Acute Exposure Guideline Levels for Selected Airborne Chemicals

Volume 4

Subcommittee on Acute Exposure Guideline Levels

Committee on Toxicology

Board on Environmental Studies and Toxicology

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Preface

Extremely hazardous substances (EHSs)[1] can be released accidentally as a result of chemical spills, industrial explosions, fires, or accidents involving railroad cars and trucks transporting EHSs. The people in communities surrounding industrial facilities where EHSs are manufactured, used, or stored and in communities along the nation's railways and highways potentially are at risk of being exposed to airborne EHSs during accidental releases. Pursuant to the Superfund Amendments and Reauthorization Act of 1986, the U.S. Environmental Protection Agency (EPA) has identified approximately 400 EHSs on the basis of acute lethality data in rodents.

As part of its efforts to develop acute exposure guideline levels for EHSs, EPA and the Agency for Toxic Substances and Disease Registry (ATSDR) in 1991 requested that the National Research Council (NRC) develop guidelines for establishing such levels. In response to that request, the NRC published *Guidelines for Developing Community Emergency Exposure Levels for Hazardous Substances* in 1993.

Using the 1993 NRC guidelines report, the National Advisory Committee (NAC) on Acute Exposure Guideline Levels for Hazardous Substances —consisting of members from EPA, the Department of Defense (DOD), the Department of Energy (DOE), the Department of Transportation, other federal and state governments, the chemical industry, academe, and other

[1]As defined pursuant to the Superfund Amendments and Reauthorization Act of 1986.

organizations from the private sector—has developed acute exposure guideline levels (AEGLs) for approximately 80 EHSs.

In 1998, EPA and DOD requested that the NRC independently review the AEGLs developed by NAC. In response to that request, the NRC organized within its Committee on Toxicology the Subcommittee on Acute Exposure Guideline Levels, which prepared this report. This report is the fourth volume in the series *Acute Exposure Guideline Levels for Selected Airborne Chemicals*. It reviews the AEGLs for chlorine, hydrogen chloride, hydrogen fluoride, toluene 2,4- and 2,6-diisocyanate, and uranium hexafluoride for scientific accuracy, completeness, and consistency with the NRC guideline reports.

This report was reviewed in draft by individuals selected for their diverse perspectives and technical expertise, in accordance with procedures approved by the NRC's Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published report as sound as possible and to ensure that the report meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process. We wish to thank the following individuals for their review of this report: David H. Moore of Battelle Memorial Institute; Sam Kacew of University of Ottawa; and Rakesh Dixit of Merck and Company, Inc.

Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations nor did they see the final draft of the report before its release. The review of this report was overseen by Janice E. Chambers of Mississippi State University, appointed by the Division on Earth and Life Studies, who was responsible for making certain that an independent examination of this report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the authoring committee and the institution.

The subcommittee gratefully acknowledges the valuable assistance provided by the following people: Ernest Falke and Paul Tobin, EPA; George Rusch, Honeywell, Inc.; Sylvia Talmage, Cheryl Bast, and Carol Wood, Oak Ridge National Laboratory; and Aida Neel, senior project assistant for the Board on Environmental Studies and Toxicology. Kelly Clark edited the report. We are grateful to James J. Reisa, director of the Board on Environmental Studies and Toxicology, for his helpful comments. The subcommittee particularly acknowledges Kulbir Bakshi, project director for

the subcommittee, for bringing the report to completion. Finally, we would like to thank all members of the subcommittee for their expertise and dedicated effort throughout the development of this report.

Daniel Krewski, *Chair*
Subcommittee on Acute Exposure
Guideline Levels

Bailus Walker, *Chair*
Committee on Toxicology

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Acute Exposure Guideline Levels for Selected Airborne Chemicals

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Introduction

This report is the fourth volume in the series *Acute Exposure Guideline Levels for Selected Airborne Chemicals.*

In the Bhopal disaster of 1984, approximately 2,000 residents living near a chemical plant were killed and 20,000 more suffered irreversible damage to their eyes and lungs following accidental release of methyl isocyanate. The toll was particularly high because the community had little idea what chemicals were being used at the plant, how dangerous they might be, and what steps to take in case of emergency. This tragedy served to focus international attention on the need for governments to identify hazardous substances and to assist local communities in planning how to deal with emergency exposures.

In the United States, the Superfund Amendments and Reauthorization Act (SARA) of 1986 required that the U.S. Environmental Protection Agency (EPA) identify extremely hazardous substances (EHSs) and, in cooperation with the Federal Emergency Management Agency and the Department of Transportation, assist Local Emergency Planning Committees (LEPCs) by providing guidance for conducting health-hazard assessments for the development of emergency-response plans for sites where EHSs are produced, stored, transported, or used. SARA also required that the Agency for Toxic Substances and Disease Registry (ATSDR) determine whether chemical substances identified at hazardous waste sites or in the environment present a public-health concern.

As a first step in assisting the LEPCs, EPA identified approximately 400 EHSs largely on the basis of their immediately dangerous to life and health (IDLH) values developed by the National Institute for Occupational Safety and Health (NIOSH) in experimental animals. Although several public and private groups, such as the Occupational Safety and Health Administration (OSHA) and the American Conference of Governmental Industrial Hygienists (ACGIH), have established exposure limits for some substances and some exposures (e.g., workplace or ambient air quality), these limits are not easily or directly translated into emergency exposure limits for exposures at high levels but of short duration, usually less than 1 h, and only once in a lifetime for the general population, which includes infants (from birth to 3 years of age), children, the elderly, and persons with diseases, such as asthma or heart disease.

The National Research Council (NRC) Committee on Toxicology (COT) has published many reports on emergency exposure guidance levels and spacecraft maximum allowable concentrations for chemicals used by the Department of Defense (DOD) and the National Aeronautics and Space Administration (NASA) (NRC 1968, 1972, 1984a,b,c,d, 1985a,b, 1986a,b, 1987, 1988, 1994, 1996a,b, 2000). COT has also published guidelines for developing emergency exposure guidance levels for military personnel and for astronauts (NRC 1986b, 1992). Because of COT's experience in recommending emergency exposure levels for short-term exposures, in 1991 EPA and ATSDR requested that COT develop criteria and methods for developing emergency exposure levels for EHSs for the general population. In response to that request, the NRC assigned this project to the COT Subcommittee on Guidelines for Developing Community Emergency Exposure Levels for Hazardous Substances. The report of that subcommittee, *Guidelines for Developing Community Emergency Exposure Levels for Hazardous Substances* (NRC 1993), provides step-by-step guidance for setting emergency exposure levels for EHSs. Guidance is given on what data are needed, what data are available, how to evaluate the data, and how to present the results.

In November1995, the National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances (NAC)[1] was established to identify, review, and interpret relevant toxicologic and other scientific data and to develop acute exposure guideline levels (AEGLs) for high-priority, acutely toxic chemicals. The NRC's previous name for acute exposure levels—community emergency exposure levels (CEELs)—was re-

[1]NAC is composed of members from EPA, DOD, many other federal and state agencies, industry, academe, and other organizations. The roster of NAC is shown on page 8.

placed by "AEGLs" to reflect the broad application of these values to planning, response, and prevention in the community, the workplace, transportation, the military, and the remediation of Superfund sites.

AEGLs represent threshold exposure limits (exposure levels below which adverse health effects are not likely to occur) for the general public and are applicable to emergency exposures ranging from 10 min to 8 h. Three levels—AEGL-1, AEGL-2, and AEGL-3—are developed for each of five exposure periods (10 min, 30 min, 1 h, 4 h, and 8 h) and are distinguished by varying degrees of severity of toxic effects. The three AEGLs are defined as follows:

> AEGL-1 is the airborne concentration (expressed as ppm [parts per million] or mg/m^3 [milligrams per cubic meter]) of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic nonsensory effects. However, the effects are not disabling and are transient and reversible upon cessation of exposure.
>
> AEGL-2 is the airborne concentration (expressed as ppm or mg/m^3) of a substance above which it is predicted that the general population, including susceptible individuals, could experience irreversible or other serious, long-lasting adverse health effects or an impaired ability to escape.
>
> AEGL-3 is the airborne concentration (expressed as ppm or mg/m^3) of a substance above which it is predicted that the general population, including susceptible individuals, could experience life-threatening adverse health effects or death.

Airborne concentrations below AEGL-1 represent exposure levels that can produce mild and progressively increasing but transient and nondisabling odor, taste, and sensory irritation or certain asymptomatic, nonsensory adverse effects. With increasing airborne concentrations above each AEGL, there is a progressive increase in the likelihood of occurrence and the severity of effects described for each corresponding AEGL. Although the AEGL values represent threshold levels for the general public, including susceptible subpopulations, such as infants, children, the elderly, persons with asthma, and those with other illnesses, it is recognized that individuals, subject to unique or idiosyncratic responses, could experience the effects described at concentrations below the corresponding AEGL.

SUMMARY OF REPORT ON GUIDELINES FOR DEVELOPING AEGLS

As described in the *Guidelines for Developing Community Emergency Exposure Levels for Hazardous Substances* (NRC 1993) and the NAC guidelines report *Standing Operating Procedures on Acute Exposure Guideline Levels for Hazardous Substances*(NRC 2001), the first step in establishing AEGLs for a chemical is to collect and review all relevant published and unpublished information available on that chemical. Various types of evidence are assessed in establishing AEGL values for a chemical. They include information from (1) chemical-physical characterizations, (2) structure-activity relationships, (3) in vitro toxicity studies, (4) animal toxicity studies, (5) controlled human studies, (6) observations of humans involved in chemical accidents, and (7) epidemiologic studies. Toxicity data from human studies are most applicable and are used when available in preference to data from animal studies and in vitro studies. Toxicity data from inhalation exposures are most useful for setting AEGLs for airborne chemicals because inhalation is the most likely route of exposure and because extrapolation of data from other routes would lead to additional uncertainty in the AEGL estimate.

For most chemicals, actual human toxicity data are not available or critical information on exposure is lacking, so toxicity data from studies conducted in laboratory animals are extrapolated to estimate the potential toxicity in humans. Such extrapolation requires experienced scientific judgment. The toxicity data from animal species most representative of humans in terms of pharmacodynamic and pharmacokinetic properties are used for determining AEGLs. If data are not available on the species that best represents humans, the data from the most sensitive animal species are used to set AEGLs. Uncertainty factors are commonly used when animal data are used to estimate risk levels for humans. The magnitude of uncertainty factors depends on the quality of the animal data used to determine the no-observed-adverse-effect level (NOAEL) and the mode of action of the substance in question. When available, pharmacokinetic data on tissue doses are considered for interspecies extrapolation.

For substances that affect several organ systems or have multiple effects, all end points, including reproductive (in both genders), developmental, neurotoxic, respiratory, and other organ-related effects, are evaluated, the most important or most sensitive effect receiving the greatest attention. For carcinogenic chemicals, excess carcinogenic risk is estimated, and the AEGLs corresponding to carcinogenic risks of 1 in 10,000 (1×10^{-4}), 1 in

100,000 (1×10^{-5}), and 1 in 1,000,000 (1×10^{-6}) exposed persons are estimated.

REVIEW OF AEGL REPORTS

As NAC began developing chemical-specific AEGL reports, EPA and DOD asked the NRC to review independently the NAC reports for their scientific validity, completeness, and consistency with the NRC guideline reports (NRC 1993, 2001). The NRC assigned this project to the COT Subcommittee on Acute Exposure Guideline Levels. The subcommittee has expertise in toxicology, epidemiology, pharmacology, medicine, industrial hygiene, biostatistics, risk assessment, and risk communication.

The AEGL draft reports are initially prepared by ad hoc AEGL Development Teams consisting of a chemical manager, two chemical reviewers, and a staff scientist of the NAC contractor—Oak Ridge National Laboratory. The draft documents are then reviewed by NAC and elevated from "draft" to "proposed" status. After the AEGL documents are approved by NAC, they are published in the *Federal Register* for public comment. The reports are then revised by NAC in response to the public comments, elevated from "proposed" to "interim" status, and sent to the NRC Subcommittee on Acute Exposure Guideline Levels for final evaluation.

The NRC subcommittee's review of the AEGL reports prepared by NAC and its contractors involves oral and written presentations to the subcommittee by the authors of the reports. The NRC subcommittee provides advice and recommendations for revisions to ensure scientific validity and consistency with the NRC guideline reports (NRC 1993, 2001). The revised reports are presented at subsequent meetings until the subcommittee is satisfied with the reviews.

Because of the enormous amount of data presented in the AEGL reports, the NRC subcommittee cannot verify all the data used by NAC. The NRC subcommittee relies on NAC for the accuracy and completeness of the toxicity data cited in the AEGLs reports.

This report is the fourth volume in the series *Acute Exposure Guideline Levels for Selected Airborne Chemicals*. AEGL documents for chlorine, hydrogen chloride, hydrogen fluoride, toluene 2,4- and 2,6-diisocyanate, and uranium hexafluoride are published as an appendix to this report. The subcommittee concludes that the AEGLs developed in those documents are scientifically valid conclusions based on the data reviewed by NAC and are consistent with the NRC guideline reports. AEGL reports for additional chemicals will be presented in subsequent volumes.

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Appendixes

4

Toluene 2,4- and 2,6-Diisocyanate[1]

Acute Exposure Guideline Levels

SUMMARY

Toluene diisocyanate (TDI) is among a group of chemicals, the isocyanates, that are highly reactive compounds containing an ⁻NCO group. TDI exists as both the 2,4- and 2,6- isomers, which are available commercially, usually in ratios of 65:35 or 80:20 (Karol 1986; WHO 1987). TDI has been used in the manufacture of polyurethane foam products as well as paints, varnishes, elastomers, and coatings (WHO 1987).

Inhaled TDI causes irritation and sensitization of the respiratory tract. Sensitization may occur from either repeated exposure over a relatively long

[1]This document was prepared by the AEGL Development Team comprising Carol Wood (Oak Ridge National Laboratory) and National Advisory Committee (NAC) on Acute Exposure Guideline Levels for Hazardous Substances member Steven Barbee (Chemical Manager). The NAC reviewed and revised the document and AEGL values as deemed necessary. Both the document and the AEGL values were then reviewed by the National Research Council (NRC) Subcommittee on Acute Exposure Guideline Levels. The NRC subcommittee concludes that the AEGLs developed in this document are scientifically valid conclusions on the basis of the data reviewed by the NRC and are consistent with the NRC guidelines reports (NRC 1993, 2001).

period of time (i.e., years), or it may consist of an induction phase precipitated by a relatively high concentration followed by a challenge phase in which sensitized individuals react to extremely low concentrations of TDI. Only irritation effects were considered in establishing AEGL values, because sensitized individuals are considered to be hypersusceptible. Although individuals with existing TDI sensitization are present in the general population, that presensitization cannot be estimated. If the number of individuals sensitized to TDI in the general population were quantifiable, a different approach to derivation of AEGL values might have been considered. At any of the AEGL levels, there might be individuals who have a strong reaction to TDI, and those individuals might not be protected within the definition of effects for each level.

Human data were available for the derivation of AEGL-1 and AEGL-2. Fifteen asthmatic subjects were exposed to TDI at 0.01 parts per million (ppm) for 1 hour (h), and then after a rest of 45 minutes (min), they were exposed at 0.02 ppm for 1 h. A nonasthmatic referent group of 10 individuals was exposed at 0.02 ppm for 2 h (Baur 1985). None of the individuals had a history of isocyanate exposure, and the asthmatic subjects were not sensitized to TDI. Although no statistically significant differences in lung function parameters were observed among asthmatic subjects during or after exposure, nonpathological bronchial obstruction was indicated in several individuals. In the referent group, there was a significant increase in airway resistance immediately and at 30 min after the initiation of exposure, but none of the subjects developed bronchial obstruction. Both groups reported eye and throat irritation, cough, chest tightness, rhinitis, dyspnea, and/or headache, but time to onset of symptoms was not given. There was also no indication whether symptoms were more severe in asthmatic subjects that inhaled 0.01 or 0.02 ppm. Therefore, the 0.02-ppm concentration was identified as the basis for the 10-min, 30-min, and 1-h AEGL-1 values. The 0.01-ppm concentration was identified as the basis for the 4- and 8-h AEGL-1 values. It should be noted that the AEGL-1 values are below a reported odor detection threshold of 0.05 ppm (Henschler et al. 1962).

Derivation of AEGL-2 was based on human data. Exposure of volunteers to TDI at 0.5 ppm for 30 min resulted in severe eye and throat irritation and lacrimation (Henschler et al. 1962). A higher exposure concentration was intolerable. Extrapolations were made using the equation $C^n \times t = k$ (C = concentration, t = time, and k is a constant), where n ranges from 0.8 to 3.5 (ten Berge et al. 1986). In the absence of an empirically derived, chemical-specific exponent, scaling was performed using $n = 3$ for extrapolating to the 10-min time point and $n = 1$ for the 1-h and 4-h time points.

The 4-h value was used for the 8-h value, because extrapolation to 8 h resulted in a concentration similar to that shown to be tolerated for >7 h with only mild effects. An uncertainty factor (UF) of 3 was applied to account for sensitive individuals; use of a greater UF results in values below those supported by human data for AEGL-2 effects.

No human data were available for derivation of AEGL-3 values. Human fatalities attributed to TDI-induced chemical pneumonitis have occurred under unusual circumstances. Exposure concentrations in those accidents were not measured. Therefore, animal data were used to derive AEGL-3 values. On the basis of LC_{50} values (concentrations lethal to 50% of subjects), the species most sensitive to the effects of TDI is the mouse. The 4-h mouse LC_{50} of 9.7 ppm (Duncan et al. 1962) was divided by 3 to estimate a threshold of lethality based on the regression plot of mortality vs concentration. This estimated 4-h lethality threshold was used to extrapolate to the 30-min and 1- and 8-h AEGL-3 time points. Values were scaled using the equation $C^n \times t = k$, where n ranges from 0.8 to 3.5 (ten Berge et al. 1986). In the absence of an empirically derived, chemical-specific exponent, scaling was performed using $n = 3$ for extrapolating to the 30-min and 1-h time points and $n = 1$ for the 8-h time point. A total UF of 10 was applied, which includes 3 to account for sensitive individuals and 3 for interspecies extrapolation (use of a greater UF would result in values below those supported by human data for AEGL-3 effects). According to Section 2.7 of the standing operating procedures for the derivation of AEGLs (NRC 2001), 10-min values are not to be scaled from an experimental exposure time of ≥4 h. Therefore, the 30-min AEGL-3 value was also adopted as the 10-min value.

1. INTRODUCTION

TDI is among a group of chemicals, the isocyanates, that are highly reactive compounds containing an -NCO group. TDI exists as both 2,4- and 2,6- isomers, which are available commercially, usually in ratios of 65:35 or 80:20 (Karol 1986; WHO 1987). An estimated 1,225 million pounds of TDI were produced in 2000, and greater than 90% was used in the manufacture of flexible urethane foams (CPS 2001). TDI is produced from the reaction of diaminotoluenes with phosgene in a closed system, and TDI has also been used in the manufacture of urethane paints, varnishes, elastomers, and coatings. The chemical may dimerize slowly at ambient temper-

TABLE 4-1 Summary of AEGLs Values for Toluene 2,4- and 2,6-Diisocyanate (ppm [mg/m^3])

Classification	10 min	30 min	1 h	4 h	8 h	End Point (Reference)
AEGL-1 (Nondisabling)	0.02 (0.14)	0.02 (0.14)	0.02 (0.14)	0.01 (0.07)	0.01 (0.07)	Chest tightness, eye and throat irritation (Baur 1985)
AEGL-2 (Disabling)	0.24 (1.71)	0.17 (1.21)	0.083 (0.59)	0.021 (0.15)	0.021 (0.15)	Severe eye and throat irritation, lacrimation (Henschler et al. 1962)
AEGL-3 (Lethal)	0.65 (4.63)	0.65 (4.63)	0.51 (3.63)	0.32 (2.28)	0.16 (0.93)	4-h LC_{50} in the mouse (Duncan et al. 1962)

Abbreviations: mg/m^3, milligrams per cubic meter; ppm, parts per million.

atures and more rapidly at higher temperatures, and trimerization occurs at 100-200°C (WHO 1987).

The odor threshold for 2,4- and 2,6-TDI was found to be 0.05 ppm (Henschler et al. 1962). In early human primary irritation testing with 2,4-TDI, 50% of subjects reported the least detectable odor at 0.4 ppm. Irritation of the nose and throat occurred at 0.5 ppm, and an appreciable odor was noted at 0.8 ppm (Zapp 1957; Wilson and Wilson 1959).

Toxicological effects to the respiratory tract from inhaled TDI may be divided into two distinct categories: (1) primary irritation and (2) immunologic hypersensitivity. The chemically reactive isocyanate group has been suggested as the cause of both effects. The primary irritation associated with inhaled TDI is a nonspecific inflammatory response characteristic of that produced by other primary irritants. Inflammation is also a consequence of sensitization, but it is caused by an immunologically mediated reaction leading to antibody formation (Karol 1986; WHO 1987), and that response is individual-specific. Sensitization consists of an induction phase precipitated by a relatively high concentration, followed by a challenge phase in which immunologically sensitized individuals react to extremely low concentrations of TDI that are, in some persons, below the current ACGIH Threshold Limit Value (TLV) of 5 ppb. Some studies showed detection of IgE antibodies in sensitized individuals, although others found variable or negative results (Karol 1986). IgG antibodies specific to TDI have been detected in both asymptomatic and symptomatic workers (Baur 1985). The immune-mediated inflammatory response of the respiratory

TABLE 4-2 Physicochemical Data for Toluene Diisocyanate

Parameter	Value	Reference
Synonyms	TDI; tolylene diisocyanate	Budavari et al. 1996
CAS registry no.	584-84-9 (2,4-TDI) 91-08-7 (2,6-TDI)	
Chemical formula	$C_9H_6N_2O_2$	Budavari et al. 1996
Molecular weight	174.16	Budavari et al. 1996
Physical state	Clear yellow liquid	Shiotsuka 1987b
Vapor pressure	0.011 mm Hg at 25°C 3.2 mm Hg at 100°C	Woolrich 1982
Vapor density (air = 1)	6.0	ACGIH 1991
Specific gravity	1.22 g/cm^3	Shiotsuka 1987b
Boiling/flash point	251°C/132°C (open cup)	ACGIH 1991
Solubility in water	Reacts with water	ACGIH 1991
Conversion factors	1 ppm = 7.12 mg/m^3 1 mg/m^3 = 0.14 ppm	Hartung 1994

tract has been characterized by persistent activation of lymphocytes, chronic expression of certain cytokines (Maestrelli et al. 1995), neutrophilia, eosinophilia (Fabbri et al. 1987), and decreased lymphocyte cAMP levels (Butcher et al. 1979).

The physicochemical properties of TDI are given in Table 4-2 (above).

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

Human fatalities from TDI exposure are not common. Accidents have involved unusual circumstances. TDI concentrations were not measured, and the isomer was not always identified. In one case, a worker was trapped in a room following the explosion of a storage vessel. The victim was unconscious for an unknown but extended exposure duration (Horspool and Doe 1977). A second report involved a salvage diver who was blowing polyurethane foam in the hold of a ship. When his air supply failed, he removed his mask and was exposed to an atmosphere containing a high (but

unknown) concentration of Freon and 2,4-TDI. The diver was unconscious and submerged in sea water when rescued. He died 4 days (d) later despite extensive resuscitative efforts (Linaweaver 1972). Deaths in both of those cases appeared to be due to pulmonary edema subsequent to chemical pneumonitis.

2.2. Nonlethal Toxicity

2.2.1. Case Reports

A 50-y-old male was drenched in TDI (isomer mixture not specified) when a hose detached from a tanker truck he was helping to unload. The individual had no history of respiratory illness, asthma, or allergic disease. Shortly after exposure, he developed shortness of breath, wheezing, and cough. Evaluation 12 y later showed persistent asthma and variable airway obstruction despite no further exposure to isocyanates. However, his asthma became more severe after exposure to other irritants in the workplace. An asthmatic attack was provoked by challenge with 10 ppb (71.2 $\mu g/m^3$) TDI for 8 min (Moller et al. 1986).

In contrast to the above report, TDI sensitivity was lost in a worker 11 months (mo) after removal from exposure, and nonspecific bronchial hyperresponsiveness resolved after 17 mo despite the continued presence of serum IgE antibodies (Butcher et al. 1982). The TDI isomer was not reported for either the occupational exposure or the experimental challenge testing.

Isocyanate vapor concentrations have been measured to estimate worker exposure during the spray application of polyurethane foam. Personal samplers were attached to the sprayers, but the exact location of the samplers (i.e., breathing zone) was not specified. Average exposure concentrations ranged from 0.021 ppm to 0.045 ppm, and exposure durations ranged from 105 min to 442 min. No head or eye protection was provided except for the voluntary use of plastic bags over the heads of the sprayers. Reddening of the eyes and lacrimation were observed in "numerous" workers during the course of the study (Hosein and Farkas 1981). This study neither identified the isocyanate isomers nor correlated the prevalence of clinical signs in the workers and the exposure concentrations and durations.

Case reports of TDI intoxication at 15 plants involved in polyurethane operations (most likely involving mixed isomers) were investigated by the Massachusetts Department of Labor and Industries (Elkins et al. 1962).

Workers complained of eye and throat irritation, tightness of the chest, nausea and vomiting, nonproductive cough, and restlessness despite the control of TDI vapor concentrations according to the standard in effect at that time. Milder effects were documented in plants with maximum workroom concentrations at 0.02 ppm, and more severe effects were documented in plants with maximum workroom concentrations at ≥0.07 ppm. The authors concluded that the maximum allowable concentration of 0.1 ppm was too high and recommended that a limit of 0.01 ppm be adopted. Current occupational exposure standards are given in Section 8.2 of this document.

Workers in a manufacturing plant involved in the production of isocyanate foam complained of coughing, sore throat, dyspnea, fatigue, and night sweats (Hama 1957). A change in the manufacturing process placed workers in a poorly ventilated room, which resulted in symptoms in 12 of 12 workers. Isocyanate concentrations (isomer not specified) ranging from 0.03 ppm to 0.07 ppm were measured in the room (assumed to be area samples). Following the return to previous manufacturing processes, no complaints or symptoms of exposure have occurred, and measured concentrations of isocyanates were found to be <0.03 ppm.

Seven men developed cough, dyspnea, chest pain, wheezing, and hemoptysis following exposure to a plastic varnish containing TDI (isomer not specified). Air samples taken in the work area—after temporary measures had been implemented to improve ventilation—contained 0.08 ppm to 0.1 ppm. Six of the seven individuals had varying degrees of respiratory impairment, as determined by timed vital capacity. Improvement was noted in five when reexamined at 2-2.5 mo after exposure (Maxon 1964).

2.2.2. Epidemiologic Studies

Numerous occupational studies have evaluated pulmonary function in workers exposed to TDI. However, most have failed to account for confounding factors such as smoking status, sampling methods that failed to detect and quantify both isomers, high rates of annual FEV_1 (forced expiratory volume in 1 second) decline in control populations, and high intra- and interindividual variation in lung-function testing (EPA 1996). A study by Diem et al. (1982, as cited in EPA 1996) accounted for those factors and followed TDI production workers prospectively over a 5-y period. Investigators identified two exposure groups, defined as low and high, with arithmetic mean concentrations for never-smokers of 0.9 ppb and 1.9 ppb (6.41 $\mu g/m^3$ and 13.53 $\mu g/m^3$), respectively. Never-smokers in the high TDI exposure category had a significant ($p \leq 0.001$) decline in FEV_1 and forced

expiratory flow at 25-75% when compared with never-smokers in the low-exposure category. Similar results in FEV_1 were found when the same groups were recategorized on the basis of time spent inhaling workplace air containing a concentration above 20 ppb (142.4 $\mu g/m^3$). The U.S. Environmental Protection Agency (EPA) (1996) used the Diem et al. (1982, as cited in EPA 1996) study to calculate a reference concentration (RfC) of 0.98×10^{-5} ppm. EPA (1996) concluded that "[a]lthough the mean exposure values determined in this study are close to the detection limit of the sampling and detection method, the values are considered accurate because they were obtained by continuous monitoring over the entire workday."

One of the largest occupational studies of polyurethane foam workers was conducted by Bugler et al. (1991). That 5-y study was designed to investigate the risk of sensitization to isocyanates and the longitudinal change in ventilatory capacity. Personal exposures were measured using modified MCM paper tape monitors. Low, intermediate, and high exposure groups were identified with average TDI exposures of 0.3, 0.6, and 1.2 ppb (2.14, 4.27, and 8.54 $\mu g/m^3$), respectively. There were no significant effects of exposure as measured by changes in the rate of decline in several parameters of pulmonary function. Over 5 y, the rate of sensitization among the original subjects was 3.1%, or 0.6% per year. Of note is the 4% rate of sensitization among new hires. Overall, in 47% of workers diagnosed, sensitization occurred after exposure to TDI concentrations less than 20 ppb (142.4 $\mu g/m^3$) (Bugler et al. 1991). A major problem with this study was that the limit of detection was only 4 ppb (28.48 $\mu g/m^3$), indicating that estimates of cumulative daily exposures were based on measurements below the limit of quantitation (Garabrant and Levine 1994).

A comprehensive review of the epidemiological studies on TDI was prepared by Garabrant and Levine (1994). Those authors concluded that respiratory sensitization occurs in less than 1% of subjects per year who are exposed to TDI at levels below 20 ppb (142 $\mu g/m^3$), and that sensitization is almost entirely attributable to short-term excursions above that level.

2.2.3. Experimental Studies

Provocative inhalation challenge tests using 2,4- and 2,6-TDI (80:20) were administered to 15 asthmatic subjects and 10 healthy controls (Baur 1985). None of the individuals had a history of isocyanate exposure, and the asthmatic subjects were not sensitized to TDI. All individuals classified as asthmatic had a history of asthmatic episodes and a significant response to acetylcholine challenge test. Asthmatic subjects were exposed to TDI at

0.01 ppm for 1 h, and then, after a rest of 45 min, they were exposed at 0.02 ppm (0.142 milligrams per cubic meter [mg/m^3]) for 1 h. Controls were exposed to TDI at 0.02 ppm for 2 h. In the control group, there was a statistically significant ($p \leq 0.05$) increase in airway resistance (R_{aw}) immediately after and 30 min after the beginning of exposure. For the asthmatic group, no statistically significant differences were observed from pretest group mean values for lung function parameters during or after exposure. However, eight of 15 individuals had an increase in R_{aw} of >50%, and four of those subjects had significant bronchial obstruction, which was defined as an increase in specific airway resistance of >50%. Specific airway resistance was calculated as the product of the R_{aw} multiplied by the intrathoracic gas volume. More important, among the asthmatics, no individual decrease in FEV_1 of more than 20% was observed. The increases in R_{aw} and decreases in FEV_1 are not considered pathologic for the asthmatic subjects because the changes were relatively minor and inconsistent within individuals. Individual values for R_{aw} and FEV_1 in several of the asthmatic subjects following TDI exposure are given in Table 4-3. Increases in R_{aw} did not correspond with decreases in FEV_1, and neither parameter could be used as an indication of reported discomfort. For example, individual 8 had the greatest increase in R_{aw} (3.2 times), but the FEV_1 showed essentially no decline (3.51 L vs 3.41 L). Individual 9 also showed no decline in FEV_1 (4.01 L vs 3.91 L) and had a 1.5-time increase in R_{aw}. Individual 5, who had the greatest decline in FEV_1, reported no symptoms of discomfort.

Five of the asthmatic individuals complained of chest tightness, rhinitis, cough, dyspnea, throat irritation, and/or headache during exposure; three controls reported eye irritation and/or cough. Some of the symptoms lasted for several hours post-exposure. The study author concluded that some people with pre-existing bronchial hyper-reactivity respond to TDI at or below the ACGIH short-term exposure limit (STEL = 0.02 ppm) (see Section 8.2) with bronchial obstruction (Baur 1985).

Henschler et al. (1962) exposed six healthy male volunteers to 2,4- and 2,6-TDI (65:35), 2,4-TDI, or 2,6-TDI at measured concentrations ranging from 0.01 ppm to 1.3 ppm for 30 min. The volunteers were exposed at all concentrations, but at only one concentration per day, and the concentrations were randomly selected. Volunteers had no prior knowledge of the isomer or concentration selected. The results are summarized in Table 4-4. The odor threshold was found to be 0.05 ppm. A concentration-dependent increase in sensory irritation was reported. There was slight eye and nose irritation at 0.1 ppm and marked discomfort at $\geq$0.5 ppm. 2,6-TDI appeared slightly more irritating than the 2,4- isomer, but was similar to the mixture.

TABLE 4-3 Increase in R_{aw} Compared with FEV_1 Following Exposure to Toluene Diisocyanate in Asthmatic Subjects

		FEV_1 (L)		
Individual	Maximum increase in R_{aw}	Before TDI Exposure	Lowest Value After TDI Exposure[a]	Symptoms
3	1.5×	3.0	2.5	Rhinitis, throat burning sensation, mild cough
5	2.0×	3.7	3.1	None
6	1.7×	4.8	4.4	Chest tightness
8	3.2×	3.5	3.4	Cough, chest tightness, dyspnea
9	1.5×	4.0	3.9	None

[a]None of the individuals experienced a >20% decline in FEV_1.
Source: Data from Baur 1985.

No adverse effects were reported in two healthy men exposed to 2,4- and 2,6-TDI (30:70) at up to 9.8 ppb (70 μg/m^3) for 4 h (Brorson et al. 1991) or in five healthy men exposed to 2,4- and 2,6-TDI (65:35) at 5.6 ppb (40 μg/m^3) for 7.5 h (Skarping et al. 1991). No further details of those studies were reported.

In 10 individuals with positive methacholine challenge tests, 2,4-TDI inhalation challenge testing at up to 20 ppb (142 μg/m^3) for 15 min resulted in no change in FEV_1 (Moller et al. 1986). No further details of this study were reported.

Four adults with occupational asthma associated with exposure to isocyanates were challenged with TDI (isomer not specified), and their responses were assessed (Vandenplas et al. 1993). The duration of work exposure ranged from 7 to 17 y, and the duration of symptoms ranged from 0.5 to 10 y. Subjects were exposed at varying concentrations (5, 10, 15, and 20 ppb [35.6, 71.2, 106.8, 142.4 μg/m^3]) for 1-90 min such that the $C \times t$ product remained constant. A positive asthmatic response was defined as a ≥20% drop in FEV_1. Although the effective $C \times t$ was highly variable between individuals (45-450 ppb·min), it remained constant for each person. Therefore, the authors concluded that both concentration and duration of exposure determined the occurrence of an asthmatic reaction in sensitized

TABLE 4-4 Effects of Controlled Inhalation Exposure to Toluene Diisocyanate in Volunteers[a]

Concentration (ppm)	Effect
0.01 or 0.02	2,4/2,6; 2,4; 2,6: no odor perception, no effects
0.05	2,4/2,6: odor noted immediately upon entering the room; after about 5 min of exposure, 3/6 volunteers experienced a slight "tingling" sensation of the eyes described as lacrimation urge without tears
	2,4: weak odor perception, no eye irritation
	2,6: odor was stronger as compared with the 2,4- isomer
0.075	2,6/2,4: odor became stronger; slight burning of the eyes occurred after 1-6 min, but there was no lacrimation; with deeper breaths, volunteers experienced tickling or a slight stabbing pain in the nose
0.08	2,4: slight conjunctival irritation and tickling of nose
	2,6: eye and nose irritation more severe as compared with same concentration of the 2,4- isomer; effects on throat were perceived as dryness, not scratching sensation
0.10	2,4/2,6: eye and nose irritation became more severe described as resembling a cold (catarrh)
	2,4: more pronounced conjunctival irritation and tickling of nose
	2,6: eye and nose irritation more severe as compared with same concentration of the 2,4- isomer; effects on throat were perceived as dryness, not scratching sensation
0.20	2,4: eye irritation was perceived by 2/5 as stinging and uncomfortable
	2,6: eye and nose irritation more severe as compared with same concentration of the 2,4- isomer; effects on throat were perceived as dryness, not scratching sensation
0.50	2,4/2,6: lacrimation, but eye irritation was still tolerable; one had copious nasal secretion that was associated with "stinging" nasal pain; all had scratchy and burning sensations in the throat, without cough
	2,4: eye irritation was perceived by all as stinging and uncomfortable with lacrimation
	2,6: effects similar to the 2,4- isomer
1.3	2,4/2,6: two individuals were able to remain in the room for 10 min; irritation was intolerable; several hours later, cold-like symptoms with cough persisted

[a]Six healthy male volunteers were exposed to one concentration per day in random order.
Source: data from Henschler et al. 1962.

individuals. This study group is considered a hypersusceptible population and was, therefore, not utilized in setting AEGL values.

Results of early human primary irritation testing with 2,4-TDI were summarized by Zapp (1957) and Wilson and Wilson (1959). Fifty percent of subjects reported the least detectable odor at 0.4 ppm, irritation of the nose and throat occurred at 0.5 ppm, and an appreciable odor was noted at 0.8 ppm. Exposure durations were not given.

2.3. Developmental and Reproductive Toxicity

No information was found regarding the potential developmental or reproductive toxicity of TDI in humans.

2.4. Genotoxicity

No information was found regarding the potential genotoxicity of TDI in humans.

2.5. Carcinogenicity

No information was found regarding the potential carcinogenicity of TDI in humans.

2.6. Summary

Fatalities have been reported following accidental exposures to high concentrations of TDI under unusual circumstances. Human responses to TDI were summarized by Woolrich (1982) from data on worker exposures, case reports, and experimental single exposure studies. Pulmonary effects after TDI inhalation may be either a direct irritant response or the result of an immunologic sensitivity that develops over time. Generally, exposure at $\leq$0.02 ppm does not elicit a response; however, asthmatic subjects may develop minor irritation and subclinical increases in R_{aw} at that concentration. At concentrations between 0.02 ppm and 0.1 ppm, a portion of the population may develop sensitivity with prolonged exposure. Exposure at >0.1 ppm causes irritation of the respiratory tract, and the severity is de-

pendent on the concentration (Woolrich 1982). It is important to note that the odor threshold of 0.05 ppm (Henschler et al. 1962) is approximately the same concentration that causes slight eye irritation. However, an older study reported 0.40 ppm as the least detectable odor in 50% of subjects (Wilson and Wilson 1959).

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

3.1.1. Guinea Pigs

A 4-h LC_{50} for the guinea pig was calculated to be 12.7 ppm. Exposures were by whole body and concentrations were measured at 0.1, 1.0, 2, 5, 10, 20, or 34 ppm. A total of 76 animals were used in the experiment (gender and number of animals not stated). Animals exhibited concentration-dependent signs of toxicity, such as mouth-breathing, lacrimation, profuse salivation, and restlessness, during exposure. At concentrations above 5 ppm, mouth-breathing was observed after 1 h of exposure. Histopathologic examinations of the respiratory tracts of five animals per group per time point revealed focal coagulation necrosis and desquamation of the superficial epithelial lining of the trachea and major bronchi. The degree of injury and subsequent repair was dependent on exposure concentration. Inflammation cleared by day 7 post-exposure in the 2-ppm group. Advanced bronchiolitis fibrosia obliterans and bronchopneumonia were evident at the higher concentrations. The specific TDI isomers studied were not identified (Duncan et al. 1962).

3.1.2. Rabbits

A 4-h LC_{50} for the rabbit was estimated to be 11 ppm. Exposures were by whole body and concentrations were measured at 0.1, 1.0, 2, 5, 10, 20, or 34 ppm. A total of 41 animals were used in the experiment (gender and numbers of animals not stated). Animals exhibited concentration-dependent signs of toxicity during exposure such as mouth-breathing, lacrimation, salivation, and restlessness. At concentrations above 5 ppm, mouth-breathing was observed after 1 h of exposure. Histopathologic examinations of

the respiratory tracts of two animals per group per time point revealed focal coagulation necrosis and desquamation of the superficial epithelial lining of the trachea and major bronchi. The degree of injury and subsequent repair was dependent on exposure concentration. Inflammation cleared by day 7 post-exposure in the 2-ppm group. Advanced bronchiolitis fibrosia obliterans and bronchopneumonia were evident at the higher concentrations. The specific TDI isomers studied were not identified (Duncan et al. 1962).

3.1.3. Rats

A 4-h LC_{50} for the rat was calculated to be 13.9 ppm. Exposures were by whole body and concentrations were measured at 0.1, 1.0, 2, 5, 10, 20, or 34 ppm. A total of 86 animals were used in the experiment (gender and numbers of animals not stated). Animals exhibited concentration-dependent signs of toxicity during exposure such as mouth-breathing, lacrimation, salivation, and restlessness. At concentrations above 5 ppm, mouth-breathing was observed after 1 h of exposure. Among surviving animals, histopathologic examination of the respiratory tracts of five animals per group per time point revealed focal coagulation necrosis and desquamation of the superficial epithelial lining of the trachea and major bronchi. The degree of injury and subsequent repair was dependent on exposure concentration. Inflammation cleared by day 7 post-exposure in the 2-ppm group, but advanced bronchiolitis fibrosia obliterans and bronchopneumonia were observed at higher concentrations. The TDI isomer mix was not specified (Duncan et al. 1962).

In contrast to the above report, Kimmerle (1976) calculated 4-h LC_{50}s for male and female Wistar II rats (n = 10/gender) to be 49.2 ppm and 50.6 ppm, respectively. Labored breathing was noted during the whole-body exposure, and lung edema and pneumonia were observed at necropsy. The TDI used was identified only by the trade name T 65. The results are higher than the 4-h LC_{50}s reported by Duncan et al. (1962).

A 1-h LC_{50} for Alderley Park male and female albino rats (n = 4/gender; whole-body exposure) was reported at 66 ppm for 2,4- and 2,6-TDI (80:20). No differences were observed between males and females, and most deaths occurred by 36 h post-exposure. At necropsy, all animals showed hemorrhagic edema in the lungs (Horspool and Doe 1977).

Albino rats were exposed by whole body for 6 h to analyzed concentrations of TDI at 2, 4, or 13.5 ppm (mixed isomer, ratio not specified). At

both the middle and high concentrations, three of six rats died, those deaths occurring by post-exposure days 7 and 15, respectively. No deaths occurred at 2 ppm. Ocular and nasal irritation and labored breathing were observed at all concentrations. Deaths resulted from severe pulmonary hemorrhage, emphysema, and pneumonia (Wazeter 1964a).

A calculated concentration of 2,4-TDI at 600 ppm for 6 h resulted in pulmonary congestion and edema and was lethal to rats (Zapp 1957).

3.1.4. Mice

A 4-h LC_{50} for the mouse was calculated to be 9.7 ppm. Exposures were by whole body and concentrations were measured at 0.1, 1.0, 2, 5, 10, 20, or 34 ppm. A total of 120 animals were used in the experiment (gender and numbers of animals not stated). Animals exhibited concentration-dependent signs of toxicity during exposure such as mouth-breathing, lacrimation, salivation, and restlessness. At concentrations above 5 ppm, mouth-breathing was observed after 1 h of exposure. Histopathologic examination of the respiratory tracts of five animals per group per time point revealed focal coagulation necrosis and desquamation of the superficial epithelial lining of the trachea and major bronchi. The degree of injury and subsequent repair was dependent on exposure concentration. Inflammation cleared by day 7 post-exposure in the 2-ppm group. Advanced bronchiolitis fibrosia obliterans was evident at the higher concentrations. The specific TDI isomers studied were not identified (Duncan et al. 1962).

3.2. Nonlethal Toxicity

3.2.1. Dogs

As part of a subchronic study, four male dogs were exposed 35-37 times over a period of 4 mo to analytical concentrations of 2,4-TDI averaging 1.5 ppm. Daily exposures were limited to 30 min to 2 h because of the resulting lacrimation, coughing, restlessness, and profuse frothy white secretions from their mouths. The onset of those clinical signs was not specifically noted except that they "continued throughout the entire course of exposure." No deaths were reported (Zapp 1957).

3.2.2. Guinea Pigs

Female albino Dunkin-Hartley guinea pigs (n = 10) were exposed by whole body to 2,4- and 2,6-TDI (80:20) at 3 ppm for 1 h. Clinical signs of toxicity during exposure, if there were any, were not reported. Increased bronchial responsiveness to acetylcholine was evident within 30 min after exposure and lasted up to 48 h. Bronchoalveolar lavage revealed an influx of neutrophils beginning at 1 h post-exposure and lasting approximately 48 h. In related experiments, following continuous exposure at 0.08 ppm for 48 h or at 0.046 ppm for 1 week (wk), bronchial hyper-responsiveness occurred in the absence of neutrophil influx (Gagnaire et al. 1996).

As part of an immunologic study on sensitization to TDI (isomer not specified), female English smooth-haired guinea pigs (n = 8-16) were exposed head-only for 5 d, 3 h/d at concentrations ranging from 0.12 ppm to 7.60 ppm. Sensory irritation was measured as decreased respiratory rate. During a single 3-h exposure, the decrease in respiratory rate was concentration dependent from 0.12 ppm to 0.93 ppm, with maximal response during the first 2 h. At higher concentrations, the maximal respiratory rate decrease (approximately 60%) occurred within the first 30 min (Karol et al. 1980; Karol 1983).

Albino guinea pigs (gender and numbers of animals not stated) were exposed to TDI (method of exposure not stated, mixed isomers assumed) at concentrations ranging from 0.02 ppm to 0.5 ppm for three exposures lasting 6 h each. During a single exposure, concentrations up to 0.05 ppm did not affect the breathing rate. However, at concentrations of $\geq$0.18 ppm, the breathing rate dropped by 50% after the first 40 min of exposure and by an additional 10% over the next 3.5 h (Stevens and Palmer 1970). It should be noted that the authors did not state whether that pattern developed at the first exposure or whether similar or more severe results occurred with subsequent exposures.

Female English smooth-haired guinea pigs (n = 8) were exposed head-only to 2,4- and 2,6-TDI (80:20) at 1.4 ppm for 3 h/d for 5 consecutive days. Body-weight loss occurred during the exposure period and body weights remained lower than the unexposed controls until termination on day 50 post-exposure. The ventilatory response of exposed animals to 10% CO_2, as measured by pressure change (ΔP), was diminished by 30-50% on day 5 of exposure but gradually recovered during the following 40 d. At sacrifice, exposed animals had multifocal interstitial inflammation of the

lungs. In contrast, no adverse effects were observed in animals exposed at 0.02 ppm 6 h/d, 4 d/wk for 70 d (Wong et al. 1985).

Respiratory sensitization was studied in groups of 11-12 male Hartley guinea pigs (Warren 1994a,b). Animals were sensitized with either room air, 2,4-TDI, or 2,6-TDI by nose-only exposure for 3 h/d for 5 d at analytical TDI concentrations of 1.29-1.4 ppm. Clinical signs of toxicity from sensitization exposure included rapid breathing (2,6-TDI), ataxia (2,4-TDI), tremors (2,4- and 2,6-TDI), and death of two animals (one with each isomer). The animals were then challenged by whole-body exposure for 1 h three times at 1 wk intervals with 2,4-TDI or 2,6-TDI at concentrations ranging from 18 ppb to 46 ppb. Challenge concentrations were low enough to avoid sensory irritation and to avoid interfering with a hypersensitivity reaction. Increased respiratory rate was taken as an indicator of hypersensitivity response. No immediate- or delayed-type hypersensitivity reactions were observed in the sham-sensitized animals. On the other hand, both delayed- and immediate-type hypersensitivity reactions occurred in all sensitized groups. Furthermore, the data showed that both 2,4- and 2,6-TDI caused sensitization in the guinea pigs, and that either isomer elicited a hypersensitive reaction regardless of the isomer used for sensitization. However, at necropsy, only the animals given sensitization and challenge exposures to 2,6-TDI showed an increase in red zones in the lungs, suggesting that 2,6-TDI is more irritating than 2,4-TDI.

3.2.3. Hamsters

Male and female Syrian hamsters (n = 5/gender) were exposed to TDI at 0.1 ppm or 0.3 ppm for 6 h/d, 5 d/wk for 4 wk. The TDI isomer or mixture and the method of exposure were not stated. At the high dose, both genders had focal hyperplasia accompanied by slight inflammation of the nasal turbinates and peribronchiolar aggregates of primary mononuclear cells in the lung. Female hamsters also had slight inflammation of the respiratory epithelium of the nasal turbinates from exposure at 0.1 ppm (Kociba et al. 1979).

3.2.4. Rats

Male Sprague-Dawley rats (n = 4) were exposed by head only to 2,4-TDI for 3 h at 0.29, 0.88, 1.41, or 3.20 ppm. Lacrimation and rhinorrhea

were observed at all concentrations, labored breathing occurred at ≥1.41 ppm, red swollen conjunctiva were seen at 3.20 ppm, and rales were heard at 0.88 ppm and 3.20 ppm. No mortality occurred. Post-exposure decreases in weight gains occurred in animals exposed at ≥0.88 ppm, but recovery was complete by day 7, except at the highest dose. The respiratory frequency of the rats was concentration-dependent and indicated upper respiratory irritation. The 3-h RD_{50} (concentration which resulted in a 50% decrease in the respiratory rate) was estimated to be 1.37 ppm (Shiotsuka 1987a). In a similar experiment, male Sprague-Dawley rats (n = 4) were exposed head-only for 3 h to a 2,4- and 2,6-TDI mixture (80:20). Concentrations ranged from 0.10 ppm to 1.45 ppm. Transient decreases in weight gain occurred post-exposure at the two highest concentrations, and rales were heard in one animal exposed at 1.45 ppm. The estimated RD_{50} was 2.12 ppm (Shiotsuka 1987b). It should be noted that the estimated RD_{50} for the second study was outside the range of exposure concentrations. Of particular interest, however, was the initial sharp drop in respiratory rate during the first 15 min, followed by a gradual decline during the remainder of the exposure period.

Male Fischer-344 rats (n = 4) exposed head-only to 2,4-TDI at 2 ppm for 4 h appeared lethargic and were not drinking water or eating. However, 12 h post-exposure the animals appeared normal and had resumed eating and drinking (Timchalk et al. 1992). No deaths were reported in rats exposed to a calculated concentration of 2,4-TDI at 60 ppm for 6 h (Zapp 1957).

Albino rats (n = 6) exposed by whole body to TDI (mixed isomer not defined) at 2 ppm for 6 h exhibited ocular and nasal irritation and labored breathing within 2 h of initiation of exposure (Wazeter 1964a). No signs of clinical toxicity were observed at concentrations <1 ppm for 6 h (Wazeter 1964a) or at 0.25 ppm for 8 h (Wazeter 1964b).

3.2.5. Mice

Male Swiss-Webster mice (n = 4) were exposed head-only to concentrations of 2,4-TDI ranging from 0.007 ppm to 2.0 ppm for up to 240 min (Sangha and Alarie 1979) or to varying concentrations of 2,6-TDI for 3 h (Weyel et al. 1982). Respiratory irritation was measured as a reduction in respiratory rate. At concentrations of 2,4-TDI above 0.07 ppm, the degree of the response was concentration-dependent with a first maximum reached after 10 min. Following this initial 10-min period, a further decline in

respiratory rate was measured gradually for the next 30 min, approximately. The results with 2,6-TDI were described as similar to those with 2,4-TDI indicating respiratory irritation. RD_{50} concentrations at various time points are given in Table 4-5. It is apparent from the development of the response and the $C \times t$ values that respiratory irritation is mainly dependent on concentration and only slightly dependent on duration of exposure. In another series of experiments, those same authors showed that the decrease in respiratory rate was due to irritation of the upper respiratory tract, because exposure by intratracheal instillation failed to result in decreased respiratory rate (Sangha and Alarie 1979). The effect of exposure on respiratory rate also was investigated using concentrations above or below the 1979 TLV (0.02 ppm) for 3 h on each of 5 consecutive days. At exposure concentrations above the 1979 TLV, the level of response was increased and the onset of reaction was faster on each subsequent day. Below the 1979 TLV, no response at all was observed on the first or subsequent days.

3.3. Developmental and Reproductive Toxicity

Pregnant Sprague-Dawley rats (n = 25) were exposed by whole-body inhalation to technical grade TDI (80% 2,4-TDI, 20% 2,6-TDI) at 0.021, 0.120, or 0.480 ppm for 6 h/d on gestation days 6-15. Maternal toxicity at the highest concentration was evident by decreased body weight and weight gain, reduced food consumption, nasal discharge, and audible respiratory distress. Signs of respiratory irritation did not appear until 5 d after treatment began. Fetotoxicity was evinced by delayed ossification of cervical centrum 5 in fetuses from high-concentration litters. No other signs of developmental toxicity were observed (Tyl 1988).

Male and female Sprague-Dawley rats (n = 28/gender) were exposed continuously by whole-body inhalation to technical grade TDI (80% 2,4-TDI, 20% 2,6-TDI) at 0.02, 0.08, or 0.3 ppm for two generations. Exposure of F_0 and F_1 females was discontinued from gestation day 19 through lactation day 4. Clinical signs of toxicity in the adult animals consisted of nasal discharge in F_0 males and red-tinged fur on the head in F_0 females at 0.3 ppm and perinasal encrustation in F_1 females at 0.08 ppm and 0.3 ppm. Histopathologic examination revealed rhinitis in the nasal turbinates of the F_0 adults and the F_1 females at $\geq$0.08 ppm and in the F_1 males at all dose levels. F_2 pup body weights and weight gains were reduced at 0.08 ppm and 0.3 ppm during lactation. There were no treatment-related effects on

TABLE 4-5 Calculated RD_{50} Values in Mice

Exposure time (min)	RD_{50} (ppm)	$C \times t$
2,4-TDI[a]		
10	0.813	8.13
30	0.498	14.94
60	0.386	11.58
120	0.249	29.88
180	0.199	35.82
240	0.199	47.76
2,6-TDI[b]		
180	0.26	46.8

[a]Data from Sangha and Alarie 1979.
[b]Data from Weyel et al. 1982.

the reproductive parameters of either generation (Tyl and Neeper-Bradley 1989).

3.4. Genotoxicity

No information was found regarding potential genotoxicity of TDI in laboratory animals.

3.5. Chronic Toxicity and Carcinogenicity

Results of oncogenicity bioassays with TDI are conflicting and depend on the route of administration. In an NTP (1986) study, groups of 50 male and female F-344/N rats and $B6C3F_1$ mice were given 2,4- and 2,6-TDI (80:20) by gavage 5 d/wk for 2 y. Doses were 60 mg/kg or 120 mg/kg for female rats and mice, 30 mg/kg or 60 mg/kg for male rats, and 120 mg/kg or 240 mg/kg for male mice. Reduced survival was seen in all treated rats and high-dose male mice. Increased subcutaneous fibromas or fibrosarcomas in male rats, mammary fibroadenomas in female rats, and hemangiomas or hemangiosarcomas and hepatocellular adenomas in female mice were observed. In contrast to the NTP (1986) results, a study commis-

sioned by the International Isocyanate Institute (Loeser 1983; Owen 1983) failed to show any evidence of carcinogenicity in Sprague-Dawley CD rats (n = 104-105/gender) or CD-1 mice (n = 89-90/gender) exposed to 2,4- and 2,6-TDI (80:20) by inhalation at 0.05 ppm or 0.15 ppm 6 h/d, 5 d/wk for approximately 2 y. Histopathologic analyses of the nasal turbinates showed a concentration-related increase in rhinitis in both mice (Loeser 1983) and rats (Owen 1983).

The studies described above have been criticized on technical and toxicologic merit. Corn oil was used as vehicle in the gavage study, even though a precipitate of unknown composition formed with the TDI, and TDI is known to breakdown in corn oil (CMA 1989). In the inhalation study, clinical effects were minimal, indicating that exposure concentrations may have been inadequate, but the histopathology of rhinitis confirms that a maximum tolerated dose was achieved (CMA 1989). Despite the suggested scientific flaws of both studies, the route-specific dependence of carcinogenicity may be due to the formation of toluene diamine (TDA), which is the major metabolite produced following oral exposure, but not inhalation exposure (Timchalk et al. 1992, 1994). TDA has previously been shown to be a carcinogen to rats and mice in chronic feeding studies producing tumors similar to those seen in the oral TDI study (NCI 1979, as cited in Timchalk et al. 1994). From histopathologic evaluation, the upper respiratory tract appears to be the target organ following inhalation exposure to TDI, with the response attributable to local irritation.

EPA (1996) has not classified the carcinogenicity of TDI. Based only on the oral studies and the similarity in the tumor response of mice and rats to TDI and TDA, IARC (1985) classified TDI in Group 2B, sufficient evidence of carcinogenicity in animals but inadequate evidence in humans.

3.6. Summary

Animal data on the toxicity of TDI are summarized in Table 4-6. Results of several animal experiments confirm that TDI is a respiratory tract irritant. That was characterized in studies in rats (Shiotsuka 1987a,b) and mice (Sangha and Alarie 1979) showing initial rapid decreases in respiratory rate followed by continued gradual decline. In a series of LC_{50} experiments with rats, mice, guinea pigs, and rabbits, animals exhibited concentration-dependent signs of toxicity during exposure such as mouth-breathing, lacrimation, salivation, and restlessness. Histopathologic examination of the respiratory tract revealed focal coagulation necrosis and

TABLE 4-6 Summary of Animal Toxicity Data

Species	Duration and End Point	Concentration (ppm)	Isomer	Reference
Rat	4-h LC_{50}	13.9	Unknown	Duncan et al. 1962
Male rat	4-h LC_{50}	49.16	Unknown	Kimmerle 1976
Female rat	4-h LC_{50}	50.56	Unknown	Kimmerle 1976
Male and female rat	1-h LC_{50}	66	2,4- and 2,6- (80:20)	Horspool and Doe 1977
Mouse	4-h LC_{50}	9.7	Unknown	Duncan et al. 1962
Guinea pig	4-h LC_{50}	12.7	Unknown	Duncan et al. 1962
Rabbit	4-h LC_{50}	11	Unknown	Duncan et al. 1962
Dog	30-120 min; coughing, lacrimation, restlessness	1.3	2,4-	Zapp 1957
Rat	3-h RD_{50}	1.37	2,4-	Shiotsuka 1987a
Rat	3-h RD_{50}	2.12	2,4- and 2,6- (80:20)	Shiotsuka 1987b
Rat	6 h; ocular and nasal irritation, labored breathing 6 h; 3/6 dead	2 4 and 13.5	Mixed, not defined	Wazeter 1964a
Mouse	10-min RD_{50}	0.813	2,4-	Sangha and Alarie 1979
Mouse	4-h RD_{50}	0.199	2,4-	Sangha and Alarie 1979

desquamation of the superficial epithelium lining the trachea and major bronchi. The degree of injury and subsequent repair was dependent on exposure concentration. Inflammation cleared by day 7 post-exposure in the 2-ppm group, but advanced bronchiolitis fibrosia obliterans was observed at higher concentrations. All species but the mouse developed bronchopneumonia following TDI inhalation (Duncan et al. 1962).

Subchronic or chronic inhalation studies in rats, mice, and hamsters indicate that the nasal turbinates are the primary target organ, and the nasal histopathology can be attributed to irritation.

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

In two related studies, healthy men (ages 36-50) were exposed to TDI at concentrations of approximately 3.5, 7, and 9.8 ppb (25, 50, and 70 $\mu g/m^3$) for 4 h at 1 wk intervals (Brorson et al. 1991) or at 5.6 ppb (40 $\mu g/m^3$) for 7.5 h (Skarping et al. 1991). Acetylator phenotype was assessed in the subjects of the Skarping et al. (1991) study. The isomeric composition of the air in the test chamber was 30% 2,4-TDI and 70% 2,6-TDI in the first study and 48% 2,4-TDI and 52% 2,6-TDI in the second study. Plasma concentrations of 2,4- and 2,6-TDA were analyzed over a period of up to 5 wk after the initial exposure. There were concentration- and time-dependent increases in plasma levels of TDA, with 2,6-TDA appearing after exposure at 5.6 ppb or 7.02 ppb (40 $\mu g/m^3$ or 50 $\mu g/m^3$) and 2,4-TDA detectable after exposure at 5.6 ppb or 9.8 ppb (40 $\mu g/m^3$ or 70 $\mu g/m^3$). Similar or slightly higher plasma levels were detected 24 h after exposure. The plasma elimination half-life for the initial rapid phase was calculated to be about 4-5 h for 2,6-TDA and 2-3 h for 2,4-TDA. Half-life for the slower elimination phase was not given. Inhaled doses were calculated from ventilation rates and exposure concentrations and durations. Cumulative urinary excretion of 2,4- and 2,6-TDA directly correlated with the concentrations of 2,4- and 2,6-TDI, respectively, in the test chamber. Over 24-28 h, the cumulative amount of 2,4-TDA excreted in the urine was 8-19% of the estimated inhaled dose of 2,4-TDI, and that of 2,6-TDA was 14-23% of the estimated inhaled dose of 2,6-TDI. No differences were observed between fast and slow acetylators (Brorson et al. 1991; Skarping et al. 1991).

Male Hartley guinea pigs were exposed by whole-body inhalation to ^{14}C-labeled 2,4-TDI for 1 h. The rate of uptake into the bloodstream was

linear over a concentration range of 0.004-0.146 ppm, and there was a continued slight increase post-exposure. The level of radioactivity in the bloodstream declined gradually over 72 h but did not show a significant decline over the subsequent 11 d period. Immediately following exposure, most of the radioactivity was distributed to the trachea, and smaller amounts were found in the lung, kidney, heart, spleen, and liver. Elimination was mainly through the urine (Kennedy et al. 1989).

Male Fischer-344 rats were exposed by inhalation to ^{14}C-labeled 2,4-TDI at 2 ppm for 4 h. It was estimated that essentially all of the inhaled TDI was retained by the animal. The half-life for urinary elimination was approximately 20 h. Acid labile conjugates accounted for about 90% of the urinary metabolites, and 10% was acetylated TDA. In contrast, the major urinary metabolite following oral administration was 2,4-TDA (Timchalk et al. 1992, 1994).

In summary, although the systemic uptake of TDI follows linear $C \times t$ kinetics, that relationship does not hold for the onset of signs of toxicity over the same concentration range. For sensory irritation (Sangha and Alarie 1979) and for development of sensitization (Karol 1983; Garabrant and Levine 1994), the response is mainly concentration-dependent.

4.2. Mechanism of Toxicity

Inhaled TDI is corrosive, and the parent material acts as a direct chemical irritant. The degree of irritation appears to be dependent on concentration rather than duration of exposure (Duncan et al. 1962; Sangha and Alarie 1979; Bernstein 1982). In both human and animal studies, an immediate decline in respiratory rate occurs with onset of exposure, followed by a continued, more gradual decline (Baur 1985; Sangha and Alarie 1979; Weyel et al. 1982). Subchronic or chronic inhalation studies in rats, mice, and hamsters indicate that the nasal turbinates are the primary target organ in rodents and that the frank pathology there can be attributed to direct chemical deposition and irritation (Kociba et al. 1979; Loeser 1983; Owen 1983).

It has long been established that repeated inhalation contact with TDI can provoke asthmatic reactions in humans (Zapp 1957). Immediate, late, and dual asthmatic responses have been documented in sensitized individuals (Butcher et al. 1979; Karol 1986). Karol (1986) concluded that although TDI does not cause asthma by a nonspecific irritant effect, concomitant irritation or hyper-reactivity of the airways may produce heightened respiratory tract responsiveness in isocyanate-sensitive individuals. A review of

epidemiological studies that reported sensitization rate found that in five of six worker populations the rate of sensitization was between 0 and 1.5% per year. In the sixth worker population, a majority of air samples showed TDI exposures above 20 ppb (142 $\mu g/m^3$) and a rate of sensitization of 5% per year (Garabrant and Levine 1994). Two distinct populations with occupational asthma were identified on the basis of the duration of exposure to TDI before the onset of symptoms. One group developed asthma after an average of 2.4 y, while the other developed asthma after an average of 21.6 y (Di Stefano et al. 1993).

The mechanism by which TDI induces asthmatic symptoms is not entirely known, but it appears to include both immunologic and nonimmunologic mechanisms (Bernstein 1982). Proposed mechanisms include pharmacologic bronchoconstriction, allergic or immunologically mediated bronchoconstriction, and hyper-reactive airways (Karol 1986). In general, isocyanates are reactive substances capable of antigenic activity (Woolrich 1982). Although, the guinea pig has been widely used as a model for TDI-induced asthma, pulmonary hyper-reactivity in guinea pigs only works for sensitized animals challenged with TDI-protein conjugate, whereas sensitized humans react to TDI alone (Karol et al. 1980). Some studies showed detection of IgE antibodies in sensitized individuals, although others found variable or negative results (Karol 1986). IgG antibodies have been detected in both healthy and symptomatic workers (Baur 1985). The inflammatory response of the respiratory tract has been characterized by persistent activation of lymphocytes, chronic expression of certain cytokines (Maestrelli et al. 1995), neutrophilia, eosinophilia (Fabbri et al. 1987), and decreased lymphocyte cAMP levels (Butcher et al. 1979). Individuals that developed asthma after short-term exposure were shown to have a greater number of mast cells in their airway mucosa than individuals that developed asthma after longer-term exposure (Di Stefano et al. 1993). Direct application of TDI in vitro induced the release of tachykinins from sensory nerves in the isolated mouse trachea (Scheerens et al. 1996). The mechanisms behind TDI-induced asthma have been thoroughly reviewed elsewhere (Karol 1986), but several major areas are discussed below.

Guinea pigs were sensitized by exposure to TDI at concentrations ranging from 0.12 ppm to 10 ppm for 3 h/d for 5 consecutive days (Karol et al. 1980; Karol 1983). All animals exposed at 10 ppm died following exposure on day 3. Twenty-two days later, animals were evaluated for TDI-specific antibodies. No antibodies were detected in animals that inhaled 0.12 ppm. However, 55% of animals exposed at $\geq$0.36 ppm had serum antibodies. Higher concentrations of TDI resulted in a greater percentage of animals producing antibodies and in higher antibody titers. When challenged, a

significant association was found with lung sensitivity (increased respiratory rate) and the presence of circulating antibodies, rather than with the antibody titer (Karol 1983). Increased respiratory rate is a well-documented phenomenon that occurs in immunologically sensitized animals and humans following inhalation of specific antigens. Increased respiration is probably a reflex due to the hypoxia resulting from narrowing of the airway lumen.

In a similar experiment, respiratory sensitization was studied in groups of 11-12 male Hartley guinea pigs (Warren 1994a,b). Animals were sensitized with room air, 2,4-TDI, or 2,6-TDI by exposure at analytical TDI concentrations of 1.29-1.4 ppm for 3 h/d for 5 d. The animals were then challenged with 2,4- or 2,6-TDI protein conjugates at concentrations ranging from 18 to 46 ppb for 1 h three times at 1 wk intervals. Challenge concentrations were low enough to avoid sensory irritation and to avoid interfering with a hypersensitivity reaction. Increases in respiratory rate were taken as indicators of hypersensitivity responses. No immediate- or delayed-type hypersensitivity reactions were observed in the sham-sensitized animals. Both delayed- and immediate-type hypersensitivity reactions occurred in all sensitized groups. Furthermore, the data showed that both 2,4-TDI and 2,6-TDI caused respiratory sensitization in the guinea pigs, and that either isomer elicited a hypersensitive reaction regardless of the isomer used for sensitization.

Both of the above studies used guinea pigs as a model for TDI-induced pulmonary hypersensitivity. But, despite the presence of circulating antibodies demonstrated by Karol (1983), inhalation challenge of animals elicited pulmonary sensitivity only when sensitized animals were challenged with TDI-protein conjugates and not TDI alone.

Another study in guinea pigs showed that dose-response relationships exist for both induction and challenge concentrations for production of TDI sensitization as measured by histamine release and mast cell degranulation (Huang et al. 1993).

4.3. Structure-Activity Relationships

TDI exists in both the 2,4- and 2,6- isomeric forms, which are available commercially as 65:35 or 80:20 mixtures. Most studies with TDI fail to specify the isomer or mixture employed. However, in the studies that did state which isomer was used, there appeared to be little difference in toxicity between the two. In humans, 2,6-TDI was slightly more irritating than 2,4-TDI, but the irritant potential of the 2,6-isomer was similar to that of the mixture (Henschler et al. 1962). Studies by Warren (1994a,b) showed that

both 2,4- and 2,6-TDI caused sensitization in the guinea pigs and that either isomer elicited a hypersensitive reaction regardless of the isomer used for sensitization. Animals in that study that were sensitized and challenged with 2,6-TDI developed gross lung lesions (red zones), indicating that the 2,6- isomer is the more irritating. However, the 3-h RD_{50} in mice was approximately 0.2 ppm for both the 2,4- (Sangha and Alarie 1979) and 2,6- (Weyel 1982) isomers.

Kimmerle (1976) found that the LC_{50} for the TDI polymer was about 10 times greater than the LC_{50} for monomeric TDI (designated T 65 with no isomer identification) in rats. The polymers used in that study were Desmodur L 67, Desmodur IL, and Desmodur HL.

Little information was found on cross-reactivity with other isocyanates in individuals sensitized to TDI. Karol (1986) noted that in the workplace, individuals are neither exposed to nor sensitized by monoisocyanates; rather, sensitization is a result of exposure to diisocyanates. However, the monoisocyanates have been successfully used as haptens in detecting antibodies to the corresponding diisocyanate (Karol 1986), and *p*-tolyl isocyanate has been used to detect antibodies in TDI-sensitized individuals (Karol et al. 1980).

TDI is structurally similar to methyl isocyanate (MIC). The databases for these isocyanates are robust and each contains animal and human studies. However, their only consistent similarity is that both are irritants when inhaled, and the available data suggest differing mechanisms of action beyond irritation. TDI is a proven sensitizer, MIC is not. Systemic effects have been well-documented after MIC inhalation exposure but not after TDI exposure. For example, in laboratory animal studies, the fetal and neonatal deaths resulting from inhalation exposure to MIC did not occur following maternal exposure to TDI. Cardiac arrhythmias reported after MIC exposures have not been seen after exposures to TDI. For MIC, systemic effects may occur at concentrations equal to or below those that cause irritation. Therefore, although TDI and MIC are both isocyanates, the end points chosen for the derivation of AEGL values differed for each chemical based on the available data from inhalation exposures.

4.4. Other Relevant Information

4.4.1. Species Variability

Although 4-h LC_{50} values for the rat and mouse do not differ appreciably (13.9 ppm and 9.7 ppm, respectively) (Duncan et al. 1962), the RD_{50}

values for rats (Shiotsuka 1987a,b) are approximately 10 times greater than those for mice (Sangha and Alarie 1979). Animal models have been validated for the mouse (Alarie 1981) and guinea pig (Borm et al. 1990). On the basis of those data, it appears that the mouse is the common laboratory animal most sensitive to the irritating effects of TDI.

The guinea pig has been studied extensively as a model for TDI-induced asthma. However, pulmonary hyper-reactivity in guinea pigs only develops in sensitized animals challenged with TDI-protein conjugate (Karol et al 1980). In contrast, sensitized humans react to TDI alone.

4.4.2. Sensitive Subpopulations

As discussed in Section 4.2, TDI produces asthmatic reactions in sensitized individuals. Rates of sensitization in workers were found to range from 0 to 5%, and the highest rate correlated to TDI exposures above 20 ppb (Garabrant and Levine 1994). The mechanism by which TDI induces asthma is not known, nor are data available to quantify the rate of sensitization in the general population. The presence of circulating antibodies has not proved to be a reliable indicator of sensitization or symptomology (Karol 1986). Therefore, at the AEGL levels there may be individuals that have a strong reaction to TDI, and those individuals may not be protected.

4.4.3. Unique Physicochemical Properties

Several physicochemical properties of TDI minimize the opportunity for acute inhalation exposure to high concentrations. The low vapor pressure (0.01 mm Hg at 20°C) corresponds to a saturated atmospheric concentration of 14.9 ppm (Horspool and Doe 1977). Temperature must be increased before higher concentrations are possible. Also, TDI readily reacts with water vapor resulting in a "fall-out" of reaction product that is probably TDI-urea (Zapp 1957; Wazeter 1964a; Horspool and Doe 1977). Deposition and reaction with moisture can act to reduce the atmospheric concentration of TDI. These phenomena are responsible for large differences in theoretical vs analytical exposure concentrations (Wazeter 1964a) and probably explain the lack of effects reported by Zapp (1957) at concentrations that resulted in clear effects, including death, in other studies (Wazeter 1964a,b; Duncan et al. 1962; Sangha and Alarie 1979).

4.4.4. Concentration-Exposure Duration Relationship

The concentration-exposure duration relationship for an irritant gas such as TDI can be described by the equation $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5 (ten Berge et al. 1986). In the absence of a chemical-specific, empirically derived exponent, a default value of $n = 1$ can be used when extrapolating to longer time points, and a default value of $n = 3$ can be used when extrapolating to shorter time points. This method will yield the most conservative AEGL estimates.

5. DATA ANALYSIS AND AEGL-1

AEGL-1 is the airborne concentration (expressed as ppm or mg/m^3) of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic, nonsensory effects. However, the effects are not disabling and are transient and reversible upon cessation of exposure.

5.1. Summary of Human Data Relevant to AEGL-1

The human data most relevant to AEGL-1 are those of the Baur (1985) study in which both asthmatics and healthy volunteers were exposed to controlled concentrations of 2,4- and 2,6-TDI (80:20). Asthmatic subjects were exposed to TDI at 0.01 ppm for 1 h. Then, after a rest of 45 min, they were exposed at 0.02 ppm for 1 h. A referent group of nonasthmatic subjects was exposed to TDI at 0.02 ppm for 2 h. Although no statistically significant differences in lung function parameters were observed among asthmatic subjects during or after exposure, bronchial obstruction was indicated in several subjects. Individually, no decrease in FEV_1 of more than 20% was observed. The magnitude of airway resistance was not considered clinically significant for the asthmatic subjects, indicating that those effects fall within the definition of AEGL-1. In the healthy referent group, there was a significant increase in airway resistance immediately after and 30 min after the beginning of exposure, but none of the subjects developed bronchial obstruction. Both groups reported eye and throat irritation, cough, chest tightness, rhinitis, dyspnea, and/or headache, but time to onset of symptoms was not given.

Similar symptoms were reported among spray-foam workers exposed to average isocyanate (isomer not identified) concentrations of up to 0.043 ppm for as long as 7.4 h (Hosein and Farkas 1981). Symptoms of exposure were reported when workplace air concentrations exceeded 0.03 ppm (Hama 1957). Healthy subjects tolerated approximately 0.01 ppm for 4 h with no adverse effects (Brorson et al. 1991).

5.2. Summary of Animal Data Relevant to AEGL-1

None of the available animal data was relevant to derivation of AEGL-1.

5.3. Derivation of AEGL-1

The data of Baur (1985) were used for derivation of AEGL-1 values. Asthmatic individuals tolerated exposure at 0.01 ppm for 1 h, and then, after a rest, 0.02 ppm for another hour. Because the time to onset of symptoms was not identified, it is assumed that the effects began immediately upon TDI exposure. This assumption is supported by the fact that significant differences in lung function occurred in the healthy population immediately after and 30 min after initiation of exposure, but resolved with longer duration of exposure. There was also no indication whether the effects were worse in asthmatic subjects at 0.01 ppm or at 0.02 ppm. Therefore, the 0.02-ppm concentration was identified as the basis for the 10-min, 30-min, and 1-h AEGL-1 values, and the 0.01-ppm concentration was identified as the 4- and 8-h AEGL-1s. Extrapolations across time were not performed. Because the asthmatic subjects tolerated 0.02 ppm for 1 h after pre-exposure at 0.01 ppm, it is assumed that the asthmatic population could tolerate the lower concentration for a longer duration. However, it is recognized that individuals with pre-existing allergic sensitization to TDI might not be protected at those concentrations and might experience airway reactivity with symptoms characteristic of an asthmatic attack, such as coughing, wheezing, chest tightness, and difficulty breathing. It should also be noted that AEGL-1 values are below any reported odor threshold concentrations (Henschler et al. 1962; Wilson and Wilson 1959). AEGL-1 values are presented in Table 4-7.

The AEGL-1 values are considered protective of public health as defined under AEGL-1. Asthmatic subjects were studied, making the use of

TABLE 4-7 AEGL-1 Values for Toluene 2,4- and 2,6-Diisocyanate (ppm [mg/m^3])

10 min	30 min	1 h	4 h	8 h
0.02 (0.14)	0.02 (0.14)	0.02 (0.14)	0.01 (0.07)	0.01 (0.07)

uncertainty factors unnecessary because asthmatic people are considered a sensitive subpopulation. The 0.01-ppm exposure concentration for the longer time points is reasonable because data suggest that the adverse health effects of inhaled TDI are more concentration-dependent than duration-dependent. Controlled inhalation at 0.02 ppm was tolerated by asthmatic subjects for 1 h. For comparison, the spray foam applicators in the Hosein and Farkas (1981) study tolerated up to 4 times the AEGL-1 values (0.04 ppm) for up to 7.5 h with reports of eye irritation only. Assuming that the applicators in the Hosein and Farkas (1981) study were healthy adults (i.e., nonasthmatic), and assuming that the isocyanates measured were TDI, minimal effects would be expected in normal individuals at the AEGL-1 concentrations. Also, healthy subjects tolerated approximately 0.01 ppm for 4 h with no adverse effects (Brorson et al. 1991). A slightly higher concentration of 0.03 ppm resulted in symptoms in 100% of workers at a manufacturing plant (Hama 1957). The AEGL-1 single-exposure values are below the concentrations expected to cause sensitization with repeated long-term exposure (Garabrant and Levine 1994). Figure 4-1 is a plot of the derived AEGLs and all of the human and animal data on TDI.

6. DATA ANALYSIS AND AEGL-2

AEGL-2 is the airborne concentration (expressed as ppm or mg/m^3) of a substance above which it is predicted that the general population, including susceptible individuals, could experience irreversible or other serious, long-lasting adverse health effects or an impaired ability to escape.

6.1. Summary of Human Data Relevant to AEGL-2

The most appropriate human data for use in derivation of AEGL-2 values are those of Henschler et al. (1962). Human subjects were exposed to analytical concentrations of 2,4- and 2,6-, 2,4-, or 2,6-TDI ranging from 0.01 to 1.3 ppm for 30 min. At 0.5 ppm, volunteers experienced ocular

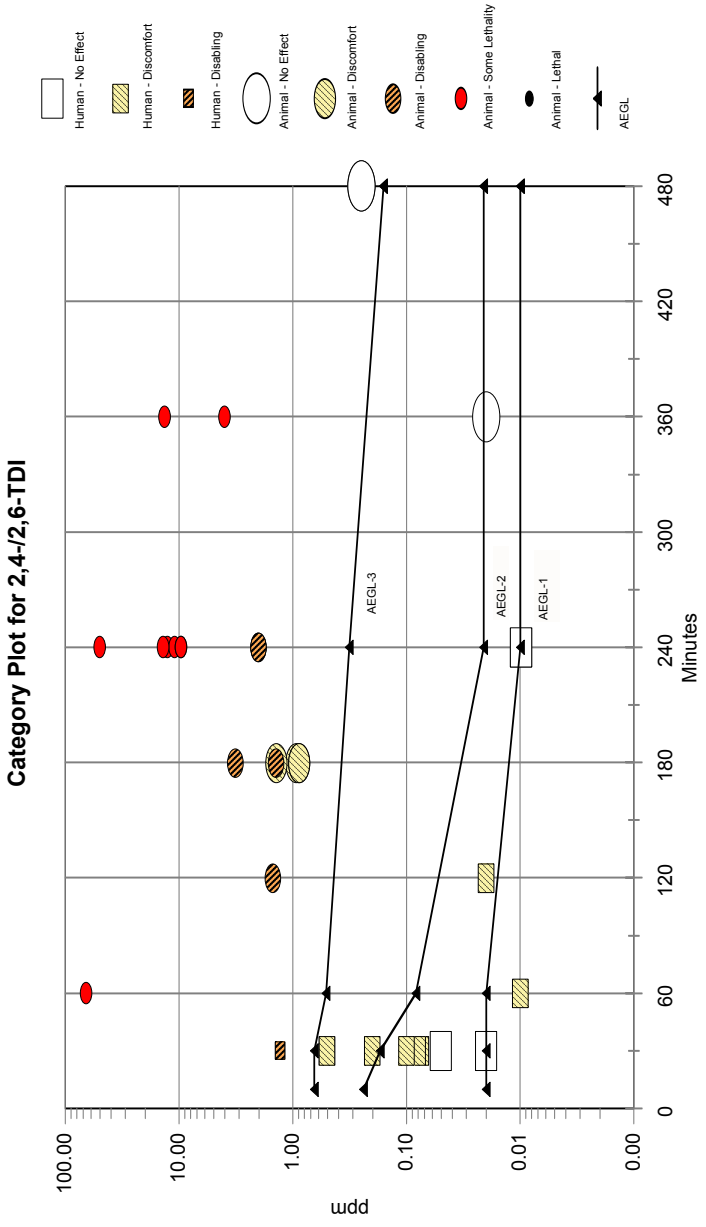

FIGURE 4-1 Toxicity data and AEGL values for toluene 2,4- and 2,6-diisocyanate. Toxicity data include both human and animal studies.

irritation with lacrimation and throat irritation in the absence of cough. Irritation was intolerable at the next higher concentration tested (1.3 ppm), forcing subjects to leave the room after only 10 min; cough persisted for several hours.

6.2. Summary of Animal Data Relevant to AEGL-2

Mouse and rat RD_{50} values were considered for calculation of AEGL-2 values. Decreased respiratory rate in the mouse model has been shown to correspond with sensory irritation in humans. When an irritant such as TDI enters the nasal mucosa, the trigeminal nerve endings are stimulated, resulting in an inhibition of respiration (Alarie 1981). The 10-min and 1-h RD_{50}s for TDI in male Swiss-Webster mice are 0.8 ppm and 0.39 ppm, respectively (Sangha and Alarie 1979). The 3-h RD_{50} in male Sprague-Dawley rats ranged from 1.37 ppm to 2.12 ppm (Shiotsuka 1987a,b). In those experiments, there was an initial sharp drop in respiratory rate during the first 15 min followed by a gradual decline during the remainder of the exposure period. This effect is indicative of concentration-dependent irritation. Fischer-344 rats exposed at 2 ppm for 4 h appeared lethargic and were not drinking water or eating. However, 12 h post-exposure, the animals appeared normal and had resumed eating and drinking (Timchalk et al. 1992). In the series of experiments by Duncan et al. (1962) that exposed four species of laboratory animals at 2 ppm, clearing of the inflammation and respiratory tract injury was apparent by day 7 post-exposure.

6.3. Derivation of AEGL-2

Because rigorous human data are available, they were used to calculate the AEGL-2. Exposure at 0.5 ppm for 30 min resulted in eye and throat irritation and lacrimation. A higher concentration was intolerable after 10 min. Although the extent of lacrimation at 0.5 ppm was not described, any amount could impair the ability to escape. Therefore, that is probably close to a NOAEL for AEGL-2. In addition, the ocular and respiratory tract irritation associated with TDI exposure appears to be more concentration-dependent than duration-dependent. However, exposure for longer periods can result in excessive fluid accumulation in the respiratory tract, which could lead to more severe consequences than those defined under AEGL-2.

Extrapolations across time were made using the equation $C^n \times t = k$, where n ranges from 0.8 to 3.5 (ten Berge et al. 1986). In the absence of an empirically derived, chemical-specific exponent, scaling was performed using $n = 3$ for extrapolating to the 10-min time point and $n = 1$ for the 1- and 4-h time points. The 4-h value was used for the 8-h because extrapolation to 8 h resulted in a concentration similar to one that caused mild effects in polyurethane foam sprayers exposed for >7 h (Hosein and Farkas 1981) and in manufacturing workers on 8-h shifts (Hama 1957). An intraspecies uncertainty factor (UF) of 3 was applied to account for sensitive individuals; use of a greater UF would result in values below those supported by the human data. The values for AEGL-2 are presented in Table 4-8.

An intraspecies UF of 3 has been used before in establishing AEGL values for chemicals that are rapidly acting respiratory irritants. Although some individuals with pre-existing bronchial hyper-reactivity have been shown to respond to TDI with nonpathological bronchial obstruction (4/15), no significant differences were observed in lung function parameters. Also, complaints of respiratory irritation occurred in both asthmatic subjects and healthy controls (Baur 1985).

Borm et al. (1990) used animal data for various toxic end points resulting from TDI exposure to calculate exposure levels for humans. The end points included were respiratory irritation, sensitization, airway hyper-responsiveness, and gradual loss of pulmonary function. The authors found that use of respiratory irritation resulted in the most conservative estimates for protection of human health (Borm et al. 1990). Using one-tenth of the mouse or rat RD_{50}, a measure of respiratory irritation, for calculation of AEGL-2, and applying an intraspecies UF of 3 results in values that are below concentrations shown to affect humans (Hosein and Farkas 1981; Henschler et al. 1962). However, similar results to the AEGL-2 values are obtained by starting with a 4-h exposure at 2 ppm. At that exposure regimen, clearing of respiratory tract lesions was observed in four laboratory species (Duncan et al. 1962). Therefore, the animal data strongly support the AEGL-2 values derived from human experiments.

7. DATA ANALYSIS AND AEGL-3

AEGL-3 is the airborne concentration (expressed as ppm or mg/m^3) of a substance above which it is predicted that the general population, including susceptible individuals, could experience life-threatening health effects or death.

TABLE 4-8 AEGL-2 Values for Toluene 2,4- and 2,6-Diisocyanate (ppm [mg/m^3])

10 min	30 min	1 h	4 h	8 h
0.24 (1.71)	0.17 (1.21)	0.083 (0.59)	0.021 (0.15)	0.021 (0.15)

7.1. Summary of Human Data Relevant to AEGL-3

No reliable human data were available for derivation of AEGL-3 values. Reported human fatalities occurred under unusual circumstances, and exposure concentrations were not measured. Acute exposure reports emphasize that the respiratory tract is the primary target, and pulmonary edema develops subsequent to the irritation brought on by the corrosive properties of TDI.

7.2. Summary of Animal Data Relevant to AEGL-3

On the basis of LC_{50} values, the mouse is the species most sensitive to the effects of TDI. The 4-h LC_{50} for the mouse was 9.7 ppm. Death was preceded by severe pathology in the respiratory tract (Duncan et al. 1962). Mouse RD_{50} values are considered equivalent to AEGL-3 values for humans (Alarie 1981). The 10-min and 1-h RD_{50}s of TDI in male Swiss-Webster mice are 0.8 ppm and 0.39 ppm, respectively (Sangha and Alarie 1979).

7.3. Derivation of AEGL-3

The 4-h mouse LC_{50} of 9.7 ppm (Duncan et al. 1962) was divided by 3 to estimate a threshold of lethality from the regression plot. The LC_{50} probit plot from Duncan et al. (1962) is shown in Appendix A. Extension of the regression line for the mouse data to the x-intercept shows that a concentration at approximately 4 ppm would result in 1% lethality. Therefore, one-third of the LC_{50} is considered to be a reasonable estimate of the threshold for lethality (NRC 2001).

The estimated 4-h lethality threshold, 3.23 ppm, was used to extrapolate to the 30-min and 1- and 8-h AEGL-3 time points. Values were scaled using the equation $C^n \times t = k$, where n ranges from 0.8 to 3.5 (ten Berge et

al. 1986). In the absence of an empirically derived, chemical-specific exponent, scaling was performed using $n = 3$ for extrapolating to the 30-min and 1-h time points and $n = 1$ for the 8-h time point. A total UF of 10 was applied, which includes 3 to account for sensitive individuals and 3 for interspecies extrapolation (use of a greater UF would result in values similar to concentrations that produced mild irritation in human inhalation studies). According to Section 2.7 of the standard operating procedures for the derivation of AEGLs (NRC 2001), 10-min values are not to be scaled from an experimental exposure time of ≥4 h. Therefore, the 30-min AEGL-3 value was adopted as the 10-min value. The values for AEGL-3 are given in Table 4-9.

Individuals already sensitized to TDI may exist in the general population. No data are available to quantify or estimate the rate of sensitization. At the AEGL-3 levels, individuals who have a stronger reaction to TDI might not be protected from severe effects.

Using the mouse RD_{50}, a measure of respiratory irritation, to calculate AEGL-3 and applying an intraspecies UF of 3 results in values that are similar to concentrations shown to affect humans in controlled experimental studies (Henschler et al. 1962).

8. SUMMARY OF AEGLS

8.1. AEGL Values and Toxicity End Points

The derived AEGLs for various levels of effects and durations of exposure are summarized in Table 4-10. AEGL-1 and AEGL-2 were based on sensory irritation in humans. The basis for AEGL-3 was a calculated 4-h LC_{50} in the mouse. Presensitized individuals might exist in the general population, but the rate of TDI sensitization cannot be predicted. If the rate of sensitization in the general population were quantifiable, the committee might have considered a different approach to derivation of AEGL values.

TABLE 4-9 AEGL-3 Values for Toluene 2,4- and 2,6-Diisocyanate (ppm [mg/m^3])

10 min	30 min	1 h	4 h	8 h
0.65 (4.63)	0.65 (4.63)	0.51 (3.63)	0.32 (2.28)	0.16 (1.14)

TABLE 4-10 Summary of AEGL Values (ppm [mg/m^3])

	Exposure Duration				
Classification	10 min	30 min	1 h	4 h	8 h
AEGL-1 (Nondisabling)	0.02 (0.14)	0.02 (0.14)	0.02 (0.14)	0.01 (0.07)	0.01 (0.07)
AEGL-2 (Disabling)	0.24 (1.71)	0.17 (1.21)	0.083 (0.59)	0.021 (0.15)	0.021 (0.15)
AEGL-3 (Lethal)	0.65 (4.63)	0.65 (4.63)	0.51 (3.63)	0.32 (2.28)	0.16 (1.14)

At each of the AEGL levels, individuals who have a strong reaction to TDI might not be protected within the definition of effects for each level.

8.2. Comparison with Other Standards and Criteria

Existing guideline exposure levels for TDI are listed in Table 4-11. NIOSH has not set exposure limits for 2,4-TDI but recommends limiting exposure to the lowest feasible concentration (NIOSH 1997). The OSHA ceiling limit (concentration that should not be exceeded at any time) for 2,4-TDI is 0.02 ppm (OSHA 1995).

The IDLH is based on acute inhalation toxicity data in animals, but was not based on data obtained from the exposures of humans or animals sensitized to TDI (NIOSH 1996). Four-hour LC_{50} values in four laboratory animal species ranged from 9.7 ppm to 13.9 ppm (Duncan et al. 1962). To calculate the IDLH, these LC_{50}s were adjusted to 30 min by multiplying by a correction factor of 2. The adjusted values were divided by a UF of 10 to yield derived values of 1.9-2.8 ppm. Therefore, the IDLH was set at 2.5 ppm (NIOSH 1996). Those same data were used in derivation of AEGL-3; however, the resulting 30-min AEGL-3 is approximately one-third of the IDLH because an estimation of the threshold for lethality was obtained by dividing the mouse LC_{50} by 3.

ACGIH (2001) classifies the chemical as a sensitizer, which refers to the potential for an agent to produce sensitization. The sensitizer notation does not imply that sensitization is the critical effect on which the Threshold Limit Value (TLV) is based, nor does it imply that the effect is the sole basis for the TLV (ACGIH 2001). The 8-h TLV of 0.005 ppm is intended to both protect against possible sensitization in workers and reduce the opportunity for accidental TDI exposure.

TABLE 4-11 Extant Standards and Guidelines for Toluene 2,4- and 2,6-Diisocyanate (ppm)

	Exposure Duration				
Guideline	10 min	30 min	1 h	4 h	8 h
AEGL-1	0.02	0.02	0.02	0.01	0.01
AEGL-2	0.24	0.17	0.083	0.021	0.021
AEGL-3	0.65	0.65	0.51	0.32	0.16
PEL-TWA (OSHA)[a]					0.02 (C)
IDLH (NIOSH)[b]		2.5			
TLV-TWA (ACGIH)[c]					0.005 (SEN)
TLV-STEL (ACGIH)[d]	0.02 (SEN)				
MAC (The Netherlands)[e]	0.02 (15-min)				0.005

[a]OSHA PEL-TWA (permissible exposure limit-time-weighted average of the Occupational Health and Safety Administration) (29 CFR § 1910.1000). The PEL-TWA is defined analogous to the ACGIH TLV-TWA but is for exposures of no more than 10 h/d, 40 h/wk. (C) denotes a ceiling limit.

[b]IDLH (immediately dangerous to life and health of the National Institute of Occupational Safety and Health) (NIOSH 1996). The IDLH represents the maximum concentration from which one could escape within 30 min without any escape-impairing symptoms or any irreversible health effects. The IDLH for TDI is based on acute inhalation toxicity data in animals, but is not based on data obtained from the exposures of individuals or animals already sensitized to TDI.

[c]ACGIH TLV-TWA (Threshold Limit Value–time-weighted average of the American Conference of Governmental Industrial Hygienists) (ACGIH 1996, 2001). The TLV-TWA is the time-weighted average concentration for a normal 8-h work day and a 40-h work week to which nearly all workers may be repeatedly exposed, day after day, without adverse effect. SEN notation refers to the potential for an agent to produce sensitization.

[d]ACGIH TLV-STEL (Threshold Limit Value–short-term exposure limit) (ACGIH 2001). The TLV-STEL is defined as a 15-min TWA exposure that should not be exceeded at any time during the work day even if the 8-h TWA is within the TLV-TWA. Exposures above the TLV-TWA up to the STEL should not be longer than 15 min and should not occur more than 4 times per day. There should be at least 60 min between successive exposures in that range. SEN notation refers to the potential for an agent to produce sensitization.

[e]MAC (Maximaal Aanvaaarde Concentratie [Maximal Accepted Concentration]) (SDU Uitgevers [under the auspices of the Ministry of Social Affairs and Employment], The Hague, The Netherlands 2000). The MAC is defined analogous to the ACGIH TLV-TWA.

ERPG values for TDI were under consideration as of year 2000 but had not been derived by 2002. The German Research Council (2000) has not recommended a current MAK but lists the chemical as an airway sensitizer.

8.3. Data Adequacy and Research Needs

Limited quantitative data in humans were available for use in deriving AEGLs. Experimental studies in humans included one that used both asthmatic subjects and healthy subjects and another that reported a concentration-response assessment. However, those are the only human studies available. Generally, very low concentrations of TDI were reported in occupational studies. Animal data have shown concentration-dependent effects, including irritation and histologic lesions of the respiratory tract and lethality. Because the nonlethal and lethal effects in humans and animals are qualitatively similar, the animal data were considered relevant and appropriate for developing AEGL values as described in the standing operating procedures of the National Advisory Committee for AEGLs (NRC 2001).

The most notable data deficiencies were the absence of quantitative human exposure data, the absence of a well-defined exposure-response curve for the toxic effects in animals, a lack of understanding of individual variability in the toxic response to TDI, and a lack of information on the extent of cross-reactivity between isocyanates.

Critical research needs include defining thresholds for effects and how those thresholds might vary with exposure concentration and duration. Such data would be valuable for affirming the AEGL values. In addition, a scientifically verifiable estimate of the number of individuals in the general population who are presensitized to TDI would be instrumental in reducing uncertainties in quantitative health risk issues.

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APPENDIX A

LC_{50} Probit Plot

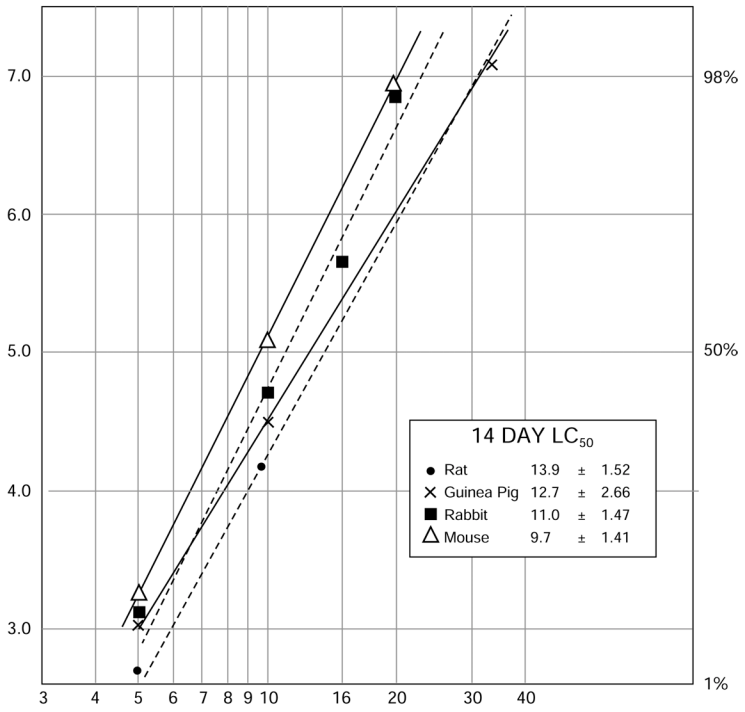

FIGURE 4A-1 LC_{50} probit plot. Source: Duncan et al. 1962. Reprinted with permission from the *American Industrial Hygiene Association Journal*; copyright 1962, AIHA.

APPENDIX B

Derivation of AEGL Values

Derivation of AEGL-1

Key study:	Baur 1985
Toxicity end point:	Asthmatic subjects experienced cough, rhinitis, chest tightness, dyspnea, throat irritation, and/or headache from exposure at 0.01 ppm for 1 h, and then, after a rest, at 0.02 ppm for another hour.
Time-scaling:	None
Uncertainty factors:	None—asthmatic people are considered a sensitive population
Modifying factor:	None
10-min AEGL-1:	0.02 ppm
30-min AEGL-1:	0.02 ppm
1-h AEGL-1:	0.02 ppm
4-h AEGL-1:	0.01 ppm
8-h AEGL-1:	0.01 ppm

Derivation of AEGL-2

Key study:	Henschler et al. 1962
Toxicity end points:	Severe eye and throat irritation in humans exposed at 0.5 ppm for 30 min

Time-scaling: $C^n \times t = k$ (ten Berge et al. 1986; NRC 2001), $n = 3$ for extrapolating to the 10-min time point, $n = 1$ for extrapolating to the 1-, 4-, and 8-h time points

Uncertainty factors: 3 for intraspecies variability (not protecting hypersusceptible individuals)

Calculations: *10-min time point*
$(C/\text{UFs})^3 \times t = k$
$(0.5/3)^3 \times 0.5 \text{ h} = 0.0023 \text{ ppm}^3\cdot\text{h}$

1-, 4-, and 8-h time points
$(C/\text{UFs})^1 \times t = k$
$(0.5/3)^1 \times 0.5 \text{ h} = 0.083 \text{ ppm}\cdot\text{h}$

10-min AEGL-2: $(0.0023 \text{ ppm}^3\cdot\text{h}/0.167 \text{ h}) = 0.24 \text{ ppm}$

30-min AEGL-2: 0.5 ppm/3 = 0.17 ppm

1-h AEGL-2: $(0.083 \text{ ppm}\cdot\text{h}/1 \text{ h}) = 0.083 \text{ ppm}$

4-h AEGL-2: $(0.083 \text{ ppm}\cdot\text{h}/4 \text{ h}) = 0.021 \text{ ppm}$

8-h AEGL-2: 0.021 ppm

Derivation of AEGL-3

Key Study: Duncan et al. 1962

Toxicity end point: The 4-h LC_{50} of 9.7 ppm in mice was used for derivation of AEGL-3 values. An approximate threshold for lethality is obtained by dividing the LC_{50} by 3.

Time-scaling: $C^n \times t = k$ (ten Berge et al. 1986)

	n = 3 for extrapolating to the 10-min, 30-min, and 1-h time points; $(3.23)^3 \times 4.0 = 135.21$ ppm·h
	n = 1 for extrapolating to the 8-h time point; $(3.23)^1 \times 4.0 = 12.92$ ppm·h
Uncertainty factors:	10 (3 for intraspecies variability and 3 for interspecies variability
Calculations:	*10-min, 30-min, and 1-h time points* $(C/\text{UFs})^3 \times t = k$ $(3.23/10)^3 \times 4$ h = 0.135 ppm^3·h
	8-h time point $(C/\text{uncertainty factors})^1 \times t = k$ $(3.23/10)^1 \times 4$ h = 1.292 ppm·hr
10-min AEGL-2:	0.65 ppm
30-min AEGL-2:	(0.135 ppm^3·h/0.5 h) = 0.65 ppm
1-h AEGL-2:	(0.135 ppm^3·h/1 h) = 0.51 ppm
4-h AEGL-2:	(3.23 ppm/10) = 0.32 ppm
8-h AEGL-2:	(1.292 ppm·h/8 h) = 0.16 ppm

APPENDIX C

DERIVATION SUMMARY

ACUTE EXPOSURE GUIDELINE LEVELS FOR TOLUENE 2,4- AND 2,6-DIISOCYANATE (CAS Nos. 584-84-9 and 91-08-7)

AEGL-1				
10 min	30 min	1 h	4 h	8 h
0.02 ppm	0.02 ppm	0.02 ppm	0.01 ppm	0.01 ppm
Key reference: Baur, X. 1985. Isocyanate hypersensitivity. Final report to the International Isocyanate Institute. III File No. 10349; III Project: E-AB-19.				
Test species/strain/number: Human subjects, gender not given;10 healthy controls and 15 asthmatics				
Exposure route/concentrations/durations: Inhalation; 0.02 ppm for 2 h (controls); 0.01 ppm for 1 h, 45 min rest, 0.02 ppm for 1 h (asthmatics)				
Effects: Controls—significant increase in airway resistence (R_{aw}) immediately and 30 min after beginning of exposure; eye irritation and/or cough. Asthmatics—no change in lung function parameters; chest tightness, rhinitis, cough, dyspnea, throat irritation, and/or headache				
End point/concentration/rationale: Some (5/15) asthmatic humans exposed for 1 h at 0.01 ppm and, after a 45 min rest, at 0.02 ppm for another hour experienced chest tightness, rhinitis, cough, dyspnea, throat irritation, and/or headache.				
Uncertainty factors/rationale: Total uncertainty factor: None Interspecies: Not applicable, human data used Intraspecies: 1, asthmatics were used as the test population				
Modifying factor: None				
Animal to human dosimetric adjustment: Not applicable				
Time-scaling: Extrapolation to time points was not conducted. Because the asthmatics tolerated 0.02 ppm for 1 h after pre-exposure at 0.01 ppm, it is assumed that this population could tolerate the lower concentration for a longer duration.				
Data quality and support for the AEGL values: AEGL-1 values are considered conservative and should be protective of the toxic effects of TDI outside those expected as defined under AEGL-1.				

AEGL-2				
10 min	30 min	1 h	4 h	8 h
0.24 ppm	0.17 ppm	0.083 ppm	0.021 ppm	0.02 ppm
Key reference: Henschler, D., Assman, W., and Meyer, K.-O. 1962. On the toxicology of toluenediisocyanate [in German]. Archiv. für Toxikologie 19:364-387				
Test species/strain/number: Human, healthy male, 6				
Exposure route/concentrations/durations: 0.01-1.3 ppm 2,4/2,6-, 2,4-, or 2,6-TDI for 30 min				
Effects: Effects were similar for both isomers and the mixture. 0.1 ppm: eye and nose irritation; ≥0.5 ppm: marked discomfort, lacrimation, nasal secretion (determinant for AEGL-2); 1.3 ppm: intolerable.				
End point/concentration/rationale: Humans exposed at 0.5 ppm for 30 min experienced pronounced irritation (marked discomfort, lacrimation, nasal secretion)				
Uncertainty factors/rationale: Total uncertainty factor: 3 Interspecies: Not applicaple, human data used Intraspecies: 3. The use of a higher uncertainty factor would make the AEGL-2 values similar to AEGL-1 values, which are based on levels that asthmatic humans can tolerate.				
Modifying factor: Not applicable				
Animal to human dosimetric adjustment: Not applicable				
Time-scaling: $C^n \times t = k$ where n ranges from 0.8 to 3.5 (ten Berge et al. 1986). In the absence of an emphirically derived, chemical-specific exponent, scaling was performed using $n = 1$ for extrapolating to the 10-min time point and $n = 3$ for the 1- and 4-h time points. The 4-h value is also used for the 8-h value because extrapolation to 8 h resulted in a concentration similar to that causing mild effects in polyurethane foam sprayers exposed for >7 h (Hosein and Farkas 1981) and in manufacturing workers on 8-h shifts (Hama 1957).				
Data quality and support for the AEGL values: Some individuals with pre-existing bronchial hyper-reactivity have been shown to respond to TDI with nonpathologic bronchial obstruction (4/15), but no significant differences were observed in lung function parameters. AEGL-2 values also supported by animal data.				

AEGL-3				
10 min	30 min	1 h	4 h	8 h
0.65 ppm	0.65 ppm	0.51 ppm	0.32 ppm	0.16 ppm
Key reference: Duncan, B., Scheel, L.D., Fairchild, E.J., Killens, R., and Graham, S. 1962. Toluene diisocyanate inhalation toxicity: pathology and mortality. Am. Indus. Hygiene Assoc. J. 23:447-456.				
Test species/strain/number: Mice, 120 total animals				
Exposure route/concentrations/durations: Inhalation, 0.1, 1.0, 2, 5, 10, 20, or 34 ppm for 4 h				
Effects: 9.7 ppm 4-h LC_{50} in the mouse: concentration dependent signs of toxicity included mouth breathing, lacrimation, salivation, and restlessness; Histopathologic examination of surviving animals: coagulation necrosis and desquamation of the superficial epithelial lining of the trachea and major bronchi, cleared by day 7 post-exposure in the 2 ppm group.				
End point/concentration/rationale: 3.23 ppm is an estimated lethality threshold obtained by dividing the 4-h mouse LC_{50} by 3. That is approximately equal to the LC_{01} obtained by extrapolating the probit plot in the Duncan et al. (1962) paper.				
Uncertainty factors/rationale: Total uncertainty factor: 10 Interspecies: 3. The LC_{50} was determined in the rat, guinea pig, rabbit, and mouse. The 4-h LC_{50} values ranged from 9.7 ppm in the mouse to 13.9 ppm in the rat. These results argue for low variability between species. In addition, the use of a higher uncertainty factor would place the AEGL-3 levels in the range of the AEGL-2 values, which were set based on human data. The most sensitive species, the mouse, was used to derive the AEGL-3 values. Intraspecies: 3. Use of a greater uncertainty factor would result in values below those supported by human data for AEGL-3 effects.				
Modifying factor: Not applicable				
Animal to human dosimetric adjustment: Not applicable				
Time-scaling: $C^n \times t = k$ where n ranges from 0.8 to 3.5 (ten Berge et al. 1986). In the absence of an empirically derived, chemical-specific exponent, scaling was performed using $n = 1$ for extrapolating to the 30-min and 1-h time points and $n = 3$ for the 8-h time point. The 10-min AEGL-3 value was flatlined from the 30-min value.				
Data quality and support for the AEGL values: Presensitized individuals might exist in the general population, but the rate of sensitization cannot be predicted. If the rate of sensitization to TDI in the general population were				

AEGL-3 *Continued*
quantifiable, the committee might have considered lower values for AEGL-3. At the AEGL-3 levels, individuals who have a stronger reaction to TDI might not be protected from severe effects. The mouse appears to be the most sensitive species tested, although LC_{50} values did not vary greatly.