulted in "rare" cases of sensitization (Peschel, 1970) and in subsequent respiratory tract hypersensitivity (Karol et al., 1981). Dermal contact sensivity developed by the 7th day, following applications of 1 - 100% solutions of 80:20 mixture (diluted with olive oil) to the dorsal skin of the guinea-pig. After 14 days, animals were evaluated for toluene diisocyanates sensitivity by serological analysis and by bronchial provocation challenge. Bronchial challenge with 0.03 mg toluene diisocyanates/m^3, or aerosols of TDI-protein conjugates, or p-tolyl isocyanate resulted in respiratory hypersensitivity (Karol et al., 1981). These responses were immediate; the respiratory rate increases were 3 times those in non-sensitive guinea-pigs. In challenges using isocyanate conjugates, TDI-specific pulmonary reactions were elicited more effectively when the hapten-protein conjugates rather than the toluene diisocyanates vapour served as the challenging agent.

Koschier et al. (1983) evaluated the dose-dependent eliciting of dermal sensitization in young adult guinea-pigs treated with 2,4-TDI (2,6-isomer was $\leq$ 2.5%). Induction was by cutaneous application (25 µl) of 8 - 40% 2,4-TDI in n-butyl ether on 2 separate uncovered dorsal sites. Five days later, animals were challenged with 0 - 0.4% 2,4-TDI (25 µl per site). All challenge applications from 0.025% (6.25 µg) elicited a positive response in 75 - 100% of the animals. The results demonstrated that 2,4-TDI induced sensitization and that the severity of the dermal response was correlated with the concentration used at induction and challenge. In a second study, in the group induced with 4% 2,4-TDI, no effects were elicited after a dermal challenge application of 3 µg,

and a minimum effect was seen with 6.25 µg 2,4-TDI (Koschier et al., 1983).

8.2.2.2 Mouse

In a dose-response study (Tanaka, 1979), a 100% increase in ear-swelling in C3H/He mice, 24 h after challenge with 0.5 ml of 5% TDI, was reduced to 50% after 72 h. In a second trial, 81% ear-swelling resulted from a 5% challenge with TDI; there was a 6.5% ear-swelling response to a 1% TDI challenge, compared with 2.4% in vehicle controls. There was a cross-reactivity between TDI and monodiisocyanate (MDI), so that sensitization with either diisocyanate resulted in equal ear-swelling responses to challenge with the opposite diisocyanate. The degree of response in cross-reactivity was 4-times that in controls and about 35% of a challenge response by the same diisocyanate used for sensitization. Thymectomy did not change the ear-swelling responses to TDI. In a subsequent study, Tanaka et al. (1984) reported that TDI induced a delayed-type hypersensitivity reaction in the ear skin of male ICR mice, and that 7-week-old mice sensitized with 1 - 5% (100 µl/dose) TDI solutions showed ear-swelling with a challenge of 1% (2 µl) TDI solution. The responses in 5-, 7-, and 13-week-old mice were the same but were very slight in 16-week-old mice. Seven-week-old BalB/C mice showed similar responses to ICR mice, but reactions in ddY mice were much weaker.

Allergic dermatitis developed in mice by sensitization to toluene diisocyanates, followed by inhalation exposure to the test compound to determine if a delayed type allergy plays a role in lung disorders caused by toluene diisocyanates. At a concentration of 4.27 mg/m^3, inhaled for 2 h, allergic dermatitis did develop, but without noticeable pathological changes in the respiratory organs (Ohsawa, 1983).

8.2.3 Oral

Oral gavage of 1500 mg/kg per day resulted in the death of 50% of rats within a total of 10 treatments. Pathological examination revealed injury to the gastrointestinal tract and liver (Zapp, 1957). No other toxic effects were reported from these studies.

8.3 Long-Term Exposure

8.3.1 Inhalation

8.3.1.1 Mouse

A dose-related increase in the incidence and severity of either chronic or necrotic rhinitis occurred in mice exposed

through inhalation to the 80:20 mixture of toluene diisocyanates at 0.36 or 1.07 mg/m³, for 6 h/day, 5 days/week, over 2 years. In addition, lesions of variable incidence and severity were seen in the lower respiratory tract (interstitial pneumonitis, catarrhal bronchitis) and eyes (keratitis) of some mice, with a higher incidence in the 1.07 mg/m³ group. Morbidity and mortality due to rhinitis occurred in both treated groups (Loeser, 1983).

8.3.1.2 Dog

Patterson et al. (1983) immunized 3 dogs (by endotracheal tube) with an aerosol of toluene diisocyanates at 1 mg/kg body weight, every 2 weeks, for 4 months (2 - 3 times the maximal TLV for occupational exposure). Thereafter, 2 dogs were dosed with 1 mg/kg body weight every 4 weeks for 6 months (stated to be the cumulative dose analagous to long-term exposure to 0.14 mg/m³). Systemic immune responses to TDI-dog serum-albumin, including elevated specific antibody titers of IgG, IgA, IgM, and development of specific lymphocyte reactivity, were seen in all animals. Elevated IgG and IgA titers were persistent. Although increased, the lower titer of IgM antibody was of short duration. The antibody IgE was detected, but levels fluctuated and became negative, even with continued exposure to toluene diisocyanates. Airway responses that occurred immediately after exposure to the aerosol included abnormalities of selected pulmonary function parameters. They were clearly not immunologically mediated, because they occurred with initial exposure. However, other immediate airway responses occurred that qualitatively simulated IgE-mediated, antigen-induced airway responses in dogs. There was a statistically-significant correlation between the latter airway responses and immediate skin reactions (Patterson et al., 1983).

8.4 Reproduction, Embryotoxicity and Teratogenicity

No published data were found on the effects of toluene diisocyanates on reproduction, or on the embryotoxicity or teratogenicity of these compounds.

8.5 Mutagenicity and Related End-Points

8.5.1 Bacterial mutagenicity

There are conflicting reports about the mutagenicity of toluene diisocyanates. Anderson & Styles (1978) reported that toluene diisocyanate of unknown purity was non-mutagenic in a

study of 120 chemicals tested by Purchase et al. (1978), but the fact that several known mutagens failed to give positive results means that the original report was suspect. Andersen et al. (1980) later optimized the procedures to test the reactive isocyanates and showed that a mixture of 2,4- and 2,6-toluene diisocyanates caused a dose-dependent mutagenic response, using S-9 activation, in S. typhimurium strains TA 98, TA 100, and TA 1538. The positive control for these mutagen tests was the hydrolysis product of 2,4-TDI, 2,4-diaminotoluene, reported by Ames et al. (1975) to be mutagenic. The NTP has also tested toluene diisocyanates using the Salmonella test system and found that both 2,6-TDI and a mixture of 2,4- and 2,6-TDI (80:20) were mutagenic in S. typhimurium strains TA 98 and TA 100 in the presence (but not the absence) of Aroclor 1254-induced male Sprague Dawley or Syrian hamster liver S9. Neither sample was mutagenic in S. typhimurium strains TA 1535 or TA 1537, with or without metabolic activation.

8.5.2 Mammalian cell transformation

Toluene diisocyanates were negative in two in vitro cell transformation assays using human lung and hamster kidney cells (Styles, 1978).

8.5.3 Mammalian in vivo study

Studies by Loeser (1983) failed to show a dose- or treatment-related percentage increase in micronucleated erythrocytes from the bone marrow of rats and mice exposed through inhalation to 80:20 mixture at 0.35 or 1.06 mg/m^3, for 6 h/day, 5 days/week, over 4 weeks.

8.6 Carcinogenicity

8.6.1 Oral

Long-term oral (gavage) administration of the 80:20 mixture of 2,4-, 2,6-TDI in corn oil resulted in increased incidences of various types of tumours in Fischer 344/N rats and B6C3F1 mice (NTP, 1986). Female rats and mice were dosed with 60 or 120 mg/kg body weight; male rats received 30 or 60 mg/kg body weight; and male mice were dosed with 120 or 240 mg/kg body weight, for 5 days per week, over 2 years. However, it is worth noting that the reaction of toluene diisocyanates with the moisture in the corn oil resulted in unknown reaction products and in doses qualitatively and quantitatively different from those reported, possibly as much as 23% below the target dose. Long-term treatment, by gavage,

with the TDI-corn oil mixture caused dose-related reductions in body weight gain. A dose-dependent pattern of cumulative toxicity began at weeks 70 - 75, culminating at 103 weeks in the following percentage mortality in control, low-, and high-dose groups, respectively: male rats: 28%, 72%, and 84%; female rats: 28%, 62%, and 88%; male mice: 8%, 20%, and 48%; and female mice: 32%, 14%, and 34%.

Significant increases were noted in the incidence of subcutaneous fibromas and fibrosarcomas (combined) in male and female rats; pancreatic acinar-cell adenomas in male rats; pancreatic islet-cell adenomas, neoplastic nodules of the liver, and mammary gland fibroadenomas in female rats; haemangiomas and haemangiosarcomas (combined), and hepatocellular adenomas in female mice (NTP, 1986). It was concluded that the 80:20 mixture of 2,4-, 2,6-TDI in corn oil was carcinogenic for male and female rats and female mice, when administered orally by gavage. The 1986 NTP report was reviewed during its preparation by Rampy et al. (1983).

8.6.2 Inhalation

In a long-term inhalation study, Sprague Dawley CD rats and CD-1 mice were exposed to the 80:20 isomer mixture at nominal levels of 0.356 mg/m^3 (0.05 ppm) or 1.068 mg/m^3 (0.15 ppm), for 6 h/day, 5 days per week, for 108 weeks (female rats), 110 weeks (male rats), or 104 weeks (male and female mice) (Loeser, 1983). The type and incidence of tumours and the number of tumour-bearing animals of either species did not indicate any carcinogenic effect. The main pathological changes in mice occurred in the nasal cavity and included dose-related incidences of epithelial atrophy, mucuous and squamous metaplasia, inflammation, and focal destructive rhinitis with debris.

In this study, there was an unexplained high mortality in both the control and treated rats and mice. In the high-exposure groups (1.068 mg/m^3), significantly lower weight gains were noted throughout the study in mice and during the first 12 weeks in rats. Haematological indices, clinical chemistry, and urinalyses were not affected by the doses of 80:20 mixture used, nor were there dose-related changes in organ weights. It was tentatively concluded that, under these experimental conditions, the 80:20 mixture at 0.356 or 1.068 mg/m^3 did not lead to a carcinogenic response or to other adverse clinical responses. Although some reductions in weight gain were noted, the doses used were probably below maximal tolerated doses. In addition, the high mortality rate reported reduced the sensitivity of this bioassay.

8.7 Special Studies and Mechanisms of Toxicity

On the basis of the possible reactions to toluene diisocyanates (section 7.5), it is most likely that covalent binding and slow recovery could follow reaction of toluene diisocyanates with hydroxyl and amino groups of receptor proteins in the nasal mucosa. Under the conditions proposed by Brown & Wold (1971), it is possible that only the first "reversible noncovalent" complex may have been formed after short durations of exposure to toluene diisocyanates, since recovery was rapid (Sangha & Alarie, 1979) (section 8.2.1.2). With longer exposure, the slow recovery would be due to the formation of the covalent irreversible complex (Brown & Wold, 1971).

In a subsequent study, McKay & Brooks (1984) reported a significant difference in carbachol-stimulated tracheal smooth muscle strips from guinea-pigs exposed to toluene diisocyanates (0.02 mg/m^3, 5 h/day, for 20 days) compared with controls. The observed increase in maximal tension and the shift of the dose-effect curve for exposed animals suggested a direct effect of toluene diisocyanates on tracheal smooth muscle. The toluene diisocyanate tested had an isomer content of 97.8% 2,4-TDI and 2.2% 2,6-TDI.

Kido et al. (1983a) measured histamine release from the leukocytes of guinea-pigs exposed to a toluene diisocyanate level of less than 7 mg/m^3 (1 ppm), to study the mechanism of induction of asthma by toluene diisocyanates. In guinea-pigs with IgE antibody, histamine release was > 20% with an average peak value (apv) of 40% compared with < 20% and an apv of 8.8% in controls, and a histamine release of approximately 20% with an apv of 24.1% in guinea-pigs without elevated IgE antibody levels.

The authors hypothesized that, after exposure to toluene diisocyanates, the IgE antibody, which is homocytotropic to basophils, resulted in histamine release in vitro by the TDI-human serum-albumin (TDI-HSA) conjugated antigen, and that it is possible that an immediate-type allergic reaction by the IgE antibody is involved in the mechanism of induction of TDI-asthma.

Studies by Chen & Bernstein (1982) have shown the presence of hapten-specific IgE antibodies in the sera of guinea-pigs immunized with either toluene-diisocyanate-human serum-albumin or hexamethylene diisocyanate-human serum-albumin or hexamethylene diisocyanate-human serum-albumin and subsequently challenged with conjugates of the respective ligands coupled to transferrin. In these studies, both homocytotropic (IgG and IgE), and precipitating antibodies were produced under appropriate conditions of parenteral immunization. The authors postulated that the complex nature of the immune

response generated by diisocyanate compounds in guinea-pigs might also serve as an appropriate model for isocyanate-induced human sensitivity reactions, which are known to involve diverse immunological and nonimmunological mechanisms.

Tanaka et al. (1984) induced nasal allergy in guinea-pigs by painting a 10% solution of toluene diisocyanates in ethyl acetate on the bilateral nasal vestibules, once a day, for 5 days. After waiting 3 weeks, the animals were challenged in a similar manner with a 5% toluene diisocyanates solution; the process was repeated 2 times per week, for 3 months. Sneezing and rhinorrhea occurred in guinea-pigs, either with or without dyspnoea, and many eosinophils were found in nasal smears. Histopathology indicated enhanced secretory function, eosinophil infiltration, and probable degranulation of mast cells in the nasal mucosa. A significant release of histamine from the nasal mucosa in TDI-sensitized guinea-pigs was noted, when stimulated in vitro by TDI-guinea-pig serum-albumin.

9. EFFECTS ON MAN

9.1 General Population Exposure - Controlled Human Studies

9.1.1 Single exposures

In human volunteers, eye and nose irritation began at acute concentrations of 0.35 - 0.92 mg/m^3, while skin irritation generally occurred at higher levels (Brugsch & Elkins, 1963; Bruckner et al., 1968; Sittig, 1981; Woolrich, 1982). The odour threshold for aerosols of toluene diisocyanates was tested in human volunteers by several investigators (Munn, 1960; Henschler et al., 1962; Brugsch & Elkins, 1963). The responses were not uniform, probably because of differences in chemical purity, protocol, etc. Ehrlicher's group reported the following: slight odour = 0.92 mg/m^3 (0.13 ppm); odour without irritation = 4.28 mg/m^3 (0.60 ppm); burning eyes and nose = 13.57 mg/m^3 (1.9 ppm); and severe irritation of eyes and respiratory tract = 27.8 mg/m^3 (3.9 ppm). Henschler et al. (1962) reported values that were about 10 times lower for the irritation effects of TDI in human exposure. In a 30-min exposure of 6 persons, levels of 0.07 and 0.14 mg/m^3 (0.01 and 0.02 ppm) were not perceived, a level of 0.35 mg/m^3 (0.05 ppm) was recognized by everyone, slight irritation of the eye, nose, and throat occurred at concentrations of between 0.35 and 0.7 mg/m^3 (0.05 and 0.1 ppm), secretions in the eye and nose occurred in most persons at 0.7 mg/m^3 (0.1 ppm) and always at 3.5 mg/m^3 (0.5 ppm), and, overall, the irritative effect was greater in response to 2,6- than to 2,4-TDI. The difference in threshold response can perhaps be attributed to more accurate analytical procedures used by Henschler et al. (1962).

Brugsch & Elkins (1963) reported that the minimum concentration of toluene diisocyanates for irritation was 0.35 - 0.7 mg/m^3 (0.05 - 0.1 ppm) and that all subjects were irritated at 3.5 mg/m^3 (0.5 ppm).

Odour threshold values varied from 0.35 to 0.92 mg/m^3 (0.05 to 0.13 ppm) in these studies.

9.2 Occupational Exposure

9.2.1 Acute toxicity

The signs and symptoms of acute exposure are non-specific and include: complaints of irritation of the nose and throat,

shortness of breath, choking, coughing, retrosternal discomfort or pain, and gastrointestinal stress (e.g., nausea, vomiting, and abdominal pain). The onset of signs and symptoms may be delayed following exposure, and may persist for several days, months, or years following removal from the contaminated environment (Ehrlicher & Pilz, 1956; Walworth & Virchow, 1959; Munn, 1960, 1968; NIOSH, 1978).

Eye contact with toluene diisocyanates (vapour, aerosols, or liquids) causes mild irritation, characterized by itching and lachrymation, which may progress to conjunctivitis and keratoconjunctivitis (Brugsch & Elkins, 1963; Luckenbach & Kieler, 1980). Oculorhinitis may also occur and be delayed by a few hours (Paggiaro et al., 1985).

Systemic symptoms, which developed after acute occupational exposure to toluene diisocyanates, have been reported by Axford et al. (1976) and Le Quesne et al. (1976). These two reports describe the findings from one accident in which the victims were firemen involved in both fire-fighting and clean-up operations at a polyurethane foam factory, where a large quantity of toluene diisocyanates (4500 litres) had leaked.

Exposed firemen experienced symptoms during and/or after the fire. Symptomatology included 15 cases of gastrointestinal distress, 4 of which, though asymptomatic during the fire, developed gastrointestinal symptoms the following day, 3 experiencing abdominal pain with diarrhoea, while the other complained of nausea and vomiting. All symptoms eased within 2 days without any apparent long-term effects (following 4 years of monitoring).

In addition to gastrointestinal symptoms, 23 firemen complained of neurological symptoms. Five firemen experienced symptoms (i.e., euphoria, ataxia, intermittent shaking of the limbs, dizziness, and loss of consciousness) immediately on exposure. Symptoms such as headaches, difficulty in concentrating, poor memory, and confusion persisted for 3 weeks in 14 of the firemen. After 4 years, poor memory was the most common complaint, followed by personality change, irritability, or depression, in a total of 13 firemen (Le Quesne et al., 1976). Interpretation of these findings is complicated by simultaneous exposure to other toxic components released during these types of fires.

In an earlier investigation, Hama (1957) reported cold-like symptoms and nocturnal sweating, without fever, in addition to the gastrointestinal and neurological symptoms described above.

9.2.2 Effects of short- and long-term occupational exposure - epidemiological studies

9.2.2.1 Ocular

Luckenbach & Kieler (1980) reported evidence of microcystic corneal oedema and conjuctival infection in both eyes in a polyurethane foam worker (40-year-old female). Clouded vision, decreased visual acuity, and loss of light perception developed within one week of employment. Both corneas and conjunctivae returned to normal after 3 days without exposure to the occupational chemicals. Similar visual effects have been attributed to some amine catalysts (Belin et al., 1983).

9.2.2.2 Dermal

Skin sensitization on repeated exposure to toluene diisocyanates may occur. Urticaria, dermatitis, and allergic contact dermatitis have been reported in workers exposed to toluene diisocyanates-based photopolymerized resins (Brugsch & Elkins, 1963; Calas et al., 1977). The dermatological symptoms included skin lesions of an eczematous, and also, of an irritant, pruriginous and erythaematous nature.

A 21-year-old female developed a rash following direct skin contact with toluene diisocyanates. The urticaria or maculopapular lesions occurred primarily over exposed areas, but occasionally spread to covered areas and lasted for up to 10 days after exposure. Titers of specific IgE antibodies gradually declined over the period of observation from a high level of 1050 net cpm [by radioallergosorbent test (RAST)] to 270 net cpm after occupational exposure ceased. The lower level corresponds to those found in non-sensitized toluene diisocyanates workers (Karol et al., 1978).

9.2.2.3 Respiratory tract

Occupational exposure to toluene diisocyanates has produced a variety of respiratory effects in workers including irritation of the upper and lower respiratory tract, an asthma-like sensitization response, dyspnoea, cyanosis, and pulmonitis and decreases in lung function (Swensson et al., 1955; Brugsch & Elkins, 1963; Gandevia, 1963; Peters et al., 1968, 1969; Peters, 1970; Gaffuri & Brugnone, 1971; Charles et al., 1976; Wegmen et al., 1977; Burge et al., 1979; Burge, 1982). Short-term, as well as long-term exposures to toluene diisocyanates, in some instances at levels < 0.007 mg/m^3, have been reported to result in significant decreases in lung function (NIOSH, 1978). However, the results of more recent studies by Musk et al. (1982) failed to support such effects

at levels of isocyanates of the order of 0.007 mg/m³ (0.001 ppm). Sensitization after a single exposure was not demonstrated by Pepys (1980). Irritation of the respiratory tract can occur at levels ranging between 0.712 and 3.560 mg/m³ (Henschler et al., 1962). The asthmatic response, evident in up to 10% of previously exposed individuals, may occur at levels of toluene diisocyanates > 0.0356 mg/m³ (Bernstein, 1982). The basis for this response is still uncertain, but there is evidence supporting either immunological or pharmacological mechanisms, or a combination of both (Scheel et al., 1964; Weill et al., 1975; Butcher et al., 1977, 1980; Cockcroft & Mink, 1979; Chadwick & Cleveland, 1981; NIOSH, 1981; Bernstein, 1982; Karol, 1983).

Toluene diisocyanate-induced asthma may not be evident until after many years of exposure (Salvaggio, 1979). However, TDI may cause immediate, delayed, or biphasic asthmatic reactions (Baur et al., 1983; NIOSH, 1981). The immediate reaction reaches a peak within minutes. Late reactions occur from 2 to 8 h after exposure and may show a recurring pattern. Most affected people have non-specific bronchial hyperreactivity, as measured by mechanical intratracheal challenge tests. This reaction may continue for several years after cessation of exposure implying persisting asthmatic symptoms. Immunologically sensitized workers can be identified by means of RAST and skin testing.

A 43-year-old non-smoking molder (female) first exhibited throat irritation and a non-productive cough after 4 months of exposure to toluene diisocyanates. Dyspnoea was noted, which worsened during work-days, resulting finally in an episode that required emergency treatment. One month later, after cessation of exposure, the patient was without symptoms, and pulmonary function had returned to normal. Subsequent symptomatic episodes were successfully treated with isoproterenol (Smith et al., 1980). Other symptoms, such as faintness, nausea, vomiting of "foamy" materials, anxiety, rapid pulse rate, elevated blood pressure, fever, and cyanosis, were reported by Brugsch & Elkins (1963). The patient, who was a 62-year-old spray painter, was coating the inside of a large tank for 7 days without respiratory protection. An ECG showed hypertrophy of the left ventrical, and a chest roentgenogram showed prominent bronchovesicular markings and an enlarged cardiac silhouette. The patient improved and was discharged after 4 days.

Epidemiological studies of health effects from occupational exposure to toluene diisocyanates are summarized in Table 8.

Table 8. Epidemiological studies of health effects from occupational exposure to toluene diisocyanates

Concentration (mg/m^3)	Effects	Reference
$\leq$ 0.213 (0.03 ppm); mostly $\leq$ 0.142 (0.02 ppm)	38 workers at a polyurethane foam factory; after 1 day exposure (Monday), statistically significant decreases in FVC, FEV_1 peak-flow rate, and $FEF_{25-50\%}$; after 5 days' exposure (Friday), in 34 workers, the FVC returned to baseline, the FEV_1 was still depressed, and the respiratory flow rates were more depressed; diurnal variation could not account for these changes; workers with respiratory symptoms showed greater decreases in FEV_1	Peters et al. (1968)
0.014 - 0.093 (0.002 - 0.013 ppm)	111 workers at a polyurethane foam factory; changes measured in FEV_1 between Monday AM and PM of work day; 51 workers (0.014 mg/m^3 exposure): 78 ml decrease; 43 workers (0.028 mg/m^3 exposure): 106 to 112 ml decrease; 17 workers (0.064 - 0.093 mg/m^3 exposure): 180 ml decrease	Wegman et al. (1974); Peters & Wegman (1975)
0.072 (0.001 ppm) (time-weighted average)	107 workers from 2 polyurethane manufacturing plants; 5-year change in FEV did not exceed that expected for aging; no significant change in FEV was noted between Monday AM and PM of work day	Musk et al. (1982)

Table 8 (contd).

Concentration (mg/m^3)	Effects	Reference
0.356 - 0.712	287 workers in 2 TDI plants; lung function (FEV_1 and FVC) measured anually for 8 years; 180 workers with no respiratory symptoms: FEV_1 and FVC normal; 46 workers with respiratory symptoms and still employed: only questioned and reported more respiratory effects than controls; 61 workers with respiratory symptoms no longer at plant: FEV_1 averaged 271 ml and FVC averaged 269 ml lower than predicted from 608 controls	Adams (1975)
< 0.01 - > 0.025 (≤ 0.0015 - ≥ 0.0035 ppm)	57 workers at toluene diisocyanates plant; a dose-response relationship observed; exposure to < 0.01 mg/m^3 did not affect FEV_1; exposure to > 0.025 mg/m^3 resulted in decrease in FEV_1 of 103 ml/year, which exceeded expected value by 3 - 4 times; workers exposed to < 0.01 mg/m^3 showed normal 2-year decline (-12 ml in 2 years); differences in FEV_1 not explained by age, time employed, smoking habits, or lung size	Wegman et al. (1977)

Table 8 (contd).

0.0007 - 0.178 (0.0001 - 0.025 ppm) (TWA)	223 workers at a new TDI plant; measured for pulmonary function, with 3 or more data points to calculate slope of annual response (during 5-year exposure); low and high cumulative exposure groups exposed for 2% and 15% of time, respectively, toluene diisocyanates exceeding 0.036 mg/m³; significant effects of smoking on spirometric tests and lung volumes; after adjustment for pack-years smoking, the FEV_1, %FEV, and $FEF_{25-75\%}$ declined more in "high" exposure group (74 workers) than in "low" exposure group (149 workers); in non-smokers, average FEV_1 decline was 38 ml/year greater in high- compared with low-exposure groups; a 24 ml/year excess average decline attributed to longer exposure to levels above 0.014 mg/m³	Diem et al. (1982)
0.007 - > 0.014 (0.007 - > 0.002 ppm)	145 workers at TDI plant surveyed for lung function in 1980 and workers re-examined in 1982; short-term exposure to > 0.014 mg/m³ occurred in 9.3% of samples in 1980, and 1.9% in 1982; no dose response in loss of pulmonary function; 0.007 mg/m³ was not associated with acute or chronic effects on pulmonary function	Omae (1984)

Note: Diem et al. (1982) clarified that the toluene diisocyanates workers were compared according to cumulative exposure, not concentration categories, and that the low-exposure group's 8-h TWA was spent at < 0.036 mg TDI/m³ and the high-exposure at > 0.036 mg TDI/m³. There was a mean increase in FEV_1 of 1 ml/year for the low-exposure category and a mean decrease in FEV_1 of 1 ml/year for the high-exposure category. They indicated that, because of variations in daily exposure to toluene diisocyanates, an average 8-h TLV < 0.036 mg/m³ might be necessary to achieve compliance.

FVC = forced vital capacity.
FEV_1 = forced expiratory volume in 1 second.
$FEV_1/FVC\%$ = ratio of FEV_1/FVC x 100.
$FEF_{25-50\%}$ and $FEF_{25-75\%}$ = forced expiratory flow between 25% and 50% or 25% and 75% of FVE, respectively.

9.2.2.4 Cancer epidemiology

No epidemiological studies of mortality or cancer incidence among workers exposed to toluene diisocyanates were available to the Task Group.

One case report of adenocarcinoma in a 47-year-old non-smoking spray-painter has been published. The subject had been exposed to toluene diisocyanate and 4,4-methylene diisocyanate for 15 years. The levels of exposure to isocyanates were not reported and neither were other chemicals to which the subject may have been exposed (Mortillaro & Schiavon, 1982).

9.2.2.5 Immunotoxicity

Several investigators have detected toluene diisocyanates sensitization with the lymphocyte transformation test and other immunoassays, but have been unable to consistently demonstrate elevated antibody titers (Bruckner et al., 1968; Avery et al., 1969; Danks et al., 1981; Game, 1982). Studies on the immune response following exposure to toluene diisocyanates are summarized in Table 9.

The results of these studies indicated that exposure to low concentrations of toluene diisocyanates ($\geq$ 0.14 mg/m^3) induced hypersensitivity in a variable and unknown percentage of the individuals at risk. The duration of exposure to toluene diisocyanates necessary to induce hypersensitivity was also highly variable, sometimes occurring immediately or requiring months or even years of exposure. There has been some success in evaluating the hypersensitivity to toluene diisocyanates with RAST assays using the TDI-HSA antigen, but neither the antibody responses to this specific antigen, nor the level of IgE antibody were consistently elevated in individuals with hypersensitivity and asthmatic responses (Baur, 1983; Belin et al., 1983; Barkman et al., 1984). Present immunoassay techniques will not detect all susceptible individuals.

9.2.3 Potential mechanisms of action

Irritation and toxic effects are presumed to stem from the reactivity of the isocyanate groups (i.e., -NCO) on toluene diisocyanates and their quasipolymers (Brugsch & Elkins, 1963). Wegman et al. (1974) demonstrated a dose-response relationship for these symptoms. Irritation will stimulate mucous-secreting goblet cells, with a proportional decrease in ciliated epithelial cells. Impaired clearance and mucal

Table 9. Immune response in workers exposed to toluene diisocyanates

Level (mg/m^3)	Sample number	Immune response	References
0.028 - 0.142	32 workers	hypersensitive responses correlated with TDI levels > 0.35 mg/m^3; IgG antibodies present and bronchoconstriction occurred	Porter et al. (1975)
frequently > 0.14	166 workers; increased incidence of TDI-specific IgE antibodies	pulmonary function normal; positive skin test and bronchoconstriction noted	Butcher et al. (1977)
0.142 dhallenge	23 workers (4 sensitive to TDI)	specific IgE antibodies in 3 out of 4 sensitive workers; 19 non-sensitized workers had antibody titers comparable with controls; high levels to specific IgE antibodies not correlated with serum-IgE levels	Karol et al. (1978)
< 0.175	87 workers	respiratory symptoms with reduction in FEV_1; tolyl-specific IgE detected in 2 workers only; RAST indicated generally low levels in all sensitized workers	Kido et al. (1983b)
0.119 - 0.147	39 workers	Significant elevation of serum-IgE levels in only 4 out of 10 workers exposed for less than 1 year, all having obstructive impairment of liver function	Hobara et al. (1984)

stagnation may result, followed by epithelial desquamation, submucosal glandular hypertrophy, and basement membrane thickening as in chronic tracheo-bronchitis (Braman & Teplitz, 1978).

The mechanisms concerned (immunological or pharmacological) in the production of asthma and hypersensitivity pneumonitis through occupational exposure to toluene diisocyanates are still the subject of debate. The controversy stems from the paradoxical nature of the sensitivity reactions. Karol et al. (1978) reported specific IgE antibodies in sera from workers sensitive to toluene diisocyanates, suggesting an IgE-mediated mechanism for sensitivity to the compound. It was reported by Thurman et al (1978) that toluene diisocyanates induced lymphocytes to undergo blastogenesis, suggesting antigenic stimulation. In many instances, no specific IgE antibodies against TDI-HSA conjugates were demonstrated (Gaffuri & Brugnone, 1971; Butcher et al., 1977, 1980). Positive results were observed in 14-19% of toluene diisocyanates reactors, depending on the method of evaluation (Butcher et al., 1980; Baur et al., 1983). Smith et al. (1980) also found a worker sensitized to toluene diisocyanates, but with no IgE antibodies, leukocyte inhibition factor for isocyanate antigen, or even bronchial hyperreactivity to methacholine, an important component of bronchial asthma. Asthma resulting from toluene diisocyanates exposure appears to be a complex syndrome with several possible mechanisms of causation, including an IgE mechanism in some individuals.

Salvaggio (1979) suggests that preexisting asthmatic conditions, together with partial andrenergic blockage or abnormal cholinergic receptor activity, may increase bronchial airway hyperreactivity to irritants, such as toluene diisocyanates. A significant decrease in erythrocyte-cholinestrase activity was found in in vitro studies in 70% of a group of 30 workers exposed to toluene diisocyanates (Brown et al. 1982; Dewair et al., 1983; Manno & Lotti, 1976).

The results of several in vitro studies showed evidence of inhibition of elevated levels of intracellular cyclic AMP production by TDI at doses as low as 6.7×10^{-7} mol (Butcher et al., 1977; Davies et al., 1977). The explanation for these responses is unclear.

The controversy over immune-controlled versus pharmacologically mediated response to toluene diisocyanates in sensitized workers has yet to be resolved.

10. EVALUATION OF HUMAN HEALTH RISKS AND EFFECTS ON THE ENVIRONMENT

10.1 Exposure to Toluene Diisocyanates

In the USA, it has been estimated that approximately 40 000 workers are involved in the manufacture or processing of toluene diisocyanates. Occupational exposure levels have been reported to range from 0.001 to 1 mg/m³.

Figures are not available on the total discharge of unreacted TDI into the environment. However, releases into the air ranging from 0.1 to 17.7 mg/m³ have been measured in stack gases emitted from a plant manufacturing polyurethane foams. It has been reported that approximately 50 g of TDI are released per tonne of processed TDI in the manufacture of polyurethane foams, the manufacture of which consumes about 90% of TDI produced.

As far as the general population is concerned, intake of toluene diisocyanates, apart from their use in the form of polyurethane lacquers and paints, is of a very low order, because of the short persistence of TDI.

10.1.1 Acute and short-term effects

The odour threshold for toluene diisocyanates in human beings is estimated to range between 0.35 and 0.92 mg/m³ (0.05 and 0.13 ppm).

The lowest levels of TDI associated with acute effects were reported to be: 0.035 - 0.70 mg/m³, eye and nose irritation, burning nose and throat, and a choking sensation; 0.70 - 3.5 mg/m³, a respiratory response of irritation, cough, and chest discomfort. At higher levels, chemical pneumonitis may be expected.

10.1.2 Health risks of long-term exposure to toluene diisocyanates

Risk of respiratory toxicity from repeated exposure can be summarized as follows: (a) chronic loss of ventilatory capacity as measured by forced expiratory volume and forced vital capacity; (b) immediate and/or delayed asthmatic responses.

In many epidemiological studies, past mean exposures to TDI have been estimated in an attempt to quantify dose-response relationships for respiratory ill health. Because of the uncertainties in the sampling procedures and analytical measurements used in past industrial health surveys, it is difficult to be confident about the exact levels at which TDI

causes the above-mentioned health effects. It should be remembered that fluctuations in the true individual exposure occur and, as both the size and extent of the intermittent peaks are unknown, their biological significance cannot be evaluated.

Once individuals are sensitized to toluene diisocyanates, low concentrations, much below current occupational exposure limits, can induce asthma. Studies on experimental animal have shown that skin application of TDI can lead to pulmonary sensitization; thus, it is prudent to avoid repeated skin contact.

No data were available on the carcinogenic effects of toluene diisocyanates in human beings.

No carcinogenic effects of TDI were noted in an inhalation study on rats and mice. However, the 80:20 mixture in corn oil, administered by gavage, was carcinogenic for male and female rats and female mice in a dose-related manner. It is considered that there is sufficient evidence for the carcinogenicity of TDI for experimental animals.

There is evidence of mutagenicity in two bacterial tests.

10.2 Evaluation of Effects on the Environment

An evaluation of the hazards for non-human targets from environmental levels of TDI is not possible on the basis of available data.

10.3 Conclusions and Recommendations

1. There is sufficient knowledge about TDI to classify it as a very toxic compound by inhalation, and TDI should be treated as a potential human carcinogen and as a known animal carcinogen. Consequently, the greatest priority should be given to safe methods of use, the education, training, and supervision of operatives, and state enforcement of legislation by an effective inspectorate. Special attention should be paid to the prevention and adequate treatment of unscheduled releases and spills.

2. Additional animal carcinogenicity testing by the inhalation route should be carried out.

3. Morbidity and mortality studies are required on occupational groups for whom reliable exposure data are available, to address the question of cancer and to evaluate the potential of toluene diisocyanates to cause long-term human health hazards under current standards of good working practice.

4. Because it is not possible to reach confident conclusions from the data on the neurotoxicity of TDI, neurophysiological and behavioural studies should be carried out on asymptomatic workers, exposed at current hygiene standards.

5. For the foreseeable future, exposed workers require health monitoring by systematic symptom enquiry and by standardized measurement of ventilatory function, with subsequent analysis of trends for individuals and for group mean values.

6. Appropriate sampling strategies together with existing analytical methods have to be developed and used to obtain better information about exposure, with special reference to the detection and characterization of peak values. The results of these analyses need to be evaluated in special studies in parallel with careful health studies.

7. Further metabolic studies of a qualitative and quantitative nature should be carried out with a view to developing methods of measuring TDI uptake and monitoring exposure.

8. Whether TDI produces sensitization in human beings by pharmacological or immune mechanisms needs to be elucidated with a view to determining whether restrictions placed on the employment of atopic subjects, in areas where TDI is produced or used, are justified.

9. Studies are required to determine whether TDI has embryotoxic and teratogenic properties or has adverse reproductive effects at current exposure levels.

10. Further environmental studies are required to monitor general environmental levels of TDI in the neighbourhood of sources and to collect ecotoxicity data.

11. PREVIOUS EVALUATIONS BY INTERNATIONAL BODIES

IARC (1979) evaluated the data on the carcinogenicity of toluene diisocyanates and found insufficient experimental animal or human data on which to base an evaluation. An evaluation of additional data by IARC (1986) led to the conclusion that there is sufficient evidence for the carcinogenicity of toluene diisocyanates for experimental animals.

In the absence of adequate case reports or epidemiological studies, there is insufficient data to assess the carcinogenicity of toluene diisocyanates for human beings (IARC 1986).

REFERENCES

ADAMS, W.G.F. (1975) Long-term effects on the health of men engaged in the manufacture of tolylene di-isocyanate. Br. J. ind. Med., 32: 72-78.

ALARIE, Y. (1973) Sensory irritation of the upper airways by airborne chemicals. Toxicol. appl. Pharmacol., 24: 279-297.

ALDER, J.F. & ISAAC, C.A. (1981a) Detection of toluene diisocyanate in air with a coated piezoelectric crystal. Part 1. A study of coating materials. Anal. Chim. Acta, 129: 163-174.

ALDER, J.F. & ISAAC, C.A. (1981b) Detection of toluene diisocyanate in air with a coated piezoelectric crystal. Part 2. Development of an instrumental method for personal monitoring. Anal. Chim. Acta, 129: 175-188.

AMES, B.N., KAMMEN, H.O., & YAMASAKI, E. (1975) Hair dyes are mutagenic: identification of a variety of mutagenic ingredients. Proc. Natl Acad. Sci. (USA), 72: 2423-2327.

ANDERSEN, M., BINDRUP, M., KIEL, P., LARSEN, H., & MAXILD, J. (1980) Mutagenic action of isocyanates used in the production of polyurethanes. Scand. J. Work environ. Health, 6: 221-226.

ANDERSON, D. & STYLES, J.A. (1978). Appendix II. The bacterial mutation test. Br. J. Cancer, 37: 924-930.

ANON. (1983) Polyurethane markets may be maturing. Chem. Eng. News, 61(46): 16.

ARAGON, J.J., FELIU, J.E., FRENKEL, R.A., & SOLS, A. (1980) Permeabilization of animal cells for kinetic studies of intracellular enzymes: in situ behavior of the glycolytic enzymes of erythrocytes. Proc. Natl Acad. Sci. (USA), 77(11): 6324-6328.

AUDUNSSON, G. & MATHIASSON, L. (1983) Simultaneous determination of amines and isocyanates in working atmospheres by gas-liquid chromatography. J. Chromatogr., 261: 253-264.

AVERY, S.B., STETSON, D.M., PAN, P.M., & MATHEWS, K.P. (1969) Immunological investigation of individuals with toluene diisocyanate asthma. Clin. exp. Immunol., 4: 585-596.

AXFORD, A.T., MCKERROW, C.B., JONES, P.A., & LE QUESNE, P.M. (1976) Accidental exposure to isocyanate fumes in a group of firemen. Br. J. ind. Med., 33: 65-71.

BAGON, D.A. & HARDY, H.L. (1978) Determination of free monomeric toluene diisocyanate (TDI) and 4,4'-diisocyanate-diphenylmethant (MDI) prepolymers, respectively, by high performance liquid chromatography. J. Chromatogr., 152(2): 560-564.

BARKMAN, H.W., BANKS, D.E., HENDRICK, D.J., JONES, R.N., ABDELKADER, H.M., HAMMAD, Y.Y., GLINDMEYER, H.W., & WEILL, H. (1984) Inhalation challenge testing with 2,4 and 2,6 toluene diisocyanate isomers. Chest, 86(2): 340.

BAUR, X. (1983) Immunologic cross-reactivity between different albumin-bound isocyanates. J. Allergy clin. Immunol., 71(2): 197-205.

BAUR, X. & FRUHMANN, G. (1981) Specific IgE antibodies in patients with isocyanate asthma. Chest, 80: 73-76.

BAUR, X., DEWAIR, M., & FRUHMANN, G. (1983) Detection of immunologically sensitized isocyanate workers by RAST and intracutaneous skin tests. J. clin. Immunol., 73: 610.

BEALL, J.R. & ULSAMER, A.G. (1981) Toxicity of volatile organic compounds present indoors. Bull N.Y. Acad. Med., 57(1): 978-996.

BELIN, L., WASS, U., AUDUNSSON, G., & MATHIASSON, L. (1983) Amines: possible causative agents in the development of bronchial hyperreactivity in workers manufacturing polyurethanes from isocyanates. Br. J. ind. Med., 40: 251-257.

BENGTSSON, B.-E. & TARKPEA, M. (1983) The acute aquatic toxicity of some substances carried by ships. Mar. Pollut. Bull., 14(6): 213-214.

BERNSTEIN, I. (1982) Isocyanate-induced pulmonary diseases: a current perspective. J. Allergy clin. Immunol., 70(1): 25-31.

BRAMAN, S.S. & TEPLITZ, C. (1978) Occupational lung disease. Primary Care, 5(3): 425-445.

BRANDT, G.H. (1972) Soil stabilizers. In: Goring, C.A.I. & Hamaker, J.W., ed. Organic chemicals in the soil environment, New York, Marcel Dekker, pp. 692-693, 719-720.

BROCHHAGEN, F.K. & GRIEVESON, B.M. (1983) Environmental aspects of isocyanates in water and soil. Cell. Polym., 3: 11-17.

BROWN, W.E. & WOLD, F. (1971) Alkyl isocyanates as active-site specific inhibitors of chymotrypsim and elastase. Science, 174: 608-610.

BROWN, W.E. & WOLD, F. (1973) Alkyl isocyanates as active-site-specific reagents for serine proteases. Biochemistry, 12: 828-834.

BROWN, W.E., GREEN, A.H., KAROL, M.H., & ALARIE, Y.C.E (1982) Inhibition of cholinesterase activity by isocyanates. Toxicol. appl. Pharmacol., 63: 45-52.

BRUCKNER, H.C., AVERY, S.B., STETSON, D.M., & DODSON, V.N. (1968) Clinical and immunologic appraisal of workers exposed to diisocyanates. Arch. environ. Health, 16: 619-625.

BRUGSCH, H.G. & ELKINS, H.B. (1963) Toluene di-isocyanate (TDI) toxicity. New Engl. J. Med., 268(7): 353-357.

BUCKLEY, L.A., JIANG, X.Z., JAMES, K.T., MORGAN, K.T., & BARROW, C.S. (1984) Respiratory tract leisons induced by sensory irritants at the RD_{50} concentration. Toxicol. appl. Pharmacol., 74: 417-429.

BUNGE, W., EHRLICHER, H., & KIMMERLE, G. (1977) Medical aspects of work with surface coating systems using the spraying technique. Z. Arbeitsmed. Arbeitsschutz Prophyl., 4(special ed.): 1-46

BURGE, P.S. (1982) Non-specific bronchial hyper-reactivity in workers exposed to toluene di-isocyanate, diphenyl methane di-isocyanate and colophony. Eur. J. respir. Dis., 63(123): 91-96.

BURGE, P.S., O'BRIEN, I.M., & HARRIES, M.G. (1979) Peak flow rate records in the diagnosis of occupational asthma due to isocyanates. Thorax, 34: 317-323.

BUTCHER, B.T., JONES, R.N., O'NEIL, C.E., GLINDMEYER, H.W., DIEM, J.E., DHARMARAJAN, V., WEILL, H., & SALVAGGIO, J.E. (1977) Longitudinal study of workers employed in the manufacture of toluene-diisocyanate. Am. Rev. respir. Dis., 116: 411-421.

BUTCHER, B.T., KARR, R.M., O'NEIL, C.E., WILSON, M.R., DHARMARAJAN, V., SALVAGGIO, J.E., & WEILL, H. (1979) Inhalation challenge and pharmacologic studies of toluene diisocyanate (TDI)-sensitive workers. J. Allergy clin. Immunol., 64(2): 146-152.

BUTCHER, B.T., O'NEIL, C.E., REED, M.A., & SALVAGGIO, J.E. (1980) Radioallergosorbent testing of toluene diisocyanate-reactive individuals using p-tolyl isocyanate antigen. J. Allergy clin. Immunol., 66(3): 213-216.

CALAS, E., CASTELAIN, P.Y., LAPOINTE, H.R., DUCOS, P., CAVELIER, C., DUPRAT, P., & POITOU, P. (1977) Allergic contact dermatitis to a photopolymerizable resin used in printing. Contact Dermat., 3(4): 186-194.

CHADWICK, D.H. & CLEVELAND, T.H. (1981) Isocyanates, organic. In: Kirk-Othmer encyclopedia of chemical technology, 3rd ed., New York, John Wiley and Sons, Vol. 13, pp. 789-818.

CHARLES, J., BERNSTEIN, A., JONES, B., JONES, D.J., EDWARDS, J.H., SEAL, R.M.E., & SEATON, A. (1976) Hypersensitivity pneumonitis after exposure to isocyanates. Thorax, 31: 127-136.

CHEN, S.E. & BERNSTEIN, I.L. (1982) The guinea-pig model of diisocyanate sensitization immunologic studies. J. Allergy clin. Immunol., 70(5): 383-392.

COCKCROFT, D.W. & MINK, J.T. (1979) Isocyanate-induced asthma in an automobile spray painter. Can. Med. Assoc. J., 121(5): 602-604.

CONTE, A. & COSSI, G. (1981) Gas chromatographic determination of free toluene diisocyanate in flexible urethane foams. J. Chromatogr., 213: 162-165.

CURTIS, M.W., COPELAND, T.L., & WARD, C.H. (1979) Acute toxicity of 12 industrial chemicals to freshwater and saltwater organisms. Water Res., 13: 137-141.

DANKS, J.M., CROMWELL, O., BUCKINGHAM, J., NEWMAN-TAYLOR, A., & DAVIES, R. (1981) Toluene-diisocyanate induced asthma: evaluation of antibodies in the serum of affected workers against a tolyl mono-isocyanate protein conjugate. Clin. Allergy, 11: 161-168.

DAVEY, J.E. & EDWARDS, A.D. (1983) Determination of toluene-2,4-diisocyanate in rubber fumes. Analyst, 108: 407-411.

DAVIES, R.J., BUTCHER, B.T., O'NEIL, C.E., & SALVAGGIO, J.E. (1977) The *in vitro* effects of toluene diisocyanate on lymphocyte cyclic adenosine monophosphate production by isoproterenol, prostaglandin, and histamine. J. Allergy clin. Immunol., 60(4): 223-229.

DE PASCALE, A., COBELLI, L., PALADINO, R., PASTORELLO, L., & FRIGERIO, A. (1983) Quantitative determination of airborne 2,4-toluene diisocyanate. J. Chromatogr., 256: 352-358.

DEWAIR, M., BAUR, X., & MAUERMAYER, R. (1983) Inhibition of acetylcholinesterase by diisocyanates and its spontaneous reactivation. Int. Arch. occup. environ. Health, 52: 257-261.

DHARMARAJAN, V., WEIL, H., & SELF, C.W. (1978) Environmental characterization of toluene diisocyanate (TDI) in a manufacturing plant. Am. Ind. Hyg. Assoc. J., 39(5): 414-418.

DIEM, J.E., JONES, R.N., HENDRICK, D.J., GLINDMEYER, H.W., DHARMARAIAN, V., BUTCHER, B.T., SALVAGGIO, J.E., & WEILL, H. (1982) Five-year longitudinal study of workers employed in a new toluene diisocyanate manufacturing plant. Am. Rev. respir. Dis., 126(3): 426-428.

DUFF, P.B. (1983) The fate of TDI in the environment. In: Proceedings of the Society of the Plastic Industry's 6th International Technical Conference, San Diego, California, New York, Society of Plastics Industry, pp. 408-412.

DUNCAN, B., SCHEEL, L.D., FAIRCHILD, E.J., RILLENS, R., & GRAHAM, S. (1962) Toluene diisocyanate inhalation toxicity: Pathology and mortality. Am. Ind. Hyg. Assoc. J., 23: 447-456.

DUNLAP, K.L., SANDRIDGE, R.L., & KELLER, J. (1976) Determination of isocyanates in working atmospheres by high speed liquid chromatography. Anal. Chem., 48: 497-499.

DUPRAT, P., GRADISKI, B., & MARIGNAC, B. (1976) Pouvoir irritant et allergisant de deux isocyanates: toluène diisocyanate (TDI) and diphénylméthane diisocyanate (MDI). Eur. J. Toxicol., 9(1): 41-53.

DYSON, W.L. & HERMANN, E.R. (1971) Reduction of atmospheric toluene diisocyanate by water vapor. Am. Ind. Hyg. Assoc. J., 32(1): 741-744.

FIELDEN, P.R., MCCALLUM, J.J., STANIOS, T., & ALDER, J.F. (1984) Detection of toluene diisocyanate with a coated quartz piezoelectric crystal. Anal. Chim. Acta, 162: 85-96.

FRIEBEL, H. & LUCHTRALH H. (1955) [The effect of toluene diisocyanate (Desmodur T) on the respiratory airways.] Arch. exp. Pathol. Pharmakol., 277: 93-110 (in German).

FRY, A. (1953) A tracer study of the reaction of isocyanates with carboxylic acids. J. Am. Chem. Soc., 75: 2686-2688.

GAFFURI, E. & BRUGNONE, F. (1971) [Respiratory troubles from isocyanates in varnishers.] Med. Lav., 62(2-3): 151-157 (in Italian).

GAME, C.J.A. (1982) Australian TDI workers' sera assayed for IgE against a p-tolyl-isocyanate-human serum albumin conjugate. Am. Ind. Hyg. Assoc. J., 43(10): 759-763.

GANDEVIA, B. (1963) Studies of ventilatory capacity and histamine response during exposure to isocyanate vapour in polyurethane foam manufacture. Br. J. ind. Med., 20: 204-209.

GRANATEK, C.H., CORRY, P.M., & GOLKIN, E.M. (1975) Use of fluorescent x-ray spectroscopy to quantitate binding of anti-embryonic antibody to human tumor cells. AACR Abstr., 16: 47.

GRANT, W.A. (1974) Toxicology of the eye, 2nd ed., Springfield, Illinois, Charles C. Thomas, p. 1028.

GRIEVESON, B.M. & REEVE, B. (1983) Isocyanate emissions: a review of work on environmental aspects of handling toluene diisocyanate. Cell. Polym., 2: 165-175.

GRIM, K.E. & LINCH, A.L. (1964) Recent isocyanate-in-air analysis studies. Ind. Hyg. J., May-June: 285-290.

HAMA, G.M. (1957) Symptoms in workers exposed to isocyanates: suggested exposure concentrations. Am. Med. Assoc. Arch. Ind. Health, 16: 232-233.

HARDY, H.L. & PURNELL, C.J. (1978) Use of foam for the emergency suppression of vapour emissions from organic isocyanate liquid surfaces. Ann. occup. Hyg., 21: 95-98.

HARTON, E.E., Jr & RAWL, R.R. (1976) Toxicological and skin corrosion testing of selected hazardous materials, Springfield, Virginia, US Department of Commerce (Final report NTIS Publication 264 975).

HARTUNG, R. (1982) Cyanides and nitriles. In: Clayton, G.D. & Clayton, I.I., ed. Patty's industrial hygiene and

toxicology, 3rd revised ed., New York, John Wiley and Sons, pp. 4845-4850, 4892-4893, 4898-4900.

HENSCHLER, D., ASSMANN, W., & MEYER, K.-O. (1962) [Toxicology of toluene diisocyanate.] Arch. Toxikol., 19: 364-387 (in German).

HOBARA, T., KOBAYASHI, H., HIGASHIHARA, E., KAWAMOTO, T., IWAMOTO, S., SHIMAZU, W., & SAKAI, T. (1984) Health hazard by exposure to toluene-diisocyanate in the shipyard. Bull. environ. Contam. Toxicol., 32: 134-139.

HOLDREN, M.W., SPICER, C.W., & RIGGIN, R.M. (1984) Gas phase reaction of toluene diisocyanate with water vapor. Am. Ind. Hyg. Assoc. J., 45(9): 626-633.

HOSEIN, H.R. & FARKAS, S. (1981) Risk associated with the spray application of polyurethane foam. Am. Ind. Hyg. Assoc. J., 42(9): 663-665.

IARC (1979) Some monomers, plastics and synthetic elastomers, and acrolein, Lyons, International Agency for Research on Cancer, p. 303 (Monographs on The Evaluation of the Carcinogenic Risk of Chemicals to Humans, Vol. 19).

IARC (1986) Toluene diisocyanate. In: Some chemicals used in plastics and elastomers, Lyons, International Agency for Research on Cancer, pp. 287-323 (Monographs on The Evaluation of the Carcinogenic Risk of Chemicals to Humans, Vol. 39).

III (1980) Technical information: recommendations for the handling of toluene diisocyanate (TDI), New York, International Isocyanate Institute Inc.

KAROL, M.H. (1983) Concentration-dependent immunologic response to toluene diisocyanate (TDI) following inhalation exposure. Toxicol. appl. Pharmacol., 68: 229-241.

KAROL, M.H., IOSET, H.H., & ALARIE, Y.C. (1978) Tolyl-specific IgE antibodies in workers with hypersensitivity to toluene diisocyanate. Am. Ind. Hyg. Assoc. J., 39: 454-458.

KAROL, M.H., DIXON, C., BRADY, M., & ALARIE, Y.C. (1980) Immunologic sensitization and pulmonary hypersensitivity by repeated inhalation of aromatic isocyanates. Toxicol. appl. Pharmacol., 53: 260-270.

KAROL, M.H., HAUTH, B.A., RILEY, E.J., & MAGRENI, C.M. (1981) Dermal contact with toluene diisocyanate (TDI)

produces respiratory tract hypersensitivity in guinea-pigs. Toxicol. appl. Pharmacol., 58: 221-230.

KIDO, T., YAMADA, Y., & TERANISHI, H. (1983a) [Studies on toluene diisocyanate asthma. Part 2. Histamine release from guinea pig leukocytes by toluene diisocyanate.] Jpn. J. Allergol., 32: 131-137 (in Japanese).

KIDO, T., YAMADA, Y., TERANISHI, H., DAIMON, N., & SHIMIZU, T. (1983b) [Studies on toluene diisocyanate asthma. I. Clinico- allergological Tests.] Jpn. J. Allergol., 32: 111-120 (in Japanese).

KOSCHIER, F.J., BURDEN, E.J., BRUNKHORST, C.S., & FRIEDMAN, M.A. (1983) Concentration-dependent elicitation of dermal sensitization in guinea pigs treated with 2,4-toluene diisocyanate. Toxicol. appl. Pharmacol., 67: 401-407.

LE QUESNE, P.M., AXFORD, A.T., MCKERROW, C.B., & PARRY JONES, A. (1976) Neurological complications after a single severe exposure to toluene diisocyanates. Br. J. ind. Med., 33: 72-78.

LINDEN, E., BENGTSSON, B.E., SVANBERG, O., & SUNDSTROM, G. (1979) The acute toxicity of 78 chemicals and pesticide formulations against 2 brackish water organisms the Bleak (Alburnus alburnus) and the Harpacticoid (Nitocra spinipes). Chemosphere, 8: 843-851.

LOESER, E. (1983) Long-term toxicity and carcinogenicity studies with 2,4/2,6-toluene-diisocyanate (80/20) in rats and mice. Toxicol. Lett., 15: 71-81.

LUCKENBACH, M. & KIELER, R. (1980) Toxic corneal epithelial edema from exposure to high atmospheric concentration of toluene diisocyanates. Am. J. Ophthalmol., 90: 682-686.

MCFADYEN, P. (1976) Determination of free toluene diisocyanate in polyurethane prepolymers by high-performance liquid chromatography. J. Chromatogr., 123: 468-473.

MACKAY, D. (1979) Finding fungacity feasible. Environ. Sci. Technol., 13(10): 1218-1223.

MCKAY, R.T. & BROOKS, S.M. (1983) Induction of tracheal smooth-muscle hyperresponsiveness to carbachol following exposure to toluene diisocyanate (TDI) vapors. Am. Rev. respir. Dis., 127(4): 174.

MANNO, M. & LOTTI, M. (1976) Cholinesterases in human toluene diisocyanate exposure. Int. Arch. occup. environ. Health, 38: 55-60.

MARCALI, K. (1957) Microdetermination of toluene diisocyanates in atmosphere. Anal. Chem., 29: 552-558.

MARTENS, R. & DOMSCH, K.H. (1981) Microbial degradation of polyurethane foams and isocyanate based polyureas in different media. Water Air Soil Pollut., 15: 503-509.

MAZUR, G., BAUR, X., PFALLER, A., & ROMMELT, H. (1986) Determination of toluene diisocyanate in air by HPLC on band-tape monitors. Int. Arch. occup. environ. Health, 58: 269-276.

MEDDLE, D.W. & WOOD, R. (1970) A method for the determination of aromatic isocyanates in air in the presence of primary aromatic amines. Analyst, 95: 402-407.

MEYER, S.D. & TALLMAN, D.E. (1983) The determination of toluene diisocyanate in air by high-performance liquid chromatography with electrochemical detection. Anal. Chim. Acta, 146: 227-236.

MORTILLARO, P.T. & SCHIAVON, M. (1982) [One case of lung cancer that developed in the course of a bronchopulmonary disease due to isocyanates.] Med. Lav., 3: 207-209 (in Italian).

MUNN, A. (1960) Experiences with diisocyanates. Trans. Assoc. Ind. Med. Off., 9: 134-138.

MUNN, A. (1968) Health hazards from isocyanates. Adv. Polyurethane Technol., 16: 299-306.

MUSK, A.W., PETERS, J.M., DEBERARDINIS, L., & MURPHY, R.L.H. (1982) Absence of respiratory effects in subjects exposed to low concentrations of TDI and MDI. J. occup. Med., 24(10): 746-749.

NIOSH (1978) Criteria for a recommended standard occupational exposure to diisocyanates, Rockville, Maryland, US National Institute for Occupational Safety and Health (NIOSH 78-215; PB 81-226615).

NIOSH (1981) Respiratory and immunologic evaluation of isocyanate exposure in a new manufacturing plant, Washington DC, US National Institute of Occupational Safety and Health,

Department of Health and Human Services, (DHHS (NIOSH) Publication No. 81-125).

NTP (1985) Disposition of 2,6-toluene diisocyanate in fischer 344 rats, Research Triangle Park, North Carolina, US National Toxicology Program (Project Report No. 7; Contract No. N01-ES-1-5007, RTI/2227/00-06P).

NTP (1986) Toxicology and carcinogenesis studies of commercial grade 2,4(80%)- and 2,6(20%)-toluene diisocyanate (CAS No. 26471-62-5) in F344/N rats and B6C3F1 mice (gavage studies), Research Triangle Park, North Carolina, US National Toxicology Program (Technical Report No. 251; NIH Publication No. 86-2507).

OHSAWA, T. (1983) [Experimental studies of the biological effects on TDI: an inhalation study in skin-sensitized mice.] J. Tokyo Women Med. Coll., 53(3): 237-246 (in Japanese).

OMAE, K. (1984) Two-year observation of pulmonary function in workers exposed to low concentrations of toluene diisocyanate. Int. Arch. occup. environ. Health, 55: 1-12.

OZAWA, H. (1967) Bridging reagent for protein. I. The reaction of diisocyanates with lysine and enzyme protein. J. Biochem., 62(4): 419-423.

PAGGIARO, P.L., ROSSI, O., LASTRUCCI, L., PARDI, F., PEZZINI, A., & BUSCHIERI, L. (1985) TDI-induced oculorhinitis and bronchial asthma. J. occup. Med., 27: 51-52.

PATTERSON, R., ZEISS, C.R., & HARRIS, K.E. (1983) Immunologic and respiratory responses to airway challenges of dogs with toluene diisocyanate. J. Allergy clin. Immunol., 71: 604-611.

PEPYS, J. (1980) Occupational asthma: a review of present clinical and immunologic status. J. Allergy clin. Immunol., 66: 179-185.

PESCHEL, H. (1970) [Skin alterations by isocyanate (Desmodur).] Derm. Mschr., 156: 691-697 (in German).

PETERS, J.M. (1970) Cumulative pulmonary effects in workers exposed to tolylene (sic) diisocyanate. Proc. R. Soc. Med., 63: 372-375.

PETERS, J.M. & MURPHY, R.L.H. (1971) Hazards to health: do it yourself polyurethane foam. Am. Rev. respir. Dis., 104: 432-433.

PETERS, J.M. & WEGMAN, D.H. (1975) Epidemiology of toluene diisocyanate (TDI)-induced respiratory disease. Environ. Health Perspect., 11: 97-100.

PETERS, J.M., MURPHY, R.L.H., PAGNOTTO, L.D., & VAN GANSE, W.F. (1968) Acute respiratory effects in workers exposed to low levels of toluene diisocyanate (TDI). Arch. environ. Health, 16: 642-647.

PETERS, J.M., MURPHY, R.L.H., & FERRIS, B.G. (1969) Ventilatory function in workers exposed to low levels of toluene diisocyanate (TDI). Br. J. ind. Med., 26: 115-120.

POLLOCK, J.R.A. & STEVENS, R. (1974) Dictionary of organic compounds, 4th ed., New York, Oxford University Press, Suppl. 10, p. 337.

PORTER, C., HIGGINS, R.L., & SCHEEL, L.D. (1975) A retrospective study of clinical, physiologic and immunologic changes in workers exposed to toluene diisocyanate. Am. Ind. Hyg. Assoc. J., 36: 159-163.

PURCHASE, I.F.H., LONGSTAFF, E., ASHBY, J., STYLES, J., ANDERSON, D., LEFEVRE, P., & WESTWOOD, F. (1978) An evaluation of six short-term tests for detecting organic chemical carcinogens. Br. J. Cancer, 37(6): 873-959.

RAMPY, L.W., LOESER, E., LYON, J.P., & CARNEY, I. (1983) Two carcinogenicity studies of toluene diisocyanate. In: Proceedings of the Society of the Plastic Industry's 6th International Technical Conference, San Diego, California, New York, Society of Plastics Industry.

RANDO, R.J. & HAMMAD, Y.Y. (1985) Modified Marcali method for the determination of total toluene diisocyanate in air. Am. Ind. Hyg. Assoc. J., 46(4): 206-210.

REILLY, D.A. (1968) A test-paper method for the determination of tolylene diisocyanate vapour in air. Analyst, 93: 178-185.

ROSENBERG, C. (1984) Direct determination of isocyanates and amines as degradation products in the industrial production of polyurethane-coated wire. Analyst, 109: 859-866.

ROSENBERG, C. & SAVOLAINEN, H. (1985) Detection of urinary amine metabolites in toluene diisocyanate exposed rats. J. Chromatogr., 323: 429-433.

ROSENBERG, C. & SAVOLAINEN, H. (1986) Determination of occupational exposure to toluene diisocyanate by biological monitoring. J. Chromatogr., 367: 385-392.

SALVAGGIO, J.E. (1979) Occupational asthma: overview of mechanisms. J. Allergy clin. Immunol., 64: 646-649.

SANGHA, G.K. & ALARIE, Y. (1979) Sensory irritation by toluene diisocyanate in single and repeated exposures. Toxicol. appl. Pharmacol., 50: 533-547.

SANGO, C. & ZIMERSON, E. (1980) A new reagent for determination of isocyanates in working atmosphere by HPLC using UV or fluorescence detection. J. liq. Chromatogr., 3(7): 971-990.

SCHAFER, E.W., Jr, BOWLES, W.A., Jr, & HURLBUT, J. (1983) The acute oral toxicity, repellency, and hazard potential of 998 chemicals to one or more species of wild & domestic birds. Arch. environ. Contam. Toxicol., 12: 355-382.

SCHEEL, L.D., KILLENS, R., & JOSEPHSON, A. (1964) Immunochemical aspects of toluene diisocyanate (TDI) toxicity. Am. Ind. Hyg. Assoc. J., 25: 179-184.

SHARONOVA, Z.V. & KRYZHANOVSKAYA, N.A. (1976) [Tolylene diisocyanate induced occupational liver pathology.] Gig. Tr. prof. Zabol., 11: 27-31 (in Russian).

SHARONOVA, Z.V., PENKNOVICH, A.A., DOROFEEVA, E.D., KRYZHANOVSKAYA, N.A., MELNIKOVA, N.D., VOLKOVA, I.D., GOLOVA, I.A., ARZYAEVA, E.YA., KLIMOVA, E.I., & MAZE, E.N. (1982) [Changes in the cardiovascular system of workers engaged in the manufacture of toluyene diisocyanate.] Gig. Tr. prof. Zabol., 1: 16-19 (in Russian).

SITTIG, M. (1979) Isocyanates. In: Hazardous and toxic effects of industrial chemicals, Park Ridge, New Jersey, Noyes Data Corporation, pp. 266-277.

SITTIG, M. (1981) Handbook of toxic and hazardous chemicals, Park Ridge, New Jersey, Noyes Publications, pp. 664-665.

SMITH, A.B., BROOKS, S.M., BLANCHARD, J., BERNSTEIN, I.L.L., & GALLAGHER, J. (1980) Absense of airway hyperreactivity to methacholine in a worker sensitized to toluene diisocyanate (TDI). J. occup. Med., 22: 327-331.

STEINMETZ, P.R., AL-AWQATI, Q., & LAWTON, W.J. (1976) Specialty rounds. Nephrology rounds. University of Iowa

Hospitals: renal tubular acidosis. Am. J. med. Sci., 271(1): 40-54.

STYLES, J.A. (1978) Appendix III. Mammalian cell transformation in vitro. Br. J. Cancer, 37: 931-936.

SWENSSON, A., HOLMQUIST, C.-E., & LUNDGREN, K.-D. (1955) Injury to the respiratory tract by isocyanates used in making lacquers. Br. J. ind. Med., 12: 50-53.

TANAKA, K.-I. (1979) [On the induction of contact sensitivity by tolylene diisocyanate (TDI) in mice.] Jpn. J. ind. Health, 21: 456-457 (in Japanese).

TANAKA, K.-I., OKAMOTO, Y., TAKEOKA, A., & INO, T. (1984) [Nasal allergy observed in an asthma model by toluene diisocyanate.] Jpn. J. Allergol., 33(4): 199-206 (in Japanese).

TED TSE, C.S. & PESCE, A.J. (1979) Chemical characterization of isocyanate-protein conjugates. Toxicol. appl. Pharmacol., 51: 39-46.

THURMAN, G.B., SIMMS, B.G., & GOLDSTEIN, A.L. (1978) The effects of organic compounds used in the manufacture of plastics on the responsivity of murine and human lymphocytes. Toxicol. appl. Pharmacol., 44: 617-641.

TUCKER, S.P. & ARNOLD, J.E. (1982) Sampling and determination of 2,4-Bis (carbonylamino)toluene and 4,4'-bis(carbonylamino)diphenylmethane in air. Anal. Chem., 54: 1137-1141.

TWE, J. & WOLD, F. (1973) Butyl isocyanate, an active-site-specific reagent for yeast alcohol dehydrogenase. Biochemistry, 12(3): 381-386.

ULRICH, H. (1983) Urethane polymers. In: Kirk-Othmer encyclopedia of chemical technology, 3rd ed., New York, John Wiley and Sons, Vol. 23, pp. 576-608.

US EPA (1984) Toluene diisocyanates (TDI) 584-84-9; 91-08-7; 26471-62-5; 1321-38-6, Washington DC, US Environmental Protection Agency (Chemical Hazard Information Profile Report).

US ITC (1985) Preliminary report on US production of selected synthetic organic chemicals. Imports, exports and sales, Washington DC, US International Trade Commission.

WALKER, R.F. & PINCHES, M.A. (1981) Chemical interference effects in the measurement of atmospheric toluene diisocyanate

concentrations when sampling with an impregnated paper tape. Am. Ind. Hyg. Assoc. J., 42: 392-397.

WALWORTH, H.T. & VIRCHOW, W.E. (1959) Industrial hygiene experiences with toluene diisocyanate. Am. Ind. Hyg. Assoc. J., 20: 205-210.

WARWICK, C.J., BAGON, D.A., & PURNELL, C.J. (1981) Application of electrochemical detection to the measurement of free monomeric aromatic and aliphatic isocyanates in air by high-performance liquid chromatography. Analyst, 106: 676-685.

WEGMAN, D.H., PAGNOTTO, L.D., FINE, L.J., & PETERS, J.M. (1974) ' dose-response relationship in TDI workers. J. occup. Med., 1 258-260.

WEGMAN, D.H. PETERS, J.M., PAGNOTTO, L.D., & FINE, L.J. (1977) Chroni. pulmonary function loss from exposure to toluene diisocyanate. Br. J. ind. Med., 34: 195-200.

WEILL, H., SALVAGGIO, J., NEILSON, A., BUTCHER, B., & ZISKIND, . (1975) Respiratory effects in toluene diisocyanate manufacture: a multidisciplinary approach. Environ. Health Perspect., 11: 101-108.

WEILL, H., BUTCHER, B., DIEM, J.E., ET AL. (1979) Respiratory and immunologic evaluation of isocyanate exposure in a new manufacturing plant, Cincinnati, Ohio, US National Institute for Occupational Safety and Health (Final Report, NIOSH Contract No. 210-75-006).

WEYEL, D.A., RODNEY, B.S., & ALARIE, Y. (1982) Sensory irritation, pulmonary irritation, and acute lethality of a polymeric isocyanate and sensory irritation of 2,6-toluene diisocyanate. Toxicol. appl. Pharmacol., 64: 423-430.

WHITE, W.G., MORRIS, M.J., SUGDEN, E., & ZAPATA E. (1980) Isocyanate-induced asthma in a car factory. Lancet, 1(8171): 756-760.

WINDHOLZ, M., ed. (1983) The Merck Index: an encyclopedia of chemicals and drugs, 10th ed., Rahway, New Jersey, Merck and Company, p. 1363.

WOOLRICH, P.F. (1982) Toxicology, industrial hygiene and medical control of TDI, MDI and PMPPI. Am. Ind. Hyg. Assoc. J., 43(1): 89-97.

WOOLRICH, P.F. & RYE, W.A. (1969) Urethanes. Engineering, medical control and toxicologic consideration. J. occup. Med., 11(4): 184-190.

ZAPP, J.A., Jr (1957) Hazards of isocyanates in polyurethane foam plastic production. Arch. ind. Health, 15(4): 324-330.

WHO publications may be obtained, direct or through booksellers, from:

ALGERIA: Entreprise nationale du Livre (ENAL), 3 bd Zirout Youcef, ALGIERS

ARGENTINA: Carlos Hirsch, SRL, Florida 165, Galerías Güemes, Escritorio 453/465, BUENOS AIRES

AUSTRALIA: Hunter Publications, 58A Gipps Street, COLLINGWOOD, VIC 3066 — Australian Government Publishing Service *(Mail order sales)*, P.O. Box 84, CANBERRA A.C.T. 2601; *or over the counter from*: Australian Government Publishing Service Bookshops *at*: 70 Alinga Street, CANBERRA CITY A.C.T. 2600; 294 Adelaide Street, BRISBANE, Queensland 4000; 347 Swanston Street, MELBOURNE, VIC 3000; 309 Pitt Street, SYDNEY, N.S.W. 2000; Mt Newman House, 200 St. George's Terrace, PERTH, WA 6000; Industry House, 12 Pirie Street, ADELAID, SA 5000; 156–162 Macquarie Street, HOBART, TAS 7000 — R. Hill & Son Ltd., 608 St. Kilda Road, MELBOURNE, VIC 3004; Lawson House, 10–12 Clark Street, CROW'S NEST, NSW 2065

AUSTRIA: Gerold & Co., Graben 31, 1011 VIENNA I

BANGLADESH: The WHO Representative, G.P.O. Box 250, DHAKA 5

BELGIUM: *For books:* Office International de Librairie s.a., avenue Marnix 30, 1050 BRUSSELS. *For periodicals and subscriptions:* Office International des Périodiques, avenue Louise 485, 1050 BRUSSELS — *Subscriptions to World Health only:* Jean de Lannoy, 202 avenue du Roi, 1060 BRUSSELS

BHUTAN: *see* India, WHO Regional Office

BOTSWANA: Botsalo Books (Pty) Ltd., P.O. Box 1532, GABORONE

BRAZIL: Centro Latinoamericano de Informação em Ciencias de Saúde (BIREME), Organização Panamericana de Saúde, Sector de Publicações, C.P. 20381 - Rua Botucatu 862, 04023 SÃO PAULO, SP

BURMA: *see* India, WHO Regional Office

CANADA: Canadian Public Health Association, 1335 Carling Avenue, Suite 210, OTTAWA, Ont. K1Z 8N8. (Tel: (613) 725–3769. Telex: 21–053–3841)

CHINA: China National Publications Import & Export Corporation, P.O. Box 88, BEIJING (PEKING)

DEMOCRATIC PEOPLE'S REPUBLIC OF KOREA: *see* India, WHO Regional Office

DENMARK: Munksgaard Export and Subscription Service, Nørre Søgade 35, 1370 COPENHAGEN K (Tel: + 45 1 12 85 70)

FIJI: The WHO Representative, P.O. Box 113, SUVA

FINLAND: Akateeminen Kirjakauppa, Keskuskatu 2, 00101 HELSINKI 10

FRANCE: Librairie Arnette, 2 rue Casimir-Delavigne, 75006 PARIS

GERMAN DEMOCRATIC REPUBLIC: Buchhaus Leipzig, Postfach 140, 701 LEIPZIG

GERMANY FEDERAL REPUBLIC OF: Govi-Verlag GmbH, Ginnheimerstrasse 20, Postfach 5360, 6236 ESCHBORN — Buchhandlung Alexander Horn, Friedrichstrasse 39, Postfach 3340, 6200 WIESBADEN

GHANA: Fides Enterprises, P.O. Box 1628, ACCRA

GREECE: G.C. Eleftheroudakis S.A., Librairie internationale, rue Nikis 4, ATHENS (T. 126)

HONG KONG: Hong Kong Government Information Services, Beaconsfield House, 6th Floor, Queen's Road, Central, VICTORIA

HUNGARY: Kultura, P.O.B. 149, BUDAPEST 62

INDIA: WHO Regional Office for South-East Asia, World Health House, Indraprastha Estate, Mahatma Gandhi Road, NEW DELHI 110002

INDONESIA: P.T. Kalman Media Pusaka, Pusat Perdagangan Senen, Block I, 4th Floor, P.O. Box 3433/Jkt, JAKARTA

IRAN (ISLAMIC REPUBLIC OF): Iran University Press, 85 Park Avenue, P.O. Box 54/551, TEHERAN

IRELAND: TDC Publishers, 12 North Frederick Street, DUBLIN 1 (Tel: 744835–749677)

ISRAEL: Heiliger & Co., 3 Nathan Strauss Street, JERUSALEM 94227

ITALY: Edizioni Minerva Medica, Corso Bramante 83–85, 10126 TURIN; Via Lamarmora 3, 20100 MILAN; Via Spallanzani 9, 00161 ROME

JAPAN: Maruzen Co. Ltd., P.O. Box 5050, TOKYO International, 100–31

JORDAN: Jordan Book Centre Co. Ltd., University Street, P.O. Box 301 (Al-Jubeiha), AMMAN

KUWAIT: The Kuwait Bookshops Co. Ltd., Thunayan Al-Ghanem Bldg, P.O. Box 2942, KUWAIT

LAO PEOPLE'S DEMOCRATIC REPUBLIC: The WHO Representative, P.O. Box 343, VIENTIANE

LUXEMBOURG: Librairie du Centre, 49 bd Royal, LUXEMBOURG

MALAWI: Malawi Book Service, P.O. Box 30044, Chichiti, BLANTYRE 3

WHO publications may be obtained, direct or through booksellers, from:

MALAYSIA: The WHO Representative, Room 1004, 10th Floor, Wisma Lim Foo Yong (formerly Fitzpatrick's Building), Jalan Raja Chulan, KUALA LUMPUR 05-10; P.O. Box 2550, KUALA LUMPUR 01-02; Parry's Book Center, 124-1 Jalan Tun Sambanthan, P.O. Box 10960, 50730 KUALA LUMPUR

MALDIVES: *See* India, WHO Regional Office

MEXICO: Libreria Internacional, S.A. de C.V., Av. Sonora 206, 06100-MEXICO, D.F.

MONGOLIA: *see* India, WHO Regional Office

MOROCCO: Editions La Porte, 281 avenue Mohammed V, RABAT

NEPAL: *see* India, WHO Regional Office

NETHERLANDS: Medical Books Europe BV, Noorderwal 38, 7241 BL LOCHEM

NEW ZEALAND: New Zealand Government Printing Office, Publishing Administration, Private Bag, WELLINGTON; Walter Street, WELLINGTON; World Trade Building, Cubacade, Cuba Street, WELLINGTON. *Government Bookshops at*: Hannaford Burton Building, Rutland Street, Private Bag, AUCKLAND; 159 Hereford Street, Private Bag, CHRISTCHURCH; Alexandra Street, P.O. Box 857, HAMILTON; T & G Building, Princes Street, P.O. Box 1104, DUNEDIN — R. Hill & Son Ltd, Ideal House, Car Gillies Avenue & Edee Street, Newmarket, AUCKLAND 1

NORWAY: Tanum — Karl Johan A.S., P.O. Box 1177, Sentrum, N-0107 OSLO 1

PAKISTAN: Mirza Book Agency, 65 Shahrah-E-Quaid-E-Azam, P.O. Box 729, LAHORE 3

PAPUA NEW GUINEA: The WHO Representative, P.O. Box 646, KONEDOBU

PHILIPPINES: World Health Organization, Regional Office for the Western Pacific, P.O. Box 2932, MANILA

PORTUGAL: Livraria Rodrigues, 186 Rua do Ouro, LISBON 2

REPUBLIC OF KOREA: The WHO Representative, Central P.O. Box 580, SEOUL

SINGAPORE: The WHO Representative, 144 Moulmein Road, SINGAPORE 1130; Newton P.O. Box 31, SINGAPORE 9122

SOUTH AFRICA: *Contact major book stores*

SPAIN: Ministerio de Sanidad y Consumo, Centro de publicaciones, Documentación y Biblioteca, Paseo del Prado 18, 28014 MADRID — Comercial Atheneum S.A., Consejo de Ciento 130-136, 08015 BARCELONA; General Moscardó 29, MADRID 20 — Librería Internacional de Summa, P.O. Box 6050, 28006 MADRID; Balmes 417 y 419, 08022 BARCELONA

SRI LANKA: *see* India, WHO Regional Office

SWEDEN: *For books*: Aktiebolaget C.E. Fritzes Kungl. Hovbokhandel, Regeringsgatan 12, 103 27 STOCKHOLM. *For periodicals*: Wennergren-Williams AB, Box 30004, 104 25 STOCKHOLM

SWITZERLAND: Medizinischer Verlag Hans Huber, Länggassstrasse 76, 3012 BERN 9

THAILAND: *see* India, WHO Regional Office

UNITED KINGDOM: H.M. Stationery Office, 49 High Holborn, LONDON WC1V 6HB; 13a Castle Street, EDINBURGH EH2 3AR; 80 Chichester Street, BELFAST BT1 4JY; Brazennose Street, MANCHESTER M60 8AS; 258 Broad Street, BIRMINGHAM B1 2HE; Southey House, Wine Street, BRISTOL BS1 2BQ. *All mail orders should be sent to*: HMSO Publications Centre, 51 Nine Elms Lane, LONDON SW8 5DR

UNITED STATES OF AMERICA: *Copies of individual publications (not subscriptions)*: WHO Publications Center USA, 49 Sheridan Avenue, ALBANY, NY 12210. *Subscription orders and correspondence concerning subscriptions should be addressed to the* World Health Organization, Distribution and Sales, 1211 GENEVA 27, Switzerland. *Publications are also available from the* United Nations Bookshop, NEW YORK, NY 10017 *(retail only)*

USSR: *For readers in the USSR acquiring Russian editions*: Komsomolskij prospekt 18, Mezhdunarodnaja Kniga, MOSCOW — *For readers outside the USSR acquiring Russian editions*: Kuznetskij most 18, Mezhdunarodnaja Kniga, MOSCOW G-200

VENEZUELA: Libreria Medica Paris, Apartado 60.681, CARACAS 106

YUGOSLAVIA: Jugoslavenska Knjiga, Terazije 27/II, 11000 BELGRADE

Special terms for developing countries are obtainable on application to the WHO Representatives or WHO Regional Offices listed above or to the World Health Organization, Distribution and Sales Service, 1211 Geneva 27, Switzerland. Orders from countries where sales agents have not yet been appointed may also be sent to the Geneva address, but must be paid for in pounds sterling, US dollars, or Swiss francs. Unesco book coupons may also be used. Prices are subject to change without notice.

Price: Sw.fr. 9.—

ISBN 92 4 154275 6