TOXICOLOGICAL PROFILE FOR TOLUENE DIISOCYANATE AND METHYLENEDIPHENYL DIISOCYANATE

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Agency for Toxic Substances and Disease Registry

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DISCLAIMER

Use of trade names is for identification only and does not imply endorsement by the Agency for Toxic Substances and Disease Registry, the Public Health Service, or the U.S. Department of Health and Human Services.

UPDATE STATEMENT

A Toxicological Profile for Toluene Diisocyanate and Methylenediphenyl Diisocyanate, Draft for Public Comment was released in September 2015. This edition supersedes any previously released draft or final profile.

Toxicological profiles are revised and republished as necessary. For information regarding the update status of previously released profiles, contact ATSDR at:

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FOREWORD

This toxicological profile is prepared in accordance with guidelines* developed by the Agency for Toxic Substances and Disease Registry (ATSDR) and the Environmental Protection Agency (EPA). The original guidelines were published in the *Federal Register* on April 17, 1987. Each profile will be revised and republished as necessary.

The ATSDR toxicological profile succinctly characterizes the toxicologic and adverse health effects information for these toxic substances described therein. Each peer-reviewed profile identifies and reviews the key literature that describes a substance's toxicologic properties. Other pertinent literature is also presented, but is described in less detail than the key studies. The profile is not intended to be an exhaustive document; however, more comprehensive sources of specialty information are referenced.

The focus of the profiles is on health and toxicologic information; therefore, each toxicological profile begins with a public health statement that describes, in nontechnical language, a substance's relevant toxicological properties. Following the public health statement is information concerning levels of significant human exposure and, where known, significant health effects. The adequacy of information to determine a substance's health effects is described in a health effects summary. Data needs that are of significance to the protection of public health are identified by ATSDR.

Each profile includes the following:

(A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a toxic substance to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects;

(B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine levels of exposure that present a significant risk to human health of acute, subacute, and chronic health effects; and

(C) Where appropriate, identification of toxicologic testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans.

The principal audiences for the toxicological profiles are health professionals at the Federal, State, and local levels; interested private sector organizations and groups; and members of the public.

This profile reflects ATSDR's assessment of all relevant toxicologic testing and information that has been peer-reviewed. Staffs of the Centers for Disease Control and Prevention and other Federal scientists have also reviewed the profile. In addition, this profile has been peer-reviewed by a nongovernmental panel and was made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.

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*Legislative Background

The toxicological profiles are developed under the Comprehensive Environmental Response, Compensation, and Liability Act of 1980, as amended (CERCLA or Superfund). CERCLA section 104(i)(1) directs the Administrator of ATSDR to "…effectuate and implement the health related authorities" of the statute. This includes the preparation of toxicological profiles for hazardous substances most commonly found at facilities on the CERCLA National Priorities List and that pose the most significant potential threat to human health, as determined by ATSDR and the EPA. Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list. In addition, ATSDR has the authority to prepare toxicological profiles for substances not found at sites on the National Priorities List, in an effort to "…establish and maintain inventory of literature, research, and studies on the health effects of toxic substances" under CERCLA Section 104(i)(1)(B), to respond to requests for consultation under section 104(i)(4), and as otherwise necessary to support the site-specific response actions conducted by ATSDR.

QUICK REFERENCE FOR HEALTH CARE PROVIDERS

Toxicological Profiles are a unique compilation of toxicological information on a given hazardous substance. Each profile reflects a comprehensive and extensive evaluation, summary, and interpretation of available toxicologic and epidemiologic information on a substance. Health care providers treating patients potentially exposed to hazardous substances may find the following information helpful for fast answers to often-asked questions.

Primary Chapters/Sections of Interest

Chapter 1: Public Health Statement: The Public Health Statement can be a useful tool for educating patients about possible exposure to a hazardous substance. It explains a substance's relevant toxicologic properties in a nontechnical, question-and-answer format, and it includes a review of the general health effects observed following exposure.

Chapter 2: Relevance to Public Health: The Relevance to Public Health Section evaluates, interprets, and assesses the significance of toxicity data to human health.

Chapter 3: Health Effects: Specific health effects of a given hazardous compound are reported by type of health effect (e.g., death, systemic, immunologic, reproductive), by route of exposure, and by length of exposure (acute, intermediate, and chronic). In addition, both human and animal studies are reported in this section.
NOTE: Not all health effects reported in this section are necessarily observed in the clinical setting. Please refer to the Public Health Statement to identify general health effects observed following exposure.

Pediatrics: Four new sections have been added to each Toxicological Profile to address child health issues:

Chapter 1	**How Can (Chemical X) Affect Children?**
Chapter 1	**How Can Families Reduce the Risk of Exposure to (Chemical X)?**
Section 3.7	**Children's Susceptibility**
Section 6.6	**Exposures of Children**

Other Sections of Interest:

Section 3.8	**Biomarkers of Exposure and Effect**
Section 3.11	**Methods for Reducing Toxic Effects**

ATSDR Information Center

Phone: 1-800-CDC-INFO (800-232-4636) or 1-888-232-6348 (TTY)
Internet: http://www.atsdr.cdc.gov

The following additional materials are available online:

Case Studies in Environmental Medicine are self-instructional publications designed to increase primary health care providers' knowledge of a hazardous substance in the environment and to aid in the evaluation of potentially exposed patients (see https://www.atsdr.cdc.gov/csem/csem.html).

Managing Hazardous Materials Incidents is a three-volume set of recommendations for on-scene (prehospital) and hospital medical management of patients exposed during a hazardous materials incident (see https://www.atsdr.cdc.gov/MHMI/index.asp). Volumes I and II are planning guides to assist first responders and hospital emergency department personnel in planning for incidents that involve hazardous materials. Volume III—*Medical Management Guidelines for Acute Chemical Exposures*—is a guide for health care professionals treating patients exposed to hazardous materials.

Fact Sheets (ToxFAQs™) provide answers to frequently asked questions about toxic substances (see https://www.atsdr.cdc.gov/toxfaqs/Index.asp).

Other Agencies and Organizations

The National Center for Environmental Health (NCEH) focuses on preventing or controlling disease, injury, and disability related to the interactions between people and their environment outside the workplace. Contact: NCEH, Mailstop F-29, 4770 Buford Highway, NE, Atlanta, GA 30341-3724 • Phone: 770-488-7000 • FAX: 770-488-7015 • Web Page: https://www.cdc.gov/nceh/.

The National Institute for Occupational Safety and Health (NIOSH) conducts research on occupational diseases and injuries, responds to requests for assistance by investigating problems of health and safety in the workplace, recommends standards to the Occupational Safety and Health Administration (OSHA) and the Mine Safety and Health Administration (MSHA), and trains professionals in occupational safety and health. Contact: NIOSH, 395 E Street, S.W., Suite 9200, Patriots Plaza Building, Washington, DC 20201 • Phone: 202-245-0625 or 1-800-CDC-INFO (800-232-4636) • Web Page: https://www.cdc.gov/niosh/.

The National Institute of Environmental Health Sciences (NIEHS) is the principal federal agency for biomedical research on the effects of chemical, physical, and biologic environmental agents on human health and well-being. Contact: NIEHS, PO Box 12233, 104 T.W. Alexander Drive, Research Triangle Park, NC 27709 • Phone: 919-541-3212 • Web Page: https://www.niehs.nih.gov/.

Clinical Resources (Publicly Available Information)

The Association of Occupational and Environmental Clinics (AOEC) has developed a network of clinics in the United States to provide expertise in occupational and environmental issues. Contact: AOEC, 1010 Vermont Avenue, NW, #513, Washington, DC 20005 • Phone: 202-347-4976 • FAX: 202-347-4950 • e-mail: AOEC@AOEC.ORG • Web Page: http://www.aoec.org/.

The American College of Occupational and Environmental Medicine (ACOEM) is an association of physicians and other health care providers specializing in the field of occupational and environmental medicine. Contact: ACOEM, 25 Northwest Point Boulevard, Suite 700, Elk Grove Village, IL 60007-1030 • Phone: 847-818-1800 • FAX: 847-818-9266 • Web Page: http://www.acoem.org/.

The American College of Medical Toxicology (ACMT) is a nonprofit association of physicians with recognized expertise in medical toxicology. Contact: ACMT, 10645 North Tatum Boulevard,

Suite 200-111, Phoenix AZ 85028 • Phone: 844-226-8333 • FAX: 844-226-8333 • Web Page: http://www.acmt.net.

The Pediatric Environmental Health Specialty Units (PEHSUs) is an interconnected system of specialists who respond to questions from public health professionals, clinicians, policy makers, and the public about the impact of environmental factors on the health of children and reproductive-aged adults. Contact information for regional centers can be found at http://pehsu.net/findhelp.html.

The American Association of Poison Control Centers (AAPCC) provide support on the prevention and treatment of poison exposures. Contact: AAPCC, 515 King Street, Suite 510, Alexandria VA 22314 • Phone: 701-894-1858 • Poison Help Line: 1-800-222-1222 • Web Page: http://www.aapcc.org/.

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THE PROFILE HAS UNDERGONE THE FOLLOWING ATSDR INTERNAL REVIEWS:

1. Health Effects Review. The Health Effects Review Committee examines the health effects chapter of each profile for consistency and accuracy in interpreting health effects and classifying end points.

2. Minimal Risk Level Review. The Minimal Risk Level Workgroup considers issues relevant to substance-specific Minimal Risk Levels (MRLs), reviews the health effects database of each profile, and makes recommendations for derivation of MRLs.

3. Data Needs Review. The Environmental Toxicology Branch reviews data needs sections to assure consistency across profiles and adherence to instructions in the Guidance.

4. Green Border Review. Green Border review assures the consistency with ATSDR policy.

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PEER REVIEW

A peer review panel was assembled for toluene diisocyanate and methylenediphenyl diisocyanate. The panel consisted of the following members:

1. Dr. Mark Pemberton; Systox, Ltd.; Wilmslow, Cheshire, United Kingdom;

2. Robyn Prueitt, Ph.D., DABT; Gradient Corporation; Cambridge, Massachusetts; and

3. John Weeks, DABT; S.C. Johnson & Son, Inc.; Racine, Wisconsin.

These experts collectively have knowledge of toluene diisocyanate and methylenediphenyl diisocyanate physical and chemical properties, toxicokinetics, key health end points, mechanisms of action, human and animal exposure, and quantification of risk to humans. All reviewers were selected in conformity with the conditions for peer review specified in Section 104(I)(13) of the Comprehensive Environmental Response, Compensation, and Liability Act, as amended.

Scientists from the Agency for Toxic Substances and Disease Registry (ATSDR) have reviewed the peer reviewers' comments and determined which comments will be included in the profile. A listing of the peer reviewers' comments not incorporated in the profile, with a brief explanation of the rationale for their exclusion, exists as part of the administrative record for this compound.

The citation of the peer review panel should not be understood to imply its approval of the profile's final content. The responsibility for the content of this profile lies with the ATSDR.

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1. PUBLIC HEALTH STATEMENT

This Public Health Statement summarizes the Agency for Toxic Substances and Disease Registry's (ATSDR) findings on toluene diisocyanate (TDI) and methylenediphenyl diisocyanate (MDI), including chemical characteristics, exposure risks, possible health effects from exposure, and ways to limit exposure.

The U.S. Environmental Protection Agency (EPA) identifies the most serious hazardous waste sites in the nation. These sites make up the National Priorities List (NPL) and are sites targeted for long-term federal clean-up activities. The EPA has found TDI in at least 4 of the 1,854 current or former NPL sites. MDI was not found in any of the current or former NPL sites. The total number of NPL sites evaluated for TDI and MDI is not known. But the possibility remains that as more sites are evaluated, the number of sites at which TDI and MDI are found may increase. This information is important because these future sites may be sources of exposure, and exposure to TDI and MDI may be harmful.

If you are exposed to TDI or MDI, many factors determine whether you'll be harmed. These include how much you are exposed to (dose), how long you are exposed (duration), how often you are exposed (frequency), and how you are exposed (route of exposure). You must also consider the other chemicals you are exposed to and your age, sex, diet, family traits, lifestyle, and state of health.

WHAT ARE TDI AND MDI?

TDI and MDI do not occur naturally in the environment. TDI is a clear, colorless to pale yellow liquid. MDI is a light yellow crystalline solid. There are several forms of TDI and MDI, which are called isomers. The two most common TDI isomers are 2,4-TDI and 2,6-TDI. The most common isomer of MDI is 4,4'-MDI.

TDI and MDI are used to make many household products. They combine with other chemicals to produce various polyurethanes. Some of the products made with these polyurethanes include foam for furniture cushions and carpet padding and waterproof sealants.

WHAT HAPPENS TO TDI AND MDI WHEN THEY ENTER THE ENVIRONMENT?

TDI and MDI can be released into the air, water, and soil at places where they are produced or used. TDI and MDI are extremely reactive chemicals and are not likely to stay in the environment. In air, TDI and

MDI have half-lives of less than 1 day (half-life is the amount of time needed for the amount of TDI or MDI in air to be reduced by one-half). TDI and MDI rapidly react with water to form other compounds in a process called hydrolysis. The half-lives of TDI and MDI in water range from a few minutes to a few hours. Significant concentrations are not likely to be found in moist soil or sediment due to the rapid hydrolysis of these compounds; however, small amounts may be detected near point sources such as industrial waste streams and hazardous waste sites. TDI and MDI will not bioaccumulate in the food chain and are therefore not expected to be found in significant concentrations in fish and foods.

HOW MIGHT I BE EXPOSED TO TDI AND MDI?

TDI and MDI are used to make a number of different types of polyurethane products that are used by consumers ranging from foams for insulation, foam cushions, and sealants. In products such as cushions, the diisocyanates are cured, meaning that they are not reactive. It is unlikely that consumers would be exposed to diisocyanates from cured products. However, you can be exposed to TDI in the air from uncured polyurethane products such as adhesives, sealants, coatings, paints, craft materials, and insulating foams. The percentage of monomeric isocyanates in pre-polymer products is low (generally <5% for consumer products). Consumer products that contain low levels of diisocyanates warn against dermal exposure and recommend use of protective gloves. Workers involved in the manufacture of cured and uncured polyurethane products or involved in other industries using uncured diisocyanates may be exposed to higher levels. You are unlikely to be exposed to TDI or MDI in food or water.

HOW CAN TDI AND MDI ENTER AND LEAVE MY BODY?

When you breathe air containing TDI or MDI, some will enter your body through your lungs, but there is limited information on how much and how fast these compounds enter the body. TDI may enter your body through the digestive tract if you ingest it. There are no data on whether MDI will enter your body after ingestion. If your skin comes in contact with TDI or MDI, it is possible that a small amount may enter the body through the skin.

Once TDI or MDI enters your body, it reacts with large molecules, called macromolecules to form TDI- or MDI-conjugates. These conjugates are widely distributed throughout the body. TDI or MDI can also be reactive with itself to form compounds called polyureas, which are not absorbed. TDI and MDI conjugates and polyureas primarily leave the body in the feces; a small amount also leaves the body in the urine.

HOW CAN TDI AND MDI AFFECT MY HEALTH?

The health effects of TDI and MDI depend on how much you are exposed to and the length of that exposure. Respiratory effects, including a decrease in lung function, have been reported in workers exposed to TDI or MDI. Some workers have become sensitized to TDI and/or MDI; they are particularly sensitive to the toxicity of TDI and MDI and may experience adverse effects at much lower concentrations than the concentrations that may affect non-sensitized individuals. Asthma and symptoms of asthma, such as wheezing and shortness of breath, have been observed in some individuals who are particularly sensitive to the toxicity of TDI and MDI.

An excess of lung cancer has been observed in some workers at a polyurethane foam manufacturing plant. However, it is not known if exposure to TDI was the cause. A study in animals exposed by gavage to TDI reported increases in tumors in the pancreas, mammary gland, and liver. The Department of Health and Human Services (HHS) considers TDI as reasonably anticipated to be a human carcinogen and the International Agency for Research on Cancer has classified TDI as possibly carcinogenic to humans. EPA has not classified the carcinogenicity of TDI.

There are limited data to determine whether exposure to MDI can cause cancer. An animal study reported an increase in lung tumors in rats exposed by inhalation to polymeric MDI. The exposure levels tested in this study are much higher than concentrations found in work environments. IARC has determined that MDI is not classifiable as to its carcinogenicity in humans. EPA notes that the carcinogenicity of MDI cannot be determined, but there is suggestive evidence that raises concern for carcinogenic effects.

See Chapters 2 and 3 for more information on health effects of TDI and MDI.

HOW CAN TDI AND MDI AFFECT CHILDREN?

This section discusses potential health effects of TDI and MDI exposure in humans from when they're first conceived to 18 years of age.

We do not have any information on the effects of TDI or MDI in children. We expect that the effects in children will be similar to those seen in adults; exposure to TDI or MDI in the air could result in lung effects. A delay in bone growth has been observed in offspring of animals exposed to high levels of TDI in air that also caused decreases in body weight gain or respiratory effects in the mothers. Exposure to

high levels of MDI in air during gestation also resulted in bone effects in the offspring; the MDI concentration causing these effects also resulted in decreased food consumption in the mothers.

HOW CAN FAMILIES REDUCE THE RISK OF EXPOSURE TO TDI AND MDI?

If your doctor finds that you have been exposed to significant amounts of TDI or MDI, ask whether your children might also be exposed. Your doctor might need to ask your state health department to investigate. You may also contact the state or local health department with health concerns.

You are unlikely to be exposed to TDI and MDI from food, drinking water, contaminated groundwater, or soil.

TDI and MDI are used to make many products; however, most of these products are cured and should not have unreacted diisocyanates remaining in them. Primary users and bystanders should be made aware of the potential risks and appropriate precautions to take when uncured TDI or MDI products (such as spray foam or sealants) are being used because use of these professional products can result in exposure to TDI or MDI. Always follow the manufacturers' instruction or product labels when using these products. Wear personal protective equipment (chemical resistant goggles/gloves/ clothing) to prevent direct contact with skin and eyes.

ARE THERE MEDICAL TESTS TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO TDI OR MDI?

TDI and MDI exposures can be measured in blood and urine by hydrolyzing the TDI and MDI reaction products to the corresponding diamine. However, the detection of the diamine products cannot predict the kind of health effects that might develop from that exposure. Because TDI and MDI reaction products leave the body fairly rapidly (within hours or days), the tests need to be conducted soon after exposure. For more information on the reaction products of TDI and MDI and on tests to detect these substances in the body, see Chapters 3 and 7.

WHAT RECOMMENDATIONS HAS THE FEDERAL GOVERNMENT MADE TO PROTECT HUMAN HEALTH?

The federal government develops regulations and recommendations to protect public health. Regulations can be enforced by law. Federal agencies that develop regulations for toxic substances include the

Environmental Protection Agency (EPA), the Occupational Safety and Health Administration (OSHA), and the Food and Drug Administration (FDA). Recommendations provide valuable guidelines to protect public health but are not enforceable by law. Federal organizations that develop recommendations for toxic substances include the Agency for Toxic Substances and Disease Registry (ATSDR) and the National Institute for Occupational Safety and Health (NIOSH).

Regulations and recommendations can be expressed as "not-to-exceed" levels; that is, levels of a toxic substance in air, water, soil, or food that do not exceed a critical value usually based on levels that affect animals; levels are then adjusted to help protect humans. Sometimes these not-to-exceed levels differ among federal organizations. Different organizations use different exposure times (e.g., an 8-hour workday or a 24-hour day), different animal studies, or emphasize some factors over others, depending on their mission.

Recommendations and regulations are also updated periodically as more information becomes available. For the most current information, check with the federal agency or organization that issued the regulation or recommendation.

OSHA has set a legal ceiling limit of 0.02 parts per million (ppm) for TDI and MDI in air; these are "not-to-exceed" levels. NIOSH has set a recommended limit of 0.005 ppm for monomeric 4,4'-MDI in air for workers exposed 10 hours/day during a 40 hour/day workweek. The EPA has not recommended any drinking water guidelines for TDI or MDI.

WHERE CAN I GET MORE INFORMATION?

If you have any questions or concerns, please contact your community or state health or environmental quality department, or contact ATSDR at the address and phone number below. You may also contact your doctor if experiencing adverse health effects or for medical concerns or questions. ATSDR can also provide publicly available information regarding medical specialists with expertise and experience recognizing, evaluating, treating, and managing patients exposed to hazardous substances.

- Call the toll-free information and technical assistance number at 1-800-CDCINFO (1-800-232-4636) or

- Write to:
  Agency for Toxic Substances and Disease Registry
  Division of Toxicology and Human Health Sciences
  1600 Clifton Road NE
  Mailstop F-57
  Atlanta, GA 30329-4027

Toxicological profiles and other information are available on ATSDR's web site: http://www.atsdr.cdc.gov.

2. RELEVANCE TO PUBLIC HEALTH

2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO TDI AND MDI IN THE UNITED STATES

Diisocyanates have widespread commercial use due to their reactivity and versatility. These compounds are predominantly used in the production of polyurethane materials. Two diisocyanates, TDI and MDI, and their related polyisocyanates make up >90% of the commercial market. Commercial-grade TDI comprises an 80:20 mixture of isomers 2,4- and 2,6-TDI and represents >95% of TDI industrial use. There are several isomers of MDI, including 4,4'-, 2,4'-, and 2,2'-MDI, as well as oligomers and polymeric compounds. The principal commercial product of MDI is made up of a mixture of all of these components, with a typical composition in the range of 40–50% 4,4'-MDI, 2.5–4.0% 2,4'-MDI, and 0.1–0.2% 2,2'-MDI; the remainder is oligomers. 4,4'-MDI is the most commercially common isomer and is referred to as pure MDI.

The dominant process affecting the overall environmental fate, transport, and bioaccumulation potential of TDI and MDI is hydrolysis. Diisocyanates react with water forming the respective amines, which in turn may react with more diisocyanates to produce inert, insoluble polyureas. Hydrolysis half-lives of MDI and TDI have been measured to be on the order of a few minutes to a few hours. Due to the rapid hydrolysis of these compounds, they are not expected to persist or bioaccumulate in the environment.

Almost all of the potential exposures to these compounds are associated with the production, handling, use, and disposal of diisocyanates and products containing unreacted diisocyanates. TDI and MDI are most frequently detected in occupational settings, mainly by inhalation of aerosol and vapor (TDI only). Diisocyanates are used in the production of polyurethane foam during foaming, casting, spraying, and other processes. Exposure may also occur after production when the polymer is processed. Thermal degradation of polyurethane foam during processes such as heat cutting of foam blocks, flame lamination with textiles, and welding, cutting, or grinding of polyurethane-coated metal, can also release diisocyanates into the air. Another route is through dermal exposure by contact with uncured polyurethane foams.

Exposure of the general population to diisocyanates could potentially result from industrial exposures, as well as the use of consumer products containing uncured TDI and MDI. There has been an increase in the number of uncured diisocyanate-containing products used by consumers. TDI emissions were not

detected in a study of polyurethane products such as carpet padding, furniture cushions, and varnishes. However, application of a concrete water solvent did result in elevated TDI levels.

2.2 SUMMARY OF HEALTH EFFECTS

TDI. Epidemiology studies and laboratory animal studies have investigated the toxicity of TDI and identified the respiratory tract as the most sensitive target of toxicity. A 6-hour exposure of healthy adults to 0.005 ppm did not result in respiratory symptoms, but did result in slight declines in lung function (specific airway conductance and maximal expiratory flow [MEF]). A shorter duration exposure to a higher concentration (0.02 ppm for 20 minutes) did not result in alterations in specific airway resistance in healthy or asthmatic subjects. Occupational exposure studies primarily report three types of respiratory effects: occupational asthma, asthma-like symptoms, and declines in lung function. Occupational asthma, which is characterized by airflow limitations and/or airway hyperresponsiveness, is seen in individuals who become hypersensitive to TDI. In sensitized individuals, exposure to low, non-irritating concentrations of TDI can result in wheezing and dyspnea, a marked decrease in lung function, and nonspecific airway hyperresponsiveness. In some workers, removal from TDI exposure can result in improvement in symptoms and a lack of response to a TDI challenge (a brief exposure to a non-irritating concentration); however, a fair percentage of workers still reported asthma symptoms. One study of TDI-sensitized subjects reported an improvement in respiratory symptoms 11 years after removal from TDI exposure; however, 60% of the workers still complained of asthmatic symptoms. Subjects who are diagnosed with occupational asthma shortly after the onset of symptoms, immediately discontinue TDI exposure after diagnosis, and have a milder degree of airway hyperresponsiveness are more likely to recover from the respiratory symptoms. Recovery has not been reported in workers who continue to be exposed to TDI; continued exposure may result in further declines in lung function. TDI concentrations resulting in sensitization are not known, but the sensitization is believed to be due to a brief exposure to a very high concentration or prolonged exposure to lower concentrations. Prior to 1970 when occupational exposure levels were higher, the prevalence of TDI-induced asthma was 5–6%; after the mid-1970s when the occupational limit was typically maintained at 0.005 ppm, rates of <1% have been reported. Some workers report asthma-like symptoms such as wheezing, dyspnea, and chest tightness but do not respond to a TDI challenge; several studies have found that approximately half of the subjects with asthma-like symptoms will have a positive response to a TDI challenge.

The primary health effect observed in nonsensitized workers exposed to TDI is a decline in lung function, particularly the forced expiratory volume in 1 second (FEV_1). Two longitudinal studies provide

suggestive evidence that the greatest declines in lung function occur within the first couple of years of exposure to lower TDI concentrations. A decline in FEV_1 and forced vital capacity (FVC) was found in workers with no previous history of occupational exposure to TDI who were exposed to an 8-hour time-weighted average (TWA) TDI level of 0.0012 ppm. However, no declines in lung function were found in the cohort, which mostly consisted of workers with prior TDI exposure. Additionally, when the naïve workers were followed for another several years, no additional declines in lung function were found. Declines in lung function were observed in workers with an 8-hour TWA TDI exposure level of 0.0082 ppm, but no effects were observed in workers with an 8-hour TWA TDI level of 0.0017 ppm.

Animal studies have reported histological lesions in the nasal cavity and lungs after acute, intermediate, or chronic TDI exposure. The nasal lesions typically consisted of rhinitis, necrosis, ulceration, and metaplasia; the severity of the lesions and location within the nasal cavity appear to be concentration- and duration-related. Rhinitis was reported at 0.02 ppm in intermediate-duration studies; chronic or necrotic rhinitis was reported at 0.05 ppm in a chronic mouse study. Interstitial pneumonitis and catarrhal bronchitis was observed at slightly higher concentrations in the chronic mouse study. In addition to the histological alterations, airway hyperresponsiveness and increases in respiratory rates have been observed in laboratory animal studies exposed for acute or intermediate durations.

A limited number of other adverse health effects have been reported in humans and animals. A chronic study in rats and mice examined major tissues and organs and only reported adverse effects in the respiratory tract. Dermal irritation and ocular irritation have also been reported in TDI workers. Reproductive and developmental toxicity of TDI has been investigated in rats. No evidence of reproductive toxicity was observed in a 2-generation study in which rats were exposed to concentrations as high as 0.3 ppm. An increase in litters with poorly ossified cervical centrum was observed in the offspring of rats exposed to 0.5 ppm on gestation days (GDs) 6–15; this concentration was also associated with significant maternal toxicity, including a 45% decrease in maternal weight gain and labored breathing.

Although the carcinogenicity of TDI specifically has not been investigated in occupational exposure studies, three studies have examined workers at polyurethane foam manufacturing facilities and found associations between work in the polyurethane foam manufacturing facility and lung cancer in female workers; none of the studies examined associations specifically with TDI exposure. A chronic-duration study in rats and mice did not find significant increases in neoplastic tumors. HHS has classified TDI as reasonably anticipated to be a human carcinogen based on sufficient evidence of carcinogenicity from

studies in experimental animals. The International Agency for Research on Cancer (IARC) has classified TDI as a Group 2B carcinogen (possibly carcinogenic to humans) based on inadequate evidence of carcinogenicity in humans and sufficient evidence of carcinogenicity in experimental animals. EPA has not classified the carcinogenicity of TDI.

TDI is rapidly hydrolyzed in water and is not likely to be detected in aquatic environments; thus, it is unlikely that the general population will be exposed via this route. The oral toxicity of commercial-grade TDI has been investigated in a series of gavage studies in rats and mice; there is some question regarding the relevance of these data to humans due to likely pharmacokinetic differences between ingestion of TDI and gavage administration directly into the acidic environment of the stomach, which could result in the formation of 2,4-toluene diamine (TDA). Mucoid bronchopneumonia was observed in rats following intermediate exposure to 240 mg/kg/day, 5 days/week for 13 weeks or following chronic exposure 30 or 60 mg/kg/day, 5 days/week for 2 years; decreases in survival were also observed at these doses. Bronchopneumonia was not observed in mice; however, an increased incidence of cytomegaly in the renal tubules was observed in male mice administered 120 mg/kg/day, 5 days/week for 2 years. Decreases in survival were also observed in mice chronically exposed to 240 mg/kg/day. The chronic study also found clear evidence of carcinogenicity in rats and female mice. In rats, there were increases in the incidence of subcutaneous fibromas and fibrosarcomas, pancreatic acinar cell adenomas and islet cell adenomas, mammary gland fibroadenomas, and neoplastic nodules of the liver. In the female mice, the incidences of hemangiomas or hemangiosarcomas and hepatocellular adenomas were increased.

MDI. Similar to TDI, the respiratory tract is the primary target of toxicity for MDI. Occupational exposure can result in occupational asthma, asthma-like symptoms, and decreases in lung function. Although a number of studies have reported MDI-induced asthma or asthma-like symptoms, no reliable concentration-response data or prevalence data are available. As with TDI, occupational asthma likely results from exposure to very high concentrations of MDI or prolonged exposure to high levels that result in sensitization. Approximately half of workers reporting asthma-like symptoms such as wheezing, dyspnea, and chest tightness have a positive response to a short MDI-challenge. Many MDI-sensitized workers also respond to nonspecific irritants; the prevalence of subjects with asthma-like symptoms exhibiting bronchial hyperresponsiveness following exposure to methacholine was significantly higher than in non-exposed subjects or other MDI workers. Unlike TDI, a small number of workers with asthma-like symptoms also reported chills, fever, and malaise, which are considered symptoms of hypersensitivity pneumonitis.

Decreases in lung function were observed in MDI workers. Other studies have not found decreases in lung function when pre-shift levels were compared to post-shift levels; one of these studies that examined 27 workers noted that the MDI levels at the facility ranged from 0.0005 to 0.001 ppm.

A limited number of studies have been conducted in laboratory animals. A study measuring respiratory rates in mice reported increases in respiratory rates at 7 mg/m^3, which were followed by a gradual decline in respiratory rate; the investigators suggested that this pattern was indicative of pulmonary irritation rather than sensory irritation. Airway hyperresponsiveness to acetylcholine was observed in guinea pigs exposed to 0.01 ppm MDI 6 hours/day for 5 days or 6 hours/day, 5 days/week for 4 weeks. A chronic-duration study with polymeric MDI containing about 50% monomeric MDI found increases in nasal lesions (basal cell hyperplasia and Bowman's gland hyperplasia) and lung lesions (localized fibrosis and alveolar duct epithelialization in rats exposed to 1.0 mg/m^3 polymeric MDI 6 hours/day, 5 days/week for 2 years. Many of these lesions were observed after 1 year of exposure to 6.0 mg/m^3. An unpublished study reported similar lung effects in female rats exposed to 0.23 mg/m^3 monomeric MDI 18 hours/day, 5 days/week for 2 years.

The chronic study in rats did not find any other systemic effects. In a rat developmental toxicity study, an increased incidence of litters with fetuses displaying asymmetric sternebrae was observed at 9 mg/m^3 MDI administered on GDs 6–15; a decrease in maternal food consumption was also observed at that exposure level.

No occupational exposure studies have examined the possible association between MDI exposure and cancer risk. As discussed in the TDI section, a possible association between lung cancer and employment at polyurethane foam manufacturing facilities was reported in female workers. The chronic inhalation rat study found increases in lung adenomas in male rats exposed to 6.0 mg/m^3 polymeric MDI; one incident of lung adenocarcinoma was also found. IARC has classified 4,4'-MDI as a Group 3 carcinogen (not classifiable as to its carcinogenicity to humans) based on inadequate evidence of carcinogenicity in humans and inadequate or limited evidence in experimental animals. EPA has characterized the carcinogenicity of MDI/polymeric MDI as "cannot be determined, but for which there is suggestive evidence that raises concern for carcinogenic effects".

2.3 MINIMAL RISK LEVELS (MRLs)

Estimates of exposure levels posing minimal risk to humans (MRLs) have been established for TDI and MDI. An MRL is defined as an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (noncarcinogenic) over a specified duration of exposure. MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration within a given route of exposure. MRLs are based on noncancerous health effects only and do not consider carcinogenic effects. MRLs can be derived for acute, intermediate, and chronic duration exposures for inhalation and oral routes. Appropriate methodology does not exist to develop MRLs for dermal exposure.

Although methods have been established to derive these levels (Barnes and Dourson 1988; EPA 1990), uncertainties are associated with these techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of the procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for health effects that are delayed in development or are acquired following repeated acute insults, such as hypersensitivity reactions, asthma, or chronic bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

Inhalation MRLs for TDI

Acute Duration

- An MRL of $1x10^{-5}$ ppm has been derived for acute-duration inhalation exposure (≤14 days) to TDI.

A limited number of human studies have evaluated the acute toxicity of TDI. No respiratory symptoms were reported in healthy subjects exposed to 0.005 ppm TDI for 6 hours followed by a 20-minute exposure to 0.02 ppm TDI; however, slight, but statistically significant, decreases in specific airway conductance and MEF at 25% of FVC were observed (Vandenplas et al. 1999). No alterations in specific airway resistance were observed in healthy or asthmatic subjects exposed to 0.02 ppm for 20 minutes (Chester et al. 1979). Acute-duration animal inhalation studies have reported rhinitis, lung damage, and airway hyperresponsiveness. The severity of rhinitis was concentration-related; moderate rhinitis was observed in mice exposed to 0.07 ppm 6 hours/day for 4 days (Zissu 1995), moderate-to-severe rhinitis was observed in mice exposed to 0.4 ppm 6 hours/day for 5 days (Buckley et al. 1984), and severe nasal

lesions were observed in mice exposed to 1 ppm 6 hours/day for 3 days (Arts et al. 2008). Interstitial inflammation, pleural thickening, and goblet cell hyperplasia were observed in the lungs of guinea pigs exposed to 1.4 ppm TDI 3 hours/day for 3 days (Wong et al. 1985). Airway hyperresponsiveness to methacholine or acetylcholine was also observed in guinea pigs and mice exposed to ≥0.01 ppm (Gagnaire et al. 1996; Gordon et al. 1985; Marek et al. 1999); a no-observed-adverse-effect level (NOAEL) of 0.005 ppm for airway hyperresponsiveness was identified in guinea pigs exposed to TDI 6 hours/day for 5 days (Marek et al. 1999). An increase in the incidence of litters with poorly ossified cervical centrum was observed in the offspring of rats exposed to 0.5 ppm commercial-grade TDI 6 hours/day on GDs 6–15 (Tyl et al. 1999a); this concentration was also associated with maternal toxicity including a marked decrease in body weight gain and signs of nasal irritation and audible respiration.

The Vandenplas et al. (1999) human study identified the lowest lowest-observed-adverse-effect level (LOAEL) (0.005 ppm) for respiratory effects caused by acute inhalation exposure to TDI; the lowest LOAEL in animals is approximately 10-fold higher. The Vandenplas et al. (1999) study was considered suitable for derivation of an MRL. The LOAEL of 0.005 ppm was adjusted to continuous 24-hour exposure; the resulting $LOAEL_{ADJ}$ was 0.00125 ppm. The MRL of 0.00001 ppm ($1x10^{-5}$ ppm) was calculated by dividing the $LOAEL_{ADJ}$ by an uncertainty factor of 100 (10 for the use of a LOAEL and 10 for human variability). There is some uncertainty whether the acute-duration MRL based on the Vandenplas et al. (1999) single exposure study would be protective of continuous exposure to TDI for 14 days. Chronic-duration occupational exposure studies provide some support for this MRL. The lowest LOAEL values identified in longitudinal studies of workers exposed to TDI are 0.0012 and 0.0019 ppm (Clark et al. 1998; Diem et al. 1982); the effects observed at these concentrations included decreases in lung function (FEV_1 and/or FVC). These LOAELs are roughly 2–4 times lower than the LOAEL from the Vandenplas et al. (1999) study. However, since there is uncertainty that the MRL would be protective for continuous exposure for 14 days, it is recommended that measured air concentrations should not exceed the MRL of $1x10^{-5}$ ppm during a 24-hour period.

Intermediate Duration. No human studies have examined the intermediate-toxicity of TDI; several animal studies have examined the respiratory tract following intermediate-duration exposure. Nasal and lung inflammation were observed in mice exposed to 0.02 ppm commercial-grade TDI 4 hours/day, 5 days/week for 6 weeks (Matheson et al. 2005); increased airway hyperresponsiveness was also observed at this concentration. At a slightly higher concentration (0.07 ppm), severe rhinitis with metaplasia and necrosis of the nasal respiratory epithelium was observed (Zissu 1995). The LOAELs in the animal studies are >10 times higher than the LOAELs identified in occupational exposure studies (see Chronic

Duration section) and may not be protective for declines in lung function. In a study by Clark et al. (1998), lung function declines were observed within the first couple of months of exposure. Thus, the data were not considered suitable for an intermediate-duration inhalation MRL for TDI.

Chronic Duration

- An MRL of $3x10^{-6}$ ppm has been derived for chronic-duration inhalation exposure (≥1 year) to TDI.

A number of studies of workers at TDI production facilities and polyurethane foam manufacturing facilities have reported respiratory effects consisting of asthma, asthma-like symptoms, and declines in lung function. TDI-induced asthma is a type of occupational asthma characterized as bronchial inflammation and/or airway hyperresponsiveness. The wheezing, dyspnea, and chest tightness observed in individuals with asthma often persists for years after exposure termination (Mapp et al. 1988; Moller et al. 1986; Moscato et al. 1991; Padoan et al. 2003; Paggiaro et al. 1984). Individuals with TDI-induced asthma are considered to be sensitized to TDI, in that brief exposures to nonirritating concentrations can result in a worsening of symptoms and a decline in lung function. Other workers reported asthma-like symptoms of wheezing and dyspnea, but do not respond to a TDI inhalation challenge; although the workers may not have asthma, the observed respiratory effects may still be indicative of TDI sensitization. The exposure level resulting in TDI sensitization is not known; TDI sensitization may result from a brief exposure to very high TDI concentrations or prolonged exposure to lower concentrations. It is believed that <10% of workers become sensitized to TDI; lower rates of sensitization (<1%) have been found since the occupational exposure limit has been lowered to 0.005 ppm (Ott et al. 2003).

The available data suggest that the primary effect in non-sensitized workers is a decline in lung function. Several longitudinal studies have evaluated the effect of TDI exposure on the annual decline in lung function (Adams 1975; Bodner et al. 2001; Butcher et al. 1977; Clark et al. 1998, 2003; Diem et al. 1982; Jones et al. 1992; Omae et al. 1992; Ott et al. 2000; Peters et al. 1970; Wegman et al. 1977, 1982). Although the results across studies are not consistent, several factors may contribute to this inconsistency, including differences in peak exposure levels, difference in the length of exposure, exposure to higher TDI levels prior to the start of the study, and inclusion of sensitized workers. A 5-year study of a new TDI manufacturing facility found greater annual declines in FEV_1 and forced expiratory flow at 25–50% of FVC ($FEF_{25–50\%}$) among nonsmoking workers with a cumulative TDI exposure of ≥0.0682 ppm-months (Diem et al. 1982). Another study that examined workers at a polyurethane foam manufacturing

facility with no prior TDI exposure found significant annual declines in FEV_1 and FVC; however, no significant alterations in lung function were observed in the entire cohort. The mean 8-hour TWA TDI concentration for the entire cohort (naïve workers and workers with prior TDI exposure) was 0.0012 ppm (Clark et al. 1998). When the naïve worker subcohort was examined several years later, the declines in lung function did not significantly vary from predicted levels (Clark et al. 2003). Clark et al. (1998) suggested that the decline in lung function observed in the naïve subcohort may have been due to respiratory irritation. Another study found greater-than-expected declines in maximal midexpiratory flow (MMF), ratio of FEV_1 to FVC, and peak expiratory flow (PEF) in polyurethane foam manufacturing workers with an 8-hour TWA TDI level of 0.0082 ppm, with peak levels of 0.02–0.03 ppm (Omae et al. 1992). No alterations were found in workers with a TWA level of 0.0017 ppm with peak levels of 0.0003–0.004 ppm. A fourth study found significant declines in FEV_1 levels in workers with TDI exposure levels ≥0.0035 ppm (Wegman et al. 1977, 1982). No alterations in lung function were observed in other longitudinal studies with TDI levels of 0.0015–0.015 ppm (Bodner et al. 2001; Butcher et al. 1977; Jones et al. 1992; Ott et al. 2000).

Only one study examined the chronic toxicity of airborne TDI in laboratory animals; significant increases in the incidence and severity of chronic or necrotic rhinitis with epithelial atrophy and mucous and squamous metaplasia were observed in mice exposed to ≥0.05 ppm TDI 6 hours/day, 5 days/week for 2 years (Loeser 1983). Interstitial pneumonitis and catarrhal bronchitis was also noted in mice exposed to 0.15 ppm; however, the incidence was not reported.

The adverse effect levels for declines in lung function in TDI workers were about 5 times lower than the LOAEL for nasal effects in mice; thus, the occupational exposure studies were selected as the basis of the MRL. The results of the Diem et al. (1982) and Clark et al. (1998) studies suggest that the greatest declines in lung function occur during the first several years of exposure to TDI; thereafter, the declines are not significantly different from predicted levels. Thus, these studies were considered as the basis of the MRL. The Clark et al. (1998) study was selected over the Diem et al. (1982) because it identified a slightly lower adverse effect level (0.0012 versus 0.0019 ppm) and did not rely on unpublished monitoring data. The mean daily exposure level of the exposed group of 0.0012 ppm was adjusted for intermittent exposure (8 hours/day, 5 days/week). This adjusted adverse effect level of 0.00029 ppm was divided by a total uncertainty factor of 100 (10 for use of an adverse effect level and 10 for human variability) resulting in an MRL 0.000003 ppm ($3x10^{-6}$ ppm or 0.003 ppb).

Oral MRLs for TDI

TDI is rapidly hydrolyzed in water and is not likely to be detected in aquatic environments. Thus, oral exposure to TDI in humans is unlikely, thereby lessening the need for oral MRLs.

Inhalation MRLs for MDI

Acute Duration. Several case reports of acute-duration inhalation exposure to MDI have been identified (Banks et al. 1986; Chang and Karol 1984; Stingeni et al. 2008; Suojalehto et al. 2011). The reports described breathing difficulties (Stingeni et al. 2008), asthma (Chang and Karol 1984; Suojalehto et al. 2011), and asthma-like respiratory symptoms (Banks et al. 1986). Although the exposure levels were not reported, they were likely to be relatively high based on the severity of the observed effects. In guinea pigs, exposure to 0.01 ppm MDI 6 hours/day for 5 days resulted in increased airway hyperresponsiveness; a NOAEL of 0.005 ppm was identified for this effect (Marek et al. 1999). The Marek et al. (1999) study was not considered a suitable basis for an MRL because the study did not include a histological examination of the respiratory tract and it is possible that histological alterations, particularly in the nasal cavity, may occur at lower concentrations than airway hyperresponsiveness.

Intermediate Duration. Bascom et al. (1985) reported a case of a male who exhibited dyspnea, fever, malaise, and hypoxemia, effects characteristic of hypersensitivity pneumonitis, 2 months after beginning a job involving the use of a polyurethane foam containing MDI. Malo and Zeiss (1982) also described a case of a foundry worker who developed dyspnea and restrictive breathing 1 month after beginning work. Neither case included information on exposure levels. Exposure of guinea pigs to 0.01 ppm MDI 6 hours/day, 5 days/week for 4 weeks resulted in increased airway hyperresponsiveness to acetylcholine (Marek et al. 1999). This study did not include a histological examination of the respiratory tract. As noted in the discussion for the acute-duration MRL, the lack of a histological examination precludes using the Marek et al. (1999) study as the basis for deriving an MRL.

Chronic Duration

- An MRL of 0.001 mg/m^3 has been derived for chronic-duration inhalation exposure (≥1 year) to polymeric MDI.

The primary effects of MDI observed in occupational exposure studies include occupational asthma in sensitized individuals and decreases in lung function. Asthma and/or asthma-like symptoms were

reported by several investigators (Hur et al. 2008; Wang and Petsonk 2004; Woellner et al. 1997; Zammit-Tabona et al. 1983); none of these studies provided exposure information. Symptoms of hypersensitivity pneumonitis (e.g., chills, fever, malaise) have also been reported in a study of workers with asthma-like symptoms (Baur 1995). Liss et al. (1988) found a significant decrease in FEV_1 levels when pre-shift levels were compared to post-shift levels in workers at a steel foundry using MDI; the study did not provide monitoring data. Comparison of pre- and post-shift lung function levels did not reveal significant differences in a study of 27 polyurethane foam workers (Sulotto et al. 1990); the MDI levels ranged from 0.0005 to 0.001 ppm. Musk et al. (1982) also found no differences in lung function when pre- and post-shift values were compared in workers at two polyurethane plastic manufacturing facilities. Monitoring data were provided by the facilities and were measured by the investigators; however, there was a large discrepancy between the values.

The chronic toxicity of inhaled MDI has been investigated in rats exposed to an aerosol of polymeric MDI, which contained 44.8–50.2% monomeric MDI 6 hours/day, 5 days/week for 2 years (Reuzel et al. 1994). Exposure to 1.0 mg/m^3 resulted in significant increases in the incidence of basal cell hyperplasia and Bowman's gland hyperplasia in the nasal cavity and mild to moderate localized fibrosis in the lungs and alveolar duct epithelialization. Localized alveolar bronchiolization was also observed at 6.0 mg/m^3. The study identified a NOAEL of 0.2 mg/m^3. An unpublished study conducted by Hoyemann and associates and reviewed by Feron et al. (2001) found similar results in female rats exposed to monomeric MDI 18 hours/day, 5 days/week for 2 years. In this study, an increased incidence of bronchiolo-alveolar hyperplasia and fibrosis were observed at $\geq$0.23 mg/m^3. After adjusting for intermittent exposure, the LOAEL value identified in the Reuzel et al. (1994) study (0.178 mg/m^3) is very similar to the LOAEL from the Hoyemann study (0.123 mg/m^3).

The NOAELs from the Sulotto et al. (1990) occupational exposure study and the Reuzel et al. (1994) rat study were both considered as possible points of departure for the chronic-duration inhalation MRL (the Hoyemann study was not considered as the basis of the MRL because the study was not available to ATSDR for review). Two TDI studies (Clark et al. 1998; Diem et al. 1982) showed that the greatest declines in lung function occurred within the first year of exposure to TDI. Sulotto et al. (1990) is not a prospective study, so it is possible that exposure to 0.005–0.001 ppm might have resulted in a decline in lung function in naïve workers that would have gone undetected. Due to this uncertainty, the Reuzel et al. (1994) study was selected as the basis of the MRL. The incidence data for basal cell hyperplasia in the nasal cavity, Bowman's duct hyperplasia in the nasal cavity, and lung fibrosis were fit to all available dichotomous models in EPA's Benchmark Dose Software (BMDS, version 2.4.0) using the extra risk

option. The $BMCL_{10}$ values predicted from the selected models for basal cell hyperplasia and lung fibrosis were 0.48 and 0.70 mg/m^3, respectively; none of the models provided an adequate fit to the incidence data for Bowman's gland hyperplasia. The $BMCL_{10}$ of 0.48 mg/m^3 was selected as the point of departure for the MRL and was adjusted for intermittent exposure (6 hours/day, 5 days/week) resulting in a $BMCL_{ADJ}$ of 0.086 mg/m^3. A human equivalent concentration ($BMCL_{HEC}$) was calculated by multiplying the $BMCL_{ADJ}$ by a regional deposited dose ratio (RDDR) of 0.453. The chronic-duration inhalation MRL of 0.001 mg/m^3 for polymeric MDI was derived by dividing the $BMCL_{HEC}$ of 0.039 mg/m^3 by a total uncertainty factor of 30 (3 for extrapolation from animals to human with dosimetric adjustments and 10 for human variability).

Oral MRLs for MDI

MDI is rapidly hydrolyzed in water and is not likely to be detected in aquatic environments. Thus, oral exposure to MDI in humans is unlikely, thereby lessening the need for oral MRLs.

3. HEALTH EFFECTS

3.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective on the toxicology of TDI and MDI. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health.

A glossary and list of acronyms, abbreviations, and symbols can be found at the end of this profile.

3.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

To help public health professionals and others address the needs of persons living or working near hazardous waste sites, the information in this section is organized first by route of exposure (inhalation, oral, and dermal) and then by health effect (e.g., death, systemic, immunological, neurological, reproductive, developmental, and carcinogenic effects). These data are discussed in terms of three exposure periods: acute (14 days or less), intermediate (15–364 days), and chronic (365 days or more).

Levels of significant exposure for each route and duration are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELs have been classified into "less serious" or "serious" effects. "Serious" effects are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). "Less serious" effects are those that are not expected to cause significant dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether an end point should be classified as a NOAEL, "less serious" LOAEL, or "serious" LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify these end points. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between "less serious" and "serious" effects. The distinction between "less serious" effects and "serious" effects is considered to be important because it helps the users of the profiles to identify levels of exposure at which major health effects start to appear. LOAELs or NOAELs should also help in determining whether or not

the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

The significance of the exposure levels shown in the Levels of Significant Exposure (LSE) tables and figures may differ depending on the user's perspective. Public health officials and others concerned with appropriate actions to take at hazardous waste sites may want information on levels of exposure associated with more subtle effects in humans or animals (LOAELs) or exposure levels below which no adverse effects (NOAELs) have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels or MRLs) may be of interest to health professionals and citizens alike.

Levels of exposure associated with carcinogenic effects (Cancer Effect Levels, CELs) of TDI and MDI are indicated in Tables 3-2 and 3-5 and Figures 3-2, and 3-3.

A User's Guide has been provided at the end of this profile (see Appendix B). This guide should aid in the interpretation of the tables and figures for Levels of Significant Exposure and the MRLs.

3.2.1 Inhalation Exposure

The highest NOAEL values and all LOAEL values from each reliable study for each end point in each species and duration category are recorded in Tables 3-1 and 3-2 and plotted in Figures 3-1 and 3-2 for TDI and MDI, respectively.

3.2.1.1 Death

Available literature did not include human studies evaluating lethality after inhalation exposure to TDI or MDI.

TDI. Acute-duration exposure to commercial-grade TDI at concentrations up to 1.0 ppm did not result in any deaths when groups of eight pregnant CD rats were exposed during GDs 6–15 in a dose-range finding study (Tyl et al. 1999a). Likewise, exposure concentrations up to 0.5 ppm did not result in maternal deaths in the main developmental toxicity study (Tyl et al. 1999a) or in F0 or F1 parental animals in a 2-generation reproductive toxicity study using rats (Tyl et al. 1999b). Chronic (2-year) exposure to 0.15 ppm production-grade TDI (80:20 mix of 2,4- and 2,6-TDI) did not affect survival rates of Sprague-Dawley rats (Loeser et al. 1983). In CD-1 mice, a significantly increased rate of mortality was seen with

Table 3-1. Levels of Significant Exposure to Toluene Diisocyanate - Inhalation

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
ACUTE EXPOSURE								
Systemic								
1	Human	6 hr	Resp		0.005[b] (slight decrease in specific airway conductance)		Vandenplas et al. 1999 TDI, not specified	
2	Rat (Wistar)	4 hours/day 5 days	Resp		0.41 F (hypersensitivity symptoms, central airway goblet cell metaplasia, central and peripheral airway eosinophil infiltration)		Kouadio et al. 2014 2,4-TDI	
3	Rat (CD)	6 hr/d Gd 6-15	Resp		0.02 F (red nasal discharge in 5/21 dams)		Tyl et al. 1999a 2,4/2,6-TDI	80: 20 mixture of 2,4- and 2,6-TDI
			Hepatic	0.5 F				
			Bd Wt			0.5 F (45% decrease in maternal body weight gain during exposure)		
4	Rat (CD)	6 hr/d Gd 6-15	Resp		1 F (maternal nasal discharge and labored respiration; blood gas changes indicative of respiratory acidosis)		Tyl et al. 1999a 2,4/2,6-TDI	80: 20 mixture of 2,4- and 2,6-TDI
			Bd Wt			1 F (27% decrease in body weight)		

Table 3-1. Levels of Significant Exposure to Toluene Diisocyanate - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
5	Mouse (BALB/c)	45, 90, 180, or 360 min/d 3 d	Resp		1 M (severe nasal lesions and slight laryngeal lesions)		Arts et al. 2008 2,4/2,6-TDI	80: 20 mixture of 2,4- and 2,6-TDI
6	Mouse (Swiss-Webster)	6 hr/d 5 d	Resp		0.4 M (moderate to severe nasal lesions)		Buckley et al. 1984 TDI, not specified	
7	Mouse (C57BL/6N)	4 hr/d 12 d	Resp		0.05 F (cellular inflammation and hyperplasia in anterior nasal cavity)		Johnson et al. 2007 TDI, not specified	
8	Mouse (C57BL/6N)	2 hr	Resp		0.5 F (nasal and lung inflammation, airway hyperresponsiveness)		Matheson et al. 2005 2,4/2,6-TDI	80: 20 mixture of 2,4- and 2,6-TDI
9	Mouse (Swiss-Webster)	3 hr/d 5 d	Resp	0.031 M 0.018 M	0.25 M (histological damage to nasal respiratory epithelium) 0.023 M (decreased respiratory rate)		Sangha and Alarie 1979 2,4-TDI	

Table 3-1. Levels of Significant Exposure to Toluene Diisocyanate - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
10	Mouse (Swiss)	6 hr/d 4 d	Resp		0.07 M (moderate rhinitis with metaplasia and necrosis in the nasal respiratory epithelium)		Zissu 1995 2,4/2,6-TDI	80: 20 mixture of 2,4- and 2,6-TDI
11	Gn Pig (Hartley)	3 hr/d 5 d	Resp	0.02 F	0.2 F (pulmonary response to TDI challenge)		Aoyama et al. 1994 2,4/2,6-TDI	
12	Gn Pig (Dunkin-Hartle	1 hr	Resp		3 F (airway hyperresponsiveness)		Gagnaire et al. 1996 2,4/2,6-TDI	80: 20 mixture of 2,4- and 2,6-TDI
13	Gn Pig (Dunkin-Hartle	continuously 48 hr	Resp		0.1 F (airway hyperresponsiveness)		Gagnaire et al. 1996 2,4/2,6-TDI	80: 20 mixture of 2,4- and 2,6-TDI
14	Gn Pig (Dunkin-Hartle	continuously 1 wk	Resp		0.05 F (airway hyperresponsiveness)		Gagnaire et al. 1996 2,4/2,6-TDI	80: 20 mixture of 2,4- and 2,6-TDI
15	Gn Pig (Hartley)	1 hr	Resp		2 M (airway hyperresponsiveness, tracheal epithelial damage, acute airway inflammation)		Gordon et al. 1985 TDI, not specified	

Table 3-1. Levels of Significant Exposure to Toluene Diisocyanate - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
16	Gn Pig (Dunkin Hartley)	6 hr/d 5 d	Resp	0.005 F	0.01 F (increased airway responsiveness)		Marek et al. 1999 2,4/2,6-TDI	80: 20 mixture of 2,4- and 2,6-TDI
17	Gn Pig (English smooth haired)	3 hr/d 5 d	Resp		1.4 F (diminished response to CO2, pulmonary hypersensitivity, interstitial inflammation, pleural thickening and goblet cell hyperplasia in the lungs)		Wong et al. 1985 2,4/2,6-TDI	80: 20 mixture of 2,4- and 2,6-TDI
Developmental								
18	Rat (CD)	6 hr/d Gd 6-15		0.1	0.5 (increased incidence of litters with poorly ossified cervical centrum no. 5)		Tyl et al. 1999a 2,4/2,6-TDI	80: 20 mixture of 2,4- and 2,6-TDI
INTERMEDIATE EXPOSURE								
Systemic								
19	Rat (CD)	2-generation, 19 wk 5 or 7 d/wk 6 hr/d	Resp		0.02 (rhinitis in F1 parental animals)		Tyl et al. 1999b 2,4/2,6-TDI	80: 20 mixture of 2,4- and 2,6-TDI
			Hepatic	0.3				
			Renal	0.3 F				
			Endocr	0.3				
			Bd Wt	0.3				

Table 3-1. Levels of Significant Exposure to Toluene Diisocyanate - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
20	Mouse (C57BL/6N)	4 hr/d 5 d/wk 6 wk	Resp		0.02 F (nasal and lung inflammation, airway hyperresponsiveness)		Matheson et al. 2005 2,4/2,6-TDI	80: 20 mixture of 2,4- and 2,6-TDI
21	Mouse (Swiss)	6 hr/d 5 d/wk 9 or 14 exposures	Resp		0.07 M (severe rhinitis with metaplasia and necrosis in the nasal respiratory epithelium)		Zissu 1995 2,4/2,6-TDI	80: 20 mixture of 2,4- and 2,6-TDI
22	Gn Pig (English smooth haired)	6 hr/d 4 d/wk 14 wk	Resp	0.2 F			Wong et al. 1985 2,4/2,6-TDI	80: 20 mixture of 2,4- and 2,6-TDI
Developmental								
23	Rat (CD)	2-generation, 19 wk 5 or 7 d/wk 6 hr/d			0.08 (9% lower body weight gain of F2 pups during lactation)		Tyl et al. 1999b 2,4/2,6-TDI	80: 20 mixture of 2,4- and 2,6-TDI
CHRONIC EXPOSURE								
Death								
24	Mouse (CD-1)	104 wk 5 d/wk 6 hr/d				0.05 F (significantly increased mortality, 77% vs 60% in controls)	Loeser 1983 2,4/2,6-TDI	80: 20 mixture of 2,4- and 2,6-TDI
Systemic								
25	Human	occupational exposure	Resp	0.0023			Bodner et al. 2001 2,4/2,6-TDI	

Table 3-1. Levels of Significant Exposure to Toluene Diisocyanate - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
26	Human	occupational exposure	Resp		0.015	(respiratory symptoms)	Butcher et al. 1977 2,4/2,6-TDI	
27	Human	occupational exposure	Resp		0.0012[c]	(decline in FEV1 in naive subjects)	Clark et al. 1998 2,4/2,6-TDI	
28	Human	occupational exposure	Resp		0.00105	(increased reporting of wheezing)	Clark et al. 2003 2,4/2,6-TDI	
29	Human	occupational exposure	Resp		0.0082	(decreased lung function)	Omae et al. 1992 2,4/2,6-TDI	
30	Human	occupational exposure	Resp	0.0042			Ott et al. 2000 2,4/2,6-TDI	
31	Human	occupational exposure	Resp		0.0035	(decreased lung function)	Wegman et al. 1977, 1982 2,4/2,6-TDI	

Table 3-1. Levels of Significant Exposure to Toluene Diisocyanate - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
32	Rat (Sprague-Dawley)	108-110 wk 5 d/wk 6 hr/d	Cardio	0.15			Loeser 1983 2,4/2,6-TDI	80: 20 mixture of 2,4- and 2,6-TDI
			Gastro	0.15				
			Hemato	0.15				
			Musc/skel	0.15				
			Hepatic	0.15				
			Renal	0.15				
			Endocr	0.15				
			Bd Wt	0.15				
33	Mouse (CD-1)	104 wk 5 d/wk 6 hr/d	Resp			0.05 (chronic or necrotic rhinitis)	Loeser 1983 2,4/2,6-TDI	80: 20 mixture of 2,4- and 2,6-TDI
			Cardio	0.15				
			Gastro	0.15				
			Hemato	0.15				
			Musc/skel	0.15				
			Hepatic	0.15				
			Renal	0.15				
			Endocr	0.15				

Table 3-1. Levels of Significant Exposure to Toluene Diisocyanate - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
			Bd Wt		0.15 (significantly reduced weight gain)			

a The number corresponds to entries in Figure 3-1.

b Used to derive an acute-duration inhalation MRL of 0.00001 ppm. The LOAEL was adjusted for intermittent exposure (6 hours/day) and divided by an uncertainty factor of 100 (10 for the use of a LOAEL and 10 for human variability).

c Used to derive a chronic-duration inhalation MRL of 0.000003 ppm. The mean daily exposure level was adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for the use of a LOAEL and 10 for human variability).

Bd Wt = body weight; Cardio = cardiovascular; d = day(s); Endocr = endocrine; F = Female; FEV1 = forced expiratory volume in 1 second; Gastro = gastrointestinal; Gd = gestational day; Gn Pig = guinea pig; Hemato = hematological; hr = hour(s); LOAEL = lowest-observed-adverse-effect level; M = male; min = minute(s); Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; Resp = respiratory; wk = week(s)

Figure 3-1. Levels of Significant Exposure to Toluene Diisocyanate - Inhalation

Acute (≤14 days)

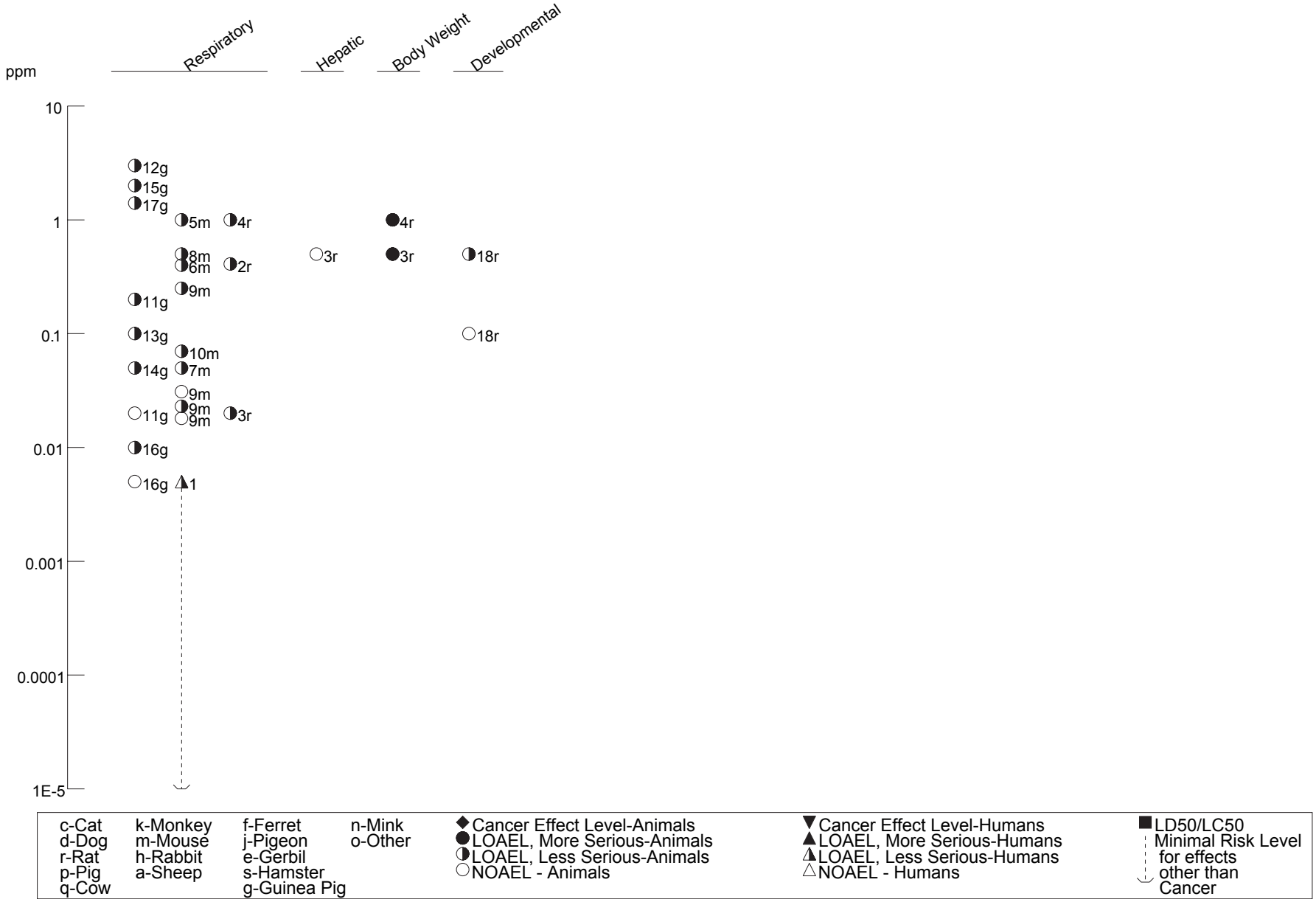


Figure 3-1. Levels of Significant Exposure to Toluene Diisocyanate - Inhalation *(Continued)*

Intermediate (15-364 days)

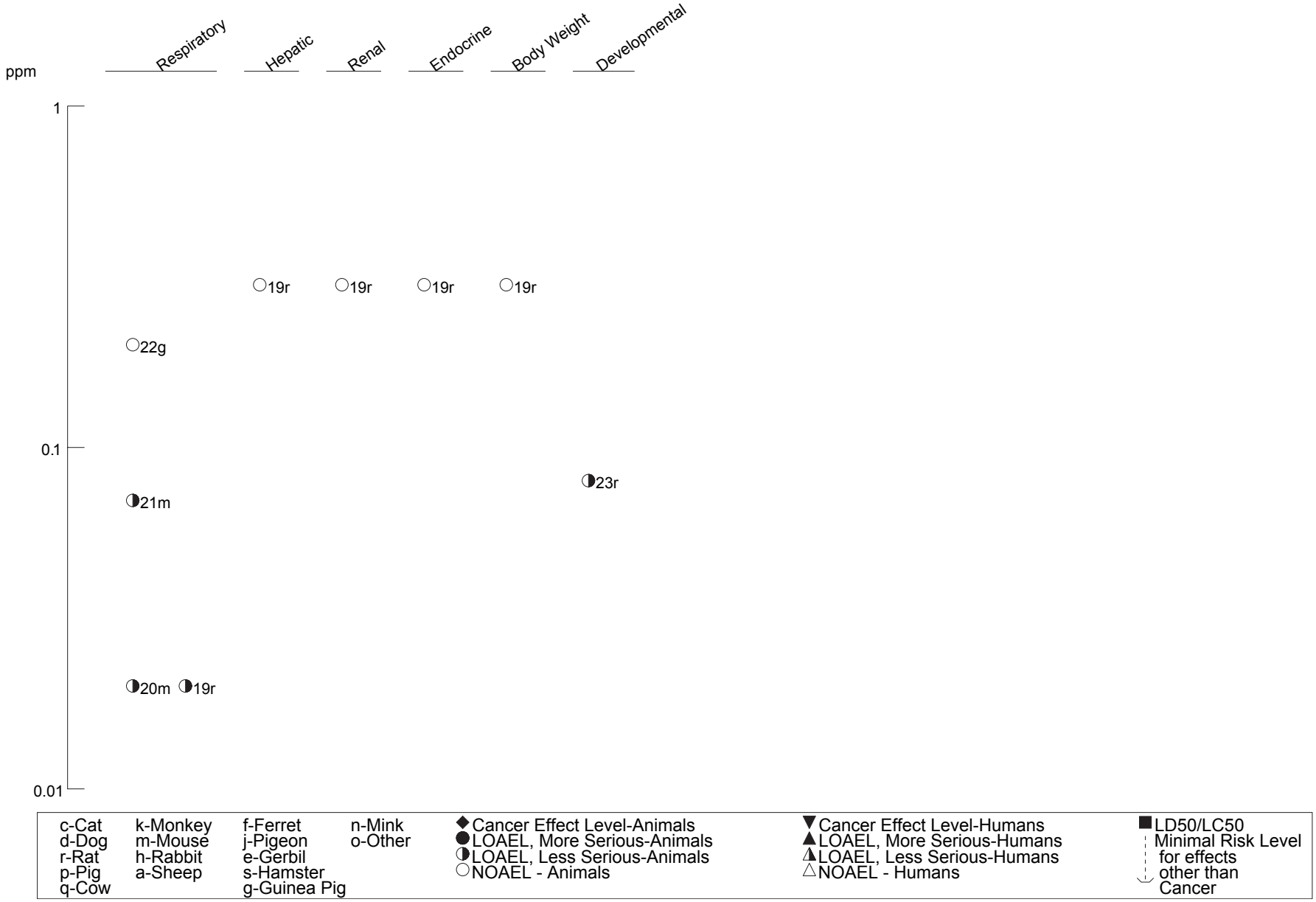


Figure 3-1. Levels of Significant Exposure to Toluene Diisocyanate - Inhalation *(Continued)*

Chronic (≥365 days)

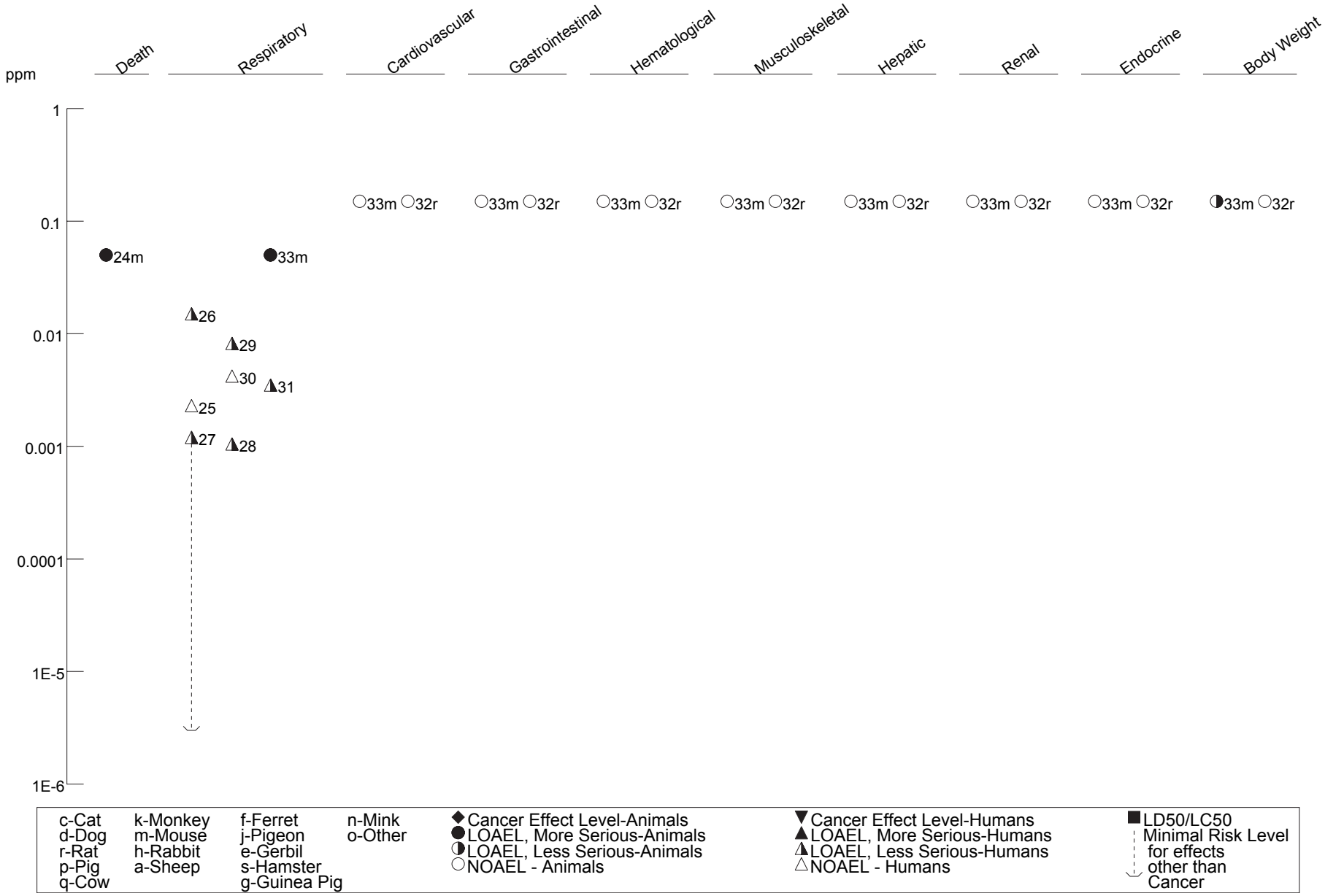


Table 3-2. Levels of Significant Exposure to Methylene Diphenyl Diisocyanate - Inhalation

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form	Comments
ACUTE EXPOSURE								
Death								
1	Rat (Wistar)	Gd 6-15 6 hr/d		9 F			Buschmann et al. 1996 4,4'-MDI	
Systemic								
2	Rat (Wistar)	Gd 6-15 6 hr/d	Resp		9 F (24% increase in relative lung weight)		Buschmann et al. 1996 4,4'-MDI	
			Bd Wt	9 F				
3	Gn Pig (Dunkin Hartley)	6 hr/d 5 d	Resp	0.0005 F	0.001 F (increased airway responsiveness)		Marek et al. 1999 4,4'-MDI	
Developmental								
4	Rat (Wistar)	Gd 6-15 6 hr/d			9 (increased litter incidence of asymmetric sternebrae)		Buschmann et al. 1996 4,4'-MDI	
INTERMEDIATE EXPOSURE								
Systemic								
5	Gn Pig (Dunkin Hartley)	6 hr/d 5 d/wk 4 wk	Resp		0.001 F (increased airway responsiveness)		Marek et al. 1999 4,4'-MDI	
CHRONIC EXPOSURE								
Death								
6	Rat (Wistar)	24 mo 5 d/wk 6 hr/d		6			Reuzel et al. 1994 Polymeric MDI, aerosolized	

Table 3-2. Levels of Significant Exposure to Methylene Diphenyl Diisocyanate - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form	Comments
Systemic								
7	Human	occupational exposure	Resp	0.0005			Sulotto et al. 1990 4,4'-MDI	
8	Rat (Wistar)	24 mo 5 d/wk 6 hr/d	Resp	0.2[b]	1 (minimal to mild pulmonary fibrosis and macrophage accumulation; alveolar duct epithelialization; basal cell and Bowman's gland hyperplasia in the nasal cavity)		Reuzel et al. 1994 Polymeric MDI, aerosolized	
			Cardio	6				
			Hemato	6				
			Hepatic	6				
			Renal	6				
			Endocr	6				
			Bd Wt	6				
Immuno/ Lymphoret								
9	Rat (Wistar)	24 mo 5 d/wk 6 hr/d		0.2 M	1 M (minimal to mild macrophage accumulation in mediastinal lymph nodes)		Reuzel et al. 1994 Polymeric MDI, aerosolized	
Neurological								
10	Rat (Wistar)	24 mo 5 d/wk 6 hr/d		6			Reuzel et al. 1994 Polymeric MDI, aerosolized	

Table 3-2. Levels of Significant Exposure to Methylene Diphenyl Diisocyanate - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form	Comments
Reproductive								
11	Rat (Wistar)	24 mo 5 d/wk 6 hr/d		6 M			Reuzel et al. 1994 Polymeric MDI, aerosolized	
Cancer								
12	Rat (Wistar)	24 mo 5 d/wk 6 hr/d				6 M (CEL: lung adenomas and adenocarcinomas)	Reuzel et al. 1994 Polymeric MDI, aerosolized	

a The number corresponds to entries in Figure 3-2.

b Used to derive a chronic-duration inhalation MRL of 0.001 mg/m3 for polymeric MDI based on a BMDL of 0.48 mg/m3. The BMDL was adjusted for intermittent exposure and multiplied by the regional deposited dose ratio for extrathoracic effects to calculate the human equivalent concentration (HEC). The BMDL(HEC) of 0.039 mg/m3 was divided by an uncertainty factor of 30 (3 for extrapolation from animals to humans with dosimetric adjustment and 10 for human variability).

Bd Wt = body weight; Cardio = cardiovascular; CEL = cancer effect level; d = day(s); Endocr = endocrine; F = female; Gd = gestational day; Gn Pig = guinea pig; Hemato = hematological; hr = hour(s); Immuno/Lymphoret = immunological/lymphoreticular; LOAEL = lowest-observed-adverse-effect level; M = male; mo = month(s); NOAEL = no-observed-adverse-effect level; Resp = respiratory; wk = weeks(s)

Figure 3-2. Levels of Significant Exposure to Methylene Diphenyl Diisocyanate - Inhalation

Acute (≤14 days)

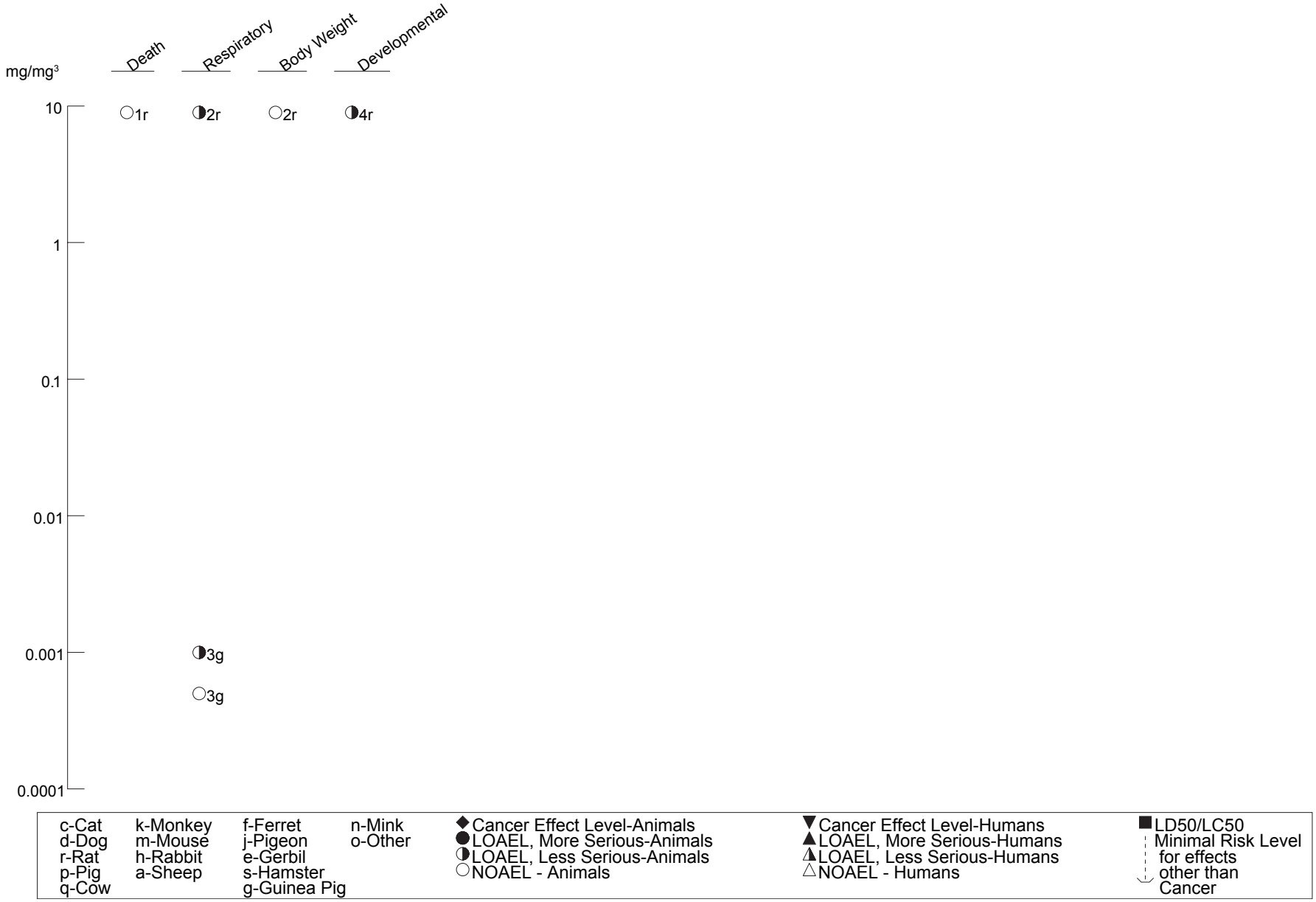
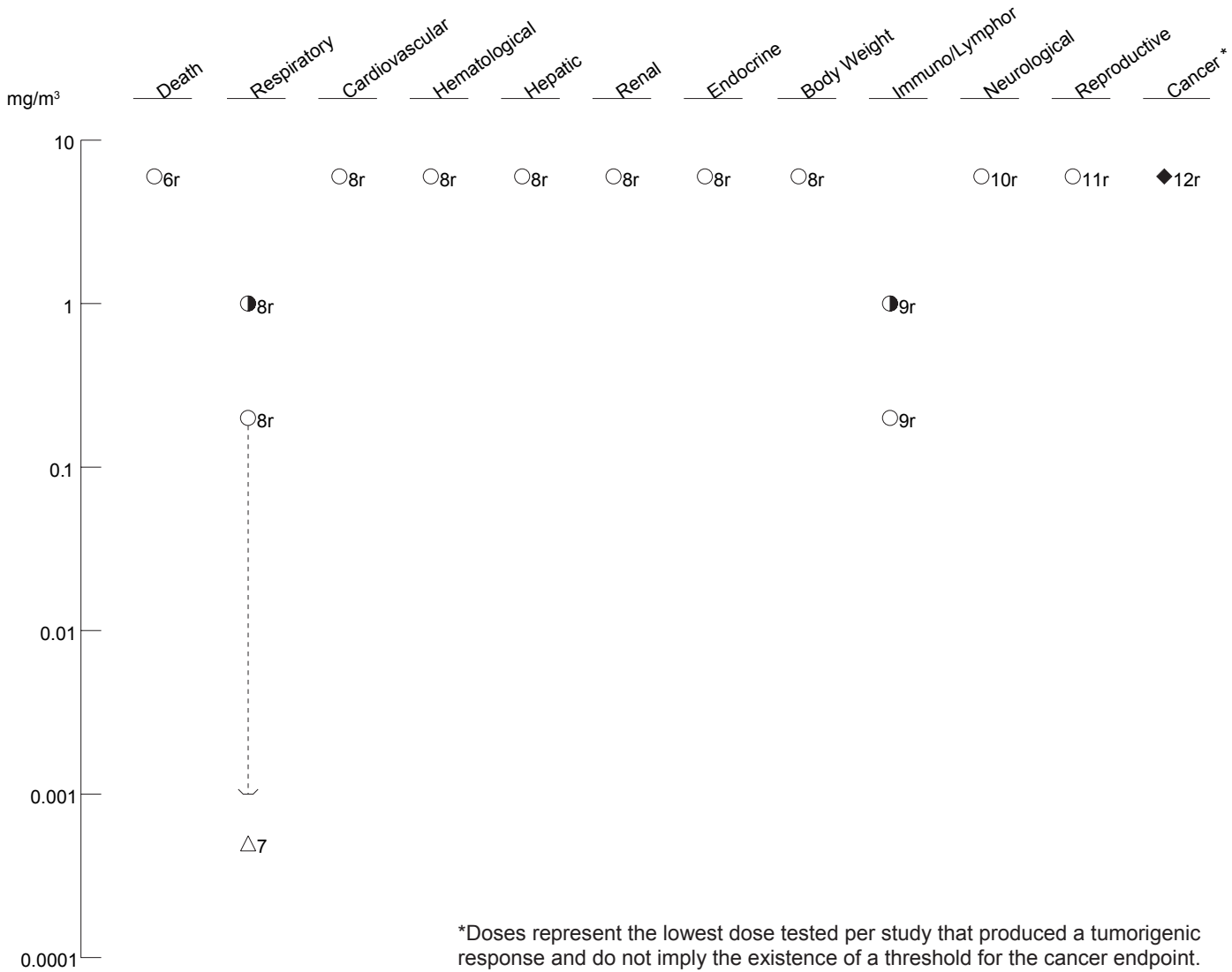


Figure 3-2. Levels of Significant Exposure to Methylene Diphenyl Diisocyanate - Inhalation *(Continued)*

Intermediate (15-364 days)

Figure 3-2. Levels of Significant Exposure to Methylene Diphenyl Diisocyanate - Inhalation *(Continued)*

Chronic (≥365 days)



*Doses represent the lowest dose tested per study that produced a tumorigenic response and do not imply the existence of a threshold for the cancer endpoint.

c-Cat d-Dog r-Rat p-Pig q-Cow	k-Monkey m-Mouse h-Rabbit a-Sheep	f-Ferret j-Pigeon e-Gerbil s-Hamster g-Guinea Pig	n-Mink o-Other	◆ Cancer Effect Level-Animals ● LOAEL, More Serious-Animals ◑ LOAEL, Less Serious-Animals ○ NOAEL - Animals	▼ Cancer Effect Level-Humans ▲ LOAEL, More Serious-Humans ◮ LOAEL, Less Serious-Humans △ NOAEL - Humans	■ LD50/LC50 Minimal Risk Level for effects other than Cancer

chronic exposure to ≥0.05 ppm production-grade TDI; deaths occurred in 60% of controls and in 77 and 74% of low- and high-exposure females, respectively (Loeser et a. 1983).

MDI. No deaths were observed in acute- or intermediate-duration studies in guinea pigs exposed up to 20 ppb 4,4'-MDI (Marek et al. 1999), in a developmental toxicity study in which rats were exposed to 9 mg/m^3 4,4'-MDI aerosol on GDs 6–15 (Buschmann et al. 1996), or in a chronic-duration study in which rats were exposed to 6.0 mg/m^3 for 2 years (Reuzel et al. 1994).

3.2.1.2 Systemic Effects

Respiratory Effects.

TDI. A large number of epidemiology and experimental studies have examined the toxicity of TDI to the respiratory tract. Data from a limited number of acute-duration studies identify respiratory irritation as the primary effect at low concentrations and severe respiratory symptoms and possibly asthma occurring after exposure to high concentrations. As reviewed by Ott et al. (2003), a 30-minute exposure to TDI resulted in the following effects in healthy subjects: ocular irritation at 0.050 ppm, nasal irritation at 0.080 ppm, eye, nose, and throat irritation, which was considered tolerable, at 0.100 ppm; tearing and burning in the throat at 0.50 ppm, and nasal discharge and severe cough after several minutes of exposure to 1.3 ppm. Another study reviewed by Ott et al. (2003) reported chest tightness, cough, and burning of the throat in asthmatics (asthma was not due to occupational exposure to TDI) exposed to 0.01 or 0.02 ppm TDI for 1 hour. By comparison, another study reported a mild cough in 1/10 healthy subjects exposed to 0.02 ppm TDI for 2 hours. A longer study in healthy subjects exposed to 0.005 ppm TDI for 6 hours followed by a 20-minute exposure to 0.02 ppm did not result in respiratory symptoms (Vandenplas et al. 1999). However, slight, but statistically significant, decreases in specific airway conductance (sG_{AW}) and MEF at 25% of FVC ($MEF_{25\%}$) were observed. The decreases in sG_{AW} and $MEF_{25\%}$ started within the first 60 minutes of exposure. Another study (Chester et al. 1979) did not find alterations in specific airway resistance (sR_{AW}) in healthy or asthmatic (not TDI-induced) subjects exposed to 0.02 ppm TDI for 20 minutes.

The primary respiratory effects observed following longer-term occupational exposure are TDI-induced bronchial asthma, asthma-like respiratory symptoms, and a decline in pulmonary function. TDI-induced asthma is a type of occupational asthma that can be characterized as bronchial inflammation and/or airway hyperresponsiveness. Respiratory symptoms often reported in workers with TDI-induced asthma

include wheezing, dyspnea, coughing, and chest tightness, which often persist after TDI exposure has ceased (Mapp et al. 1988; Moller et al. 1986; Moscato et al. 1991; Padoan et al. 2003; Paggiaro et al. 1984). Individuals with TDI-induced asthma are considered to be sensitized to TDI, in that brief exposures to nonirritating concentrations can result in a worsening of symptoms and a decline in lung function. TDI exposure can result in four types of asthmatic reactions in sensitized individuals: an immediate response, a late response, a dual response (individuals having immediate and late responses), or an irregular response. Two studies, each examining about 100 workers suspected of having TDI-induced asthma based on respiratory symptoms (e.g., wheezing, dyspnea, chest tightness, or dry cough), found that more workers (41 or 44% of responders) had a late response to a TDI challenge (0.011 ppm for 30 minutes or 0.015–0.025 ppm for 10–15 minutes) than had a dual response (35 or 41%) or immediate response (28 or 21%) (Moscato et al. 1991; Paggiaro et al. 1986). A smaller scale study of 10 subjects reported that 8/10 workers had a late reaction to a TDI challenge (0.005–0.006 ppm) and 2/10 had a dual reaction (Saetta et al. 1995). Siracuse et al. (1978) reported a case of a worker who had recurrent nocturnal asthma as a result of TDI exposure. Although the cause of the different responses is not known, Paggiaro et al. (1986) noted that subjects who had a dual response to a TDI challenge had a significantly longer duration of symptoms before diagnosis than the immediate or late responders.

The prevalence of TDI-induced asthma among TDI workers has not been well established. A comparison of the prevalence of TDI-induced asthma across studies is difficult due to differences in the criteria used to define asthma. Some studies define asthma as removal from workplace or job due to respiratory symptoms, particularly wheezing and dyspnea, and others as a decrease in lung function following a TDI-challenge. Ott et al. (2003) calculated annual induction rates of TDI-induced asthma using data from a number of cross-sectional and longitudinal studies and found rates of approximately 5–6% prior to the 1970s and rates of <1% since the mid-1970s when TDI levels were typically maintained at ≤0.005 ppm and many of the cases were attributable to incidents involving exposure to TDI levels well above 0.02 ppm. In a study of 49 workers at a new TDI polyurethane foam manufacturing facility, new symptoms of asthma were observed in 7.1% of the workers after 6 months of exposure (Gui et al. 2014). The investigators noted that 90% of the air samples were less than the 0.0001 ppm detection limit, with a maximum exposure level of 0.01 ppm.

Inhalation challenge testing in which subjects with respiratory symptoms characteristic of asthma are exposed to a non-irritating concentration of TDI (typically ≤0.02 ppm) for a short period is often used to diagnose TDI-induced asthma. However, not all subjects have a positive reaction, such as a decline in FEV_1, to the challenge test (Banks et al. 1989; Burge 1982; Mapp et al. 1988; Moller et al. 1986; Moscato

et al. 1991; O'Brien et al. 1979). For example, a study of 58 workers reporting wheezing and dyspnea found that only 43% had a positive response in the TDI challenge test (Banks et al. 1989). Another study of 51 workers with respiratory symptoms found a positive reaction to the TDI challenge in 52% of the workers (Burge 1982).

The mechanism of TDI sensitization has not been elucidated; some investigators have suggested that immune mechanisms may be involved. Specific IgG antibodies to TDI-human serum albumin (HSA) conjugates (Park et al. 1999) or IgE antibodies to TDI-HSA (Baur and Fruhmann 1981; Cvitanovic et al. 1989; Park and Nahm 1996; Park et al. 1999; Pezzini et al. 1984; Sharifi et al. 2013) have been found in workers with TDI-induced asthma. However, TDI-HSA-specific IgG or IgE antibodies were typically found in less than half of the sensitized workers (16–57%).

A number of studies have tracked the prognosis of workers with probable TDI-induced asthma. Some recovery from respiratory symptoms and/or an absence of a response to a TDI challenge have been observed (Banks and Rando 1988; Banks et al. 1990; Lemiere et al. 1996; Mapp et al. 1998; Moller et al. 1986; Padoan et al. 2003; Paggiora et al. 1984, 1993; Park and Nahm 1997; Saetta et a. 1995). A small improvement in the prevalence of respiratory symptoms was observed 2 years after exposure termination in workers with verified TDI-induced asthma (Paggiaro et al. 1984). Dyspnea and wheezing were reported by 8/12 subjects, as compared to 12/12 subjects at the initial examination. In 16 asthmatic subjects who left the workplace, 56% did not respond to a TDI challenge administered 4 years after leaving the workforce (Paggiaro et al. 1993). Padoan et al. (2003) also reported a decline in the prevalence of respiratory symptoms of asthma and hyperresponsiveness to methacholine in subjects who ceased TDI exposure for an average of 11 years. However, 60% of the subjects removed from TDI exposure for >10 years still complained of asthmatic symptoms. Improvement in respiratory symptoms or response to a TDI challenge was not observed in workers who continued TDI exposure (Banks et al. 1990; Mapp et al. 1988; Padoan et al. 2003; Paggiaro et al. 1984). A study of 35 subjects with TDI-induced asthma monitored for 2 years after cessation of exposure found that 49% were no longer hyperresponsive to methacholine, 31% had significant improvements in the first year, and 20% did not show evidence of improvement. Subjects who recovered had a shorter duration of asthmatic symptoms before diagnosis, immediately ceased TDI exposure after diagnosis, had a milder degree of airway hyperresponsiveness, and had specific IgE antibodies to TDI-HSA (Park and Nahm 1997). A case report suggested that re-exposure to TDI may result in a reversal of the recovery (Banks and Rando 1988). Eleven years after a worker with asthma ceased TDI exposure, there were no respiratory symptoms and

no response when challenged with a subirritant concentration of TDI. However, within 5 months of returning to work, the subject developed asthma and had a positive response to a TDI challenge.

TDI-induced asthma is typically associated with acute exposure to very high concentrations or prolonged exposure to lower concentrations. Two studies have examined communities near a polyurethane foam manufacturing facility in Finland (Nuorteva et al. 1987) or TDI-emitting sources in North Carolina (Wilder et al. 2011). In the Finnish study of 3,153 adults living near the facility, asthma was diagnosed in 2.2% of the subjects, compared to 2.4% of the 1,029 subjects living in a referent area. In the subjects with asthma, IgE antibodies specific to TDI, MDI, or hexamethylene diisocyanate (HDI) were only found in one subject who was occupationally exposed. No differences in the prevalence of respiratory symptoms were found. Wilder et al. (2011) did not find a significant increase in the prevalence of asthma or asthma-like respiratory symptoms in the residents living near TDI sources compared to the referent communities. Of the 161 residents living near TDI sources, only 1 had IgG antibodies specific to TDI and none had IgE antibodies specific to TDI.

The primary effect in workers not sensitized to TDI is a decline in lung function. Ott et al. (2003) noted that the decline in lung function, particularly airflow limitations, may be due to increased airway wall thickness, subepithelial fibrosis, obstruction of airway lumen by exudate or mucus, and changes in elastic properties of airway walls or loss of the interdependence between airways and surrounding parenchyma. Longitudinal studies, summarized in Table 3-3, have examined possible changes in lung function in TDI workers over time and found mixed results based on reported 8-hour TWA TDI levels (Adams 1975; Bodner et al. 2001; Butcher et a. 1977; Clark et al. 1998, 2003; Diem et al. 1982; Jones et al. 1992; Omae et al. 1992; Ott et al. 2000; Peters et al. 1970; Wegman et al. 1977, 1982). Conflicting results may be due to differences in peak exposure levels, length of exposure, historical TDI exposure, or inclusion of subjects with possible TDI-induced asthma. Diem et al. (1982) conducted a 5-year study of a new TDI manufacturing facility and found a greater decline in FEV_1 and $FEF_{25–50\%}$ among workers with a cumulative TDI exposure of ≥0.0682 ppm-months and who never smoked. A greater decline in FEV_1 was also observed in smokers with high cumulative exposure; however, the mean annual decline was similar to expected values from cross-sectional studies of normal populations. Based on unpublished information from Janet Hughes, EPA (IRIS 2003) reported a mean 8-hour TWA TDI level in the high cumulative exposure, never-smoking group of 0.0019 ppm; the mean 8-hour TWA TDI level for the low cumulative exposure, never-smoking group was 0.0009 ppm. Clark et al. (1998) found a significant

Table 3-3. Summary of Occupational Exposure Studies Examining the Effects of TDI on Lung Function

Study	Exposure	Effect
Adams 1975 Longitudinal study 565 TDI workers at two TDI manufacturing facilities examined between 1961 and 1972	Exposure levels not reported; the percentage of TDI levels that exceeded 0.02 ppm was 58–67% in 1962–1964 (most readings between 0.05 and 0.1 ppm) in plant 1, 21% and 13% in 1965 in plants 1 and 2, and 1–4 and 2-8% in 1966–1970 in plants 1 and 2	No association between exposure and decline in FVC and FEV_1 levels
Bodner et al. 2001 Longitudinal study 305 TDI manufacturing workers employed for at least 3 consecutive months; referent group consisted of 581 workers in hydrocarbon departments at the same facility; workers were examined every 1–2 years for 26 years	Mean TDI level at the last study examination was 0.0023 ppm	No correlations between lung function (FEV_1 and FVC) and TDI exposure
Butcher et al. 1977 Longitudinal study 166 TDI manufacturing workers examined prior to working in TDI-related job and at 6-month intervals for a total of 2.5 years	The TWA TDI level was estimated to be 0.015 ppm based on area monitoring; a comparison between some area monitoring and personal monitoring data suggests that the area monitoring may overestimate the worker's exposure levels	No exposure-related decline in lung function
Clark et al. 1998 Longitudinal study 644 workers at 12 polyurethane foam manufacturing facilities and 136 referents examined over a 5-year period	The mean daily 8-hour TWA was 0.0012 ppm	No exposure-related decline in lung function; in a subset of 157 workers who entered the study after the first year, longitudinal analysis showed a significant decline in FEV_1 and FVC
Clark et al. 2003 Longitudinal study 251 polyurethane foam manufacturing workers (217 workers were part of the Clark et al. 1988 cohort)	Workers divided into three groups; mean 8-hour TWA TDI levels were 0.00105, 0.0006, and 0.00029 ppm	No effect of exposure on FEV_1 levels for the full cohort
Diem et al. 1982 Longitudinal study 114 TDI workers and 54 referents working at a new TDI manufacturing facility; workers divided in to low, medium, and high exposure groups and into high and low cumulative exposure groups; workers examined 9 times in 5-year period	Mean 8-hour TWA TDI levels were 0.0016, 0.0032, and 0.0068 ppm TDI levels in the low and high cumulative exposure groups were <0.0682 and ≥0.0682 ppm-months	Greater decline in FEV_1 and $FEF_{25–50\%}$ in never-smokers in the high cumulative exposure group, as compared to low cumulative exposure group; no effect on FEV_1 when TDI was expressed as a continuous variable

Table 3-3. Summary of Occupational Exposure Studies Examining the Effects of TDI on Lung Function

Study	Exposure	Effect
Gui et al. 2014 Longitudinal study 49 workers at a new TDI manufacturing facility	90% air samples had TDI levels below the detection limit of 0.0001 ppm	No significant alteration in FEV_1, FVC, or FEV_1/FVC; decline in FEV_1 levels of >15% in 9.1% workers after 12 months of exposure
Huang et al. 1991a Cross-sectional study 15 painters applying polyurethane varnish; included 7 workers with chronic bronchitis and 4 workers with dyspnea and wheezing	TDI levels ranged from 0.07 to 0.17 ppm	Decreased FVC, FEV_1, and FEV_1%
Huang et al. 1991b Cross-sectional study 48 workers at spraying polyurethane varnish at three facilities included workers at facilities A and B with chronic bronchitis (46.7 and 15%), dyspnea and wheezing (26.7 and 15%)	Mean TDI levels at facilities A, B, and C were 0.11, 0.043, and 0.015 ppm, respectively	Decreased FEV_1, and MMF at facilities A and B
Jones et al. 1992 Longitudinal study 386 workers at polyurethane foam manufacturing facility examined ≥1 time in a 2-year period; 227 examined at least 3 times and initial lung function testing performed on 294 workers	Mean TDI levels ranged from 0.00117 to 0.00447 ppm	No relationship between TDI exposure and decline in FVC or FEV_1 (excluded workers with TDI-induced asthma)
Olsen et al. 1989 Cross-sectional study 57 workers at TDI manufacturing facility and 89 referents	Exposure levels not reported; TDI levels did not exceed the permissible level of 0.02 ppm	No association between TDI exposure (current, highest career, or cumulative) and FEV_1 levels.
Omae et al. 1992 Longitudinal study 57 polyurethane foam manufacturing workers and 24 referents followed for 4 years	Mean TWA TDI levels in low and high exposure groups were 0.0001 and 0.0057 ppm High exposure group further divided into high-1 and high-2 groups; TWA TDI concentrations were 0.0082 ppm (maximum TWA TDI level of 0.02–0.03 ppm) and 0.0017 ppm (maximum TWA TDI level of 0.003–0.004 ppm)	Larger than expected annual losses of MMF, ratio of FEV_1%, $FEF_{25\%}$, and PEF in high-1 group; MMF, FEV_1%, and $PEF_{25\%}$ in the high-1 group were significantly higher than low exposure group
Ott et al. 2000 Longitudinal study 219 TDI manufacturing workers and 77 referents examined over a 16-year period (average duration of employment was 4.7–5.7 years)	TWA TDI level across jobs and times was 0.0042 ppm	No association between FVC and FEV_1 and exposure (annual or cumulative exposure measures) in smokers or nonsmokers

Table 3-3. Summary of Occupational Exposure Studies Examining the Effects of TDI on Lung Function

Study	Exposure	Effect
Peters et al. 1970 Longitudinal study 28 workers at a polyurethane foam manufacturing facility examined every 6 months for 2 years	Maximum TDI levels at examinations 1, 2, 3, and 4 were 0.003, 0.012, 0.0015, and 0.0145 ppm, respectively	FEV_1 levels on Monday morning were significantly lower at the second examination than first examination
Peters et al. 1968 Cross-sectional study 38 workers at a polyurethane foam manufacturing facility	TDI levels ranged from 0.0001 to 0.003 ppm (levels were approximately 10-fold higher the previous year)	Decreased FVC, FEV_1, $FR_{50\%}$, and $FR_{25\%}$ during the workday
Świerczyńska-Machura et al. 2015 Cross sectional study 30 workers at polyurethane foam manufacturing facility	Arithmetic mean TDI levels at different work areas ranged from 0.0005 to 0.0037 ppm	Changes indicative of mild bronchial obstruction noted in 17% of workers
Wegman et al. 1977 Longitudinal study 57 polyurethane foam manufacturing workers originally examined in 1972 were re-examined in 1974	TDI levels were ≤0.0015, 0.0025-0.0030, and ≥0.0035 ppm	Decline in FEV_1 was dose-related and exceeded predicted levels in the highest two groups
Wegman et al. 1982 Longitudinal study 48 TDI workers from Wegman et al. (1977) re-examined in 1976	TDI levels were ≤0.0015, 0.0025-0.0030, and ≥0.0035 ppm	4-Year change in FEV_1 was significantly greater in ≥0.0035 ppm group than low exposure group; most of the decline occurred in the first 2 years of the study
White et al. 1980 Cross-sectional study 147 machinists making seat covers with a fabric backed with flame-bonded polyurethane foam; 30% workers reported wheezing and/or dyspnea	TDI levels ranged from 0.0003 to 0.003 ppm	Higher prevalence of peak flow rates <90% of predicted, as compared to 45 workers who never machined polyurethane foam

$FEF_{25–75\%}$ = forced expiratory flow between 25 and 75% of FVC; FEV_1 = forced expiratory volume in 1 second; FEV_1% = ratio of FEV_1 to FVC; $FR_{50\%}$ = flow rate at 50% vital capacity; $FR_{25\%}$ = flow rate at 25% vital capacity; FVC = forced vital capacity; MMF = maximal mid-expiratory flow; PEF = peak expiratory flow; TDI = toluene diisocyanate; TWA = time-weighted average

increase in annual declines in FEV_1 and FVC among workers at a polyurethane foam manufacturing facility who entered the study with no prior exposure to TDI (naïve group). It was noted that the greatest decline in lung function occurred during the first few months of employment. The mean 8-hour TWA TDI level for the entire cohort of exposed workers was 0.0012 ppm. No exposure-related effects on lung function were found in the whole cohort of exposed workers. A follow-up of this cohort (Clark et al. 2003) did not find significant increases in annual declines in lung function in the whole cohort or the naïve group in subsequent years. Another study of polyurethane manufacturing workers found larger-than-expected annual losses of MMF, ratio of FEV_1 to FVC (FEV_1%), and PEF in workers with an 8-hour TWA TDI level of 0.0082 ppm with maximal TWA peak concentrations of 0.02–0.03 ppm (Omae et al. 1992). Annual declines in lung function parameters were not observed in workers with an 8-hour TWA TDI level of 0.0017 ppm with maximal TWA peak concentrations of 0.0003–0.004 ppm. In another study of a new polyurethane foam production facility, no significant alterations in FEV_1, FVC, or FEV_1/FVC ratio were found after 6 or 12 months of exposure (Gui et al. 2014). However, it was noted that in 9.1% of the 33 workers, there was a decrease in FEV_1 of >15% between 6 and 12 months of exposure. TWA TDI levels were not reported; the investigators noted that the TDI levels in >90% of the air samples were below the detection limit of 0.0001 ppm.

Other longitudinal studies of workers at TDI manufacturing facilities (Adams 1975; Bodner et al. 2001; Butcher et al. 1977; Ott et al. 2000) or polyurethane foam manufacturing facilities (Clark et al. 2003; Jones et al. 1992) have not found significant associations between TDI exposure and declines in lung function (Table 3-3). In longitudinal analysis of FVC and FEV_1 levels and TDI exposure, Ott et al. (2000) did not find statistically significant associations in TDI manufacturing workers with a TWA TDI level of 0.0042 ppm. Similar findings were reported in another study of TDI manufacturing workers with a mean TDI exposure level of 0.0023 ppm (Bodner et al. 2001). Ott et al. (2003) concluded that among nonsensitized TDI workers, exposure to ≤5 ppb (8-hour TWA) was not associated with decreases in FEV_1. However, it is noted that the investigators did not consider the possibility of increased toxicity among naïve workers, as found by Clark et al. (1998) and Diem et al. (1982).

Cross-sectional studies, summarized in Table 3-3, also examined declines in lung function due to TDI exposure (Huang et al. 1991a, 1991b; Olsen et al. 1989; Peters et al. 1968; Świerczyńska-Machura et al. 2015; White et al. 1989). The interpretation of the results of some of the studies is limited by the inclusion of workers with asthma-like respiratory symptoms (Huang et al. 1991a, 1991b; White et al. 1980) or the lack of controls (Świerczyńska-Machura et al. 2015). Olsen et al. (1989) did not find associations between TDI exposure (current exposure, highest career exposure, cumulative exposure, or

cumulative highest-to-date exposure) and FEV_1 levels in a study of TDI manufacturing workers. Although the TDI levels were not reported, the investigators noted that TDI levels at the facility did not exceed the permissible level of 0.02 ppm; the investigators did not provide definitions of highest career exposure, cumulative exposure, or cumulative highest-to-date exposure or information on how they were calculated. In a study of polyurethane foam manufacturing workers, Peters et al. (1968) reported significant decreases in FVC, FEV_1, flow rate at 50% vital capacity ($FR_{50\%}$), and $FR_{25\%}$ when end-of-shift values were compared to start-of-shift values. Further declines in FVC, peak flow rate (PFR), $FR_{50\%}$, and $FR_{25\%}$ were found when Monday afternoon values were compared to Monday morning values. The TDI levels ranged from 0.0001 to 0.003 ppm.

Animal studies support the findings from human studies that the respiratory tract is a sensitive target of TDI toxicity. Signs of irritation and histological damage have been observed following acute-, intermediate-, and chronic-duration exposure. Acute studies in mice and rats demonstrated that TDI was a sensory irritant and that the level of response was related to the concentration and the duration of exposure (Pauluhn 2014; Sangha and Alarie 1979). RD_{50} values (concentration resulting in a 50% decrease in respiration rate) in mice exposed for 10, 30, 60, 120, 180, or 240 minutes were 0.813, 0.498, 0.386, 0.249, 0.199, and 0.199 ppm, respectively (Sangha and Alarie 1979). When the animals were repeatedly exposed, the RD_{50} values were lower on subsequent days; after 3 days of exposure to 0.023–1.18 ppm, pre-exposure respiratory rates were lower than day 1, indicating an incomplete recovery.

Histological alterations have been observed in the nasal cavity (Arts et al. 2008; Buckley et al. 1984; Johnson et al. 2007; Loeser 1983; Matheson et al. 2005; Sangha and Alarie 1979; Zissu 1995), trachea (Gordon et al. 1985), and lung (Loeser 1983; Wong et al. 1985) in laboratory animals. The nasal lesions consist of inflammation, hyperplasia, degeneration, ulceration, and metaplasia; the severity and the location of the damage appear to be concentration and duration related. At lower concentrations and shorter durations, only the nares (most anterior region of the nasal cavity) are affected; at high concentrations, the damage extends to the olfactory epithelium. The only NOAEL identified for nasal effects is 0.031 ppm in mice exposed 3 hours/day for 5 days (Sangha and Alarie 1979). When the duration was extended to at least 6 weeks (4 hours/day, 5 days/week), exudate, goblet cell metaplasia, and inflammation were observed in the nares of mice exposed to 0.02 ppm (Matheson et al. 2005). Rhinitis was also observed in rats exposed to 0.02 ppm in a 2-generation study (Tyl et al. 1999b). Exposure to 0.05 ppm 4 hours/day for 12 days resulted in extensive inflammatory cell infiltration into the lamina propria in the nasoturbinates and maxilloturbinates of mice; goblet cell metaplasia was also observed in the maxilloturbinates (Johnson et al. 2007). Extending exposure to 0.07 ppm from 4 to 9 days resulted in

an increase in the severity of the rhinitis and respiratory epithelia metaplasia and necrosis observed in mice (Zissu 1995). The TDI concentration associated with olfactory epithelial damage was 0.4 ppm (6 hours/day for 5 days), which resulted in moderate olfactory epithelial ulceration and necrosis and slight degeneration of the olfactory nerve (Buckley et al. 1984). Concentration-related increases in the incidence and severity of chronic or necrotic rhinitis with epithelial atrophy and mucous and squamous metaplasia were observed in mice exposed to ≥0.05 ppm TDI for 2 years (Loeser 1983).

Slight laryngeal epithelial hyperplasia was observed in mice exposed to 1.0 ppm TDI for 6 hours (Arts et al. 2008). Exposure of guinea pigs to 2 ppm for 1 hour resulted in patchy loss of cilia and disruption of the surface epithelium in the trachea (Gordon et al. 1985). Matheson et al. (2005) reported goblet cell inflammation, epithelial hyperplasia, regeneration, and loss of structure in the lungs of mice exposed to 0.5 ppm for 2 hours. However, other acute studies at similar (0.4 ppm 6 hours/day for 5 days) or higher (1 ppm for 6 hours) concentrations did not find histological alterations in the lungs (Arts et al. 2008; Buckley et al. 1984). Interstitial inflammation, localized pleural thickening, and goblet cell hyperplasia were observed in the lungs of guinea pigs 50 days after exposure to 1.4 ppm 3 hours/day for 5 days (Wong et al. 1985). Similarly, goblet cell metaplasia in the central airway mucosa and eosinophil infiltration in the central and peripheral airways were observed in rats exposed to 0.41 ppm 2,4-TDI 4 hours/day for 5 days (Kouadio et al. 2014); the severity of the lesions increased with exposure concentration. In a chronic mouse study, interstitial pneumonitis and catarrhal bronchitis were observed in “some mice,” with a higher incidence at 0.15 ppm (Loeser 1983).

In addition to the histological alterations, studies in guinea pigs, rats, and mice have demonstrated TDI sensitization (Aoyama et al. 1994), bronchial hyperresponsiveness (Gagnaire et al. 1996; Gordon et al. 1985; Kouadio et al. 2014; Marek et al. 1999; Matheson et al. 2005), and nasal hyperresponsiveness (Kouadio et al. 2014). An increase in respiratory rate was observed in guinea pigs exposed to 0.2 ppm TDI 3 hours/day for 5 days and challenged with 0.02 ppm TDI (15-minute exposure) 26 days after the initial exposure (Aoyama et al. 1994). The TDI challenge concentration did not elucidate a response in guinea pigs previously exposed to 0.02 ppm for 5 days. Challenge tests with acetylcholine or methacholine resulted in airway hyperresponsiveness in guinea pigs and mice previously exposed to a TDI concentration as low as 0.01 ppm (6 hours/day for 5 days) (Marek et al. 1999); a NOAEL of 0.005 ppm was identified in the same study. Airway hyperresponsiveness was also observed following a 1-hour exposure to a relatively high concentration (3 ppm) (Gagnaire et al. 1996). The effects were observed 30 minutes after exposure and persisted for 48 hours. A TDI challenge following 4-hour/day exposure to 2,4-TDI resulted in severe labored breathing as evidenced by gasping and breathing with an

open mouth after 4 days of exposure to 1.14 ppm (Kouadio et al. 2014); the severity of the labored breathing was less severe after 2 or 3 exposure days. Labored breathing was also observed in rats similarly exposed to 0.41 ppm for 4 or 5 days. Symptoms of nasal hyperresponsiveness (sneezing and hyperrhinorrhea) were also observed at both concentrations (Kouadio et al. 2014).

MDI. The toxicity of MDI to the respiratory tract has not been as well investigated as TDI, but the effects appear to be similar. The primary effects observed include occupational asthma in sensitized individuals and decreased lung function. MDI-induced asthma has been reported in occupational exposure studies and case reports (Bonauto et al. 2005; Burge 1982; Chang and Karol 1984; Helaskoski et al. 2015; Hur et al. 2008; Liss et al. 1988; Suojalehto et al. 2011; Woellner et al. 1997; Zammit-Tabona et al. 1983); however, no reliable dose-response data are available. Asthma symptoms were noted in 18 of the 106 workers at a wood products plant using heated MDI in the manufacture of synthetic wood (Woellner et al. 1997). Symptoms occurred within the first 12 months of operation; half reported symptoms within the first 7 months of operation when operational problems would likely have resulted in MDI levels that exceeded the permissible level of 0.02 ppm. Bonauto et al. (2005) used worker's compensation claims to estimate the rate of asthma in the spray-on truck bed lining industry. A rate of 200 per 10,000 full-time employees was found; however, no testing was done on any of the claims to determine whether MDI was causative agent. Approximately half of subjects reporting asthma-like symptoms (wheezing, dyspnea, and/or cough) had a positive response in a methacholine-challenge test. A study of 11 foundry workers with asthma-like symptoms found that 6 had a positive response in a MDI-challenge test (Zammit-Tabona et al. 1983). Another study of 40 MDI workers found that 24 responded to MDI challenge at test atmospheres of up to 0.02 ppm (Burge 1982). A third study (Hur et al. 2008) diagnosed MDI-induced asthma or eosinophilic bronchitis in 6 of 13 car upholstery factory workers with lower respiratory symptoms. The incidence of nonspecific bronchial hyperresponsiveness to a challenge with methacholine was significantly higher among MDI workers with asthma-like symptoms, as compared to controls and TDI workers (Jang et al. 2000). Several case reports of MDI workers (Bascom et al. 1985; Baur et al. 1984; Malo and Zeiss 1982; Zeiss et al. 1980) and a study of MDI workers (Baur 1995) with asthma-like symptoms also reported chills, fever, and malaise, which are consistent with symptoms of hypersensitivity pneumonitis.

Several occupational exposure studies have examined the effect of MDI exposure on lung function (Liss et al. 1988; Musk et al. 1982; Sulotto et al. 1990). Lung function was examined in 27 polyurethane foam workers who were asymptomatic for asthma; the MDI concentrations ranged from 0.0005 to 0.001 ppm. A comparison of lung function values of the workers to an age-matched control group of 27 clerks did not

show statistically significant differences between the groups. Additionally, no differences in the change in lung function over a work week (Monday values compared to Friday values) or over the work shift were found. Musk et al. (1982) examined 107 workers at two polyurethane plastic manufacturing facilities over a 5-year period; 25 of the subjects were only exposed to MDI, 17 to only TDI, 6 to MDI and TDI, and 42 were not exposed to diisocyanates. The geometric mean MDI levels reported by the plants during the last year of the study were 0.0006 and 0.0003 ppm at plants 1 and 2, respectively; however, the mean MDI levels measured by the investigators ranged from 0.001 to 0.003 ppm. It should be noted that MDI exists as an aerosol; thus, the method used to measure MDI air levels (impinged method) may have underestimated MDI levels (EPA 1998a). Lung function tests were conducted on Monday morning and afternoon and on Monday morning and afternoon following a 2-week vacation. No significant alterations in FEV_1 or FVC levels were found over the 5-year period, over a workday, or after a 2-week non-exposure period among the MDI-only exposed group.

Several studies of MDI workers have examined the possible association between specific immunoglobulin antibodies to MDI and MDI-induced asthma (Hur et al. 2008; Pezzini et al. 1984; Tse et al. 1985; Zeiss et al. 1980). In a study of 76 foundry workers (10 with asthma-like symptoms and bronchial hyperreactivity, 40 with respiratory symptoms but no evidence of bronchial hyperreactivity, and 26 with no respiratory symptoms), specific IgE antibodies to MDI-HSA conjugates were found in 2 workers (1 with asthma-like symptoms and one with other symptoms) and specific IgG antibodies to MDI-HSA conjugates were found in 5 workers (3 with asthma-like symptoms, 1 with other symptoms, and 1 with no symptoms) (Tse et al. 1985). Another study of car upholstery factory workers found specific IgG antibodies to MDI-HSA conjugates in 20.7% of the 58 workers (4/12 of the responders were diagnosed with MDI-induced asthma or eosinophilic bronchitis) and specific IgE antibodies to MDI-HSA conjugates in 8.6% of the workers (2/5 of the responders were diagnosed with MDI-induced asthma or eosinophilic bronchitis) (Hur et al. 2008).

A limited number of laboratory animal studies have examined the toxicity of MDI to the respiratory tract. An RD_{50} of 32 mg/m^3 in mice exposed to 4,4'-MDI for 4 hours was calculated (Weyel and Schaffer 1985). Exposure to concentrations as low as 7 mg/m^3 initially resulted in increases in respiratory rate followed by a gradual decline in respiratory rate; a similar respiratory pattern was observed in mice administered 4,4'-MDI via tracheal cannulation. The investigators suggested that this respiratory pattern was indicative of a pulmonary irritant rather than a sensory irritant. Increases in airway hyper-responsiveness to acetylcholine were observed in guinea pigs exposed to 0.01 ppm MDI 6 hours/day for

5 days or 6 hours/day, 5 days/week for 4 weeks (Marek et al. 1999); a NOAEL of 0.005 ppm was identified in the 5-day study.

In a chronic-duration study (Reuzel et al. 1994), rats were exposed to polymeric MDI (containing 44.8–50.2% monomeric MDI) for 1 or 2 years. After 2 years of exposure, nasal and pulmonary lesions were observed at 1.0 and 6.0 mg/m^3 and no alterations were observed at 0.2 mg/m^3. The nasal lesions consisted of basal cell hyperplasia and Bowman's gland hyperplasia in males at ≥1.0 mg/m^3 (basal cell hyperplasia was also observed in females at 6.0 mg/m^3) and minimal to severe olfactory epithelial degeneration in males and females at 6.0 mg/m^3; after 1 year of exposure, the only nasal lesion with a significantly increased incidence was minimal to moderate olfactory epithelial disarrangement in males exposed to 6.0 mg/m^3. The lung lesions in rats exposed to 1.0 or 6.0 mg/m^3 for 2 years consisted of mild to moderate localized fibrosis and alveolar duct epithelialization; exposure to 6.0 mg/m^3 also resulted in localized alveolar bronchiolization. Additionally, an accumulation of macrophages with yellow pigment was observed at 1.0 and 6.0 mg/m^3. After 1 year of exposure, minimal to moderate localized fibrosis, alveolar duct epithelialization, and localized alveolar bronchiolization were observed at 6.0 mg/m^3; alveolar duct epithelialization was also observed in the females exposed to 1.0 mg/m^3.

An unpublished study conducted by Hoyemann and associates in 1995 also evaluated the chronic toxicity of MDI in rats; this study was reviewed by Feron et al. (2001). Groups of 80 female Wistar rats were exposed to 0, 0.23, 0.70, or 2.05 mg/m^3 monomeric MDI aerosols (mass median aerodynamic diameter [MMAD] of approximately 1.0 μm) 18 hours/day, 5 days/week for approximately 2 years. As reviewed by Feron et al. (2001), significant increases in absolute and relative lung weight were observed at 2.05 mg/m^3. A number of histological alterations were observed at 0.23 mg/m^3 including bronchiolo-alveolar hyperplasia, mononuclear cell infiltration, and fibrosis; the incidence and severity of the lesions appeared to be concentration related. These effects are similar to those observed in Reuzel et al. (1994). The LOAELs from the two studies are similar after adjusting for intermittent exposure: 0.178 mg/m^3 for the Reuzel et al. (1994) study and 0.123 mg/m^3 for the Hoyemann study.

Cardiovascular Effects.

TDI. No histological alterations were observed in the aorta or heart of rats or mice exposed to 0.15 ppm commercial-grade TDI for 2 years (Loeser 1983).

MDI. No histological alterations were observed in the heart of rats exposed to 6.0 mg/m^3 polymeric MDI for 2 years (Reuzel et al. 1994).

Gastrointestinal Effects.

TDI. Workers with accidental exposure to unknown quantities of TDI spilled from tanks have reported nausea and vomiting during exposure (Axford et al. 1976; Singer and Scott 1987).

Shadnia et al. (2013) reported a case of intestinal obstruction in a 16-year-old male worker in an Iranian sponge production factory. The subject's symptoms began after he was exposed to TDI for 2 hours; details of his exposure prior to this incident, or coexposures during the incident, were not provided. The authors noted that the subject had a past history of surgery for stomach lymphoma, and during surgery to correct the obstruction, mild adhesions from the previous surgery were seen. However, the authors noted that the surgery did not identify any possible causes of the obstruction; they postulated several possible mechanisms by which TDI may have induced the effect, including triggering an inflammatory response, interrupting parasympathetic nervous system function, or decreasing bowel motility via an effect on intestinal smooth muscle.

No gastrointestinal lesions were observed in rats or mice exposed to 0.15 ppm commercial-grade TDI for 2 years (Loeser 1983).

MDI. No histological alterations were observed in the gastrointestinal tract of rats exposed to 6.0 mg/m^3 polymeric MDI for 2 years (Reuzel et al. 1994).

Hematological Effects.

TDI. No hematological alterations were noted in rats or mice exposed to 0.15 ppm commercial-grade TDI for 2 years (Loeser 1983).

MDI. No hematological alterations were observed in rats exposed to 6.0 mg/m^3 polymeric MDI for 2 years (Reuzel et al. 1994).

Musculoskeletal Effects.

TDI. No histological alterations were observed in the femur or skeletal muscle (quadriceps) of rats or mice exposed to 0.15 ppm commercial-grade TDI for 2 years (Loeser 1983).

MDI. Reuzel et al. (1994) examined 43 organs and tissues, which likely included bones and skeletal muscles, of rats exposed to 6.0 mg/m^3 polymeric MDI for 2 years and did not find histological alterations outside of the respiratory tract.

Hepatic Effects.

TDI. No histological alterations in the liver or alterations in serum chemistry parameters were observed in rats or mice exposed to 0.15 ppm commercial-grade TDI for 2 years (Loeser 1983).

MDI. No histological alterations were observed in the liver of rats exposed to 6.0 mg/m^3 polymeric MDI for 2 years (Reuzel et al. 1994); additionally, no alterations in serum clinical chemistry parameters were observed.

Renal Effects.

TDI. No histological alterations were observed in the kidneys in rats or mice exposed to 0.15 ppm commercial-grade TDI for 2 years (Loeser 1983).

MDI. No histological alterations in the kidneys or alterations in urinalysis parameters were observed in rats exposed to 6.0 mg/m^3 polymeric MDI for 2 years (Reuzel et al. 1994).

Dermal Effects.

TDI. In a study of 114 workers at a flexible foam manufacturing facility (Daftarian et al. 2002), production workers who were exposed to TDI reported skin conditions such as dermatitis, eczema, or other red rash in the previous 12 months more than twice as often as unexposed non-production workers (prevalence rate ratio of 2.66; 95% confidence interval [CI] 1.14–16.32, $p<0.02$). Skin patch testing and blood samples for specific IgG or IgE antibodies to TDI were largely negative (only 2/100 workers had a

positive result to any of these tests, and only for specific IgG); thus, the effects were considered to be related to irritation rather than an immune response.

MDI. Stingeni et al. (2008) reported a case of facial urticaria in a worker using a polyurethane glue containing MDI.

Ocular Effects.

TDI. In a case series of ocular effects in humans or animals exposed to diisocyanates, Luckenbach and Kielar (1980) evaluated visual acuity and ophthalmologic status in nine workers exposed to TDI during the production of polyurethane foam. No information on exposure levels was provided; the various cases had worked in the facility for durations ranging from 10 days to 2 years. All nine workers reported ocular symptoms such as "smoky" or "foggy" vision or eye irritation, usually resolving during weekends or overnight. In all nine, microcystic edema of the corneas and conjunctival injection (dilation of conjunctival blood vessels leading to appearance of redness) were observed upon ophthalmologic examination, with more severe cases associated with diminished visual acuity. None of the cases exhibited abnormal Schirmer I tear test or tear break-up time (Luckenbach and Kielar 1980).

Littorin et al. (2007) noted a significant association between self-reported eye symptoms and continuous measures of TDI exposure in workers. When the 2,4-TDI and 2,6-TDI levels were examined separately, a stronger association was found between eye symptoms and 2,4-TDI levels than with 2,6-TDI levels.

MDI. No information was located regarding ocular effects in humans or animals following inhalation exposure to MDI.

Body Weight Effects.

TDI. Significant decreases (45% relative to controls) in maternal body weight gain were seen in CD rats during exposure (6 hours/day on GDs 6–15) to 0.5 ppm commercial-grade TDI in a developmental toxicity study (Tyl et al. 1999a); in a range-finding study, significant weight loss was observed at 1 ppm. In a 2-generation reproductive toxicity study, intermediate-duration exposure (19 weeks including premating, mating, gestation, and lactation) to 0.3 ppm commercial-grade TDI did not alter body weight of male or female F0 or F1 parental CD rats (Tyl et al. 1999b). Chronic exposure of rats to 0.15 ppm commercial-grade TDI resulted in significant reductions in body weight gain (Loeser et al. 1983).

However, the magnitude of change was not reported; the investigators did not report any changes in body weight gain at 0.05 ppm.

MDI. Acute-duration exposure of Wistar rats to 4,4'-MDI during gestation (6 hours/day on GDs 6–15) did not alter maternal body weight or body weight gain at exposure concentrations up to 9 mg/m^3 (Buschmann et al. 1996). No significant alterations in body weight gain were observed in rats exposed to 6.0 mg/m^3 polymeric MDI for 2 years (Reuzel et al. 1994).

3.2.1.3 Immunological and Lymphoreticular Effects

Although the exact mechanism of toxicity of TDI and MDI has not been elucidated, there is some indication that occupational asthma observed in some workers has an immune component, and several studies have reported alterations in TDI or MDI specific IgG and IgE antibodies in workers with asthma (Baur and Fruhmann 1981; Cvitanovic et al. 1989; Hur et al. 2008; Park and Nahm 1996; Park et al. 1999; Pezzini et al. 1984; Sharifi et al. 2013; Tse et al. 1985; Zeiss et al. 1980). These findings are discussed in detail in the Respiratory Effects section.

3.2.1.4 Neurological Effects

TDI. Le Quesne et al. (1976) described the immediate and long-term neurological effects in 23 firefighters who were "heavily exposed" during a fire at a polyurethane foam factory; approximately 4,500 L of TDI had spilled from storage tanks during the fire (Axford et al. 1976). The firefighters were exposed via inhalation, and some also had dermal contact. Other chemicals were stored at the factory, but the spillage was apparently limited to TDI; however, exposure to other chemicals cannot be ruled out. Additionally, exposure to carbon monoxide or anoxia may have contributed to the observed effects; the investigators noted that there was no evidence that the fumes were sufficiently dense for the firefighters to become anoxic. Five of the exposed men reported symptoms during the fire including euphoria, ataxia, and transient loss of consciousness; two reported headache the next day. Seventeen of the firefighters were medically evaluated 3 weeks later and 14 of these men reported symptoms of confusion, poor memory, headache, irritability, difficulty concentrating, or depression. Neurological examination showed slight changes including ataxia and mild sensory loss; electroencephalography recordings on nine men were unremarkable. At follow-up of 18 men 4 years later, memory problems were still reported by most of the subjects, and some reported persistence of concentration difficulty, irritability, and depression. No abnormalities were seen on neurological examination; however, a statistically significant ($p<0.02$) impairment in long-term recall was noted in the Wechsler memory scale when tests in exposed men who

reported persistent effects were compared with unexposed firemen from another area (Le Quesne et al. 1976).

Singer and Scott (1987) reported neurological symptoms and neuropsychological and electrophysiology test results for three male wharf workers who were exposed to spilled TDI. Both dermal contact and inhalation exposure were described, and the total duration of exposure was about 4 hours for all three workers. The workers reported feeling dizzy during exposure. The workers were evaluated 2 and 16 months after exposure using neuropsychological tests and nerve conduction velocity measurements. Test results showed statistically significant decreases ($p<0.0003$) in verbal, performance, and full-scale IQ at 16 months postexposure compared with 2 months postexposure (full scale IQ dropped between 20 and 26 points in all three subjects); while the tests administered at each time were slightly different (WAIS at 2 months versus WAIS-R at 16 months), on average, these tests differ only by 7–8 points (Singer and Scott 1987). In addition to IQ change, statistically significant impairments in both the Benton Visual Retention and Wechsler Memory Scale: Logical Memory were observed. Two of the three subjects exhibited significantly reduced nerve conduction velocities, one in the median sensory nerve and the other in the sural nerve, while the third showed no change in nerve conduction. The study authors also reported that testing at 16 months postexposure showed severe deficits in manual dexterity, visuomotor tracking, mental flexibility, ability to detect figure-ground relationships, and word fluency (additional details of these findings were not provided). The small number of subjects, lack of a control group, and small magnitude of the effects limit the interpretation of the results.

Hughes et al. (2014) recently evaluated the available data on the neurotoxicity of diisocyanates to determine whether a causal association could be established between diisocyanate exposure (the studies involved exposure to TDI, MDI, HDI, or unspecified diisocyanates) and neurotoxicity. Using the Hill criteria for causality, Hughes et al. (2014) concluded that there was limited evidence for strength of association and consistency, and the data were inadequate to establish a casual association between diisocyanates and neurotoxicity. The investigators noted several limitations of the studies included in their systematic review such as limited exposure information (including the lack of objective exposure measures and no dose-response assessment), co-exposure to known neurotoxicants, and lack of objective measures of neurotoxicity. Additionally, they noted that no plausible mechanisms of toxicity were identified.

No animal studies have examined the potential of TDI to induce neurological effects. No histological alterations were observed in the brain, sciatic nerve, or spinal cord of rats or mice exposed to 0.15 ppm commercial-grade TDI for 2 years (Loeser 1983).

MDI. Information on the neurotoxicity of MDI is limited to a chronic study that did not find histological alterations in the brain of rats exposed to 6.0 mg/m^3 polymeric MDI for 2 years (Reuzel et al. 1994).

3.2.1.5 Reproductive Effects

TDI. No information was located regarding reproductive effects in humans following inhalation exposure to TDI. When groups of 28 CD rats were exposed via inhalation to commercial-grade TDI (80:20 mix of 2,4- and 2,6-TDI), no effects on reproductive toxicity parameters (including mating, fecundity, or fertility indices; gestation length; numbers of live litters or live birth indices; gross necropsy findings; or histopathology of reproductive organs) were seen at exposures up to 0.3 ppm, 6 hours/day, 5 days/week for 2 generations (Tyl et al. 1999b). A 2-year study in rats and mice did not find histological alterations in the gonads of male and female rats and mice (Loeser 1983).

MDI. No information was located regarding reproductive effects in humans following inhalation exposure to MDI. A 2-year study in male and female rats did not find histological alterations in the gonads at 6.0 mg/m^3 polymeric MDI (Reuzel et al. 1994).

3.2.1.6 Developmental Effects

TDI. No information was located regarding developmental effects in humans following inhalation exposure to TDI. Exposure of rats to 0.5 ppm TDI (80:20 mix of 2,4- and 2,6-TDI) during GDs 6–15 resulted in an increased incidence of litters with poorly ossified cervical centrum no. 5, but no other treatment-related increases in anomalies or variations (Tyl et al. 1999a). Maternal toxicity, including markedly reduced body weight gain and respiratory symptoms, was seen at 0.5 ppm, and the observed developmental effects may have been secondary to the maternal toxicity.

MDI. No information was located regarding developmental effects in humans following inhalation exposure to MDI. After exposure of rats to 9 mg/m^3 4,4'-MDI aerosol for 6 hours/day on GDs 6–15, there was an increase in the incidence of litters with fetuses displaying asymmetric sternebrae (10/23 litters versus 2/25 control litters, $p<0.05$); no effects of treatment were seen on other gestational parameters or on malformation or variation incidences at lower exposure concentrations (Buschmann et

al. 1996). The investigators noted that the incidence was within the limits of biological variability. Apart from reduced food consumption, dams did not exhibit signs of toxicity at any exposure concentration in this study; an increase in lung weight was also observed in the dams.

3.2.1.7 Cancer

Human data on the potential association between inhalation exposure to diisocyanates and cancer are available from studies of three cohorts of workers engaged in polyurethane foam manufacture. Studies of these cohorts (Mikoczy et al. 2004; Schnorr et al. 1996; Sorahan and Nichols 2002) have suggested an association between work in the polyurethane foam manufacturing industry and lung cancer in female workers, but an association with diisocyanate exposure was not established. Significant limitations of all three studies included lack of control for confounding factors such as smoking and alcohol consumption and coexposure to mixtures of compounds including those other than diisocyanates.

Cohort studies of cancer and diisocyanate exposure include: a cohort of 4,611 workers from 4 plants in the United States (Schnorr et al. 1996); a cohort of 4,175 workers from 9 plants in Sweden (Mikoczy et al. 2004; Hagmar et al. 1993a, 1993b); and a cohort of 8,288 workers in 11 plants in the United Kingdom (Sorahan and Nichols 2002; Sorahan and Pope 1993). Sorahan and Nichols (2002) reported data on the largest number of person-years at risk (200,262); Schnorr et al. (1996) reported on 90,393 person-years at risk, and Mikoczy et al. (2004) reported on 83,023 person-years at risk. None of the studies provided quantitative estimates of individual exposures. Workers in all three cohorts were exposed to a mixture of TDI isomers, and those at some plants were also exposed to unspecified isomers of MDI. In addition, all of the cohorts included workers who may have been exposed to other airborne contaminants such as methylene chloride, aliphatic amines, acrolein, acrylonitrile, styrene, amine accelerators such as bis(2-dimethylaminoethyl) ether, and others (Mikoczy et al. 2004; Schnorr et al. 1996).

Table 3-4 shows the results of the most recent studies in the three cohorts. Increased standardized mortality ratios (SMRs) for lung cancer were reported for women in all three cohorts; the increases were statistically significant in the U.K. (Sorahan and Nichols 2002) and Swedish (Mikoczy et al. 2004) cohorts, but not the U.S. cohort (Schnorr et al. 1996). Mikoczy et al. (2004) also reported a significantly increased incidence of lung cancer in females (standardized incidence ratio [SIR] of 3.0; 95% CI 1.55–5.24) compared with the expected incidence in the general Swedish population. However, when stratified

Table 3-4. Results of Cohort Studies of Diisocyanate Exposure and Mortality from Specific Cancers

	U.S. cohort		U.K. cohort		Swedish cohort	
Reference	Schnorr et al. 1996		Sorahan and Nichols 2002		Mikoczy et al. 2004	
Cohort size (number of plants)	4,611 (4)		8,288 (11)		4,175 (9)	
Time period of follow-up	1958–1993		1958–1998		1959–1998	
Person-years at risk	90,393		200,262		83,023	
Cancer site	Number of cases	SMR (95% CI)	Number of cases	SMR (95% CI)	Number of cases	SMR (95% CI)
Females						
Lung	8	173	35	181[a] (126–251)	10	352[a] (169–648)
Rectum	0	NA	2	53 (6–192)	–	–
Non-Hodgkin's lymphoma	–	–	3	110 (23, 321)	–	–
Hodgkin's disease	–	–	0	NA	–	–
Males						
Lung	12	79	134	107 (90–127)	7	49 (20–101)
Rectum	3	390	10	65 (31–120)	–	–
Non-Hodgkin's lymphoma	–	–	6	65 (24–142)	–	–
Hodgkin's disease	–	–	1	44 (1–243)	–	–
Females and males (combined)						
Lung	20[b]	101 (62–156)	–	–	17	99 (58–159)
Rectum	3	278 (57–813)	–	–	–	–
Non-Hodgkin's lymphoma	4	154 (42–395)	–	–	–	–
Hodgkin's disease	2	232 (28–838)	–	–	–	–

[a]Significantly different from null hypothesis at $p<0.05$.
[b]Includes tumors of the lung, trachea, and bronchus.

– = not reported; CI = confidence interval; SMR = standardized mortality ratio

by "apparent" versus "no or low" exposure to TDI or MDI, women with "apparent" exposure did not exhibit a higher risk of lung cancer. In addition, Mikoczy et al. (2004) conducted a nested case-referent study of the 12 lung cancer cases among female workers, and observed no greater prevalence of exposure to polyurethane dust in cases compared with referents. Similarly, Sorahan and Nichols (2002) observed a statistically significant increased incidence of lung and bronchus cancer in women (standardized registration ratios [SRR] 199; 95% CI 135–282), but reported that all of the female lung cancers in the cohort were in women who did not work for any period in an isocyanate-exposed setting. Schnorr et al. (1996) did not evaluate the effect of isocyanate exposure duration on lung cancer risk in women alone, but in both male and female workers, there was no trend of increased lung cancer mortality by duration of exposure or time since first exposure.

Schnorr et al. (1996) reported nonsignificant increases in the SMRs for rectal cancer, Hodgkin's disease, and non-Hodgkin's lymphoma in the U.S. cohort; however, studies of the Swedish and U.K. cohorts (Mikoczy et al. 2004 and Sorahan and Nichols 2002, respectively) did not support these findings, as SMRs for these neoplasms were reduced in the exposed workers of these cohorts (Table 3-4).

TDI. When groups of 126/sex Sprague-Dawley rats and 120/sex CD-1 mice were exposed to vapors of commercial-grade TDI via whole-body inhalation on 6 hours/day, 5 days/week for 108–110 weeks (Loeser 1983), there were no treatment-related increased tumor incidences in rats or mice.

The authors noted that histopathology of the nasal turbinates in rats was still in progress, but that there were no grossly visible effects of treatment on the upper respiratory tract. No follow-up study was identified in the literature search. This study lacked some details in methodology, and did not describe the approach to statistical analysis.

MDI. Groups of 60 Wistar rats per sex were exposed to aerosolized polymeric MDI at nominal concentrations of 0, 0.2, 1.0, or 6.0 mg/m^3 via whole-body inhalation 6 hours/day, 5 days/week for 2 years (Reuzel et al. 1994). A significantly increased incidence (6/60) of lung adenoma, as well as one lung adenocarcinoma, was observed in male rats exposed to 6.0 mg/m^3 polymeric MDI. No lung tumors occurred in control, 0.2, or 1.0 mg/m^3 exposure groups of male or female rats. In female rats exposed to 6.0 mg/m^3, 2/59 animals developed lung adenomas; there were no adenocarcinomas (Reuzel et al. 1994).

In a second study conducted by Hoyemann and associates (reviewed by Feron et al. 2001) in which female Wistar rats were exposed to monomeric MDI 18 hours/day, 5 days/week for 2 years, the

occurrence of lung tumors was limited to a bronchiolo-alveolar adenoma observed in 1/80 rats exposed to 2.05 mg/m^3.

3.2.2 Oral Exposure

It is noted that TDI and MDI are rapidly hydrolyzed in aqueous environments and it is unlikely that humans will be exposed to these compounds in water. The only available information on the toxicity of TDI administered via the oral route comes from gavage studies in which rats and mice were administered TDI in corn oil for 14 days, 13 weeks, or 2 years (NTP 1986). There is some question regarding the applicability of the results of the gavage studies to humans due to likely differences in the metabolism of ingested TDI compared to gavage administered TDI. Direct instillation of TDI into the acidic stomach could result in the formation of 2,4-TDA, which is unlikely to occur following ingestion because TDI is likely to react with itself and macromolecules to form urea and polyurea in the neutral pH milieu of the mouth. No information was located regarding health effects in humans or animals following oral exposure to MDI.

The highest NOAEL values and all LOAEL values for TDI from each reliable study for each end point in each species and duration category are recorded in Table 3-5 and plotted in Figure 3-3.

3.2.2.1 Death

No information was located regarding death in humans following oral exposure to TDI. In acute-duration gavage studies of commercial-grade TDI administered in corn oil (NTP 1986), treatment-related deaths occurred at doses ≥240 mg/kg/day in rats and ≥500 mg/kg/day in mice exposed for up to 14 consecutive days; however, because sporadic deaths among male mice at lower doses (as low as 30 mg/kg/day), it is difficult to identify a clear and reliable effect level for death in mice. Data on effect levels for death of mice and rats exposed for intermediate durations are also uncertain as a consequence of sporadic deaths occurring at low doses; however, based on the study authors' determinations, treatment-related deaths of female rats and mice occurred at doses of 240 and 120 mg/kg/day, respectively (NTP 1986). In 2-year studies of commercial-grade TDI, doses ≥30 mg/kg/day reduced survival of male and female rats, while the high dose of 240 mg/kg/day reduced the survival of male mice (NTP 1986). Importantly, NTP (1986) reported that analysis of the test material in the chronic study showed that the TDI had reacted with the corn oil vehicle, yielding actual gavage doses 77–90% of nominal doses. It is reasonable to assume that similar reactions occurred in the acute- and intermediate-duration studies.

Table 3-5. Levels of Significant Exposure to Toluene Diisocyanate - Oral

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
ACUTE EXPOSURE								
Death								
1	Rat (F344/N)	single dose (G)				2150 M (2/5 M died)	NTP 1986 2,4/2,6-TDI	80: 20 mixture of 2,4- and 2,6-TDI
2	Rat (F344)	14 d, 1 x/d (G)				240 (1/5 males and 1/5 females died)	NTP 1986 2,4/2,6-TDI	80: 20 mixture of 2,4- and 2,6-TDI
3	Mouse (B6C3F1)	single dose (G)				4640 (4/5 M and 1/5 F died)	NTP 1986 2,4/2,6-TDI	80: 20 mixture of 2,4- and 2,6-TDI
Systemic								
4	Rat (F344)	14 d, 1 x/d (G)	Bd Wt	60 M	120 M (12% decrease in body weight)		NTP 1986 2,4/2,6-TDI	80: 20 mixture of 2,4- and 2,6-TDI
5	Mouse (B6C3F1)	14 d, 1 x/d (G)	Bd Wt	500			NTP 1986 2,4/2,6-TDI	80: 20 mixture of 2,4- and 2,6-TDI
INTERMEDIATE EXPOSURE								
Systemic								
6	Rat (Fischer- 344)	13 wk, 5 d/wk (G)	Bd Wt	60 M	120 M (10% decrease or greater in body weight)		NTP 1986 2,4/2,6-TDI	80: 20 mixture of 2,4- and 2,6-TDI
CHRONIC EXPOSURE								
Death								
7	Rat (F344/N)	105 wk, 5 d/wk (G)				30 (significantly decreased survival)	NTP 1986 2,4/2,6-TDI	80: 20 mixture of 2,4- and 2,6-TDI
8	Mouse (B6C3F1)	105 wk, 5 d/wk (G)				240 M (significantly decreased survival)	NTP 1986 2,4/2,6-TDI	80: 20 mixture of 2,4- and 2,6-TDI

Table 3-5. Levels of Significant Exposure to Toluene Diisocyanate - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
Systemic								
9	Rat (F344/N)	105 wk, 5 d/wk (G)	Resp		30 M (bronchopneumonia)		NTP 1986 2,4/2,6-TDI	80: 20 mixture of 2,4- and 2,6-TDI
			Cardio	120 F				
			Gastro	120 F				
			Musc/skel	120 F				
			Hepatic	120 F				
			Renal	120 F				
			Bd Wt		30 M (12% decrease in terminal body weight)			

Table 3-5. Levels of Significant Exposure to Toluene Diisocyanate - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
10	Mouse (B6C3F1)	105 wk, 5 d/wk (G)	Resp	240 F			NTP 1986 2,4/2,6-TDI	80: 20 mixture of 2,4- and 2,6-TDI
			Cardio	240 F				
			Musc/skel	240 F				
			Hepatic	240 F				
			Renal	120 M	240 M (cytomegaly of tubular epithelium)			
			Endocr	240 F				
			Bd Wt	120 M	240 M (body weight decrement of ~10% throughout most of the study)			
Cancer								
11	Rat (F344/N)	105 wk, 5 d/wk (G)				60 CEL: subcutaneous fibromas/fibrosarcomas (M); pancreatic acinar cell adenomas (M); mammary gland fibroadenomas (F); pancreatic islet cell adenomas (F); neoplastic nodules of liver (F)	NTP 1986 2,4/2,6-TDI	80: 20 mixture of 2,4- and 2,6-TDI
12	Mouse (B6C3F1)	105 wk, 5 d/wk (G)				120 F CEL: hemangiomas, hemangiosarcomas, and hepatocellular adenomas	NTP 1986 2,4/2,6-TDI	80: 20 mixture of 2,4- and 2,6-TDI

a The number corresponds to entries in Figure 3-3.

Bd Wt = body weight; Cardio = cardiovascular; CEL = cancer effect level; d = day(s); Endocr = endocrine; F = Female; (G) = gavage; Gastro = gastrointestinal; LOAEL = lowest-observed-adverse-effect level; M = male; Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; Resp = respiratory; wk = week(s); x = time(s)

Figure 3-3. Levels of Significant Exposure to Toluene Diisocyanate - Oral

Acute (≤14 days)

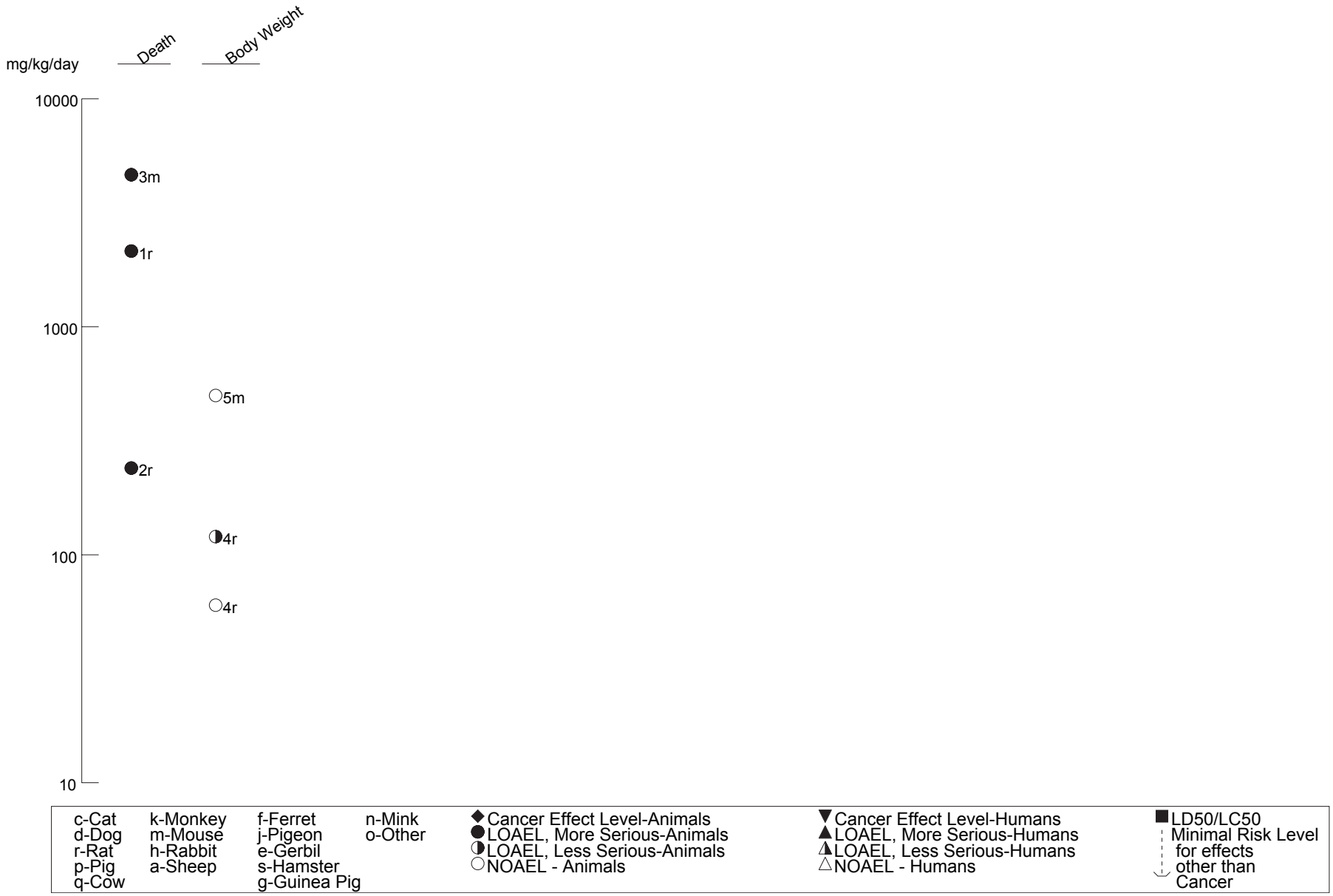
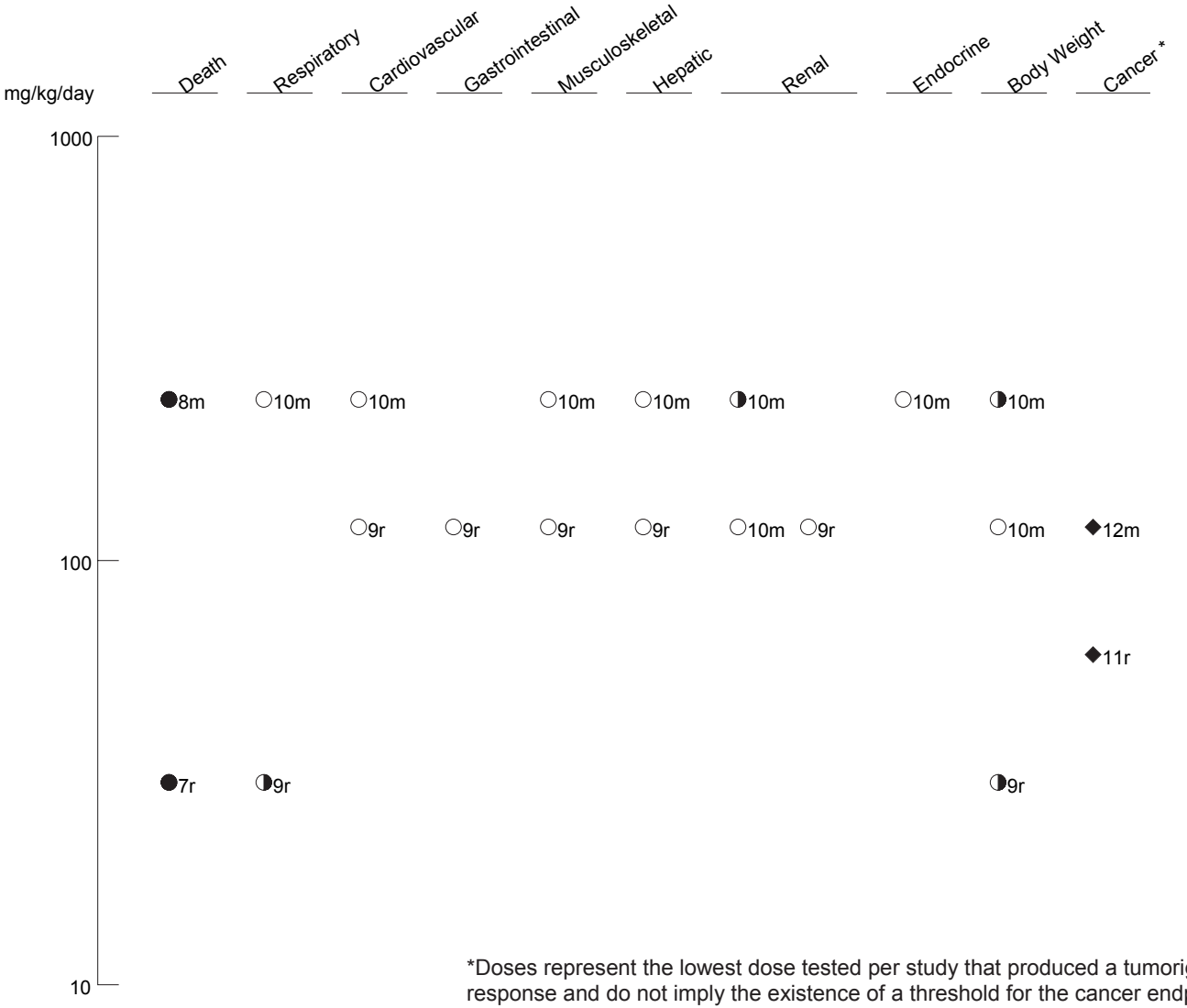


Figure 3-3 Levels of Significant Exposure to Toluene Diisocyanate - Oral *(Continued)*

Intermediate (15-364 days)

Figure 3-3 Levels of Significant Exposure to Toluene Diisocyanate - Oral *(Continued)*

Chronic (≥365 days)



*Doses represent the lowest dose tested per study that produced a tumorigenic response and do not imply the existence of a threshold for the cancer endpoint.

c-Cat d-Dog r-Rat p-Pig q-Cow	k-Monkey m-Mouse h-Rabbit a-Sheep	f-Ferret j-Pigeon e-Gerbil s-Hamster g-Guinea Pig	n-Mink o-Other	◆ Cancer Effect Level-Animals ● LOAEL, More Serious-Animals ◑ LOAEL, Less Serious-Animals ○ NOAEL - Animals	▼ Cancer Effect Level-Humans ▲ LOAEL, More Serious-Humans ◭ LOAEL, Less Serious-Humans △ NOAEL - Humans	■ LD50/LC50 Minimal Risk Level for effects other than Cancer

In an acute lethality study using five animals/sex/dose, two of five male F344 rats given a single gavage dose of 2,150 mg/kg (the lowest dose tested) commercial-grade TDI in corn oil died on days 5 and 9 of the observation period (NTP 1986). No females died at this dose, but at 3,160 mg/kg, two of five female rats died. Dose-related increases in mortality were observed in both sexes at higher doses. There were no untreated controls in this study. In a 14-day gavage study of rats by NTP (1986), there were clear dose-related increases in mortality at doses ≥500 mg/kg/day. A second study by this group reported that one male and one female each in the 30 and 240 mg/kg/day dose groups, and one female in the 500 mg/kg/day group died prematurely, but there were no deaths at 60 or 120 mg/kg/day. Taken together with the first study, these data suggest a severe LOAEL of 240 mg/kg/day for death in rats (NTP 1986).

In the acute lethality study of mice performed by NTP (1986), a dose-related increase in mortality was observed at doses ≥ 4,640 mg/kg. At 4,640 mg/kg, one of five female mice and four of five male mice died between days 2 and 8 of the observation period. No deaths occurred at doses of 2,150 mg/kg (males only were exposed to this dose) or 3,160 mg/kg (males and females). As with the rat study, there were no untreated controls in this study. In 14-day gavage studies of commercial-grade TDI in mice (NTP 1986), all animals died in the first study using doses 500 mg/kg/day. A second study using doses of 30–500 mg/kg/day was performed, and deaths of one to two male mice per group were seen at all doses. Two females died at 240 mg/kg/day, but there were no female deaths at any other dose. An effect level for death is difficult to ascertain from this study due to the lack of a dose-response relationship in the male deaths at doses between 30 and 500 mg/kg/day in the second study and the deaths of all animals at ≥500 mg/kg/day in the first study.

Intermediate-duration (13 weeks, 5 days/week) gavage studies of commercial-grade TDI in rats and mice were performed by NTP (1986). In both species, the 13-week studies were repeated due to mortality in the first study. As with the 14-day studies, deaths occurred at various doses without a clear dose-response relationship. The study authors considered a single female rat death at 240 mg/kg/day, and deaths of 1/10 and 2/10 female mice exposed to 120 and 240 mg/kg/day (respectively), to be treatment-related (NTP 1986).

Chronic (2-year) exposure to gavage doses ≥30 mg/kg/day TDI for 5 days/ week significantly decreased survival of F344 rats (NTP 1986). At termination, survival of male rats was 36/50, 14/50, and 8/50 at 0, 30, and 60 mg/kg/day, respectively; survival of female rats was 36/50, 19/50, and 6/50 at 0, 60, and 120 mg/kg/day, respectively. In the chronic study of mice (NTP 1986), survival of high-dose (240 mg/kg/day) male mice was significantly lower than controls; at termination, 46/50 controls, 40/50 in

the 120 mg/kg/day group, and 26/50 in the 240 mg/kg/day group remained. Survival of female mice was not diminished by treatment.

3.2.2.2 Systemic Effects

No information was located regarding systemic effects in humans following oral exposure to TDI.

Respiratory Effects. No information on respiratory effects of acute-duration oral exposure to TDI in animals was located. In rats exposed via gavage to commercial-grade TDI for 13 weeks (5 days/week), mucoid bronchopneumonia was reported in one of 2 male rats that received 120 mg/kg/day and died prematurely; this effect was also seen in 8/10 males and 2/10 females exposed to 240 mg/kg/day (NTP 1986). Histopathology examination was not performed on other rats in the 120 mg/kg/day group or in any rats of the lower dose groups; thus, an effect level cannot be determined for this end point. In the 13-week study of mice, few results of the histopathology examination of high dose animals were reported, but results that were reported did not indicate lesions of the respiratory tract at 240 mg/kg/day.

When F344 rats were exposed via gavage to commercial-grade TDI on 5 days/week for 2 years, acute bronchopneumonia was seen in both sexes (NTP 1986). The incidences of bronchopneumonia in male rats were 2/50, 6/50, and 14/50 (control, 30, and 60 mg/kg/day groups, respectively) and incidences in female rats were 1/50, 10/50, and 25/49 (control, 60, and 120 mg/kg/day groups, respectively). In contrast, B6C3F1 mice exhibited no respiratory effects when exposed for 2 years to commercial-grade TDI doses up to 120 mg/kg/day in females and 240 mg/kg/day in males (NTP 1986).

Cardiovascular Effects. No histological alterations were observed in the hearts of rats or mice administered doses up to 120 or 240 mg/kg/day commercial-grade TDI 5 days/week for 2 years (NTP 1986).

Gastrointestinal Effects. Chronic gavage studies with TDI in rats and mice did not result in gastrointestinal lesions (NTP 1986).

Hematological Effects. No information was located regarding hematological effects in animals following oral exposure to TDI.

Musculoskeletal Effects. No histological alterations were observed in the musculoskeletal system of rats or mice administered doses up to 120 or 240 mg/kg/day commercial-grade TDI 5 days/week for 2 years (NTP 1986).

Hepatic Effects. No non-neoplastic lesions resulted from a 2-year administration of commercial-grade TDI to rats and mice (NTP 1986).

Renal Effects. No histological alterations were observed in the kidneys of administered doses up to 120 mg/kg/day commercial-grade TDI 5 days/week for 2 years (NTP 1986). An increased incidence of cytomegaly of tubular epithelium was observed in male mice administered 240 mg/kg/day commercial-grade TDI 5 days/week for 2 years (NTP 1986); no alterations were observed in male or female mice exposed to 120 mg/kg/day.

Dermal Effects. Administration of commercial-grade TDI for 2 years did not result in dermal lesions in rats or mice (NTP 1986).

Ocular Effects. Administration of commercial-grade TDI for 2 years did not result in ocular lesions in rats or mice (NTP 1986).

Body Weight Effects. Decreases in body weight gain were observed in male and female rats administered via gavage ≥30 mg/kg/day commercial-grade TDI 5 days/week for 2 years (NTP 1986). A similar exposure of mice resulted in decreases in body weight gain at 240 mg/kg/day (males only); no alterations in weight gain were observed in male or female mice at 120 mg/kg/day (NTP 1986).

3.2.2.3 Immunological and Lymphoreticular Effects

No information was located regarding immunological and lymphoreticular effects in humans or animals following oral exposure to TDI.

3.2.2.4 Neurological Effects

No information was located regarding neurological effects in humans or animals following oral exposure to TDI.

3.2.2.5 Reproductive Effects

No information was located regarding reproductive effects in humans or animals following oral exposure to TDI.

3.2.2.6 Developmental Effects

No information was located regarding developmental effects in humans or animals following oral exposure to TDI.

3.2.2.7 Cancer

Data on cancer effects of diisocyanates in humans and animals orally exposed to diisocyanates are limited to bioassays in rats and mice exposed to commercial-grade TDI via gavage (NTP 1986). Based on the bioassays, NTP (1986) concluded that there was clear evidence that commercial-grade TDI in corn oil was carcinogenic to female mice and to rats of both sexes. Tumor types occurring at increased incidences in the exposed rats included subcutaneous fibromas and fibrosarcomas, pancreatic acinar cell adenomas and islet cell adenomas, mammary gland fibroadenomas, and neoplastic nodules of the liver. In exposed female mice, the following tumor types occurred at increased incidences: hemangiomas or hemangiosarcomas and hepatocellular adenomas. The findings of the study are limited by reduced survival in rats and high dose male mice, as well as instability of the test material in the vehicle.

NTP (1986) administered commercial-grade TDI in corn oil via gavage to groups of 50/sex F344 rats and B6C3F1 mice on 5 days/week for 104 weeks. Doses were 0, 60, or 120 mg/kg/day in female rats and mice; 0, 30, or 60 mg/kg/day in male rats; and 0, 120, or 240 mg/kg/day in male mice. Analysis of the administered material indicated that the TDI had reacted with corn oil, yielding actual gavage doses 77–90% of nominal doses. In rats, survival was significantly lower than controls in all exposed groups; NTP (1986) concluded that the maximum tolerated dose had been exceeded. Statistically significant increases in the incidence of neoplasia were observed in both male and female rats; the data are shown in Table 3-6. Increased incidences of subcutaneous tissue fibromas or fibrosarcomas and pancreatic acinar cell adenomas occurred in male rats. In female rats, mammary gland fibroadenomas, pancreatic islet cell adenomas, and neoplastic nodules of the liver were observed; mammary gland and pancreatic tumor incidences were significantly higher than controls at both doses, while the incidence of hepatic neoplastic nodules was significantly increased only at the high dose in female rats (NTP 1986). Survival of high-dose male mice was significantly lower than controls, but survival of female mice was not diminished by

treatment (NTP 1986). Statistically significant increases in the incidence of neoplasia were observed only in high dose female mice, and included hemangiosarcomas or hemangiomas and hepatocellular adenomas or carcinomas (Table 3-6). NTP (Dieter et al. 1990) noted that the liver, mammary gland, and subcutaneous tissue tumors observed in rats and hemangiomas and liver tumors observed in mice were the same types of tumors observed in rats and mice exposed to 2,4-diaminotoluene, a known carcinogen. Dieter et al. (1990) suggested that the carcinogenic activity observed in the NTP (1986) study could be attributed to the metabolism of 2,4-TDI to products identical to those of 2,4-diaminotoluene metabolism. An industry-sponsored statistical analysis of the results of the NTP TDI study and NTP 2,4-diamino-toluene study concluded that hydrolyzation of 5% of the TDI dose to form 2,4-aminotoluene could explain carcinogenic responses observed in the NTP TDI study (Sielken et al. 2012).

3.2.3 Dermal Exposure

3.2.3.1 Death

No information was located regarding deaths in humans or animals following dermal exposure to TDI or MDI.

3.2.3.2 Systemic Effects

No information was located regarding systemic effects in humans or animals following dermal exposure to TDI. Data on the dermal toxicity of MDI are limited to a human study that reported respiratory effects.

Respiratory Effects.

MDI. Workers at a newly established wood products facility with no prior exposure to MDI were asked to complete symptom questionnaires prior to beginning work and 2, 9, 14, and 20 months after production began (Petsonk et al. 2000; Wang and Petsonk 2004); the workers were exposed to liquid MDI resin.

Asthma-like symptoms were reported by 15 of the 56 workers with the highest potential for exposure to liquid MDI and prepolymer, as compared to 0 of 43 workers with the lowest exposure potential. MDI-exposed workers had significantly increased odds of dyspnea with wheezing, dyspnea or cough at rest, chest tightness, and phlegm after adjusting for age, smoking, and wood dust exposure (Wang and Petsonk 2004). There were no increases in the prevalence of eye or nasal symptoms. MDI exposure was likely via the inhalation and dermal routes of exposure. The workers wore respirators; however, the incidence

Table 3-6. Tumor Incidences in Rats and Mice Exposed to Commercial-Grade Toluene Diisocyanate for 2 Years by Gavage[a,b]

	Control	30 mg/kg/day	60 mg/kg/day	120 mg/kg/day
Male rats				
Subcutaneous fibroma or fibrosarcoma	3/50 (6%)	6/50[b] (12%)	12/50[b] (24%)	Not tested
Pancreatic acinar cell adenoma	1/47 (2%)	3/47 (6%)	7/49[b] (14%)	Not tested
Pancreatic islet cell adenoma or carcinoma	1/47 (2%)	0/47 (0%)	4/49[b] (8%)	Not tested
Female rats				
Subcutaneous fibroma or fibrosarcoma	2/50 (4%)	Not tested	1/50 (2%)	5/50[b] (10%)
Mammary gland tumors	17/50 (34%)	Not tested	25/50[b] (50%)	21/50[b] (42%)
Pancreatic islet cell adenoma	0/50 (0%)	Not tested	6/49[b] (12%)	2/47 (4%)
Hepatic neoplastic nodules	3/50 (6%)	Not tested	8/50[b] (16%)	8/48[b] (17%)
Female mice				
Hemangioma or hemangiosarcoma	0/50 (0%)	Not tested	1/50 (2%)	5/50[b] (10%)
Hepatocellular adenoma or carcinoma	4/50 (8%)	Not tested	5/50 (10%)	15/50[b] (30%)

[a]Data are presented as the number of animals with tumor per total number of animals examined in each exposure group (percentages in parentheses).
[b]Significantly different from control by either life table or incidental tumor test or both, $p<0.05$.

Source: NTP 1986

of asthma symptoms was significantly higher among those who reported removing their respirator during work. The incidence of asthma symptoms was also significantly higher in workers reporting skin or clothing MDI staining (Petsonk et al. 2000).

3.2.3.3 Immunological and Lymphoreticular Effects

No information was located regarding immunological and lymphoreticular effects in humans following dermal exposure to TDI or MDI.

In mice, dermal exposure to 2,4-TDI or MDI followed by an oral challenge dose resulted in airway hyperreactivity, lung tissue hyperreactivity, and increases in serum IgE levels (Pollaris et al. 2016). However, no evidence of cross-reactivity was observed in mice exposed to 2,4-TDI and challenged with MDI or exposed to MDI and challenged with 2,4-TDI.

3.2.3.4 Neurological Effects

No information was located regarding neurological effects in humans or animals following dermal exposure to TDI or MDI.

3.2.3.5 Reproductive Effects

No information was located regarding reproductive effects in humans or animals following dermal exposure to TDI or MDI.

3.2.3.6 Developmental Effects

No information was located regarding developmental effects in humans or animals following dermal exposure to TDI or MDI.

3.2.3.7 Cancer

No information was located regarding cancer in humans or animals following dermal exposure to TDI or MDI.

3.3 GENOTOXICITY

TDI. Results of *in vitro* genotoxicity testing of TDI are shown in Table 3-7. 2,4-TDI, 2,6-TDI, and the commercial-grade mixture (80:20 mixture of 2,4- and 2,6-TDI) have all been tested for mutagenicity in various strains of *Salmonella typhimurium* (Anderson and Styles 1978; Anderson et al. 1980; NTP 1986; Seel et al. 1999; Zeiger et al. 1987). All of the studies have shown negative results in the absence of metabolic activation.

All of the studies other than Seel et al. (1999) used dimethylsulfoxide (DMSO) as a solvent for the test compounds, and these studies suggested that each of the individual isomers and the mixture was mutagenic with metabolic activation in at least one strain of *S. typhimurium* (NTP 1986; Zeiger et al. 1987). Seel et al. (1999) showed that 2,4-TDI is not stable in DMSO (a hygroscopic solvent that increases reaction of TDI with water), and that use of this solvent yielded a variety of degradation products, including 2,4-TDA (a known mutagen), in the reaction medium. To assess the role of toluene diamines in the observed responses of TDI in these tests, Seel et al. (1999) conducted parallel mutagenicity tests using DMSO and ethylene glycol dimethylether (EGDE) as solvents and quantifying levels of TDI and TDA in the first 45 seconds after the test was started. These tests showed that 2,6-TDI was relatively more stable in EGDE than in DMSO; when DMSO was used as a solvent, only 12.3% of dose of 2,6-TDI remained at the start of mutagenicity testing, while 9.1% of the dose existed as 2,6-TDA (other reaction products were not analyzed). In contrast, when EGDE was used, 99.5% of the dose existed as 2,6-TDI at the start of testing, with only 0.5% as 2,6-TDA (Seel et al. 1999). Analyses over time showed formation of TDA in mixtures using either DMSO or EGDE; levels of TDA were lower when EGDE was used, but not substantially lower after the first 45 seconds (2,6-TDA was 5.6% of the TDI dose in the EGDE mixture, compared with 8.3% of the TDI dose in the DMSO mixture). These experiments indicated that mutagenicity testing of TDI using DMSO as a solvent yields unreliable results due to the conversion of TDI to TDA prior to plating.

In mutagenicity tests using EGDE as the solvent (Seel et al. 1999) and with metabolic activation, all three test materials tested positive in TA98 and TA100 and all three tested negative in TA1535. 2,4-TDI was also positive in strain TA1537, and the 80:20 mixture was weakly positive in this strain, while 2,6-TDI was negative. The authors attributed the positive and weakly positive results to the TDA formed over time even when EGDE was used.

Table 3-7. Genotoxicity of TDI and MDI *In Vitro*

Species (test system)	End point	Results: With activation	Results: Without activation	Purity	Vehicle	Reference
2,6-TDI						
Prokaryotic organisms:						
Salmonella typhimurium (TA100, TA98)	Gene mutation	+	–	94%	DMSO	NTP 1986; Zeiger et al. 1987
S. typhimurium (TA98)	Gene mutation	+	–	NR	EGDE	Seel et al. 1999
S. typhimurium (TA1535, TA1537[a])	Gene mutation	–	–	94%	DMSO	NTP 1986; Zeiger et al. 1987
S. typhimurium (TA1537)	Gene mutation	–	–	NR	EGDE	Seel et al. 1999
Mammalian cells:						
L5178Y mouse lymphoma cells	Gene mutation	+	+	NR	DMSO	McGregor et al. 1991
Chinese hamster ovary cells	Sister chromatid exchange	–	+	99%	DMSO	Gulati et al. 1989
Chinese hamster ovary cells	Chromosomal aberrations	–	+	99%	DMSO	Gulati et al. 1989
2,4-TDI						
Prokaryotic organisms:						
S. typhimurium (TA100, TA98)	Gene mutation	+	–	99%	DMSO	Zeiger et al. 1987
S. typhimurium (TA1535, TA97)	Gene mutation	(+/–)	–	99%	DMSO	Zeiger et al. 1987
S. typhimurium (TA98, TA100, TA1535, TA1538)	Gene mutation	–	NT	NR	DMSO	Anderson and Styles 1978
S. typhimurium (TA1537, TA98)	Gene mutation	+	–	NR	EGDE	Seel et al. 1999
Mammalian cells:						
L5178Y mouse lymphoma cells	Gene mutation	+	+	NR	DMSO	McGregor et al. 1991
Chinese hamster ovary cells	Sister chromatid exchange	–	(+/–)	94%	DMSO	Gulati et al. 1989
Chinese hamster ovary cells	Chromosomal aberrations	–	–	94%	DMSO	Gulati et al. 1989

Table 3-7. Genotoxicity of TDI and MDI *In Vitro*

Species (test system)	End point	Results: With activation	Results: Without activation	Purity	Vehicle	Reference
Commercial-grade 2,4- and 2,6-TDI (80:20 mixture)						
Prokaryotic organisms:						
S. typhimurium (TA100, TA98)	Gene mutation	+	–	Commercial grade	DMSO	NTP 1986; Zeiger et al. 1987
S. typhimurium (TA100, TA98, TA1537)	Gene mutation	+	–	Commercial grade	EGDE	Seel et al. 1999
S. typhimurium (TA100, TA98, TA1538)	Gene mutation	+	–	Commercial grade	DMSO	Anderson et al. 1980
S. typhimurium (TA1537)	Gene mutation	–	–	Commercial grade	DMSO	Anderson et al. 1980
S. typhimurium (TA1535, TA1537)	Gene mutation	–	–	Commercial grade	DMSO	NTP 1986; Zeiger et al. 1987
Mammalian cells:						
F-344 rat hepatocyte primary cultures	Unscheduled DNA synthesis	–	–	NR	DMSO	Shaddock et al. 1990
4,4'-MDI (monomer)						
Prokaryotic organisms:						
S. typhimurium (TA100, TA98)	Gene mutation	+	–	NR	DMSO	Herbold et al. 1998
S. typhimurium (TA100, TA98)	Gene mutation	+	–	98%	DMSO	Shimizu et al. 1985
S. typhimurium (TA100, TA98)	Gene mutation	+	–	Commercial grade	DMSO	Anderson et al. 1980
S. typhimurium (TA100, TA98)	Gene mutation	–	–	NR	EGDE	Herbold et al. 1998
S. typhimurium (TA1535, TA1537, TA1538)	Gene mutation	–	–	98%	DMSO	Shimizu et al. 1985
S. typhimurium (TA1535, TA1537)	Gene mutation	–	–	NR	DMSO, EGDE	Herbold et al. 1998
S. typhimurium (TA1537)	Gene mutation	–	–	Commercial grade	DMSO	Anderson et al. 1980
Mammalian cells:						
Human lung epithelial cells (A549)	DNA double-strand breaks	NT	–(c)	NR	EGDE	Vock et al. 1998

Table 3-7. Genotoxicity of TDI and MDI *In Vitro*

Species (test system)	End point	Results: With activation	Results: Without activation	Purity	Vehicle	Reference
2,4-MDI						
S. typhimurium (TA98, TA1538)	Gene mutation	+	–	NR	DMSO	Herbold et al. 1998
S. typhimurium (TA98, TA1538)	Gene mutation	–	–	NR	EGDE	Herbold et al. 1998
S. typhimurium (TA100)	Gene mutation	–	–	NR	DMSO, EGDE	Herbold et al. 1998
Mixture of isomers monomeric MDI (4,4'-, 2,4'-, and 2,2'-)						
S. typhimurium (TA100, TA98)	Gene mutation	+	–	NR	DMSO	Herbold et al. 1998
S. typhimurium (TA100, TA98, TA1535, TA1537)	Gene mutation	–	–	NR	EGDE	Herbold et al. 1998
S. typhimurium (TA1535, TA1537)	Gene mutation	–	–	NR	DMSO	Herbold et al. 1998
Polymeric MDI						
S. typhimurium (TA100, TA98)	Gene mutation	+	–	NR	DMSO	Herbold et al. 1998
S. typhimurium (TA100, TA98, TA1535, TA1537)	Gene mutation	–	–	NR	EGDE	Herbold et al. 1998
S. typhimurium (TA1535, TA1537)	Gene mutation	–	–	NR	DMSO	Herbold et al. 1998

[a]Zeiger et al. (1987) incorrectly show the tested strain as TA97; the data shown are identical to those shown for TA1537 in the original report (NTP 1986).

– = negative result; +/– = mixed results; + = positive result; –(c); positive only at cytotoxic concentrations;
DMSO = dimethylsulfoxide; DNA = deoxyribonucleic acid; EGDE = ethylene glycol dimethylether;
MDI = methylenediphenyl diisocyanate; NR = not reported; NT = not tested; TDI = toluene diisocyanate

Experiments conducted by Seel et al. (1999) also included using two different S9 microsome quantities: 10 and 30%. The authors observed that the mutagenic responses were slightly diminished in the tests with higher S9 content, and postulated that the higher protein content in the 30% S9 mix provided alternative substrates for TDI reaction, yielding relatively lower amounts of the mutagenic TDA degradation products.

TDI has also been tested in mammalian cell systems for mutagenicity (McGregor et al. 1991), chromosomal aberrations, and sister chromatid exchanges (Gulati et al. 1989), as well as unscheduled DNA synthesis (Shaddock et al. 1990), as shown in Table 3-7. All of the tests used DMSO as the test material solvent.

Only commercial-grade TDI has been tested for *in vivo* genotoxicity (see Table 3-8); data on the individual isomers are not available. In workers exposed occupationally to TDI (0.007–0.016 mg/m^3) during plastic production, significantly increased numbers of sister chromatid exchanges, micronuclei, and structural chromosomal aberrations were observed in peripheral blood lymphocytes, when compared with unexposed persons from the same geographic area (Bilban et al. 2004). The study did not adjust for the statistically significant differences in average age and smoking index (number of cigarettes smoked per day per years of smoking) between the exposed and unexposed groups; the exposed group was older and had a higher smoking index. In a controlled exposure experiment, Marczynski et al. (2005) compared the frequency of DNA strand breaks in lymphocytes before and after exposure of 5 workers with prior diisocyanate exposure and airway symptoms and 10 subjects without prior exposure but with asthma or bronchial hyperresponsiveness. The subjects were exposed to industrial-grade TDI (80:20 mixture of 2,4- and 2,6-TDI) in the following sequence: 30 minutes at 5 ppb, 30 minutes at 10 ppb, 90-minute break, 30 minutes at 20 ppb, 90-minute break, and ending with 30 minutes at 30 ppb. Blood was sampled for use in the comet assay before as well as 30 minutes and 19 hours after the end of exposure. Blood was also collected at the same time points from a group of 10 healthy subjects who were not subjected to any exposure. Mean values of the olive tail moment before and after exposure did not differ significantly, nor were there significant differences between the groups. In workers exposed to isocyanates, primarily TDI and MDI (mean TDI levels ranged from <1 to 60 μg/m^3), and several tertiary amines, no significant increases in chromosomal aberrations, sister chromatid exchanges, or micronuclei frequency in peripheral lymphocytes were observed, as compared to a referent group (Holmen et al. 1988). Exposing *S. typhimurium* T98 or *E. coli* WP2 uvrA to urinary samples from the exposed workers did not result in increases in mutagenic activity.

Table 3-8. Genotoxicity of TDI and MDI *In Vivo*

Species (test system)	End point	Results	Purity or grade	Route of exposure	Reference
2,6-TDI					
No data					
2,4-TDI					
No data					
Commercial-grade 2,4- and 2,6-TDI (80:20 mixture)					
Humans					
Peripheral blood lymphocytes	Micronuclei	+	NA	Inhalation	Bilban 2004
Peripheral blood lymphocytes	Structural chromosomal aberrations	+	NA	Inhalation	Bilban 2004
Peripheral blood lymphocytes	Sister chromatid exchange	+	NA	Inhalation	Bilban 2004
Peripheral blood lymphocytes	DNA strand breaks	–	Industrial grade	Inhalation	Marczynski et al. 2005
Non-human mammals					
Mouse bone marrow	Micronuclei	–	Production grade	Inhalation	Loeser et al. 1983
Mouse bone marrow	Micronucleated PCEs	–	NR	Inhalation	Lindberg et al. 2011
Mouse bone marrow	Chromosomal aberrations	+	95%	Inhalation	Ji et al. 2008
Mouse bone marrow	Sister chromatid exchange	+	95%	Inhalation	Ji et al. 2008
Mouse peripheral blood	Micronucleated PCEs	–	NR	Inhalation	Lindberg et al. 2011
Rat bone marrow	Micronuclei	–	Production grade	inhalation	Loeser et al. 1983
Non-mammalian systems					
Drosophila melanogaster post-meiotic and meiotic germ cells	Sex-linked recessive lethal mutation	+	99%	Feeding (ethanol vehicle)	Foureman et al. 1994
D. melanogaster post-meiotic and meiotic germ cells	Translocation	+	99%	Feeding (ethanol vehicle)	Foureman et al. 1994

Table 3-8. Genotoxicity of TDI and MDI *In Vivo*

Species (test system)	End point	Results	Purity or grade	Route of exposure	Reference
4,4'-MDI (monomer)					
Peripheral blood lymphocytes	DNA strand breaks	–	Industrial grade: 60% methylene-diphenyl diisocyanate, 30% triiso-cyanates, 10% diisocyanates	Inhalation	Marczynski et al. 2005
Mouse bone marrow	Micronucleated PCEs	–	98%	Inhalation	Lindberg et al. 2011
Mouse peripheral blood	Micronucleated PCEs	–	98%	Inhalation	Lindberg et al. 2011
Rat bone marrow	Micronucleated PCEs	+		Inhalation	Zhong and Siegel 2000
Rat bone marrow	Micronuclei	–	99%	Inhalation	Pauluhn et al. 2001
Rat epidermis and liver	DNA adduct formation	–	NR	Dermal	Vock and Lutz 1997
Rat epidermis	DNA adduct formation	–	NR	Dermal	Vock et al. 1995

– = negative result; + = positive result; (+/–) = mixed results; DNA = deoxyribonucleic acid; MDI = methylenediphenyl diisocyanate; NA = not applicable; NR = not reported; NT = not tested; PCE = polychromated erythrocyte; TDI = toluene diisocyanate

Lindberg et al. (2011) observed no increase in the frequency of micronucleated polychromatic erythrocytes (PCEs) in mouse bone marrow or peripheral blood after five daily 1-hour periods of exposure to TDI vapor (63% 2,4-TDI and 37% 2,6-TDI) at concentrations up to 2.4 mg/m^3 (0.34 ppm). Similarly, Loeser et al. (1983) did not observe an increase in micronucleated erythrocytes in bone marrow of rats or mice exposed for 4 weeks to vapor concentrations of 0, 0.05, or 0.15 ppm, 6 hours/day for 5 days/week. Ji et al. (2008) reported a significant increase in the frequencies of chromosomal aberrations and sister chromatid exchanges in bone marrow of mice exposed for 4 hours/day on 14 consecutive days to TDI vapor (composition not specified, but reported as 95% pure) at a concentration characterized as one-fourth of the LC_{50} (no other exposure details were provided). However, given the lack of study details, especially the absence of information on exposure concentration, the results reported by Ji et al. (2008) cannot be evaluated in the context of the other available data.

In *in vivo* tests of sex-linked recessive lethal mutation and translocation using male *Drosophila* exposed by feeding, commercial-grade TDI (mixture of 2,4- and 2,6- isomers of unknown composition, administered in ethanol) yielded positive results (Foureman et al. 1994).

MDI. Studies of the *in vitro* genotoxicity of MDI are shown in Table 3-7. As was seen with experiments on TDI, stability testing of MDI in DMSO showed diminished levels of free MDI as a function of time in the solvent (Herbold et al. 1998). However, in contrast to TDI, the rate of MDI degradation in both DMSO and EGDE was much slower. In fact, MDI was stable in EGDE; even in the presence of 12.78 mM water, <1% of the tested mass of MDI (tested as 4,4'-MDI, monomeric MDI isomers, and polymeric MDI) had degraded after 4 hours (Herbold et al. 1998). Consistent with its greater stability in EGDE, MDI was uniformly negative in mutagenicity testing using this solvent (Herbold et al. 1998), while positive results (in TA98 and TA100 for monomeric and polymeric MDI and 4,4'-MDI and in TA1538 for 2,4-MDI) were observed when DMSO was used as the solvent (Anderson et al. 1980; Herbold et al. 1998; Shimizu et al. 1985).

Only 4,4'-MDI has been tested for genotoxicity in mammalian cells; Vock et al. (1998) observed double-strand DNA breaks in human lung epithelial cells (A549) at 4,4'-MDI concentrations (in EGDE) that were cytotoxic. The authors noted that cytotoxicity in the test system was exacerbated both by the slight toxicity of the EGDE solvent and by the lack of nutrients and growth factors in the test solution (phosphate-buffered saline was used instead of growth medium to minimize reaction between MDI and

medium constituents like proteins). The study authors concluded that the observed DNA damage was a function of cytotoxicity rather than direct genotoxicity.

Likewise, 4,4'-MDI is the only isomer or composition that has been tested for genotoxicity in *in vivo* systems (Table 3-8). Marczynski et al. (2005) assessed the potential of MDI to induce DNA strand breaks. MDI workers (n=25) and controls (n=10) were exposed to 4,4'-MDI in the same sequences as the TDI study: 30-minute exposure to 5 ppb, 30-minute exposure to 10 ppb, 90-minute break, 30-minute exposure to 20 ppb, 90-minute break, and 30-minute exposure to 30 ppb. 4,4'-MDI exposure did not significantly increase DNA strand breaks, as assessed using olive tail moment comet assay. Lindberg et al. (2011) observed no increase in the frequency of micronucleated PCEs in mouse bone marrow or peripheral blood after five daily 1-hour periods of exposure to 4,4'-MDI aerosol at concentrations up to 23.3 mg/m^3. Zhong and Siegel (2000) reported a concentration-dependent increase in the frequency of micronucleated PCEs in the bone marrow of male Brown-Norway rats 7 days following exposure to 4,4'-MDI. The rats were exposed for 3 weeks, 1 hour/week to concentrations of 7 and 113 mg/m^3 4,4'-MDI aerosol. Pauluhn et al. (2001) also exposed male Brown-Norway rats for 1 hour/week for 3 weeks at concentrations up to 118 mg/m^3 of 4,4'-MDI aerosol. Pauluhn et al. (2001) sacrificed the rats on post-exposure days 1, 2, and 7; no increase in micronucleated PCEs was seen at any time point. Vock and colleagues (Vock and Lutz 1997; Vock et al. 1995) observed minimal to no induction of isocyanate-DNA adducts (assessed by ^{32}P postlabelling) in the skin liver, kidney, lung, and bladder of female Wistar rats exposed to 6.9–9 mg 4,4'-MDI in acetone via topical application.

3.4 TOXICOKINETICS

Both TDI and MDI combine readily with biological macromolecules including hemoglobin, albumin, and others. As a consequence of their reactivity, these compounds or their reaction products are often found at higher concentrations at the site of entry into the body early in exposure, and may continue to be distributed from the site of entry long after exposure has terminated.

Many studies in humans and laboratory animals use levels of diamines (TDA or methylenediphenyl diamine [MDA]) as a biomarker to evaluate TDI and MDI toxicokinetic properties. Most studies are not measuring free TDA or MDA levels that are the result of TDI or MDI metabolism. Rather, the studies are treating the plasma and urine samples with acids or bases to hydrolyze the diisocyanate-protein or diamine-protein conjugates and acetylated diamines, resulting in the formation of free diamine (Sennbro et al. 2004; Sepai et al. 1995).

TDI is absorbed after human exposure, but available data are not adequate to permit estimation of the rate or extent of absorption. In rats, absorption of inhaled 2,4-TDI was estimated to be between 61 and 90% (Timchalk et al. 1994). One study in rats exposed to monomeric 4,4'-MDI as an aerosol estimated that 32% of an inhaled dose of 0.078 mg was systemically available (Gledhill et al. 2005). Limited data are available on the oral absorption of TDI or MDI. Following gavage administration of 2,4-TDI, 12–20% of the dose was absorbed (Timchalk et al. 1994); no data on the oral absorption of MDI are available. There is evidence that both TDI and MDI are absorbed across the skin to some extent, but the available data do not provide clear estimates of the rate or extent of absorption.

Once absorbed into the body, TDI is bound to macromolecules, forming adducts with hemoglobin, albumin, glutathione, and other macromolecules. The binding of TDI to glutathione appears to be reversible (Day et al. 1997), and may represent a mechanism by which TDI is transported between tissues. After inhalation (Kennedy et al. 1994; Timchalk et al. 1994) and gavage administration (Timchalk et al. 1994) exposure of rats to radiolabeled TDI, radioactivity was detected in a number of tissues, albeit at low levels. Systemic distribution of low levels of radioactivity has also been observed after inhalation (Gledhill et al. 2005) and dermal exposure (Vock et al. 1997) of rats to radiolabeled MDI.

The metabolic fate of TDI depends on the exposure route. After oral exposure, TDI is hydrolyzed in the gastrointestinal tract to TDA, and subsequently either absorbed and metabolized further or reacted with unhydrolyzed TDI to form polyurea polymers that pass unabsorbed through the gastrointestinal tract. However, after inhalation exposure, the primary fate of TDI appears to be conjugation reactions; little to no TDI is hydrolyzed to TDA. Little information on the metabolism of MDI was located; the single available study (Gledhill et al. 2005) indicated that after inhalation exposure of rats to MDI aerosol, the primary metabolites in the urine and bile were N-acetylated and N-acetylated hydroxylated products of MDI, and the primary product in feces is believed to be mixed molecular weight polyureas resulting from spontaneous reaction of MDI.

In humans exposed experimentally, TDA levels in hydrolyzed urine exhibits a biphasic pattern, with an initial rapid phase followed by a slower phase. The primary route of TDI elimination after inhalation or oral exposure of rats is via the feces, which may include material absorbed and excreted via the bile. Data on the elimination of MDI are limited. Like TDI, MDI is excreted primarily in the feces of rats after inhalation exposure, and there is evidence for biliary excretion of MDI. No studies of MDI elimination after oral exposure were located in the available literature.

3.4.1 Absorption

3.4.1.1 Inhalation Exposure

TDI. Two studies reporting urinary concentrations of diisocyanate-derived amines in volunteers exposed to mixtures of TDI in exposure chambers showed absorption of both the 2,4- and 2,6-TDI isomers (Brorson et al. 1991; Skarping et al. 1991). These studies show that at least 20%, and possibly more, of an inhaled dose of TDI is absorbed, based on analysis of TDA levels in hydrolyzed urine. Brorson et al. (1991) exposed each of two men to a mixture of 70% 2,6-TDI with 30% 2,4-TDI in an exposure chamber at concentrations of 25, 50, and 70 μg/m^3 for 4-hour periods. Hydrolyzed plasma samples collected immediately after exposure showed detectable levels of 2,4-TDA after exposure to the highest concentration and detectable levels of 2,6-TDA after exposure to 50 and 70 μg/m^3. Analysis of 24-hour hydrolyzed urine samples showed excretion of 2,4-TDA estimated to represent 14–19% of the inhaled 2,4-TDI dose and levels of 2,6-TDA estimated to represent 17–23% of the inhaled 2,6-TDI dose. In another experiment, Skarping et al. (1991) exposed five men to a mixture of 52% 2,6-TDI and 48% 2,4-TDI at a concentration of 36 to 43 μg/m^3 for 7.5 hours, and measured TDA levels in hydrolyzed urine samples. Urinary levels of 2,4-TDA was estimated to represent 8–14% of the inhaled dose of 2,4-TDI and urinary levels of 2,6-TDA was estimated to represent 14–18% of the inhaled 2,6-TDI dose. As these urinary excretion levels reflected only the first 24–28 hours of excretion and fecal levels of TDI were not measured, the total absorption of 2,4- and 2,6-TDI may have been higher than estimated.

The results of a study in male F344 rats exposed to ^{14}C ring-labeled 2,4-TDI vapor (2 ppm) via inhalation for 4 hours suggest that approximately 61–90% of the radioactivity was absorbed; the remaining radioactivity was likely rapidly cleared from the respiratory tract and swallowed (Timchalk et al. 1994).

Using guinea pigs, Kennedy et al. (1989) showed a linear relationship between ^{14}C TDI exposure concentrations multiplied by exposure duration and radioactivity levels in blood samples taken immediately after 1-hour exposure to concentrations ranging from 0.0005 to 0.146 ppm, suggesting that absorption via the lung is not saturable in this concentration range. Blood samples taken during exposure via arterial cannula showed steady, essentially linear uptake during the 60-minute exposure period (Kennedy et al. 1989).

MDI. A single study examined the toxicokinetics of inhaled MDI in rats (Gledhill et al. 2005). The male Wistar rats were exposed, head only, to ^{14}C-4,4'-MDI (monomeric, as a condensation aerosol) at a

concentration of 2 mg/m^3 for 6 hours. A separate group of bile-cannulated rats was similarly exposed. Using data on urinary, biliary, and fecal excretion as well as radioactivity in the carcass measured 168 hours after exposure, the authors estimated that approximately 32% of the inhaled dose (calculated to be equivalent to 0.078 mg MDI per animal) was systemically available.

3.4.1.2 Oral Exposure

TDI. The absorption of TDI after oral exposure has only been examined in one gavage administration study. Timchalk et al. (1994) administered a single gavage dose of ^{14}C ring-labeled 2,4-TDI (60 mg/kg) to male F344 rats and analyzed excreta collected over the next 48 hours for radioactivity. Based on the measured radioactivity in the urine and carcass, at least 12% of the oral dose was absorbed; the investigators suggested that another 8% may have been eliminated through biliary excretion into the feces (Timchalk et al. 1994). It was also suggested that the radioactivity was absorbed as ^{14}C-2,4-TDA rather than as the parent compound. TDI absorption is likely to differ between ingestion and gavage administration due to differences in the pH of the oral cavity and stomach. Installation of TDI directly into the acidic stomach is likely to favor the formation of TDA, ureas, and polyureas. Comparatively, the neutral pH of the oral cavity would likely favor the binding of TDI to macromolecules and the formation of urea and polyureas.

MDI. No data on the absorption of MDI after oral exposure were located in the available literature.

3.4.1.3 Dermal Exposure

TDI. The limited available data demonstrate that TDI is absorbed across the skin, but the data are not adequate to estimate the rate and extent of absorption. Hoffman et al. (2010) detected <1% of a dermally-applied dose of 350 mg/kg body weight (12 mg/cm^2) ^{14}C-2,4-TDI in the urine, plasma, and carcasses of male rats exposed for 0.5, 1, or 8 hours; no detectable radioactivity was found in the feces. However, the animals were sacrificed immediately after exposure. Yeh et al. (2008) demonstrated dermal absorption of 2,4- and 2,6-TDI in male rats by measuring TDA levels in hydrolyzed urine for 6 days after a 5-hour dermal exposure to commercial-grade TDI at concentrations of 0.2, 1, and 5%. The maximum concentration in urine, as well as the area under the urinary concentration versus time curve both showed dose-related increases, providing evidence for dermal absorption.

MDI. Henriks-Eckerman et al. (2015) suggested that a comparison between urinary acetylated MDA levels at the end of the workshift to levels after a day off from work provides evidence of dermal

absorption of MDI since the workers wore respiratory protection. However, the investigators also noted that respiratory protection only reduced the inhalable amount by 60%.

When male rats were exposed to a topical dose of 15 or 165 mg/kg ^{14}C-4,4'-MDI and sacrificed at the end of the 8-hour exposure, or 24 or 120 hours after the commencement of exposure, <1% of the applied radioactivity was detected in the urine, feces, tissues, gut and its contents, and carcass (Hoffman et al. 2010). At both doses, the estimated amount of 4,4'-MDI absorbed was higher in rats sacrificed at later time points; for example, absorbed amounts were estimated to be 0.21, 0.66, and 0.88% of the applied dose of 165 mg/kg in rats sacrificed at 8, 24, and 120 hours after the beginning of exposure, respectively. However, in female rats exposed to topical doses of ~30 mg/kg ^{14}C-4,4'-MDI for 48 hours, 29–30% of the applied radioactivity was recovered in the feces during the first 48 hours after treatment, indicating significant dermal uptake (Vock and Lutz 1997). It is not clear whether the greater absorption suggested by the study by Vock and Lutz (1997) reflects a gender difference or an impact of longer exposure, or whether the rats in that study had unintended oral exposure via grooming. Hoffman et al. (2010) took measures to prevent oral exposure, while Vock and Lutz (1997) did not.

3.4.2 Distribution

3.4.2.1 Inhalation Exposure

TDI. Immediately after inhalation exposure to 2 ppm ^{14}C ring-labeled TDI for 4 hours, radioactivity levels were highest in the carcass, skin, gastrointestinal contents, and gastrointestinal tracts of male F344 rats (Timchalk et al. 1994). When examined 48 hours later, the highest percentage of recovered dose was found in the gastrointestinal contents (~17%), followed by the carcass (10%) and skin (6%). Table 3-9 shows the distribution of radioactivity immediately after exposure and 48 hours after exposure. Kennedy et al. (1994) measured radioactivity in tissues immediately after 4-hour exposure of rats to concentrations of 0.026, 0.143, and 0.821 ppm ^{14}C-2,4-TDI. The highest specific activities (μgEq/g) were located in the airways (trachea and lung) followed by the gastrointestinal tract (esophagus and stomach) and systemic circulation (blood, liver, kidney, spleen, and heart). When expressed as percent of dose /total tissue, the highest level was in the blood, followed by the liver or stomach, kidney or lung, and trachea. In guinea pigs exposed to ^{14}C-2,4-TDI concentrations ranging from 0.00005 to 0.146 ppm for 1, 4, or 5 hours, the highest levels of radioactivity were detected in the trachea and lung, followed by the kidney, heart, spleen, and liver (Kennedy et al. 1989).

Table 3-9. Tissue Distribution of ^{14}C in Male F344 Rats Exposed to ^{14}C Ring-Labelled 2,4-Toluene Diisocyanate Via Gavage or Inhalation

	Percent of administered dose after oral exposure (60 mg/kg)		Percent of recovered dose after inhalation exposure (2 ppm, 4 hours)	
Tissue	2 hours postdosing	48 hours postdosing	Immediately after exposure	48 hours postexposure
Blood	NA	0.05±0.02	NA	0.23±0.15
Gastrointestinal contents	65.82±8.35	2.56±0.84	9.76±2.31	16.63±9.18
Carcass	5.50±3.62	0.77±0.20	71.54±2.99	10.02±2.69
Gastrointestinal tract	10.10±3.09	0.10±0.05	3.75±1.56	0.76±0.37
Skin	1.12±0.53	0.15±0.02	9.86±3.12	5.59±1.61
Lung	0.99±0.52	<0.01	2.50±1.13	0.28±0.12
Liver	0.50±0.15	0.11±0.00	1.68±0.13	0.37±0.01
Kidney	0.08±0.02	0.02±0.00	0.69±0.08	0.25±0.04
Fat	<0.01	<0.01	0.02±0.00	<0.01
Total	83.18±7.19	3.77±0.87	–	34.14±11.53

Source: Timchalk et al. 1994

Kennedy et al. (1994) quantified the distribution of radioactivity in blood components after a 4-hour inhalation exposure of rats to ^{14}C-2,4-TDI. Radioactivity was primarily recovered from the plasma (74–87%), but radioactivity was also detected in the cell pellet. The plasma was fractionated by molecular weight, showing that the vast majority of the radioactivity (97–100%) was associated with high molecular weight (>10 kDa) components; electrophoresis was then used to demonstrate that the majority of the radioactivity was associated with a 70 kDa protein, which the authors suggested was likely albumin. Analysis of stomach contents by fractionation and electrophoresis showed that a higher proportion of the radioactivity in the stomach (28%) was in the low molecular weight fraction (<10 kDa) compared with the fraction in plasma. High performance liquid chromatography (HPLC) analysis of the low molecular weight fraction showed a TDA peak in addition to other products, demonstrating that TDA is not the primary reaction product after inhalation exposure. The authors postulated that the inhaled TDI reacted with macromolecules in the airway prior to being transported to the stomach, where proteolysis occurred, yielding the low molecular weight adducts.

Day et al. (1996) analyzed hemoglobin adducts of TDI in guinea pigs exposed to 1 ppm 2,4-TDI for 3 hours/day on 5 consecutive days, and identified several TDI-derived adducts that demonstrated that the isocyanate moiety was capable being transported from the lung into the blood and across the erythrocyte membrane to form a hemoglobin adduct.

MDI. Systemic distribution of radioactivity was measured in male Wistar rats exposed head-only for 6 hours to an aerosol of ^{14}C-4,4'-MDI (2 mg/m^3) (Gledhill et al. 2005). The results are shown in Table 3-10. As the table indicates, the largest percentages of received radioactivity were recovered from the respiratory and gastrointestinal tracts, but radioactivity was detected in all of the tissues examined (Gledhill et al. 2005). The authors suggested that the radioactivity in the gastrointestinal tract and its contents likely resulted from oral intake during grooming after the exposure period and/or mucociliary clearance of material from the respiratory tract (Gledhill et al. 2005).

3.4.2.2 Oral Exposure

TDI. In male F344 rats given a single gavage dose of 60 mg/kg ^{14}C ring-labeled TDI, the highest proportion of administered dose was recovered from the gastrointestinal tract and contents when sampled 2 or 48 hours postdosing (Timchalk et al. 1994). Radioactivity levels in the skin, lung, liver, and kidney reflected 1.1, 1.0, 0.5, and 0.08% of the administered dose, respectively, at 2 hours postdosing; lower concentrations were seen at 48 hours postdosing (Timchalk et al. 1994).

Table 3-10. Tissue Distribution of ^{14}C in Male Wistar Rats Exposed to ^{14}C Ring-Labelled 4,4'-Methylenediphenyl Diisocyanate Aerosol Via Inhalation

	Percent of received radioactivity		
Tissue	0 hours postexposure	24 hours postexposure	168 hours postexposure
Adrenals	0.025±0.01	0.021±0.005	0.025±0.004
Brain	0.051±0.018	0.031±0.007	<0.016±<0.006
Gastrointestinal	4.173±0.801	0.992±0.406	<0.141±<0.007
Gonads	0.356±0.022	0.201±0.032	0.054±0.021
Heart	0.375±0.068	0.157±0.041	0.053±0.013
Kidneys	0.524±0.089	0.363±0.03	0.103±0.014
Liver	3.379±0.756	2.004±0.408	0.424±0.058
Lungs	12.771±2.521	5.558±0.944	3.558±0.503
Nasal tissue (olfactory)	0.115±0.018	0.047±0.017	0.029±0.032
Nasal tissue (respiratory)	1.44±1.873	0.182±0.247	0.058±0.01
Esophagus	0.074±0.02	0.014±0.005	<0.039±<0.048
Pancreas	0.046±0.008	0.031±0.005	0.021±0.009
Spleen	0.102±0.021	0.071±0.012	0.043±0.009
Stomach	0.335±0.22	0.234±0.185	0.039±0.026
Thyroid	0.024±0.021	0.004±0.001	0.004±0.003
Trachea	0.167±0.168	0.095±0.103	0.012±0.002
Residual carcass	37.106±9.752	18.539±4.058	5.001±1.187
Total	61.063	54.901	5.159
Stomach contents	<0.921±<1.564	0.351±0.358	<0.103±<0.039
Gastrointestinal contents	31.787±5.133	13.177±5.487	0.617±0.13

Source: Gledhill et al. 2005

MDI. No data on the distribution of MDI after oral exposure were located in the available literature.

3.4.2.3 Dermal Exposure

TDI. The carcasses of male rats exposed to 330 mg/kg ^{14}C-2,4-TDI for 0.5, 1,0, or 8.0 hours via topical application contained 0.25, 0.44, and 0.52% of the applied radioactivity, respectively (Hoffman et al. 2010).

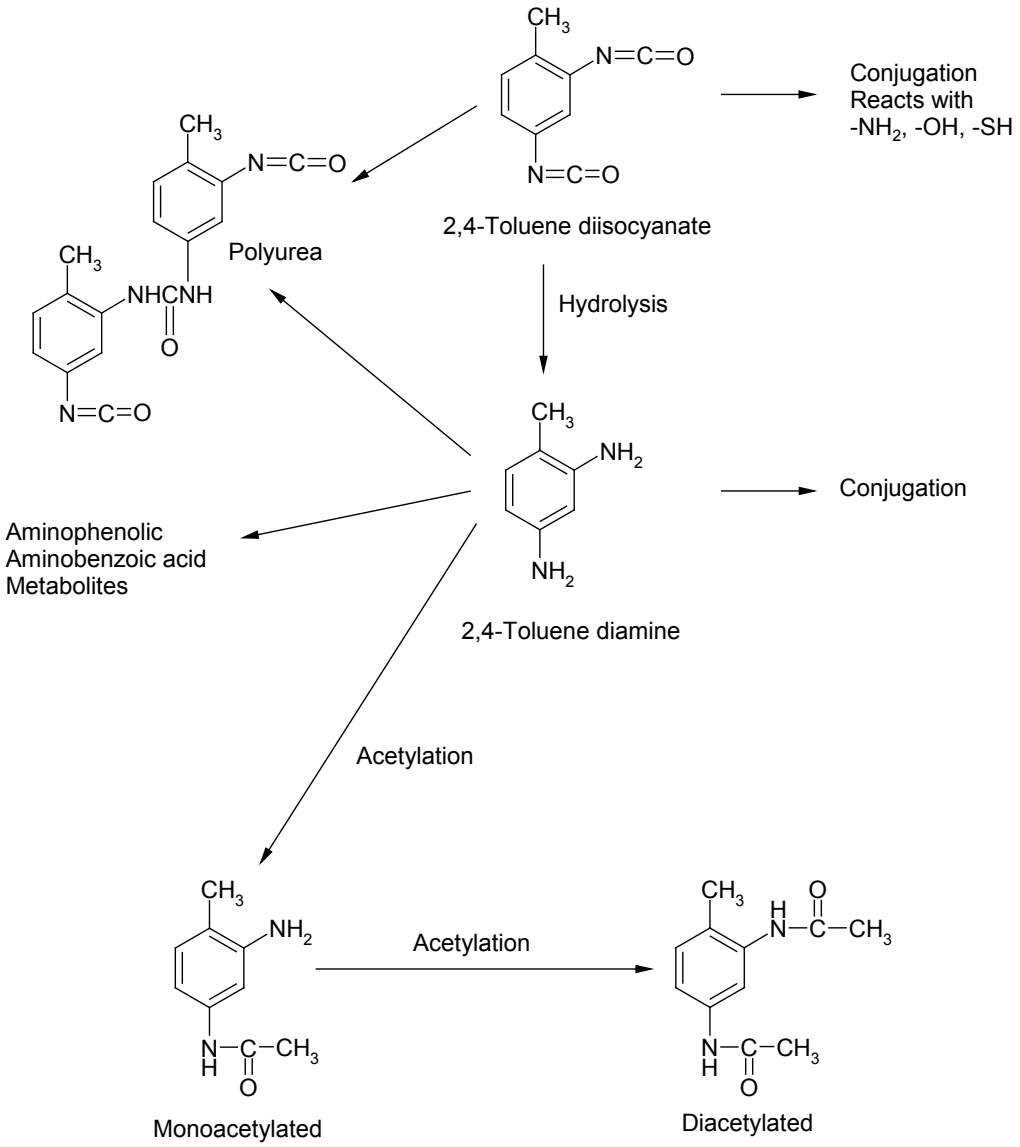
MDI. No radioactivity was detected in the tissues of male rats exposed for 8 hours to a topical dose of 15 or 165 mg/kg ^{14}C-4,4'-MDI and sacrificed 8, 24, or 120 hours after the commencement of exposure (Hoffman et al. 2010). Vock and Lutz (1997) detected small amounts of radioactivity (≤ 1% of applied radioactivity in total) in the lung, liver, kidney, and muscle of female rats exposed to topical doses of 11–15 mg/kg ^{14}C-4,4'-MDI for 24 hours or to 29–30 mg/kg for 48 hours. Of the applied radioactivity, 9–12% was recovered in the epidermis (Vock and Lutz 1997).

3.4.3 Metabolism

TDI reacts readily with sulfhydryl, amine, and hydroxyl groups, forming adducts with hemoglobin, glutathione, albumin, and other macromolecules. After gavage exposure, TDI is hydrolyzed in the gastrointestinal tract to TDA, which may be absorbed and metabolized further (acetylated, conjugated, or metabolized to aminophenolic or aminobenzoic acid compounds) (Timchalk et al. 1994). In the gut, TDA may also react with unhydrolyzed TDI to form polyurea polymers that pass unabsorbed through the gastrointestinal tract. In contrast, after inhalation exposure, little TDI, if any, is hydrolyzed to TDA; conjugation reactions are believed to represent be the primary fate of inhaled TDI. These route-specific differences in the fate of TDI were observed when rat urine was analyzed after gavage and inhalation exposure; after gavage exposure to TDI, 35% of the detected metabolites were free or acetylated TDA (the balance reflected acid-labile conjugates of TDI or TDA), while only 10% of the metabolites detected after inhalation exposure were acetylated TDA (Timchalk et al. 1994). The acidic pH of the stomach favors the hydrolysis of TDI to form TDA. At neutral pH levels, TDI is more likely to form polyurea polymers (as discussed in Sielken et al. 2012); thus, TDA formation may not occur following inhalation, ingestion, or dermal exposure to TDI.

Figure 3-4 shows the proposed metabolic scheme for 2,4-TDI in the rat.

Figure 3-4. Proposed Metabolic Scheme for 2,4-Toluene Diisocyanate in the Rat



Source: Timchalk et al. 1994

A single study evaluating the metabolism of MDI was located. In male rats exposed via inhalation to MDI aerosol, five metabolites were identified in the urine, feces, and bile (Gledhill et al. 2005). Table 3-11 shows the percentage of administered dose represented by each metabolite. Four metabolites were identified as N-acetylated and N-acetylated hydroxylated products of MDI, while the fifth could not be identified. The primary product detected in feces was proposed to be mixed molecular weight polyureas resulting from spontaneous reaction of MDI. No free MDA was detected in excreta or bile (Gledhill et al. 2005).

3.4.3.1 Inhalation Exposure

TDI. When rats were exposed by inhalation to 2 ppm 2,4-TDI for 4 hours, no free TDA was detected in the urine (Timchalk et al. 1994). A total of 0.26 μg equivalents of 2,4-TDA were detected in the hydrolyzed urine as mono- and diacetylated products, while 2.53 μg equivalents were detected as acid-labile conjugates of 2,4-TDI or TDA. Another inhalation study (Kennedy et al. 1994) showed that 95% of the TDI in plasma was conjugated to macromolecules, which the investigators suggested demonstrated that macromolecules successfully competed with hydrolysis to form the diamine.

In one study, TDI was shown to induce a decrease in CYP2B1 expression. Exposure of male Sprague-Dawley rats to commercial-grade TDI (80:20 mix of 2,4- and 2,6-TDI) at a concentration of 1 ppm for 8 hours resulted in decreased CYP2B1 mRNA (33%) and protein (40%) levels in the lung when compared with control rats (Pons et al. 2000). TDI exposure did not alter expression of other CYPs investigated (1A1, 2E1, or 3A1) or glutathione S-transferase (GST).

MDI. A total of five metabolites of 4,4'-MDI monomer were observed in the urine, feces, and bile of male rats exposed to 2 mg/m^3 radiolabeled MDI aerosol for 6 hours; four were identified by liquid chromatography-mass spectrometry (LC-MS) and LC-MS^3 analysis as N-acetylated and N-acetylated hydroxylated products of MDI, while the fifth could not be identified (Gledhill et al. 2005). The primary product detected in feces was proposed to be mixed molecular weight polyureas resulting from spontaneous reaction of MDI. Free MDA was not detected in excreta or bile. After acid hydrolysis of the 6-, 12-, and 24-hour urine samples, MDA was detected at concentrations of 483, 120, and 131 ng/mL, respectively. Analysis of the acid-hydrolyzed urine also revealed deacetylated products of the metabolites N,N'-diacetyl-4,4'-diaminobenzhydrol and N,N'-diacetyl 4,4'-diaminobenzophenone (Gledhill et al. 2005).

Table 3-11. Metabolites of Methylenediphenyl Diisocyanate (MDI) in Male F344 Rats Exposed to ^{14}C Ring-Labelled 4,4'-MDI Monomer Via Inhalation

	Percentage of administered dose in intact rats		Percentage of administered dose in bile-cannulated rats		
Metabolite	Urine	Feces	Urine	Bile	Feces
N,N'-Diacetyl-4,4'-diaminobenzhydrol	1	ND	6	1	ND
N,N'-Diacetyl-4,4'-diaminophenyl-methane	0.5	ND	4	4	ND
N-Acetyl-4, 4'-diaminophenylmethane	0.3	ND	ND	ND	ND
N,N'-Diacetyl 4,4'-diaminobenzophenone	0.4	ND	ND	ND	ND
Metabolite V; not identified	0.2	ND	<1	ND	ND
Proposed as mixed molecular weight polyureas derived from MDI	ND	56	ND	9	24
Total	2.4	56	10	14	24

ND = not detected

Source: Gledhill et al. 2005

3.4.3.2 Oral Exposure

TDI. After rats were given a single gavage dose of 60 mg/kg 2,4-TDI, 2,4-TDA was detected (by HPLC) in the urine collected during the first 12 hours postdosing (Timchalk et al. 1994). In the urine, 2.08 μg equivalents of free 2,4-TDA were detected, while monoacetylated, and diacetylated 2,4-TDA were measured to be 5.12 and 8.17 μg equivalents of 2,4-TDA. Approximately 44.51 μg equivalents existed in the urine as acid-labile conjugates of 2,4-TDA and/or 2,4-TDI (Timchalk et al. 1994). The relevance of these gavage data in which the TDI is instilled into the acidic stomach to human ingestion is questionable. At neutral pH levels, such as found in the mouth, TDI is more likely to react with other TDI molecules to form polyurea polymers than to hydrolyze to TDA (as discussed in Sielken et al. 2012).

MDI. No data on the metabolism of MDI after oral exposure were located in the available literature.

3.4.3.3 Dermal Exposure

TDI. No data on the metabolism of TDI after dermal exposure of humans or animals were located in the available literature.

MDI. No data on the metabolism of MDI after dermal exposure of humans or animals were located in the available literature.

3.4.4 Elimination and Excretion

3.4.4.1 Inhalation Exposure

TDI. Budnik et al. (2011) evaluated urinary excretion of diamines following specific inhalation challenge exposure to known concentrations ranging from 0.5 to 30 ppb of 2,4-TDI (n=18) or 2,6-TDI (n=18). The subjects were workers with prior exposure to these compounds who were being evaluated for occupational asthma. Levels of TDA in the spot urine samples collected over the following 24 hours were subjected to acid hydrolysis prior to analysis by gas chromatography (GC)/MS. In subjects exposed to 2,4- and 2,6-TDI, creatinine-corrected urinary levels of the corresponding diamines peaked at 4.1 and 4.8 hours, respectively. The half-life for TDA in urine was estimated to be 6 hours. Subjects exposed to higher concentrations of either isomer of TDI (mean exposure 1,569 ppb) did not exhibit correspondingly higher urinary peak levels of TDA when compared with the low exposure group (496 ppb).

The plasma elimination rate for both 2,4- and 2,6-TDI was estimated to average 21 days in workers chronically exposed to airborne concentrations between 0.4 and 4 μg/m^3 TDI (mixture of 2,4- and 2,6-TDI with varying composition) (Lind et al. 1996).

TDA levels in hydrolyzed urine in humans experimentally exposed for 4–7.5 hours to mixtures of 2,4- and 2,6-TDI exhibited a biphasic pattern, with an initial rapid phase followed by a slower phase (Brorson et al. 1991; Skarping et al. 1991). The half-time for urinary excretion in the initial rapid phase was estimated to be between 1.6 and 2.5 hours for 2,6-TDI and between 1.9 and 5 hours for 2,4-TDI (Brorson et al. 1991; Skarping et al. 1991). The half-time for the slower phase was reportedly about 5 hours for both isomers (Skarping et al. 1991).

In guinea pigs, 2,3-TDI is cleared slowly from the blood. Kennedy et al. (1989) observed a gradual decline in blood radioactivity over the course of 72 hours following exposure of guinea pigs to concentrations of ^{14}C-2,4-TDI ranging from 0.004 to 0.336 ppm. Radioactivity remaining in the blood at 72 hours postexposure persisted at that level for a second week, suggesting that the molecule to which the radioactivity was bound was saturated, and that the adduct did not have a rapid turnover rate (Kennedy et al. 1989).

The primary excretory pathway for 2,4-TDI in rats exposed via inhalation was fecal (Timchalk et al. 1994). Forty-eight hours after a 4-hour exposure to 2 ppm ^{14}C ring-labeled 2,4-TDI, male F344 rats excreted 47% of the recovered radioactivity in the feces and 15% in the urine. No radioactivity was detected in exhaled CO_2 or volatile organics (Timchalk et al. 1994). Detection of significant amounts of radioactivity in the gastrointestinal contents both immediately after exposure (10% of recovered dose) and 48 hours later (17% of recovered dose) (Timchalk et al. 1994) suggests biliary excretion of 2,4-TDI.

MDI. In addition to evaluating urinary excretion of diamines in workers undergoing specific inhalation challenge with TDI, Budnik et al. (2011) measured levels of 4,4'-MDA in acid hydrolyzed urine following specific inhalation challenge exposure to 4,4'-MDI (0.5–30 ppb; n=36 subjects). The peak level of 4,4'-MDA in urine occurred at 14 hours after exposure. Urinary excretion of 4,4'-MDA was slower and more prolonged than that of the TDAs, and excretion was not complete during the 24-hour study period. In addition, the excretion time course was longer in those subjects exposed to higher concentrations of 4,4'-MDI (mean exposure 1,569 ppb) compared with those exposed to lower concentrations (mean exposure 496 ppb).

Male rats exposed (head only) to aerosols of ^{14}C-4,4'-MDI monomer for 6 hours at 2 mg/m^3 excreted the majority of the received radioactivity in the feces (80%), with about 5% excreted in urine during the 168-hour follow-up time (Gledhill et al. 2005). In bile duct-cannulated rats exposed similarly, biliary excretion was estimated to be 14% of the dose and urinary excretion was 12%.

3.4.4.2 Oral Exposure

TDI. After gavage exposure to a 60 mg/kg ^{14}C ring-labeled 2,4-TDI, 81% of the administered dose was recovered in the feces and 8% was recovered in the urine of male F344 rats; total radioactivity recovered represented 94% of the administered dose (Timchalk et al. 1994). Quantifiable levels of radioactivity were not detected in exhaled CO_2 or volatile organics.

MDI. No data on the elimination of MDI after oral exposure were located in the available literature.

3.4.4.3 Dermal Exposure

TDI. Hoffman et al. (2010) detected <1% of a dermally-applied dose of 330 mg/kg ^{14}C-TDI in the urine of rats after exposure durations up to 8 hours; no radioactivity was detected in the feces. Yeh et al. (2008) evaluated the kinetics of urinary excretion of 2,4- and 2,6-TDI in male rats by measuring urinary TDA for 6 days after topical application of commercial-grade TDI (80:20 mixture of 2,4- and 2.6-TDI) at concentrations of 0.2, 1, and 5%. 2,4- and 2,6-TDA were measured in acid-hydrolyzed urine samples collected at 12-hour intervals. The results are shown in Table 3-12. For both compounds and regardless of applied concentration, the maximum concentration in urine was reached during the first 12-hour interval. At the highest exposure level, urinary excretion was not complete at the end of the 6-day collection period, but was essentially complete at the lower concentrations. The half-life for urinary elimination of 2,4- and 2.6-TDA ranged between 18.4 and 26.6 hours. The data readily fit a first-order kinetic linear model ($p<0.05$), but the pattern at the highest exposure demonstrated a non-linear saturation at 60 hours after Cmax was reached (Yeh et al. 2008).

MDI. Hoffman et al. (2010) detected only small amounts of radioactivity in the feces of male rats exposed via dermal application of 15 or 165 mg/kg ^{14}C-4,4'-MDI for 8 hours and sacrificed 8, 24, or 120 hours after treatment. In contrast, approximately 29–30% of the applied radioactivity was recovered in the feces during a 48-hour exposure of female rats to topical doses of ~30 mg/kg ^{14}C-4,4'-MDI (Vock

Table 3-12. Kinetics of Urinary Toluene Diamine (TDA) Excretion in Rats Exposed to Toluene Diisocyanate Via Topical Application

	2,4-TDA			2,6-TDA		
Applied dose	0.2%	1%	5%	0.2%	1%	5%
Tmax (hours)	12	12	12	12	12	12
Cmax (μg/mL)	0.062± 0.009	0.238± 0.060	6.116± 0.429	0.056± 0.004	0.268± 0.060	3.777± 0.384
AUC (μg*hour/mL)	2.186± 0.376	8.395± 0.919	158.599± 5.517	2.046± 0.263	10.558± 0.538	133.994± 20.35
Accumulative amount (μg)	2.682± 0.631	12.940± 4.224	83.843± 29.542	2.622± 0.779	14.978± 2.628	69.810± 11.541
k (1/hour)	0.0376± 0.002	0.0341± 0.003	0.0325± 0.003	0.0329± 0.0020	0.0339± 0.0027	0.0264± 0.004
t1/2 (hours)	18.4±0.8	20.4±01.5	21.5±2.2	21.1±1.3	20.5±1.6	26.6±3.7

Source: Yeh et al. 2008

and Lutz 1997). Hoffman et al. (2010) took measures to prevent oral exposure of the rats via grooming, while Vock and Lutz (1997) did not. In both studies, recovery of radioactivity in the urine was <1% of the applied dose (Hoffman et al. 2010; Vock and Lutz 1997).

3.4.5 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models

Physiologically based pharmacokinetic (PBPK) models use mathematical descriptions of the uptake and disposition of chemical substances to quantitatively describe the relationships among critical biological processes (Krishnan et al. 1994). PBPK models are also called biologically based tissue dosimetry models. PBPK models are increasingly used in risk assessments, primarily to predict the concentration of potentially toxic moieties of a chemical that will be delivered to any given target tissue following various combinations of route, dose level, and test species (Clewell and Andersen 1985). Physiologically based pharmacodynamic (PBPD) models use mathematical descriptions of the dose-response function to quantitatively describe the relationship between target tissue dose and toxic end points.

PBPK/PD models refine our understanding of complex quantitative dose behaviors by helping to delineate and characterize the relationships between: (1) the external/exposure concentration and target tissue dose of the toxic moiety, and (2) the target tissue dose and observed responses (Andersen and Krishnan 1994; Andersen et al. 1987). These models are biologically and mechanistically based and can be used to extrapolate the pharmacokinetic behavior of chemical substances from high to low dose, from route to route, between species, and between subpopulations within a species. The biological basis of PBPK models results in more meaningful extrapolations than those generated with the more conventional use of uncertainty factors.

The PBPK model for a chemical substance is developed in four interconnected steps: (1) model representation, (2) model parameterization, (3) model simulation, and (4) model validation (Krishnan and Andersen 1994). In the early 1990s, validated PBPK models were developed for a number of toxicologically important chemical substances, both volatile and nonvolatile (Krishnan and Andersen 1994; Leung 1993). PBPK models for a particular substance require estimates of the chemical substance-specific physicochemical parameters, and species-specific physiological and biological parameters. The numerical estimates of these model parameters are incorporated within a set of differential and algebraic equations that describe the pharmacokinetic processes. Solving these differential and algebraic equations provides the predictions of tissue dose. Computers then provide process simulations based on these solutions.

The structure and mathematical expressions used in PBPK models significantly simplify the true complexities of biological systems. However, if the uptake and disposition of the chemical substance(s) are adequately described, this simplification is desirable because data are often unavailable for many biological processes. A simplified scheme reduces the magnitude of cumulative uncertainty. The adequacy of the model is, therefore, of great importance, and model validation is essential to the use of PBPK models in risk assessment.

PBPK models improve the pharmacokinetic extrapolations used in risk assessments that identify the maximal (i.e., the safe) levels for human exposure to chemical substances (Andersen and Krishnan 1994). PBPK models provide a scientifically sound means to predict the target tissue dose of chemicals in humans who are exposed to environmental levels (for example, levels that might occur at hazardous waste sites) based on the results of studies where doses were higher or were administered in different species. Figure 3-5 shows a conceptualized representation of a PBPK model.

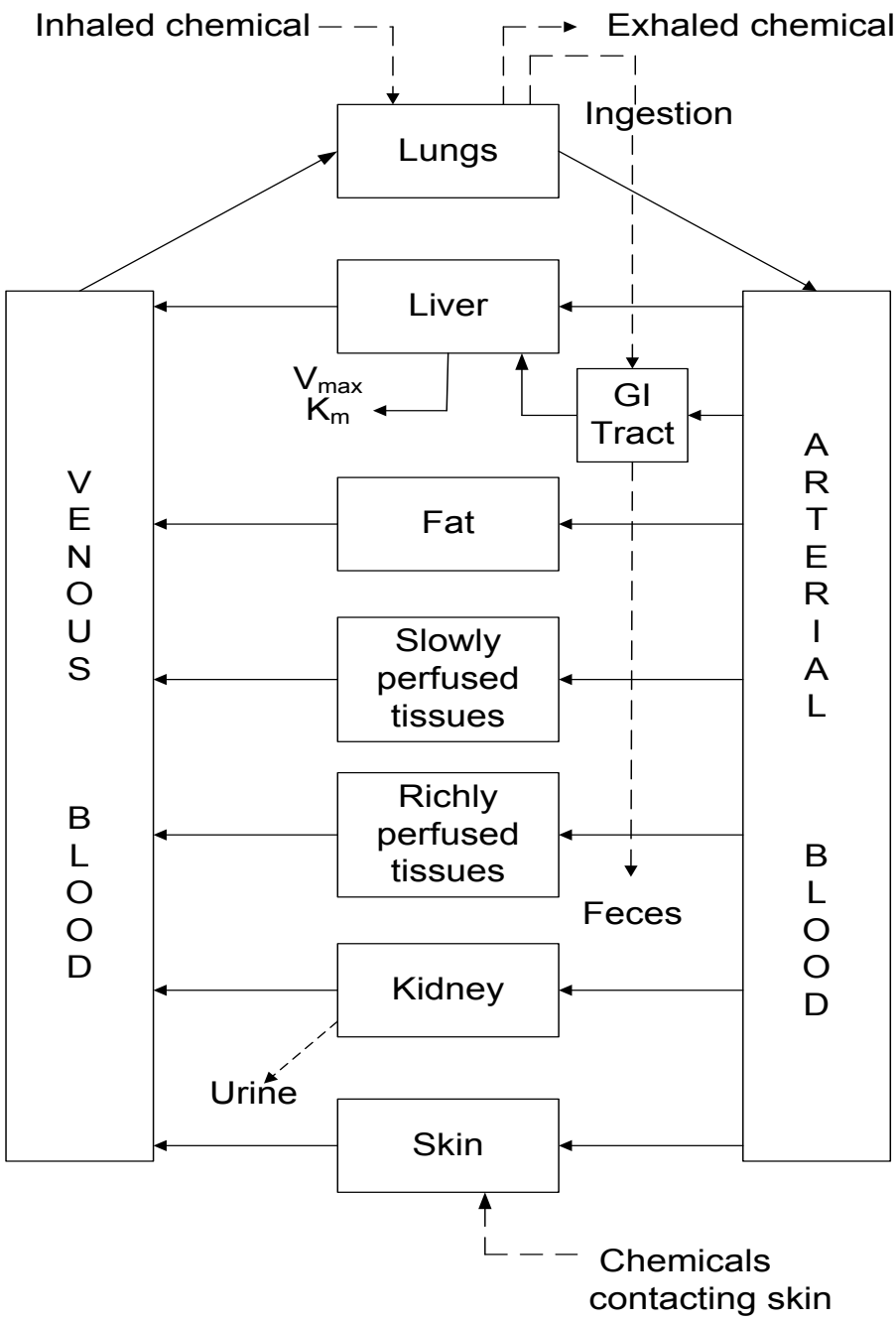
No physiologically based pharmacokinetics models for TDI or MDI were located in the available literature.

3.5 MECHANISMS OF ACTION

3.5.1 Pharmacokinetic Mechanisms

The metabolic fate of TDI is route-dependent. After oral exposure, TDI is hydrolyzed in the gastrointestinal tract to TDA, which may be absorbed and metabolized further (acetylated, conjugated, or metabolized to aminophenolic or aminobenzoic acid compounds) (Timchalk et al. 1994). In the gut, TDA may also react with unhydrolyzed TDI to form polyurea polymers that pass unabsorbed through the gastrointestinal tract. In contrast, after inhalation exposure, little TDI, if any, is hydrolyzed to TDA; conjugation reactions are believed to represent be the primary fate of inhaled TDI. As a consequence of these route differences, exposure to TDI via the gastrointestinal tract will likely result in higher tissue concentrations of TDA and its downstream products than would occur after inhalation exposure.

Figure 3-5. Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance



Note: This is a conceptual representation of a physiologically based pharmacokinetic (PBPK) model for a hypothetical chemical substance. The chemical substance is shown to be absorbed via the skin, by inhalation, or by ingestion, metabolized in the liver, and excreted in the urine or by exhalation.

Source: Krishnan and Andersen 1994

3.5.2 Mechanisms of Toxicity

The respiratory tract is the primary target of TDI and MDI toxicity resulting in declines in lung function and occupational asthma; chronic airway inflammation likely plays a key role in both effects. The mechanisms of diisocyanate-induced occupational asthma have been more extensively investigated than those involved in reduced lung function. The pathogenesis of TDI/MDI asthma has not been fully elucidated; it appears to be multifaceted and involves a number immunological and non-immunological mechanisms. TDI/MDI occupational asthma has many similar features to allergic asthma, including persistent airway inflammation and subsequent airway hyperresponsiveness; however, there are several features present in TDI/MDI asthma not seen in allergic asthma including airway neutrophilia, increases in interleukin (IL)-8 levels, low prevalence of diisocyanate-specific IgE antibodies, and lack of association with atopy (Furusho et al. 2006). It is believed that diisocyanates bind to airway cell proteins and are taken up by epithelial cells resulting in cytokine and chemokine production and cellular recruitment, which leads to airway inflammation (Kim et al. 2010). Wisnewski et al. (2013) speculated that albumin is the primary protein target of diisocyanate reactivity; the diisocyanate-albumin conjugate can trigger innate and adaptive cellular responses associated with airway inflammation and asthma. Glutathione serves as a carbamoylating intermediate through which diisocyanate is transported from the airways to the blood where there are higher levels of albumin. This shuttle mechanism could explain the rapid accumulation of diisocyanate-albumin conjugates in the peripheral blood in animals exposed to diisocyanates (Wisnewski et al. 2013).

The immunological mechanisms appear to involve hypersensitivity response, although other types of immune response are likely involved. There is suggestive evidence that all types of hypersensitivity are involved. An immediate response to a diisocyanate challenge is likely indicative of Type 1 hypersensitivity, which is mediated by IgE. Specific IgE antibodies to TDI-HSA (Baur and Fruhmann 1981; Cvitanovic e t al. 1989; Park and Nahm 1996; Park et al. 1999; Pezzini et al. 1984; Sharifi et al. 2013) or MDI-HSA (Hur et al. 2008; Pezzini et al. 1984; Tse et al. 1985) have been found. However, only a small percentage of TDI and MDI workers with occupational asthma have elevated levels of IgE, suggesting that other mechanisms are likely involved. The delayed response to a TDI or MDI challenge is suggestive of one or more subtype of Type IV hypersensitivity. This type of response is typically driven by leukotrienes, chemokines, and cytokines synthesized by activated mast cells and CD4+ Th2 cells. A study of CD4 knockout mice sensitized to TDI showed a significant reduction in airway hyperresponsiveness to a TDI challenge as compared to wild-type controls. A marked reduction of pulmonary inflammation by neutrophils, lymphocytes, eosinophils, and macrophage infiltration and

decreases in Th2 cytokines—IL-4, IL-5, and IL-13—were also observed in the CD4 knockout mice (Matheson et al. 2005). The role of CD4+ Th2 subtype of Type IV hypersensitivity in diisocyanate-induced asthma is supported by the findings of increased IL-4 and IL-6 levels in the bronchoalveolar lavage (BAL) fluid of rats sensitized to TDI (Zheng et al. 2001a, 2001b). Increases in the production of IL-1β, IL-1α, and tumor necrosis factor (TNF)-α expression were observed in the lungs of mice with TDI-induced asthma; increases in IL-1β and TNF-α expression were also observed in the lung biopsy samples from workers with TDI-induced asthma (Johnson et al. 2005). Studies in TDI-sensitized mice in which IL-1β or IL-1α was suppressed showed that they have unique and overlapping roles (Johnson et al. 2005). A central role for TNF-α in the propagation of airway inflammation and hyperresponsiveness is supported by a study of TNF-α deficient mice that found a reduction in TDI-induced inflammation, airway hyperresponsiveness, and migration of airway dendritic cells to the draining lymph nodes (Matheson et al. 2002). The increases in IFN-γ and TNF-α observed in TDI sensitized mice also support a Th1 response mechanism (Świerczyńska-Machura et al. 2014). There is also some evidence to support mechanisms for the other two subtypes of Type IV hypersensitivity. A significant reduction in the Th1 cytokine, interferon-γ (INF-γ), was observed in CD4 knockout mice (Matheson et al. 2005). In contrast, Zheng et al. (2001a) did not find significant differences in Th1 cytokines (IL-2 or IFN-γ) levels in TDI-sensitized rats, as compared to controls. The Matheson et al. (2005) study also provides some evidence of the CD8+ subtype of Type IV hypersensitivity; reductions in airway hyperresponsiveness and pulmonary inflammation were observed in CD8 knockout mice sensitized to TDI as compared to TDI-sensitized wild-type mice.

In addition to immune hypersensitivity mechanism, there is evidence to suggest that other immune and non-immune mechanisms are involved in TDI/MDI-induced inflammation and airway hyperresponsiveness. *In vitro* studies in bronchial epithelial cells have showed enhanced production of IL-8 in the presence of TDI-HSA conjugate (Lee et al. 2003; Ogawa et al. 2006). The IL-8 attracts and activates neutrophils, and increased neutrophil counts have been observed in the BAL fluid of sensitized workers exhibiting a delayed response to a TDI challenge (Fabbri et al. 1987). A marked infiltration of eosinophils, as well as neutrophils, was observed in the central and peripheral airways of TDI-sensitized rats (Zheng et al. 2001a); in sensitized mice, increased leukocyte levels were observed in the BAL fluid with the eosinophils having the greatest increase (Zheng et al. 2004). De Vooght et al. (2013) showed that granulocytes played a key role in TDI-induced airway hyperresponsiveness. Ogawa et al. (2006) showed that TDI-HSA increased cytokine and chemokine production through the epidermal growth factor (EGFR) and p38 mitogen-activated protein kinase (MAPK) pathways. Results from studies conducted by

Pham et al. (2014) suggest that TDI can bind to tissue transglutaminase and that this conjugate can induce specific IgG antibody production, which can increase airway inflammation.

Intercellular adhesion molecule-1 (ICAM-1) plays a key regulatory role in TDI-induced inflammation by mediating the adhesion of blood leukocytes to the vascular epithelium (Furusho et al. 2006). In ICAM-1 knockout mice sensitized and challenged with TDI, there is a reduction in neutrophil, lymphocyte, eosinophil, and macrophage airway infiltration, a blocking of airway hyperresponsiveness, and marked decreases in TNF-α, IL-4, IL-5, and IFN-γ levels in the BAL fluid. Another mediator of airway inflammation that is overexpressed in response to TDI-HSA conjugates is vascular endothelial growth factor (VEGF) (Zhao et al. 2009). Overexpression of VEGF can result in increased vascular permeability and Th2 cell sensitization. Incubating bronchial cells with TDI-HSA resulted in increased cell permeability; however, neutralizing VEGF partially inhibited this increase in cell permeability (Zhao et al. 2009). Kim et al. (2011) found higher VEGF levels in workers with TDI-induced asthma, as compared to asymptomatic TDI-exposed workers.

Several investigators have shown that oxidative stress plays an essential role in diisocyanate-induced inflammation. Studies of workers with TDI- or MDI-induced asthma have shown increased transferrin levels and decreased ferritin levels (Hur et al. 2009; Kim et al. 2010). Ferritin is used for detoxification during oxidative stress-induced inflammation. Kim et al. (2010) found that TDI suppressed the synthesis of ferritin light chain in human airway epithelial cells. Several other antioxidant proteins were also found to be downregulated by TDI, including heme oxygenase-1, thioredoxins-1, glutathione peroxidase, peroxiredoxin-1, and catalase. Heme oxygenase-1/ferritin light chain expression was likely suppressed through the MAPK-Nrf2 signaling pathway (Kim et al. 2010). Studies in epithelial cells have also shown that TDI exposure induces the generation of reactive oxygen species (Hur et al. 2009).

3.5.3 Animal-to-Human Extrapolations

Kennedy et al. (1994) compared the quantities of TDI-derived components (as radioactivity) in the blood of guinea pigs, rats, and humans exposed by inhalation to ^{14}C- 2,4-TDI in several studies, and observed a linear relationship between the log-transformed microgram equivalents of the tolyl group per mL of blood and the log-transformed exposure concentration x time metric (ppm-hours). This observation suggests limited interspecies differences in the absorption of inhaled TDI into the blood stream. No data on interspecies differences in the pharmacokinetic behavior of MDI were located in the available literature.

3.6 TOXICITIES MEDIATED THROUGH THE NEUROENDOCRINE AXIS

Recently, attention has focused on the potential hazardous effects of certain chemicals on the endocrine system because of the ability of these chemicals to mimic or block endogenous hormones. Chemicals with this type of activity are most commonly referred to as *endocrine disruptors*. However, appropriate terminology to describe such effects remains controversial. The terminology *endocrine disruptors*, initially used by Thomas and Colborn (1992), was also used in 1996 when Congress mandated the EPA to develop a screening program for "...certain substances [which] may have an effect produced by a naturally occurring estrogen, or other such endocrine effect[s]...". To meet this mandate, EPA convened a panel called the Endocrine Disruptors Screening and Testing Advisory Committee (EDSTAC), and in 1998, the EDSTAC completed its deliberations and made recommendations to EPA concerning *endocrine disruptors*. In 1999, the National Academy of Sciences released a report that referred to these same types of chemicals as *hormonally active agents*. The terminology *endocrine modulators* has also been used to convey the fact that effects caused by such chemicals may not necessarily be adverse. Many scientists agree that chemicals with the ability to disrupt or modulate the endocrine system are a potential threat to the health of humans, aquatic animals, and wildlife. However, others think that endocrine-active chemicals do not pose a significant health risk, particularly in view of the fact that hormone mimics exist in the natural environment. Examples of natural hormone mimics are the isoflavinoid phytoestrogens (Adlercreutz 1995; Livingston 1978; Mayr et al. 1992). These chemicals are derived from plants and are similar in structure and action to endogenous estrogen. Although the public health significance and descriptive terminology of substances capable of affecting the endocrine system remains controversial, scientists agree that these chemicals may affect the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body responsible for maintaining homeostasis, reproduction, development, and/or behavior (EPA 1997). Stated differently, such compounds may cause toxicities that are mediated through the neuroendocrine axis. As a result, these chemicals may play a role in altering, for example, metabolic, sexual, immune, and neurobehavioral function. Such chemicals are also thought to be involved in inducing breast, testicular, and prostate cancers, as well as endometriosis (Berger 1994; Giwercman et al. 1993; Hoel et al. 1992).

No studies were located regarding endocrine disruption in humans and/or animals after exposure to TDI or MDI. No *in vitro* studies were located regarding endocrine disruption of TDI or MDI.

3.7 CHILDREN'S SUSCEPTIBILITY

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans, when most biological systems will have fully developed. Potential effects on offspring resulting from exposures of parental germ cells are considered, as well as any indirect effects on the fetus and neonate resulting from maternal exposure during gestation and lactation. Relevant animal and *in vitro* models are also discussed.

Children are not small adults. They differ from adults in their exposures and may differ in their susceptibility to hazardous chemicals. Children's unique physiology and behavior can influence the extent of their exposure. Exposures of children are discussed in Section 6.6, Exposures of Children.

Children sometimes differ from adults in their susceptibility to adverse health effects from exposure to hazardous chemicals, but whether there is a difference depends on the chemical(s) (Guzelian et al. 1992; NRC 1993). Children may be more or less susceptible than adults to exposure-related health effects, and the relationship may change with developmental age (Guzelian et al. 1992; NRC 1993). Vulnerability often depends on developmental stage. There are critical periods of structural and functional development during both prenatal and postnatal life that are most sensitive to disruption from exposure to hazardous substances. Damage from exposure in one stage may not be evident until a later stage of development. There are often differences in pharmacokinetics and metabolism between children and adults. For example, absorption may be different in neonates because of the immaturity of their gastrointestinal tract and their larger skin surface area in proportion to body weight (Morselli et al. 1980; NRC 1993); the gastrointestinal absorption of lead is greatest in infants and young children (Ziegler et al. 1978). Distribution of xenobiotics may be different; for example, infants have a larger proportion of their bodies as extracellular water, and their brains and livers are proportionately larger (Altman and Dittmer 1974; Fomon 1966; Fomon et al. 1982; Owen and Brozek 1966; Widdowson and Dickerson 1964). Past literature has often described the fetus/infant as having an immature (developing) blood-brain barrier that is leaky and poorly intact (Costa et al. 2004). However, current evidence suggests that the blood-brain barrier is anatomically and physically intact at this stage of development, and the restrictive intracellular junctions that exist at the blood-CNS interface are fully formed, intact, and functionally effective (Saunders et al. 2008, 2012).

However, during development of the brain, there are differences between fetuses/infants and adults that are toxicologically important. These differences mainly involve variations in physiological transport

systems that form during development (Ek et al. 2012). These transport mechanisms (influx and efflux) play an important role in the movement of amino acids and other vital substances across the blood-brain barrier in the developing brain; these transport mechanisms are far more active in the developing brain than in the adult. Because many drugs or potential toxins may be transported into the brain using these same transport mechanisms—the developing brain may be rendered more vulnerable than the adult. Thus, concern regarding possible involvement of the blood-brain barrier with enhanced susceptibility of the developing brain to toxins is valid. It is important to note however, that this potential selective vulnerability of the developing brain is associated with essential normal physiological mechanisms; and not because of an absence or deficiency of anatomical/physical barrier mechanisms.

The presence of these unique transport systems in the developing brain of the fetus/infant is intriguing; whether these mechanisms provide protection for the developing brain or render it more vulnerable to toxic injury is an important toxicological question. Chemical exposure should be assessed on a case-by-case basis. Research continues into the function and structure of the blood-brain barrier in early life (Kearns et al. 2003; Saunders et al. 2012; Scheuplein et al. 2002).

Many xenobiotic metabolizing enzymes have distinctive developmental patterns. At various stages of growth and development, levels of particular enzymes may be higher or lower than those of adults, and sometimes unique enzymes may exist at particular developmental stages (Komori et al. 1990; Leeder and Kearns 1997; NRC 1993; Vieira et al. 1996). Whether differences in xenobiotic metabolism make the child more or less susceptible also depends on whether the relevant enzymes are involved in activation of the parent compound to its toxic form or in detoxification. There may also be differences in excretion, particularly in newborns given their low glomerular filtration rate and not having developed efficient tubular secretion and resorption capacities (Altman and Dittmer 1974; NRC 1993; West et al. 1948). Children and adults may differ in their capacity to repair damage from chemical insults. Children also have a longer remaining lifetime in which to express damage from chemicals; this potential is particularly relevant to cancer.

Certain characteristics of the developing human may increase exposure or susceptibility, whereas others may decrease susceptibility to the same chemical. For example, although infants breathe more air per kilogram of body weight than adults breathe, this difference might be somewhat counterbalanced by their alveoli being less developed, which results in a disproportionately smaller surface area for alveolar absorption (NRC 1993).

Limited data for TDI and MDI on children's susceptibility were identified. In the absence of data, it is assumed that the respiratory tract would be the most sensitive target of toxicity for both compounds. Two studies have examined the developmental toxicity and both reported skeletal effects. Exposure to TDI on GDs 6–15 resulted in poorly ossified cervical vertebrae at a concentration also resulting in markedly reduced maternal weight gain and respiratory symptoms (Tyl et al. 1999a). An increase in the occurrence of asymmetric sternebrae was observed in rats; maternal toxicity was limited to a decrease in food consumption (Buchsmann et al. 1996).

3.8 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility (NAS/NRC 1989).

A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself, substance-specific metabolites in readily obtainable body fluid(s), or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to TDI and MDI are discussed in Section 3.8.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly

adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by TDI and MDI are discussed in Section 3.8.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 3.10, Populations That Are Unusually Susceptible.

3.8.1 Biomarkers Used to Identify or Quantify Exposure to TDI and MDI

A number of potential urinary and plasma biomarkers of exposure to TDI and MDI have been investigated. TDA, likely released by hydrolysis of protein adducts, has been measured in plasma and in acid- or alkaline-hydrolyzed urine as a biomarker of exposure to 2,4- and 2,6-TDI (Austin et al. 2007; Brorson et al. 1991; Geens et al. 2012; Sennbro et al. 2004; Sepai et al. 1995; Skarping et al. 1991; Tinnerberg et al. 1997, 2014). Both Geens et al. (2012) and Sennbro et al. (2004) observed strong correlations (coefficients ranging from 0.75 to 0.88) between personal air concentrations of 2,4- and 2,6-TDI and plasma and urinary levels of 2,4-, 2,6-, and total TDA in occupationally exposed persons. Similarly, the diamine metabolite of MDI (MDA) has been studied as a biomarker of exposure (Sabbioni et al. 2007; Schutze et al. 1995; Sennbro et al. 2003, 2006; Sepai et al. 1995). Sennbro et al. (2006) reported statistically significant, but not strong, correlation coefficients of 0.51–0.65 for the association between personal air measurements of MDI and plasma or urinary levels of MDA (samples collected the same day as the air measurements; urinary samples were hydrolyzed). The authors noted that there was significant interindividual variation. Tinnerberg et al. (2014) also found correlations between TDA levels in hydrolyzed urine (creatinine adjusted or specific gravity adjusted) and TDA levels in hydrolyzed plasma; strong correlations were also found for MDA levels in hydrolyzed urine and hydrolyzed plasma. It was noted that GSTM1 polymorphisms modified the association between urine and plasma TDA levels.

To facilitate the distinction between background levels of exposure and occupational exposure, Sennbro et al. (2005) measured plasma and hydrolyzed urinary 2,4- and 2,6-TDA and MDA in workers with and without occupational exposure to isocyanates. Upper reference limits on the background biomarker levels were calculated using the receiver operator characteristic curve method; the results are shown in Table 3-13. TDA was detected infrequently in unexposed persons (detection frequencies ranging from

2 to 15%), while MDA was detected in nearly all (97%) urinary and plasma samples (Sennbro et al. 2005).

Diamines may be present in the plasma and urine as a result of exposure to the corresponding diisocyanate or exposure to the diamine itself; thus, this biomarker is not specific to isocyanate exposure. Sabbioni et al. (2010, 2012) and Kumar et al. (2009) developed methods for measuring TDI and MDI adducts of albumin that are specific to isocyanates. Sabbioni et al. (2012) detected 2,4- and 2,6-TDI adducts with the lysine of albumin in blood samples taken from 10 workers 26 days after they were accidentally exposed to TDI (details of the exposure were not provided). Three lysine adducts were detected: N^{ε}-[({3-amino-4-methylphenyl}amino)carbonyl]-lysine (3A4MP-Lys); N^{ε}-[({5-amino-2-methylphenyl}amino)carbonyl]-lysine (5A2MP-Lys); and N^{ε}-[({3-amino-2-methylphenyl}amino)-carbonyl]-lysine (3A2MP-Lys). The adducts were detected at concentrations ranging from 29 to 269 fmol/mg. Repeat analysis of selected samples showed coefficients of variation ranging from 2.1 to 6.6% for the three adducts. Half-lives of the albumin adduct levels were estimated to be 21.7 days for 3A4MP-Lys, 40.3 days for 5A2MP-Lys, and 19.6 days for 3A2MP-Lys.

Sabbioni et al. (2010, 2016) likewise detected albumin adducts of MDI in workers exposed to MDI; the adducts were identified as N^{6}-[({4-[4-aminobenzyl]phenyl}amino)carbonyl]lysine (MDI-Lys) and N^{6}-[({4-[4-acetylaminobenzyl]phenyl}amino)carbonyl]lysine (AcMDI-Lys). The level of MDI-Lys was correlated with MDA in acid- and alkaline-hydrolyzed urine, but not with measurements of hemoglobin adducts of MDA. The authors (Sabbioni et al. 2010) noted that measurement of hemoglobin adducts only would have underestimated the number of exposed workers; only 27% of workers exhibited hemoglobin adducts of MDI, while albumin adducts were observed in 64% of workers.

In summary, recent exposure to diisocyanates may be reflected in TDA or MDA levels in acid- or alkaline-hydrolyzed urine or plasma, but these biomarkers may also be present in urine and plasma as a result of exposure to the diamines themselves (TDA and MDA). Background levels of TDA and MDA in urine and plasma should be considered in the interpretation of measured values from subjects with

Table 3-13. Upper Reference Limits for Biomarkers of Exposure to Toluene Diisocyanate and Methylenediphenyl Diisocyanate

Biomarker	Median[a] (μg/L)	Range[a] (μg/L)	Frequency of detection[a] (%)	Upper reference limit (μg/L)	Sensitivity (%)	Specificity (%)
Urinary 2,4-TDA	<0.1	<0.1–0.4	7	0.4	94	100
Plasma 2,4-TDA	<0.1	<0.1–0.1	2	0.1	100	100
Urinary 2,6-TDA	<0.1	<0.1–0.2	15	0.2	97	100
Plasma 2,6-TDA	<0.1	<0.1–0.1	2	0.2	99	100
Urinary MDA	0.2	<0.05–3.0	97	0.5	100	97
Plasma MDA	0.2	<0.05–0.4	97	0.4	88	100

[a]TDA and MDA measured in 120 unexposed workers from five workplaces in Sweden.

MDA = methylenediphenyl amine; TDA = toluene diamine

Source: Sennbro et al. 2005

unknown exposure. Finally, serum levels of albumin adducts of TDI or MDI are specific to diisocyanate exposure and, due to their longer half-life, may be useful in assessing exposure over the preceding weeks. These biomarkers have been shown to be useful for identifying exposure to TDI or MDI; however, no biomarkers have been identified that allow for quantification of exposure.

3.8.2 Biomarkers Used to Characterize Effects Caused by TDI and MDI

One of the prominent health effects associated with inhalation exposure to TDI or MDI is the induction of occupational asthma. Several tests have been developed to diagnosis occupational asthma; these include measurement of peak expiratory flow rate, nonspecific bronchial provocation testing, specific immunological testing, skin-prick testing, specific inhalational challenge testing, and nasal lavage testing (Jolly et al. 2015; Ott et al. 2007). With the exception of the specific immunological and specific inhalational challenge tests, these tests are not specific to TDI or MDI exposure. Although specific inhalational challenge testing is considered one of the better tests for diagnosing sensitizer-induced occupational asthma (Jolly et al. 2015; Ott et al. 2007; Vandenplas et al. 2014), the American College of Occupational and Environmental Medicine notes that it is a highly technical test and has the potential for inducing severe adverse effects, including fatalities (Jolly et al. 2015). Several investigators have evaluated the usefulness of specific immunological tests, TDI-/MDI-specific IgE and IgG levels, for diagnosing TDI-/MDI-induced occupational asthma. As discussed in Section 3.2.1.2, a number of occupational exposure studies have reported IgG- or IgE-specific antibodies to TDI-HSA in workers with TDI-induced asthma (Baur and Fruhmann 1981; Cvitanovic et al. 1989; Park and Nahm 1996; Park et al. 1999; Pezzini et al. 1984; Sharifi et al. 2013) or MDI-HSA in MDI workers (Hur et al. 2008; Pezzini et al. 1984; Tse et al. 1985; Zeiss et al. 1980). However, specific IgG or IgE antibodies were typically observed in a small percentage of TDI workers (16–57%). In a small study of MDI workers (Budnik et al. 2013), MDI-specific IgE antibodies were detected in four of seven workers with confirmed MDI-induced asthma, none of the four workers with hypersensitivity pneumonitis, and none of the six asymptomatic workers. In contrast, IgG antibody levels were detected in four of seven workers with asthma, four of four subjects with hypersensitivity pneumonitis, and one of six asymptomatic workers. In a review conducted by Wisnewski (2007), isocyanate-specific serum IgE has been found in up to 50% of workers. It is noted that isocyanate-specific IgE levels have a half-life of approximately 2 days and levels can drop below the detection limit following brief periods with no exposure (Wisnewski 2007). Palikhe et al. (2011) also noted that the prevalence of IgG antibodies was not a reliable biomarker because the prevalence was too low. This is less of an issue for IgG, which has a half-life of approximately 30 days. The American College of Occupational and Environmental Medicine concluded that there is insufficient

evidence to assess the usefulness of IgE testing for low molecular weight antigens (Jolly et al. 2015); it is noted that this recommendation is not specific to isocyanates.

Several studies have examined other biomarkers that could be used for early diagnosis of TDI-induced asthma. Significantly lower matrix metalloproteinase-9 (MMP-9) level and higher VEGF levels were found in workers with TDI-induced asthma, as compared to asymptomatic workers (Kim et al. 2011; Palikhe et al. 2011). The sensitivity and specificity of the MMP-9 were 79.7 and 80.0%, respectively (Kim et al. 2011). Combining several variables (MMP-9, VEGF, and interleukin-8) increased the sensitivity to 82.6%, but decreased the specificity to 75.8%. Kim et al. (2012) found that the levels of vitamin D-binding protein (VDBP) were significantly higher in workers with isocyanate-induced occupational asthma, as compared to asymptomatic workers from the same working environment, or in unexposed healthy subjects; the sensitivity and specificity was 69 and 81%, respectively. Ye et al. (2006) examined the usefulness of three cytokeratins (CK8, CK18, and CK19) for identifying TDI-induced asthma. Significantly higher IgG antibody levels of CK8, CK18, and CK19 were found in the workers with TDI-induced asthma as compared to asymptomatic workers, subjects with allergic asthma, and healthy subjects. The sensitivity and specificity for C8, CK18, and CK19 antibodies were 18.2 and 95.2%, 26.2 and 93.5%, and 26.2 and 93.5%, respectively.

3.9 INTERACTIONS WITH OTHER CHEMICALS

No studies were identified examining the influence of other chemical on the toxicity or toxicokinetics of TDI or MDI.

3.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to TDI or MDI than will most persons exposed to the same level of TDI or MDI in the environment. Factors involved with increased susceptibility may include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters result in reduced detoxification or excretion of TDI and MDI, or compromised function of organs affected by TDI and MDI. Populations who are at greater risk due to their unusually high exposure to TDI and MDI are discussed in Section 6.7, Populations with Potentially High Exposures.

There are data to suggest that there is a genetic susceptibility factor that may predispose certain individuals to develop occupational asthma as a result of exposure to TDI or MDI. Several investigators

have examined possible associations between genetic polymorphisms and diisocyanate-induced asthma. Vucesoy et al. (2012) demonstrated that genetic variants of antioxidant defense genes are associated with increased susceptibility to diisocyanate (TDI, MDI, or HDI)-induced asthma in a study of diisocyanate workers with confirmed occupational asthma, workers reporting respiratory symptoms who did not react to diisocyanate challenge, and asymptomatic HDI workers. Significant associations between diisocyanate-induced asthma and three types of variant genotypes (manganese superoxide dismutase [SOD2] rs4880, microsomal epoxide hydrolase [EPHX1] 2740171, and a glutathione S-transferase [GSTP1] rs1695) were noted. Blindow et al. (2015) also found greater responses to specific inhalation challenges among symptomatic isocyanate workers with GST1 deletions and a higher risk of developing IgE-mediated reactions in workers with GSTM1 deletions. In a study of 84 workers with TDI-induced occupational asthma, higher bronchial hyperresponsiveness was observed in TDI workers with asthma with polymorphisms of catenin alpha 3, alpha-T-catenin (CTNNA3) (Kim et al. 2009). Similar results were observed in a second study of diisocyanate workers; increased risks of CTNNA3 polymorphisms were found among workers with occupational asthma, but not among workers without asthma (Bernstein et al. 2013).

Several studies have examined the frequency of human leukocyte antigen class II (HLA) haplotypes among with TDI-induced asthma. Higher frequencies of haplotypes DRB1*15-DPB1*05 (Kim et al. 2006) and DRB1*1501-DQB1*0602-DPB1*0501 (Choi et al. 2009) and the allele DQB1*0503 and the allelic combination of DQB1*0201/0301 (Bignon et al. 1994) were found among workers with TDI-induced asthma. Similarly, Yucesoy et al. (2014) found increases in the susceptibility to diisocyanate-induced asthma among diisocyanate workers with single nucleotide polymorphisms in HLA-E HLA-DPB1, HLA-DOA, or HLA-DQA2 genes. Both Kim et al. (2006) and Beghe et al. (2004) found an alteration in the distribution of HLA class I antigens in subjects with TDI-induced asthma. Ye et al. (2010) found no differences in the allelic, genotypic, or haplotypic frequencies of beta 2-adrenergic receptor gene (ADRB2) polymorphisms among TDI workers with occupational asthma, asymptomatic workers, or controls with no TDI exposure. However, significant associations between two ADRB2 polymorphisms (Arg16Gly and Arg173Arg single nucleotide polymorphisms) and the prevalence of specific IgE antibodies to TDI-HSA were found among TDI workers and a significantly higher TDI-HSA specific IgE sensitization was found in workers with the ADRB2 ht1/ht1 homozygote. Broberg et al. (2008) found that an increased risk of eye symptoms was associated with the CYP1A1*2A variant and an increased risk of wheezing was associated with CYP1A1*2B. Studies by Yucesoy et al. (2015, 2016) identified several gene and single nucleotide polymorphisms that may be associated with susceptibility to diisocyanate-induced asthma. Single nucleotide polymorphisms mapping to several genes including

TNFα, TGB1, PTGS1, PTGS2, HERC2, CDH17, and ODZ3 have been found to contribute to diisocyanate-induced asthma susceptibility.

Studies examining clinical features of subjects with suspected occupational asthma found no differences in the incidence of atopy among workers who reacted to a TDI challenge and workers not reacting to the TDI challenge (Mapp et al. 1988; Moscato et al. 1991; Paggiaro et al. 1984). Significantly fewer subjects reacting to TDI were found to be current smokers; although a higher percentage of ex-smokers were found among the TDI reactors (Moscato et al. 1991; Paggiaro et al. 1984). One study found a higher number of workers with positive skin tests to common allergens among the reactors (Paggiaro et al. 1984).

3.11 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to TDI and MDI. Because some of the treatments discussed may be experimental and unproven, this section should not be used as a guide for treatment of exposures to TDI and MDI. When specific exposures have occurred, poison control centers, board certified medical toxicologists, board-certified occupational medicine physicians and/or other medical specialists with expertise and experience treating patients overexposed to TDI and MDI can be consulted for medical advice. The following texts provide specific information about treatment following exposures to TDI and MDI:

Blanc PD. 2018. Section II: Specific poisons and drugs: Diagnosis and treatment: Isocyanates. In: Poisoning & drug overdose. 7th ed. McGraw-Hill Education. https://accessmedicine.mhmedical.com/book.aspx?bookid=2284. May 30, 2018.

Leikin JB, Paloucek FP. 2008. Methylene diisocyanate and toluene diisocyanate. In: Poisoning and toxicology handbook. 4th ed. Boca Raton, FL: CRC Press, 824; 857-858.

Vena J, McKay C. 2007. Isocyanates and related compounds. In: Haddad and Winchester's clinical management of poisoning and drug overdose. 4th ed. Philadelphia, PA: Saunders Elsevier, 1317-1322.

Additional relevant information can be found in the front section of this profile under QUICK REFERENCE FOR HEALTH CARE PROVIDERS.

3.11.1 Reducing Peak Absorption Following Exposure

No studies were identified that examined reducing peak absorption of TDI or MDI following exposure.

3.11.2 Reducing Body Burden

No studies were identified that examined reducing body burden of TDI or MDI following exposure.

3.11.3 Interfering with the Mechanism of Action for Toxic Effects

Several studies have examined the effectiveness of asthma medication or corticosteroid medication inhibiting the asthmatic reaction and nonspecific airway reactivity associated with TDI exposure in sensitized individuals. An acute treatment course with ketotifen, atropine, slow-release verapamil, or cromolyn did not prevent dual and/or late asthmatic reactions in TDI-sensitized individuals receiving an inhalation challenge with TDI (Mapp et al. 1987; Paggiaro et al. 1987; Tossin et al. 1989). Ketotifen, verapamil, and cromolyn also did not alter bronchial responsiveness to methacholine (Mapp et al. 1987; Tossin et al. 1989). In contrast, administration of beclomethasone or prednisone prevented the asthmatic reaction and airway hyperresponsiveness following a TDI inhalation challenge (Boschetto et al. 1987; Mapp et al. 1987). Slow-release theophylline partially inhibited the immediate and late asthmatic reaction to TDI but did not alter airway hyperresponsiveness (Mapp et al. 1987). In subjects receiving a 5-month treatment with beclomethasone, there was an improvement in the response to TDI inhalation challenge 1 month post-treatment; however, a similar improvement was found in untreated controls (Maestrelli et al. 1993). However, beclomethasone treatment did improve airway hyperresponsiveness to methacholine, a finding not observed in the untreated controls.

3.12 ADEQUACY OF THE DATABASE

Section 104(I)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of TDI and MDI is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the adverse health effects (and techniques for developing methods to determine such health effects) of TDI and MDI.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health risk assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

3.12.1 Existing Information on Health Effects of TDI and MDI

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to TDI and MDI are summarized in Figure 3-6 and 3-7, respectively. The purpose of these figures is to illustrate the existing information concerning the health effects of TDI and MDI. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not necessarily imply anything about the quality of the study or studies, nor should missing information in this figure be interpreted as a "data need". A data need, as defined in ATSDR's *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (ATSDR 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

3.12.2 Identification of Data Needs

Acute-Duration Exposure. Although several case reports of single exposures to TDI (Axford et al. 1976; Le Quesne et al. 1976; Schmidt-Nowara et al. 1973; Singer and Scott 1987; Vandenplas et al. 1992; Yoshizawa et al. 1989) and MDI (Chang and Karol 1984; Suojalehto et al. 2011) have reported respiratory effects following an acute exposure, they did not include monitoring data. Several acute exposure experimental studies have examined lung function following a single exposure to TDI (Chester et al. 1979; Vandenplas et al. 1999). Animal studies have examined the toxicity of TDI (Aoyama et al. 1994; Arts et al. 2008; Buckley et al. 1984; Gagnaire et al. 1996; Gordon et al. 1985; Johnson et al. 2007; Marek et al. 1999; Sangha and Alarie 1979; Wong et al. 1985; Zissu 1995) and MDI (Marek et al. 1999); the observed effects on the respiratory system include histological damage to the nasal cavity and lungs and increased airway responsiveness. In general, these studies did not examine end points outside of the target tissues, the respiratory tract. The database for TDI was considered adequate for derivation of an acute-duration inhalation MRL; however, a repeated exposure study examining lung function in humans would provide support for this MRL. The database was not considered adequate for derivation of an acute-duration inhalation MRL for MDI and studies are needed that provide concentration-response data. Acute-duration data on the toxicity of TDI following oral exposure are limited to single and 14-day exposure studies that found increases in mortality and decreases in body weight gain (NTP 1986); other

Figure 3-6. Existing Information on Health Effects of Toluene Diisocyanate

	Systemic									
	Death	Acute	Intermediate	Chronic	Immunologic/Lymphoretic	Neurologic	Reproductive	Developmental	Genotoxic	Cancer
Inhalation	●	●	●	●	●	●			●	●
Oral										
Dermal										

Human

	Systemic									
	Death	Acute	Intermediate	Chronic	Immunologic/Lymphoretic	Neurologic	Reproductive	Developmental	Genotoxic	Cancer
Inhalation	●	●	●	●	●		●	●	●	●
Oral	●	●	●	●	●					●
Dermal										

Animal

● Existing Studies

Figure 3-7. Existing Information on Health Effects of Methylenediphenyl Diisocyanate

	Death	Systemic								
		Acute	Intermediate	Chronic	Immunologic/Lymphoretic	Neurologic	Reproductive	Developmental	Genotoxic	Cancer
Inhalation		●	●	●	●					
Oral										
Dermal										

Human

	Death	Systemic								
		Acute	Intermediate	Chronic	Immunologic/Lymphoretic	Neurologic	Reproductive	Developmental	Genotoxic	Cancer
Inhalation	●	●	●	●						●
Oral										
Dermal										

Animal

● Existing Studies

end points were not examined. No studies examined the acute-duration oral toxicity of MDI. Studies that examine the dermal toxicity of TDI and MDI are needed, particularly since ocular and dermal irritation has been reported in workers exposed to airborne TDI and MDI.

Intermediate-Duration Exposure. Occupational exposure studies typically involve chronic-duration exposure; however, there is suggestive evidence that effects can occur after several months of exposure (Clark et al. 1998). Three studies have examined the toxicity of TDI to the respiratory tract of animals following intermediate-duration exposure (Matheson et al. 2005; Wong et al. 1985; Zissu 1995). The studies reported histological damage in the nasal cavity and lungs and an increase in airway hyperresponsiveness. One study examined the intermediate-duration toxicity of MDI in animals (Marek et al. 1999), but the study was limited to the examination of airway hyperresponsiveness and did not include a histological examination of the respiratory tract. Although the database was considered inadequate for the derivation of intermediate-duration inhalation MRLs, the chronic-duration inhalation MRLs could be used for intermediate duration.

Chronic-Duration Exposure and Cancer. The chronic toxicity of TDI and MDI has been extensively investigated in occupational studies of production facilities and polyurethane manufacturing facilities and in workers applying polyurethane varnishes (Bodner et al. 2001; Burge 1982; Clark et al. 1998, 2003; Diem et al. 1982; Jang et al. 2000; Liss et al. 1988; Mapp et al. 1998; Moscato et al. 1991; Musk et al. 1982; Ott et al. 2000; Paggiaro et al. 1986, 1993; Sulotto et al. 1990; Zammit-Tabona et al. 1983). These studies provide strong evidence that the respiratory tract is the most sensitive target of TDI or MDI toxicity. Longitudinal studies of TDI workers provide sufficient monitoring data to allow for the derivation of a chronic-duration inhalation MRL (Clark et al. 1998; Diem et al. 1982). Monitoring data in the MDI studies were not considered adequate. The chronic toxicity of TDI and MDI has also been investigated in two animal studies (Loeser 1983; Reuzel et al. 1994); these studies also identify the respiratory tract as the most sensitive target. A chronic-duration rat study (Reuzel et al. 1994) was used to derive a chronic-duration inhalation MRL for MDI. Data on the chronic toxicity of orally administered TDI was investigated by NTP (1986). No long-term studies on the dermal toxicity of TDI or MDI were located.

There are limited human data on the carcinogenicity of TDI or MDI. Three studies of polyurethane foam manufacturing workers provide some suggestive evidence of an increased lung cancer risk, but the association with diisocyanates was not established (Mikoczy et al. 2004; Schnorr et al. 1996; Sorahan and Nichols 2002). No significant increases in lung cancer were observed in animals following TDI (Loeser

1983) or MDI (Reuzel et al. 1994) exposure. Increases in tumor incidence were observed in a chronic-duration gavage study of TDI (NTP 1986). The relevance of the findings in this gavage study to humans exposed to TDI via ingestion has been questioned due to likely toxicokinetic differences between ingestion and gavage administration of this very reactive compound. Additional studies are needed to address these concerns.

Genotoxicity. Both TDI and MDI have been tested for genotoxicity in prokaryotic and mammalian systems *in vitro*. TDI is not stable in most *in vitro* test systems; TDA is formed rapidly in the vehicles used in available genotoxicity tests, and it has been suggested that TDA is responsible for positive mutagenicity tests of TDI (Seel et al. 1999). Mixed results have been found in *in vivo* tests for genotoxic end points. However, the interpretation of the results of some of the studies is limited by methodological problems or poor reporting. Additional *in vivo* studies would facilitate assessing the interpretation of the genotoxicity data.

MDI also degrades to MDA in *in vitro* test systems using DMSO or EGDE, but at a much slower rate than TDI does. When MDI was tested for genotoxicity in EGDE (in which MDI is more stable), the results were negative, while positive results were seen when DMSO was used as the solvent (Herbold et al. 1998). There is little information on genotoxicity of MDI in humans or non-human mammalian systems tested *in vivo*.

Reproductive Toxicity. The available data on the reproductive toxicity of TDI consists of a 2-generation study in rats exposed via inhalation (Tyl et al. 1999b) in which no effects on reproductive parameters were observed. No data on the reproductive toxicity of MDI in humans or animals exposed by any route were located in the available literature.

Developmental Toxicity. A single developmental toxicity study of TDI in rats exposed via inhalation (Tyl et al. 1999a) showed poorly ossified cervical centra at an exposure concentration that also resulted in maternal toxicity; no other exposure-related effects were seen in the offspring. Similarly, there is one study of MDI developmental toxicity in rats exposed via inhalation (Buchsmann et al. 1996); an increased incidence of litters with asymmetric sternebrae was the only treatment-related effect. There are no data on the developmental toxicity of TDI or MDI via oral or dermal exposure routes.

Immunotoxicity. Available literature did not include human or animal studies evaluating immunological effects after exposure to TDI or MDI. Occupational asthma observed in TDI (Mapp et al.

1988; Moller et al. 1986; Moscato et al. 1991; Padoan et al. 2003; Paggiaro et al. 1984, 1986; Saetta et al. 1995) and MDI (Bonauto et al. 2005; Burge 1982; Chang and Karol 1983; Hur et al. 2008; Liss et al. 1988; Suojalehto et al. 2011; Woellner et al. 1997; Zammit-Tabona et al. 1983) workers may be the result of immunotoxicity; however, additional research is needed to identify the mechanism of toxicity.

Neurotoxicity. The database for diisocyanates (including both TDI and MDI) does not include any information on neurological effects of chronic-duration exposure. Human and/or animal studies are warranted given the suggestive evidence for long-term impairment after acute exposure (Le Quesne et al. 1976; Singer and Scott 1987). In addition, no information on potential neurotoxicity of MDI was located; animal and/or mechanistic studies are needed to evaluate this end point.

Epidemiological and Human Dosimetry Studies. Numerous studies have examined the toxicity of TDI (Bodner et al. 2001; Clark et al. 1998, 2003; Diem et al. 1982; Mapp et al. 1998; Moscato et al. 1991; Ott et al. 2000; Paggiaro et al. 1986, 1993) and MDI (Burge 1982; Jang et al. 2000; Liss et al. 1988; Musk et al. 1982; Sulotto et al. 1990; Zammit-Tabona et al. 1983) in occupationally exposed subjects; additionally, two studies have examined possible adverse health outcomes in residents living near TDI sources (Nuorteva et al. 1987; Wilder et al. 2011). These studies provide strong evidence that the respiratory tract is the most sensitive target resulting in occupational asthma, respiratory symptoms, and impaired lung function. However, many studies are lacking reliable monitoring data, particularly in studies examining workers exposed to MDI. Several occupational exposure studies have also assessed the potential association between inhalation exposure to diisocyanates and cancer (Mikoczy et al. 2004; Schnorr et al. 1996; Sorahan and Nichols 2002) and found suggestive evidence between work in the polyurethane foam manufacturing industry and lung cancer in female workers, but an association with diisocyanate exposure was not established. Significant limitations of all three studies included the lack of control for confounding factors, such as smoking and alcohol consumption, and coexposure to mixtures of compounds including those other than diisocyanates. Continued epidemiological research focused on improving exposure estimates (for example, using biomarkers of exposure) and control for confounding is recommended.

Biomarkers of Exposure and Effect.

Exposure. Biomarkers of exposure to TDI and MDI include the diamine hydrolysis products (TDA and MDA) as well as hemoglobin and albumin adducts of the isocyanates. Improvements in the standardization of methods used to pretreat biological samples (e.g., acid- and alkaline-hydrolysis) prior

to analysis could help to refine the predictive relationship between levels of metabolites or adducts in the samples and exposure.

Effect. Given the continued decline in lung function and the delay in recovery when TDI- or MDI-sensitized workers remain in jobs involving TDI/MDI exposure (Banks et al. 1990; Mapp et al. 1988; Padoan et al. 2003; Paggiaro et al. 1984; Park and Nahm 1997), biomarkers that would allow for early detection of sensitization are needed. Investigators have identified several potential biomarkers of effect including MMP-9 (Kim et al. 2011), VEGF (Kim et al. 2011), cytokeratins (Ye et al. 2006), which may be useful for early detection of occupational asthma. Additional studies in sensitized workers are needed to evaluate the usefulness of these biomarkers and others for early detection of TDI and/or MDI sensitization.

Absorption, Distribution, Metabolism, and Excretion. Human and animal data suggest that TDI and MDI are absorbed to some extent via all exposure routes. Both TDI and MDI combine readily with biological macromolecules including hemoglobin, albumin, and others. As a consequence of their reactivity, these compounds or their reaction products are often found at higher concentrations at the site of entry into the body early in exposure, and may continue to be distributed from the site of entry long after exposure has terminated. Once in the body, conjugated TDI and MDI are distributed to a large number of tissues, albeit at low levels.

The metabolic fate of TDI depends on the exposure route. After oral exposure, TDI is hydrolyzed in the gastrointestinal tract to TDA, and subsequently either absorbed and metabolized further or reacted with unhydrolyzed TDI to form polyurea polymers that pass unabsorbed through the gastrointestinal tract. However, after inhalation exposure, the primary fate of TDI appears to be conjugation reactions; little TDI, if any, is hydrolyzed to TDA. In humans exposed experimentally, urinary excretion of the TDI metabolite TDA exhibits a biphasic pattern, with an initial rapid phase followed by a slower phase. The primary route of TDI elimination after inhalation or oral exposure of rats is via the feces, which may include material absorbed and excreted via the bile.

Few data on the metabolism and elimination of MDI were identified in the available literature. Like TDI, MDI is excreted primarily in the feces of rats after inhalation exposure, and there is evidence for biliary excretion of MDI. As there are no data on the pharmacokinetic behavior of MDI after oral exposure in humans or animals, research on the route-dependence of MDI metabolism would be particularly beneficial.

PBPK models of TDI and MDI pharmacokinetics have not yet been developed.

Comparative Toxicokinetics. There are few data on species differences in the toxicokinetics of TDI, and no data on this issue for MDI. Research to assess species differences in MDI toxicokinetics would provide important information regarding the extrapolation from animal toxicity information to human effects.

Methods for Reducing Toxic Effects. Several investigators have examined the effectiveness of asthma medication or corticosteroids for treating occupational asthma induced by TDI (Boschetto et al. 1987; Maestrelli et al. 1993; Mapp et al. 1987; Paggiaro et al. 1987; Tossin et al. 1989). Although some beneficial effects were observed when asthmatic subjects were challenged with TDI during the treatment course (Boschetto et al. 1987; Mapp et al. 1987), long-term benefits have not been found (Maestrelli et al. 1993). Since a large number of subjects with occupational asthma do not recover even after exposure cessation, additional research is needed on the treatment of TDI- or MDI-induced occupational asthma. In addition, studies are needed to assess the treatment of other TDI- or MDI-related health effects such as decreased lung function.

Children's Susceptibility. Data needs relating to both prenatal and childhood exposures, and developmental effects expressed either prenatally or during childhood, are discussed in detail in the Developmental Toxicity subsection above.

No information on children's susceptibility to TDI or MDI toxicity was identified and it is not known if children would be more susceptible to the irritating properties of TDI or MDI. Although TDI/MDI exposure primarily occurs in the workplace, communities living near TDI or MDI sources or the commercial use of products containing uncured TDI or MDI can result in exposure to children. Two studies have examined communities living near a TDI source (Nuorteva et al. 1987; Wilder et al. 2011), one of these studies included children (Nuorteva et al. 1987); however, the data were not analyzed by age group. Given the potential for exposure, studies are needed to address this data gap.

Child health data needs relating to exposure are discussed in Section 6.8.1, Identification of Data Needs: Exposures of Children.

3.12.3 Ongoing Studies

The following ongoing studies pertaining to TDI and MDI have been identified in the National Institutes of Health (NIH) Research Portfolio Online Reporting Tools (RePORTER 2016) database.

Adam Wisnewski at L2 Diagnostics, LLC is developing two immunoassays that can be used to biomonitor MDI exposure in the workplace. The two biomarkers being investigated are MDI-specific IgG antibodies and MDI albumin conjugates

4. CHEMICAL AND PHYSICAL INFORMATION

4.1 CHEMICAL IDENTITY

Information regarding the chemical identity of TDI and MDI is provided in Table 4-1.

TDI and MDI have widespread commercial use due to their reactivity and versatility. TDI and MDI and their related polyisocyanates make up >90% of the commercial market (EPA 2011a). Commercial-grade TDI is made up of an 80:20 mixture of isomers 2,4- and 2,6-TDI and represents >95% of TDI industrial use (NIOSH 1989).

Commercial-grade MDI consists of several isomers, including 4,4'-, 2,4'-, and 2,2'-MDI, as well as oligomers and polymeric compounds. The principal commercial product of MDI is made up of a mixture of all of these components, with a typical composition in the range of 40–50% 4,4'-MDI, 2.5–4.0% 2,4'-MDI, and 0.1–0.2% 2,2'-MDI; the remainder is oligomers. 4,4'-MDI is the most commercially common isomer and is referred to as pure MDI (IARC 1999a).

4.2 PHYSICAL AND CHEMICAL PROPERTIES

Information regarding the physical and chemical properties of TDI and MDI is provided in Table 4-2.

Table 4-1. Chemical Identity of Toluene Diisocyanate and Methylenediphenyl Diisocyanate[a]

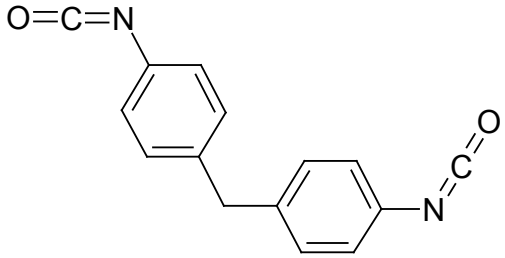
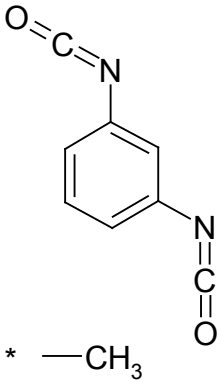
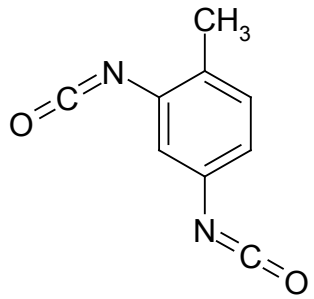
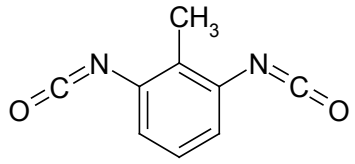
Characteristic	Methylenediphenyl diisocyanate	Toluene diisocyanate
Chemical name	Benzene, 1,1'-methylenebis(4-isocyanato-)	Benzene, 1,3-diisocyanato-methyl-
Synonyms(s)	4,4'-Methylenedi(phenyl isocyanate); 4,4'-methylenebis(phenyl isocyanate); 4,4'-methylenediphenyl diisocyanate; bis(4-isocyanatophenyl)methane; isocyanic acid, methylenedi-p-phenylene ester; MDI	Diisocyanatotoluene; isocyanic acid, methylphenylene ester; methylphenylene isocyanate; TDI
Registered trade name(s)	Caradate 30; Desmodur 44; Hylene M; Isonate M; Nacconate	TDI 80/20; Mondur TD; Hylene T; Rubinate TDI; Niax TDI
Chemical formula	$C_{15}H_{10}N_2O_2$	$C_9H_6N_2O_2$
Chemical structure		
Identification numbers:		
CAS registry	101-68-8 9016-87-9 (polymeric MDI)	26471-62-5 (mixture of 2,4-TDI and 2,6-TDI)
NIOSH RTECS	NQ9350000[b]	NQ9490000[e]
EPA hazardous waste	No data	U223
OHM/TADS	No data	No data
DOT/UN/NA/IMCO shipping	UN 2489[c] IMO 6.1[d]	UN 2078 IMO 6.1
HSDB	2630	6003
NCI	C50668	No data

Table 4-1. Chemical Identity of Toluene Diisocyanate and Methylenediphenyl Diisocyanate[a]

Characteristic	2,4-Toluene diisocyanate	2,6-Toluene diisocyanate
Chemical name	Benzene, 2,4-diisocyanato-1-methyl	Benzene, 1,3-diisocyanato-2-methyl
Synonyms(s)	2,4-Diisocyanatotoluene; isocyanic acid, 4-methyl-m-phenylene ester; 4-methyl-phenylene diisocyanate; toluene-2,4-diisocyanate; 2,4-TDI	2,6-Diisocyanatotoluene; 2,6-diisocyanto-1-methylbenzene; 2-methyl-phenylene diisocyanate; toluene-2,6-diisocyanate; 2,6-TDI
Registered trade name(s)	Hylene T; Mondur TDS	Hylene T; Mondur TDS
Chemical formula	$C_9H_6N_2O_2$	$C_9H_6N_2O_2$
Chemical structure		
Identification numbers:		
CAS registry	584-84-9	91-08-7
NIOSH RTECS	CZ6300000[f]	CZ6310000[g]
EPA hazardous waste	U223	U223
OHM/TADS	No data	No data
DOT/UN/NA/IMCO shipping	UN 2206/2207/2478/3080[d] IMO 6.1	UN 2207[d] IMO 6.1
HSDB	874	5272
NCI	C50533	No data

[a]All information obtained from HSDB (2012), unless otherwise noted.
[b]RTECS 2009a
[c]ChemSpider 2013
[d]Lewis 2004
[e]NIOSH 1989
[f]RTECS 2009b
[g]RTECS 2009c

CAS = Chemical Abstracts Services; DOT/UN/NA/IMCO = Department of Transportation/United Nations/North America/Intergovernmental Maritime Dangerous Goods Code; EPA = Environmental Protection Agency; HSDB = Hazardous Substances Data Bank; NCI = National Cancer Institute; NIOSH = National Institute for Occupational Safety and Health; OHM/TADS = Oil and Hazardous Materials/Technical Assistance Data System; RTECS=Registry of Toxic Effects of Chemical Substances

Table 4-2. Physical and Chemical Properties of Toluene Diisocyanate and Methylenediphenyl Diisocyanate[a]

Property	Methylenediphenyl diisocyanate	Toluene diisocyanate
Molecular weight	250.252	174.16
Color	Light-yellow	Clear, colorless to pale yellow
Physical state	Solid/crystals	Liquid
Melting point	37°C	11–14°C
Boiling point	196°C (at 5 mm Hg)	250°C
Density:		
at 25°C	No data	1.22 g/mL
at 70°C	1.197 g/cm^3	No data
Odor	Odorless	Pungent
Odor threshold:		
Water	Not applicable[b]	Not applicable[b]
Air	No data	360–920 μg/m^3
Solubility:		
Water at 25°C	Not applicable[b]	Not applicable[b]
Organic solvents	Soluble in acetone, benzene, kerosene, and nitrobenzene	Miscible with alcohol, ether, acetone, carbon tetrachloride, benzene, and kerosene
Partition coefficients:		
Log K_{ow}	Not applicable[b]	Not applicable[b]
Log K_{oc}	Not applicable[b]	Not applicable[b]
Vapor pressure at 25°C	5.1x10^{-6} mm Hg	2.30x10^{-2} mm Hg
Henry's law constant at 25°C	Not applicable[b]	Not applicable[b]
Autoignition temperature	No data	No data
Flashpoint	202°C (open cup)	132°C (closed cup)
Flammability limits	Flammable[c]	0.9–9.5 volume %
Conversion factors	1 ppm=10.24 mg/m^3	No data
Explosive limits	No data	Explosive (vapor)

Table 4-2. Physical and Chemical Properties of Toluene Diisocyanate and Methylenediphenyl Diisocyanate[a]

Property	2,4-Toluene diisocyanate	2,6-Toluene diisocyanate
Molecular weight	174.16	174.16
Color	Colorless to pale yellow	Colorless to pale yellow
Physical state	Liquid	Liquid
Melting point	20.5°C	18.3°C
Boiling point	251°C	129–133°C (at 18 mm Hg)
Density:		
at 20°C/4°C	1.2244	No data
at 25°C	No data	1.22
Odor	Sharp, pungent	Pungent
Odor threshold:		
Water	Not applicable[b]	Not applicable[b]
Air	0.4–2.14 ppm	No data
Solubility:		
Water at 25°C	Not applicable[b]	Not applicable[b]
Organic solvents	Miscible with alcohol (decomposition), ether, acetone, benzene, carbon tetrachloride, chlorobenzene, diglycol monomethyl ether, kerosene, and olive oil	Soluble in acetone and benzene
Partition coefficients:		
Log K_{ow}	Not applicable[b]	Not applicable[b]
Log K_{oc}	Not applicable[b]	Not applicable[b]
Vapor pressure at 25°C	8.0×10^{-3} mm Hg (20°C)	2.09×10^{-2} mm Hg
Henry's law constant at 25°C	Not applicable[b]	Not applicable[b]
Autoignition temperature	620°C	No data
Flashpoint	132°C (open cup)[c]	No data
Flammability limits	0.9–9.5 volume %	Flammable
Conversion factors	No data	1 mg/m^3=0.14 ppm
Explosive limits	Explosive (vapor)	No data

[a]All information obtained from HSDB (2012), unless otherwise noted.
[b]Diisocyanates hydrolyze rapidly in water; therefore, these end points are not applicable.
[c]Lewis 2004

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5. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

5.1 PRODUCTION

TDI is manufactured via the dinitration of toluene with mixed acid to produce a mixture of 2,4- and 2,6-dinitro isomers in a 80:20 ratio. Catalytic reduction of these isomers under hydrogen pressure forms the corresponding diamines, which are then treated with phosgene to yield TDI, made up of an 80:20 mixture of isomers 2,4- and 2,6-TDI (HSDB 2012).

MDI is produced through a two-step process starting with the condensation reaction between aniline and formaldehyde in the presence of hydrochloric acid to yield MDA, followed by the phosgenation to MDI. The production of polymeric MDI also proceeds via this reaction, with the percent distribution of homologues and isomers being dependent on the ratio of aniline to formaldehyde, the acid concentration, and the reaction conditions (HSDB 2012).

The worldwide production of polyurethanes was around 15.9 million tons in 2007, which corresponds to a total consumption of 1.9 million tons of TDI (Geens et al. 2012). The worldwide production volume of MDI in 2008 was approximately 1.4 million tons (Gries and Leng 2013). Also in 2008, the demand for pure MDI and polymeric MDI was 192.1 and 1,418 million pounds, respectively, in the United States (EPA 2011a). The demand for TDI in 2008 in the United States was 425.2 million pounds (EPA 2011b). 2,4-TDI, 2,6-TDI, and 4,4'-MDI are listed by the EPA as High Production Volume (HPV) chemicals. Chemicals listed under the HPV Challenge Program were produced or imported into the United States in quantities >1 million pounds in 1990 and/or 1994 (HSDB 2012). The aggregated national production volumes reported for 2,4-TDI, 2,6-TDI, and 4,4'-MDI under the EPA's 2010 Inventory Update Rule were 10–<50, <500,000, and 100–<500 million pounds (EPA 2010). TDI (mixed isomers) had a reported aggregated national production volume of ≥1 billion pounds (EPA 2010).

TDI (mixed isomers), 2,4-TDI, and 2,6-TDI are chemicals that manufacturing and processing facilities would be required to report under Section 313 of the Emergency Planning and Community Right-to-Know Act (Title III of the Superfund Amendments and Reauthorization Act of 1986 [SARA]) (EPA 1998a). Tables 5-1, 5-2, and 5-3 list the production year, number of facilities, the state where each facility is located, and the range (in pounds) for each domestic manufacturer that reported the production or formulation of TDI (mixed isomers), 2,4-TDI, and 2,6-TDI, respectively in 2016 (TRI16 2017). The TRI category diisocyanates contains data for MDI and 20 other diisocyanates (not including TDI); however, since there is no way to parse out the data for MDI separately, it was not included.

Table 5-1. Facilities that Produce, Process, or Use Toluene Diisocyanate (Mixed Isomers)

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
AR	1	100,000	999,999	6
AZ	1	No data	No data	No data
CA	11	100	9,999,999	6, 7, 8, 11
DE	2	10,000	99,999	6, 7
FL	3	10,000	999,999	6, 7
GA	6	10,000	999,999	6
IA	2	10,000	999,999	6, 7
IL	3	1,000	999,999	6, 7, 12
IN	6	1,000	9,999,999	6, 7
KS	2	1,000	9,999,999	6
KY	2	100,000	49,999,999	6, 9
LA	3	100,000	9,999,999	1, 4, 6, 12
MA	4	10,000	9,999,999	6, 7
MD	2	100,000	999,999	6, 7
ME	2	10,000	99,999	6
MI	5	10,000	9,999,999	6, 7, 9, 10, 11
MN	1	1,000	9,999	6, 7, 8
MO	5	100,000	999,999	6
MS	6	100,000	9,999,999	6, 7
NC	11	10,000	9,999,999	6, 7
NH	1	1,000	9,999	6
NJ	7	10,000	999,999	6, 7
NM	2	100,000	999,999	6, 7
OH	8	1,000	999,999	6, 7, 8, 9, 12
OR	1	100,000	999,999	6
PA	7	1,000	999,999	6, 7
PR	1	No data	No data	No data
SC	2	10,000	99,999	6
TN	4	1,000	999,999	6, 7, 9
TX	14	1,000	9,999,999	1, 3, 6, 7, 12
VA	4	100,000	9,999,999	6, 7, 9, 12
WA	2	10,000	999,999	6, 7

Table 5-1. Facilities that Produce, Process, or Use Toluene Diisocyanate (Mixed Isomers)

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
WI	2	100,000	999,999	6, 7
WV	1	1,000,000	9,999,999	6, 7, 9

[a]Post office state abbreviations used.
[b]Amounts on site reported by facilities in each state.
[c]Activities/Uses:

1. Produce
2. Import
3. Onsite use/processing
4. Sale/Distribution
5. Byproduct
6. Impurity
7. Reactant
8. Formulation Component
9. Article Component
10. Repackaging
11. Chemical Processing Aid
12. Manufacturing Aid
13. Ancillary/Other Uses
14. Process Impurity

Source: TRI16 2017 (Data are from 2016)

Table 5-2. Facilities that Produce, Process, or Use 2,4-Toluene Diisocyanate

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
AL	1	10,000	99,999	7
AR	2	100,000	999,999	9, 12
CO	1	1,000,000	9,999,999	6, 8
CT	1	1,000	9,999	6
GA	2	100,000	999,999	10
IA	1	1,000	9,999	10
IL	1	No data	No data	No data
IN	2	1,000	999,999	6
KS	1	No data	No data	No data
KY	1	10,000	99,999	6
MA	1	10,000	99,999	6
MD	1	1,000	9,999	6, 7
MI	5	10,000	999,999	6, 7, 11
MN	1	10,000	99,999	12
MO	2	10,000	99,999	6, 7, 12
MS	4	0	9,999,999	6, 7, 12
NC	1	100,000	999,999	6
NE	1	100,000	999,999	6
NJ	3	10,000	99,999	6
NY	1	10,000	99,999	6, 7
OH	5	1,000	99,999	6, 7, 8, 12
PA	4	1,000	999,999	6, 7, 8
RI	1	No data	No data	No data
TN	2	1,000	999,999	6, 10, 11
TX	3	1,000	9,999,999	9, 12
UT	1	10,000	99,999	12
VA	1	10,000	99,999	8
WI	2	0	99	12
WV	1	100,000	999,999	2, 3, 7

[a]Post office state abbreviations used.
[b]Amounts on site reported by facilities in each state.
[c]Activities/Uses:

1. Produce
2. Import
3. Onsite use/processing
4. Sale/Distribution
5. Byproduct
6. Impurity
7. Reactant
8. Formulation Component
9. Article Component
10. Repackaging
11. Chemical Processing Aid
12. Manufacturing Aid
13. Ancillary/Other Uses
14. Process Impurity

Source: TRI16 2017 (Data are from 2016)

Table 5-3. Facilities that Produce, Process, or Use 2,6-Toluene Diisocyanate

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
AR	1	10,000	99,999	12
CO	1	100,000	999,999	6, 8
GA	1	10,000	99,999	10
IL	1	No data	No data	No data
IN	1	10,000	99,999	6
KS	1	No data	No data	No data
MA	1	1,000	9,999	6
MD	1	1,000	9,999	6, 7
MI	4	10,000	999,999	6, 7, 8
MO	2	1,000	99,999	6, 7
MS	2	10,000	9,999,999	6, 7
NE	1	10,000	99,999	6
OH	5	100	99,999	6, 7, 8, 12
PA	1	10,000	99,999	6, 7, 1
TN	2	1,000	999,999	6, 7, 10, 11
TX	1	No data	No data	No data
WI	2	0	99	12
WV	1	10,000	99,999	2, 3, 6, 7

[a]Post office state abbreviations used.
[b]Amounts on site reported by facilities in each state.
[c]Activities/Uses:

1. Produce
2. Import
3. Onsite use/processing
4. Sale/Distribution
5. Byproduct
6. Impurity
7. Reactant
8. Formulation Component
9. Article Component
10. Repackaging
11. Chemical Processing Aid
12. Manufacturing Aid
13. Ancillary/Other Uses
14. Process Impurity

Source: TRI16 2017 (Data are from 2016)

Table 5-4. Facilities that Produce, Process, or Use Diisocyanates

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
AL	32	1,000	9,999,999	1, 3, 4, 6, 7, 8, 10, 11, 12
AR	13	0	999,999	2, 4, 6, 7
AZ	12	1,000	999,999	6, 10
CA	63	100	9,999,999	2, 4, 6, 7, 8, 9, 10, 11
CO	8	10,000	9,999,999	6, 7, 8
CT	13	1,000	999,999	6, 7, 8, 9, 10, 11
DE	4	10,000	99,999	6, 7
FL	28	100	9,999,999	6, 7, 8, 9, 14
GA	54	1,000	9,999,999	2, 3, 4, 6, 7, 8, 9, 10
IA	20	1,000	999,999	6, 7, 8, 11, 12
ID	3	10,000	999,999	8, 12
IL	49	0	9,999,999	2, 3, 6, 7, 8, 9, 11, 12
IN	84	100	9,999,999	1, 2, 3, 5, 6, 7, 8, 9, 10, 11, 12, 14
KS	15	10,000	999,999	6, 7, 8, 11, 12
KY	25	10,000	9,999,999	1, 4, 6, 7, 8, 9, 10, 11
LA	14	0	49,999,999	1, 2, 3, 4, 6, 7, 9, 12
MA	23	1,000	9,999,999	6, 7, 8, 9, 11
MD	5	1,000	999,999	6, 7, 9, 11
ME	3	10,000	9,999,999	1, 5, 6, 8
MI	90	100	9,999,999	1, 2, 3, 5, 6, 7, 8, 9, 10, 11, 12, 14
MN	40	1,000	999,999	2, 3, 4, 6, 7, 8, 9, 11, 12
MO	55	100	9,999,999	2, 3, 6, 7, 8, 9, 10, 11, 12
MS	22	1,000	999,999	6, 7, 8, 10, 11, 12
MT	2	No data	No data	No data
NC	54	1,000	49,999,999	6, 7, 8, 9, 10, 11, 12
ND	2	10,000	9,999,999	7
NE	10	1,000	9,999,999	6, 8, 9, 10, 12
NH	5	1,000	999,999	2, 3, 6, 7, 8, 9
NJ	17	100	999,999	6, 7, 8, 11
NM	2	100,000	999,999	6
NV	7	10,000	999,999	6, 7, 12
NY	23	1,000	9,999,999	2, 3, 6, 7, 8, 9
OH	89	100	499,999,999	1, 5, 6, 7, 8, 9, 10, 11, 12
OK	15	1,000	999,999	6, 7, 8, 11
OR	23	0	9,999,999	1, 2, 3, 4, 6, 7, 8, 9, 10, 12, 13
PA	64	0	9,999,999	2, 3, 6, 7, 8, 9, 10, 11, 12
PR	2	1,000	9,999	12
RI	7	1,000	999,999	6, 7, 8, 9
SC	32	0	9,999,999	1, 3, 5, 6, 7, 8, 9, 10, 11, 12
SD	2	No data	No data	No data

Table 5-4. Facilities that Produce, Process, or Use Diisocyanates

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
TN	58	100	9,999,999	2, 3, 6, 7, 8, 9, 11, 12
TX	85	100	499,999,999	1, 2, 3, 4, 6, 7, 8, 9, 10, 11, 12
UT	14	1,000	9,999,999	2, 3, 6, 7, 8, 9, 10, 12
VA	20	1,000	999,999	6, 7, 8, 9, 10, 11, 12
VT	1	No data	No data	No data
WA	11	1,000	9,999,999	6, 7, 11, 12
WI	71	1,000	9,999,999	2, 3, 6, 7, 8, 9, 10, 11, 12
WV	13	1,000	9,999,999	2, 3, 6, 7, 8, 9, 11

[a]Post office state abbreviations used.
[b]Amounts on site reported by facilities in each state.
[c]Activities/Uses:

1. Produce
2. Import
3. Onsite use/processing
4. Sale/Distribution
5. Byproduct
6. Impurity
7. Reactant
8. Formulation Component
9. Article Component
10. Repackaging
11. Chemical Processing Aid
12. Manufacturing Aid
13. Ancillary/Other Uses
14. Process Impurity

Source: TRI16 2017 (Data are from 2016)

Manufacturers are required to report Toxics Release Inventory (TRI) data to satisfy EPA requirements. The TRI data should be used with caution since only certain types of facilities are required to report (EPA 2005). This is not an exhaustive list.

5.2 IMPORT/EXPORT

U.S. imports of mixed isomers of TDI were 984,000 kg (2.1 million pounds) in 1989, and decreased to 1,000 kg (2,200 pounds) in 1996 but increased again to 15 million kg (32 million pounds) in 2006; 2008 imports were reported as 500,000 kg (1.1 million pounds) (NTP 2011). U.S. imports of unmixed isomers of TDI were reported as 426,000 kg (939,000 pounds) in 1989, and reached a low of 9,000 kg (19,800 pounds) in 1998. U.S. imports of unmixed isomers peaked at 1.3 million kg (2.8 million pounds) in 2004; 2008 imports were 130,000 kg (286,000 pounds). U.S. exports of mixed isomers of TDI were 62 million kg (125 million pounds) in 1989, rising to 277 million kg (609 million pounds) in 2003. U.S. exports of unmixed isomers of TDI peaked in 1994 at 46 million kg (101 million pounds), falling to a low of 3.9 million kg (8.6 million pounds) in 2008 (NTP 2011).

It was reported that 5% of the total U.S. production volume of MDI was exported in 2000 (HSDB 2012). No export data could be located for MDI in the available literature.

5.3 USE

TDI and MDI have widespread commercial use due to their reactivity and versatility. TDI and MDI and their related polyisocyanates make up >90% of the commercial market (EPA 2011a). Commercial- grade TDI is made up of an 80:20 mixture of isomers 2,4- and 2,6-TDI and represents >95% of TDI industrial use (NIOSH 1989). Technical MDI products vary in composition and consist of several MDI isomers and oligomeric derivatives with increasing number of aromatic rings (Bobeldijk et al. 2008).

Diisocyanates, such as MDI and TDI, are generally supplied as raw materials to formulators who use their reactivity to combine them with other chemicals to create various polyurethanes with a wide diversity of applications (EPA 2011a, 2011b).

TDI is a widely used industrial intermediate in the manufacture of polyurethane products (Bilban 2004). In the presence of amines, TDI reacts rapidly with polyols to form polyurethane foam for the furniture, bedding, and automotive industries (Austin 2007).

MDI, polymeric MDI, and TDI are used predominantly in the production of flexible and rigid polyurethane foams. Rigid foams are mainly used for insulation, while flexible foams are used for cushioning. A smaller amount of the total production volume of MDI, polymeric MDI, and TDI is used in the non-foam polyurethane sector, including coatings, adhesives, binders, and sealants (EPA 2011a, 2011b).

Prior to reaching the consumer market, the majority of polyurethane products made with TDI and MDI undergo a curing process (process by which TDI and MDI react with other product components to form polyurethane). However, polyurethane products such as spray foams, coatings, sealants, and adhesives may be sold and used containing uncured TDI and MDI (EPA 2011a, 2011b). In general, polyurethane products sold to the consumer have low concentrations of uncured TDI and MDI and are generally accompanied by product safety information.

5.4 DISPOSAL

TDI is designated with an EPA hazardous waste number U223, and therefore, generators of waste containing this contaminant must conform with EPA regulations in storage, transport, treatment, and disposal (HSDB 2012).

TDI and MDI wastes from distillation equipment are preferably sent to special waste incinerators for burning. Hydrolysis reaction products of TDI and MDI contained in waste waters can be biodegraded by treatment with activated sludge. Recommended methods of TDI and MDI disposal include incineration, and alkaline hydrolysis. Disposal to landfills is not recommended (HSDB 2012).

A study was conducted to assess the effectiveness of using wet sand in the event of a spill to detoxify TDI *in situ*. A 30-L container holding 5 kg of TDI was covered with a mixture of 30 kg of sand and 5 kg of water at ambient temperature. After 24 hours, it was observed that only 5.5% of the TDI remained unreacted. The reaction degradation product, TDA, was not present above the detection limit (10 ppb) (Duff 1983).

Another study described a procedure to decontaminate diisocyanates by which liquid TDI or MDI was added to a decontamination solution containing water (90%), concentrated ammonia solution (8%), and liquid detergent (2%) to effect safe disposal (Duff 1983).

The EPA proposed “low part per million concentration level” criteria of 10 ppm for TDI, which would allow a pronouncement that the spilled TDI residues treated *in situ* could be considered nonhazardous, if the criteria are achieved (Duff 1983).

6. POTENTIAL FOR HUMAN EXPOSURE

6.1 OVERVIEW

TDI has been identified in 4 of the 1,854 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (ATSDR 2017). Diisocyanates were not found at the sites most likely due to their rapid hydrolysis in the environment. The frequency of these sites can be seen in Figure 6-1.

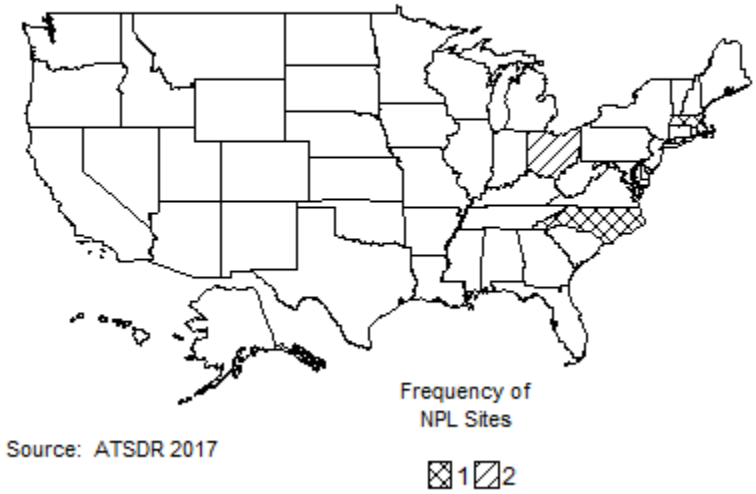
TDI and MDI are extremely reactive compounds that are widely used in the production of polyurethane materials. There are no natural sources of diisocyanates. Almost all of the potential exposures to these compounds are associated with the production, handling, use, and disposal of diisocyanates and diisocyanate-containing products and material. Exposure of the general population to diisocyanates could potentially result from industrial exposures, as well as from the use of consumer products containing uncured TDI and MDI (EPA 2011a, 2011b).

The dominant process affecting the overall environmental fate, transport, and bioaccumulation potential of diisocyanates is hydrolysis (EPA 2011a, 2011b). Diisocyanates react with water forming the respective amines, which in turn may react with more diisocyanates to produce inert, insoluble polyureas (WHO 2000). Hydrolysis half-lives of MDI and TDI have been measured to be on the order of a few minutes to a few hours (HSDB 2012).

6.2 RELEASES TO THE ENVIRONMENT

The Toxics Release Inventory (TRI) data should be used with caution because only certain types of facilities are required to report (EPA 2005). This is not an exhaustive list. Manufacturing and processing facilities are required to report information to the TRI only if they employ 10 or more full-time employees; if their facility is included in Standard Industrial Classification (SIC) Codes 10 (except 1011, 1081, and 1094), 12 (except 1241), 20–39, 4911 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4931 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4939 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4953 (limited to facilities regulated under RCRA Subtitle C, 42 U.S.C. section 6921 et seq.),

Figure 6-1. Frequency of NPL Sites with 1,3-Toluene Diisocyanate Contamination



Source: ATSDR 2017

5169, 5171, and 7389 (limited S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited to facilities primarily engaged in solvents recovery services on a contract or fee basis); and if their facility produces, imports, or processes ≥25,000 pounds of any TRI chemical or otherwise uses >10,000 pounds of a TRI chemical in a calendar year (EPA 2005).

TDI can enter the environment through industrial releases, such as through vent stacks of facilities handling this compound or as an accidental spillage to land or surface waters during transit (Duff 1983).

EPA's National Emission Inventory (NEI) database contains comprehensive and detailed estimates regarding sources that emit criteria air pollutants and their precursors, and hazardous air pollutants (HAPs) for the 50 United States, Washington DC, Puerto Rico, and the U.S. Virgin Islands. The NEI database includes point and non-point source emissions, on-road sources, non-road sources, and event sources such as emissions from wildfires. According to data from the 2014 NEI, 26,0381 pounds of MDI were released and 764,987 pounds of TDI were released (EPA 2014f).

6.2.1 Air

Estimated releases of 19,050, 737, and 381 pounds (~8.64, 0.33, and 0.17 metric tons) of TDI (mixed isomers), 2,4-TDI, and 2,6-TDI to the atmosphere from 134, 53, and 29 domestic manufacturing and processing facilities in 2016 (TRI16 2017) are summarized in Tables 6-1, 6-2, and 6-3. Table 6-4 summarizes releases of 207,137 pounds (~93.96 metric tons) of the diisocyanates category, which consists of MDI and 19 other substances, to the atmosphere from 1,304 domestic manufacturing and processing facilities in 2016 (TRI16 2017).

There is no information on releases of MDI to the atmosphere from manufacturing and processing facilities because these releases are not required to be reported (EPA 1998a).

During processing in a polyurethane foam plant, TDI emissions are removed from the workplace air by ventilation systems. However, any residual TDI leaving the plant vent stack is then dispersed into the atmosphere (Duff 1983).

Researchers studying six flexible foam manufacturing plants in Germany found that discharge concentrations of TDI emitted in factory exhaust gases ranged from 3 to 8 mg/m^3. Concentrations

Table 6-1. Releases to the Environment from Facilities that Produce, Process, or Use Toluene Diisocyanate (Mixed Isomers)[a]

		Reported amounts released in pounds per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
AR	1	373	0	0	0	0	373	0	373
AZ	1	No data	No data	No data	No data	No data	No data	No data	No data
CA	11	1,993	0	0	70	32	1,993	102	2,095
DE	2	4	0	0	0	0	4	0	4
FL	3	1,230	0	0	0	9,563	1,230	9,563	10,793
GA	6	623	0	0	0	209	623	209	832
IA	2	382	0	0	0	0	382	0	382
IL	3	234	0	0	3	0	234	3	237
IN	6	960	0	0	0	0	960	0	960
KS	2	295	0	0	0	0	295	0	295
KY	2	2,555	0	0	7	0	2,561	0	2,561
LA	3	37	0	0	77	0	37	77	114
MA	4	167	0	0	0	0	167	0	167
MD	2	294	0	0	0	0	294	0	294
ME	2	5	0	0	0	574	5	574	579
MI	5	48	0	0	11	0	59	0	59
MN	1	325	0	0	0	0	325	0	325
MO	5	121	0	0	0	0	121	0	121
MS	6	2,070	0	0	0	0	2,070	0	2,070
NC	11	894	0	0	0	0	894	0	894
NH	1	1	0	0	0	352	1	352	353
NJ	7	625	0	0	0	9,129	625	9,129	9,754
NM	2	214	0	0	0	2,195	214	2,195	2,409
OH	8	468	0	0	14,195	0	14,363	300	14,663
OR	1	122	0	0	0	0	122	0	122
PA	7	1,547	0	0	0	430	1,547	430	1,977
PR	1	No data	No data	No data	No data	No data	No data	No data	No data
SC	2	No data	No data	No data	No data	No data	No data	No data	No data
TN	4	676	0	0	0	0	676	0	676
TX	14	916	0	892	223	52	916	1,167	2,084
VA	4	610	0	0	0	0	610	0	610
WA	2	276	0	0	0	0	276	0	276
WI	2	500	0	0	0	0	500	0	500

Table 6-1. Releases to the Environment from Facilities that Produce, Process, or Use Toluene Diisocyanate (Mixed Isomers)[a]

		Reported amounts released in pounds per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
WV	1	486	0	0	0	0	486	0	486
Total	134	19,050	0	892	14,586	22,536	32,963	24,101	57,064

[a]The TRI data should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list. Data are rounded to nearest whole number.
[b]Data in TRI are maximum amounts released by each facility.
[c]Post office state abbreviations are used.
[d]Number of reporting facilities.
[e]The sum of fugitive and point source releases are included in releases to air by a given facility.
[f]Surface water discharges, waste water treatment-(metals only), and publicly owned treatment works (POTWs) (metal and metal compounds).
[g]Class I wells, Class II-V wells, and underground injection.
[h]Resource Conservation and Recovery Act (RCRA) subtitle C landfills; other onsite landfills, land treatment, surface impoundments, other land disposal, other landfills.
[i]Storage only, solidification/stabilization (metals only), other off-site management, transfers to waste broker for disposal, unknown.
[j]The sum of all releases of the chemical to air, land, water, and underground injection wells.
[k]Total amount of chemical transferred off-site, including to POTWs.

RF = reporting facilities; UI = underground injection

Source: TRI16 2017 (Data are from 2016)

Table 6-2. Releases to the Environment from Facilities that Produce, Process, or Use 2,4-Toluene Diisocyanate[a]

		Reported amounts released in pounds per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
AL	1	5	0	0	0	0	5	0	5
AR	2	1	0	0	2	0	1	2	3
CO	1	5	0	0	0	0	5	0	5
CT	1	1	0	0	0	0	1	0	1
GA	2	255	250	0	0	0	505	0	505
IA	1	No data	No data	No data	No data	No data	No data	No data	No data
IL	1	No data	No data	No data	No data	No data	No data	No data	No data
IN	2	47	0	0	0	0	47	0	47
KS	1	No data	No data	No data	No data	No data	No data	No data	No data
KY	1	10	0	0	0	0	10	0	10
MA	1	0	0	0	0	545	0	545	545
MD	1	10	0	0	0	0	10	0	10
MI	5	28	0	0	0	0	28	0	28
MN	1	0	0	0	1,020	0	0	1,020	1,020
MO	2	59	0	0	0	0	59	0	59
MS	4	173	0	0	0	0	173	0	173
NC	1	No data	No data	No data	No data	No data	No data	No data	No data
NE	1	22	0	0	0	0	22	0	22
NJ	3	10	0	0	0	0	10	0	10
NY	1	10	0	0	0	0	10	0	10
OH	5	28	0	0	4,745	0	4,773	0	4,773
PA	4	1	0	0	0	540	1	540	541
RI	1	No data	No data	No data	No data	No data	No data	No data	No data
TN	2	23	0	0	0	250	23	250	273
TX	3	22	0	0	0	0	22	0	22
UT	1	No data	No data	No data	No data	No data	No data	No data	No data
VA	1	21	0	0	0	0	21	0	21
WI	2	1	0	0	0	0	1	0	1

Table 6-2. Releases to the Environment from Facilities that Produce, Process, or Use 2,4-Toluene Diisocyanate[a]

		Reported amounts released in pounds per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
WV	1	2	0	0	0	0	2	0	2
Total	53	737	250	0	5,767	1,335	5,732	2,357	8,088

[a]The TRI data should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list. Data are rounded to nearest whole number.
[b]Data in TRI are maximum amounts released by each facility.
[c]Post office state abbreviations are used.
[d]Number of reporting facilities.
[e]The sum of fugitive and point source releases are included in releases to air by a given facility.
[f]Surface water discharges, waste water treatment-(metals only), and publicly owned treatment works (POTWs) (metal and metal compounds).
[g]Class I wells, Class II-V wells, and underground injection.
[h]Resource Conservation and Recovery Act (RCRA) subtitle C landfills; other onsite landfills, land treatment, surface impoundments, other land disposal, other landfills.
[i]Storage only, solidification/stabilization (metals only), other off-site management, transfers to waste broker for disposal, unknown
[j]The sum of all releases of the chemical to air, land, water, and underground injection wells.
[k]Total amount of chemical transferred off-site, including to POTWs.

RF = reporting facilities; UI = underground injection

Source: TRI16 2017 (Data are from 2016)

Table 6-3. Releases to the Environment from Facilities that Produce, Process, or Use 2,6-Toluene Diisocyanate[a]

		Reported amounts released in pounds per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
AR	1	No data	No data	No data	No data	No data	No data	No data	No data
CO	1	1	0	0	0	0	1	0	1
GA	1	255	5	0	0	0	260	0	260
IL	1	No data	No data	No data	No data	No data	No data	No data	No data
IN	1	11	0	0	0	0	11	0	11
KS	1	No data	No data	No data	No data	No data	No data	No data	No data
MA	1	1	0	0	0	2,365	1	2,365	2,366
MD	1	10	0	0	0	0	10	0	10
MI	4	8	0	0	0	0	8	0	8
MO	2	2	0	0	0	0	2	0	2
MS	2	27	0	0	0	0	27	0	27
NE	1	11	0	0	0	0	11	0	11
OH	5	3	0	0	1,726	0	1,729	0	1,730
PA	1	No data	No data	No data	No data	No data	No data	No data	No data
TN	2	47	0	0	0	250	47	250	297
TX	1	No data	No data	No data	No data	No data	No data	No data	No data
WI	2	3	0	0	0	0	3	0	3
WV	1	2	0	0	0	0	2	0	2
Total	29	381	5	0	1,726	2,615	2,112	2,615	4,727

[a]The TRI data should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list. Data are rounded to nearest whole number.
[b]Data in TRI are maximum amounts released by each facility.
[c]Post office state abbreviations are used.
[d]Number of reporting facilities.
[e]The sum of fugitive and point source releases are included in releases to air by a given facility.
[f]Surface water discharges, waste water treatment-(metals only), and publicly owned treatment works (POTWs) (metal and metal compounds).
[g]Class I wells, Class II-V wells, and underground injection.
[h]Resource Conservation and Recovery Act (RCRA) subtitle C landfills; other onsite landfills, land treatment, surface impoundments, other land disposal, other landfills.
[i]Storage only, solidification/stabilization (metals only), other off-site management, transfers to waste broker for disposal, unknown
[j]The sum of all releases of the chemical to air, land, water, and underground injection wells.
[k]Total amount of chemical transferred off-site, including to POTWs.

RF = reporting facilities; UI = underground injection

Source: TRI16 2017 (Data are from 2016)

Table 6-4. Releases to the Environment from Facilities that Produce, Process, or Use Diisocyanates[a]

		Reported amounts released in pounds per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
AL	32	301	5	0	251	2,921	306	3,172	3,478
AR	13	1,554	0	0	18,609	0	1,554	18,609	20,163
AZ	12	7	0	0	0	0	7	0	7
CA	63	399	0	0	5,036	6,526	400	11,561	11,961
CO	8	7	0	0	0	3,672	7	3,672	3,679
CT	13	659	0	0	0	180	659	180	839
DE	4	4	0	0	0	2,015	4	2,015	2,019
FL	28	44	0	0	26,109	43,418	44	69,527	69,570
GA	54	15,813	0	0	26,578	0	15,813	26,578	42,391
IA	20	11,548	0	0	750	2,291	11,548	3,041	14,589
ID	3	4	0	0	45,081	0	45,085	0	45,085
IL	49	13,788	0	0	172	1,118	13,836	1,242	15,079
IN	84	4,666	0	0	50,317	1,285	4,786	51,482	56,267
KS	15	491	0	0	250	0	491	250	741
KY	25	12,781	0	0	99,504	0	12,781	99,504	112,285
LA	14	2,142	0	0	13,200	17,998	2,142	31,198	33,340
MA	23	411	0	0	4	15,799	411	15,803	16,214
MD	5	1,300	0	0	0	28,549	1,300	28,549	29,849
ME	3	2,223	0	0	0	3,675	2,223	3,675	5,898
MI	90	28,009	0	0	790,863	58,974	28,044	849,802	877,846
MN	40	2,430	0	0	77,725	23,754	2,430	101,479	103,910
MO	55	58,809	0	0	12,306	20,397	58,819	32,693	91,512
MS	22	2,583	0	0	5,736	0	2,583	5,736	8,319
MT	2	No data	No data	No data	No data	No data	No data	No data	No data
NC	54	1,166	0	0	12,125	18,204	1,166	30,329	31,495
ND	2	44	0	0	0	0	44	0	44
NE	10	896	0	0	673	0	896	673	1,569
NH	5	3	0	0	0	1,500	3	1,500	1,503
NJ	17	1,390	0	0	5	0	1,395	0	1,395
NM	2	2	0	0	0	2,512	2	2,512	2,514
NV	7	59	0	0	16,324	40	14,847	1,576	16,423
NY	23	1,224	0	0	403	2,365	1,224	2,768	3,992
OH	89	7,483	0	0	68,334	126,119	13,683	188,253	201,936
OK	15	3,841	0	0	0	594	3,841	594	4,435
OR	23	3,293	0	0	0	566	3,293	566	3,859
PA	64	6,188	0	0	146,145	12,487	6,188	158,632	164,819
PR	2	No data	No data	No data	No data	No data	No data	No data	No data

Table 6-4. Releases to the Environment from Facilities that Produce, Process, or Use Diisocyanates[a]

		Reported amounts released in pounds per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
RI	7	0	0	0	0	5,512	0	5,512	5,512
SC	32	2,097	0	0	5,013	0	2,097	5,013	7,110
SD	2	No data	No data	No data	No data	No data	No data	No data	No data
TN	58	1,687	0	0	102,845	622	1,687	103,467	105,154
TX	85	6,936	38	0	130,388	5,839	87,152	56,049	143,201
UT	14	1,154	0	0	0	723	1,154	723	1,877
VA	20	564	0	0	2	5,609	564	5,611	6,175
VT	1	No data	No data	No data	No data	No data	No data	No data	No data
WA	11	272	0	0	0	250	272	250	522
WI	71	2,234	0	0	10,263	121,093	2,234	131,356	133,590
WV	13	6,634	0	0	44,014	1,500	6,634	45,514	52,147
Total	1,304	207,137	43	0	1,709,025	538,106	353,646	2,100,666	2,454,312

[a]The TRI data should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list. Data are rounded to nearest whole number.
[b]Data in TRI are maximum amounts released by each facility.
[c]Post office state abbreviations are used.
[d]Number of reporting facilities.
[e]The sum of fugitive and point source releases are included in releases to air by a given facility.
[f]Surface water discharges, waste water treatment-(metals only), and publicly owned treatment works (POTWs) (metal and metal compounds).
[g]Class I wells, Class II-V wells, and underground injection.
[h]Resource Conservation and Recovery Act (RCRA) subtitle C landfills; other onsite landfills, land treatment, surface impoundments, other land disposal, other landfills.
[i]Storage only, solidification/stabilization (metals only), other off-site management, transfers to waste broker for disposal, unknown
[j]The sum of all releases of the chemical to air, land, water, and underground injection wells.
[k]Total amount of chemical transferred off-site, including to POTWs.

RF = reporting facilities; UI = underground injection

Source: TRI16 2017 (Data are from 2016)

released were dependent on the foam density produced at a given time. The study reported that only 0.005% of all of the TDI processed within the facilities was lost to the atmosphere (Duff 1983).

It has been reported that 2,6-TDI dominates TDI emissions to air from newly manufactured polyurethane foams, despite the 80:20 ratio of 2,4-TDI to 2,6-TDI in the original TDI formulation used. This is due to the lower reactivity of 2,6-TDI (Kelly et al. 1999). This information mainly relates to releases to indoor air.

Due to the diversity of applications and wide variety of MDI formulations, typical emission levels of MDI are difficult to quantify. Emissions may be comprised of MDI vapor, MDI aerosol, or a reacting mix of aerosol and vapor, which is predominantly converted to polyurethane. Emission levels are generally much lower than those of TDI flexible foam processes. A survey conducted in the United Kingdom of polyurethane production facilities (comprising 50% of total U.K. rigid foam manufacture) producing insulation board by spray and liquid laydown techniques and rigid foam slabstock produced by both continuous and discontinuous processes found typical emission levels to be ≤0.2 mg/m^3 (Gilbert 1988). The American Chemistry Council Center for the Polyurethane Industry has developed an emissions calculator to estimate emissions from typical process applications and activities, which may be downloaded at https://polyurethane.americanchemistry.com. Tury et al. (2003) estimated that typical environmental loadings are less than 1 gram per metric ton of MDI used and about 25 grams per metric ton of TDI used.

Developments in polyurethane processing to control emissions of TDI and MDI include increasing the use of reaction injection moulding closed-circuit technology and advancement in the carbon absorption of emissions (Gilbert 1988).

During the application of MDI in foam or film coating of surfaces by spray gun techniques, the measured environmental contamination during application showed levels of total MDI as high as 5 mg/m^3. More than 95% of air samples contained MDI particulates of respirable size, and counts were from 2 to 8 million parts/feet^3 (ACGIH 2001).

Available information on the releases of TDI and MDI to the air in occupational settings and indoor air, along with exposure levels, are discussed in Section 6.5.

6.2.2 Water

Estimated releases of 0, 250, and 5 pounds (~0, 0.11, and 0.002 metric tons) of TDI (mixed isomers), 2,4-TDI, and 2,6-TDI to surface water from 134, 53, and 29 domestic manufacturing and processing facilities in 2016 (TRI16 2017) are summarized in Tables 6-1, 6-2, and 6-3. Table 6-4 summarizes releases of 43 pounds (~0.02 metric tons) of the diisocyanates category, which consists of MDI and 19 other substances, to surface water from 1,304 domestic manufacturing and processing facilities in 2016 (TRI16 2017).

Because of their reactivity with water, TDI and MDI are not likely to be found in waste water streams or in other aquatic environments, except possibly near point sources after immediate release.

6.2.3 Soil

Estimated releases of 14,586, 5,767, and 1,726 pounds (~6.62, 2.62, and 0.78 metric tons) of TDI (mixed isomers), 2,4-TDI, and 2,6-TDI to soils from 134, 53, and 29 domestic manufacturing and processing facilities in 2016 (TRI16 2017) are summarized in Tables 6-1, 6-2, and 6-3. Table 6-4 summarizes releases of 1,709,025 pounds (~775.2 metric tons) of the diisocyanates category, which consists of MDI and 19 other substances, to soils from 1,304 domestic manufacturing and processing facilities in 2016 (TRI16 2017). Estimated releases of 892, 0, and 0 pounds (~0.4, 0, and 0 metric tons) of TDI (mixed isomers), 2,4-TDI, and 2,6-TDI via underground injection from 134, 53, and 29 domestic manufacturing and processing facilities in 2016 (TRI16 2017) are summarized in Tables 6-1, 6-2, and 6-3. There were no releases of the diisocyanates category, which consists of MDI and 19 other substances, via underground injection (TRI16 2017). These releases are summarized in Tables 6-4.

6.3 ENVIRONMENTAL FATE

Diisocyanates are extremely reactive compounds (Geens et al. 2012), especially with water. The dominant process affecting the overall environmental fate, transport, and bioaccumulation potential of diisocyanates is hydrolysis (EPA 2011b).

6.3.1 Transport and Partitioning

Based on their vapor pressures (see Table 4-2), MDI is expected to exist in both the vapor and particulate phases in the ambient atmosphere, while TDI isomers are expected to exist solely as a vapor (Bidleman

1988; Eisenreich et al. 1981). Based on a study of the atmospheric hydrolysis of TDI (Dyson and Hermann 1971), it is likely that wet deposition of particulate-phase MDI from the atmosphere is not an important removal process because of its reactivity with water. TDI and MDI may be stable enough to be transported some distances under conditions of low humidity (EPA 2011a, 2011b); however, no studies were found on long distance transport in the available literature.

If released to water or moist soil/sediment, TDI and MDI will rapidly undergo hydrolysis (EPA 2011a, 2011b), and therefore, the potential to volatilize to air and leaching or adsorption to soil and sediments will be negligible. The rapid hydrolysis of these compounds also suggests that they will not bioconcentrate in aquatic organisms or bioaccumulate in the food chain. This is supported by a study using three artificial ponds to determine the fate and biological effects from a simulated accidental pollution event with MDI on an aquatic ecosystem. MDI did not accumulate in fish after 119 days post-MDI addition due to its rapid reaction on the sediment surface with water to form polyurea and carbon dioxide (Heimbach et al. 1996). Also, during another study by the International Isocyanate Institute (1981), no accumulation of TDI or its respective amine hydrolysis product was found in the whole bodies of carp after 8 weeks of exposure in a model river system with an initial TDI concentration of 0.1 ppm. No bioconcentration factors (BCFs) for TDI or MDI were found in the available literature.

Volatilization from dry soil surfaces is not expected to be an important fate process for TDI, TDI isomers, or MDI based on their vapor pressures (see Table 4-2).

6.3.2 Transformation and Degradation

TDI and MDI are extremely reactive compounds and are well known to react with water (Yakabe et al. 1999). Hydrolysis is the dominant environmental process for TDI and MDI (EPA 2011a, 2011b), forming the respective amines, which in turn may react with more diisocyanates to produce inert, insoluble polyureas (WHO 2000).

6.3.2.1 Air

Kelly et al. (1994) reported that TDI and MDI have half-lives of <1 day due to reaction with OH radicals in the atmosphere. The International Isocyanate Institute (1987) also measured the rate constant for the reaction of TDI with OH radicals in the atmosphere to be 7.4×10^{-12} cm^3/molecule-second, which corresponds to a half-life of 26 hours. These experimental half-lives are in good agreement with estimated half-lives for the reaction with photochemically produced hydroxyl radicals of 20 and 11 hours

based on vapor phase reaction rate constants of 7.07×10^{-12} and 1.2×10^{-11} cm^3/molecule-second at 25°C, for TDI and MDI respectively, determined using a structure estimation method (HSDB 2012). Aromatic isocyanates, such as TDI and MDI, do not absorb light in the ultraviolet region (wavelengths >290 nm) (Lyman et al. 1990), and therefore, direct photolysis by sunlight is not expected to be an important degradation process in the atmosphere.

In an experiment using an environmental chamber to assess the impact of photolysis, reaction with free radicals, and adsorption onto particulate matter as atmospheric removal processes of TDI, the loss rate of TDI in irradiated clean air was first order, with a half-life of 3.3 hours. It was shown that free radicals were responsible for removal, not photolysis. The removal rate was not altered by the addition of an urban surrogate hydrocarbon mixture to simulate urban air, demonstrating that adsorption onto particulate matter had minimal effect (Duff 1985).

Gas-phase TDI was originally thought to react with water vapor in the atmosphere to form TDA. One study measured a maximum reduction of 50% for TDI concentrations of 0.4 and 0.034 ppm after 8 seconds and showed that the disappearance of TDI in air depends almost solely on the water vapor concentration. The percent reduction of TDI increased 3.2% per unit increase in absolute humidity (g water/kg dry air) and a 50% reduction was obtained at 15 g water/kg dry air (Dyson and Hermann 1971). A study conducted by Holdren et al. (1984) contradicts early findings of TDI reaction with water vapor, indicating that TDI loss was likely due to gas-surface or heterogeneous reactions in reaction chambers with large surface to volume ratios. In this study, gas-phase reactions between TDI and water vapor were observed in a room-sized environmental chamber. It was found that the loss rate of TDI was independent of humidity, measured over a relative humidity range of 7–70%, and that no TDA or other hydrolysis product could be detected. Loss was stated to be caused by the adsorption of TDI to the chamber walls. These studies, however, did not investigate the condensed phase atmospheric hydrolysis of TDI, such as reactions with rain drops, fog, or clouds. The average hydrolysis half-lives of TDI and MDI are on the order of a few minutes to a few hours (HSDB 2012), which suggests that the heterogeneous condensed phase atmospheric hydrolysis of these compounds may be rapid.

6.3.2.2 Water

Diisocyanates that are released to water hydrolyze rapidly, forming amines that can react with residual diisocyanates, ultimately producing inert insoluble polyureas (WHO 2000). Polyureas have been reported to be the main degradation products resulting from environmental contact of TDI and MDI with water,

with smaller amounts of soluble diamines being formed (Yakabe et al. 1999). Hydrolysis half-lives of MDI and TDI have been measured to be on the order of a few minutes to a few hours (HSDB 2012). The hydrolysis half-lives of polyureas are on the order of millennia (Sendijarevic et al. 2004).

TDI added to a model river system and a seawater system at initial concentrations of 50 ppm was monitored over the course of 30 days. In the freshwater system, the concentration of TDI declined rapidly ranging from not detected to 0.1 ppm after 1 day. Low levels of diamine degradation products were detectable only during early sampling periods. In the seawater system, the concentration of TDI also declined rapidly to 0.1 ppm after 1 day (Duff 1983). The concentration of MDI added to a model marine system and a model river to simulate spill situations fell to a maximum of 5% of the initial value within 1 day (Gilbert 1988).

Yakabe et al. (1999) examined the kinetics of the hydrolysis of TDI and MDI in well-stirred and unstirred environments, with unstirred reactions representing conditions of an environmental spill. The reported half-life was 30 seconds for 28 mg/L of TDI in a well-stirred water system, while with less efficient stirring, the half-life for TDI was in the region of 3–5 minutes. At a loading of 1,000 mg/L, the half-lives of 2,4- and 2,6-TDI were about 0.7 and 1.7 hours, respectively, demonstrating that reaction rate was a function of the concentration of TDI. After 30 minutes in well-stirred water, the extent of TDI reacted varied from 85% at 10 mg/L to 20% at 10,000 mg/L. The observed half-life of about 20 hours for polymeric MDI was much slower than TDI, due to its greater viscosity. Because of the viscosity and difficulty mixing with water, the reaction rate was affected by surface area contact with water and not on concentration. The well-stirred, homogeneous environments showed that TDI and MDI are expected to be rapidly degraded in water and never attain any significant concentrations. However, the complete reaction of both TDI and MDI may take several weeks under poorly mixed conditions, typical of an environmental spill, due to the formation of insoluble, solid polyurea crusts. These predictions are consistent with field observations. For example, when 14 tons of TDI were accidentally spilled onto marshy woodland in 1975, the material was covered with wet sand and monitored for 6 years. The TDI was converted to polyureas within 6 weeks, while no TDA was detected in soil (<3 mg/kg) or water (<50 μg/L) at any point and no adverse environmental effects were reported. In another accidental spill involving 20 tons of TDI into a fast-moving stream, the TDI reacted to form polyureas that were distributed for 2–3 km downstream, while TDA was detected at 5 mg/L downstream after 2 days, but fell below the detection limit after 2 weeks. In 1991, about 50 tons of prepolymeric MDI was spilled into a river and a majority was reported to have formed solid polyureas when it was scooped out after 2 days. The EPA testing of the river ceased after 3 days and the material in the river was declared nonhazardous.

During a study using three artificial ponds to determine the fate and biological effects from a simulated accidental pollution event with MDI on an aquatic ecosystem, MDI was not detected in water after 119 days post-MDI addition due to its rapid reaction on the sediment surface with water to form polyurea and carbon dioxide (Heimbach et al. 1996).

TDI and MDI are expected to be hydrolyzed much more quickly than they would undergo biodegradation in water, although the resulting diamines should be subject to biodegradation (HSDB 2012). TDI, MDI, and prepolymeric MDI, at concentrations of 50 ppm each, were reported to be completely biodegraded within 15 days at 25 °C in a freshwater model river system with bottom sludge, and in a saltwater system, TDI could not be detected after 4 days, while MDI disappeared after 1 day (International Isocyanate Institute 1980, 1983, 1987). However, hydrolysis was not taken into account during these experiments, and it should be the predominant degradation process, not biodegradation.

6.3.2.3 Sediment and Soil

No studies of the transformation and degradation of TDI and MDI in dry soil could be located in the available literature. When monomeric MDI, and under many circumstances TDI, are handled as a liquid, they will solidify on contact with soil (Gilbert 1988). TDI and MDI will hydrolyze in moist soil and sediment due to their rapid reaction with water to form diamines and polyureas (HSDB 2012; WHO 2000) and hydrolysis is expected to occur much more rapidly than biodegradation (HSDB 2012). Therefore, reaction with water is expected to be the only significant fate process in moist soil and sediment.

In a laboratory experiment involving TDI in undisturbed moist sand, 5.5 and 3.5% of unreacted TDI remained after 24 hours and 8 days, respectively, indicating that TDI is converted to polyureas at a decreasing rate. The diamine hydrolysis product was not found above the detection limit (0.01 ppm). These results suggest the encapsulation of unreacted TDI within a rapidly forming water-insoluble polyurea crust (Gilbert 1988).

Ten days after a spill of 13 tons of TDI onto swampy, wet forest soil, the TDI solidified and the area was covered with sand. The concentration of TDI and degradation product, TDA, combined declined from the parts per thousand to the parts per million range in the soil between 10 days and 12 weeks after the spill.

After 6 years, soil samples showed only TDI-derived polyureas (Brochhagen and Grieveson 1984; HSDB 2012).

6.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

Reliable evaluation of the potential for human exposure to TDI and MDI depends in part on the reliability of supporting analytical data from environmental samples and biological specimens. Concentrations of TDI and MDI in unpolluted atmospheres and in pristine surface waters are often so low as to be near the limits of current analytical methods. In reviewing data on TDI and MDI levels monitored or estimated in the environment, it should also be noted that the amount of chemical identified analytically is not necessarily equivalent to the amount that is bioavailable. The analytical methods available for monitoring TDI and MDI in a variety of environmental media are detailed in Chapter 7.

6.4.1 Air

Most monitored TDI and MDI concentrations in air are found in occupational settings (see Section 6.5). Limited data were located in the available literature on measured concentration of TDI and MDI in the ambient atmosphere, likely due to their relatively short half-lives (<1 day) (Kelly et al. 1994) from reaction with hydroxyl radicals.

Detectable concentrations may be found near point sources of TDI and MDI, such as near waste streams from manufacturing and processing facilities and hazardous waste sites. In an exposure assessment to TDI from a polyurethane foam manufacturing plant in North Carolina conducted in 1997, concentrations of TDI in ambient air were as high as 29 ppbv at a monitoring station approximately 100 feet outside the facilities fence line (MMWR 1998). Stack exhaust streams from a polyurethane foam manufacturing plant had reported concentrations of 100–17,700 $\mu g/m^3$ of TDI (HSDB 2012). In a study conducted by the North Carolina Department of Health and Human services from 2007 to 2010, TDI was detected in only one air sample at a concentration of 0.001 ppbv near polyurethane foam plants in North Carolina (NCDHHS 2017). Levels of MDI and TDI were monitored at six schools in the United States in order to assess outdoor air quality in representative schools (EPA 2017). MDI and TDI were not detected in the outdoor air near these schools.

A monitoring study conducted from 1984 to 1999 analyzed 4,551 area and 3,583 personal air samples in which airborne MDI concentrations were measured in a wide variety of manufacturing processes that use either polymeric MDI (PMDI) or monomeric (pure) MDI (Booth et al. 2009). Nearly 50% of the area

samples were below the level of quantification. Detectable levels ranged from $8.5x10^{-5}$ to 9.5 mg/m^3, with an arithmetic mean (standard deviation) of 0.057 (0.32) mg/m^3 (Booth et al 2009).

Both MDI and TDI are included in EPA's National Air Toxics Assessment (NATA), which is an ongoing comprehensive evaluation of air toxics in the United States. Emissions inventory statistics are collected from data reported by large individual facilities (point sources) and estimated for area and mobile sources using various emissions inventory models. Ambient air levels are estimated using the air dispersion model, AERMOD. Nationwide estimated average concentrations of MDI and TDI from point sources were $7.3x10^{-5}$ and $1.4x10^{-5}$ mg/m^3, respectively, for the 2011 assessment (EPA 2015).

6.4.2 Water

No information on the concentration of TDI or MDI in natural water was located in the available literature. Significant concentrations are not likely to be found in the aquatic environment due to the rapid hydrolysis of these compounds; however, small amounts may be detected near point sources such as industrial waste streams and hazardous waste sites immediately after release.

6.4.3 Sediment and Soil

No information on the concentration of TDI or MDI in soil or sediment was located in the available literature. Significant concentrations are not likely to be found in moist soil or sediment due to the rapid hydrolysis of these compounds; however, small amounts may be detected near point sources such as industrial waste streams and hazardous waste sites.

6.4.4 Other Environmental Media

Commercial TDI has been detected in a urethane foam fabric coating in concentrations of <200 mg/kg (HSDB 2012). Application of a water sealant to a concrete slab resulted in measured TDI emission rates of 319,000 or 257,000 $\mu g/m^2$/hour in 30-minute tests at 21°C and 360,000 $\mu g/m^2$/hour in a 1-hour test at 27°C (Kelly et al. 1999). These emission rates corresponded to 35, 38, and 179 µg of total TDI emitted, respectively; 75.2, 97.8, and 79.2% of the TDI emitted was 2,6-TDI. MDI emissions were detected at 60 ppt for aluminum and wood substrates cured with polyurethane glue in the first 8 hours of sampling, but was below the detection limit (20 ppt) thereafter (Parekh and Karoly 2001). No data on the concentrations of TDI or MDI in other environmental media, including food, were found in the available

literature. Due to the rapid hydrolysis of these compounds, TDI and MDI will not bioaccumulate in the food chain and are therefore not expected to be found in significant concentration in fish and foods.

6.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

Exposure of the general population to TDI from its use in polyurethane products in household materials was once thought to be negligible. An increase in the number of uncured diisocyanate-containing products used by consumers has been noted by researchers. These researchers also noted that exposure of the general population to TDI and MDI could potentially result from industrial exposures, as well as from the use of consumer products containing uncured TDI and MDI (EPA 2011a). In a study of the emission rates from polyurethane household product and materials, TDI emissions were not detectable from carpet padding, mattress and sheet foam, furniture cushion foam, spray varnishes, brush-on varnishes, general purpose water sealers, mastic construction adhesive, or high-performance caulk (Kelly et al. 1999). The only product with a large, detectable TDI emission rate was a concrete sealant. Total TDI emitted from these samples were 35 and 38 μg over 30 minutes at 21°C and 179 μg over 1 hour at 27°C, where 75–98% of the TDI released was the 2,6-isomer (Kelly et al. 1999). The predominant possible sources of exposure to MDI to the general population comes from its use in the construction and installation of foams, glue and putty, dyes, varnishes, and furniture (EPA 2011a).

Due to the concern about the presence of TDI and MDI in an uncured form in products used by or around consumers, the EPA created Action Plans to address the use of MDI, TDI, and related compounds that may result in consumer and general population exposures. The Action Plans are intended to describe courses of action to pursue to mitigate concerns over exposure (EPA 2011a, 2011b). It should be noted that these Action Plans are focused on concerns for unreacted uncured TDI and MDI products, as the completely cured products are considered inert and nontoxic.

Exposure to TDI and MDI is mainly an occupational problem due to their manufacturing and processing in many different industries. Diisocyanates are used in the production of polyurethane foam during foaming, casting, spraying, and other processes. Exposure may also occur after production when the polymer is processed. Thermal degradation of polyurethane foam during processes such as heat cutting of foam blocks, flame lamination with textiles, and welding, cutting, or grinding of polyurethane-coated metal, can also release diisocyanates into the air (Dahlin et al. 2008). MDI emission levels due to thermal degradation from the use of polyurethane core binder materials in foundry molds was reported to be <0.02–1.0 mg/kg (Renman et al. 1986).

Workers may be predominantly exposed to TDI and MDI by inhalation of aerosol and vapor (TDI only). Another route is through dermal exposure (Tinnerberg et al. 1997). Most occupational diisocyanate exposure studies have focused on TDI because of its widespread industrial use in the manufacture of polyurethane foam (Tinnerberg et al. 1997). A common way of assessing workplace exposure is through air monitoring. The average air concentration of TDI measured in a TDI flexible foam plant was 29.8 $\mu g/m^3$, while the highest exposure peak was approximately 3 mg TDI/m^3 (Tinnerberg et al. 1997). Mean TDI levels ranged from 0.7 to 180 $\mu g/m^3$ for workplace air in U.S. factories manufacturing TDI between 1973 and 1978 (IARC 1985). Mean TDI levels ranged from not detected to 540 $\mu g/m^3$ for personal and workplace air in U.S. factories producing polyurethane foam between 1972 and 1981 (IARC 1985). A monitoring study conducted from 1984 to 1999 analyzed 3,583 personal air samples in which airborne MDI concentrations were measured in a wide variety of manufacturing processes that use either PMDI or monomeric (pure) MDI (Booth et al. 2009). Nearly 75% of the personal samples were below the level of quantification, and detectable levels ranged from $2x10^{-5}$ to 3.9 mg/m^3 (Booth et al 2009). The highest airborne levels tended to occur when MDI was heated or sprayed, and control measures such as appropriate ventilation and protective equipment were recommended to reduce occupational exposures.

Diem et al. (1982) performed a 5-year (April 1973 to October 1978) longitudinal study of 277 workers in a new TDI manufacturing plant in Louisiana in which over 2,000 personal air samples were measured for TDI concentrations. The 8-hour TWAs ranged from 0.1 to 25 ppb. Different jobs in the facility fell into low, moderate, and high TWA exposure categories. The average time periods spent above 20 ppb were 1.3, 8.6, and 28.2 minutes per 8-hour shift for workers in the low, moderate, and high exposure categories, respectively.

In a study conducted in 2000 involving a plastic production plant using TDI, the concentration of TDI detected in the air ranged from 0.007 to 0.016 mg/m^3 (Bilban 2004). Ambient air concentrations that included 60 personal breathing zone samples collected from workers in a petrochemical industrial complex in Korea contained mean TDI and MDI concentrations of 0.0174 and 0.0013 mg/m^3, respectively (Jang et al. 2000). Tarlo et al. 1997 reported an air sampling study of 223 companies in Ontario, Canada that had potential diisocyanate exposure to workers during 1984–1988. The highest exposure levels of MDI in 123 companies were <0.005 ppm in 95 companies and ≥0.005 ppm in 38 companies. The highest exposure levels of TDI in 78 companies were <0.005 ppm in 58 companies and ≥0.005 ppm in 20 companies (Tarlo et al. 1997).

At a facility that manufactures refrigerated tractor trailers in the United States, MDI was detected in the personal breathing zone of workers in the polyurethane foaming area at levels ranging from not detected to 9.1 μg/m^3, with a mean concentration of 1.5 μg/m^3 (Lushniak et al. 1998). Workplace air sampled during spraying operations had MDI concentrations of 21.4, 5.9, and 2.1 mg/m^3 at distances of 2, 6, and 10 m away from production machinery, respectively (D'Eril et al. 1995).

A study determining the workplace air exposure concentrations of MDI to sprayers, helpers, and personnel produced during the spray application of polyurethane foam during typical indoor and outdoor construction operations was conducted by Bilan et al. (1989). In outdoor locations (three rooftops), sprayers were exposed to MDI air concentrations ranging from 0.003 to 0.05 ppm, helpers were exposed to 0.013–0.038 ppm, area personnel 5–40 feet away were exposed to 0.003–0.006 ppm, and area personnel 45 feet away were in an area with no detectable MDI. In five indoor locations ranging from 750 to 3,375 square feet, sprayers were exposed to MDI air concentrations ranging from 0.008 to 0.129 ppm, helpers were exposed to 0.001–0.018 ppm, area personnel 6–<25 feet away were exposed to 0.007–0.093 ppm, and area personnel 25–100 feet away were in an area with no detectable MDI to 0.002 ppm. This study determined that the dominant factor in worker exposure to MDI was the distance from the spray operation and the time spent near the spray operation (Bilan et al. 1989). In another study measuring the exposure of sprayers and helpers to MDI during applications of polyurethane foam to dwellings and office buildings, MDI was measured in the personal air samples of sprayers at concentrations of 0.018–0.077 and 0.017–0.400 mg/m^3 during outdoor and indoor applications, respectively (Crespo and Galan 1999). Helpers were exposed to MDI concentrations of 0.034–0.045 and 0.025–0.308 mg/m^3 during outdoor and indoor applications, respectively. Maximum airborne MDI concentrations measured 15, 45, and >45 minutes after spray foam application inside five single-family homes were 0.019 mg/m^3, 0.003 mg/m^3, and below the limit of quantification (LOQ) (0.036 μg/sample), respectively (Lesage et al. 2007). Measured MDI concentrations sampled 1–3, 3–6, and 6–12 m away from application in this study were 0.147–1.55, 0.005–1.12, and <LOQ–0.822 mg/m^3, respectively (Lesage et al. 2007). During the application of MDI in foam or film coating of surfaces by spray gun techniques, >95% of air samples contained MDI particulates of respirable size, and counts were from 2 to 8 million parts/feet^3.

In general, MDI levels decreased rapidly and were undetectable 1 hour postapplication. Many of the airborne MDI samples collected in the breathing zone of the applicators during spraying exceeded the OSHA permissible exposure limit (PEL) of 0.2 mg/m^3, and thus, there are recommendations that workers use an air-purifying respirator equipped with a combination organic vapor cartridge and prefilter during

application. Additionally, in order to decrease dermal exposure, personal protective equipment such as gloves, coveralls, and goggles are recommended. Additional industry recommendations when spray polyurethane foam (SPF) insulation is being applied to buildings are to vacate the structure and ventilate the area following installation. Building occupants should not return until after the manufacturer's recommended re-occupancy time (typically 24 hours) has elapsed.

Air monitoring methods may not fully characterize exposure patterns to workers, as they do not take into account possible dermal absorption (Austin 2007). In a study of 19 workers at an iron foundry, the average personal air concentration of MDI was 0.55 μg/m^3 and dermal exposure to MDI ranged from 0.006 to 0.34 μg, indicating that dermal exposure can be a significant exposure pathway (Liljelind et al. 2010). Therefore, biological markers of isocyanates in urine and plasma may be valuable indicators in the work environment (Austin 2007). TDI in biological samples are hydrolyzed to form TDA for analysis (Tinnerberg et al. 1997). Austin (2007) conducted a study that showed how urinary TDA was a useful indication of the contribution of skin exposure to total TDI exposure in a polyurethane foam plant using 80:20 mixture of 2,4- and 2,6-TDI. This was done by comparing urinary TDA levels in two groups: 13 workers who had physical contact with uncured polyurethane foam (handlers) and 13 workers in the same plant environment who had no physical contact with uncured foam (non-handlers) on the day of sampling. Both groups were exposed to the same TDI air concentrations, ranging from <3.5 to 8.4 μg/m^3. In hydrolyzed post-shift urine samples, 10 handlers were found to have urinary TDA above detection limits with a mean level of 2.21 μmol/mol creatinine, compared to only 2 non-handlers (mean 0.11 μmol/mol creatinine).

Hydrolyzed post-shift urine samples collected from 15 workers in a polyurethane foam plant had TDA concentrations of 0.6–4.0 μg/L, while all urine samples from 12 people with no known history of TDI exposure had urinary TDA concentrations of below the detection limit of 0.1 μg/L (Carbonnelle et al. 1996).

In a study of four exposed workers and one volunteer working 8-hour shifts in a TDI flexible foam plant using an 80:20 mixture of 2,4- and 2,6-TDI, plasma concentrations were 1–38 and 7–24 μg/L for 2,4- and 2,6-TDA, respectively. Over a 3-day period, the individual plasma levels among the workers varied between 7 and 73%. An increase in plasma TDA for each workday was observed for the volunteer, and reached a maximum concentration 24 hours after the last exposure. The half-life in plasma was estimated to be about 10 days (Tinnerberg et al. 1997). In the urine samples of the workers, TDA concentrations varied greatly with time and exposure, reaching a maximum shortly after exposure. Measured

concentrations of TDA in urine ranged from not detected to about 2.0 μg/mmol creatinine (Tinnerberg et al. 1997). Lind et al. (1996) performed a study monitoring 2,4- and 2,6-TDA in plasma from 11 workers at two separate flexible foam polyurethane production plants after their occupational exposure to 2,4- and 2,6-TDI. The TDI concentration and relative percent concentrations of 2,4- and 2,6-TDI were 0.4–4 μg/m^3 and 60/40–5/95% in plant 1, respectively, and 10–120 μg/m^3 and 65/35–30/70% in plant 2, respectively. The lower exposure levels in plant 1 compared to plant 2 was reflected in the plasma TDA concentrations. Plasma 2,4- and 2,6-TDA concentrations were 0.4–1.3 and 1.8–5.6 ng/mL, respectively, in plant 1 and 2–23 and 7.0–23 ng/mL, respectively, in plant 2 before a summer holiday.

In a study comparing the exposure to TDI in air and the concentration of TDA in urine of nine workers from two production lines in a polyurethane foam production plant using an 80:20 mixture of 2,4- and 2,6-TDI, it was reported that exposure to TDI in personal air during a shift resulted in an increase in TDA in the urine of the workers (Geens et al. 2012). Sampled over 4 days, personal air TDI concentrations ranged from 4.2 to 141.9 μg/m^3 and hydrolyzed pre- and post-shift urine TDA concentrations were 1.0–19.5 and 4.4–142.6 μg/L, respectively (Geens et al. 2012). Kaaria et al. (2001a) performed another study on the determination of airborne TDI and urinary 2,4- and 2-6-TDA during the production of flexible foam in two separate plants in which samples were collected during one work shift on 2 consecutive days. Plant 1, which applied high-pressure molding, had TDI air concentrations ranging from not detected (LOD 0.2 μg/m^3) to 230 μg/m, while Plant 2, which applied low-pressure molding, had concentrations ranging from not detected to 41 μg/m^3. The proportions of 2,4-and 2,6-TDI in the total exposure varied during different stages of the production process, but 2,6-TDI constituted about 75% of all TDI detected. In urine samples collected from 17 workers, total TDA (2,4- and 2,6-TDA) was detected at concentrations of 0.11–39 nmol/mmol creatinine in Plant 1 and <0.05–7.1 nmol/mmol creatinine in Plant 2. The higher urinary TDA concentrations in Plant 1 compared to Plant 2 parallels the higher TDI concentrations in Plant 1. Kaaria et al. (2001b) observed similar results in the study of exposure to airborne MDI during the molding of rigid polyurethane foam in a refrigerator and freezer manufacturing plant. MDI was below the limit of detection (3 μg/m^3) in 64% of air samples collected from the workers' breathing zone, with detectable samples containing 0.03–3.3 μg/m^3 MDI. However, detectable amounts of urinary MDA were found in 97% of urine samples ranging from 0.12 to 0.20 nmol/mmol creatinine, showing that monitoring of MDA in urine may be a useful method of assessing MDI exposure in workplaces that have low MDI concentrations in air.

During a study assessing MDI exposure by monitoring a specific MDI hemoglobin adduct, 5-isopropyl-3-[4-(4-aminobenzyl)phenyl]hydantoin (ABP-Val-Hyd), in human blood, blood samples from 25 workers

from an MDI plant had ABP-Val-Hyd marker concentrations ranging from 0.15 to 16.2 pmol/g, while 40 people from the general population with no known exposure had no detectable amounts of ABP-Val-Hyd (limit of detection of 0.062 pmol/g) (Gries and Leng 2013).

The National Occupational Exposure Survey (NOES) conducted by NIOSH in 1983 estimated that 53,321 workers employed at 2,896 facilities were potentially exposed to MDI in the United States (RTECS 2009a). The 1983 NOES also estimated that 10,921 and 2,872 workers employed at 838 and 415 facilities were potentially exposed to 2,4- and 2,6-TDI in the United States, respectively (RTECS 2009b, 2009c). The NOES database does not contain information on the frequency, concentration, or duration of exposure; the survey provides only estimates of workers potentially exposed to chemicals in the workplace.

6.6 EXPOSURES OF CHILDREN

This section focuses on exposures from conception to maturity at 18 years in humans. Differences from adults in susceptibility to hazardous substances are discussed in Section 3.7, Children's Susceptibility.

Children are not small adults. A child's exposure may differ from an adult's exposure in many ways. Children drink more fluids, eat more food, breathe more air per kilogram of body weight, and have a larger skin surface in proportion to their body volume than adults. A child's diet often differs from that of adults. The developing human's source of nutrition changes with age: from placental nourishment to breast milk or formula to the diet of older children who eat more of certain types of foods than adults. A child's behavior and lifestyle also influence exposure. Children crawl on the floor, put things in their mouths, sometimes eat inappropriate things (such as dirt or paint chips), and may spend more time outdoors. Children also are generally closer to the ground and have not yet developed the adult capacity to judge and take actions to avoid hazards (NRC 1993).

Exposure to TDI and MDI is mainly an occupational problem due to their manufacturing and processing in many different industries. There is limited data pertaining to the use and exposure of consumer and commercial products containing uncured TDI and MDI. Because of this, exposure levels to children have not been well characterized (EPA 2011a, 2011b).

6.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Exposure to TDI and MDI is mainly an occupational problem. Workers involved in the production of MDI and TDI, as well as those involved in the production of polyurethane foams, have the potential for high exposure, mostly via inhalation (Dahlin et al. 2008). However, the general population could be exposed to higher than background levels through the use of uncured polyurethane consumer products such as adhesives, sealants, paints, craft materials, and insulating foams.

Diisocyanates, such as MDI and TDI, are generally supplied as raw materials to formulators who use their reactivity to combine them with other chemicals to create various polyurethanes with a wide diversity of applications. This diversity of applications leads to worker exposures in a broad range of production facilities, from small businesses to automated production lines. Diisocyanates are commonly available in unreacted, uncured forms as part of product mixtures that require an end-use reaction to form a final product. Since some of these applications can occur beyond the confines of a controlled production facility, workers and formulators need to be careful to prevent exposures (EPA 2011a).

6.8 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of TDI and MDI is available. Where adequate information is not available, ATSDR, in conjunction with NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of TDI and MDI.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

6.8.1 Identification of Data Needs

Physical and Chemical Properties. The physical-chemical properties of TDI and MDI are provided in Chapter 4. Important properties such as melting point, boiling point, and vapor pressure are available.

Other properties such as water solubility and octanol/water partition coefficient are not applicable due to the rapid rate of hydrolysis. No data needs are identified.

Production, Import/Export, Use, Release, and Disposal. According to the Emergency Planning and Community Right-to-Know Act of 1986, 42 U.S.C. Section 11023, industries are required to submit substance release and off-site transfer information to the EPA. This database is updated yearly and should provide a list of industrial production facilities and emissions.

Production, use, and import/export data are available (EPA 2011a; NTP 2011). Continuous updated information regarding these quantities is necessary.

Environmental Fate. The environmental fate and transport of TDI and MDI is well understood. Hydrolysis is the dominant process affecting the overall environmental fate, transport, and bioaccumulation potential. Additional research on the heterogeneous condensed phase atmospheric hydrolysis of TDI and MDI would be helpful in determining the significance of atmospheric hydrolysis for these compounds.

Bioavailability from Environmental Media. The rapid hydrolysis of TDI and MDI suggests that these compounds will not be biologically available in the environment. No data needs are identified.

Food Chain Bioaccumulation. The rapid hydrolysis of TDI and MDI suggests that these compounds will not bioconcentrate in aquatic organisms or bioaccumulate in the food chain. No data needs are identified.

Exposure Levels in Environmental Media. Reliable monitoring data for the levels of TDI and MDI in contaminated media at hazardous waste sites are needed so that the information obtained on levels of TDI and MDI in the environment can be used in combination with the known body burden of TDI and MDI to assess the potential risk of adverse health effects in populations living in the vicinity of hazardous waste sites.

Exposure Levels in Humans. In order to evaluate the possible correlation between the air levels of diisocyanates and the urine and plasma levels of the amine metabolites, more studies monitoring the concentration in workplace air and concentration in biological samples of workers exposed to diisocyanates are needed (Tinnerberg et al. 1997).

There is limited exposure data pertaining to the use and exposure of consumer and commercial products containing uncured TDI and MDI (EPA 2011a, 2011b). Additional studies on the personal air and dermal exposure characterizing the concentration of TDI and MDI during application of these products is needed to assess the exposure to the general population.

This information is necessary for assessing the need to conduct health studies on these populations.

Exposures of Children. There are limited data pertaining to the use and exposure of consumer and commercial products containing uncured TDI and MDI. Because of this, exposure levels to children have not been well characterized (EPA 2011a, 2011b). Additional studies on the personal air and dermal exposure characterizing the concentration of TDI and MDI during application of these products is needed to assess the exposure to children.

Child health data needs relating to susceptibility are discussed in Section 3.12.2, Identification of Data Needs: Children's Susceptibility.

Exposure Registries. The information amassed in the National Exposure Registry facilitates the epidemiological research needed to assess adverse health outcomes that may be related to exposure to these substances; however, no exposure registries for TDI and MDI were located. TDI and MDI are not currently compounds for which a sub-registry has been established in the National Exposure Registry. TDI and MDI will be considered in the future when chemical selection is made for sub-registries to be established.

6.8.2 Ongoing Studies

No ongoing environmental fate studies for TDI or MDI were identified using the NIH RePORTER (2014) or the Defense Technical Information Center (DTIC) online database.

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7. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting, measuring, and/or monitoring TDI and MDI, their metabolites, and other biomarkers of exposure and effect to TDI and MDI. The intent is not to provide an exhaustive list of analytical methods. Rather, the intention is to identify well-established methods that are used as the standard methods of analysis. Many of the analytical methods used for environmental samples are the methods approved by federal agencies and organizations such as EPA and the National Institute for Occupational Safety and Health (NIOSH). Other methods presented in this chapter are those that are approved by groups such as the Association of Official Analytical Chemists (AOAC) and the American Public Health Association (APHA). Additionally, analytical methods are included that modify previously used methods to obtain lower detection limits and/or to improve accuracy and precision.

7.1 BIOLOGICAL MATERIALS

Some of the methods used for determining TDI and MDI in biological media are reported in Table 7-1.

Since diisocyanates react much more rapidly with the sulfhydryl, amino, and hydroxyl groups present on proteins than with water in physiological situations, they are primarily eliminated from the body as protein adducts. TDI and MDI can be effectively assayed in urine by first carrying out a strong acid extraction of the urine samples, which releases the corresponding free amine (i.e., TDA or MDA) (Rosenberg and Savolainen 1986b). The urine hydrolysate is then extracted with toluene and a perfluoroalkyl anhydride, commonly heptafluorobutyric anhydride or pentafluoropropionic anhydride, is added to produce perfluoroacylated amide derivatives that are analyzed by gas chromatography (GC)/mass spectrometry (MS) (Dalene et al. 1997; Rosenberg and Savolainen 1986b). Instead of using GC/MS, these amide derivatives may also be evaporated from the toluene solution and then dissolved in a mobile phase consisting of 0.1 M ammonium acetate in 55/20/25% acetonitrile/methanol/water for analysis by liquid chromatography (LC)/MS (Skarping et al. 1994).

Alkaline hydrolysis of diisocyanates protein adducts to amines has also been used for quantification in urine. A method involving strongly alkaline conditions to hydrolyze TDI protein adducts to toluene diamines followed by extraction with toluene and analysis using reverse phase high performance liquid chromatography (HPLC) and electrochemical detection has been described (Carbonelle et al. 1996).

Table 7-1. Analytical Methods for Determining TDI and MDI in Biological Materials

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Human urine (diisocyanate-derived amines)	Heat with sulfuric acid; adjust pH to ~9.2; cleanup on SPE silica cartridge; solvent extraction with toluene; derivatization with heptafluorobutyric anhydride	GC/MS	0.2 pmol per injection	No data	Rosenberg and Savolainen 1986a
Human urine (2,6-TDA)	Heat with sulfuric acid; solvent extraction with toluene; derivatization with heptafluorobutyric anhydride	GC/MS	2 pg for a 1 μL sample	96% (3% RSD)	Rosenberg and Savolainen 1986b
Human urine (4,4'-MDA)	Acidic hydrolysis with sulfuric acid; extraction with toluene; derivatization with pentafluoropropionic anhydride; evaporation; dissolution in 0.1 M ammonium acetate in 55/20/25% ACN/methanol/ water	LC/PSP-MS	0.1 pg/μL	No data	Skarping et al. 1994
Human urine (TDAs)	Alkaline hydrolysis with sodium hydroxide; extraction with toluene; purification with a cation-exchange column containing methanol and phosphoric acid solution	RP-HPLC/ED	0.1 μg/L (2,6-TDA); 0.15 μg/L (2,4-TDA)	87.6% (7.9% RSD) (2,6-TDA); 88.3% (5.3% RSD) (2,4-TDA)	Carbonnelle et al. 1996
Human urine, plasma (TDA, MDA)	Acidic hydrolysis with sulfuric acid; extraction with toluene; derivatization with pentafluoropropionic anhydride	GC/MS	No data	No data	Dalene et al. 1997
Human blood (MDI adduct ABP-Val-Hyd)	Blood sample centrifuged and washed with 2.5 mL of 0.9% sodium chloride solution; hydrolysis with HCl; derivatization with heptafluorobutyric anhydride	GC/MS-NCI	0.02 ng ABP-Val-Hyd/g globin	99.8% (3.0–9.3% RSD)	Gries and Leng 2013

ABP-Val-Hyd = 5-isopropyl-3-[4-(4-aminobenzyl)phenyl]hydantoin; ACN = acetonitrile; ED = electrochemical detection; GC = gas chromatography; HCl = hydrochloric acid; LC = liquid chromatography; MDA = methylene dianiline; MDI = methylenediphenyl diisocyanate; MS = mass spectrometry; NA = not applicable; NCI = negative chemical ionization; PSP = plasma spray; RP-HPLC = reverse phase high performance liquid chromatography; RSD = relative standard deviation; SPE = solid-phase extraction; TDA = toluene diamine; TDI = toluene diisocyanate

Amine hydrolysis products may also be detected in plasma. Similar to urinalysis, sample preparation involves heating the plasma with sulfuric acid to hydrolyze the amines diisocyanate-protein adducts, which are extracted with toluene and then pentafluoropropionic anhydride is added to produce perfluoroacylated amide derivatives that are analyzed by GC/MS (Dalene et al. 1997).

Gries and Leng (2013) have described a method for detecting the MDI-hemoglobin adduct ABP-Val-Hyd in human blood as a marker for MDI exposure. In this technique, a blood sample is centrifuged to separate the erythrocytes from the plasma, which are then washed with 2.5 mL of 0.9% sodium chloride solution. A globin residue is produced, which is hydrolyzed using 2 mL of 2 M hydrochloric acid and derivatization was done by adding heptafluorobutyric anhydride to produce a perfluoroacylated amide. Analysis is performed by GC and high-resolution MS with negative chemical ionization.

7.2 ENVIRONMENTAL SAMPLES

Methods of analysis are available for the determination of TDI and MDI in air. These include HPLC, GC, and spectrophotometry. The use of a bubbler that collects air through an impinger containing an absorbent solution is the most common sampling procedure (Rosenberg and Savolainen 1986b). A critical review of sampling and analysis methods for TDI and MDI in air is presented in Levine et al. (1995). A summary of analytical methods is shown in Table 7-2.

Analysis of aromatic diisocyanates was historically performed using Marcali or Ranta colorimetric methods, with the Marcali method being the method of choice. However, these methods are limited by their lack of specificity. The Marcali method uses an acidified aqueous bubbler solution to collect diisocyanates in air and convert them into their respective diamines. The diamines then couple with N-1-naphthyl ethylenediamine to produce a colored complex. The intensity of the color measured at two different wavelengths is a measure of the amount of diisocyanates in the bubble. The inability to distinguish the diisocyanates from the produced diamines is the major limitation of this method (OSHA 1980).

The first sensitive and diisocyanate-specific method of analysis is employed by OSHA as Method 18 (OSHA 1980). Diisocyanates in air are trapped in a bubbler solution consisting of a nitro reagent (0.0002 M p-nitrobenzyl-N-n-propylamine) in toluene. This amine reacts with the diisocyanates to

Table 7-2. Analytical Methods for Determining TDI and MDI in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Air (diisocyanates)	Air drawn through a glass tube with a glass fiber filter and 0.1 mg of 1-2PP adsorbent; extraction with 90:10 (v/v) ACN/DMSO	HPLC/UV (Method 42)	1.6 μg/m^3 (2,6-TDI); 1.3 μg/m^3 (2,4-TDI); for a 15-L sample	86.4% (1.6% RSD) (2,6-TDI); 80.3% (2.4% RSD) (2,4-TDI)	OSHA 1989a
Air (MDI)	Air drawn through a glass tube with a glass fiber filter and 1.0 mg of 1-2PP adsorbent; extraction with 90:10 (v/v) ACN/DMSO	HPLC/UV (Method 47)	0.8 μg/m^3 for a 15-L sample	94.8% (4.5% RSD)	OSHA 1989b
Air (diisocyanates)	Air drawn into a bubbler containing nitro reagent in toluene	HPLC (Method 18)	0.15 ppb (1 μg/m^3) (2,4-TDI); 0.10 ppb (1 μg/m^3) (MDI); for a 20-L sample	100% (2,4-TDI and MDI)	OSHA 1980
Air (total diisocyanates)	Air collected on fiberglass filters impregnated with nitro reagent (4-nitro-N-propylbenzylamine); SPE with 4:6:1 methanol/water/0.2M hydrochloric acid	DPP	8 μg/m^3 for a 50-L sample	98% (1.9% RSD)	Corbini et al. 1991
Air (total diisocyanates)	Air drawn through a glass tube with a glass fiber filter and 0.13–1.1 mg of MAP adsorbent; acetylation with acetic anhydride; extraction with 65:35 (v/v) ACN/ triethylammonium phosphate/formate	RP-HPLC/UV/FD (Method 5525)	17 ng/sample; for a 15-L sample	97–99% (1.0–3.5% RSD)	NIOSH 2003
Air (2,4-TDI)	Air drawn through a tube with 200 mg of Tenax-TA adsorbent; thermal desorption	capGC/ FID-ITD	<0.001 μg/sample for a 1-L sample	99.5% (3.4–7% RSD)	Bianchi and Joyner 1997

Table 7-2. Analytical Methods for Determining TDI and MDI in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Air (2,4-TDI)	Air drawn into traps containing silica gel coated with phosphoric acid; elution with sodium hydroxide and methanol; separation with 60:40 (v/v) phosphate buffer/ methanol	HPLC/UV	0.2 μg/m^3 for a 20-L sample	100% (<3% RSD)	Colli et al. 1993
Air (TDI)	Air collected into a glass tube; simultaneous absorption and derivatization with p-aminophenol	HPLC/ ECHD	94 pg/sample	75–80% (<2% RSD)	Meyer and Tallman 1983
Air (TDI vapor and aerosols)	Air collected onto a denuder coated with dimethylpolysiloxane (adsorbent) and dibutylamine (derivatization reagent) in series with a glass fiber filter; extraction with ACN	LC-ESI/ MS-MS	1.9 ng/m^3 (2,4-TDI); 1.5 ng/m^3 (2,6-TDI)	99.4% (2,4-TDI); 99.7% (2,6-TDI)	Nordqvist et al. 2005
Air (MDI vapor and aerosols)	Air collected onto a denuder coated with N-4-nitrobenzyl-N-1-propylamine in series with a glass fiber filter; extraction with ACN	HPLC/UV	0.7 μg/m^3 (vapor phase); 3.3 μg/m^3 (condensed phase)	No data	Rando and Poovey 1994
Air (diisocyanates)	Air drawn through a glass tube with a glass fiber filter and di-n-butylamine in toluene; extraction with ACN	LC/MS	5–10 ng/mL	92% (2,6-TDI); 96% (2,4-TDI); 86% (MDI)	Bobeldijk et al. 2008
Occupational air (TDI)	Air collected on a 15-mg 1-2MPP-impregnated glass fiber filter; extraction with 1 mL ACN with 0.5% acetic anhydride	RP-HPLC/ UV	0.1 ng per injection	No data	Rosenberg and Savolainen 1986b

Table 7-2. Analytical Methods for Determining TDI and MDI in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Occupational air (diisocyanates)	Air collected using midget impinge flasks and derivatized with di-n-butylamine in toluene followed by a glass fiber filter; evaporation; dissolution in ACN	LC/MS	0.002 μg/m^3 (TDI and MDI)	~95% (<4% RSD for TDI); (12% RSD for MDI)	Karlsson et al. 2000
Occupational air (diisocyanates)	Air collected with an impinger and derivatized with 1-2MPP in toluene; acetylation; evaporation; dissolution in ACN/methanol buffer	HPLC/ ECHD/UV (Method 5521)	0.2 μg/sample (2,4- and 2,6-TDI) 0.09 μg/sample (MDI)	No data	NIOSH 1994
Occupational air (diisocyanates)	Air collected using an impinger and derivatized with tryptamine in DMSO; dissolution in ACN/ sodium acetate buffer	HPLC/FD/ ECHD (Method 5522)	0.1 μg/sample (2,4-TDI); 0.2 μg/sample (2,6-TDI); 0.3 μg/sample (MDI)	90.5% (2,4-TDI); 102.8% (2,6-TDI); 96.4% (MDI)	NIOSH 1996
Occupational air (MDI)	Air drawn into traps containing silica gel coated with phosphoric acid; elution with sodium hydroxide and methanol	GC/NPD	0.7 μg/m^3 for a 20-L sample	100% (<5% RSD)	D'Eril et al. 1995
Occupational vapor (2,4-TDI)	Air drawn through a glass tube with a 1-2PP/methylene chloride adsorbent; extraction with methanol/water	RP-HPLC/ UV	1 ppb for a 15-L sample	106.3% (10% RSD)	Chang and Burg 1982
Chemical products (TDI and MDI)	Derivatized with 9-(methyl aminomethyl)-anthracene (1% v/v) in dichloromethane	HPLC/UV	50 ppb (MDI) 5 ppb (TDI)	92–97% (<5% RSD)	Rastogi 1989

1-2MPP = 1-(2-methoxyphenyl)piperazine; 1-2PP = 1-(2-pyridyl)piperazine; ACN = acetonitrile; capGC = capillary gas chromatography; DMSO = dimethyl sulfoxide; DPP = differential-pulse polarography; ECHD = electrochemical detector; ED = electron capture detector; ESI = electrospray interface; FD = fluorescence detector; FID = flame ionization detector; GC = gas chromatography; HPLC = high performance liquid chromatography; ITD = ion-trap detector; LC = liquid chromatography; MAP = 1-(9-anthracenylmethyl)piperazine; MDI = methylenediphenyl diisocyanate; MS = mass spectrometry; NPD = nitrogen-phosphorus detector; RP-HPLC = reverse-phase high performance liquid chromatography; RSD = relative standard deviation; SPE = solid-phase extraction; TDI = toluene diisocyanate; UV = ultraviolet absorbance detection

produce ultraviolet (UV)-absorbing urea derivatives that can be easily analyzed by HPLC (OSHA 1980). Another nitro reagent method describes the analysis of diisocyanate monomers by collecting air onto fiberglass filters impregnated with 4-nitro-N-propylbenzylamine, followed by solid-phase extraction and determination of total diisocyanate concentration by differential-pulse polarography (Corbini et al. 1991).

A modified Marcali technique was described that allowed for the ability to isolate specific diisocyanates. Colli et al. (1993) reported this method for the determination of 2,4-TDI concentrations in air. In this procedure, air is collected in traps containing silica gel coated with phosphoric acid to form 2,4-TDA, followed by elution with methanol and sodium hydroxide and analysis using HPLC and UV detection. A similar method was described for the determination of MDI in workplace air, particularly spraying operations, which employs analysis by GC and a nitrogen-phosphorus detector (D'Eril et al. 1995).

Other sampling techniques collect air onto a solid sorbent media by using an impinger and a reagent-impregnated glass-fiber filter. These methods employ the use of a derivatizing agent, such as 1-(2-methoxyphenyl)piperazine, to form stable derivatives of the diisocyanates for HPLC and electrochemical detection (Rosenberg and Savolainen 1986b). Three NIOSH methods (Methods 5521, 5522, and 5525) have been used to analyze diisocyanates and employ the use of HPLC with UV, or UV and fluorescence detection (NIOSH 1994, 1996, 2003). Derivatizing agents in these methods include 1-(2-methoxyphenyl)piperazine, 1-(9-anthracenylmethyl)piperazine, and tryptamine. Several methods use 1-(2-pyridyl)piperazine as a derivatizing agent to form stable urea derivatives for detection by HPLC with UV (Chang and Burg 1982; OSHA 1989a, 1989b). Karlsson et al. (2000) described a method using a di-n-butylamine derivatizing agent followed by LC/MS analysis. This method was validated by Bobeldijk et al. (2008).

A method employing a chemosorptive denuder in series with a glass fiber filter in order to sample personal exposure to TDI vapor and aerosols was described (Nordqvist et al. 2005). This method used a dimethylpolysiloxane denuder coating with dibutylamine as a derivatizing agent. Analysis is performed using LC with an electrospray interface with MS. The advantages of this method include a wide sampling concentration range and accurate vapor-particulate-phase distribution measurements (Nordqvist et al. 2005). Rando and Poovey (1994) described a similar method using a denuder in series with a glass fiber

filter coated with nitro reagent, N-4-nitrobenzyl-N-1-propylamine, for collection and derivatization of MDI vapor and aerosol followed by HPLC analysis and UV detection.

Bianchi and Joyner (1997) describe a method for detecting TDI in air that collects samples directly onto an adsorbent tube packed with Tenax-TA followed by thermal desorption and then uses capillary GC with simultaneous flame ionization and ion-trap detection.

A method for determining TDI and MDI in various types of chemical products, such as adhesives, insulating foam, sealing waxes, surface coatings, etc., has been described (Rastogi 1989). This method involves the reaction of the chemical product with 9-(methyl aminomethyl)-anthracene to form urea derivatives from the diisocyanates present, followed by HPLC and UV detection.

Analytical methods for the detection of diisocyanates in other media were not located. Diisocyanates hydrolyze rapidly in water, so it is therefore unlikely that significant amounts would be found in other environmental media, such as water, soil, sediment, or food.

7.3 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of TDI and MDI is available. Where adequate information is not available, ATSDR, in conjunction with NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of TDI and MDI.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

7.3.1 Identification of Data Needs

Methods for Determining Biomarkers of Exposure and Effect.

Exposure. TDI-protein adducts in biological samples are hydrolyzed to form TDA. (Tinnerberg et al. 1997). Methods of measuring this biomarker of exposure are available (Austin 2007; Carbonelle et al. 1996).

Effect. Respiratory exposure to diisocyanates can lead to occupationally induced asthma. Workers diagnosed with diisocyanate-induced asthma manifest characteristic physiological responses after specific bronchoprovocation, which correlate to changes in their airways (Bernstein 1996).

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. Analytical methods for measuring diisocyanates in air are available (Levine et al. 1995; NIOSH 1994, 1996, 2003). Diisocyanates hydrolyze rapidly in water and it is unlikely that significant amounts would be found in environmental media, such as water, soil, and sediment.

7.3.2 Ongoing Studies

L2 Diagnostics, LLC (A. Wisnewski, Principal Investigator) are developing innovative biomonitoring approaches to exposure surveillance for MDI. Specifically, they aim to develop blood tests that measure two different MDI exposure biomarkers. The first biomarker is MDI-specific antibodies (IgG), produced by the immune system in response to exposure. The second biomarker is the chemical (MDI) itself conjugated to albumin, the major "protein adduct" *in vivo* (NIH RePORTER 2014).

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8. REGULATIONS, ADVISORIES, AND GUIDELINES

MRLs are substance-specific estimates that are intended to serve as screening levels. They are used by ATSDR health assessors and other responders to identify contaminants and potential health effects that may be of concern at hazardous waste sites.

ATSDR has derived an acute-duration inhalation MRL of $1x10^{-5}$ ppm for TDI. The MRL is based on LOAEL of 0.005 ppm for decreases in lung function in healthy volunteers exposed to TDI for 6 hours (Vandenplas et al. 1999). The LOAEL was adjusted to continuous 24-hour exposure (from 6 hours/day) and divided by a total uncertainty factor of 100 (10 for the use of a LOAEL and 10 for human variability). Since there is uncertainty that the MRL would be protective for continuous exposure for 14 days, it is suggested that measured air concentrations should not exceed the MRL of $1x10^{-5}$ ppm during a 24-hour period.

ATSDR has derived a chronic-duration inhalation MRL of $3x10^{-6}$ ppm for TDI. The MRL is based on the mean daily exposure level of 0.0012 ppm, which resulted in decreases in lung function in workers at flexible foam producing facilities (Clark et al. 1998). The adverse effect level of 0.0012 ppm was adjusted for intermittent exposure (8 hours/day, 5 days/week) and divided by a total uncertainty factor of 100 (10 for the use of a LOAEL and 10 for human variability).

EPA (IRIS 2003) has derived a chronic-duration reference concentration (RfC) of $7x10^{-5}$ mg/m^3 ($1x10^{-5}$ ppm) based on a NOAEL of 0.0009 ppm and a LOAEL of 0.0019 ppm for decreases in lung function in workers at a TDI manufacturing facility (Diem et al. 1982). The NOAEL was adjusted for intermittent exposure ([10 m^3/day]/[20 m^3/day], 5 days/week) and divided by a total uncertainty factor of 30 (3 to account for both extrapolation from a subchronic study and the lack of developmental toxicity data in a second species and 10 for intrahuman variability).

ATSDR has derived a chronic-duration inhalation MRL of 0.001 mg/m^3 for polymeric MDI. The MRL is based on a $BMCL_{10}$ of 0.48 mg/m^3 for basal cell hyperplasia in the nasal cavity observed in rats exposed to polymeric MDI for 2 years (Reuzel et al. 1994). The $BMCL_{10}$ was adjusted for intermittent exposure (6 hours/day, 5 days/week) and multiplied by a regional deposited dose ratio for extrathoracic effect ($RDDR_{ET}$) of 0.453 to calculate the human equivalent concentration ($BMCL_{HEC}$). The $BMCL_{HEC}$ of 0.039 mg/m^3 was divided by a total uncertainty factor of 30 (3 to extrapolate from animals to humans

with dosimetric adjustments and 10 for human variability); EPA notes that "the two UFs of 3 each coalesce to a 10, yielding a total UF of 100."

EPA (IRIS 2002) has derived a chronic-duration RfC of 0.0006 mg/m^3 based on a $BMCL_{ADJ}$ of 0.14 mg/m^3 for basal cell hyperplasia in rats exposed to polymeric MDI for 2 years (Reuzel et al. 1994). The $BMCL_{HEC}$ was calculated by multiplying the $BMCL_{ADJ}$ of 0.14 mg/m^3 by a $RDDR_{ET}$ of 0.453. The $BMCL_{HEC}$ of 0.06 mg/m^3 was divided by a total uncertainty factor of 100 (10 for intraindividual variation, 3 for the lack of reproductive data, and 3 for "interspecies variation inasmuch as dosimetric adjustments had been made").

The international and national regulations, advisories, and guidelines regarding TDI and MDI in air, water, and other media are summarized in Table 8-1.

Table 8-1. Regulations, Advisories, and Guidelines Applicable to TDI and MDI

Agency	Description	Information	Reference
International			
Guidelines:			
IARC	Carcinogenicity classification		
	TDI	Group 2B[a]	IARC 1999b
	4,4'-MDI	Group 3[b]	IARC 1999a
WHO	Air quality guidelines	Not listed	WHO 2010
	Drinking water quality guidelines	Not listed	WHO 2017
National			
Regulations and guidelines:			
a. Air			
ACGIH	TLV-TWA[c,d,e]		
	2,4-TDI or 2,6-TDI (or as a mixture)	0.001 ppm[f]	ACGIH 2016a
	Monomeric 4,4'-MDI	0.005 ppm	ACGIH 2001
	STEL		
	2,4-TDI or 2,6-TDI (or as a mixture)	0.005 ppm[f]	ACGIH 2016a
DOE	PAC-1[g]		DOE 2016b
	TDI, mixed isomers	0.020 ppm	
	2,4-TDI	0.020 ppm	
	2,6-TDI	0.020 ppm	
	Monomeric 4,4'-MDI	0.45 mg/m^3	
	Polymeric 4,4'-MDI	29 mg/m^3	
	PAC-2[g]		
	TDI, mixed isomers	0.083 ppm	
	2,4-TDI	0.083 ppm	
	2,6-TDI	0.083 ppm	
	Monomeric 4,4'-MDI	5 mg/m^3	
	Polymeric 4,4'-MDI	40 mg/m^3	
	PAC-3[g]		
	TDI, mixed isomers	0.51 ppm	
	2,4-TDI	0.51 ppm	
	2,6-TDI	0.51 ppm	
	Monomeric 4,4'-MDI	55 mg/m^3	
	Polymeric 4,4'-MDI	240 mg/m^3	

Table 8-1. Regulations, Advisories, and Guidelines Applicable to TDI and MDI

Agency	Description	Information	Reference
EPA	2,4-TDI		EPA 2016a
	AEGL-1[h]		
	10 minutes	0.020 ppm	
	30 minutes	0.020 ppm	
	60 minutes	0.020 ppm	
	4 hours	0.010 ppm	
	8 hours	0.010 ppm	
	AEGL-2[h]		
	10 minutes	0.24 ppm	
	30 minutes	0.17 ppm	
	60 minutes	0.083 ppm	
	4 hours	0.021 ppm	
	8 hours	0.021 ppm	
	AEGL-3[h]		
	10 minutes	0.65 ppm	
	30 minutes	0.65 ppm	
	60 minutes	0.51 ppm	
	4 hours	0.32 ppm	
	8 hours	0.16 ppm	
	2,6-TDI		
	AEGL-1[h]		
	10 minutes	0.020 ppm	
	30 minutes	0.020 ppm	
	60 minutes	0.020 ppm	
	4 hours	0.010 ppm	
	8 hours	0.010 ppm	
	AEGL-2[h]		
	10 minutes	0.24 ppm	
	30 minutes	0.17 ppm	
	60 minutes	0.083 ppm	
	4 hours	0.021 ppm	
	8 hours	0.021 ppm	
	AEGL-3[h]		
	10 minutes	0.65 ppm	
	30 minutes	0.65 ppm	
	60 minutes	0.51 ppm	
	4 hours	0.32 ppm	
	8 hours	0.16 ppm	
	Hazardous air pollutant		EPA 2016c 42 USC 7412
	2,4-TDI	Yes	
	Monomeric 4,4'-MDI	Yes	

Table 8-1. Regulations, Advisories, and Guidelines Applicable to TDI and MDI

Agency	Description	Information	Reference
	NAAQS	Not listed	EPA 2018b
NIOSH	REL		NIOSH 2016a, 2016b
	2,4-TDI	Potential occupational carcinogens	
	Monomeric 4,4'-MDI	0.05 mg/m^3	
	Ceiling limit (10-minute)		
	Monomeric 4,4'-MDI	0.2 mg/m^3	
	IDLH		
	2,4-TDI	2.5 ppm	
	Monomeric 4,4'-MDI	75 mg/m^3	
OSHA	Ceiling limit (15-minute TWA) for general industry		OSHA 2017b 29 CFR 1910.1000, Table Z-2
	2,4-TDI	0.02 ppm	
	Monomeric 4,4'-MDI	0.02 ppm	
	Highly hazardous chemicals	Not listed	OSHA 2017a 29 CFR 1910.119, Appendix A
b. Water			
EPA	Designated as hazardous substances in accordance with Section 311(b)(2)(A) of the Clean Water Act	Not listed	EPA 2017b 40 CFR 116.4
	Drinking water contaminant candidate list		EPA 2016b 81 FR 81099
	TDI	Yes	
	Drinking water standards and health advisories	Not listed	EPA 2012
	National primary drinking water standards	Not listed	EPA 2009b
	National recommended water quality criteria: human health for the consumption of (at 10^{-4} risk)	Not listed	EPA 2018c
	Reportable quantities of hazardous substances designated pursuant to Section 311 of the Clean Water Act	Not listed	EPA 2017d 40 CFR 117.3
c. Food			
FDA	Bottled water	Not listed	FDA 2017 21 CFR 165.110
	EAFUS[i]	Not listed	FDA 2013
d. Other			
ACGIH	Carcinogenicity classification		ACGIH 2016a
	2,4-TDI or 2,6-TDI (or as a mixture)	A3[j]	

Table 8-1. Regulations, Advisories, and Guidelines Applicable to TDI and MDI

Agency	Description	Information	Reference
EPA	Carcinogenicity classification		IRIS 2002, 2003
	TDI (toluene 2,4- (2,6-) diisocyanate)	No data	
	MDI (monomeric MD) and polymeric MDI)	Group D[k]	
	RfC		
	2,4-/2,6-TDI	$7x10^{-5}$ mg/m^3	
	MDI (monomeric MDI and polymeric MDI)	$6x10^{-4}$ mg/m^3	
	RfD		
	2,4-/2,4-TDI (toluene 2,4- (2,6-) diisocyanate)	Not listed	
	MDI (monomeric MDI and polymeric MDI)	Not listed	
	Identification and listing of hazardous waste		EPA 2017c 40 CFR 261, Appendix VIII
	TDI (toluene 2,4- (2,6-) diisocyanate)	U223	
	Master Testing List		EPA 1996
	Monomeric 4,4'-MDI	Yes	
	Polymethylene polyphenyl isocyanate	Yes	
	Polymeric 4,4'-MDI	Yes	
	RCRA waste minimization PBT priority chemical list	Not listed	EPA 1998b 63 FR 60332
	Standards for owners and operators of hazardous waste TSD facilities; groundwater monitoring list	Not listed	EPA 2017e 40 CFR 264, Appendix IX
	Superfund, emergency planning, and community right-to-know		
	Designated CERCLA hazardous substance and reportable quantity		EPA 2017f 40 CFR 302.4
	TDI (toluene 2,4- (2,6-) diisocyanate)[l]	100 pounds	
	2,4-TDI[l]	100 pounds	
	2,6-TDI[l]	100 pounds	
	Monomeric 4,4'-MDI[m]	5,000 pounds	
	Effective date of toxic chemical release reporting		EPA 2017g 40 CFR 372.65
	TDI (toluene 2,4- (2,6-) diisocyanate)	01/01/1990	
	2,4-TDI	01/01/1987	
	2,6-TDI	01/01/1987	
	Monomeric 4,4'-MDI	01/01/1987	
	Diisocyanates category (including MDI and polymeric MDI)	01/01/1995	

Table 8-1. Regulations, Advisories, and Guidelines Applicable to TDI and MDI

Agency	Description	Information	Reference
	Extremely hazardous substances and its threshold planning quantity		EPA 2017h 40 CFR 355, Appendix A
	2,4-TDI	500 pounds	
	2,6-TDI	100 pounds	
	TSCA chemical lists and reporting periods		EPA 2017i 40 CFR 712.30
	Monomeric 4,4'-MDI		
	Effective date	10/29/1990	
	Reporting date	12/27/1990	
	Polymeric 4,4'-DMDI		
	Effective date	10/29/1990	
	Reporting date	12/27/1990	
	TSCA health and safety data reporting		EPA 2017j 40 CFR 716.120
	TDI (2,4 and 2,6 mixed isomers); 2,4-TDI; monomeric 4,4'-MDI; polymeric 4,4'-MDI		
	Effective date	06/01/1987	
	Reporting date	06/01/1997	
	2,6-TDI		
	Effective date	06/01/1987	
	Reporting date	12/19/1995	
NTP	Carcinogenicity classification		NTP 2016
	TDI	Reasonably anticipated to be a human carcinogen	

[a]Group 2B: possibly carcinogenic to humans.
[b]Group 3: not classifiable as to its carcinogenicity to humans.
[c]Skin notation: refers to potential significant contribution to the overall exposure by the cutaneous route (ACGIH 2016b).
[d]Dermal sensitization notation: refers to potential for agent to produce dermal sensitization (ACGIH 2016b).
[e]Respiratory sensitization notation: refers to potential for agent to produce respiratory sensitization (ACGIH 2016b).
[f]Inhalable fraction and vapor: material exerts sufficient vapor pressure such that it may be present in both particle and vapor phases, with each contributing a significant portion of the dose at the TLV-TWA concentration (ACGIH 2016b).
[g]Definitions of PAC terminology are available from DOE (2016a).
[h]AEGL-1 is the airborne concentration 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 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 of a substance above which it is predicted that the general population, including susceptible individuals, could experience life-threatening health effects or death (EPA 2018a).
[i]The EAFUS list of substances contains ingredients added directly to food that FDA has either approved as food additives or listed or affirmed as GRAS.
[j]A3: confirmed animal carcinogen with unknown relevance to humans.
[k]Group D: not classifiable as to human carcinogenicity.

Table 8-1. Regulations, Advisories, and Guidelines Applicable to TDI and MDI

Agency	Description	Information	Reference

[l]Designated CERCLA hazardous substance and reportable quantity pursuant to Section 112 of the Clean Air Act and Section 3001 of RCRA.
[m]Designated CERCLA hazardous substance and reportable quantity pursuant to Section 112 of the Clean Air Act.

ACGIH = American Conference of Governmental Industrial Hygienists; AEGL = acute exposure guideline levels; CERCLA = Comprehensive Environmental Response, Compensation, and Liability Act; CFR = Code of Federal Regulations; DOE = Department of Energy; EAFUS = Everything Added to Food in the United States; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; FR = Federal Register; GRAS = generally recognized as safe; IARC = International Agency for Research on Cancer; IDLH = immediately dangerous to life or health; IRIS = Integrated Risk Information System; MDI = methylenediphenyl diisocyanate; NAAQS = National Ambient Air Quality Standards; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; PAC = protective action criteria; PBT = persistent, bioaccumulative, and toxic; RCRA = Resource Conservation and Recovery Act; REL = recommended exposure limit; RfC = inhalation reference concentration; RfD = oral reference dose; SIDS = Screening Information Data Set; STEL = short-term exposure limit; TDI = toluene diisocyanate; TLV = threshold limit values; TSCA = Toxic Substances Control Act; TSD = treatment, storage, and disposal; TWA = time-weighted average; USC = United States Code; WHO = World Health Organization

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9. REFERENCES

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10. GLOSSARY

Absorption—The taking up of liquids by solids, or of gases by solids or liquids.

Acute Exposure—Exposure to a chemical for a duration of 14 days or less, as specified in the Toxicological Profiles.

Adsorption—The adhesion in an extremely thin layer of molecules (as of gases, solutes, or liquids) to the surfaces of solid bodies or liquids with which they are in contact.

Adsorption Coefficient (K_{oc})—The ratio of the amount of a chemical adsorbed per unit weight of organic carbon in the soil or sediment to the concentration of the chemical in solution at equilibrium.

Adsorption Ratio (Kd)—The amount of a chemical adsorbed by sediment or soil (i.e., the solid phase) divided by the amount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed in micrograms of chemical sorbed per gram of soil or sediment.

Benchmark Dose (BMD)—Usually defined as the lower confidence limit on the dose that produces a specified magnitude of changes in a specified adverse response. For example, a BMD_{10} would be the dose at the 95% lower confidence limit on a 10% response, and the benchmark response (BMR) would be 10%. The BMD is determined by modeling the dose response curve in the region of the dose response relationship where biologically observable data are feasible.

Benchmark Dose Model—A statistical dose-response model applied to either experimental toxicological or epidemiological data to calculate a BMD.

Bioconcentration Factor (BCF)—The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same period.

Biomarkers—Broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility.

Cancer Effect Level (CEL)—The lowest dose of chemical in a study, or group of studies, that produces significant increases in the incidence of cancer (or tumors) between the exposed population and its appropriate control.

Carcinogen—A chemical capable of inducing cancer.

Case-Control Study— A type of epidemiological study that examines the relationship between a particular outcome (disease or condition) and a variety of potential causative agents (such as toxic chemicals). In a case-control study, a group of people with a specified and well-defined outcome is identified and compared to a similar group of people without the outcome.

Case Report—Describes a single individual with a particular disease or exposure. These may suggest some potential topics for scientific research, but are not actual research studies.

Case Series—Describes the experience of a small number of individuals with the same disease or exposure. These may suggest potential topics for scientific research, but are not actual research studies.

Ceiling Value—A concentration that must not be exceeded.

Chronic Exposure—Exposure to a chemical for 365 days or more, as specified in the Toxicological Profiles.

Cohort Study—A type of epidemiological study of a specific group or groups of people who have had a common insult (e.g., exposure to an agent suspected of causing disease or a common disease) and are followed forward from exposure to outcome. At least one exposed group is compared to one unexposed group.

Cross-sectional Study—A type of epidemiological study of a group or groups of people that examines the relationship between exposure and outcome to a chemical or to chemicals at one point in time.

Data Needs—Substance-specific informational needs that, if met, would reduce the uncertainties of human health risk assessment.

Developmental Toxicity—The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

Dose-Response Relationship—The quantitative relationship between the amount of exposure to a toxicant and the incidence of the adverse effects.

Embryotoxicity and Fetotoxicity—Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the insult occurs. The terms, as used here, include malformations and variations, altered growth, and *in utero* death.

Environmental Protection Agency (EPA) Health Advisory—An estimate of acceptable drinking water levels for a chemical substance based on health effects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

Epidemiology—Refers to the investigation of factors that determine the frequency and distribution of disease or other health-related conditions within a defined human population during a specified period.

Genotoxicity—A specific adverse effect on the genome of living cells that, upon the duplication of affected cells, can be expressed as a mutagenic, clastogenic, or carcinogenic event because of specific alteration of the molecular structure of the genome.

Half-life—A measure of rate for the time required to eliminate one half of a quantity of a chemical from the body or environmental media.

Immediately Dangerous to Life or Health (IDLH)—A condition that poses a threat of life or health, or conditions that pose an immediate threat of severe exposure to contaminants that are likely to have adverse cumulative or delayed effects on health.

Immunologic Toxicity—The occurrence of adverse effects on the immune system that may result from exposure to environmental agents such as chemicals.

Immunological Effects—Functional changes in the immune response.

Incidence—The ratio of new cases of individuals in a population who develop a specified condition to the total number of individuals in that population who could have developed that condition in a specified time period.

Intermediate Exposure—Exposure to a chemical for a duration of 15–364 days, as specified in the Toxicological Profiles.

***In Vitro*—**Isolated from the living organism and artificially maintained, as in a test tube.

***In Vivo*—**Occurring within the living organism.

Lethal Concentration$_{(LO)}$ (LC_{LO})—The lowest concentration of a chemical in air that has been reported to have caused death in humans or animals.

Lethal Concentration$_{(50)}$ (LC_{50})—A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

Lethal Dose$_{(LO)}$ (LD_{Lo})—The lowest dose of a chemical introduced by a route other than inhalation that has been reported to have caused death in humans or animals.

Lethal Dose$_{(50)}$ (LD_{50})—The dose of a chemical that has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time$_{(50)}$ (LT_{50})—A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

Lowest-Observed-Adverse-Effect Level (LOAEL)—The lowest exposure level of chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

Lymphoreticular Effects—Represent morphological effects involving lymphatic tissues such as the lymph nodes, spleen, and thymus.

Malformations—Permanent structural changes that may adversely affect survival, development, or function.

Minimal Risk Level (MRL)—An estimate of daily human exposure to a hazardous substance that is likely to be without an appreciable risk of adverse noncancer health effects over a specified route and duration of exposure.

Modifying Factor (MF)—A value (greater than zero) that is applied to the derivation of a Minimal Risk Level (MRL) to reflect additional concerns about the database that are not covered by the uncertainty factors. The default value for a MF is 1.

Morbidity—State of being diseased; morbidity rate is the incidence or prevalence of disease in a specific population.

Mortality—Death; mortality rate is a measure of the number of deaths in a population during a specified interval of time.

Mutagen—A substance that causes mutations. A mutation is a change in the DNA sequence of a cell's DNA. Mutations can lead to birth defects, miscarriages, or cancer.

Necropsy—The gross examination of the organs and tissues of a dead body to determine the cause of death or pathological conditions.

Neurotoxicity—The occurrence of adverse effects on the nervous system following exposure to a hazardous substance.

No-Observed-Adverse-Effect Level (NOAEL)—The dose of a chemical at which there were no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Effects may be produced at this dose, but they are not considered to be adverse.

Octanol-Water Partition Coefficient (K_{ow})—The equilibrium ratio of the concentrations of a chemical in *n*-octanol and water, in dilute solution.

Odds Ratio (OR)—A means of measuring the association between an exposure (such as toxic substances and a disease or condition) that represents the best estimate of relative risk (risk as a ratio of the incidence among subjects exposed to a particular risk factor divided by the incidence among subjects who were not exposed to the risk factor). An OR of greater than 1 is considered to indicate greater risk of disease in the exposed group compared to the unexposed group.

Organophosphate or Organophosphorus Compound—A phosphorus-containing organic compound and especially a pesticide that acts by inhibiting cholinesterase.

Permissible Exposure Limit (PEL)—An Occupational Safety and Health Administration (OSHA) regulatory limit on the amount or concentration of a substance not to be exceeded in workplace air averaged over any 8-hour work shift of a 40-hour workweek.

Pesticide—General classification of chemicals specifically developed and produced for use in the control of agricultural and public health pests (insects or other organisms harmful to cultivated plants or animals).

Pharmacokinetics—The dynamic behavior of a material in the body, used to predict the fate (disposition) of an exogenous substance in an organism. Utilizing computational techniques, it provides the means of studying the absorption, distribution, metabolism, and excretion of chemicals by the body.

Pharmacokinetic Model—A set of equations that can be used to describe the time course of a parent chemical or metabolite in an animal system. There are two types of pharmacokinetic models: data-based and physiologically-based. A data-based model divides the animal system into a series of compartments, which, in general, do not represent real, identifiable anatomic regions of the body, whereas the physiologically-based model compartments represent real anatomic regions of the body.

Physiologically Based Pharmacodynamic (PBPD) Model—A type of physiologically based dose-response model that quantitatively describes the relationship between target tissue dose and toxic end points. These models advance the importance of physiologically based models in that they clearly describe the biological effect (response) produced by the system following exposure to an exogenous substance.

Physiologically Based Pharmacokinetic (PBPK) Model—Comprised of a series of compartments representing organs or tissue groups with realistic weights and blood flows. These models require a variety of physiological information: tissue volumes, blood flow rates to tissues, cardiac output, alveolar ventilation rates, and possibly membrane permeabilities. The models also utilize biochemical information, such as blood:air partition coefficients, and metabolic parameters. PBPK models are also called biologically based tissue dosimetry models.

Prevalence—The number of cases of a disease or condition in a population at one point in time.

Prospective Study—A type of cohort study in which the pertinent observations are made on events occurring after the start of the study. A group is followed over time.

q_1*—The upper-bound estimate of the low-dose slope of the dose-response curve as determined by the multistage procedure. The q_1* can be used to calculate an estimate of carcinogenic potency, the incremental excess cancer risk per unit of exposure (usually μg/L for water, mg/kg/day for food, and μg/m^3 for air).

Recommended Exposure Limit (REL)—A National Institute for Occupational Safety and Health (NIOSH) time-weighted average (TWA) concentration for up to a 10-hour workday during a 40-hour workweek.

Reference Concentration (RfC)—An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious noncancer health effects during a lifetime. The inhalation reference concentration is for continuous inhalation exposures and is appropriately expressed in units of mg/m^3 or ppm.

Reference Dose (RfD)—An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure of the human population to a potential hazard that is likely to be without risk of deleterious effects during a lifetime. The RfD is operationally derived from the no-observed-adverse-effect level (NOAEL, from animal and human studies) by a consistent application of uncertainty factors that reflect various types of data used to estimate RfDs and an additional modifying factor, which is based on a professional judgment of the entire database on the chemical. The RfDs are not applicable to nonthreshold effects such as cancer.

Reportable Quantity (RQ)—The quantity of a hazardous substance that is considered reportable under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA). Reportable quantities are (1) 1 pound or greater or (2) for selected substances, an amount established by regulation either under CERCLA or under Section 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

Reproductive Toxicity—The occurrence of adverse effects on the reproductive system that may result from exposure to a hazardous substance. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

Retrospective Study—A type of cohort study based on a group of persons known to have been exposed at some time in the past. Data are collected from routinely recorded events, up to the time the study is undertaken. Retrospective studies are limited to causal factors that can be ascertained from existing records and/or examining survivors of the cohort.

Risk—The possibility or chance that some adverse effect will result from a given exposure to a hazardous substance.

Risk Factor—An aspect of personal behavior or lifestyle, an environmental exposure, existing health condition, or an inborn or inherited characteristic that is associated with an increased occurrence of disease or other health-related event or condition.

Risk Ratio—The ratio of the risk among persons with specific risk factors compared to the risk among persons without risk factors. A risk ratio greater than 1 indicates greater risk of disease in the exposed group compared to the unexposed group.

Short-Term Exposure Limit (STEL)—A STEL is a 15-minute TWA exposure that should not be exceeded at any time during a workday.

Standardized Mortality Ratio (SMR)—A ratio of the observed number of deaths and the expected number of deaths in a specific standard population.

Target Organ Toxicity—This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

Teratogen—A chemical that causes structural defects that affect the development of an organism.

Threshold Limit Value (TLV)—An American Conference of Governmental Industrial Hygienists (ACGIH) concentration of a substance to which it is believed that nearly all workers may be repeatedly exposed, day after day, for a working lifetime without adverse effect. The TLV may be expressed as a Time Weighted Average (TLV-TWA), as a Short-Term Exposure Limit (TLV-STEL), or as a ceiling limit (TLV-C).

Time-Weighted Average (TWA)—An average exposure within a given time period.

Toxic Dose$_{(50)}$ (TD$_{50}$)—A calculated dose of a chemical, introduced by a route other than inhalation, which is expected to cause a specific toxic effect in 50% of a defined experimental animal population.

Toxicokinetic—The absorption, distribution, and elimination of toxic compounds in the living organism.

Uncertainty Factor (UF)—A factor used in operationally deriving the Minimal Risk Level (MRL) or Reference Dose (RfD) or Reference Concentration (RfC) from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using lowest-observed-adverse-effect level (LOAEL) data rather than no-observed-adverse-effect level (NOAEL) data. A default for each individual UF is 10; if complete certainty in data exists, a value of 1 can be used; however, a reduced UF of 3 may be used on a case-by-case basis, 3 being the approximate logarithmic average of 10 and 1.

Xenobiotic—Any substance that is foreign to the biological system.

APPENDIX A. ATSDR MINIMAL RISK LEVELS AND WORKSHEETS

The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) [42 U.S.C. 9601 et seq.], as amended by the Superfund Amendments and Reauthorization Act (SARA) [Pub. L. 99–499], requires that the Agency for Toxic Substances and Disease Registry (ATSDR) develop jointly with the U.S. Environmental Protection Agency (EPA), in order of priority, a list of hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL); prepare toxicological profiles for each substance included on the priority list of hazardous substances; and assure the initiation of a research program to fill identified data needs associated with the substances.

The toxicological profiles include an examination, summary, and interpretation of available toxicological information and epidemiologic evaluations of a hazardous substance. During the development of toxicological profiles, Minimal Risk Levels (MRLs) are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified route and duration of exposure. MRLs are based on noncancer health effects only and are not based on a consideration of cancer effects. These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.

MRLs are derived for hazardous substances using the no-observed-adverse-effect level/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1–14 days), intermediate (15–364 days), and chronic (365 days and longer) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive substance-induced endpoint considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that

are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as 100-fold below levels that have been shown to be nontoxic in laboratory animals.

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology and Human Health Sciences, expert panel peer reviews, and agency-wide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published levels. For additional information regarding MRLs, please contact the Division of Toxicology and Human Health Sciences, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop F-57, Atlanta, Georgia 30329-4027.

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Toluene diisocyanate
CAS Number: 26471-62-5
Date: June 2018
Profile Status: Final
Route: [X] Inhalation [ ] Oral
Duration: [X] Acute [ ] Intermediate [ ] Chronic
Graph Key: 1
Species: Humans

Minimal Risk Level: $1x10^{-5}$ [ ] mg/kg/day [X] ppm

Reference: Vandenplas O, Delwiche J-P, Staquet P, et al. 1999. Pulmonary effects of short-term exposure to low levels of toluene diisocyanate in asymptomatic subjects. Eur Respir J 13:1144-1150.

Experimental design: In this single-blind crossover design study, 17 volunteers (8 male, 9 females) were exposed to ambient air or 0.005 ppm TDI for 6 hours followed by a 20-minute exposure to 0.020 ppm TDI. Pulmonary function testing was conducted prior to exposure and every hour during the 6-hour exposure and at the end of the 20-minute exposure to 0.020 ppm or air. Bronchial lavage (BL) and bronchoalveolar lavage (BAL) were performed 1 hour after the end of the exposure.

Effect noted in study and corresponding doses: None of the subjects reported respiratory symptoms in response to the exposure. TDI exposure was associated with a slight, but significant, decrease in specific airway conductance (sGaw) and maximal expiratory flow at 25% of forced vital capacity ($MEF_{25\%}$). No significant alterations in the volume of fluid recovered or total and differential cell counts were observed in the BL and BAL after TDI exposure, as compared to air exposure. Exposure to TDI was associated with a decrease in the proportion of CD19 cells in the BL and BAL, although there was no difference in the absolute number of cells. A slight but statistically significant increase in BAL albumin levels and BL α-2-macroglobulin levels were observed.

Dose and end point used for MRL derivation: LOAEL of 0.005 ppm for decreased lung function

[ ] NOAEL [X] LOAEL

Uncertainty Factors used in MRL derivation:

[X] 10 for use of a LOAEL
[ ] 10 for extrapolation from animals to humans
[X] 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose? Not applicable.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: Not applicable.

Was a conversion used from intermittent to continuous exposure? Yes. The LOAEL of 0.005 ppm was adjusted for intermittent exposure:

0.005 ppm x 6 hours/24 hours = 0.00125 ppm

Other additional studies or pertinent information that lend support to this MRL: In another acute-duration human study, no alterations in specific air way resistance were observed in healthy or asthmatic subjects exposed to 0.02 ppm TDI for 20 minutes (Chester et al. 1979). Acute-duration animal inhalation studies have reported rhinitis, lung damage, and airway hyperresponsiveness. The severity of rhinitis was concentration-related; moderate rhinitis was observed in mice exposed to 0.07 ppm 6 hours/day for 4 days (Zissu 1995), moderate-to-severe rhinitis was observed in mice exposed to 0.4 ppm 6 hours/day for 5 days (Buckley et al. 1984), and severe nasal lesions were observed in mice exposed to 1 ppm 6 hours/day for 3 days (Arts et al. 2008). Interstitial inflammation, pleural thickening, and goblet cell hyperplasia were observed in the lungs of guinea pigs exposed to 1.4 ppm TDI 3 hours/day for 3 days (Wong et al. 1985). Airway hyperresponsiveness to methacholine or acetylcholine was also observed in guinea pigs and mice exposed to ≥0.01 ppm (Gagnaire et al. 1996; Gordon et al. 1985; Marek et al. 1999); a NOAEL of 0.005 ppm for airway hyperresponsiveness was identified in guinea pigs exposed to TDI 6 hours/day for 5 days (Marek et al. 1999). An increase in the incidence of litters with poorly ossified cervical centrum was observed in the offspring of rats exposed to 0.5 ppm commercial-grade TDI 6 hours/day on GDs 6–15 (Tyl et al. 1999a); this concentration was also associated with maternal toxicity including a marked decrease in body weight gain and signs of nasal irritation and audible respiration.

Support for basing the MRL on a single exposure study comes from chronic occupational exposure studies. The lowest LOAEL values identified in longitudinal studies of workers exposed to TDI were 0.0012 and 0.0019 ppm (Clark et al. 1998; Diem et al. 1982); the effects observed at these concentrations included decreases in lung function (FEV_1 and/or FVC). These LOAELs are roughly 2–4 times lower than the LOAEL from the Vandenplas et al. (1999) study. However, since there is uncertainty that the MRL would be protective for continuous exposure for 14 days, it is suggested that measured air concentrations should not exceed the MRL of 1×10^{-5} ppm during a 24-hour period.

Agency Contact (Chemical Manager): Malcolm Williams

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Toluene diisocyanate
CAS Number: 26471-62-5
Date: June 2018
Profile Status: Final
Route: [X] Inhalation [ ] Oral
Duration: [ ] Acute [ ] Intermediate [X] Chronic
Graph Key: 26
Species: Humans

Minimal Risk Level: $3x10^{-6}$ [ ] mg/kg/day [X] ppm

Reference: Clark RL, Bugler J, McDermott M, et al. 1998. An epidemiology study of lung function changes of toluene diisocyanate foam workers in the United Kingdom. Int Arch Occup Environ Health 71:169-179.

Experimental design: A group of 780 (649 males, 131 females) workers employed at 12 flexible foam-producing factories in the United Kingdom were examined over a 5-year period; all subjects had taken at least three pulmonary function tests over a period of at least 1 year. Workers were divided into three groups: (1) the exposed group (472 males and 49 females), which consisted of workers employed in the manufacture of polyurethane foam or were handling freshly manufactured products still emitting measurable quantities of TDI; (2) the handling group (80 males and 43 females), consisting of workers handling cold polyurethane products from which TDI emissions could not usually be detected; and (3) the low-exposure group (97 males and 39 females), consisting of shop floor and office workers (control group). The average time in the study was 4.3 years. Workers completed respiratory questionnaires at the start of the study and at the end (or when they left the study); pulmonary function testing was conducted annually at the same time of day, same day of the week, and same month of the year. The mean daily exposure to TDI was 0.0096-hours ppm (0.0012 ppm 8-hour TWA). The investigators noted that although 4.7% of the measurements exceeded the 8-hour TWA concentration limit of 0.0058 ppm, most of the subjects were exposed to <0.00125 ppm. Additionally, 19% of the samples in the exposed group exceeded the 15-minute short-term limit of 0.02 ppm.

Effect noted in study and corresponding doses: Significant increases in the prevalence of wheezing were observed in the handling and exposed groups; however, there were only small differences between the two groups. Longitudinal analysis did not find a significant exposure-related effect on lung function. Twenty-four cases of respiratory sensitization were identified; the FEV_1 decline was greater in these subjects than those not sensitized. A study of 157 naïve subjects (workers who entered the study after the first longitudinal measurements were made) showed no difference in FEV_1 decline as compared to exposed non-naïves. However, longitudinal regression showed the mean daily exposure to be significant for annual changes in FEV_1 and FVC. These declines were more rapid in the early years of employment, frequently during the first few months of employment. Clark et al. (1998) suggested that the decline in lung function may have been due to respiratory irritation.

Dose and end point used for MRL derivation: The MRL was based on the mean daily exposure level for the exposed group of 0.0012 ppm that was associated with a significant decrease in lung function; this concentration was treated as an adverse effect level for the purposes of deriving the MRL.

[ ] NOAEL [X] Adverse Effect Level (AEL)

Uncertainty Factors used in MRL derivation:

[X] 10 for use of a AEL
[ ] 10 for extrapolation from animals to humans
[X] 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose? Not applicable.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: Not applicable.

Was a conversion used from intermittent to continuous exposure? Yes. The AEL of 0.0012 ppm was adjusted for intermittent exposure:

0.0012 ppm x 8 hours/24 hours x 5 days/7 days = 0.00029 ppm

Other additional studies or pertinent information that lend support to this MRL: The toxicity of TDI has been examined in a large number of occupational exposure studies that identify the respiratory tract as the primary target of toxicity; they are supported by a number of animal studies. In humans, the primary respiratory effects are occupational asthma, asthma-like symptoms (e.g., wheezing, dyspnea, chest tightness), and decreases in lung function. The occupational asthma and possibly the asthma-like symptoms are observed in individuals sensitized to TDI. Although the prevalence of sensitization is not known, it is likely <10% based on older literature when the occupational exposures were higher and may now be as low as <1% since the occupational exposure limit was lowered to 0.005 ppm (Ott et al. 2003). Exposure to very low concentrations of TDI can elicit an asthma response in sensitized individuals; in non-sensitized individuals, this concentration would be non-irritating. Although there is some indication of an improvement in asthma symptoms after discontinuing TDI exposure, a fair percentage of sensitized workers still report symptoms >10 years after exposure termination (Mapp et al. 1988; Moller et al. 1986; Moscato et al. 1991; Padoan et al. 2003; Paggiaro et al. 1984).

The primary effect observed in non-sensitized workers is a decline in lung function (Adams 1975; Bodner et al. 2001; Butcher et al. 1977; Clark et al. 1998, 2003; Diem et al. 1982; Jones et al. 1992; Omae et al. 1992; Ott et al. 2000; Peters et al. 1970; Wegman et al. 1977, 1982). Based on the results of the Clark et al. (1998) study and a prospective longitudinal study by Diem et al. (1982), it appears that the greatest declines in lung function occur during the first couple of years of exposure to TDI; thereafter, continued exposure to lower TDI levels does not result in further annual declines in lung function.

Chronic exposure to TDI resulted in chronic or necrotic rhinitis with epithelial atrophy and mucous and squamous metaplasia in mice exposed to 0.05 ppm TDI 6 hours/day, 5 days/week for 2 years (Loeser 1983). In the lungs, interstitial pneumonitis and catarrhal bronchitis were observed.

Agency Contact (Chemical Manager): Malcolm Williams

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Polymeric methylenediphenyl diisocyanate
CAS Number: 9016-87-9
Date: June 2018
Profile Status: Final
Route: [X] Inhalation [ ] Oral
Duration: [ ] Acute [ ] Intermediate [X] Chronic
Graph Key: 8
Species: Rat

Minimal Risk Level: 0.001 [ ] mg/kg/day [X] mg/m^3

Reference: Reuzel PGJ, Arts JHE, Lomax LG, et al. 1994. Chronic inhalation toxicity and carcinogenicity study of respirable polymeric methylene diphenyl diisocyanate (polymeric MDI) aerosol in rats. Fundam Appl Toxicol 22:195-210.

Experimental design: Groups of 70 male and 70 female Wistar rats were exposed to 0, 0.2, 1.0, or 6.0 mg/m^3 polymeric MDI for 6 hours/day, 5 days/week for 2 years; after 1 year of exposure, 10 rats/sex/group were sacrificed for interim evaluation. The test substance contained 44.8–50.2% monomeric MDI. The mass median aerodynamic diameter (MMAD) particle sizes (and geometric standard deviation [GSD]) were 0.68 (2.93), 0.70 (2.46), and 0.74 (2.31) µm, respectively. The following parameters were used to evaluate toxicity in the rats exposed for 1 year: clinical signs, body weight (weekly for the first 13 weeks and monthly thereafter), hematology (red and white blood cell counts, hemoglobin, packed cell volume, differential white blood cell count, prothrombin time), urinary parameters (volume, density, pH, protein, occult blood, glucose, ketones), clinical chemistry (albumin, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, urea nitrogen, total protein, creatinine, electrolytes, inorganic phosphate, cholesterol, triglycerides and glucose), and histopathological examination of major tissues and organs. Histopathological examination of major tissues and organs was also conducted in the control and 6.0 mg/m^3 after 2 years of exposure and the nose, lungs, and mediastinal lymph nodes were examined in the 0.2 and 1.0 mg/m^3 group after 2 years of exposure.

Effect noted in study and corresponding doses: Sniffing (no additional information provided) was observed in the 6.0 mg/m^3 group after removal from the exposure chamber during months 5 and 6. No treatment-related increases in mortality were observed, and there were no alterations in body weight gain. No alterations in hematological, clinical chemistry, or urinalysis parameters were observed. Significant increases in absolute and relative lung weights were observed in the 6.0 mg/m^3 group after 1 and 2 years of exposure. In the rats sacrificed after 1 year of exposure, histological alterations were observed in the nasal cavity, lungs, and mediastinal lymph nodes. In the lungs, the lesions consisted of pneumonitis in the 1.0 and 6.0 mg/m^3 males, alveolar duct epithelialization in males at 6.0 mg/m^3 and females at 1.0 and 6.0 mg/m^3, and minimal to moderate localized fibrosis and accumulation of macrophages with yellow pigment in the 6.0 mg/m^3 males and females. An accumulation of macrophages with yellow pigment was also observed in the lymph nodes of male and female rats exposed to 1.0 or 6.0 mg/m^3. In the nasal cavity, minimal to moderate olfactory epithelial disarrangement was observed in males at 6.0 mg/m^3. Alterations were also observed in the lungs, mediastinal lymph nodes, and nasal cavity after 2 years of exposure. Lung effects included adenoma in males exposed to 6.0 mg/m^3, accumulation of macrophages with yellow pigment in males and females at 1.0 and 6.0 mg/m^3, localized fibrosis in males at 1.0 and 6.0 mg/m^3 and females at 6.0 mg/m^3, alveolar duct epithelialization in males and females at 1.0 and 6.0 mg/^{3}, and localized alveolar bronchiolization in males and females at 6.0 mg/m^3. An accumulation of macrophages with yellow pigment was observed in the mediastinal lymph nodes in males at 1.0 and 6.0 mg/m^3 and females at 6.0 mg/m^3. Nasal effects included basal cell hyperplasia and Bowman's gland

hyperplasia in males at 1.0 and 6.0 mg/m^3, basal cell hyperplasia in females at 6.0 mg/m^3, and minimal to severe olfactory epithelial degeneration in males and females at 6.0 mg/m^3. No significant increases in tumors were observed.

Dose and end point used for MRL derivation: $BMCL_{10}$ of 0.48 mg/m^{3}for basal cell hyperplasia

[ ] NOAEL [ ] LOAEL [X] BMCL

The incidence data (Table A-1) for basal cell hyperplasia in the nasal cavity, Bowman's duct hyperplasia in the nasal cavity, and lung fibrosis were fit to all available dichotomous models in EPA's Benchmark Dose Software (BMDS, version 2.4.0) using the extra risk option. Adequate model fit was judged by three criteria: goodness-of-fit statistics (p-value >0.1), visual inspection of the dose-response curve, and scaled residual at the data point (except the control) closest to the predefined benchmark dose response (BMR). Among all of the models providing adequate fit to the data, the lowest BMCL (95% lower confidence limit on the benchmark concentration) was selected as the point of departure when the difference between the BMCLs estimated from these models were more 3-fold; otherwise, the BMCL from the model with the lowest Akaike's Information Criterion (AIC) was chosen. For all three lesion types, a BMR of 10% was used. The model predictions for basal cell hyperplasia are presented in Table A-2. The incidence data for Bowman's gland hyperplasia did not fit any of the available dichotomous models. The model predictions for the incidence of lung fibrosis are presented in Table A-3.

Table A-1. Incidence of Nasal and Pulmonary Lesions in Male Rats Exposed to Polymeric Methylenediphenyl Diisocyanate

	Exposure concentration (mg/m^3)			
	0	0.2	1.0	6.0
Basal cell hyperplasia	14/60	13/60	26/60	32/60
Bowman's gland hyperplasia	0/60	2/60	9/60	17/60
Lung fibrosis	1/60	0/60	9/60	44/60

Source: Reuzel et al. 1994

Table A-2. Model Predictions for Incidence of Basal Cell Hyperplasia in Male Rats Exposed to Polymeric Methylenediphenyl Diisocyanate (mg/m^3)

Model	DF	χ^2	χ^2 Goodness of fit p-value[a]	Scaled residuals[b] Dose below BMC	Dose above BMC	Overall largest	AIC	BMC_{10} (mg/m^3)	$BMCL_{10}$ (mg/m^3)
Gamma[c]	2	4.8	0.09	1.87	-0.45	1.87	301.60	ND	ND
Logistic	2	5.76	0.06	2.01	-0.28	2.01	302.55	ND	ND
LogLogistic[d,f]	**2**	**3.96**	**0.14**	**1.67**	**-0.62**	**1.67**	**300.81**	**0.87**	**0.48**
LogProbit[d]	2	7.56	0.02	2.30	-0.28	2.30	304.25	ND	ND
Multistage (1 degree)[e]	2	4.8	0.09	1.87	-0.45	1.87	301.60	ND	ND
Multistage (2 degree)[e]	2	4.8	0.09	1.87	-0.45	1.87	301.60	ND	ND
Multistage (3-degree)[e]	2	4.8	0.09	1.87	-0.45	1.87	301.60	ND	ND
Probit	2	5.7	0.06	2.00	-0.29	2.00	302.49	ND	ND
Weibull[c]	2	4.8	0.09	1.87	-0.45	1.87	301.60	ND	ND
Quantal-Linear	2	4.8	0.09	1.87	-0.45	1.87	301.60	ND	ND

AIC = Akaike Information Criterion; BMC = maximum likelihood estimate of the exposure concentration associated with the selected benchmark response; BMCL = 95% lower confidence limit on the BMC (subscripts denote benchmark response: i.e., $_{10}$ = exposure concentration associated with 10% extra risk); DF = degrees of freedom; ND = not determined, model does not provide adequate fit to the data

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[b]Scaled residuals at doses immediately below and above the BMD; also the largest residual at any dose.
[c]Power restricted to ≥1.
[d]Slope restricted to ≥1.
[e]Betas restricted to ≥0.
[f]Selected model. The only model that was fit to the data was the LogLogistic model (all other models had a p-value <0.1).

Table A-3. Model Predictions for Incidence of Lung Fibrosis in Male Rats Exposed to Methylenediphenyl Diisocyanate (mg/m^3)

Model	DF	χ^2	χ^2 Goodness of fit p-value[a]	Scaled residuals[b] Dose below BMC	Dose above BMC	Overall largest	AIC	BMC_{10} (mg/m^3)	$BMCL_{10}$ (mg/m^3)
Gamma[c]	1	2.04	0.15	0.63	-0.16	-1.12	139.67	0.90	0.57
Logistic	2	8.46	0.01	2.23	-0.20	2.23	144.69	ND	ND
LogLogistic[d,f]	1	1.73	0.19	0.43	-0.15	-1.06	139.22	0.87	0.57
LogProbit[d]	**2**	**1.3**	**0.52**	**0.35**	**-0.20**	**-0.84**	**136.40**	**0.87**	**0.70**
Multistage (1-degree)[e]	2	4.42	0.11	-0.65	0.73	-1.69	141.53	0.54	0.43
Multistage (2-degree)[e]	1	2.64	0.10	0.67	-0.07	-1.36	140.83	0.89	0.51
Multistage (3-degree)[e]	1	2.64	0.10	0.67	-0.07	-1.36	140.83	0.89	0.51
Probit	2	7.46	0.02	2.11	-0.23	2.11	143.53	ND	ND
Weibull[c]	1	2.2	0.14	0.64	-0.12	-1.19	139.99	0.90	0.55
Quantal-Linear	2	4.42	0.11	-0.65	0.73	-1.69	141.53	0.54	0.43

AIC = Akaike Information Criterion; BMC = maximum likelihood estimate of the exposure concentration associated with the selected benchmark response; BMCL = 95% lower confidence limit on the BMC (subscripts denote benchmark response: i.e., $_{10}$ = exposure concentration associated with 10% extra risk); DF = degrees of freedom; ND = not determined, model does not provide adequate fit to the data

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[b]Scaled residuals at doses immediately below and above the BMD; also the largest residual at any dose.
[c]Power restricted to ≥1.
[d]Slope restricted to ≥1.
[e]Betas restricted to ≥0.
[f]Selected model. All models, except for the Logistic and the Probit (p<0.1) were fit to the data. BMDLs for models providing adequate fit were sufficiently close (differed by <2–3-fold), so the model with the lowest AIC was selected (LogLogistic Model).

The $BMCL_{10}$ values predicted from the selected models for basal cell hyperplasia and lung fibrosis were 0.48 and 0.70 mg/m^3; the LogLogistic and LogProbit models for these effects are presented in Figures A-1 and A-2. The $BMCL_{10}$ of 0.48 mg/m^3 was selected as the point of departure for the MRL.

Figure A-1. Fit of LogLogistic Model to Data on Incidence of Basal Cell Hyperplasia in Male Rats Exposed to Polymeric Methylenediphenyl Diisocyanate (mg/m^3)

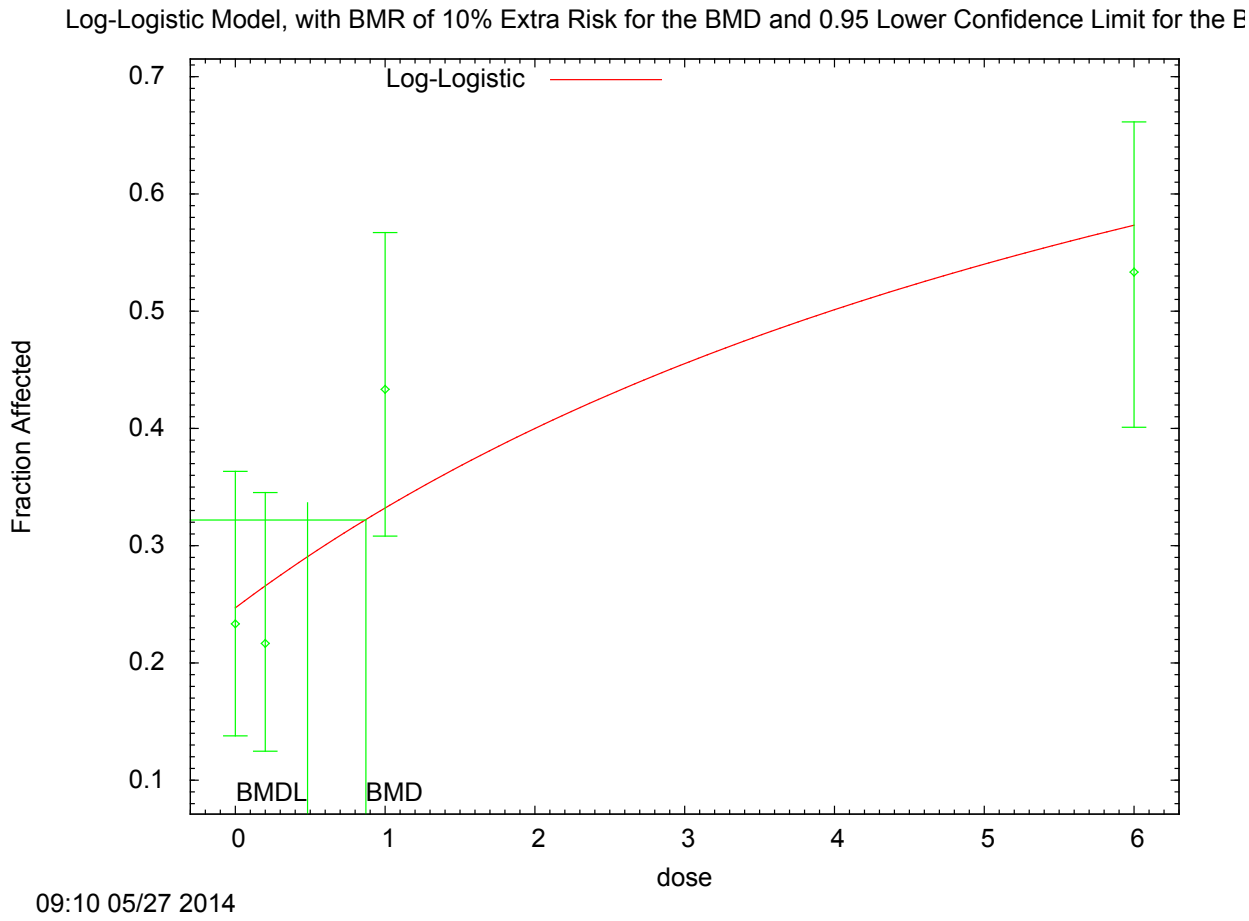
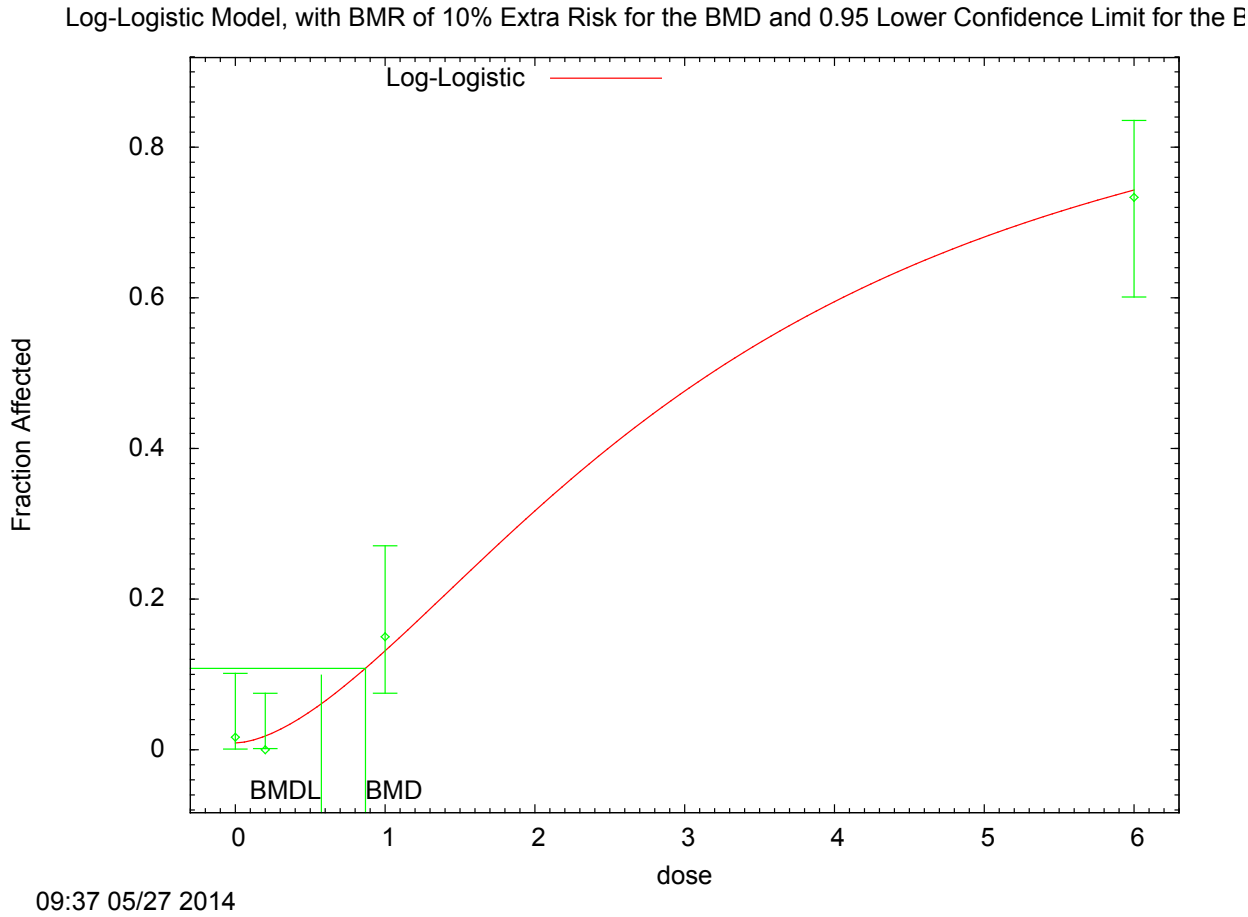


Figure A-2. Fit of LogLogistic Model to Data on for Incidence of Lung Fibrosis in Male Rats Exposed to Polymeric Methylenediphenyl Diisocyanate (mg/m^3)



Uncertainty Factors used in MRL derivation:

[ ] 10 for use of a LOAEL
[X] 3 for extrapolation from animals to humans with dosimetric adjustment
[X] 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose? Not applicable.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: Yes.

The $BMCL_{ADJ}$ of 0.086 mg/m^3 was converted to a human equivalent concentration ($BMCL_{HEC}$) of 0.039 mg/m^3 using the RDDR program (EPA 1990) as follows:

$BMCL_{HEC} = BMCL_{ADJ} \times RDDR$
$BMCL_{HEC} = 0.086 \text{ mg/m}^3 \times 0.453$
$BMCL_{HEC} = 0.039 \text{ mg/m}^3$

where:

RDDR is a multiplicative factor used to adjust an observed inhalation particulate exposure concentration of an animal to the predicted inhalation particulate exposure concentration for a human. The RDDR multiplier of 0.453 for the extrathoracic region tract was determined using the default chronic body weight of 462 g for male Wistar rats (EPA 1988) and a particle size MMAD±GSD of 0.68±2.93 μm reported in the Reuzel et al. (1994) study.

Was a conversion used from intermittent to continuous exposure? Yes.

A $BMCL_{ADJ}$ was calculated by adjusting the $BMCL_{10}$ of 0.48 mg/m^3 for intermittent exposure:

$$0.048 \text{ mg/m}^3 \times 6 \text{ hours}/24 \text{ hours} \times 5 \text{ days}/7 \text{ days} = 0.086 \text{ mg/m}^3$$

Other additional studies or pertinent information that lend support to this MRL: The respiratory tract is the primary target of MDI toxicity in humans and animals. Occupational asthma, asthma-like symptoms, and decreases in lung function have been reported in occupational exposure studies (Hur et al. 2008; Liss et al. 1988; Musk et al. 1982; Sulotto et al. 1990; Wang and Petsonk 2004; Woellner et al. 1997; Zamit-Tabona et al. 1983). The occupational asthma and asthma-like symptoms result from sensitization to MDI following a brief exposure to very high concentrations or prolonged exposure to lower concentrations; the prevalence of MDI-sensitization is believed to be low. Liss et al. (1988) reported significant declines in FEV_1 levels when pre-shift levels were compared to post-shift levels; however, the study did not provide monitoring data. Sulotto et al. (1990) and Musk et al. (1982) did not find declines in lung function in workers. Sulotto et al. (1990) reported MDI levels ranging from 0.005 to 0.001 ppm; the monitoring data provided by Musk et al. (1982) was not considered reliable.

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APPENDIX B. USER'S GUIDE

Chapter 1

Public Health Statement

This chapter of the profile is a health effects summary written in non-technical language. Its intended audience is the general public, especially people living in the vicinity of a hazardous waste site or chemical release. If the Public Health Statement were removed from the rest of the document, it would still communicate to the lay public essential information about the chemical.

The major headings in the Public Health Statement are useful to find specific topics of concern. The topics are written in a question and answer format. The answer to each question includes a sentence that will direct the reader to chapters in the profile that will provide more information on the given topic.

Chapter 2

Relevance to Public Health

This chapter provides a health effects summary based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information. This summary is designed to present interpretive, weight-of-evidence discussions for human health end points by addressing the following questions:

1. What effects are known to occur in humans?

2. What effects observed in animals are likely to be of concern to humans?

3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

The chapter covers end points in the same order that they appear within the Discussion of Health Effects by Route of Exposure section, by route (inhalation, oral, and dermal) and within route by effect. Human data are presented first, then animal data. Both are organized by duration (acute, intermediate, chronic). *In vitro* data and data from parenteral routes (intramuscular, intravenous, subcutaneous, etc.) are also considered in this chapter.

The carcinogenic potential of the profiled substance is qualitatively evaluated, when appropriate, using existing toxicokinetic, genotoxic, and carcinogenic data. ATSDR does not currently assess cancer potency or perform cancer risk assessments. Minimal Risk Levels (MRLs) for noncancer end points (if derived) and the end points from which they were derived are indicated and discussed.

Limitations to existing scientific literature that prevent a satisfactory evaluation of the relevance to public health are identified in the Chapter 3 Data Needs section.

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information is available, ATSDR has derived MRLs for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not meant to support regulatory action, but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans.

MRLs should help physicians and public health officials determine the safety of a community living near a hazardous substance emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Chapter 2, "Relevance to Public Health," contains basic information known about the substance. Other sections such as Chapter 3 Section 3.9, "Interactions with Other Substances," and Section 3.10, "Populations that are Unusually Susceptible" provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology that the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses (RfDs) for lifetime exposure.

To derive an MRL, ATSDR generally selects the most sensitive end point which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen end point are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest no-observed-adverse-effect level (NOAEL) that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor (UF) of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MRL are provided in the footnotes of the levels of significant exposure (LSE) tables.

Chapter 3

Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

Tables and figures are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species, MRLs to humans for noncancer end points, and EPA's estimated range associated with an upper- bound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. Use the LSE tables and figures for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of NOAELs, LOAELs, or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE Table 3-1 and Figure 3-1 are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

LEGEND

See Sample LSE Table 3-1 (page B-6)

(1) Route of Exposure. One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. Typically when sufficient data exist, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure, i.e., inhalation, oral, and dermal (LSE Tables 3-1, 3-2, and 3-3, respectively). LSE figures are limited to the inhalation (LSE Figure 3-1) and oral (LSE Figure 3-2) routes. Not all substances will have data on each route of exposure and will not, therefore, have all five of the tables and figures.

(2) Exposure Period. Three exposure periods—acute (less than 15 days), intermediate (15–364 days), and chronic (365 days or more)—are presented within each relevant route of exposure. In this example, an inhalation study of intermediate exposure duration is reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.

(3) Health Effect. The major categories of health effects included in LSE tables and figures include death, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the "System" column of the LSE table (see key number 18).

(4) Key to Figure. Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 18 has been used to derive a NOAEL and a Less Serious LOAEL (also see the two "18r" data points in sample Figure 3-1).

(5) Species. The test species, whether animal or human, are identified in this column. Chapter 2, "Relevance to Public Health," covers the relevance of animal data to human toxicity and Section 3.4, "Toxicokinetics," contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.

(6) Exposure Frequency/Duration. The duration of the study and the weekly and daily exposure regimens are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18), rats were exposed to “Chemical x” via inhalation for 6 hours/day, 5 days/week, for 13 weeks. For a more complete review of the dosing regimen, refer to the appropriate sections of the text or the original reference paper (i.e., Nitschke et al. 1981).

(7) System. This column further defines the systemic effects. These systems include respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. "Other" refers to any systemic effect (e.g., a decrease in body weight) not covered in these systems. In the example of key number 18, one systemic effect (respiratory) was investigated.

(8) NOAEL. A NOAEL is the highest exposure level at which no adverse effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system, which was used to derive an intermediate exposure, inhalation MRL of 0.005 ppm (see footnote "b").

(9) LOAEL. A LOAEL is the lowest dose used in the study that caused an adverse health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific end point used to quantify the adverse effect accompanies the LOAEL. The respiratory effect reported in key number 18 (hyperplasia) is a Less Serious LOAEL of 10 ppm. MRLs are not derived from Serious LOAELs.

(10) Reference. The complete reference citation is given in Chapter 9 of the profile.

(11) CEL. A CEL is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases.

(12) Footnotes. Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. Footnote "b" indicates that the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

LEGEND

See Sample Figure 3-1 (page B-7)

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure concentrations for particular exposure periods.

(13) Exposure Period. The same exposure periods appear as in the LSE table. In this example, health effects observed within the acute and intermediate exposure periods are illustrated.

(14) Health Effect. These are the categories of health effects for which reliable quantitative data exists. The same health effects appear in the LSE table.

(15) Levels of Exposure. Concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m^3 or ppm and oral exposure is reported in mg/kg/day.

(16) NOAEL. In this example, the open circle designated 18r identifies a NOAEL critical end point in the rat upon which an intermediate inhalation exposure MRL is based. The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the table) to the MRL of 0.005 ppm (see footnote "b" in the LSE table).

(17) CEL. Key number 38m is one of three studies for which CELs were derived. The diamond symbol refers to a CEL for the test species-mouse. The number 38 corresponds to the entry in the LSE table.

(18) Estimated Upper-Bound Human Cancer Risk Levels. This is the range associated with the upper-bound for lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. These risk levels are derived from the EPA's Human Health Assessment Group's upper-bound estimates of the slope of the cancer dose response curve at low dose levels (q_1*).

(19) Key to LSE Figure. The Key explains the abbreviations and symbols used in the figure.

SAMPLE

1 → **Table 3-1. Levels of Significant Exposure to [Chemical x] – Inhalation**

	Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
2 →	INTERMEDIATE EXPOSURE							
		5	6	7	8	9		10
3 →	Systemic	↓	↓	↓	↓	↓		↓
4 →	18	Rat	13 wk 5 d/wk 6 hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
	CHRONIC EXPOSURE							
	Cancer					11		
						↓		
	38	Rat	18 mo 5 d/wk 7 hr/d			20	(CEL, multiple organs)	Wong et al. 1982
	39	Rat	89–104 wk 5 d/wk 6 hr/d			10	(CEL, lung tumors, nasal tumors)	NTP 1982
	40	Mouse	79–103 wk 5 d/wk 6 hr/d			10	(CEL, lung tumors, hemangiosarcomas)	NTP 1982

12 → [a] The number corresponds to entries in Figure 3-1.
[b] Used to derive an intermediate inhalation Minimal Risk Level (MRL) of 5×10^{-3} ppm; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

SAMPLE

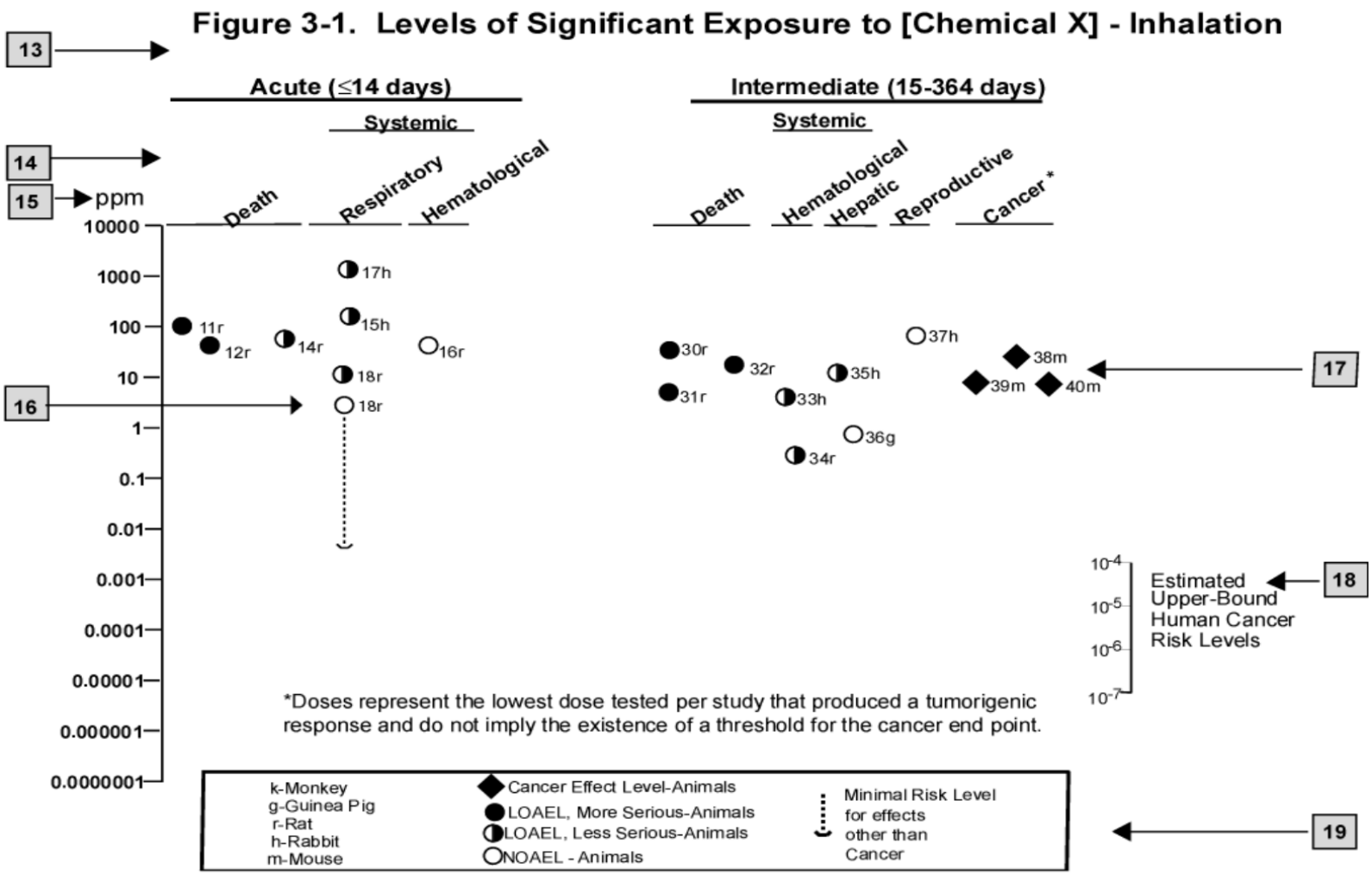
Figure 3-1. Levels of Significant Exposure to [Chemical X] - Inhalation
13
Acute (≤14 days)
Systemic
Death
Respiratory
Hematological
Intermediate (15-364 days)
Systemic
Death
Hematological
Hepatic
Reproductive
Cancer *
14
15
ppm
10000
1000
100
10
1
0.1
0.01
0.001
0.0001
0.00001
0.000001
0.0000001
16
11r
12r
14r
15h
17h
16r
18r
18r
30r
31r
32r
33h
34r
35h
36g
37h
38m
39m
40m
17
10^{-4}
10^{-5}
10^{-6}
10^{-7}
Estimated Upper-Bound Human Cancer Risk Levels
18
*Doses represent the lowest dose tested per study that produced a tumorigenic response and do not imply the existence of a threshold for the cancer end point.
k-Monkey
g-Guinea Pig
r-Rat
h-Rabbit
m-Mouse
Cancer Effect Level-Animals
LOAEL, More Serious-Animals
LOAEL, Less Serious-Animals
NOAEL - Animals
Minimal Risk Level for effects other than Cancer
19

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APPENDIX C. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ACOEM	American College of Occupational and Environmental Medicine
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AED	atomic emission detection
AFID	alkali flame ionization detector
AFOSH	Air Force Office of Safety and Health
ALT	alanine aminotransferase
AML	acute myeloid leukemia
AOAC	Association of Official Analytical Chemists
AOEC	Association of Occupational and Environmental Clinics
AP	alkaline phosphatase
APHA	American Public Health Association
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BAT	best available technology
BCF	bioconcentration factor
BEI	Biological Exposure Index
BMD/C	benchmark dose or benchmark concentration
BMD_X	dose that produces a X% change in response rate of an adverse effect
$BMDL_X$	95% lower confidence limit on the BMD_X
BMDS	Benchmark Dose Software
BMR	benchmark response
BSC	Board of Scientific Counselors
C	centigrade
CAA	Clean Air Act
CAG	Cancer Assessment Group of the U.S. Environmental Protection Agency
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	cancer effect level
CELDS	Computer-Environmental Legislative Data System
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CI	confidence interval
CLP	Contract Laboratory Program
cm	centimeter
CML	chronic myeloid leukemia
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
DOL	Department of Labor
DOT	Department of Transportation

DOT/UN/ NA/IMDG	Department of Transportation/United Nations/ North America/Intergovernmental Maritime Dangerous Goods Code
DWEL	drinking water exposure level
ECD	electron capture detection
ECG/EKG	electrocardiogram
EEG	electroencephalogram
EEGL	Emergency Exposure Guidance Level
EPA	Environmental Protection Agency
F	Fahrenheit
F_1	first-filial generation
FAO	Food and Agricultural Organization of the United Nations
FDA	Food and Drug Administration
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FPD	flame photometric detection
fpm	feet per minute
FR	Federal Register
FSH	follicle stimulating hormone
g	gram
GC	gas chromatography
gd	gestational day
GLC	gas liquid chromatography
GPC	gel permeation chromatography
HPLC	high-performance liquid chromatography
HRGC	high resolution gas chromatography
HSDB	Hazardous Substance Data Bank
IARC	International Agency for Research on Cancer
IDLH	immediately dangerous to life and health
ILO	International Labor Organization
IRIS	Integrated Risk Information System
Kd	adsorption ratio
kg	kilogram
kkg	kilokilogram; 1 kilokilogram is equivalent to 1,000 kilograms and 1 metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{50}	lethal concentration, 50% kill
LC_{Lo}	lethal concentration, low
LD_{50}	lethal dose, 50% kill
LD_{Lo}	lethal dose, low
LDH	lactic dehydrogenase
LH	luteinizing hormone
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
LT_{50}	lethal time, 50% kill
m	meter
MA	*trans,trans*-muconic acid
MAL	maximum allowable level
mCi	millicurie
MCL	maximum contaminant level

MCLG	maximum contaminant level goal
MF	modifying factor
MFO	mixed function oxidase
mg	milligram
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectrometry
mt	metric ton
NAAQS	National Ambient Air Quality Standard
NAS	National Academy of Science
NATICH	National Air Toxics Information Clearinghouse
NATO	North Atlantic Treaty Organization
NCE	normochromatic erythrocytes
NCEH	National Center for Environmental Health
NCI	National Cancer Institute
ND	not detected
NFPA	National Fire Protection Association
ng	nanogram
NHANES	National Health and Nutrition Examination Survey
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
NLM	National Library of Medicine
nm	nanometer
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPD	nitrogen phosphorus detection
NPDES	National Pollutant Discharge Elimination System
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NSPS	New Source Performance Standards
NTIS	National Technical Information Service
NTP	National Toxicology Program
ODW	Office of Drinking Water, EPA
OERR	Office of Emergency and Remedial Response, EPA
OHM/TADS	Oil and Hazardous Materials/Technical Assistance Data System
OPP	Office of Pesticide Programs, EPA
OPPT	Office of Pollution Prevention and Toxics, EPA
OPPTS	Office of Prevention, Pesticides and Toxic Substances, EPA
OR	odds ratio
OSHA	Occupational Safety and Health Administration
OSW	Office of Solid Waste, EPA
OTS	Office of Toxic Substances

OW	Office of Water
OWRS	Office of Water Regulations and Standards, EPA
PAH	polycyclic aromatic hydrocarbon
PBPD	physiologically based pharmacodynamic
PBPK	physiologically based pharmacokinetic
PCE	polychromatic erythrocytes
PEL	permissible exposure limit
PEL-C	permissible exposure limit-ceiling value
pg	picogram
PHS	Public Health Service
PID	photo ionization detector
pmol	picomole
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
PSNS	pretreatment standards for new sources
RBC	red blood cell
REL	recommended exposure level/limit
REL-C	recommended exposure level-ceiling value
RfC	reference concentration (inhalation)
RfD	reference dose (oral)
RNA	ribonucleic acid
RQ	reportable quantity
RTECS	Registry of Toxic Effects of Chemical Substances
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
SGOT	serum glutamic oxaloacetic transaminase (same as aspartate aminotransferase or AST)
SGPT	serum glutamic pyruvic transaminase (same as alanine aminotransferase or ALT)
SIC	standard industrial classification
SIM	selected ion monitoring
SMCL	secondary maximum contaminant level
SMR	standardized mortality ratio
SNARL	suggested no adverse response level
SPEGL	Short-Term Public Emergency Guidance Level
STEL	short term exposure limit
STORET	Storage and Retrieval
TD_{50}	toxic dose, 50% specific toxic effect
TLV	threshold limit value
TLV-C	threshold limit value-ceiling value
TOC	total organic carbon
TPQ	threshold planning quantity
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TWA	time-weighted average
UF	uncertainty factor
U.S.	United States
USDA	United States Department of Agriculture
USGS	United States Geological Survey
VOC	volatile organic compound
WBC	white blood cell

WHO	World Health Organization
>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
γ	gamma
δ	delta
μm	micrometer
μg	microgram
q_1^*	cancer slope factor
–	negative
+	positive
(+)	weakly positive result
(–)	weakly negative result