Evaluation of Self-Reported Skin Problems Among Workers Exposed to Toluene Diisocyanate (TDI) at a Foam Manufacturing Facility

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Toluene diisocyanate, or TDI (CAS 584-84-9) is a well-known asthmagen and respiratory irritant. TDI is also known for its ability to irritate the skin and mucous membranes. To further investigate the dermal effects of TDI, NIOSH investigators conducted a cross-sectional study at a flexible foam manufacturing plant. A total of 114 workers participated in the study. Participants completed a medical questionnaire, provided blood for antibody testing to TDI and other allergens, and a subset of participants reporting skin symptoms underwent skin patch testing to a standard diisocyanate panel. Production line workers were more than twice as likely to report skin problems as those working in nonproduction areas (PRR = 2.66; 95% CI = 1.14–16.32; P = 0.02). Age, gender and duration of employment at the plant were comparable among participants working in production and nonproduction areas. Of the 100 participants who provided blood samples for antibody testing, specific IgG antibody to TDI was detected in two individuals, and none of the samples demonstrated specific IgE antibody to TDI. Of the 26 workers who underwent skin patch testing, none developed reactions to the diisocyanate allergens. These results suggest that the skin symptoms among study participants represent an irritant rather than an immunologic reaction to TDI, or to an unidentified allergen present in the foam. (J Occup Environ Med. *2002;44:1197–1202*)

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Toluene diisocyanate (TDI) is an important industrial chemical used in the manufacture of polyurethane (PUR) foams, paints, coatings, and elastomers.[1] TDI-related health effects include asthma, rhinitis, hypersensitivity pneumonitis or alveolitis, conjunctivitis, and chronic obstructive lung disease.[2] TDI and the other diisocyanates are widely recognized for their ability to cause respiratory hypersensitivity.[3] TDI is also known to be a dermal irritant, but only rarely have cases of allergic contact dermatitis been reported.[4] In general, the potential for TDI and the other polyisocyanate monomers to act as dermal irritants and/or contact sensitizers is believed to be low.[5]

Approximately 50 cases of allergic contact dermatitis caused by a variety of diisocyanate compounds have been reported in the medical literature from 1967 to 1999. Among these are six cases of allergic contact dermatitis resulting from exposure to polyurethane chemicals. These cases were diagnosed at the Institute of Occupational Health, Helsinki, Finland, from 1974 to 1990.[6] Three of the six patients were skin patch test positive to 5 different diisocyanates, including TDI, 4,4′-diphenylmethane diisocyanate (MDI), 1,6-hexamethylene diisocyanate (HDI), and diaminodiphenylmethane (MDA); the remaining three patients were sensitized to MDI alone. All six patients displayed localization of the dermatitis on the hands and/or the

face.[6] During the period 1983 to 1986, Frosch et al (1989) skin patch-tested 83 consecutive patients with suspected occupational diseases caused by isocyanates.[4] The health effects reported by the 83 individuals included asthma ($n = 60$), contact dermatitis ($n = 21$), rhinitis ($n = 17$), urticaria and/or fever ($n = 5$), conjunctivitis ($n = 2$), and laryngitis ($n = 1$). Of the 83, two had positive skin patch tests to isocyanates. The first individual, a 28-year-old nonatopic woman with a 2-month occupational history of spraying polyurethanes and who subsequently developed a strongly pruritic dermatitis on her hands, reacted to both MDI (5%, 2%, and 1% in petrolatum) and TDI (5% and 2% in petrolatum). The second individual, a 50-year-old nonatopic male car painter who developed hand dermatitis after a 6-month exposure history to paints containing HDI, reacted to HDI at various exposure concentrations (ranging from 0.02% to 0.1% in petrolatum). A total of 3 consecutive patch tests were conducted, all of which elicited reactions to HDI.[4]

From 1997 to the present, three case reports describing individuals with allergic contact dermatitis caused by diisocyanates were published in the medical literature. The first case involved a 47-year-old female textile worker who processed raw wool containing dicyclohexylmethane-4,4′-diisocyanate (HMDI). The patient presented with a 4-year history of a pruritic, vesiculopapular rash on her hands, arms, and torso. Upon skin patch testing, the patient demonstrated strong positive reactions to HMDI.[7] The second individual was a 48-year-old male laboratory office assistant with a 3-year history of chronic dermatitis of the hands and forearms. This patient had a positive skin patch test to TDI and MDA.[8] The third case, described in 1999, involved a 32-year-old female worker who developed dermatitis of both hands, forearms and face after a 1½-year history of exposure to a 2-component adhesive containing polyurethane resins. Patch tests were positive to TDI, MDI, and MDA.[9]

Numerous animal studies have demonstrated the ability of TDI and the other diisocyanates to induce contact sensitivity when applied topically to intact animal skin.[10–17] TDI has been shown to induce marked ear swelling in both mice and rats, a response which is characteristic of delayed-type hypersensitivity.[10,13,14] Similar results, indicating dermal hypersensitivity to TDI and to the other polyisocyanate prepolymers, have also been found in various studies using the guinea pig.[11,12,17]

The National Institute for Occupational Safety and Health (NIOSH) conducted a health hazard evaluation (HHE) at a facility that manufactured flexible polyurethane foam components for use in automotive seating.[18] The diisocyanate used at the facility was TDI. The HHE request was concerned primarily with respiratory effects; however, in this article, we report the results of our evaluation of dermal and respiratory health problems among 114 workers at this facility, and the results of immunologic testing and skin patch testing among a subset of the study participants.

Materials and Methods

A cross-sectional study design was utilized to determine (1) whether workers exposed to TDI (production line workers) had a higher prevalence of dermal symptoms compared with workers not exposed to TDI (nonproduction workers); (2) whether reported dermal symptoms were consistent with allergic contact dermatitis secondary to TDI exposure; (3) whether asthma and work-related mucous membrane irritation were related to dermal symptoms; and (4) whether individuals reporting dermal symptoms were more likely to have immunologic evidence of TDI sensitization. TDI airborne exposure monitoring (including personal breathing zone and area sampling), as well as dermal exposure monitoring for TDI were performed. The protocol for this study was reviewed and approved by the NIOSH Human Subjects Review Board (HSRB).

All plant employees were invited to participate in the study. Participants completed a detailed, self-administered questionnaire addressing work and health history, as well as a history of work-related skin, respiratory and mucous membrane symptoms. Participants were asked to provide a blood sample for total immunoglobulin (IgE) antibody, which was measured using the Pharmacia CAP System™ IgE fluoroenzymeimmunoassay (FEIA) (Pharmacia AB, Uppsala, Sweden). Total IgE levels were reported in kilounits per liter (kU/L). Sera were also assayed for specific IgE against six CAP® environmental allergen mixes (with a total of 27 allergens tested): grass mix (gx1, consisting of cocksfoot grass, meadow fescue, rye grass, Timothy grass, and meadow grass/Kentucky blue antigens); house dust mix (hx2, consisting of Hollister-Stier Labs house dust, house dust mite, and German cockroach antigens); mold mix (mx1, consisting of *Penicillium*, *Cladosporium*, *Aspergillus*, and *Alternaria sp*. antigens); tree mix (tx2, consisting of box-elder, oak, elm, cottonwood, pecan, and hickory wood antigens); weed mix (wx1, consisting of common ragweed, mugwort, English plantain, lamb's quarters, and Russian thistle antigens); and epidermal mix (ex1, consisting of cat, dog, horse, and cow dander antigens). The environmental allergen mixes were chosen because they contained allergens typically found in the region of the United States where the participants lived. Reaction to each mix was scored as either positive or negative, and a positive reaction (defined as circulating allergen-specific IgE antibody levels greater than 0.35 kU_A/L) to one or more of the environmental mixes was considered evidence of atopy.[19] Additionally, sera were analyzed for the presence of specific IgE antibodies to a TDI-human serum albumin (HSA) conju-

TABLE 1
Comparison of Age, Gender, and Duration of Employment for Production versus Non-Production Participants

Exposure Group	N	Mean Age (yrs)	Age Range (yrs)	Number of Males	Percent of Males	Number of Females	Percent of Females	Mean Duration of Empl. (yrs)
Production	88	39	19–59	27	31	61	69	13
Nonprod.	26	42	24–71	13	50	13	50	15

gate using the Pharmacia CAP System™ (Pharmacia & Upjohn Diagnostics AB, Uppsala, Sweden), with the results reported in terms of kU_A/L and a value greater than 0.35 kU_A/L considered positive. Specific IgG antibodies to TDI-HSA were determined using an enzyme-linked immunosorbent assay (ELISA) in accordance with the methods described in the article by Lushniak et al.[20] For the ELISA, levels of IgG antibodies to TDI-HSA were considered significant if the optical density reading obtained on the ELISA plate reader was three standard deviations above the mean for control sera from individuals with no prior diisocyanate exposure (laboratory controls, $n = 6$).[20]

Personal breathing zone (PBZ) air sampling of plant workers was also conducted. This consisted of one full-shift TDI air sample being obtained for each participant. Area air sampling for TDI was also conducted. Dermal TDI exposures were also assessed using the Permea-Tec™ colorimetric detectors produced by Omega Specialty Instrument Company (Chelmsford, MA). These detectors have an adhesive backing that adheres to the skin, and an impregnated pad on the exposed surface that changes color when exposed to isocyanates. The limit of detection for these devices is three micrograms of isocyanate per pad, and they provide a qualitative dermal exposure measurement. The detectors were placed on the palmar side of the index finger, and/or on the palm of the worker, and read by the industrial hygienist at the conclusion of the work shift. If the worker was wearing a light-weight cotton glove, the detector was placed inside the palmar side of the glove.

Questionnaire responses were analyzed using SAS® Version 6.12 statistical software (SAS Institute, Cary, N.C.). Health outcome variables based upon questionnaire responses included the following:

1. Dermal symptoms (defined as dermatitis, eczema, or other red rash reported in the last 12 months);
2. Asthma (defined as wheezing, plus one of the following: shortness of breath, cough or chest tightness); and
3. Work-related mucous membrane symptoms (defined as an itchy, stuffy or runny nose, or frequent sneezing or eye irritation at work).

Using information from the questionnaire, employees were classified as either production line workers or nonproduction workers. These designations were used as indicators of potential TDI exposure.

Prevalence rate ratios (PRRs) were used to measure the association between health outcomes and exposures. A 95% confidence interval (CI) was calculated for each PRR point estimate. The associated *P*-value was also calculated for each exposure variable/health outcome variable pair.

Participants who reported dermatitis, hives, eczema or other red rash during the previous 12 months were asked to participate in skin patch testing. Skin patch testing was performed by a board-certified dermatologist using a six-component isocyanate skin patch testing (I-1000) series marketed by the Chemotechnique Diagnostics Company (Malmo, Sweden; distributed by Dormer Laboratories, Inc., Rexdale, Ontario, Canada). Skin patch testing was performed according to International Contact Dermatitis Research Group (ICDRG) guidelines.[21] Isocyanate series allergens included TDI (2.0% in petrolatum); diphenylmethane-4,4-diisocyanate (MDI) (2.0% in petrolatum); 1,6-hexamethylene diisocyanate (HDI) (0.1% in petrolatum); diaminodiphenylmethane (0.5% in petrolatum); isophorone diisocyanate (IPDI) (1.0% in petrolatum), and isophorone diamine (IPD) (0.1% in petrolatum). Patch tests were applied using IQ test chambers (Chemotechnique Diagnostics Co). The chambers were applied to the participant's upper back for 48 hours, after which time the patches were removed and an initial reading was made. Participants returned 96 hours after initial application for a second reading. Interpretation of patch testing results involved the use of a standard scale of 1+ to 3+, with 1+ representing erythema and edema at the site of the patch test, 2+ representing vesicles, and 3+ representing a severe reaction with bullae. A reaction of 2+ or 3+ was considered indicative of an allergic reaction.

Results

Of the 290 employees at the plant, 114 participated in the study. These 114 participants, which included 88 production and 26 nonproduction workers, completed the questionnaire. Production and nonproduction participants were similar with respect to age, gender, and duration of employment at the company (Table 1). Analysis of the questionnaires revealed that 40 subjects met the case definition for dermal symptoms. Thirty-six (90%) of these 40 subjects were production line workers, and 4 (10%) were nonproduction workers.

Workers on the production line were more than twice as likely to report dermal symptoms as workers in nonproduction areas (PRR = 2.66; 95% CI = 1.14–16.32; $P = 0.02$). Twenty-six of 40 eligible participants meeting the case definition for dermal symptoms participated in skin patch testing, and 38 provided blood samples for antibody testing. PBZ air sampling for 2,4-TDI and 2,6-TDI was obtained for 66 of the 114 study participants. Air sampling was also obtained for 38 nonparticipants.

Of the 38 participants with dermal symptoms who provided blood samples, 3 (8%) had total IgE levels above the upper limit of normal (ie, >179 kU/L). Eight (13%) of the 62 participants without reported dermal symptoms who provided blood samples had elevated total IgE. Thirteen (34%) of the 38 participants with dermal symptoms had positive IgE to one or more of the environmental allergen mixes. Of the 62 participants without reported dermal symptoms, 22 (36%) had positive IgE to one or more of the environmental allergen mixes. No specific IgE antibodies against TDI were detected among any of the 38 individuals tested. Specific IgG antibody to TDI was detected in one of the individuals who had reported dermal symptoms.

Workers meeting the case definition for asthma were almost twice as likely to report dermal symptoms as those without asthma (PRR = 1.92; 95% CI = 1.12–8.53; $P = 0.02$). Similarly, those with work-related mucous membrane symptoms were more than twice as likely as those without mucous membrane symptoms to report dermal symptoms (PRR = 2.21; 95% CI = 1.07–10.04; $P = 0.03$).

Twenty-six of the 40 eligible workers participated in skin patch testing. None developed a skin reaction to any of the 6 isocyanate test allergens at 48 or 96 hours after the skin patch tests were initially applied.

Full-shift, personal breathing zone TDI exposure measurements were collected for 104 workers over three shifts. Nine full-shift area air samples were also collected. TDI concentrations in all samples were below the current American Conference of Governmental Industrial Hygienists (ACGIH®) Threshold Limit Value (TLV®) of 36 $\mu g/m^3$, with total TDI (2,4-TDI + 2,6-TDI) exposures ranging from 0.08 to 8.07 $\mu g/m^3$ (median = 1.15 $\mu g/m^3$). Limited data were obtained from the dermal exposure assessment, due to the Permea-Tec™ detectors failing within one hour of use, with the impregnated pads separating from the adhesive backing and falling to the floor. The three pads that remained intact during the testing phase were worn by production workers in the demold area (where foam cushions are removed from their molds after the curing process is complete). For these workers (who wore the detector pads on the palmar aspect of their hands, under their light-weight cotton gloves) the pads changed color over the course of the 8-hour work shift, indicating that dermal exposure to TDI had occurred.

Discussion and Conclusion

Our results indicate that the etiology of skin symptoms among study participants does not appear to be either a type I or type IV immunologic reaction to TDI. To the extent that they are related to a workplace exposure, they could represent an irritant reaction to TDI, or a reaction to another unidentified irritant or allergen associated with the foam-manufacturing process. Workers with and without dermal symptoms had similar proportions of elevated total IgE and positive antibody responses to the CAP® environmental allergen mixes, which may indicate positive atopic status. In contrast, other studies have demonstrated that individuals with dry or hyperirritable skin, particularly atopics, are prone to develop irritant contact dermatitis.[22]

Workers meeting the case definition for asthma and those with work-related mucous membrane symptoms were more likely to report dermal symptoms than those without these conditions. These results are consistent with the known health effects of diisocyanates, and may indicate that individuals exposed to diisocyanates who develop diisocyanate-induced symptoms in one organ system (such as the lungs or mucous membranes) are likely to develop symptoms in other organ systems (such as the skin). The lack of TDI-specific IgG and IgE in this worker cohort, however, seems at odds with these findings. Perhaps the relatively low environmental levels of TDI found at this plant were sufficient to cause health symptoms among plant employees, but were not of a level sufficient to induce a vigorous IgG- or IgE-mediated immunologic response to TDI. Additionally, because the participation rate in this study was low, the medical findings that were obtained for those employees who participated in the study may not be representative of the true disease prevalence among this plant population as a whole.

Production line work was found to be significantly associated with the reporting of dermal symptoms ($P = 0.02$). Thus, skin problems may be related to production line activities which involve direct cutaneous contact with polyurethane foam or chemicals used in the foam-making or foam-repairing process (eg, solvent-based polyethylene wax coatings and various adhesive compounds). The Material Safety Data Sheets (MSDSs) for the waxes and adhesives used at the plant indicate there are components that are capable of causing skin irritation and dermatitis with prolonged or repeated contact. Dermal irritation can also be caused by amine accelerators or catalysts utilized in polyurethane synthesis, such as triethylenediamine, triethylamine, and diethanol-

amine.[2,6,23,24] Exposure of unreacted isocyanate monomer inside the polyurethane foam after curing may occur and contribute to an irritant response when the foam is manually handled.[2,23,25] During machining and cutting, polyurethane foam produces a dust containing isocyanates; when this dust is heated above 250°C, polyurethane polymers decompose into isocyanates and nitrogen oxides, which may cause dermatitis.[2] Although cutting of cured foam components was an inherent part of the foam repair process at the plant, heating of the resulting foam dust did not occur.

Although PBZ and area air sampling for TDI indicated that airborne TDI exposures in the plant were relatively low, dermal effects may be related more to direct contact with diisocyanate-containing dust, liquid, or finished product, than to the air concentrations of diisocyanate vapor. Based on the available dermal exposure data, it was evident that production line workers who handled recently-cured foam had measurable TDI on the surfaces of their palms even while wearing cloth gloves, indicating cutaneous exposure to TDI.

In conclusion, the results of our study support an irritant contact dermatitis etiology, rather than an allergic contact dermatitis to TDI, as the most likely explanation for the dermal symptoms identified in this workforce. This is consistent with other evidence indicating that isocyanates are a rare cause of allergic contact dermatitis, despite the extensive use of these chemicals.[2,7–9,22,23,26–29] This irritant contact dermatitis could be caused by either residual unreacted TDI monomer contained in the freshly cured foam, or to solvents, waxes, or adhesives used in the mold preparation or foam-repair process. To help reduce the occurrence of skin problems in this and similar facilities using TDI, measures providing appropriate dermal protection from TDI and other auxiliary irritant chemicals should be emphasized. These would include gloves made of a permeation-resistant material, such as nitrile rubber, butyl rubber, neoprene, PVC, or flexible laminates (eg, 4H™ [PE/EVAL] and Silver Shield™).[15,18,30] In combination with worker education, these measures may help to reduce the morbidity associated with isocyanate exposure.

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