

Health Effects of Diisocyanates: Guidance for Medical Personnel

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FOREWARD

This guidance document is designed specifically for medical personnel to provide current information about the potential health effects from diisocyanate⁽¹⁾ exposure, and to provide guidance to assist with medical diagnosis and management. The discussion focuses on two widely used diisocyanate-based products: diphenylmethane diisocyanate (MDI) and toluene diisocyanate (TDI)⁽²⁾⁽³⁾⁽⁴⁾.

Although this guidance reflects the current scientific knowledge and experience of medical researchers, industrial hygienists, manufacturers, and other knowledgeable experts, it is not intended to be a comprehensive or detailed discussion of all aspects of the subject, but rather an overview. Medical personnel and other health professionals can keep themselves informed of recent developments in this field by consulting the current scientific literature, as well as manufacturers' and suppliers' product safety literature (e.g., [Material] Safety Data Sheets [SDSs]).

- (1) Diisocyanates are organic compounds containing two isocyanate groups (-NCO). They are used primarily in the manufacture of polyurethane systems to make foams, elastomers, coatings, adhesives and other polymeric products.
- (2) TDI is manufactured predominantly as a mixed ratio, 80:20, of the 2,4-TDI and 2,6-TDI isomers [CAS# 26471-62-5].
- (3) MDI is the usual abbreviation for monomeric methylene diphenyl diisocyanate, [CAS# 101-68-8]. The "polymeric" forms of MDI, which typically consist of 30-70 percent monomeric diphenylmethane diisocyanate and the balance in higher molecular weight fractions [CAS # 5873-54-1] may at times be generically referred to as MDI.
- (4) For further information about the handling of TDI and MDI, consult the following bulletins published by the Center for the Polyurethanes Industry of the American Chemistry Council: *Guidance for Working with MDI and Polymeric MDI: Things You Should Know (AX-205)* and *Guidance for Working with TDI: Things You Should Know (AX-202)* available at www.polyurethane.org.

POTENTIAL HEALTH HAZARDS

RESPIRATORY EFFECTS

The predominant health effect of MDI and TDI is on the respiratory tract. Both chemicals have been shown to be portal-of-entry toxicants.

INHALATION OF VAPORS AND MISTS

MDI:

At room temperature, MDI has a relatively low vapor pressure in comparison to other organic chemicals. The vapor pressure of MDI largely explains the very low to non-detectable airborne concentrations found during most applications. Studies show that airborne concentrations of MDI are associated only with processes or applications that involve heating (well above 100 degrees F) and/or spraying (aerosolizing).

TDI:

The vapor pressure of TDI is higher than MDI and at a typical room temperature (i.e., 70°F) the concentration of vapor in the air can exceed the OSHA Permissible Exposure Limit (PEL) of 20 ppb. Thus protective measures, including the use of engineering controls (e.g., local exhaust ventilation), appropriate personal protective equipment (e.g., respiratory protection) or other workplace practices (e.g., proper handling and storage), etc., are taken whenever there is potential exposure to (unknown) airborne concentrations of TDI.

Heated or Sprayed Diisocyanates:

Exposure to heated diisocyanates can be extremely hazardous, not only because high vapor concentrations are formed, but also because condensation may result in airborne particulate, which may injure the eyes, skin, and respiratory tract. Similarly, spray mists can impose a significant health hazard.

Odor Threshold:

Reported odor threshold values for chemicals often are expressed in wide ranges because "odor" threshold testing has historically lacked a consistent approach. The reasons for the variation in reported odor thresholds include the chemical purity, the mode of presentation of the challenge agent to the individual, the influence of extraneous factors in how the odor is introduced, and the type of observer used (i.e., age, gender, race).

Two studies on the odor threshold for MDI and TDI, respectively, are summarized below:

- MDI: There is no reliable odor threshold for MDI reported. Nevertheless, the reported value of 0.4 ppm (400 ppb) suggests that if MDI is detected by smell, overexposure is likely to have occurred (Woolrich, 1982).
- TDI: In one study (Henschler et al., 1962), recognition of the odor of TDI was achieved by 90% of the panel of volunteers at 0.05 ppm (50 ppb) TDI. Thus, if TDI is detected by odor, most likely overexposure has occurred.

RESPIRATORY IRRITATION

The reactivity of the diisocyanates with the respiratory tract can cause irritation and inflammation at high concentrations. Irritating substances cause a decrease in respiratory rate in mice and rats. The RD_{50} (50% reduction in respiration rate) of MDI is 32 mg/m³ in mice (Weyel and Schaffer, 1985) and the RD_{50} of TDI is 1.4 mg/m³ (0.2ppm) in mice (Sangha and Alarie, 1979).

RESPIRATORY SENSITIZATION

Respiratory sensitization results in hyperreactivity of the airways following inhalation of an allergen. Sensitization includes two phases: the first phase is induction of specialized immunological memory in an individual by exposure to an allergen. The second phase is elicitation, i.e., production of a cell-mediated or antibody-mediated allergic response by exposure of a sensitized individual to an allergen. There are several substances in the workplace, including diisocyanates, which can cause respiratory sensitization. One of the outcomes of respiratory sensitization can be occupational asthma.

MDI and TDI-related occupational asthma can occur from overexposure in the workplace. Diisocyanates have been shown to cause bronchial reactivity of the respiratory tract, manifesting as wheezing, shortness of breath, and chest tightness in previously sensitized persons. These symptoms may occur either immediately or 6 to 8 hours post exposure. Dual reactions involving both immediate and delayed reactions, have been reported. Follow up studies have demonstrated that if diisocyanate-related asthma is diagnosed early and the affected person avoids any further exposure, recovery can be complete (Tarlo, 1997; Pisati, 2007). However, if diisocyanate exposure continues, chronic asthma, with reduced lung function, could develop. The result may be chronic lung impairment of varying severity. Therefore, studies show that medical monitoring with early removal from repeated exposure can help with recovery from diisocyanate-related asthma. Deaths have occurred in previously sensitized individuals exposed to diisocyanates (Carino, 1997; Fabbri, 1988, NIOSH, 1996).

DIAGNOSIS

It is important to correctly diagnose occupational asthma attributed to diisocyanates. The basis for a diagnosis of “diisocyanate-induced asthma” includes confirming the diagnosis of asthma and then establishing that the reaction occurs in relation to exposure to diisocyanates and not to other irritants in the workplace.

A first step toward the diagnosis is taking a careful history regarding the following:

- 1) history consistent with asthma;
- 2) relief of symptoms during weekends or vacations, and recurrence upon returning to work; and
- 3) tendency for the symptoms to be worse at the end of the workday.

Carefully controlled specific provocative inhalation tests with diisocyanates may be used, but are usually not readily available. Such bronchial provocation testing uses elaborate exposure equipment and experienced technicians. Confirming work-related bronchoconstriction by demonstrating decrement of lung function in association with workplace exposures is usually sufficient to confirm or contradict the presumptive diagnosis. Immune testing, including diisocyanate-specific IgE and IgG testing in blood serum, has not been standardized and validated and as a consequence has not shown adequate specificity and sensitivity for diagnosis (Budnik, 2012).

ALVEOLITIS OR HYPERSENSITIVITY PNEUMONITIS

On occasion, alveolitis or hypersensitivity pneumonitis, may result from diisocyanate exposure. In contrast to bronchial asthma, alveolitis has been reported in isolated case reports usually when there have been gross overexposures. Symptoms may appear 6 to 8 hours after exposure and may include malaise, joint pain, fever, cough, and shortness of breath. Chest X-rays may show “shadows” on the lungs.

The condition usually subsides upon removal from exposure.

Diagnosis of the condition requires the following criteria: clinical (a flu-like syndrome) with fever and shortness of breath, radiographic (lung infiltrates), physiologic (restrictive pattern in lung function) and immunologic (presence of specific IgG antibodies) (Baur, 1995). Other investigators have not found the IgG antibodies in all cases and concluded that the clinical syndrome in the presence of non-irritating concentrations of diisocyanates as a sensitive indicator of the disease (Vandenplas, 1993). Signs and symptoms usually disappear in a few days upon removal from exposure. However, if exposure is continued, chronic lung fibrosis, impaired gas exchange, labored breathing, and reduced physical fitness may develop.

SKIN EFFECTS

DERMAL IRRITATION

Repeated contact with liquid diisocyanates may discolor the skin or cause signs of irritation such as redness, irritation, swelling, and/or blistering. If diisocyanates accidentally come in contact with the skin, wash immediately with soap and water. Cured material is difficult to remove; however, practical experience has demonstrated that some of the best ways to remove it is with corn oil, petroleum jelly or industrial skin cleansers (e.g., D-TAM™ Safe Solvent: Colorimetric Laboratories, Inc.).

ALLERGIC CONTACT DERMATITIS

Dermal exposure to diisocyanates may also result in allergic contact dermatitis (ACD). ACD is a rare occurrence with MDI and TDI. ACD is a two-step process: the first phase is induction of specialized immunological memory in an individual by exposure to an allergen; the second phase is elicitation -- the production of a cell-mediated allergic response by re-exposure of a sensitized individual to an allergen. Persons previously sensitized can experience allergic skin reaction with the symptoms of reddening, itching, swelling, and rash upon dermal contact.

Evidence in animal studies suggests that repeated dermal exposure may also play a role in the development of respiratory sensitization. Both TDI and MDI have induced respiratory hypersensitivity responses when applied to, or injected into, the skin of animals and followed by inhalation exposure. Based on these findings, it is strongly recommended that skin contact with diisocyanates be avoided.

CARCINOGENICITY

For hazard communication purposes under OSHA Standard 29 CFR, Part 1910.1200, TDI is listed as a potential carcinogen by the National Toxicology Program (NTP) and the International Agency for Research on Cancer (IARC). Both agencies based their evaluation of TDI as a potential carcinogen primarily on an oral study in which high doses of TDI were reported to cause cancer in animals. This study, in which rats and mice were administered high doses of TDI in corn oil by oral gavage, has been found to contain deficiencies that resulted in the formation of toluene diamine (TDA), a known animal carcinogen. TDI did not cause cancer or result in the formation of detectable levels of free TDA when laboratory animals were exposed by inhalation, by far the most likely route of exposure (Loser, 1983).

A study to determine the chronic toxicity and potential carcinogenicity of MDI has been conducted. Male and female rats were exposed 6 hours/day, 5 days/week for two years to an atmosphere of respirable polymeric MDI aerosols at concentrations of 0.2 mg/m³, 1.0 mg/m³, or 6.0 mg/m³ (Reuzel et al., 1994). A low incidence of primarily benign lung tumors in Type II cells were seen at only the highest concentration. In a second study (Hoymann et al., 1995), female rats were exposed 17 hours/day, 5 days/week for 2 years to an atmosphere of respirable monomeric MDI aerosols at concentrations of 0.23 mg/m³, 0.70 mg/m³ or 2.03 mg/m³. A benign lung tumor was only observed in a single rat at 2.03 mg/m³.

Several *in vitro* studies used solvents that cause rapid hydrolysis of TDI to its diamine, a known mutagen, and the results have been discounted (Herbold et al., 1998; Seel et al., 1999). A weight of evidence assessment of *in vitro* and *in vivo* testing indicates that TDI has no mutagenic activity. Numerous *in vitro* mutagenicity studies have been done on MDI that do not show a mutagenic potential, except under conditions using solvents which cause rapid hydrolysis of MDI to its diamine, a known mutagen (Herbold et al., 1998; Seel et al., 1999). This may account for the mutagenic findings. The majority of the studies using a different solvent have not resulted in mutagenicity.

The results of these studies suggest that the incidence and delayed occurrence of lung tumors is consistent with a non-genotoxic mode of action since MDI-DNA adducts are not detected in organs with tumors or at doses associated with cell proliferation. Since lung tumors only were observed at a concentration orders of magnitude higher than established occupational exposure guidelines, MDI is unlikely to pose a significant cancer risk to workers.

Several epidemiology studies were unable to show a significant link between employment in polyurethane manufacturing and cancer deaths:

- 40-year cohort study of TDI polyurethane foam manufacturing in England and Wales (Sorahan and Pope, 1993; Sorahan and Nichols, 2002)
- 37-year cohort study of TDI polyurethane foam manufacturing in US (Schnorr et al., 1996)
- 29-year cohort study of TDI and MDI polyurethane foam manufacturing in Sweden (Hagmar et al., 1993a; Hagmar et al., 1993b)
- 40-year cohort study of TDI and MDI. Follow-up of the Hagmar et al. studies in Sweden (Mikoczy et al., 2004)

WAYS TO ADDRESS POTENTIAL HEALTH EFFECTS

EXPOSURE GUIDELINES

Irritation and sensitization are the primary hazards associated with dermal and inhalation exposures to diisocyanates. Exposure limits have been established by various regulatory agencies regarding allowable airborne concentrations of diisocyanates in the work environment. It is important to remember, however, that while these values represent the best current thinking of toxicologists and industrial hygienists, they offer no guarantee of absolute safety. Therefore, personnel who work with diisocyanates (including both TDI and MDI) need to know and understand the hazards associated with their use and follow those procedures designed to minimize the hazards involved. Since exposure guidelines are reviewed regularly by occupational health professionals, and are changed when new information dictates, users of diisocyanates need to keep themselves informed of the most current guidelines and regulations.

To minimize the risk of irritation and/or sensitization, the Occupational Safety and Health Administration (OSHA) has set a Permissible Exposure Limit (PEL) for MDI and TDI as a Ceiling Limit, which is not to be exceeded at any time during the workday. The Ceiling Limit is equivalent to the Maximum Allowable Concentration (MAC) commonly used in certain European countries. In the United States, the law requires compliance with OSHA exposure limits. In addition to the exposure limits established by OSHA, the American Conference of Governmental Industrial Hygienists (ACGIH), a voluntary standards setting organization, adopted a Threshold Limit Value (TLV) for both MDI and TDI as an 8-hour time weighted average (TWA). The TWA is an airborne concentration for a normal 8-hour workday and a 40-hour workweek and represents conditions under which nearly all workers can be exposed without adverse health effect. The ACGIH has also adopted a 15-minute Short Term Exposure Limit (STEL) for TDI. The STEL is defined as a 15-minute TWA exposure that, like the Ceiling Limit, should not be exceeded at any time during the workday, even if the 8-hour TWA is within the TLV. Things to consider regarding the STEL include: (1) exposures at the STEL should not be repeated more than four times per day, and (2) there should be at least 60 minutes between successive exposures at the STEL (See Table 1).

Table 1—Exposure Limits to 2,4-/2,6-Toluene Diisocyanate and 4,4' Methylene-diphenyl Diisocyanate

	OSHA PEL- C	ACGIH TLV - TWA	ACGIH TLV - STEL
MDI	0.02 ppm (0.214 mg/m ³) as a Ceiling Limit	0.005 ppm (0.051 mg/m ³) as an 8-hour TWA	_____
TDI	0.02 ppm (0.14 mg/m ³) as Ceiling Limit	0.005 ppm (0.036 mg/m ³) as an 8-hour TWA	0.02 ppm (0.14 mg/m ³) as a 15-minute TWA

Some articles in earlier published literature suggest that approximately 5% of persons exposed to diisocyanates develop diisocyanate-related asthma (Ott et al., 2003; Adams, 1975). Ott et al. (2003) states that since the mid-1970s, where 8-hour TDI concentrations have been maintained below 5 ppb as a TWA, annual occupational asthma incidence rates have been very low, less than 1%. The few new cases of sensitization occurred when short term exposures were above 20 ppb (Ott et al., 2000; Weill et al., 1981). In addition, in a review of the critical data for the TDI OEL, it was stated that “if the exposure concentrations of TDI are kept below 10 to 20 ppb, generally no new cases of TDI asthma are observed” (AGS, 2006). Conversely, peaks of airborne concentrations well above 20 ppb and/or gross dermal contamination seem to play a special role in the sensitization process. Therefore, controlling exposures only by the 8-hr TWA may not prevent exposures capable of producing sensitization. In addition to controlling exposures below the 8-hour TWA guidelines (5 ppb), control exposures below the OSHA Ceiling Limit (20 ppb). Finally, there also is evidence from animal studies suggesting that repeated dermal exposure may play a role in the development of respiratory sensitization. Elicitation of a respiratory response is manifested with subsequent exposure via inhalation. Once a person is sensitized to diisocyanates, inhalation exposure to challenge concentrations as low as 1 ppb, have been shown to precipitate an asthmatic response (Lemiere et al., 2002).

INDUSTRIAL HYGIENE PRACTICES TO MINIMIZE EXPOSURE

Avoiding exposure to diisocyanates through sound industrial hygiene practices is the primary measure for prevention of diisocyanate-related health problems. Good engineering controls, adherence to industrial hygiene practices and training employees to follow the manufacturer’s recommended handling procedures to minimize exposure to diisocyanates are essential for primary prevention. Inform all persons who work with these materials of the potential hazards to health and safety posed by diisocyanates and the procedures designed to minimize such hazards. Properly train all personnel and equip them to respond appropriately in an emergency, to safely clean up spills and leaks, and to protect themselves from direct contact with diisocyanate liquid, or exposure to excessive levels of diisocyanate vapors and aerosols. General experience with diisocyanates has demonstrated that healthy individuals will not be affected by diisocyanate vapor concentrations that do not exceed 0.02 ppm (Henschler et al., 1962). Thus, airborne vapor concentrations are carefully monitored and include correct sampling procedures and equipment and appropriate analytical techniques ⁽⁵⁾. Personnel also are properly trained in the administration of appropriate first aid. And finally, personnel read and understand current (Material) Safety Data Sheets (SDSs), Technical Data Sheets (TDS), and similar documents before working with diisocyanates.

[5] Eight-hour TWAs may conceal excessive “exposure peaks,” which can potentially induce sensitization when such peaks exceed 0.02 ppm. Thus, a number of regulatory agencies have established Ceiling Limits or Maximum Allowable Concentrations (MAC), which may not be exceeded at any time during the workday.

MEDICAL SURVEILLANCE

Early detection of health effects through medical surveillance is considered secondary prevention, but very important since removal from exposure carries the best prognosis for diisocyanate-related asthma. Medical surveillance consists of pre-placement and periodic medical surveillance examinations. The medical examination includes a respiratory health history, a clinical evaluation, and baseline pulmonary function testing. Contact the manufacturer for additional information.

Careful individual medical assessment by a physician knowledgeable in diisocyanates is advised prior to placement, during periodic evaluations, and for any new or worsening symptoms for workers with a pre-existing history of asthma,

which is defined as work exacerbation of pre-existing asthma, or other respiratory disease that may interfere with the safe handling of diisocyanates. The individual assessment takes into account the workplace exposure monitoring as well as the worker's past and current medical diagnosis. Atopy (allergic diathesis) has not been demonstrated to be a risk factor for the development of diisocyanate-induced asthma (Redlich et al., 2002). However, these individuals may respond to lower levels of a variety of stimuli depending on the severity of the bronchial hyperresponsiveness (Baur et al., 1982; Baur, 1985; Behr et al., 1990). Likewise, individuals with atopy or an inherited allergic tendency (including skin and/or upper respiratory allergies, manifested as hay fever, sinusitis, positive skin tests to common allergens, etc.) or a history of childhood asthma have not been demonstrated to have greater risk for development of diisocyanate-related asthma (Vandenplas et al., 1993). However, due to the difficulty of making an early diagnosis with a similar pre-existing condition, the physician may recommend restricting individuals with symptomatic nonspecific bronchial hyperresponsiveness (i.e., chest tightness, wheezing, shortness of breath) or symptomatic asthma from working with diisocyanates. Individuals with symptoms suggesting any type of bronchial hyperreactivity should consult a physician for an exact diagnosis and counseling. And finally, individuals with specific diisocyanate bronchial sensitization are restricted from any workplace contact with or exposure to diisocyanates.

MEDICAL MANAGEMENT

FIRST AID FOLLOWING OVEREXPOSURE

Remove individuals affected by overexposure to diisocyanates from the source of exposure. Remove contaminated clothing and place in a plastic bag for decontamination or safe destruction later. Administer first aid immediately.

- For breathing difficulties: Obtain medical attention immediately, but inform affected individual and medical personnel that onset of symptoms may occur several hours after exposure.
- Eye Contamination: Flush eyes using an eye wash station, several sterile eye wash bottles or copious amounts of tap water. Remove contact lenses if easily removable and continue eye irrigation for up to 15 minutes. Obtain medical attention.
- Skin Contamination: Wash immediately with soap and water. Cured material is difficult to remove; however, practical experience has demonstrated that some of the best ways to remove it is with corn oil, petroleum jelly or industrial skin cleanser (e.g., D-TAM™ Safe Solvent: Colorimetric Laboratories, Inc.).
- Swallowing: Do not induce vomiting. Wash mouth well with water. Obtain medical attention.

NOTE FOR GUIDANCE TO MEDICAL PERSONNEL

Diisocyanates are respiratory and skin irritants and potential sensitizers. There is no specific antidote. Treatment should be essentially symptomatic for irritation of skin and mucous membranes and/or bronchospasm. MDI and TDI have very low oral toxicity. Post incident follow-up is needed. For more specific information see relevant (M)SDSs.

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