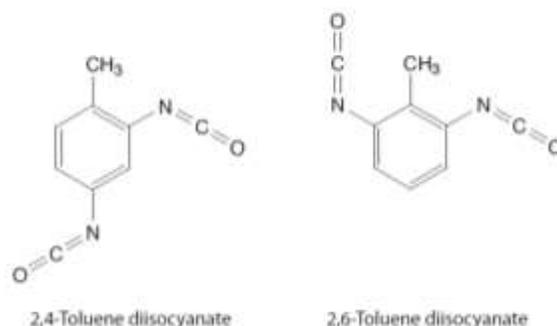


Toluene Diisocyanate Reference Exposure Levels

(2,4- and 2,6-Toluene diisocyanate, 1,3-Diisocyanatomethylbenzene, Methylphenylene isocyanate, Toluene diisocyanate)

CAS: 26471-62-5 (mixed toluene diisocyanate isomers)



1. Summary

The Office of Environmental Health Hazard Assessment (OEHHA) is required to develop guidelines for conducting health risk assessments under the Air Toxics Hot Spots Program (Health and Safety Code Section 44360 (b) (2)). OEHHA developed a Technical Support Document (TSD) in response to this statutory requirement that describes acute, 8 hour and chronic RELs and was adopted in December 2008. The TSD presents methodology for deriving Reference Exposure Levels. In particular, the methodology explicitly considers possible differential effects on the health of infants, children and other sensitive subpopulations, in accordance with the mandate of the Children's Environmental Health Protection Act (Senate Bill 25, Escutia, chapter 731, statutes of 1999, Health and Safety Code Sections 39669.5 *et seq.*). These guidelines have been used to develop the following RELs for toluene diisocyanate: this document will be added to Appendix D of the TSD.

Exposure to diisocyanates, including toluene diisocyanate, has been found to cause adverse effects to the respiratory system in both animals and humans. These effects include acute impacts such as sensory irritation and the induction of asthma in sensitive subjects. Chronic exposure can result in sensitization and long-term decrements in lung function without evidence of sensitization. Once asthma has been induced, triggering of attacks can occur following very low exposures (≤ 1 to 10 ppb) to diisocyanates. Literature summarized and referenced in this document covers the relevant published literature for toluene diisocyanate through Spring 2014.

1.1. Toluene

<i>Reference exposure level</i>	0.7 µg/m ³ (0.1 ppb)
<i>Critical effect(s)</i>	Asthmatic response in non-sensitized humans with asthma
<i>Hazard index target(s)</i>	Respiratory system

1.2. Toluene

<i>Reference exposure level</i>	0.008 µg/m ³ (0.001 ppb)
<i>Critical effect(s)</i>	Accelerated decline in lung function; TDI-induced sensitization
<i>Hazard index target(s)</i>	Respiratory system

1.3. Toluene

<i>Reference exposure level</i>	0.008 µg/m ³ (0.001 ppb)
<i>Critical effect(s)</i>	Accelerated decline in lung function; TDI-induced sensitization
<i>Hazard index target(s)</i>	Respiratory system

2. Physical & Chemical Properties (HSDB, 2013)

TDI Isomer	CAS	Vapor pressure
Toluene diisocyanate (mixed isomers)	26471-62-5	0.023 mm Hg 25°C
2,4-toluene diisocyanate	584-84-9	0.008 mm Hg 25°C
2,6-toluene diisocyanate	91-08-7	0.021 mm Hg 25°C

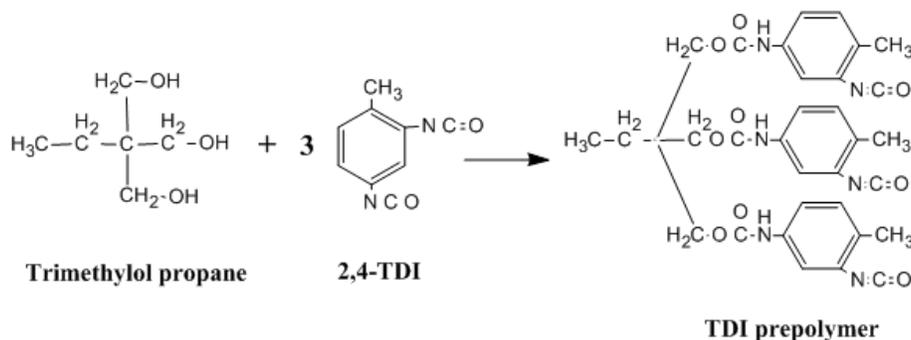
<i>Description</i>	Clear colorless to pale yellow liquid
<i>Molecular formula</i>	C ₉ H ₆ N ₂ O ₂
<i>Molecular weight</i>	174.16 g/mol
<i>Density</i>	1.22 g/cm ³ (25°C)
<i>Boiling point</i>	251°C (mixed isomers)
<i>Melting point</i>	11-14°C (mixed isomers)
<i>Odor threshold</i>	>20 to 50 ppb (Henschler et al., 1962); pungent odor
<i>Solubility</i>	Very soluble in acetone and benzene. Water solubility at 25°C, 0.038 g/L for 2,4-TDI; 2,6-TDI decomposes in water
<i>Conversion factor</i>	7.1 mg/m ³ = 1 ppm @ 25° C

3. Major Uses and Sources

Toluene diisocyanate (TDI) is used in adhesives, coatings, elastomers, and polyurethane foams. During its production and use, it may be released to the environment by volatilization and through various waste streams. Commercial TDI is an isomeric mixture typically comprising 80% 2,4-toluene diisocyanate and 20% 2,6-toluene diisocyanate. Both isomeric forms are listed as Toxic Air Contaminants (TAC) (OEHHA, 2008). U.S. EPA (2010) reported in their IUR (Inventory Update Reporting) that the aggregated national production volume of TDI was 1 billion pounds or greater in 2006. Reported release of TDI to the air in California in 2008 was at the rate of 0.28 tons/year (CARB, 2011). Given the vapor pressures of the constituent isomers, toluene diisocyanate in air will exist solely as a vapor. Vapor-phase TDI may be degraded in the atmosphere by reaction with photochemically-produced hydroxyl radicals with an estimated half-life of 2.7 days for the mixed isomers, 1.7 days for 2,4-TDI, and 2.5 days for the 2,6-isomer. Rapid degradation of low levels of TDI in water is expected to preclude leaching or adsorption to solids in moist soils, as well as bioconcentration in aquatic organisms. However, airborne TDI does not appear to react significantly with atmospheric water vapor (Tury et al., 2003).

Occupational exposure to TDI may occur through inhalation and dermal contact during its production or use. The general population may be exposed to TDI via emissions from facilities that use TDI and use of consumer products containing this compound (Darcey et al., 2002; Krone and Klingner, 2005). These may include products in which the monomeric or prepolymeric form of TDI is present by design, such as in paints and varnishes.

However, TDI manufactured as a prepolymer (Figure 1) is much less volatile but still retains a high level of reactivity. Thus, while the potential for vapor exposure is reduced with the prepolymer, exposure to aerosols generated during use remains a possibility, as does the potential for pulmonary effects.



In an attempt to minimize potentially harmful exposures, TDI has been replaced in many applications, especially consumer products, by other less volatile and reactive compounds such as methylene diphenyl diisocyanate (MDI) and

hexamethylene diisocyanate (HDI), so direct handling of TDI containing materials by consumers is less frequent. TDI and MDI are the most commonly used diisocyanates for the manufacture of polyurethanes. About 95% of all polyurethanes are based on TDI and MDI (Vandenplas et al., 1993b). HDI is another commercially important diisocyanate used principally as a hardener in spray paints and is listed on the California Toxic Air Contaminant list (Vandenplas et al., 1993b; CARB, 2010). Other diisocyanates available include naphthylene diisocyanate (NDI), isophorone diisocyanate (IPDI) and dicyclohexylmethane diisocyanate or hydrogenated MDI (HMDI) but their use is limited to more specialized applications. All of these diisocyanates are also known to cause asthma in occupational settings.

4. Metabolism

TDI is characterized by the N=C=O group which contains two double bonds and exhibits strong chemical reactivity (Raulf-Heimsoth and Baur, 1998). Animal inhalation studies with ¹⁴C-labeled TDI showed that TDI is mainly absorbed in the upper airways (Kennedy et al., 1989). Inhaled TDI was found in the epithelium and the subepithelial level from the nose down to the terminal bronchioles. The uptake of TDI into the blood is linear during exposure at concentrations ranging from 0.05 to 146 ppb.

Based on experiments in rats exposed to 2,4-TDI by inhalation, oral or iv routes, the metabolic scheme in Figure 2 was proposed by Timchalk et al. (1994). As with other isocyanates, TDI can readily react with hydroxyl, sulfhydryl and amine groups on macromolecules including hemoglobin, glutathione, laminin, serum albumin, and tubulin (Brown and Burkert, 2002). In the gut, hydrolysis of TDI generates toluene-2,4-diamine (TDA), a carcinogen. Free TDA may be absorbed and be further metabolized, or may react with TDI to form polyurea polymers that are poorly absorbed and thus eliminated in the feces. In experimental administration by the oral route, 12-20% of the dose was absorbed, while by the inhalation route, essentially all the TDI was absorbed and retained (Timchalk et al., 1994). Inhalation exposure leads preferentially to the formation of TDI conjugates and little or no measurable TDA (Timchalk et al., 1994; Lindberg et al., 2011). These route-dependent differences in fate are posited to explain the observed carcinogenicity of TDI by the oral (with conversion to TDA) but not the inhalation route in experimental animals (Collins, 2002). Exposure to TDI also occurs via dermal absorption and can lead to both dermal and pulmonary hypersensitivity (Karol et al., 1981). The metabolic fate of TDI following dermal exposure is expected to be similar to that following inhalation.

In occupational studies, a correlation between airborne exposure to TDI and urinary TDI metabolite concentrations has been found in workers (Geens et al., 2012). Urinary samples were hydrolyzed with sodium hydroxide to release the TDI-related diamines 2,4- and 2,6-TDA and then quantified as total TDA. Through regression analysis, a post-shift minus pre-shift TDA urine concentration of 18.12 µg/L corresponded to an airborne TDI concentration of 5 ppb (37 µg/m³).

A combined half-life of TDA in urine was 1.1 days, indicating that TDI metabolites may accumulate in the body of workers during the workweek.

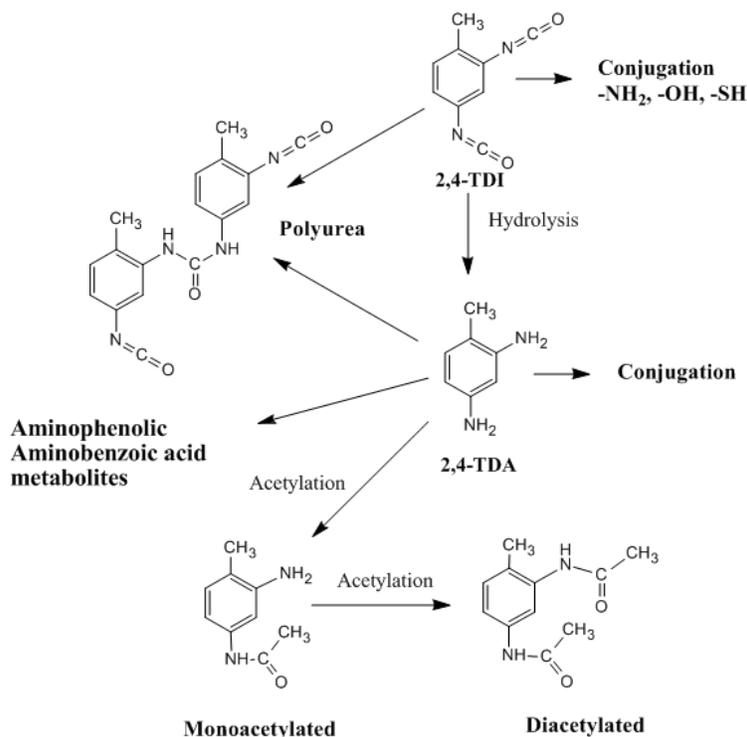


Figure 2. Metabolic Scheme for TDI in Rat (Timchalk et al., 1994)

5. Acute Toxicity of Toluene Diisocyanate

The main effect of acute exposure to TDI in previously non-exposed individuals is sensory irritation. In experimental animals, this has been measured as respiratory rate depression. However, TDI may also act as a pulmonary irritant resulting in increased respiratory rate (Castranova et al., 2002). Dermal exposure and/or inhalation exposures to acutely high levels or long-term lower levels of TDI may result in allergic sensitization. If acute exposure is severe enough, a condition known as reactive airways dysfunction syndrome (RADS) may occur that may persist for years. Subsequent exposure to low-level TDI or other irritants in these individuals result in pulmonary symptoms including bronchial hyperresponsiveness and airflow obstruction. Asthmatic cross reactivity between different isocyanates has been documented. Innocenti et al. (1988) found that nearly 50% of subjects with asthma induced by TDI also exhibited asthmatic reactions to MDI, which they were never exposed to at work. In another study, of 13 workers exclusively exposed to MDI, four also reacted to TDI (O'Brien et al., 1979a). In six workers with IgE-mediated sensitization to isocyanates, radioallergosorbent test (RAST) and/or skin-test investigations revealed the presence of IgE antibodies reacting specifically with isocyanates conjugated with human serum albumin (HSA); these isocyanates included those

to which workers were exposed as well as other isocyanates to which they had not been exposed (Baur, 1983). These results indicate the predominance of closely related antigenic determinants in HSA conjugated with different isocyanates. The common antibody-binding regions are recognized to different extents by antibodies of clinically sensitized workers, indicating individual differences in specificities and avidities of antibody populations.

There is evidence that prepolymers of isocyanates, including TDI prepolymers, can themselves cause occupational asthma. A case study showed that specific inhalation challenges with a prepolymer of TDI elicited asthmatic reactions in two subjects who were not affected by challenge with the monomer of TDI (Vandenplas et al., 1992).

5.1. Acute Toxicity to Adult Humans

Acute respiratory exposures to TDI are typically reported in occupational settings with responses ranging from upper airway irritation to toxic bronchitis (Ott et al., 2003). Eye, nose and throat irritation are often the first manifestations of acute high exposure to TDI, with dry cough, and chest pain and tightness ensuing. Patchy infiltrates may be seen on chest X-rays, and the clinical picture may approximate bronchitis, bronchiolitis, bronchial asthma, or pneumonitis (Peters and Wegman, 1975). While less likely than with chronic exposures, high acute exposure may result in allergic sensitization. In these cases a subsequent acute inhalation exposure, often considerably below the odor and sensory irritation threshold (i.e., <5-20 ppb), may provoke a potentially life-threatening pulmonary hypersensitivity response.

5.1.1. Dose-Response Chamber Studies in Humans

Henschler et al. (1962) conducted one of the only controlled human exposure studies with exposure concentrations of TDI considerably above 20 ppb. In the German article (translated into English by OEHHA), six healthy men were exposed to various concentrations of TDI 65/35 (2,4-TDI and 2,6-TDI, respectively) and to the pure isomers for 30 min in an exposure chamber. The subjects were only exposed to one concentration of TDI per day, which was randomly selected. At 0.01 and 0.02 ppm (10 and 20 ppb) neither odor nor other sensory symptoms were perceived. At 0.05 ppm, the odor of TDI was perceived immediately upon entering the chamber, but was not noticeable by the men after 4-9 min of exposure. Three of 6 subjects noted conjunctiva irritation by 15 min of exposure, which was described as "tear stimulus, but without tearing".

At 0.075 ppm TDI 65/35, the odor was stronger and took longer to become unnoticeable (12-14 min). A light burning sensation of the eye without tearing was experienced in the subjects after 1-6 min of exposure. When asked to breathe deeply, all felt a tingling or slight stinging sensation in the nose. Exposure to 0.1 ppm produced more severe eye and nose irritation described as resembling a cold. Odor disappeared after 12-15 minutes.

At 0.5 ppm, lacrimation was elicited in all subjects, but the eye irritation was still considered bearable. A strong stinging sensation and greater secretion from the nose were noted. The throat was described as scratchy or burning, but without coughing. Two subjects were exposed to 1.3 ppm TDI 65/35 for 10 min resulting in heavy eye tearing, eye reddening and eyelid closure. Several hours after exposure, significant catarrhal symptoms (mucous membrane inflammation) of the respiratory tract appeared with coughing.

Henschler et al. (1962) also exposed subjects to pure 2,4-TDI and 2,6-TDI individually. Exposure to 0.02 ppm 2,4-TDI did not result in sensory symptoms, but a weak odor was noted at 0.05 ppm. No eye irritation was noted. Irritation of the conjunctiva and nose occurred at 0.08 ppm, which was significantly stronger with exposure to 0.1 ppm. Eye irritation occurred in 2 out of 5 subjects at 0.2 ppm, while 0.5 ppm caused tearing, which was described as piercing and annoying in all subjects. Exposure to 2,6-TDI was described as having similar sensory effects as that produced by 65/35 TDI, but was considered slightly stronger than the same concentration of 2,4-TDI. At 0.5 ppm 2,6-TDI, the subjects could not differentiate from the effects produced by 2,4-TDI at the same concentration.

The threshold for odor recognition reported by Henschler et al. (1962) is supported by numerous reports of exposures of 5-20 ppb resulting in no noticeable odor. Other acute studies that were primarily conducted to assess or confirm TDI-sensitization in workers also found no sensory irritation in normal humans with exposures up to 20 ppb for 30 min or less. In support of the finding of sensory irritation at 50 ppb and above by Henschler et al. is a report by Lee and Phoon (1992) in which uncontrolled industrial exposure to a mean concentration of 160 ppb TDI (range: 10 to 500 ppb) resulted in eye and respiratory system irritation. Similarly, painters handling polyurethane varnish experienced eye, nose and throat irritation with exposure to TDI concentrations of 70-170 ppb (Huang et al., 1991).

5.1.2. Challenge Studies in Sensitized Workers

There are numerous reports in the literature in which low acute concentrations of TDI were used to study or confirm a diagnosis of probable toluene diisocyanate asthma in workers (Chester et al., 1979; Mapp et al., 1986; Moller et al., 1986a; Boschetto et al., 1987; Banks et al., 1989; Vogelmeier et al., 1991; Karol et al., 1994; Pisati et al., 2007). Concentrations of TDI in these challenge tests usually ranged between 5 and 20 ppb with exposure durations of 10 min to several hours. With the exception of a few early reports, concentrations of TDI higher than 20 ppb are not used in controlled human studies due to the potential to provoke acute allergic sensitization, sensory irritation and respiratory inflammation.

In studies in workers suspected to have TDI-induced asthma, pulmonary responses often resulted from exposures below 10 ppb TDI. The lowest

controlled exposure to TDI resulting in an asthmatic response is ≤ 1 ppb. Lemiere et al. (2002) exposed eight subjects with occupational asthma induced by specific diisocyanates (TDI, MDI or HDI) to 1 ppb using a closed circuit apparatus. The authors considered a positive result to be a 20% or greater reduction in Forced Expiratory Volume in 1 second (FEV_1). By this criterion asthma symptoms were triggered in two of the subjects with a 30 min exposure, one to MDI and the other to HDI. A third subject had asthma symptoms with a 45 min exposure to TDI. There was also a significant correlation (Spearman rank order test $\rho=0.8$, $P<0.001$) between the percentage of maximum decrease in FEV_1 after exposure to 1 ppb and the increase in sputum neutrophil count, indicating inflammatory changes as well.

In another study of workers suspected to have TDI-induced asthma, 9 out of 63 subjects responded with a fall in FEV_1 of 15% or more following exposure to a TDI concentration of ≤ 1 ppb for 30 min (O'Brien et al., 1979b). This sensitive subgroup of TDI responders also showed a significantly greater increase in bronchial reactivity to both histamine and exercise than the TDI-sensitive subgroup with asthmatic reactions to TDI concentrations of 2-20 ppm (28 subjects), and the TDI non-sensitive group (26 subjects).

5.1.3. Challenge Studies in Normals and Non-Sensitized Asthmatics

More pertinent to derivation of an acute REL for TDI, some studies also tested pulmonary response in exposed normal and asthmatic subjects with no sensitization or history of exposure to isocyanates, in addition to testing the pulmonary response in workers with probable TDI sensitization.

Vogelmeier et al., 1991; and Baur and Colleagues, 1994

Diisocyanate inhalation tests were performed in exposure chambers on 19 workers with diisocyanate-induced asthma and on 10 healthy and 15 asthmatic volunteers with no previous contact with diisocyanates (Vogelmeier et al., 1991; Baur et al., 1994). The ten healthy individuals had a negative methacholine test and were exposed to 20 ppb TDI for 2 hrs. The 15 patients with asthma had a positive methacholine test and were exposed for one hr to 10 ppb TDI, followed by a 45 min break, then a one hr exposure to 20 ppb. Pulmonary function tests included airway resistance (R_{aw}), specific airway conductance, FEV_1 , inspiratory vital capacity, total lung capacity. The pulmonary function test results of volunteers without previous contact with diisocyanates were presented by two different approaches: Vogelmeier et al. (1991) used a $\geq 50\%$ decrease in specific airway conductance from the zero value as evidence of a positive airway reaction, while Baur et al. (1994) used a 100% increase of airway resistance as evidence of a positive airway reaction.

In the approach used by Vogelmeier et al. (1991), one of 10 normal volunteers showed a positive airway reaction ($\geq 50\%$ decrease in specific airway conductance) to 20 ppb TDI, and one of 15 subjects with asthma had a positive

airway reaction to 10 ppb TDI. With subsequent exposure of the asthmatic subjects to 20 ppb for 1 hour, two of the remaining 13 asthmatic subjects had a positive reaction to 20 ppb TDI. (Baur et al. (1994) later clarified that the subject responding to 10 ppb of TDI and another subject with asthma who refused to continue did not undergo the second challenge with 20 ppb TDI). All the positive airway reactions occurred during the first hour after inhalation; late responses were not observed. Vogelmeier et al. concluded that supposedly sub-irritant concentrations of TDI may induce a marked airway reaction in healthy volunteers and patients with asthma.

Baur et al. (1994) then presented the Raw results measured by body plethysmography on the same subjects. Using 100% increase in Raw (amounting to values of ≥ 0.5 kPa/l per second) as evidence of a positive airway reaction, none of the 10 healthy controls had an asthmatic response with a two-hour exposure to 20 ppb TDI. In contrast, one of 15 asthmatics responded to 10 ppb with a severe asthmatic reaction. Another asthmatic subject from the remaining group of 13 subjects showed an asthmatic reaction to 20 ppb. Based on these results, Baur et al. presented a different conclusion from Vogelmeier et al. (1991). Baur et al. concluded that the TDI exposures in the TLV range (5 to 20 ppb) do not change lung function in healthy subjects and only rarely in previously unexposed asthmatics, indicating that asthmatic responses in TDI challenge tests are not absolutely specific to sensitized individuals.

Additional details of this study are in Baur (1985), but were unavailable to OEHHA. However, this study was summarized by NRC (2004). Of the 15 asthmatic subjects exposed to TDI, five complained of chest tightness, rhinitis, cough, dyspnea, throat irritation, and/or headache during exposure. It was unclear from the report what concentration of TDI caused these symptoms. Three normal subjects reported eye irritation and/or cough. Among the asthmatics, no decrease in FEV₁ <20% was observed, although two showed a decrease in FEV₁ between 15 and 20%. Increases in Raw did not correspond with decreases in FEV₁, and neither parameter could be used as an indication of the reported symptom discomfort.

Fruhmann et al., 1987

An apparently different group of subjects were examined using similar methodology, and was conducted by many of the same researchers in Baur et al. (1994) and Vogelmeier et al. (1991). In this German study by Fruhmann et al. (1987), translated into English by OEHHA, 15 healthy and 15 asthmatic subjects with no previous contact with diisocyanates were exposed to TDI and airway resistance (Raw) recorded periodically by whole body plethysmography. The healthy subjects were chamber-exposed to 20 ppb TDI for 2 hrs, while the asthmatic subjects were exposed to 10 ppb TDI for 1 hr, then given a break for 45 min followed by a 1 hr exposure to 20 ppb TDI. For healthy subjects, mean Raw before and after exposure was 0.12 and 0.17 kPa.s.L⁻¹, respectively, with no individual experiencing an increase in Raw above 0.25 kPa.s.L⁻¹. A normal Raw

result was considered to be $<0.35 \text{ kPa}\cdot\text{s}\cdot\text{L}^{-1}$. For the asthmatic subjects, significant changes and complaints were recorded in one-third of the subjects, although the authors did not specify what these changes and complaints were other than presenting the individual Raw results. Three of the 15 asthmatic subjects experienced a maximum Raw value greater than 100 percent of their control value taken before exposure. Raw was recorded during and up to 3 hrs post-exposure, but it was not specified exactly when the highest Raw value was recorded. Another five asthmatic subjects had a maximum increased Raw between 50-100 percent of their control value, all of which were above $0.35 \text{ kPa}\cdot\text{s}\cdot\text{L}^{-1}$.

Chester et al., 1979

Chester et al. (1979) exposed 40 subjects by facemask to 20 ppb TDI for 20 min and then assessed airway response by specific airway resistance (S_{Raw}) at regular intervals for up to six hours following exposure. Twenty of the subjects were symptomatic TDI workers and the other subjects were a nonsmoking control group without previous TDI exposure consisting of 10 healthy subjects and 10 subjects with extrinsic asthma. The authors defined symptomatic TDI workers as those that have experienced bronchoconstriction with occupational TDI exposure. Using an increase in S_{Raw} $\geq 50\%$ above baseline resistance as a positive response to the TDI challenge, Chester et al. found that 9 of the 20 TDI workers were positive responders (one immediate, five dual and three late asthmatic reactions). None of the extrinsic asthmatics or normal subjects responded to 20 ppb TDI by an increase in their S_{Raw} greater than 50%. The specific changes in S_{Raw} experienced by the asthmatics and normals were not presented by the authors.

Some control subjects and seven of the non-responding TDI workers were then assessed for small airway function by testing for maximum expiratory flow volume by breathing air and repeated when breathing helium-oxygen (Chester et al., 1979). Using the criteria of a 40% increase in the volume of isoflow and a 40% decrease in Forced Expiratory flow at 50%FVC (ΔFEF_{50}) as evidence of small airway changes, the authors observed that five of seven “non-responders” had reduced lung function. Of the normal subjects and seven subjects with extrinsic asthma examined using these pulmonary function tests, none were considered responders by the criteria applied.

Fabbri et al., 1987

Fabbri et al. (1987) exposed 6 normal subjects with no previously documented asthmatic reaction to TDI to 18 ppb TDI for 30 min. FEV₁ and airway responsiveness to methacholine were unaffected by TDI exposure.

Moller et al., 1986

Moller et al. (1986b) exposed 10 subjects with a positive methacholine challenge test, but with no apparent previous exposure to TDI, to concentrations of TDI up to 20 ppb for 15 min. A positive methacholine test was considered to be a fall in FEV₁ of 20% or greater when exposed to a total cumulative dose of <2,000 µg methacholine. No change in FEV₁ was observed with exposure to TDI in these subjects.

Mapp et al., 1986

In addition to exposing a group of 40 sensitized TDI-workers (10 each with immediate, dual, late, or no asthmatic reactions after exposure to TDI) to 18 ppb TDI for up to 30 min, Mapp et al. (1986) also exposed eight asthmatic subjects with no history of sensitization to TDI. FEV₁ was measured immediately before and after exposure and then hourly for 8 hrs. The provocative dose of methacholine that had previously caused a decrease in FEV₁ of 20% (PD20, the dose of methacholine in mg) was also measured. An asthmatic reaction was considered to occur when FEV₁ decreased by 20% from baseline, or an increase in airway responsiveness occurred when the PD20 FEV₁ decreased at least two-fold. By this measure, exposure to TDI did not elicit an asthmatic reaction in the group of asthmatic subjects not sensitized to TDI. Although airway responsiveness was markedly increased with methacholine challenge in asthmatic subjects not sensitized to diisocyanates, the authors found no further decrease in FEV₁ after TDI inhalation with challenge at the PD20.

Vandenplas et al., 1999

Vandenplas et al. (1999) exposed 17 subjects without respiratory symptoms (eight smokers and nine nonsmokers) or occupational exposure to diisocyanates to ambient air and once to 5 ppb TDI for 6 hrs followed by 20 ppb TDI for 20 min. Nonspecific bronchial responsiveness was assessed by inhalation of histamine, which was expressed as the concentration of histamine causing a 20% fall in FEV₁. Several pulmonary function tests including specific airway conductance (sGaw), functional residual capacity (FRC), total lung capacity (TLC), forced vital capacity (FVC), FEV₁, FEV₁/FVC ratio, and maximal expiratory flow at 50% of FVC (MEF_{50%}), and at 25% of FVC (MEF_{25%}), were carried out before exposure and at every hour during exposure. Bronchial lavage (BL) and bronchoalveolar lavage (BAL) were performed 1 hr after each exposure.

None of the subjects in the Vandenplas et al. (1999) study experienced significant respiratory symptoms in response to the exposures. Comparison of pre- and post-exposure pulmonary function values did not result in significant differences. The pulmonary function tests did find detectable changes in airway caliber throughout the exposure period using regression analysis of repeated measures. Compared to ambient air exposure, TDI exposure resulted in a modest decrease in sGaw (p=0.053) and in MEF_{25%} (p=0.015). Multivariate

analysis of the time-point differences in sGaw showed that the mean concentration of TDI was a significant determinant of the response, while the level of nonspecific responsiveness to histamine had a significant effect on changes to MEF_{25%} induced by TDI exposure. The authors suggest these results show that TDI could exert an effect on both small and large airways.

TDI exposure in the Vandenplas et al. (1999) study also resulted in a slight increase in BAL albumin level (TDI: 26.4±12.5 vs. air: 21.8±8.6 µg/ml, p=0.044) and in BL α₂-macroglobulin concentration (TDI: 0.07±0.061 vs. air: 0.05±0.04 µg/ml, p=0.044). The authors note that the observed increase in BAL albumin content after TDI exposure likely represents indirect evidence of changes in permeability of the epithelial barrier and slight leakage of blood plasma components into the alveolar compartment. The increase in BL α₂-macroglobulin level could reflect a selective increase in epithelial permeability associated with local production. The concentrations of potential indicators of epithelial cell dysfunction (secretory component and CC16) and pro-inflammatory cytokines (TNF- α, IL-4, IL-5, IL-6 and IL-8) were not significantly altered by TDI exposure, suggesting to the authors that the observed TDI-related changes in pulmonary function tests were not directly related to airway inflammation.

A summary of the acute studies presented above is shown in Table 1.

Table 1. Summary of Controlled Acute Exposure Studies in Non-Sensitized Subjects

Study	TDI Exposure Conditions	Pulmonary/Sensory Findings
Henschler et al. (1962)	6 subjects, 1 exposure/day 30 min exposure to: 10, 20, 50, 75, 100, 500, and 10 min exposure to 1300 ppb	No symptoms at 10 or 20 ppb; increasing sensory irritation with increasing TDI concentration starting at 50 ppb and above.
Vogelmeier et al., 1991; Baur et al., 1994	10 normal subjects, 20 ppb for 2 hrs 15 asthmatics, 10 ppb for 1 hr, 45 min break, then 20 ppb for 1 hr	Normals: No significant pulmonary decrement; 3 complained of eye irritation and/or cough Asthmatics: 1/15 had $\geq 100\%$ increase in Raw at 10 ppb; 1/13 had $\geq 100\%$ increase in Raw at 20 ppb; overall, 5 complained of chest tightness, rhinitis, cough, dyspnea, throat irritation, and/or headache
Fruhmann et al., 1987	15 normal subjects, 20 ppb for 2 hrs 15 asthmatics, 10 ppb for 1 hr, 45 min break, then 20 ppb for 1 hr	Normals: No significant increase in Raw Asthmatics: 3/15 had $\geq 100\%$ increase in Raw; one-third of subjects experienced significant, but unspecified, changes or complaints
Chester et al. (1979)	10 normal subjects and 10 asthmatics 20 ppb for 20 min	No increase in SRaw greater than 50% in any subject
Fabbri et al. (1987)	6 normal subjects 18 ppb for 30 min	No change in FEV ₁ or airway responsiveness to methacholine
Moller et al., 1986	10 subjects with positive methacholine challenge test up to 20 ppb for 15 min	No change in FEV ₁ observed with methacholine challenge after TDI exposure
Mapp et al., 1986	8 asthmatic subjects 18 ppb for 30 min	No decrease in FEV ₁ $\geq 20\%$ observed; No decrease in the PD ₂₀ FEV ₁ greater than 2-fold with methacholine challenge
Vandenplas et al. (1999)	17 normal subjects 5 ppb for 6 hrs followed by 20 ppb for 20 min, with pulmonary function test every hr	Decreased sGaw (p=0.053) and MEF _{25%} (p=0.015) measured by regression analysis of repeated measures; increased BAL albumin level (p=0.044) and BL macroglobulin (p=0.044) concentration

5.2. Acute Toxicity to Infants and Children

No studies were located that examined the effects of acute exposure to TDI in children. However, the effects due to acute TDI exposure may be expected to be similar to those reported following acute accidental exposure of school children to methylene diphenyl diisocyanate (MDI) (Jan et al., 2008). In this report, asthma-like symptoms were observed among 203 schoolchildren following acute exposure to MDI and toluene spilled during track paving with polyurethane. Of the exposed children, 70.9% reported headache, 67.5% had persistent cough, 63.5% had dyspnea, and 62.6% nausea. Chest discomfort was reported by 23.6% of the students but chest X-rays were normal. Bronchodilators were administered to 15.8% who experienced wheezing and difficulty breathing. Although no measurements of actual air MDI levels were reported, the authors observed an inverse linear relationship between the incidence of affected students in various classrooms and the distance from the site of MDI spillage ($r = -0.48$, $p < 0.05$) suggesting a dose-response.

During follow-up surveillance three days after the incident, the prevalence of residual symptoms was cough 30.0%, headache 19.7%, dyspnea 15.3%, sore throat 10.3%, and nausea 3.9%. A positive history of asthma among 10.8% of the students was strongly correlated with the incidence of dyspnea (OR 4.09; 95% CI 1.17-14.32) and an abnormal pulmonary function test (OR 3.84; 95% CI 1.09-13.5). However, none of the other symptoms during the episode was correlated with either asthma history or abnormal lung function tests. In addition, 60.8% of the children without a history of asthma also complained of dyspnea, and 16.2% required bronchodilators for symptomatic relief. Acute exposure to high levels of MDI was thus associated with reactive airway dysfunction (RADs) among previously unexposed individuals. The authors did not discuss effects seen in exposed adults, so it is unclear if children were more prone to the acute effects of MDI than adults. Also, no apparent follow-up was performed to determine if the children had been immunologically sensitized as a result of the high acute exposure.

Krone and associates have postulated that a relationship exists between exposure to polyurethane products made from isocyanates and childhood asthma (Krone and Klingner, 2005). Further discussion is presented in Section 6.2.

5.3. Acute Toxicity to Experimental Animals

The effects on the respiratory tract of a single 4-hour exposure of mice, rats, guinea pigs and rabbits to 2, 5 or 10 ppm TDI were reported by Duncan et al. (1962). Two hours following termination of the exposure to 2 ppm, focal coagulation necrosis and desquamation of the superficial epithelium lining the trachea and the major bronchi were observed. Occasionally bronchial airways were found containing acute inflammatory cells associated with sloughed epithelium. However, by one day following exposure, acute inflammatory

exudates were observed in the majority of the major bronchi, along with further desquamation of necrotic epithelium. Fibrinous strands were observed in the lumina, and an infiltration of polymorphonuclear leukocytes extended through the edematous peribronchiolar connective tissue. Acute inflammatory cells also infiltrated the edematous perivascular spaces of the accompanying vessels. By day four, there were signs of clearing of the inflammatory response and evidence of regeneration of tracheal and bronchial epithelium. By day seven, control and exposed animals were not significantly different. While the effects of exposure to 2 ppm were largely transient, exposures at 5 and 10 ppm resulted in more severe effects that were not completely reversible. The LOAEL for these effects was 2 ppm, but a NOAEL was not observed.

The effects of single, and repeated 3-hour exposures to 2,4-TDI vapor on sensory irritation at concentrations ranging from 0.007 to 2 ppm were measured as respiratory rate depression and nasal histopathology in mice (Sangha and Alarie, 1979). With single exposures, time-response relationships showed the slow development of the respiratory response with exposure duration. Concentration-response relationships also showed that the level of the response was dependent upon both exposure concentration and duration. Repeated exposures at ≥ 0.023 ppm resulted in cumulative effects. Regardless of the TDI concentration used, respiratory rates decreased relatively rapidly during the first 10 minutes of exposure, followed by a more gradual decline. As shown in Table 2, depression of the respiratory rate by 50% (RD50) was achieved in 10 min at a concentration of 0.813 ppm, in 60 min at 0.386 ppm, but took 180 minutes at 0.199 ppm.

Table 2. Respiratory Depression (RD50) Dependence on Exposure Duration

Exposure Time (min)	10	30	60	120	180	240
RD50 (ppm)	0.813	0.498	0.386	0.249	0.199	0.199

Recovery of respiratory rate following cessation of exposure was similarly duration dependent, being rapid with short exposures and slow with long exposures. This is in contrast to other sensory irritants such as acrolein, the response to which is only concentration dependent and recovery is rapid regardless of the exposure duration (Kane and Alarie, 1977). The slow rate of recovery became more evident when 3-hour exposures of 0.023, 0.078, 0.301, 0.505, 0.82, and 1.18 ppm were repeated on successive days. On the first day of exposure, the drop in respiration rate was similar to that of the single exposures: rapid during the first 10 minutes, with a more gradual descent thereafter. However, on subsequent days, the pre-exposure rates were progressively lower indicating incomplete recovery from the exposures on previous days. Recovery to baseline required at least five days after the last exposure. By contrast, with exposures in the range of 0.007 to 0.018 ppm, there were no consistent respiratory responses after the three-hour exposures, nor was there the pattern of reduced respiratory rate with repeated exposure.

Histopathological evaluation of successive transverse sections of the nasal area revealed no lesions following three days of exposure for 3 hours/day to 0.031 ppm. However, in mice similarly exposed to 0.25 ppm, damage was consistently observed in the most anterior section of the nasal passages and external nares, with 25-50% of the mucosa involved including some extension into the submucosa. The lesions were much less pronounced in more distal sections.

These results suggest that, in addition to the potential for immune hypersensitization demonstrated in other studies (Karol et al., 1980), TDI has cumulative irritant effects that result from incomplete recovery from previous exposures above a certain level in this rodent model. Both the development of and recovery from these effects are slow, possibly consistent with covalent modification of receptors as in the reaction of TDI with OH or NH₂ groups in proteins and/or specific residues on TRPA channels in sensory neurons. TRPA belongs to the family of transient receptor potential (TRP) channels that transduce sensory neurons' response to thermal, mechanical, and specific chemical stimuli.

In guinea pigs, Gagnaire et al. (1988) demonstrated that TDI-induced airway hyperresponsiveness to intravenous acetylcholine can occur with continuous exposure as short as a single 4 hr exposure to 1.2 ppm. Similar responses to acetylcholine in guinea pigs were seen with TDI exposures to 118 ppb for 48 hr, 1.08 ppm for 4 hr/day for 2 days, and continuous exposure to 23 ppb for 1 week. However, regardless of exposure concentration or duration, TDI did not modify the baseline airway resistance (Raw). The authors concluded the study results were consistent with the hypothesis of a cumulative effect of TDI on airway hyperresponsiveness.

It is important to note that the development of pulmonary sensitivity to TDI does not require inhalation exposure. Working with guinea pigs, Karol et al. (1981) demonstrated that single dermal exposures to TDI were sufficient to elicit signs of significant pulmonary sensitivity, as measured by increases in respiratory rates greater than three SD from the mean upon subsequent inhalation challenge. (Rapid shallow breathing is an early response to chemical stimulation of bronchial C-fibers (Coleridge et al., 1983)). Significant pulmonary sensitivity was seen in 2 of 12 animals challenged with 5 ppb TDI vapor, in 4 of 12 animals challenged with TDI-protein conjugates, in 5 of 12 animals challenged with toluene monoisocyanate-protein conjugates, and in none of the animals challenged with the unconjugated protein carriers alone.

Marek et al. (1995) investigated the induction of lung injury and development of airway hyperresponsiveness in rabbits with acute exposure to 5, 10 or 30 ppb TDI. Eight rabbits per group were anesthetized and intubated for pulmonary function tests to increase the effective dose in the lower airways and the lung. Exposure to TDI four times each over a period of one hour did not significantly alter airway resistance, dynamic elastance, slope of the inspiratory pressure generation, arterial pressure or arterial blood gas tensions. Airway

responsiveness to aerosols of 2% acetylcholine (ACh) was measured before and after each TDI exposure. No effect by ACh was seen in rabbits exposed to 5 ppb TDI for up to 7 hrs. With exposure to 10 ppb TDI, the amplitude of the ACh-constrictor response, indicated by changes in dynamic elastance, had increased by almost 2-fold by the third hour of TDI exposure, with similar increases in airway resistance and the slope of the inspiratory pressure generation also recorded. Exposure to 30 ppb TDI resulted in a steeper increase in these pulmonary responses following 2% ACh exposure. The authors concluded that the increased airway resistance to ACh in the rabbits exposed to TDI is an early indication for the development of obstructive lung disease.

Since TDI exposure may elicit both pulmonary and immune responses, it is of interest to compare the relative levels of exposure that elicit these respective responses. Guinea pigs received whole body exposure to 0, 0.02, 0.2, 0.6, or 1.0 ppm TDI as an aerosol comprising an 80:20 mixture of the 2,4- and 2,6-isomers 3 hr/day for 5 days (Aoyama et al., 1994). Three weeks following these induction exposures, all animals were challenged with a 15 min exposure to 0.02 ppm TDI while in a body plethysmograph to measure respiration rates. The pulmonary response was assessed as the percentage increase in respiratory rate. Compared to controls, an increase of at least 3 standard deviations measured during and 60 minutes after the challenge exposure was considered significant. By this criterion, animals induced by exposure to 0.2 ppm and above showed significant pulmonary responses. There was, however, no linear correlation between the intensity of the pulmonary responses and the dose used for induction. Whether this is related to the ability of TDI to act both as a sensory irritant, thereby decreasing respiratory rate, and as a pulmonary irritant that increases respiratory rate is not clear. Alternatively, the breathing rate during induction was not reported and may have decreased, consistent with TDI's sensory irritating properties.

The breathing rate increase measured during the subsequent challenge by Aoyama et al. (1994) may reflect pulmonary changes associated with the immune response. The number of animals responding at each dose level was also not different among exposure groups. The time course of IgG production was followed and the first TDI-specific antibodies were detected in some of the animals 6 days following the first induction exposures to 0.2 ppm and above. By 13 days, all animals in these groups had demonstrable anti-TDI IgG. In this study, 0.02 ppm represents a threshold above which both pulmonary and immune responses were observed. Although these responses were not seen when the induction dose was 0.02 ppm, once the animals had been sensitized by higher induction doses, a challenge exposure to 0.02 ppm was sufficient to elicit pulmonary responses.

In a protocol similar to Aoyama's above, Karol (1983) exposed guinea pigs to 0.02, 0.12, 0.36, 0.61, 0.93, 4.70, 7.60, or 10 ppm TDI and, beginning on day 22, examined animals for production of TDI-specific antibodies, and for dermal and pulmonary sensitivity to TDI. TDI-specific antibodies were found with exposures

of 0.36 ppm and above with the antibody titers reflecting a dose-dependent increase through 0.93 ppm. Respiration rates were observed to decrease in a dose-dependent fashion during the sensitizing exposure to TDI. At exposures of 0.61 ppm and above, respiratory rates were depressed at least 50% after one hour. However, upon subsequent inhalation challenge with 1% TDI-guinea pig serum albumin conjugate, pulmonary responsiveness was measured as an increase in respiration rate. Similar to the results for antibody production, pulmonary effects were only observed in animals sensitized with 0.36 ppm TDI and above. The pulmonary effects correlated to the presence of antibodies, but not to their titer.

Pauluhn (2014) developed a respiratory sensitization/elicitation protocol in Brown Norway rats to determine a threshold dose of TDI for elicitation of asthma-like responses in sensitized, re-challenged rats. The focus of the study was to duplicate at least some phenotypes typical of diisocyanate-asthma using two cutaneous exposures to induce and boost systemic sensitization. Pauluhn and Poole (2011) found that skin-sensitization with MDI produced a more pronounced subsequent response upon inhalation challenge with MDI as compared to repeated inhalation-only sensitization, so a similar protocol was used for TDI.

Pauluhn (2014) notes that both the priming response and the elicitation response are linked to irritation/inflammation of the susceptible lung airway tissue. Thus, the dose must be high enough to overcome the scrubbing ability of peptides and proteins in lung lining fluid of the upper airways and reach susceptible lung structures in the posterior airways. As measured by changes in tidal volume that are a result of stimulation of the C-fiber-related alveolar Paintal reflex, this TDI dose was determined to be about 81 mg/m³ or higher. Neutrophilic granulocytes (PMNs) in BAL fluid were used as the endpoint for allergic pulmonary inflammation in the rats. This was supplemented by physiological measurements characterizing nocturnal asthma-like responses and increased nitric oxide in exhaled breath.

A $C \times t$ regimen in which concentration (C) was held constant and time (t) was variable yielded the best dose-response relationship for the dermally-sensitized rats as long as C was high enough to overcome the scrubbing capacity of the upper airways (Pauluhn, 2014). In rats that were primed with three previous exposures to 85 mg/m³ TDI for 30 min each, the author identified a NOAEL of 1000 mg TDI/m³ x min for TDI-induced asthma in rats using his $C \times t$ (in which $t = 10, 30$ or 60 min) escalation challenge protocol. The author then calculated a human-equivalent 8-hour worker exposure of 3 ppb from the rat NOAEL, which included a dosimetric adjustment factor of 3 for conversion from obligate nose breathers (rats) to oronasal breathers (humans). This breathing adjustment was based on findings in HDI from Shroeter et al. (2013).

6. Chronic Toxicity of Toluene

Isocyanate exposure, including TDI exposure, is one of the leading causes of occupational asthma, characterized by bronchial inflammation with lymphocytic infiltration and eosinophilia, airway hyperresponsiveness, and airway remodeling (Chan-Yeung, 1990). In clinical investigations carried out by Baur et al. (1994) detailed evaluation of case histories and clinical data of 621 isocyanate workers, 247 of whom reported symptoms, showed that the predominant diagnosis was bronchial asthma followed by chronic bronchitis, rhinitis, conjunctivitis, and several other less common disorders including allergic alveolitis. Another pulmonary endpoint investigated by many researchers is an accelerated decline in pulmonary function (such as decreased FEV₁) with chronic TDI exposure in the absence of occupational asthma.

6.1. Chronic Toxicity to Adult Humans

6.1.1. Pulmonary Function as Measured by FEV₁

FEV₁ is one of the most common pulmonary function tests examined in occupational studies. It is helpful to review typical FEV₁ loss in worker and general populations first before comparing pulmonary function decrements in diisocyanate worker populations. In healthy adults, FEV₁ has been found to decline at a rate of about 25 ml/yr (Anees et al., 2006). In asthmatic subjects and smokers with chronic obstructive pulmonary disease, declines of about 40 ml/yr and 60 ml/yr, respectively, have been found. Examined longitudinally, the Six Cities Study observed individual rates of FEV₁ loss increased more rapidly with age in never-smoking adults (Ware et al., 1990). Their longitudinal model gave rates of loss in males increasing from 16.9 ml/yr at age 25-29 to 58.0 ml/yr at age 75-78. In females, rates of loss increased from 14.6 ml/yr at age 25-29 to 41.7 ml/yr at age 75-78.

In a large steelworker population of 475 participants, smoking, being overweight, excess weight gain over time, and dust exposure at work were all related to a lower level (as measured cross-sectionally) and a steeper rate of decline of FEV₁ loss (as measured longitudinally) of pulmonary function (Wang et al., 1996). In this worker group (age at midway 40 yrs), FEV₁ loss examined longitudinally in current-, ex- and never-smokers was 53, 44, and 37 ml/yr, respectively. In a 15-year follow-up study of a general population, the unadjusted decline in FEV₁ among subjects with asthma was 38 ml/yr, as compared with 22 ml/yr in those without asthma (Lange et al., 1998).

6.1.2. Prevalence and Characteristics of Diisocyanate-Induced Asthma

The prevalence of occupational asthma due to diisocyanates was estimated by Baur (1990) to be anywhere between 0 (seat production of a car manufacturer with no detectable TDI air concentration) and 30% (car equipment plant atmosphere with a permanent TDI concentration of 5-10 ppb). In occupational

studies where TWA TDI concentrations were kept below 5 ppb, the prevalence of asthma was generally below 1% (Ott et al., 2003).

Exposure to TDI or other diisocyanates in workers with diisocyanate-induced asthma may result in an immediate or delayed asthmatic symptom onset, or have a dual or recurrent character. Diisocyanate challenges in diisocyanate-sensitized workers do not always correlate with nonspecific bronchial hyperactivity as evaluated by the methacholine challenge test. For example, of 132 workers with an asthmatic response to methacholine 71% did not respond to diisocyanates, whereas 16% of those without methacholine hyperreactivity were positive in the diisocyanate challenge test (Baur et al., 1994). Alternatively, Karol et al. (1994) found that airways hyperresponsiveness to methacholine in TDI-sensitized workers is a strong predictor of response to TDI provocation challenge, independent of atopy and serum IgE, and that serum IgE is associated with early-onset responses to TDI provocation challenge.

Most studies find no evidence that atopy or smoking influences susceptibility to diisocyanate-induced asthma (Malo et al., 1992; Baur et al., 1994). However, a case-referent study of TDI workers found smoking or history of either hay fever, eczema, or asthma increased the risk of developing TDI-related asthma 2-3-fold (Meredith et al., 2000).

It has been proposed that brief episodes of high exposure are more likely to lead to diisocyanate asthma than long-term exposure to lower concentrations (Musk et al., 1988). Thus, many researchers recorded average TDI concentrations as well as short-term peak exposures, most often defined as time spent at or above 20 ppb. However, it is still unclear what the relative importance of short-term high exposures and low, long-term exposures are in the development of diisocyanate-induced occupational asthma. Some studies found a stronger association with continuous-type exposure leading to asthma compared to short-term high exposures (Diem et al., 1982; Meredith et al., 2000).

The persistence of pulmonary symptoms for months to years following cessation of diisocyanate exposure is not uncommon (Paggiaro et al., 1990; Paggiaro et al., 1993; Piirila et al., 2008). Follow-up studies of patients with diisocyanate induced asthma resulting from TDI exposure typically find mild to moderate inflammatory responses, as indicated by elevated numbers of lymphocytes, eosinophils, and neutrophils in the bronchial submucosa and bronchial lavage fluid, along with epithelial damage and thickening of the basement membrane (Paggiaro et al., 1990). In a long-term follow-up (11 years) study, asthma-like symptoms, bronchial hyperresponsiveness and airway obstruction improved, but did not normalize with cessation or reduction in TDI exposure (Talini et al., 2013). Improvement mainly occurred in subjects with an early diagnosis of occupational asthma and in patients with a lower baseline FEV₁ no longer exposed to TDI.

6.1.3. Latency Period for Onset of Isocyanate-Induced Symptoms

In a study of 60 workers with isocyanate-induced asthma (predominantly to TDI), the average duration of exposure to isocyanates ranged between 8 and 15 years (Mapp et al., 1988). The average duration of symptoms for these subjects before diagnosis was between two and five years showing that diagnosis was often delayed, but also that there can be a prolonged latent period between exposure and onset of respiratory symptoms. In a more detailed study of the time of exposure before onset of occupational asthma, approximately 20% of 107 subjects with isocyanate-induced asthma (principally HDI followed by MDI and TDI) had symptoms within the first year of exposure (Malo et al., 1992). Nearly 60% of subjects exposed became symptomatic after 5 years of exposure, with a mean latency period of 7.34 years between the start of exposure and the onset of symptoms.

In a case-referent study by Meredith et al. (2000), symptoms began in 11 of 27 workers (41%) in the first year of employment at a TDI plant, with nine occurring within 3 months. The median duration employed at the time symptoms of asthma developed was 30 months. The difference between cases and referents in mean 8-hr TWA exposure was most pronounced in these 11 matched sets (1.8 ppb for the early-onset asthmatics and 1.3 ppb for asymptomatic referents performing similar jobs). No difference in peak exposures between cases and referents was found. Also, there seemed to be no association between current exposure to TDI and the development of asthma more than one year from first employment. This finding suggested to the authors that the etiology of asthma due to diisocyanates which occurs soon after exposure may differ from asthma which develops after longer periods of employment.

6.1.4. Principal Occupational Studies

Longitudinal studies are the primary means for assessing asthma onset prevalence and changes in pulmonary function with time in diisocyanate workers. The following longitudinal study summaries represent the most comprehensive studies that included both TDI exposure data and the subsequent pulmonary effects. A few selected cross-sectional studies relevant for REL determination are also summarized.

Diem et al., 1982; Weill et al., 1981

The chronic REL is based on a prospective occupational study by Diem et al. (1982) of 277 male workers in a new TDI production plant. This study has several strengths over other workplace investigations of TDI exposure, including minimal co-exposure to other irritating chemicals, extensive use of personal exposure monitoring devices, accounting of TDI-sensitized workers in the cohort, and in particular, detailed longitudinal analysis of workers from the start of exposure in a new TDI production facility.

Changes in pulmonary function, measured as changes in forced expiratory volume in 1 sec (FEV_1), were assessed with nine examinations conducted over a five year period. Baseline pulmonary function was established six months prior to the start of TDI production in 168 workers with no previously reported TDI exposure. Personal 8-hr exposures were measured with continuous tape monitors (MCM Type 4000), but not until two years into the study. A total of 2,093 personal samples from 143 workers were collected. The 8-hr TWA ranged from a minimum of 0.1 ppb to a maximum of 25 ppb, with a geometric mean of 2.00 ppb and a geometric standard deviation of 2.94 ppb.

Workers were divided into two groups. The low exposure group comprised those exposed at or below 68.2 ppb-months (which is the cumulative exposure of a worker exposed to a geometric mean TDI level of 1.1 ppb for the entire 62 months of the study), while the high exposure group comprised those above this level. In the high exposure group, the 8-hr TWA concentration of TDI was above 5 ppb for 15% of the time. A further sub-grouping was based on smoking history (never, previous, current). The arithmetic mean exposure level for the non-smokers was 1.9 ppb TDI in the high-exposure group and 0.9 ppb TDI in the low-exposure group (calculated by Hughes (1993) as cited by U.S. EPA (1995)). The higher exposure group was further limited to those individuals who showed normal FEV_1 levels (i.e. FEV_1 to height ratio: FEV_1/ht^3). This was done since it has been observed that FEV_1 level is inversely related to previous annual decline in FEV_1 . Use of non-normal FEV_1 levels could result in spurious associations between annual FEV_1 decline and TDI. Data were analyzed by the maximum likelihood weighted regression approach to account for inter-individual variability in the precision of the measurements (Diem and Liukkonen, 1988).

Prevalence of bronchitis and dyspnea increased from pre-exposure baseline in the high exposure category, as measured by cumulative exposure, to a greater extent than in the low category. However, these differences in symptom increases between low and high exposure categories were not statistically significant.

Surveillance of the workers for onset of TDI sensitization was presented in Weill et al. (1981). Of 277 workers in the study population, 12 men (4.3%) became clinically sensitized to TDI during the study. Nine of these 12 men became sensitized after less than 12 months of TDI exposure; eight of those nine men were sensitized after less than four months of exposure. The incidence of sensitization over the five years of the study was 0.9% per year. Workers were identified as clinically "sensitive" if they developed recurrent respiratory signs and symptoms upon repeated exposure to low concentrations of TDI.

In data provided by Weill et al. (1981), job positions held by the workers were stratified into three categories of TWA TDI exposure intensities of 6.8, 3.2 and 1.6 ppb. By this criterion 9 of 12 workers who became sensitized were in the high or moderate exposure groups. Two other workers that became sensitized worked in low TDI exposure jobs. The last sensitized worker was said to be

exposed to high TDI levels in laboratory work that was not measured during the study. Six of the 12 workers had known major exposure in TDI spills, but the report did not specify which workers were exposed. Workers in high and moderate exposure jobs were exposed to >5 ppb TDI for at least 24% of the time. Workers in the low exposure jobs were exposed to >5 ppb TDI for only 3% of the time. It was not stated specifically which exposure group the sensitized workers belonged to when stratified by two cumulative exposure groups (i.e., ≤68.2 ppb-months group or >68.2 ppb-months group). However, the authors reported that the sensitized workers likely did not affect the overall pulmonary function results.

Linear regression analysis did not find a relationship between a decline in FEV₁ and TDI exposure when TDI exposure was treated as a continuous variable. Annual change in FEV₁ was found to be significantly related to pack-yrs of smoking (p<0.01). Table 3 presents the annual change in FEV₁ dichotomized by three smoking categories and two cumulative exposure categories after adjusting for mean age (35.6 yrs) and FEV₁ level. The mean age used for FEV₁ adjustment was 35.6 yr and assumed a 5.8-ml increase in FEV₁ annual decline per decade of age. Among workers who never smoked, FEV₁ was significantly reduced by 38 ml/year in the high-exposure group compared to the low-exposure group (p = 0.001). However, among current and previous smokers, the decline in FEV₁ was not statistically significant. Comparing within the low exposure group, current smokers showed a mean FEV₁ decline of 27 ml/year greater than never smokers (p = 0.004).

Table 3. Annual Average FEV₁ Change by Smoking and Cumulative Exposure^a

Cigarette Smoking	Cumulative TDI Exposure		Annual FEV ₁ decline	p (one-tailed)
	≤68.2 ppb-months	>68.2 ppb-months		
Never	1 ml/yr (n=35)	-37 ml/yr (n=21)	-38 ml/yr	0.001
Previously	-12 ml/yr (n=31)	-15 ml/yr (n=16)	-3 ml/yr	ND ^b
Currently	-26 ml/yr (n=64)	-37 ml/yr (n=35)	-11 ml/yr	0.10

^aBased on 202 workers with FEV₁/ht³ ≥ 550 in Table 7 of Diem et al. (1982)

^bStatistical result was not presented but was not statistically significant (p>0.05)

Similarly, in the low-exposure group, the mean annual decline in forced expiratory flow (25-75%) [FEF_(25-75%)] was 81 ml/sec-yr greater among current smokers than among never-smokers (p = 0.003). However, in the high exposure group, there was no effect of smoking history. For never-smokers, the mean annual decline in FEF_(25-75%) was 113 ml/sec-yr greater in the high exposure group than in the low-exposure group. Thus the combined effects of smoking and TDI exposure were more pronounced in the low TDI exposure group.

The association between FEV₁ annual change and time above 20 ppb dichotomized at 0.19 months was similar to that obtained using the cumulative exposure dichotomized at 68.2 ppb-months. Among never-smokers, FEV₁ was statistically significantly reduced ($p=0.033$) by 24 ml/year in the high-exposure group (>0.19 mo above 20 ppb) compared to the low-exposure group (≤ 0.19 mo above 20 ppb).

This study suggests that an annual FEV₁ and an FEF₂₅₋₇₅ decline in excess of that due to aging occurred in the high exposure group. A limitation of this study is that no unexposed reference group was included, although differences in FEV₁ were observed between low and high cumulative exposure groups.

Peters and coworkers

In one of the first studies to examine the longitudinal effects of TDI exposure on pulmonary function, Peters et al. (1968) published a series of reports following a group of polyurethane workers over three years. In the first study, the pulmonary function of 38 workers was examined at the beginning and end of the work day (Monday). Significant decrements in FVC (-190 ml, $p<0.001$) and FEV₁ (-220 ml, $p<0.001$) occurred over the work day, with both nonsmokers and smokers showing similar responses. Workers with respiratory symptoms of cough and phlegm showed greater decreases in FEV₁ than workers without symptoms.

Area exposures were determined at the time of the study by a colorimetric method called the Marcali method. Individual exposure to TDI was not assessed. The limit of detection was said to be 0.1 ppb when air was sampled for 1 hour. Exposures ranged from 0.1 to 3.0 ppb, but had been 20-30 ppb in the polyurethane pouring area the previous year before ventilation was improved. Worker exposure duration ranged from 2 weeks to more than 10 years, with a mean of about 2 years.

In a six month follow-up, 28 of the workers were again examined with the same pulmonary function tests (Peters et al., 1969). The average FEV₁ change for the group compared to six months earlier was -140 ml (annual average of -280 ml/yr). The limit of detection using the Marcali method was said to be 0.5 ppb with long sampling times. At the time of the follow-up, the TDI concentration was 9-12 ppb ($n=2$) in the pouring area and 4-5 ppb ($n=2$) near the stripping molds.

The average FEV₁ change for never-smokers (-160 ml/yr, $n=11$) was less than ever-smokers (-360 ml/yr, $n=17$), but not statistically significantly different. The authors indicated larger sample sizes are needed to properly assess smoking differences. No significant correlation was found between current smoking habits and any ventilatory function. However, both lifetime packs and duration of smoking correlated significantly with one-day and six-month changes in FEV₁.

There was also a significant correlation coefficient ($r=0.72$) between one-day changes in FEV₁ (measured six-months earlier) and six month changes in FEV₁.

In addition, workers with respiratory symptoms (cough and/or phlegm) demonstrated greater falls in FEV₁ than did asymptomatic workers. Those workers with sputum in the morning and afternoon (n=8) had an annual average FEV₁ change of -760 ml/yr. The mean annual average FEV₁ change for the other 17 workers was -100 ml/yr.

One- and two-year follow up of the workers found a change in FEV₁ of -120 ml at one year in the remaining 25 workers, and a change of -220 ml (annual average of -110 ml/yr) at two years in 20 remaining workers (Peters, 1970). Further information on TDI exposure and worker condition was not provided with the exception that the correlation for one-day changes in FEV₁ (before and after Monday work) with one year changes was still strong (r=0.71). The only data presented at the end of year three of the study showed that the decrement in FEV₁ was still persistent in the workers (number unknown) at 120 ml/yr (Peters, 1974).

A more detailed report of the 18-month follow-up was conducted by Peters et al. (1970). FEV₁ was measured in the 19 remaining workers common to the first survey. The cumulative change in FEV₁ was -220 ml, or -147 ml/yr. This change was statistically significant (p<0.02) and exceeded the expected change associated with aging and smoking. It was unclear from the study how many of the remaining workers were asymptomatic for respiratory effects of TDI. Sampling using the Marcali method found TDI concentrations of 3.0 to 14.5 ppb in the pouring area (n=9 samples), and concentrations at or below the limit of detection (0.5 ppb) to 2.0 ppb in other areas of the facility (n=14 samples).

Table 4 presents the overall summary of changes in FEV₁ found in the workers over the three years of the study.

Table 4. Mean change in FEV₁ in polyurethane workers over three years of study by Peters and coworkers

Follow-up period	Annual average change in FEV ₁ (ml/yr)	Number of workers	p-value
6 mo	-280	28	<0.02
1 yr	-120	25	<0.02
1.5 yr	-147	19	<0.02
2 yr	-110	20	<0.01
3 yr	-120	*	*

* Data not presented

This study is limited by use of area exposure sampling with a method (i.e., Marcali) that may seriously underestimate the true TDI exposure at polyurethane plants (Rando et al., 1984; Omae et al., 1992b). This colorimetric technique measures only total TDI concentration, but the signal strength is different for the two TDI isomers. The 2,6-TDI isomer gives about a 55% lower response than

2,4-TDI isomer. In occupational settings, use of high performance liquid chromatography determined that 2,4-TDI is more efficiently reacted in the polymerization process. Thus, a starting solution of 80% 2,4-TDI and 20% 2,6-TDI has been shown to produce a contaminated air concentration dominated by the 2,6-TDI isomer during end stages of polyurethane production. If the Marcali method was based on the signal given by the starting solution dominated by 2,4-TDI, as was probably the case, the air concentration of TDI will likely be underestimated.

Other limitations include lack of a control worker cohort, although the authors stated no FEV₁ changes were found when the authors tested themselves (Peters et al., 1969). The statistical analysis by the authors included workers experiencing respiratory symptoms. However, Peters (1974) noted that although many of the workers experienced cough and phlegm, none experienced symptoms of chest tightness or shortness of breath from the TDI exposures. This finding would suggest that many of the workers had chronic bronchitis. Finally, no follow-up of the workers that left the study early was conducted.

Wegman and coworkers

In 1972 Wegman et al. (1974) examined 112 polyurethane workers exposed to TDI for acute pulmonary function changes during the work shift on the first day of the work week. A follow-up of 57 remaining original workers was conducted two years later to investigate longitudinal pulmonary function changes (Wegman et al., 1977). Comparison of the retested and lost workers did not find any selection bias. Sampling included both area and personal sampling using the Marcali method, the sensitivity of which allowed the detection of TDI at 0.5 ppb. A total of 118 personal and 14 area samples were taken to characterize 20 work stations over the course of the two-year study. Ventilatory capacity was assessed on Monday morning following a three-day weekend.

The average exposure values by job ranged from 0.5 to 9 ppb TDI. To examine the results for a dose-effect relationship, three exposure categories were created, ≤ 1.5 ppb, 2-3 ppb, and ≥ 3.5 ppb TDI. Reports of symptoms collected on a standard questionnaire found the prevalence of cough and phlegm increased proportionally with increase in exposure. About 15% had responses consistent with chronic bronchitis (cough or phlegm for most days for three months of the year) but not associated with exposure. Thirty percent reported wheezing occasionally or most of the time, and 10% reported dyspnea, but neither was associated with exposure. OEHHA notes that these symptom findings suggest sensitization to TDI in some workers, but it was not investigated by the authors.

Table 5 presents the annual average change in FEV₁ over the two-year period of the study. Analysis of Variance (ANOVA) showed a significant difference in loss of FEV₁ according to exposure groupings ($F = 5.2539$, $p < 0.01$). The study authors report that possible confounding variables including age, months employed, smoking habits and lung size did not explain the differences.

Table 5. Two-year change in FEV₁ 1972-1974 and annual average change in FEV₁

Variable	Exposure Concentration (ppb)		
	≤ 1.5 (n=20)	2-3 (n=17)	≥ 3.5 (n=20)
Months in plant	51.5	55.8	55.1
# Nonsmokers	4	2	4
2-yr Δ FEV ₁ in ml, mean (±SD) ^a	-12 (204)	-85 (177)	-205 (185)
FEV ₁ in ml/yr	-6	-43	-103

^a SD = standard deviation

A follow-up examination was carried out on a Monday before work of the remaining workers (n=48) two years later in 1976 (Wegman et al., 1982). Sixty-nine personal and area samples were collected on the day of pulmonary function testing and employed the Marcali method as before to estimate TDI concentration. Personnel records were used to estimate exposure to each worker during both the 1972-1974 and 1974-1976 time intervals. Accurate information on exposure history and acceptable spirograms were obtained for 37 of the 48 workers.

Overall median TDI concentration for 1974-1976 was 3 ppb; the job identified as mixing and pouring has the highest median exposure of 7 ppb (range: 5 to 40 ppb). The population was divided into exposure categories of low (<2.0 ppb), medium (2.0-3.4 ppb), and high (>3.5 ppb) exposure.

Upper and lower respiratory symptoms were found to be unrelated to exposure category. The four-year change in FEV₁ shown in Table 6 was statistically significantly related to exposure category by the ANOVA (p=0.007, F statistic not given), with the t-test showing a difference between the low and high exposure groups (p=0.002).

Table 6. Four-year change in FEV₁ 1972-1976 and annual average change in FEV₁.

Variable	Exposure Concentration (ppb)		
	≤ 2.0 (n=13)	2.0-3.4 (n=13)	≥ 3.5 (n=11)
Months in plant	82.5	81.1	67.0
# Nonsmokers	4	2	3
4-yr Δ FEV ₁ in ml, mean (±SD) ^a	+2 (168)	-133 (184)	-242 (174) ^b
FEV ₁ (ml/yr)	~0	-33	-60

^a SD = standard deviation

^b ANOVA f, p=0.007; t-test low vs. high, p=0.002

Analysis of possible confounding variables including age, months employed, smoking habits and lung size did not explain the differences. Comparison of the

survivor group with the initial cohort indicated that the restudied group was representative of the original group from 1972. Thus no selection bias was introduced due to loss of subjects from the study.

These studies are limited by use of the Marcali method that may have considerably underestimated the true TDI exposure. OEHHA notes that the authors did not discuss the potential for TDI-sensitive workers being included in the analysis of longitudinal change in FEV₁. Also, sample size of the groups is small. The authors state that smoking had no effect on FEV₁, although this may have been a result of the small sample sizes.

Musk and coworkers

Analysis of FEV₁ and respiratory symptoms was conducted in 259 workers at two polyurethane plants in 1971, with 107 available for follow-up examination five years later (Musk et al., 1982; Musk et al., 1985). Over the five years of the study, 2,573 samples were collected by hand-held devices in breathing zone areas of subjects employed in the polyurethane pouring area. Samples were also collected at other sites during the survey where highest exposures were encountered. The sampling time was 20 to 60 min and analysis was done by the Marcali method. Mean geometric TDI exposures over the last 4 years of the study were 1.5 ppb at Plant 1 and 1.0 ppb at Plant 2. The 90th percentile concentration was 5.0 ppb at Plant 1 and 3.6 ppb at Plant 2. Very low concentrations of MDI were also present (0.6 to 0.3 ppb).

No workers described acute exposure-related symptoms with exposure to TDI. Bronchitis was found to be more prevalent in smokers. The mean annual decline in FEV₁ for all subjects was 20 ml/yr, which was concluded by the authors to approximate normal aging declines. For workers with no exposure to isocyanates (n=42), the annual average decline in FEV₁ was 22 ml/yr. The average annual decline in FEV₁ for those exposed only to TDI (n=17) was 26 ml/yr and not statistically significantly different from non-exposed workers. In addition, no excess decline in FEV₁ was reported for those workers exposed to MDI (n=25) or to both TDI and MDI (n=6). Stepwise regression analysis showed the 5 yr decrement in FEV₁ was significantly related only to current smoking. Workers that had been lost to follow-up had similar lung function to those who remained in the study.

A ten-year follow-up was carried out in 42 remaining workers by Gee and Morgan (1985) in 1981. A group of 12 additional workers at the plants with no isocyanate exposure was used as a control group. The authors indicated the rate of decline of ventilatory capacity could not be accurately calculated since many of the 1971 measurements were not valid. This assertion had been refuted by Musk et al. (1985). Nonetheless, Gee and Morgan (1985) did not detect an excess annual FEV₁ decline in the exposed workers. Follow-up of exposed workers that had left employment was not conducted, although the authors noted no worker compensation claims had been filed.

Omae, 1984

Pulmonary effects were investigated in 106 workers at TDI production plants and 39 referents in 1980, and in 64 workers and 21 referents on the 2-year follow-up in 1982 (Omae, 1984). The workers wore personal MCM 4000 paper-tape monitors for TDI during working hours. The numbers of samples collected from the followed workers were 161 in 1980 and 106 in 1982. The mean duration of TDI exposure was 9.0 years in 1980 and 11.2 years in 1982.

Arithmetic means of 8-hour TWA exposure concentrations were 0.7 ppb in 1980 and 1.0 ppb in 1982. Because the TDI process was automated, the workers spent much of their working time in clean areas. The author indicated exposures occurred only during excursion into TDI areas. As a result, only two of the TWA exposure concentrations exceeded 20 ppb. Short-term concentrations (presumably 15 minutes) exceeding 20 ppb occurred in 15 of the 161 samples in 1980 and 2 of 106 samples in 1982.

No statistically significant differences were observed in the pulmonary function between the TDI workers and the referents, or in two-year reductions in FEV₁ or FVC between TDI workers and the referents. The change in FEV₁ was -50 ml/yr among exposed and -65 ml/yr among the referents. The change in FVC was -25 ml/yr among exposed and -40 ml/yr among the referents. Eight workers had exhibited episodes of acute asthmatic reactions soon after having begun their TDI jobs (mean exposure duration 11.7 yrs) but had continued working at the plants. The authors imply these workers developed asthma prior to the start of the study in 1980 when TDI exposure was higher. Specific TDI sensitivity was not assessed in these workers. Although some of these individuals did show decreased pulmonary function (in particular, peak expiratory flow), the two-year decrement in pulmonary function in the asthmatic workers was not different from that in the other TDI workers.

The author observed that the relatively low follow-up rate could introduce biases. Reasons for losses of about 80% of TDI workers were not related to TDI exposure. However, follow-up of the remaining 20% of workers lost was not performed and appeared to fall into one of three categories: left due to plant closing, plant transfer, and absent from work on day of test. Comparison of the data in 1980 between workers successfully followed and the 42 workers lost indicated negligible differences in pulmonary parameters and that selection biases were not considered a concern.

Higher prevalence of sensory irritation was observed in the follow-up survey, but the symptoms were more often attributed to other chemical exposures. Co-exposure to other irritants included phosgene, chlorine, nitric acid and sulfuric acid, all of which are raw materials for TDI production.

Omae et al., 1992

Fifty-seven polyurethane foam manufacturing workers and 24 reference workers were followed for four years to examine the long-term effect of TDI exposure on pulmonary function (Omae et al., 1992a; Omae et al., 1992b). The workers wore personal paper-tape monitors for TDI (MCM 4000, MDA Sci.) on their chest during working hours. The numbers of samples collected from the followed workers were 59 in 1981, 48 in 1983, and 52 in 1985. The forced maximal expiratory flow-volume was examined in the same manner as in the first cross-sectional study in 1981 and the follow-up surveys. Adjustment for age and height of the forced expiratory flow-volume parameters was conducted using the prediction equations originally calculated by the authors with a group of non-exposed males.

None of these workers were considered hypersensitive to TDI. The authors noted that the polyurethane workers had been engaged in their jobs for a mean of 13.3 years and sensitized workers may have left prior to the survey. Thus, the workers examined may represent a survivor population. Greater prevalence of eye irritation during or after work, nasal stuffiness or discharge in winter, and phlegm in the morning in winter were statistically significantly greater ($p < 0.05$) in non- and ex-smoking polyurethane workers than in the non- and ex-smoking reference workers.

Exposed workers were divided into two groups, workers in mold-type manufacturing processes ($n=28$) with low-level TDI exposure (TWA 0.1 ppb), and workers in mostly slab-type factories ($n=29$) where short-term exposure to TDI often exceeded 20 ppb. The slab-type polyurethane workers were further divided into 2 subgroups, one subgroup consisted of workers ($n=15$) exposed to mean and maximal TWA concentrations of 8.2 and 30 ppb, respectively, and the other subgroup ($n=14$) was exposed to lower mean and maximal TWA concentrations of 1.7 and 4 ppb, respectively. The ranges of peak exposure levels for the high and low slab-type PF workers were 30-80 ppb and 3-14 ppb, respectively.

No differences were observed between the four exposure groups for average annual loss of FVC, MEF_{50} (forced expiratory flow at 50% FVC), and FEV_1 . However, greater than expected average annual loss in other flow-volume indices was observed (Table 7). For the high exposed slab-type PF workers, greater than expected average annual losses ($p < 0.05$) occurred for MMF (maximal mid-expiratory flow), $FEV_1\%$ ($FEV_1/FVC \times 100$), and MEF_{25} (forced expiratory flow at 25% FVC). The average annual loss in these three indices was also greater in the high exposed slab-type workers compared to workers exposed in mold-type factories ($p < 0.05$). Finally, the high exposure slab-type workers also showed a greater average annual loss in PEF (peak expiratory flow) compared to the reference workers. For the lower exposed slab-type PF workers, greater than expected average annual losses ($p < 0.05$) occurred for MMF and MEF_{25} .

Table 7. Statistically significant average annual loss indices among high-exposed and low-exposed slab-type workers, mold-type workers and reference workers.

Variable	Worker Exposure Group (mean ± SD)			
	Slab workers High exposure (n=15)	Slab workers Low exposure (n=14)	Mold workers (n=28)	Reference workers (n=24)
TWA Exposure	8.2 ppb	1.7 ppb	0.1 ppb	0 ppb
MMF	-2.39±4.13 ^a	1.91±3.02 ^b	0.11±2.96	-0.30±2.39
FEV ₁ %	-0.89±0.96 ^a	0.19±0.63	-0.10±0.94	-0.29±0.88
MEF ₂₅	-3.28±5.64 ^a	3.38±4.39 ^b	1.01±4.37	-0.50±5.49
PEF	-0.38±1.46 ^c	0.66±1.79	0.61±1.61	0.72±1.66

^a p<0.05 against expected value of average annual loss and mold workers

^b p<0.05 against expected value of average annual loss

^c p<0.05 against reference workers

The average annual loss of pulmonary function over 4 years was larger in smokers than in non-smokers, although the differences were not significant. The lack of an effect due to smoking, the authors noted, was probably because the number of subjects was too small to detect significant differences. The lack of differences in annual average loss between the low exposed slab-type workers compared to reference workers suggested to the authors that TWA concentrations of 1.7 ppb and a maximal TWA level of 4 ppb with short-term peaks up to 14 ppb may not cause long-term pulmonary function loss in those who are not hypersensitive to TDI. However, the authors concluded that pulmonary function loss occurred in workers with short-term TDI exposures above 20 ppb (i.e., 30-80 ppb) and TWA exposure to 8.2 ppb.

Co-exposure to other chemical irritants occurred in the workers during PF manufacturing processes. Some of these chemicals include tertiary amines, organic tin compounds, polyols, silicon oil, dichloromethane, freons and flame-resistant agents.

Jones et al., 1992

Exposure to TDI was studied for effects on respiratory health of workers in two plants manufacturing polyurethane foams (Jones et al., 1992). TDI levels were measured at yearly intervals for 5 yr (1982 to 1986) at Plant 1 and for 4 yr (1982 to 1985) at Plant 2. Workplace concentrations were determined using the MCM TDI-sensitive paper-tape continuous monitoring system. A total of 258 workers wore monitors on 507 shifts producing 4,845 measurements. To improve accuracy in recording peak exposures and time-weighted averages under conditions of fluctuating TDI concentrations, a sample collection pattern of 12 min on, followed by 24 min of no sampling, was repeated during the 8-hr work shifts to produce up to 14 evenly spaced 12 min samples. The lower detection limit was 1 ppb before 1983, and 0.5 ppb from 1983 on. Samples showing no detectable TDI were assigned a value of one-half the lower detection limit (LDL).

With additional limited sampling done in the 1970s, personnel records were used to track each employee's career, assigning exposures as the TDI level in ppb times the number of months worked in specific job groupings in the plants. Cumulative exposure, in units of ppb x month, is the sum of all such doses; average exposure is cumulative exposure divided by length of employment. There were 394 workers present at the start of the study, and, through the fourth examination, a total of 435 had worked in one or the other plant. Six yearly spirometry examinations were performed on the workers to assess respiratory health and estimate rates of annual change in lung function.

Of 4,845 personal TDI monitoring measurements, 50% reached or exceeded the LDL, 9% reached or exceeded 5 ppb, and 1% exceeded 20 ppb. In a group of jobs involving exposure to foam ingredients or freshly produced foam, the respective figures were 68% \geq LDL, 20% \geq 5 ppb, and 4% \geq 20 ppb. Mean TDI concentrations by specific job category ranged from 4.47 ppb for foam production (plant 2) to 1.17 ppb for "other".

At initial interview of 380 workers, a trend for increased prevalence of "chronic bronchitis" (cough or phlegm for more than 3 months yearly in the previous 2 years) with increasing cumulative exposure (hire to start of study) was observed, with prevalences in low, middle and high terciles of 2.6, 6.5, and 14.3%, respectively. Terciles refer to any of the two points that divide an ordered distribution into three parts, each containing a third of the population. The exposure terciles presumably refer to exposures of ≤ 32 , >32 and ≤ 86 , and >86 ppb x month presented later in the paper. Logistic regression analysis showed a significant association of prevalence with exposure ($p < 0.02$) after controlling for smoking, age and sex. Mean initial lung function (percent predicted) and mean decline in FEV₁ were indicated as marginally worse in those with chronic bronchitis (data not shown). At the time of follow-up examinations of the remaining workers ($n=262$), 12 workers had been identified as developing TDI-sensitization, 6 of whom were tested and confirmed by TDI challenge.

When initial pulmonary function values (hire to start) were presented by exposure tercile, the percent of predicted FEF₂₅₋₇₅ in the highest tercile (>86 ppb x month) showed a statistically significant reduction (Table 8). No differences were observed for FEV₁ and FVC as a result of cumulative exposure to TDI.

Table 8. Initial pulmonary values by exposure tercile

Variable	Tercile Exposure, Hire to Start (ppb x month)		
	≤ 32 (n=108-120)	> 32, ≤ 86 (n=109-121)	> 86 (n=112-121)
Years in plant	4.45±0.50 ^a	6.34±0.28	17.56±0.55
FEV ₁ , % pred	107.4±1.1	106.3±1.2	104.2±1.4
FVC, % pred	107.7±1.1	106.1±1.0	105.1±1.2
FEF ₂₅₋₇₅ , % pred	88.0±2.0	91.0±2.4	82.3±2.3 ^b
FEV ₁ /FVC, % pred	97.0±0.6	97.0±0.7	96.3±0.7

^a All values presented as mean±standard error

^b Difference among means: p<0.025

Mean initial FEV₁ and FVC in Table 8 were above 100% of predicted values. The reason cited by Jones et al. was the “healthy worker effect”, which often results in working populations derived from the general population that exceed the health of the general population as a whole.

When cumulative TDI exposure was treated as a continuous variable (in increments of 100 ppb x month) there was a marginally significant effect (p<0.063) on FEF₂₅₋₇₅ over all smoking categories. Each increment of 100 ppb x month was associated with a reduction in FEF₂₅₋₇₅ of 2.3% predicted. When the effect of smoking on initial pulmonary function was examined, a significant reduction was found only in current smokers; for each 100 ppb x month increment, associated reductions of 4.3% of predicted FEV₁ value (p<0.0003) and 4.4% of predicted FVC value (p<0.0001) were observed.

Jones et al. also presented a longitudinal analysis of pulmonary function change for the workers over the five years of the study (Table 9). The observed mean annual declines were steep in relation to expected values, but no statistically significant difference was observed.

Table 9. Observed mean annual change in pulmonary function values in relation to expected values

Cigarette Smoking	Lung Function (in relation to expected values)		
	FEV ₁	FVC	FEF ₂₅₋₇₅
Never	-53 ml/yr	-51 ml/yr	-76 L/sec-yr
Previously	-59 ml/yr	-59 ml/yr	-71 L/sec-yr
Currently	-67 ml/yr	-66 ml/yr	-99 L/sec-yr

When annual change was studied using weighted multiple regression followed by weighted stepwise multiple regression, the authors could find neither smoking nor measures of cumulative or average exposure were significantly related to annual change. The FEV₁ change was -6 ml/yr for current vs. never smoker (p<0.3). Examining only the highest tercile (>86 ppb x month) of exposure, mean FEV₁ annual changes were virtually identical across the smoking categories: -65, -61, and -61 ml/yr in current, ex-, and never-smokers, respectively.

The authors concluded that their study showed evidence of past and ongoing adverse effects on respiratory health, but was only attributable in part to measured and estimated TDI exposures. Although the authors discussed their confidence in the reliability of their data, they could not fully rule out misclassification of exposure or co-exposure to other workplace chemicals as contributors to effects not fully explained by TDI exposures.

Clark and coworkers

This longitudinal study represents the largest investigation of the pulmonary effects of TDI-exposed workers at low concentrations (Clark et al., 1998). A population of 780 polyurethane workers in 12 United Kingdom factories was followed for five years to determine whether longitudinal declines in ventilatory capacity and the occurrence of respiratory symptoms were related to TDI exposure. The workers were divided into three subgroups: a “high” exposed worker group that manufactured the polyurethane products, a low-exposure handling group that handled cold polyurethane after manufacture, and a control group of factory office workers with minimal background exposure. During the study, 88 workers left. The average time in the study for the remaining 692 workers was 4.3 yrs.

Continuous tape monitors (MCM type 4000) were used throughout the study and were capable of measuring TDI concentrations between 1 and 40 ppb. A total of 2,294 measurements were collected. The UK 8-hr (5.8 ppb) and 15-min (20 ppb) maximum exposure limits were exceeded in 4.7% and 19% of the samples taken, respectively. The short-term exceedances were all from the high exposed group. In all, 8.8% of the observed peak measurements were at or above the level of detection of 40 ppb. Although MCM monitors are used for short-term exposure estimates, these monitors have a minimum resolution time of 9-10 min for TDI. This duration may underestimate very short duration peaks. A portable ion-mobility spectrometer with a rapid response time (on the order of a few seconds) was used post-study to monitor the peak concentrations from some of the manufacturing processes. Transient TDI peaks of up to 200 ppb were recorded, which equated to MCM-measured peaks of up to 30 ppb.

The high-exposed group of 521 workers had an in-study mean daily cumulative exposure of 9.6 ppb-hr, and an 8-hr TWA exposure of 1.2 ppb. In a summary of the industrial report by Garabrant and Levine (2000), the in-study mean daily cumulative exposure for the handler group and the office worker group was 5.0 and 2.5 ppb-hr, respectively. Based on an 8-hr workday these were said to be equivalent to average TWA daily exposures of 0.6 ppb for the handlers and 0.3 ppb for the office workers. Clark et al. noted that some HPLC samples taken in the control and handling areas showed TDI levels were below the level of detection (0.1 ppb) for this method. Given some baseline “noise” on the MCMs, which has a higher detection limit (1 ppb), the assigned exposures for such subjects may have been overestimated.

Health questionnaire responses found a statistically significant increase in wheezing in the high-exposure group ($p < 0.01$) and the low-exposure handling group ($0.01 < p < 0.05$). Those workers who left the study from the high-exposed and low-exposed groups reported an increased incidence of breathlessness, wheeze and chest illness as compared with those not leaving. This includes 7 of 24 cases of respiratory sensitization identified during the study.

The 24 cases of TDI-sensitization identified during the course of the study were presumably from the total of 780 workers examined. Thus, 3.1% of workers became sensitized resulting in an annual incidence of 0.6% over 5 years. The published study did not indicate which exposure group these workers were in, but the industrial report by Bugler et al. (1991) and summarized by Ott (2002) indicated that 14 of 18 new hires that became sensitized after the start of surveillance had jobs with routine short-term TDI exposures above 20 ppb. Three others that became sensitized had jobs with routine short-term exposures of 10-19 ppb. The last of these 18 workers had a low exposure job, but had previous work in exposed areas with routine exposure > 20 ppb. The FEV₁ decline in sensitized workers shown in Table 10 was greater than those not sensitized, but was not found to be statistically significant ($p = 0.29$).

For the lung function measurements, linear regression analysis found no TDI-exposure related effect on FEV₁, FVC, peak flow and FEV₁/FVC% for any of the exposure groups. The mean annual decline in FEV₁ was 38 ml/yr for the exposed group of 521 workers. Mean annual declines in FEV₁ for the handler and control groups were not presented by the authors. A subgroup of male fitters and electricians in the exposed group with irregular TDI exposure, shown as maintenance workers in Table 10, did not have a different annual change in FEV₁ compared to the remaining male exposed group ($p = 0.25$). Female workers in the exposed group ($n = 49$) were not included in this analysis.

Linear regression analysis found a smoking-related effect on FEV₁, which was not considered statistically significant by the researchers ($0.05 < p < 0.1$). The smoking group represented a subset that smoked > 15 cigarettes/day; their FEV₁ declined at a rate of 7 ml/yr more than that of nonsmokers (Table 10). The authors noted there was a suggestion of an increased decline in FEV₁ with increasing TDI exposure in non- and ex-smokers as compared with smokers, but was not found to be statistically significant.

For the study population the average decline in FEV₁ determined for the 88 workers who left during the study (leavers) was not significantly different from that recorded for the other workers (non-leavers) (Table 10).

Table 10. Summary of FEV₁ Annual Change Comparisons from Clark et al. (1998)

Variable	FEV ₁ Annual Change
High- exposure group	-38 ml/yr
Low-exposure (Handler) group	NS ^a
“Control” group	NS
Nonsmoker ^b (n=157)	-29 ml/yr
Smoker (n=253)	-36 ml/yr
TDI-sensitized (n=24)	-49 ml/yr
Not TDI-sensitized (n=756)	-38 ml/yr
Non-leavers (n=692)	-38 ml/yr
Leavers (n=88)	-40 ml/yr
Exposed group naïve workers (n=119)	-34.5 ml/yr
Exposed group non-naïve workers (n=402)	-39.5 ml/yr
Exposed maintenance male worker subgroup (n=95)	-34 ml/yr
Remaining exposed male workers (n=377)	-41 ml/yr

^a NS: Not stated in the report

^b The n represents the population of nonsmokers. It was unclear from the study if ex-smokers were included in this group or analyzed separately.

Clark et al. also examined a subgroup of workers who entered the study after the first longitudinal measurements were made and had no known prior TDI exposure (naïve workers). The naïve worker population (n=157) showed a decline in FEV₁ of 36 ml/yr and non-naïves (n=623) showed a decline in FEV₁ of 39 ml/yr. The difference was not statistically significant. Additionally, exposed naïves in Table 9 did not show a significant excess decline in FEV₁ as compared to exposed non-naïves (p=0.56).

Longitudinal regressions on the data from naïve workers show an in-study mean daily excess decline in FEV₁ (p=0.016) and FVC (p=0.026) in the early years of employment. The effect sometimes occurred immediately following the first exposure and is suggestive of an irritant response affecting those already suffering from non-specific bronchial hyperreactivity, rather than being suggestive of an allergic mechanism. It was not clear in the study if all naïves were included in the analysis, or if only those exposed to TDI during manufacturing processes were included. Further analysis of naïve subjects for more than 4 years did not demonstrate an excess decline in pulmonary function as compared to non-naïves. Thus, further deterioration did not occur in naïve workers, but neither was there recovery to pre-employment values that would indicate a “spirometry-learning effect”.

A follow-up was conducted over the period of 1997-1998 on 251 workers – the majority from the original population of 780 workers (Clark et al., 2003). The authors called this a survivor population due to large attrition rates from factory closures and industry restructuring that occurred between studies. The available

survey records from about 60% of all leavers indicated that respiratory illness was the reason for leaving in 2.3% of cases. Any workers diagnosed with TDI sensitization had been removed from exposure and were no longer available in the current study. As in the previous study, workers were divided into a high-exposed (n=175), low-exposed (handling) (n=26) and low-exposure “control” (n=50) groups. Personal measurements were recorded only for the exposed group. Of the 1,004 measurements recorded as a mean cumulative exposure in ppb-hr, only 1.3% were in excess of 46.4 ppb-hr (equivalent to 5.8 ppb TDI over an 8 hr workshift). This is a reduction from the 6.9% over the period 1981-1986 observed in the previous study. Mean exposure was 8.4 ppb-hr (equivalent to 1.05 ppb TDI).

Allowing for the effects of age, gender and smoking habits, regression analysis for the high-exposed group showed no relationship between the annual losses of FEV₁ and FVC, and the mean daily exposure to TDI (Clark et al., 2003). Annual declines for the high-exposed group with a mean age of 48 yrs at the end of the study were 35 ml per year for FEV₁ and 30 ml per year for FVC. These results are similar to what was reported previously in Clark et al. (1998). The small handling group showed excess declines in both FEV₁ and FVC (data not shown in study) compared to the control subjects. The low n and the higher proportion of smokers in this group were attributed by the authors as causes for this effect. Their conclusion was that the study did not provide evidence of a TDI-related decline in FEV₁ and FVC.

Ott et al., 2000

Ott et al., (2000) conducted an analysis of employees ever assigned (n=313) to a TDI production unit at a manufacturing complex for ≥ 3 months during the period 1967 to 1992. The workers were compared to a group of frequency matched referents (n=158) without known exposure to TDI. The duration of TDI unit assignments averaged 5.7 and 4.7 years among men and women employees, respectively, with a range of 3 months to 30 years. Reports during visits to the occupational clinic of incidents related to TDI and annual periodic examination results (questionnaire, physical findings, and spirometry) were abstracted and assessed relative to industrial hygiene estimates of exposure to TDI.

Exposure estimates were initially conducted by area sampling in 1967 with a Uni-jet TDI-in-air sampler. Personal monitoring by the paper tape method (MCM4000 personal monitor) began in 1976. Starting in 1989, personal sampling for TDI was performed by OSHA method 42, which uses glass fiber filters coated with 1-(2-pyridyl)piperazine followed by solvent desorption. Analysis was by HPLC. A job-exposure matrix approach was used to estimate individual exposure to TDI. Job specific work histories were coded for each person and linked to industrial hygiene measurements. Peak exposure and TWA concentrations were aggregated on a job and time specific basis for three job groups with potentially low, medium, and high exposure to TDI. Cumulative dose estimates (ppb-months) were computed by multiplying the mean TWA concentration during a

particular job assignment by the time spent on that job (expressed in months) and summing across all job assignments.

Regression analysis showed that TWA estimates declined significantly over time for all job groups. Area sampling between 1967 and 1973 were mostly <10 ppb, with concentrations of 60 to 80 ppb in high exposure areas. Personal 8-hour samples collected by the paper tape method from 1976 to 1988 averaged 5.9 ppb TDI (n=156). Eight hour samples collected by the filter method between 1989 and 1997 averaged 2.8 ppb TDI (n=84). The TWA estimates for high exposure jobs were 9.9 ppb TDI before 1985, and <5 ppb after 1985. The average TWA concentration after 1985 across all jobs and times was 4.2 ppb TDI. Table 11 presents the distribution of the average concentration of TDI for the 313 workers over their entire work career.

Table 11. Average TDI concentration across all jobs in the TDI unit, and the number (n) and percentage of workers (%) in each exposure group.

Average TDI concentration (ppb)	n	%
<1.0	13	4.2
1.0-2.9	113	36.1
3.0-4.9	59	18.8
5.0-6.9	94	30.0
≥7.0	34	10.9

Incidents of exposure to TDI were reported by 77 different employees and included 58 incidents related to asthmatic or allergic skin reactions in 29 different workers (19 with asthmatic reactions only, nine with skin allergies only, and one person with both asthma and skin allergies). The yearly incidence of asthma induced by TDI was 1.1%, but was higher before 1980 (1.8%) than after 1979 (0.7%). The incidence for workers assigned to the TDI unit for at least 20 years was estimated to be 11.5%.

Spirometric data obtained before 1980 were judged to be unacceptable due to data quality. The average number of lung function tests per employee was 7.5 and the average interval between the earliest and most recent test was 9.3 years. Cross sectional analysis of FVC, FEV₁ and FEV₁/FVC% based on the most recent spirometry test found age, height, race, and sex were significant predictors of FVC and FEV₁. Pack years smoked was a significant risk factor for FVC, FEV₁ and FEV₁/FVC%.

The TDI concentration and cumulative dose were not significant predictive factors in the full model or in models without occupational asthma as a covariate. An additional set of analyses carried out for 119 never-smokers also found no significant relation between outcome of spirometry and either TDI concentration or dose. In addition, cross-sectional analysis was carried out with the earliest available lung function test to determine if previous exposure to TDI was

associated with lung function tests. Neither TDI concentration nor cumulative dose was significantly related to these tests. However, occurrence of previous incidents of exposure to phosgene, a chemical used in production of TDI, was associated with declines in both FEV₁ and FVC.

Longitudinal analyses were performed to estimate the annual change in FVC and FEV₁ for various subgroups of the population with ≥ 3 lung function tests covering an interval of ≥ 2 years. Declines in FVC and FEV₁ were greater among cigarette smokers than never-smokers, but cumulative dose of TDI was not significantly related to the annual decline in either FVC or FEV₁ (Table 12). The authors concluded that in agreement with other studies conducted in workplaces with exposures ranging up to 5 ppb TWA and where active medical surveillance and exposure monitoring programs were in place, there was little evidence of a relation between exposure to TDI and either FVC or FEV₁ decrement. This study, however, relied on some retrospective construction of exposures using different measurement techniques; thus, exposure misclassification could be a problem.

Table 12. Estimated annual change in FEV₁ and FVC in selected subgroups

Population Subgroup	Lung Function Value	
	FEV ₁	FVC
Men		
Exposed (n=209)	-37 ml/yr	-37 ml/yr
Referents (n=65)	-35 ml/yr	-34 ml/yr
Women		
Exposed (n=10)	-20 ml/yr	-27 ml/yr ^a
Referents (n=12)	-14 ml/yr	-14 ml/yr
Men, never smokers		
Exposed (n=67)	-31 ml/yr	-33 ml/yr
Referents (n=25)	-36 ml/yr	-34 ml/yr
Men, ≥ 20 cigarette pack-yrs		
Exposed (n=72)	-43 ml/yr	-44 ml/yr
Referents (n=24)	-44 ml/yr	-41 ml/yr

^a FVC statistically different ($p=0.03$) from controls but referent women had more pack-yrs smoking (14.8 vs. 4.6) and follow up interval nearly 5 yrs longer for referent women.

Bodner et al., 2001

In this longitudinal study at a Texas chemical manufacturing facility from 1971 through 1997, 305 TDI manufacturing workers and 581 hydrocarbons workers never employed in isocyanate processes were examined to determine if TDI was associated with changes in respiratory measures (Bodner et al., 2001). Accurate work history records and data from routine medical surveillance examinations were used to trace changes in lung function of the workers. Workers who spent at least 3 consecutive months in TDI-related departments were selected. Personal sampling over the duration of the study included the MCM Model 4000

paper-tape method, followed by use of the colorimetric Marcali method, and beginning in 1989, use of continuous monitors employing the colorimetric paper-tape based method. From 448 8-hour TWA TDI samples and known work histories, average TDI exposures and cumulative exposure estimates in ppb-months were determined for each work segment for each worker. Mean employment in TDI departments was 3.8 ± 4.1 yrs (SD).

Mean TDI exposures were 2.3 ppb (SD \pm 1.0 ppb) for 8-hour TWA, and 96.9 ppb-months (SD \pm 110.6 ppb-months) when expressed as cumulative TDI exposure per month. Maximum individual worker TDI exposure was 5.2 ppb for 8-hour TWA and 639 ppb-months. Since 1980, mean 8-hour TWA TDI exposures were at or below 3 ppb for all job categories. When exposure was expressed as cumulative TDI exposures of 1-12, 13-60, 61-120, and >120 ppb-month, no difference in FEV₁ due to TDI exposure compared to control values was observed, and no trend in FEV₁ decline with increasing cumulative TDI exposure was observed. The average annual FEV₁ decline for all workers was 30 ml/yr. The authors concluded that the decline in FEV₁ was within normal limits of age-related decline. Significant declines in FEV₁ were found among current smokers (1 ml/pack-yrs), those workers with asthma (114 ml/yr), and those with symptoms of shortness of breath (77 ml/yr).

A drawback of this study was that no short-term estimates of high TDI exposures were examined by the authors. Also, the health surveys used in this study could not adequately differentiate between occupational and nonoccupational asthma, although no workers were reportedly transferred due to TDI sensitization over the previous 10 years. The prevalence of asthma, and clinical symptoms including persistent cough and shortness of breath were not different in TDI workers when compared to the control group. Finally, pulmonary examinations of those that had left TDI operations had similar FEV₁ values as those control workers that left the hydrocarbons departments (-32 ml/yr). Thus, no negative impact on respiratory function was apparent after a worker had left the TDI operations.

Table 13 presents a summary of the findings from the longitudinal studies presented here.

Table 13. Summary of Longitudinal Studies of TDI-exposed Workers

Study	Industry type & Exposure	Incidence of Sensitization	Pulmonary Findings
Weill et al., 1981; Diem et al., 1982	TDI manufacturing 8-hr TWA: <1.1 (>5 ppb 2% of time) & >1.1 ppb (>5 ppb 15% of time)	12/277 (4.3%) 0.9%/yr	Mean FEV ₁ decline of 38 ml/yr greater in high vs. low dose never-smokers No FEV ₁ annual loss when cumulative dose treated as a continuous variable
Peters and coworkers	Polyurethane plant Area sampling, 9-12 ppb in pouring area, 4-5 ppb near stripping molds	None found, but workers that left were not examined	Mean FEV ₁ loss 120 ml/yr after 1 and 3 yrs exposure; greater in workers with respiratory symptoms (probably chronic bronchitis)
Wegman and coworkers	Polyurethane plant Area and personal sampling; ≤2.0, 2.0-3.4, & ≥3.5 ppb groups	ND*, but sensitized workers likely included in analysis	Mean FEV ₁ loss after 4 yr exposure: 60 ml/yr in ≥ 3.5 ppb group 33 ml/yr in 2.0-3.4 ppb group No change in ≤ 2.0 ppb group
Musk et al., 1982	Polyurethane plant 20-60 min sampling at peak exposure Mean 1.0-1.5 ppb (90 th %tile - 5 ppb)	No indication of sensitized workers	Mean FEV ₁ loss after 5 yr exposure: 26 ml/yr in TDI workers 22 ml/yr in controls FEV ₁ loss significantly related only to smoking
Omae, 1984	TDI manufacturing Personal monitoring 8-hr TWA 0.7-1.0 ppb	8/106 (7.5%) sensitization probably prior to study	Mean FEV ₁ loss after 2 yr exposure: 50 ml/yr in TDI workers 65 ml/yr in controls
Omae et al., 1992	Polyurethane plant 8-hr TWA personal monitoring: 0.1, 1.7 and 8.2 ppb and control groups	ND, may have only examined "survivor" population	No average annual change in FEV ₁ over 4 yrs for all groups. Lower MMF, MEF ₂₅ , and FEV ₀ in high vs. low exposure (p<0.05); lower PEF in high vs. control (p<0.05)
Jones et al., 1992	Polyurethane plant 8-hr TWA: 1.2 to 4.5 ppb depending on job Overall: 9% of samples >5 ppb In polyurethane production jobs: 20% of samples ≥5 ppb	12/262 (4.6%) 0.9%/yr	Marginal effect on FEF ₂₅₋₇₅ (p<0.063) when cumulative TDI exposure treated as a continuous variable. Ave annual FEV ₁ loss over 5 yrs: 53 ml/yr in never smokers 59 ml/yr in previous smokers 67 ml/yr in current smokers Declines steep in relation to expected values but not related to exposure

Study	Industry type & Exposure	Incidence of Sensitization	Pulmonary Findings
Clark et al., 1998	Polyurethane plants 8-hr TWA: 0.3 ppb control group 0.6 ppb low group 1.2 ppb high group 4.7% of samples exceeded 5.8 ppb	24/780 (3.1%) 0.6%/yr At least 14 sensitized were from the high exposure group	Ave. annual FEV ₁ loss over 5 yrs: 38 ml/yr in high exposed group; not different from control or low exposed groups Mean daily excess decline in FEV ₁ (p=0.016) in early exposure years of naïve workers
Clark et al., 2003	Follow-up of Clark et al., 1998 1.05 ppb for high group: 1.3% of samples exceeded 5.8 ppb No exposure data for other two groups	ND; only examined survivor population	No relationship between the annual losses of FEV ₁ and FVC, and the mean daily exposure to TDI in high exposure group. Excess declines in FEV ₁ and FVC (data not shown in study) compared to the control subjects
Ott et al., 2000	TDI manufacturing Ave 8-hr TWA 1976-88: 5.9 ppb 1989-97: 2.8 ppb	20/313 (6.4%) (1.1%/yr) incidence 1.1%/yr before 1980; incidence 0.7%/yr after 1979	Mean exposure duration 9.3 yrs Ave annual FEV ₁ loss over: 37 ml/yr all workers 35 ml/yr controls 31 ml/yr never smoker workers 36 ml/yr never smoker controls Annual FEV ₁ loss not associated with exposure
Bodner et al., 2001	TDI manufacturing 305 TDI workers: 8-hr TWA 2.3 ppb (96.9 ppb-month) 3.8 yrs mean employment 581 control workers	ND	No difference in FEV ₁ among cumulative exposure groups of 1-12, 13-60, 61-120 and >120 ppb-mo No FEV ₁ change compared to controls No trend in FEV ₁ decline with increasing cumulative TDI exposure

* ND – Not determined

6.1.5. Additional supporting studies

Surprisingly few of the longitudinal studies summarized above gave strong evidence of a quantitative exposure-response relationship for TDI-induced asthma. The following case-referent and cross-sectional studies provide the best available data for exposure levels to TDI that can result in development of occupational asthma. A few studies also provide evidence for decreased lung function in non-sensitized workers with long-term exposure.

Lee and Phoon, 1992

This cross-sectional occupational study presents evidence of pulmonary function decrements with prolonged high occupational exposures to TDI (Lee and Phoon, 1992). Pulmonary effects of TDI exposure were studied in 26 mixers from eight east Asian factories making polyurethane foam, and in 26 unexposed controls matched for age, race and smoking. Mean exposure duration for the TDI workers was 6.6 yrs. Personal breathing zone samples (n=24) were collected only during the foaming process when TDI exposure was the highest, a duration of 30 to 92 minutes. Analysis was by the Marcali method, so only mean exposure time could be determined and the exposure may be underestimated. The foaming process was carried out for 4 to 6 hours every day at 6 factories and for only about 4 hours per week at two factories that had automated the process.

The mean TDI exposure concentration during the mixing process was 160 ppb (range: 10 to 500 ppb). Prevalence of symptoms included increased eye irritation and cough in the mixers compared to unexposed controls. Only one case of clinically overt wheezing was observed in exposed workers, and this subject was negative when tested by bronchial challenge to TDI. The authors characterized the group of mixers as a survivor population in which only those workers that did not develop TDI-related asthma remained in the job.

No statistically significant differences were observed in FEV₁ or FVC between the TDI workers and the control group. FEV₁ of mixers was 3.4 L, and that of the controls was 3.5 L. There was a statistically significant reduction (p=0.01) in the average ratio of FEV₁/FVC and in diurnal variation of peak expiratory flow (PEF) rate (p=0.02). Six mixers exhibited a diurnal variation in PEF of more than 15% on at least one day compared with none among the controls (p=0.01; Fisher's exact test).

Mixers with exposure of 10 years or more (n=7) had a significantly reduced FEV₁ (2.7 L; p<0.001) compared to those with less than 10 years of exposure (FEV₁=3.5 L, n=19) and controls (FEV₁=3.5 L, n=26). FEV₁ was reduced 16.4% in this group compared to predicted values. Workers with >10 years of exposure were older (39.0 yrs) than workers with <10 years of exposure (28.8 yrs) and the controls (32.2 yrs), but FEV₁ had been adjusted for age, height, race, and cigarette-yrs. The mixers with >10 years of exposure also exhibited a reduced FVC (p<0.05 compared to mixers with <10 yrs of exposure only), FEV₁/FVC (p<0.005 compared to control group only), and diurnal variation in PEF (p<0.05 compared to controls only). The authors suggested that the longer TDI exposures were associated with chronic airways obstruction.

Huang et al., 1991

This cross-sectional study from China compared the pulmonary function of 15 painters (7 men and 8 women) exposed to high levels of TDI from polyurethane varnish with 18 referents with no history of TDI exposure (Huang et al., 1991).

The painters had a mean exposure duration of 7.5 yrs to TDI. Referents (9 men and 9 women) were matched with regard to age, height, weight and smoking habits. Area sampling with analysis by a colorimetric method on the day of pulmonary testing revealed TDI concentrations of 70-170 ppb during the 8-hr workshift.

Respiratory symptoms included eye, nose and throat irritation in all exposed painters. Seven painters with chronic bronchitis, and four with longer exposure durations (9.5-17 yrs) reported dyspnea and wheezing during work. Five painters had a positive response with patch testing to 0.1%TDI in petrolatum. All symptoms were statistically significantly different compared to referents ($p < 0.01$).

Pulmonary function testing revealed reduced FEV₁ in the painters compared to referents (2.04 L vs. 2.94 L, $p < 0.05$). The %FEV₁ and maximum mid-expiratory flow were also statistically significantly reduced in the exposed workers. The four painters exhibiting wheeze and dyspnea during work, reported by the authors to be consistent with work-related asthma, had a much greater rate of decline than the other painters (data not shown).

Meredith et al., 2000

The quantitative relationship between exposure to diisocyanates and occupational asthma was investigated at several polyurethane plants (Meredith et al., 2000). Workers with diisocyanate-induced asthma ($n=27$; 24 exposed to TDI and 3 exposed to MDI) were compared with referents ($n=51$) that were defined as workers without asthma, of the same sex as the case, who were working in the same area, both at the time the case started the job in which he developed asthma and when the diagnosis of occupational asthma was made. Exposures by job category were reconstructed based on records of personal paper-tape monitors.

No difference was found between the 27 cases and 51 matched referents in estimated peak exposure (means 21.5 ppb and 22.5 ppb respectively), defined as the highest 15-20 min TWA exposure. Mean 8-hr TWA exposure for cases (1.5 ppb) was slightly higher than for referents (1.2 ppb). The odds of occupational asthma for those for whom estimated exposure to TDI was greater than the median concentration for the control group (1.125 ppb) were 3.2 times the odds for those exposed to lower concentrations (95% confidence interval 0.96 to 10.6; $p=0.06$). The odds of occupational asthma increased by 8% for each 0.1 ppb increase in 8-hr TWA exposure ($p=0.06$). Overall, higher exposures seemed to be associated with increased risk of disease, but this was limited to those cases which occurred in the first year of employment. A history of either hay fever, eczema, or asthma at the time of employment tripled the risk of developing occupational asthma ($p=0.04$), but no single factor was associated with significantly increased risk.

This study suggests that keeping 8-hr TWA exposure below 1 ppb significantly lowers the risk of TDI-induced asthma in a worker population. A limitation of this study was that person-specific exposure measurements were not available, and so exposure was estimated from job title and date. Referents were closely matched to cases and selected from the same work areas in an attempt to ensure a similar level of surveillance and a similar chance that occupational asthma would be diagnosed if it occurred. This was done, the authors noted, to minimize the risk of selection bias, a common problem in case-control studies.

Tarlo et al., 1997

In this study conducted in Ontario, Canada, the ambient levels of isocyanates were compared between 20 plants with and 203 plants without cases of compensated isocyanate occupational asthma over a 4-year period from 1984-1988 (Tarlo et al., 1997). Sampling methods included Marcali and Nitro reagent methods. Exposure was based on the highest level identified at a plant as a result of state-mandated monitoring at plants to ensure worker exposure does not exceed 5 ppb. There were a total of 49 occupational asthma claimants in which exposure was attributed primarily or exclusively to TDI. Some claimants also had potential exposure to MDI and/or HDI. The overall estimated incidence of occupational asthma in the total 223 companies surveyed was 0.9% in the 4 years of the study (56 out of 6,308 workers).

A greater proportion of companies which had claims for occupational asthma was found in the higher exposure category (≥ 5 ppb) than in the lower exposure category (< 5 ppb). For TDI, the proportion was 30% (high) vs. 13.7% (low); the odds ratio (OR) was 2.7 (95% confidence interval (CI) of 0.7-10.6). When combined across all isocyanate types, claims were significantly more likely to be from companies in the higher exposure category; 10 of 20 companies (50%) with claims were in the high exposure category vs. 50 of 203 companies (25%) without claims, OR: 3.1 (95% CI: 1.1-8.5, two-tailed $p=0.03$).

6.2. Chronic Toxicity to Infants and Children

No studies of inhalation exposures to TDI among children were located. However, early life exposure to TDI may occur through inhalation and dermal contact with polyurethane products. Although detectable levels of free TDI emitted from bedding materials have not been found, Krone et al. (2003) applied semiquantitative tests (i.e., wipe test) for isocyanate to polyurethane products, including mattresses, mattress pads, sofa padding, carpet pads and pillows, and detected free isocyanate in these consumer products. When this bedding is used by infants, there is a potential for exposure of the developing immune system to TDI. In fact, among children with 12 or more wheezing attacks in the previous 12 months, independent associations have been reported between severe wheeze and the use of non-feather bedding, especially foam pillows (odds ratio 2.78; 95% C.I. 1.89 to 4.17) (Strachan and Carey, 1995). It has also been observed that there is a higher incidence of asthma among first children

compared with their siblings (Karmaus and Botezan, 2002). This is consistent with the use of new polyurethane products (bedding, car seats, etc.) by the first child while siblings often use hand-me-downs whose isocyanate content has diminished over time.

These early life diisocyanate exposures may be significant since at birth, humans exhibit a dominant humoral, T_H2 , responsiveness (i.e., an atopic state). During the first few years of life, the T_H2 response converts to a more cellular (T_H1) immune response characteristic of the mature adult immune system. A delay in the transition from the predominant T_H2 pattern to the more balanced T_H1/T_H2 response allows an atopic T_H2 type response to persist longer, thus extending the period of vulnerability to environmental stressors and allergens, and increasing the likelihood of subsequent disease expression including asthma (Prescott et al., 1999).

In animal models of TDI-induced asthma, T_H2 cytokines were found to be decisive in the initial phase of asthma, in the priming of T_H2 cells, and in the permeation of eosinophils into the airway lumen (Matheson et al., 2005b). In other mouse models of asthma, a T_H2 -dominated sensitization was best achieved via dermal exposure followed by tracheal exposure, while exposure exclusively by inhalation prompted more of a T_H1 type response (Ban et al., 2006). Thus if a T_H2 response predominates, whether by previous activation or due to an early developmental stage, subsequent respiratory exposure may result in a substantial pulmonary inflammatory response. Other examples of chemical stressors that can shift the immune response to a T_H2 pattern are diesel exhaust and environmental tobacco smoke, both of which are strongly associated with asthma.

6.3. Chronic Toxicity to Experimental Animals

One lifetime TDI exposure study in rodents has been carried out and reported by Loeser (1983). Groups of male and female rats and mice (~40 rats and 30 mice per sex per level) were exposed to 0.05 and 0.15 ppm TDI by whole-body inhalation for 6 hr/day, 5 days/week for approximately 2 years. In rats, termination of the study occurred at week 110 for males and week 108 for females. TDI exposure did not affect mortality, although mortality was high in all groups (64 to 75%). Male and female rats in the 0.15 ppm group gained less weight, but only during the first 12 weeks of exposure. No treatment-related changes in haematological, blood biochemical or urinary parameters were seen. Organ weights were not affected by TDI exposure and no macroscopic changes were observed in the upper respiratory tract.

Histopathology of the rat nasal turbinates in the Loeser report were reported separately by Owen (1984). Seven rats per sex per level were examined at 6-, 12- and 18-month interval sacrifices, respectively. There were 26 to 37 rats per sex per level sacrificed and examined at termination of the study at approximately 2 years. At 6-, 12- and 18-month sacrifice, nasal passages

showed a dose-related increased incidence of rhinitis mainly in the anterior portion of the nasal cavity (Table 14). The lesions at 6-, 12- and 18-months showed similar incidences and severity grades regardless of exposure duration, so the data were combined in Table 14. Rhinitis was generally characterized by squamous metaplasia/hyperplasia of the respiratory mucosa, with or without exudates in the lumen, and leukocyte infiltration. In males, there was some degree of rhinitis in about half of the controls. Female control rats were free of rhinitis.

Table 14. Summary of Incidence of Grade Scores in the Anterior Respiratory Portion of the Nasal Cavity of Rats Exposed to TDI: Six-, 12- and 18-Month Sacrifice Combined

Histopathology Score ^a	TDI Exposure Group (ppm)					
	Male 0	Male 0.05	Male 0.15	Female 0	Female 0.05	Female 0.15
# examined	21	20	21	21	21	20
Grade 0	13	12	2	21	12	7
1	3	2	0	0	4	6
2	4	4	5	0	5	5
3	1	2	11	0	0	2
4	0	0	3	0	0	0
% with grade 3-4	5	10	67	0	0	10

^a Histopathological grading scores: (0) unremarkable, (1) minimal - rhinitis present in <25% of mucosa, (2) slight - rhinitis present in 25-50% of mucosa, (3) moderate - rhinitis present in 50-75% of mucosa, and (4) marked - rhinitis present in >75% of mucosa.

At 2-year sacrifice, the dose-related increased incidence of rhinitis was still apparent, although some female control rats now showed some degree of rhinitis. In particular, the incidence and severity grade of the lesion had increased in exposed females at two years more than in exposed females in the earlier sacrifice groups (Table 15). To a lesser extent, nasal lesions were also found in the middle and posterior nasal cavity. Overall, Owen (1984) concluded that the nasal lesions were a low grade injury considered to be evidence of local irritation. The lesion was not accompanied by any unusual proliferative changes suggestive of any oncogenic effect.

Table 15. Summary of Incidence of Grade Scores in the Anterior Respiratory Portion of the Nasal Cavity of Rats Exposed to TDI: 2-Year Sacrifice

Histopathology Score ^a	TDI Exposure Group (ppm)					
	Male 0	Male 0.05	Male 0.15	Female 0	Female 0.05	Female 0.15
# examined	37	35	30	35	26	36
Grade 0	17	18	4	25	15	10
1	8	5	5	7	4	10
2	9	11	8	3	4	13
3	3	1	12	0	3	3
4	0	0	1	0	0	0
% with grade 3-4	8	3	43	0	12	44

^a Histopathological grading scores: (0) unremarkable, (1) minimal - rhinitis present in <25% of mucosa, (2) slight – rhinitis present in 25-50% of mucosa, (3) moderate – rhinitis present in 50-75% of mucosa, and (4) marked – rhinitis present in >75% of mucosa.

In mice, Loeser (1983) observed a statistically significant increase in mortality in females of both dose groups, although not strictly dose-related (60% in controls, 77% low-dose, 74% high-dose). The female mice in the 0.15 ppm group showed a high incidence of death within a 3 week period during the 10th month. Rhinitis in this group was considered to be associated with exposure and was predominantly seen in the animals dying during the study. Statistically significant reduced weight gain was observed in the high dose group for both males and females. No treatment-related changes in hematological, blood biochemical or urinary parameters were seen. The major pathological change observed in both groups was a dose-related increased incidence and severity of either chronic or necrotic rhinitis (epithelial atrophy, mucous and squamous metaplasia, inflammation, focal destructive rhinitis with debris). Lesions of variable incidence and severity were also seen in the lower respiratory tract (interstitial pneumonitis, catarrhal bronchitis) and in the eyes (keratitis) of some mice, with a higher incidence in the 0.15 ppm group. Pathology tables for the mice, including specific incidence and severity grades for respiratory tract findings, were not provided in the report.

As a result of the numerous human occupational studies that exist in the literature, animal studies conducted in the ppm range of TDI are less relevant for derivation of the chronic REL and are not summarized here. The principal chronic exposure studies (i.e., <2 year exposure) that conducted toxicity studies at TDI concentrations in the range of occupational exposures are summarized.

Animal models for TDI-induced allergic rhinitis and asthma have been developed and suggest a duration-dependent nature. Female C57BL/6 mice were given a subchronic nose-only exposure to TDI vapors (80:20 2,4:2,6 isomers) at 20 ppb

4 hr/day, 5 d/wk for 6 weeks, or a single acute, 2 hr exposure to 500 ppb (Matheson et al., 2005b). These exposures were followed 14 days later with an acute 1 hr challenge exposure to 20 ppb. In this model, 6 weeks is the period during which sensitization to TDI develops. Three control groups included air-exposed/air-challenged, TDI-exposed/air-challenged, and air-exposed/TDI-challenged mice. A portion of each group was sacrificed 24 hr after the challenge for the collection of blood and bronchioalveolar lavage fluid (BALF). Another portion was sacrificed 48 hrs after challenge for airway and pulmonary histopathology. The exposure period resulted in different immunological response patterns. Following the challenge exposure, total IgE levels were elevated 10-fold over controls ($p < 0.05$) in mice with the subchronic exposure but not significantly different from controls in acutely exposed mice. However, both subchronic and acute exposures significantly raised TDI-specific IgG antibodies ($p < 0.05$) compared to non-detectable levels in controls. Subchronically exposed mice exhibited histopathological changes in the nares and lungs consistent with an inflammatory response including significant infiltration by neutrophils, lymphocytes, eosinophils, and macrophages.

In acutely exposed mice, Matheson et al. (2005b) observed that inflammatory cells were only slightly elevated relative to controls. Consistent with this, inflammatory cytokines (IL-4, IL-5, IFN γ and TNF α) were significantly ($p < 0.05$) elevated following subchronic but not acute exposure. However, both exposure regimens resulted in significant degenerative cellular changes including loss of cilia, goblet cell metaplasia, septal exudates, hyaline droplet formation and epithelial hyperplasia. In addition, airway hyperreactivity, assessed by methacholine challenge, was significantly elevated in animals sensitized to TDI and challenged with TDI regardless of exposure duration. These results suggest that long term, low level TDI exposure caused a marked allergic response including airway inflammation, eosinophilia, goblet cell metaplasia, elevated IgE and TDI-specific IgG, and T_H1/ T_H2 cytokine expression, all characteristic of allergic asthma. Acute exposure however, did not present evidence of either T_H2 or eosinophil involvement, and the observed cellular changes likely were predominantly a result of upper airway irritation rather than an immune response.

To examine the effects of long-term, low-level exposure on bronchial hyper-responsiveness, animals were exposed to 0.02 ppm TDI 6 hr/day for 70 days resulting in a total exposure of 8.67 ppm x hr (Karol, 1983). This was comparable to the total exposure of 9.2 ppm x hr received by animals breathing 0.61 ppm for 3 hr/day for 5 days. Whereas animals receiving the higher level (0.61 ppm), short term exposure displayed bronchial hyper-responsiveness and antibody production, none of the animals with low level (0.02 ppm) TDI exposure developed antibodies or pulmonary responsiveness upon challenge. These results suggest that in the absence of a sensitizing event, chronic low level TDI exposure may not elicit either pulmonary hyper-responsiveness or immune responses. However, as observed in the occupational study by Diem et al. (1982), pulmonary effects (decreased FEV₁) were associated with a low TDI concentration of 1.9 ppb.

Pulmonary function was investigated in guinea pigs exposed to 0 or 20 ppb TDI, 6 hr/day, 4 days/wk for 14 weeks (Wong et al., 1985). Each week during exposure, eight animals were randomly selected and placed in a whole-body plethysmograph to record respiratory frequency, pressure change (which is proportional to tidal volume) and the ventilatory response to 10% CO₂. These animals were compared to guinea pigs receiving 1.4 ppm TDI 3 hr/day for 4 days, a concentration expected to cause pulmonary damage. Exposure to 20 ppb TDI had no effect on baseline pressure change, respiratory frequency or the ventilator response to CO₂, whereas exposure to 1.4 ppm TDI increased baseline pressure change and respiratory frequency, but diminished the CO₂-induced increase in pressure change. All animals exposed to 1.4 ppm showed multifocal subchronic interstitial inflammation at terminal sacrifice, whereas only 2 of 24 animals exposed to 20 ppb TDI showed patchy interstitial inflammation.

Bronchial provocation challenge was also examined by Wong et al. (1985) with TDI antigens on days 37-38. Four of 8 guinea pigs exposed to 1.4 ppm TDI exhibited pulmonary hypersensitivity. No sensitivity was apparent in animals exposed to 20 ppb TDI or control animals.

Immunologic and respiratory responses have been produced in dogs with airway challenge to TDI (Patterson et al., 1983). In this model three anesthetized dogs received 1 mg/kg aerosolized TDI via tracheal tube every 2 weeks for 4 months, and then every 4 weeks thereafter for 6 months. A dose of 1 mg/kg TDI every 4 weeks was said to approximate 4 week exposure of a human at heavy work exposed to 20 ppb TDI. After the biweekly exposures, the dogs developed systemic immune responses to TDI-dog serum albumin, which included IgG, IgA and IgM antibody responses and development of lymphocyte reactivity. Immediate-type airway responses occurred after the fourth TDI aerosolization, some of which qualitatively simulated IgE-mediated antigen-induced airway responses.

6.4. Toxicogenomics

Even though diisocyanates are one of the most common causes of occupational asthma, only 5 to 15% of exposed workers develop the disease. Thus, genetic variability has been implicated in the susceptibility to occupational asthma by TDI and other diisocyanates. A number of gene variants have been reported to be associated with increased sensitivity to the disease in workers (Table 16), which suggests that diisocyanate-induced asthma represents a complex disease phenotype determined by multiple genes. Examples of genes include, but are not limited to, genes involved in immune regulation, inflammatory regulation, and antioxidant defense (Choi et al., 2009; Yucesoy and Johnson, 2011; Yucesoy et al., 2012). The goal of genetic association studies is to provide more accurate information on interindividual variability, thereby contributing to better protection of sensitive human populations and to the establishment of more accurate exposure limits in the workplace.

A case-control study was conducted by Yucesoy et al. (2012) to investigate whether genetic variants of antioxidant defense genes are associated with increased susceptibility to diisocyanate-induced asthma (DA). The study population consisted of 353 Caucasian French-Canadians in three groups: 95 workers with specific inhalation challenge confirmed DA; 116 symptomatic diisocyanate workers with a negative specific inhalation challenge; and 142 asymptomatic exposed workers. Antioxidant defense gene variations for superoxide dismutase, glutathione-S-transferase and epoxide hydrolase and their interactions were found to contribute to DA susceptibility (Table 16).

In a study population of 109 cases of workers with DA and 73 exposed non-symptomatic controls, polymorphisms in glutathione-S-transferase genes were examined to look for associations with DA (Pirila et al., 2001). Lack of the GSTM1 gene (null) was found to be associated with increased risk of DA. In a later study on the same worker group, Wikman et al. (2002) investigated the possible role of *N*-acetyltransferase (NAT) genotypes in the development of DA. Positive associations for increased DA were found with slow acetylator genotypes and genotype combinations with a glutathione-S-transferase (GSTM1 null) genotype.

The human leucocyte antigen (HLA) class II molecules are also thought to be involved in the development of the immune response to diisocyanates. HLA class II molecules are encoded by genes located within the major histocompatibility complex and present antigens from outside of the cell to T-lymphocytes. These particular antigens stimulate the multiplication of T-helper cells, which in turn stimulate antibody-producing B-cells to produce antibodies to that specific antigen. Mapp et al. (2000) examined the distribution of markers (DQA, DQB and DRB) for HLA class II genes in European Caucasians (67 TDI-exposed workers with DA, 27 asymptomatic worker controls, and 101 normals). The frequencies of DQA1*0104 and DQB1*0503 were significantly increased in asthmatic subjects. DQB1*0503 was also more frequent among asthmatic subjects compared with normal subjects.

Kim et al. (2006) evaluated a Korean population for associations of HLA class I and II alleles with TDI-induced asthma. Statistical significance was not found with single allele analysis. However, two and three locus haplotype analysis showed several significant alleles as potential susceptible markers. The authors identified the HLA haplotype DRB1*15-DPB1*05 as the most useful marker for predicting development of TDI-induced occupational asthma (OA) in the Korean population.

A more recent study by the same Korean research group expanded on the earlier study by looking for associations of HLA class I and II alleles with TDI-induced asthma using high resolution analysis (Choi et al., 2009). The Korean study population included 84 worker with DA, 47 asymptomatic controls and 127 unexposed normal controls. No significant association was found between allele

frequencies and TDI-induced OA. However, two- and three-locus haplotype frequencies were found that were associated with TDI-induced OA compared to both asymptomatic workers and unexposed controls (DRB1*1501-DQB1*0602-DPB1*0501, DRB1*1501- DQB1*0602, and DRB1*1501- DPB1*0501).

CTNNA3 (alpha-T catenin) is a key protein of the adherence junctional complex in epithelial cells and plays an important role in cellular adherence. The function of CTNNA3 in TDI-induced asthma is not known, but it has been shown that decreased expression of CTNNA3 may lead to increased susceptibility to TDI effects and contribute to development of DA (Bernstein et al., 2013). A Caucasian study population including 132 workers with DA, 131 symptomatic workers with a negative challenge for DA, and 147 asymptomatic workers were examined to determine if genetic variants of CTNNA3 genes are associated with increased susceptibility to DA. CTNNA3 minor allele homozygotes of rs7088181 and rs10762058 SNPs were at increased risk for DA compared to the asymptomatic control workers, but not symptomatic workers with a negative challenge. These same SNP CTNNA3 polymorphisms were also significantly associated with TDI-induced asthma in a group of 84 Korean workers with DA compared to 263 normal controls (Kim et al., 2009).

Sixty-two workers with DA and 75 diisocyanate workers negative for DA were analyzed for SNPs associated with the immune response genes IL4RA, IL-13, and CD14 (Bernstein et al., 2006). The T_H2 cytokines IL-4 and IL-13 play key roles in B-cell IgE isotype class switching and are believed to at least partially determine expression of airway inflammation and allergic disease. No associations were found with individual SNPs and DA when all diisocyanate workers (TDI-, MDI- and HDI-exposed) were considered. When only HDI-exposed workers were considered (34 with DA, 62 negative for DA), associations with immune response genes and DA were found. The strongest associations were for the two-genotype variation combination IL4RA (150V) II and CD14 (C159T) CT, and the three-genotype variation combination IL4RA (150V) II, IL13 (R110Q) RR, and CD14 (C159T) CT.

Table 16. Variability in Observed Odds Ratio (OR) or *p* Value for Significant Genotype Variation Associations and Increased Susceptibility for Diisocyanate-Induced Asthma

Reference	Ratio or <i>p</i> value	Genetic associations for DA
Yucesoy et al., 2012	OR=2.70 ^a (95%CI 1.38-5.27) <i>p</i> =0.004	SOD2 (rs4880) superoxide dismutase single-nucleotide polymorphism (SNP) Ala→Val substitution on SOD2 gene that decreases the activity of SOD2
	OR=6.10 ^a (95%CI 1.31-28.4) <i>p</i> =0.021	GSTP1 (rs762803) glutathione-S-transferase SNP of unknown functional consequence
	OR=7.34 ^a (95%CI 2.04-26.5) <i>p</i> =0.002	GSTM1*EPHX1 (rs2854450) copresence of glutathione-S-transferase (GSTM1) deletion and minor allele for epoxide hydrolase (EPHX1 rs2854450)
	OR=8.55 ^a (95%CI 1.05-69.9) <i>p</i> =0.045	EPHX1 (rs2740168)*EPHX1 (rs1051741) copresence of two EPHXs, rs2740168 variant and a variation (rs1051741) that reduces enzyme activity
	OR=10.36 ^b (95%CI 1.47-72.96) <i>p</i> =0.019	EPHX1 (rs1051741) epoxide hydrolase minor allele
	OR=6.22 ^b (95%CI 1.95-19.82) <i>p</i> =0.002	EPHX1 (rs2740171) epoxide hydrolase SNP minor allele
Piirila et al., 2001	OR=1.89 (95%CI 1.00-3.52) (no <i>p</i> given)	GSTM1 (null) gene lacks enzyme activity (59 cases and 29 controls with TDI, MDI or HDI exposure)
Wikman et al., 2002	OR=7.77 (95%CI 1.18-51.6) (no <i>p</i> given)	NAT1 gene polymorphism for slow acetylation. TDI-exposed only (23 cases, 8 controls)
	OR=4.53 (95%CI 1.76-11.6) <i>p</i> =0.040	GSTM1 (null)*NAT1 copresence (43 cases and 20 controls with TDI, MDI or HDI exposure)
Mapp et al., 2000	<i>P</i> =0.005	HLA DQA1*0104 - 16 of 67 cases (23.9%), 0 of 27 asymptomatics (0%)
	<i>P</i> =0.009	HLA DQB1*0503 - 14 of 67 cases (20.9%), 0 of 27 asymptomatics (0%)
	<i>P</i> =0.027	HLA DQB1*0503 - 14 of 67 cases (20.9%), 9 of 101 normals (8.9%)
Kim et al., 2006	<i>P</i> =0.001 (cases vs. asymptomatics) <i>P</i> =0.003 (cases vs. normals)	HLA DRB1*15-DPB1*05 - 10.6% in cases (n=110), 0% in asymptomatic controls (n=94), and 2.5% in normals (n=190).

Reference	Ratio or <i>p</i> value	Genetic associations for DA
Choi et al., 2009	TDI-OA vs. AEC ^a OR=4.43 (95%CI 1.50-13.10) <i>p</i> =0.007	DRB1*1501-DQB1*0602-DPB1*0501 – 16 of 84 cases (19%), 1 of 47 asymptomatic workers (2.1%), and 4 of 127 normals (4%).
	TDI-OA vs. AEC OR=2.024 (95%CI 1.14-3.59) <i>p</i> =0.016	DRB1*1501- DQB1*0602 – 23 of 84 cases (27.4%), 6 of 47 asymptomatic workers (12.8%), and 15 of 127 normals (11.8%).
	TDI-OA vs. AEC OR=3.127 (95%CI 1.38-7.08) <i>p</i> =0.006	DRB1*1501- DPB1*0501 - 17 of 84 cases (20.2%), 2 of 47 asymptomatic workers (4.3%), and 4 of 127 normals (3.1%).
Bernstein et al., 2013	OR=9.05 (95%CI 1.69-48.54) <i>p</i> =0.01	CTNNA3 (rs7088181) – SNP minor allele homozygote (130 cases, 147 asymptotic control workers)
	OR=6.82 (95%CI 1.82-14.88) <i>p</i> =0.002	CTNNA3 (rs10762058) – SNP minor allele homozygote (130 cases, 147 asymptotic control workers)
Bernstein et al., 2006	OR=5.2 (95%CI 1.65-28.24) <i>p</i> =0.008	IL4RA (150V) II and CD14 (C159T) CT HDI workers with DA 39% vs 11% among DA-negative workers
	OR=6.4 (95%CI 1.57-26.12) <i>p</i> =0.01	IL4RA (150V) II, IL13 (R110Q) RR, and CD14 (C159T) CT HDI workers with DA 24% vs 5% among DA-negative workers

^a AEC: asymptomatic TDI-exposed control workers

7. Developmental and Reproductive Toxicity

To examine the developmental toxicity of exposure to TDI vapors, Tyl et al. (1999a) exposed mated female Sprague Dawley rats to 0, 0.02, 0.10, or 0.50 ppm (25 per dose) of an 80:20 mixture of 2,4- and 2,6-TDI for 6 hr/day on gestation days 6-15. Animals were terminated on gestational day 21 and examined for signs of fetal and maternal toxicity. At 0.50 ppm, signs of maternal toxicity included reduced feed consumption and reduced weight gain, audible breathing and, among some animals, red nasal discharge. Reduced weight gain was also observed at the lower doses but this was reportedly transient in nature. No maternal treatment-related lesions were observed at necropsy. In terms of developmental toxicity, there were no apparent treatment-related effects on the total number of corpora lutea, implants per litter, or percent live fetuses. Of 111 skeletal variations observed, the only treatment-related sign of fetal toxicity was poor ossification of cervical centrum 5 at 0.50 ppm. The reported LOAEL for maternal and fetal effects was thus 0.50 ppm, with a corresponding NOAEL of 0.10 ppm.

The potential reproductive effects of TDI exposure were investigated in a two-generation study, also by Tyl et al. (1999b). Sprague-Dawley rats (28/sex/group)

were exposed beginning at 42 days of age to TDI vapors (80:20 mix of 2,4- and 2,6-TDI) for 6 hr/day, 5 days/wk for 10 weeks at 0, 0.02, 0.08, or 0.3 ppm. This was the parental or F0 generation. During the 3-week mating period, gestation and lactation, exposures were increased to 7 days/wk. F0 maternal rats were not exposed from gestational day 20 through postnatal day 4, but exposures resumed on postnatal day 5. Randomly selected weanlings (F1) were exposed as described above for 12 weeks prior to mating, during the 3-week mating period, and throughout gestation and lactation. Males of the F1 generation were terminated after delivery of the F2 generation; F1 females were terminated upon weaning of the F2 generation.

Among F0 parents, reproductive parameters were unaffected by TDI treatment. In the production of the F1 generation, no treatment-related effects were seen on gestation length, litter sizes, sex ratios, pup body weights or weight gain. In the F2 generation, a transient significant decrease in pup body weight gain was observed at the 0.08 and 0.30 ppm level. At these exposure levels, pup body weight/litter was also depressed (transiently in females, permanently in males). In the F0 and F1, but not F2 generations, rhinitis showed a dose-dependent incidence and severity. This study found no effects of TDI exposure on reproductive parameters in either the F1 or F2 generations.

8. Derivation of Reference Exposure Levels

8.1. Toluene Diisocyanate Acute Reference Exposure Level

<i>Study</i>	Baur et al., 1994; Vogelmeier et al., 1991
<i>Study population</i>	15 asthmatic and 10 healthy volunteers with no previous contact with diisocyanates
<i>Exposure method</i>	Exposure chamber
<i>Continuity</i>	
<i>Asthmatic subjects</i>	1 hr at 10 ppb (71 $\mu\text{g}/\text{m}^3$), 45 min break, then 1 hr at 20 ppb (142 $\mu\text{g}/\text{m}^3$)
<i>Healthy subjects</i>	2 hr at 20 ppb
<i>Critical effects</i>	$\geq 100\%$ increase in Raw in asthmatics
<i>LOAEL</i>	71 $\mu\text{g}/\text{m}^3$ (10 ppb)
<i>NOAEL</i>	Not determined
<i>Time-adjusted exposure</i>	71 $\mu\text{g}/\text{m}^3$
<i>LOAEL uncertainty factor</i>	10 (for severe effect)
<i>Interspecies uncertainty factor</i>	
<i>Toxicokinetic (UF_{a-k})</i>	1
<i>Toxicodynamic (UF_{a-d})</i>	1
<i>Intraspecies uncertainty factor</i>	
<i>Toxicokinetic (UF_{h-k})</i>	1
<i>Toxicodynamic (UF_{h-d})</i>	$\sqrt{10}$ (protect children with asthma)
<i>Cumulative uncertainty factor</i>	30
<i>Reference Exposure Level</i>	2 $\mu\text{g}/\text{m}^3$ (0.3 ppb)

Acute Reference Exposure Levels (RELs) are levels at which infrequent one-hour exposures are not expected to result in adverse health effects. Sensory irritation and altered lung function of sensitive individuals are the main responses seen with acute exposure to TDI.

The key study presented by both Baur et al. (1994) and Vogelmeier et al. (1991) was among the few controlled human exposure studies in which the total dose level of TDI was sufficient to elicit sensory irritation in normal and asthmatic subjects, and an asthmatic reaction in non-sensitized asthmatic subjects. A supporting study by Fruhmann et al. (1987) observed similar results in asthmatic subjects using a similar exposure protocol.

Pulmonary function in healthy subjects was not impaired with 2 hr exposure to 20 ppb TDI, although 3 subjects reported sensory irritation. In asthmatics, 1/15 experienced a severe pulmonary response to 10 ppb during 1 hr of exposure, and 1/13 remaining asthmatics experienced a severe response to 20 ppb TDI after a 45 min break. Five of 15 asthmatics reported pulmonary symptoms of chest tightness, rhinitis, cough, dyspnea, throat irritation, and/or headache during exposure. The concentration at which these symptoms occurred was not

specified in the report. The LOAEL from this study is 10 ppb ($71 \mu\text{g}/\text{m}^3$) for a 1 hour exposure (with no NOAEL observed). Only one of 15 asthmatics exhibited severe symptoms (100% increase in Raw) at 10 ppb. However, symptoms of respiratory irritation may have occurred as low as 10 ppb (or slightly higher at 20 ppb) in several other asthmatic subjects.

A LOAEL-to-NOAEL uncertainty factor (UF) of 10 is applied for a severe effect (onset of asthma symptoms) occurring at the LOAEL. Specific exposure durations to onset of symptoms were not presented by the authors.

Concentration x duration studies in TDI-sensitized subjects observed that bronchial responsiveness was neither exclusively concentration- nor duration-dependent (Vandenplas et al., 1993a). Rather, the product of the two factors, i.e., total dose, was the main determinant. This could explain why shorter duration exposure studies (15-30 min) with similar TDI concentrations did not elicit effects in asthmatics and non-asthmatics, although all the subjects in these studies were non-sensitized individuals. No time adjustment was applied since the TDI response appears to be, at least in part, a concentration-dependent effect that is already addressed by the LOAEL-to-NOAEL uncertainty factor.

A default toxicokinetic UF=1 was applied to the NOAEL based on the key human study that examined a sensitive subpopulation (i.e., asthmatic subjects). It is not anticipated that there would be significant interindividual variability in toxicokinetics for TDI, which acts at the portal of entry. TDI primarily affects the tracheobronchial region of the respiratory system. Comprehensive data are available to show that children have lower tracheobronchial regional gas doses compared to adults (OEHHA, 2008). The tracheobronchial minute volume (MV) to surface area (SA) is equal to 1 for adults, while children age 0 to 2 years has a MV/SA ratio of 0.5. For older children age 2 to 15 years, the MV/SA ratio is roughly 0.8. The toxicogenomics data for diisocyanates show gene variants associated with increased sensitivity up to 10-fold greater in workers developing diisocyanate-induced asthma. However, these findings address long-term exposures resulting in diisocyanate-induced asthma and is applied to the 8-hour and chronic REL derivations below. An intraspecies toxicodynamic default UF of $\sqrt{10}$ was used to address any potential increased sensitivity of children with asthma compared to adults with asthma. The total UF of 100, when divided by the POD of 10 ppb, generates an acute REL of 0.1 ppb ($0.7 \mu\text{g}/\text{m}^3$).

Evidence of cross-reactivity of diisocyanates suggests that a first exposure to TDI could result in diisocyanate-induced asthma in an individual previously exposed and sensitized to a different diisocyanate. As discussed above in Krone and associates, it is conceivable that infants could be sensitized with dermal exposure to diisocyanate-containing polyurethane products. Subsequent exposure to low level airborne TDI could then result in asthmatic symptoms. However, definitive evidence that dermal sensitization resulted from exposure to these consumer products is lacking. Exposure to TDI at concentrations as low as 1 ppb ($7 \mu\text{g}/\text{m}^3$) have resulted in an asthmatic reaction in sensitized individuals. However, a study by Suojalehto et al. (2011) showed an asthmatic

reaction occurred in a sensitized individual exposed to MDI at a much lower concentration of 0.05 ppb (0.51 $\mu\text{g}/\text{m}^3$). This finding suggests that once primary sensitization occurs it is probably not possible to identify a no effect level to protect all individuals that acquired specific hypersensitivity to diisocyanates. The same conclusion was presented in an International Consensus Report on Isocyanates (ICRI, 2002). Thus, the acute REL for TDI is based on prevention of primary sensitization, but should in many cases be protective for previously sensitized individuals.

In view of the concern for sensitization by exposures to TDI (which is discussed further in the derivation of the 8-hour and chronic RELs), it is appropriate to also consider whether repeated acute exposures at the acute REL level could cause sensitization. Although acute RELs are defined for infrequent single exposures, it is possible that an acute increase in the exposure concentration might be repeated on an occasional basis, and this type of exposure pattern may promote sensitization. However, in the study upon which the chronic REL is based, 0.9 ppb was the NOAEL for five years of occupational exposure. There is a 3-fold difference between this level for a regularly repeated exposure over five years and the acute REL of 0.3 ppb meant for infrequent exposures. Therefore infrequent exposures at the level of the acute REL should be adequately protective for most individuals, although the possibility of a pulmonary response in certain hypersensitive individuals cannot be completely excluded.

8.2. Toluene 8-hour Reference Exposure Level

The 8-hour Reference Exposure Level is a concentration at or below which adverse noncancer health effects would not be anticipated for repeated 8-hour exposures.

The critical study and the time adjustment for the 8-hour REL is the same as that for the chronic REL below, resulting in the same health value for both 8-hour and chronic RELs. For many substances, higher exposure levels are tolerable if the exposures are intermittent versus chronic, thus 8-hr RELs are typically higher than chronic RELs. For TDI, the exposure level of the chronic REL was also chosen for the 8-hour REL as a more health-protective approach due to its sensitization potential, an effect that may occur with only intermittent low-level exposures. Sensitization to TDI that occurs following an acute, high-level exposure primarily represents a neurological sensitization with only non-specific involvement of the immune system. The development of TDI-specific IgE (and possibly IgG) antibodies requires longer-term exposures and may occur at low exposure levels (Matheson et al., 2005a). The manner in which airway hyperresponsiveness and remodeling occur is thus affected by the intensity and duration of exposure. For this reason, while some individuals may become sensitized to TDI in a relatively short period of time, for others sensitization may only develop following years of low-level exposure (Peters and Wegman, 1975). In the former case, neural sensitization may ultimately trigger an immune system

involvement, while in the latter case, development of a specific immune response can potentiate neural responsiveness.

8.3. Toluene Diisocyanate Chronic Reference Exposure Level

<i>Study</i>	Diem et al., 1982
<i>Study population</i>	277 adult male workers in TDI production
<i>Exposure method</i>	Discontinuous whole-body inhalation exposure to 0.9 or 1.9 ppb
<i>Continuity</i>	8 hours per day, 5 days/week
<i>Duration</i>	5 years
<i>Critical effects</i>	Accelerated decline in FEV ₁
<i>LOAEL</i>	13.5 µg/m ³ (1.9 ppb)
<i>NOAEL</i>	6.4 µg/m ³ (0.9 ppb)
<i>Time-adjusted exposure</i>	2.285 µg/m ³ (6.4 * 10/20 * 5/7)
<i>LOAEL uncertainty factor</i>	1
<i>Subchronic uncertainty factor</i>	√10
<i>Interspecies uncertainty factor</i>	
<i>Toxicokinetic (UF_{a-k})</i>	1
<i>Toxicodynamic (UF_{a-d})</i>	1
<i>Intraspecies uncertainty factor</i>	
<i>Toxicokinetic (UF_{h-k})</i>	10
<i>Toxicodynamic (UF_{h-d})</i>	10
<i>Cumulative uncertainty factor</i>	300
<i>Reference Exposure Level</i>	0.008 µg/m ³ (0.001 ppb)

The chronic REL is a concentration at which adverse noncancer health effects would not be expected from chronic exposures (see Section 7 in the Technical Support Document (OEHHA, 2008)).

The chronic REL is based on a prospective occupational study by Diem et al. (1982). This study had several strengths over the other workplace investigations of TDI exposure, including minimal co-exposure to other irritating chemicals, extensive use of personal exposure monitoring devices, accounting of TDI-sensitized workers in the cohort, and in particular, detailed longitudinal analysis of workers from the start of exposure in a new TDI production facility.

In this five year longitudinal study by Diem et al. (1982), FEV₁, Forced Percentual Expiratory Volume (FEV%), and FEF_{25-75%} annual declines were significantly related (after controlling for smoking and atopic status) to TDI dose, where dose was measured by either: (a) two cumulative exposure categories, equivalent to a mean exposure of 0.9 or 1.9 ppb; or (b) two “time above 20 ppb” categories (division point = 0.19 months). The accelerated decline in FEV₁ occurred in the absence of workers with occupational asthma. A NOAEL of 0.9 ppb (6.4 µg/m³), the arithmetic mean of the non-smoking low-exposure group (≤68.2 ppb-months), was calculated by Hughes (U. S. EPA, 1995). The LOAEL of 1.9 ppb is the

calculated arithmetic mean of the non-smoking high-exposure group. Other longitudinal studies support the findings by Diem et al. that keeping 8-hr TWA TDI exposures below a range of about 1-2 ppb does not result in a measurable accelerated decline of pulmonary function.

OEHHA's noncancer TSD (OEHHA, 2008) calls for a 3-fold subchronic uncertainty factor for exposures from 8 to <12% of a lifetime. The 5 year duration of the Diem study represents only about 7% of a worker's lifetime of 70 years. In consideration of the generally moderate but variable amount of time required for symptom manifestation, a subchronic UF of $\sqrt{10}$ was applied (rather than a UF of 10). Since the critical study is a human study, no interspecies adjustments were required.

The toxicogenomics data for TDI and other diisocyanates show gene variants associated with increased sensitivity up to 10-fold greater in workers developing diisocyanate-induced asthma. Thus, an intraspecies toxicokinetic uncertainty factor (UF_{h-k}) of 10 is applied.

The intraspecies UF_{H-d} (toxicodynamics) is used to account for pharmacodynamic variability among pregnant women and their fetuses and among infants, children, and adults. Although the critical effect was in an adult worker population, the potential greater sensitivity for lung function impairment in the developing lungs of infants and children would support an intraspecies UF_{H-d} of 10. The total intraspecies UF would equal 100. The cumulative UF of 300 results in a chronic REL of $0.008 \mu\text{g}/\text{m}^3$ (0.001 ppb).

Application of an overall intraspecies UF of 100 is supported by the toxicogenomic data in Table 15, in which odds ratios for immune/inflammatory system genotype variation associations for increased susceptibility for diisocyanate-induced asthma fall in the range of 1.89 to 10.36. However, these associations are for development of asthma rather than the critical effect of decreased lung function upon which the 8-hour and chronic RELs are based.

There is currently no consensus on the threshold-sensitizing inhalation dose for TDI and some believe there may be no lower limit of exposure at which no workers will be sensitized (Tarlo and Liss, 2002). This is due, in part, to the likely genetic predisposition for isocyanate-induced asthma at extremely low levels in some individuals (Suojalehto et al., 2011). Sensitization to TDI can occur within weeks of first exposure, or after many years of exposure. This would argue in favor of genetic predisposition for some individuals, rather than a concentration-related correlation for onset of TDI-induced asthma. Also, the role of peak exposures in workers (e.g., accidental spills) may be a factor in the onset of isocyanate-induced asthma.

In the summarized longitudinal studies above, the level of TDI at which workers may become sensitized to TDI has not been as thoroughly investigated as the accelerated loss of FEV_1 . Nevertheless, the data by Weill et al. (1981) indicate

that the NOAEL of 0.9 ppb for accelerated non-sensitized pulmonary function will also keep the prevalence of TDI-induced asthma very low. Weill et al. (1981) showed that two of 12 men that became sensitized during the 5-year study had worked in jobs with low TDI exposure (TWA 1.6 ppb). The other sensitized workers were exposed to higher TWA levels of ≥ 3.2 ppb TDI. The investigators stratified the workers by cumulative exposures of < 68.2 ppb-month and ≥ 68.2 ppb-month (equivalent to a TWA of 0.9 and 1.9 ppb, respectively); it was unclear from the report which grouping the sensitized workers were in. However, it appears likely that most of the sensitized workers, if not all, were assigned to the ≥ 68.2 ppb-month group. If that is true, then the NOAEL of 0.9 ppb for accelerated decrease in FEV₁ should protect most individuals from diisocyanate-induced sensitization. The database as a whole supports this assumption.

Supporting evidence for low prevalence of asthma at 0.9 ppb is provided by Musk et al. (1982) in the 5-year longitudinal study in which no indication of TDI-induced sensitization was found in 107 workers exposed to 20-60 min peak exposures of 1.0-1.5 ppb (90th percentile: 5.0 ppb). Examination for sensitization and follow-up of workers leaving the industry was not as rigorous as that used for the Weill et al. study. However, it was claimed by the authors that the 152 workers that left before follow-up was due to high labor turnover in unskilled occupations and the reorganization of the industry, and likely not due to symptoms of sensitization.

Ott et al. (2000) observed a decline in annual incidence of sensitization with improvement of environmental conditions. The yearly incidence of sensitization was 1.1% before 1980, and 0.7% thereafter when 8-hr TWA TDI concentrations were reduced from ≥ 5.9 ppb to about 2.8 ppb.

Other supportive evidence comes from cross-sectional or case-referent studies. Meredith et al. (2000) established a TWA exposure of 1.5 ppb (95% confidence interval 1.2-1.8) in a group of 27 workers that became sensitized primarily to TDI. Exposure above the median TDI exposure level of 1.125 ppb of a matched referent group increased the odds 3.2-fold of developing occupational asthma. Tarlo et al. (1997) found plants with at least one exposure above 5 ppb were more likely to have cases of isocyanate-induced asthma than companies in which exposures were kept below 5 ppb.

For comparison, the U.S. EPA (1995) estimated a Reference Concentration of 0.07 $\mu\text{g}/\text{m}^3$ also based on the Diem study. The 10-fold difference in the U.S. EPA derivation and the chronic REL results from OEHHA's use of intraspecies toxicodynamic and toxicokinetic UFs of 10, rather than $\sqrt{10}$, to address the respiratory susceptibility of children, and the differences in risk of diisocyanate-induced asthma in workers based on genotype for a number of enzymes including GST, NAT, and epoxide hydrolase.

8.4. TDI as a Toxic Air Contaminant Especially Affecting Infants and Children

Under Health and Safety Code Section 39669.5, OEHHA establishes and maintains a list of Toxic Air Contaminants (TACs) that may disproportionately impact infants and children. OEHHA evaluates TACs for addition to this list when developing Reference Exposure Levels for TACs. TDI was identified by the Air Resources Board as a toxic air contaminant in accordance with Section 39657(b) of the California Health and Safety Code (Title 17, California Code of Regulations, section 93001) (CCR, 2007). TDI has been shown to cause asthmatic reactions in non-sensitized asthmatic adults in controlled exposure studies (Vogelmeier et al., 1991; Baur et al., 1994), and in non-sensitized children with asthma as well as asthma-like effects in children without asthma exposed acutely to the diisocyanate MDI in an accidental exposure (Jan et al., 2008). OEHHA considers asthma a disease that disproportionately impacts children, and thus chemicals that induce or exacerbate asthma are considered more impactful for children (OEHHA, 2001). Animal models for TDI-induced asthma have produced T_H2 -dominated sensitization. In humans during the first few years of life, the dominant T_H2 response converts to a more cellular T_H1 immune response characteristic of the mature adult immune system. Any delay or shift to a T_H2 pattern during early life as a result of chemical stressors, including TDI, has been strongly associated with asthma. In view of the potential of TDI to induce or exacerbate asthma and the differential impacts of asthma on children including higher prevalence rates, and in view of the rapid development of the lung during infancy, OEHHA recommends that TDI be identified as a TAC that may disproportionally impact children pursuant to Health and Safety Code Section 39669.5(c).

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