Article

Toxicology and Industrial Health

Toxicology and Industrial Health
2022, Vol. 38(9) 622–635

DOI: 10.1177/07482337221107243
journals.sagepub.com/home/tih
SAGE

Assessment of personal inhalation and skin exposures to polymeric methylene diphenyl diisocyanate during polyurethane fabric coating

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Abstract

Methylene diphenyl diisocyanate (MDI) monomers and polymeric MDI (pMDI) are aromatic isocyanates widely used in the production of polyurethanes. These isocyanates can cause occupational asthma, hypersensitivity pneumonitis, as well as contact dermatitis. Skin exposure likely contributes toward initial sensitization but is challenging to monitor and quantitate. In this work, we characterized workers' personal inhalation and skin exposures to pMDI in a polyurethane fabric coating factory for subsequent health effect studies. Full-shift personal and area air samples were collected from eleven workers in representative job areas daily for 1–2 weeks. Skin exposure to hands was evaluated concomitantly with a newly developed reagent-impregnated cotton glove dosimeter. Samples were analyzed for pMDI by liquid chromatography-tandem mass spectrometry. In personal airborne samples, the concentration of 4,4′-MDI isomer, expressed as total NCO, had a geometric mean (GM) and geometric standard deviation (GSD) of 5.1 and 3.3 ng NCO/m^3, respectively (range: 0.5–1862 ng NCO/m^3). Other MDI isomers were found at much lower concentrations. Analysis of 4,4′-MDI in the glove dosimeters exhibited much greater exposures (GM: 10 ng/cm^2) and substantial variability (GSD: 20 ng NCO/cm^2; range: 0–295 ng NCO/cm^2). MDI inhalation exposure was well below occupational limits for MDI for all the job areas. However, MDI skin exposure to hands was substantial. These findings demonstrated the potential for substantial isocyanate skin exposure in work settings with very low airborne levels. This exposure characterization should inform future studies that aim to assess the health effects of work exposures to MDI and the effectiveness of protective measures.

Keywords

Isocyanates, methylene diphenyl diisocyanate, asthma, polyurethanes, skin exposure, inhalation

Received 2 March 2022; Revised 27 May 2022; Accepted 27 May 2022

Introduction

Methylene diphenyl diisocyanate (MDI) monomers and polymeric MDI (pMDI) are important commercial isocyanates used in a broad range of industrial applications and consumer products, including production of rigid and flexible polyurethane foams, coatings, and adhesives (Allport et al., 2003; Bello et al., 2019; Ulrich, 1997). MDI and pMDI, while less volatile than the other major commercial isocyanates (e.g., toluene diisocyanate, TDI; hexamethylene diisocyanate, HDI), are potent sensitizers known to cause asthma, hypersensitivity pneumonitis, and contact dermatitis (Tsui et al., 2020). Global production and usage, especially

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pMDI, continues to increase along with the economic demand for polyurethane products (Allport et al., 2003; Global Markets Insights Inc., 2022). Waterproof fabric coatings are another application where MDI/pMDI is used.

Isocyanates remain among the leading reported causes of occupational asthma throughout the world (Dao and Bernstein, 2018; Kwon et al., 2015; Lockey et al., 2015; Tarlo and Lemiere, 2014). The National Institute for Occupational Safety and Health (NIOSH) recommends an 8-h time weighted average (TWA) exposure limit (REL) of 50 μg MDI/m^3 (or 5 parts per billion, ppb) and a 10-min short-term exposure limit of 200 μg MDI/m^3 (20 ppb) (NIOSH, 2005). The Occupational Safety and Health Administration (OSHA) only defines a ceiling permissible exposure limit (PEL) of 200 μg MDI/m^3 (Bello et al., 2004; OSHA, 1975). The United Kingdom (UK) Health and Safety Executive (HSE) has established a total isocyanate group standard of 20 μg NCO/m^3 as an 8-h time weighted average and 70 μg NCO/m^3 as a 10-min short-term exposure limit (Jones et al., 2017).

The primary strategy for preventing isocyanate asthma is to minimize inhalation exposures. Air sampling is used for exposure surveillance and compliance and to guide selection of personal protective equipment (PPE) and engineering controls. Despite low workplace levels of airborne isocyanates, immune sensitization and asthma continue to occur in workplaces where isocyanates are used, including in settings where measured airborne exposure levels have been below permissible exposure limits (Heederik et al., 2012; Meredith et al., 2000). With ever-expanding production, usage, and applications, opportunities for workplace isocyanate exposure and disease are likely to continue.

In mice and other animal models, skin exposure to isocyanates can induce systemic immune sensitization and the development of asthmatic-like airway inflammation (asthma) following secondary respiratory tract exposure (Bello et al., 2007; Redlich and Herrick, 2008; Wisnewski et al., 2011). Notably, skin exposure has been shown to be more potent than respiratory tract exposure for inducing immune sensitization (Rattray et al., 1994; Redlich, 2010; Vanoirbeek et al., 2004; Wisnewski et al., 2011). Among workers that produce and/or use isocyanates, skin exposure is commonly observed but generally does not cause localized skin reactions and, hence, often goes unnoticed (Bello et al., 2019; Jones et al., 2017). Contact dermatitis can occur in workers exposed to isocyanates but is not common (Geier et al., 2018; Goossens et al., 2002; Kanerva et al., 1989). Despite these concerns, there is currently neither a standardized methodology for measuring isocyanate skin exposure nor regulation of workplace skin exposure levels.

In this study, we used a newly developed skin exposure dosimeter based on an interception technique that uses cotton gloves impregnated with 1-(9-anthracenylmethyl) piperazine (MAP) to measure potential isocyanate skin exposure. This new technique detects up to three orders of magnitude greater skin exposures than tape stripping (Harari et al., 2016). When combined with sensitive and specific liquid chromatography-tandem mass spectrometry techniques, very low dermal exposure detection limits can be achieved.

In this study, we aimed: (1) to assess simultaneously inhalation and potential skin exposures to MDI in a polyurethane fabric coating production facility; (2) determine exposure variability within workers and between jobs at this factory. The findings demonstrate the feasibility of an approach than can be used to assess both airborne and skin isocyanate exposures in future exposure-health effects investigation and intervention studies.

Materials and methods

Process and study population

This study was conducted in a polyurethane fabric coating factory. The polyurethane coatings process involves the application of polyurethane coating mixtures over fabric in different coating and laminating machines. MDI and/or pMDI solutions in solvents (primarily methyl ethyl ketone (MEK), toluene, tetrahydrofuran (THF), or N-methyl pyrrolidone) were formulated, applied to fabric, and cured at various temperatures to produce coatings with tailored properties.

The study population consisted of 11 male workers with different jobs in the factory: fabric coating (6 workers), coating preparation (2 workers), mixing area (1 worker), material handling (1 worker), and waste management (1 worker). The typical process flow starts in the mixing area with mixing of proprietary formulations that are then transferred to the production floor by coating preparation workers and material handlers. Coating preparation workers can further adjust these formulations near their workstations to tailor product viscosity and curing properties to the

specific product line. Machine operators dispense the pMDI mixtures over the rollers and fabric using small buckets or more automated systems. Empty containers are then transferred by the waste management worker to a nearby area for disposal and cleaning. Figure 1 depicts typical activities in applying the MDI-based coat (A, C, and D) and preparing a coating formulation. Use of gloves was variable. When in use, the most common glove type at the time was thick cotton gloves, and sometimes rubber gloves (Figure 1(d)). Workers typically did not wear coveralls. In addition to hands, wrists, forearms, head, and neck were bare and could get contaminated with MDI.

Subject recruitment and consent followed procedures approved by the Institutional Review Board at Yale University and University of Massachusetts Lowell. The study was performed during 3 consecutive weeks. In addition to sampling, the research team on the ground observed processes and collected daily contextual information about workers activities, materials, and any process changes.

Chemicals and supplies

Methanol, acetonitrile, formic acid, and ammonium acetate were supplied by VWR International (Bridgeport, NJ, USA). Trifluoroacetic acid was purchased from Thermo Fisher Scientific (Waltham, MA, USA). Butyl benzoate (99% purity) was supplied by Sigma-Aldrich (Bellefonte, PA, USA) and was run through a silica gel column for further purification before use. LC grade solvents and reagents were used in the sample preparation and analysis. High-purity 1-(9-anthracenylmethyl) piperazine (MAP) was supplied by Legacy Technical Products & Consulting (Largo, FL, USA). MDI-MAP derivatives and deuterated MDI-MAP-d8 derivatives were supplied by Dr. Robert P. Streicher at NIOSH (Cincinnati, OH, USA). Twenty-five-mm glass fiber filters (Gelman Sciences, Ann Arbor, MI, USA) were used for air sampling in an Institute of Medicine (IOMs) stainless-steel inhalable sampler and as backup filters in impingers-filter sampling trains. PTFE membrane Acrodiscs® (0.45 µm and 0.20 µm, Pall Corporation, Port Washington, NY, USA) were used for sample cleanup as described below. LC-Si Supelclean 6-mL (0.5 g) tubes from Sigma-Aldrich (Bellefonte, PA, USA) were used for impinger solvent exchange (butyl benzoate) in Solid Phase Extraction (SPE). Ultrapure deionized water was generated in-house (Barnstead Nanopure-Infinity; Thermo Scientific, Marietta, OH, USA). Twenty-five-mm IOM stainless steel air sampler holders and glass midget impingers were used for air sampling (SKC, Eighty Four, PA, USA).

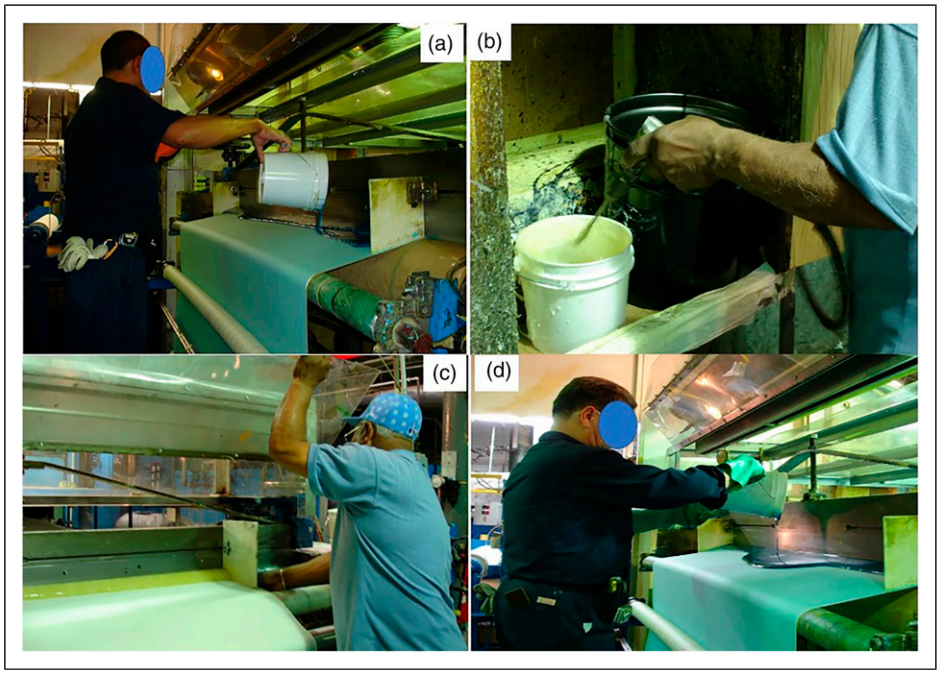

Figure 1. Representative photographs of activities in the fabric coating factory illustrating opportunities for skin exposure to MDI products. a, c, d – machine operation; b, product formulation.

Inhalation exposures

Area and personal breathing zone air samples were collected according to NIOSH Method 5525 (Bello et al., 2002; NIOSH, 2003; Streicher et al., 2000). Briefly, area air samples were collected with a glass midget impinger containing 15 mL of 1×10^{-4} M MAP solution in butyl benzoate followed by a MAP-impregnated quartz fiber filter. Impingers were operated at 1 L/min and were calibrated online with a DryCal DC-Lite primary flow meter (Bios International Co., NJ, USA). Impinger samples were located approximately 1.5 m above the floor and within 1 m of the work area/primary machine of use to represent potential inhalation exposures of workers. After sampling, the 15 mL impinger solution was transferred to a scintillation vial with a PTFE cap and stored in a cooler until delivery in the laboratory the same day. Backup filters were transferred into jars containing 10 mL of 1×10^{-4} M MAP in acetonitrile.

Personal breathing zone samples were collected with an Institute of Medicine (IOM) inhalable particulate size selective sampler operated at 2 L/min (Bello et al., 2002). The 25-mm glass fiber filters were impregnated with 500 µg MAP/filter just prior to sampling and placed in the stainless-steel IOM cassette sampler, covered, stored inside a sealed box, and transported in a cooler to the factory. The IOM samplers were placed on the lapel of each worker for the entire work shift. After sampling, the glass fiber filters and stainless-steel sample holders were placed in a 20 mL scintillation vial containing 10 mL of 1×10^{-4} MAP solution in acetonitrile, sealed with PTFE caps, and stored in a cooler until delivery to the laboratory. Once at the laboratory, area and personal samples were kept in a freezer at -20° C and analyzed within a month of collection.

Skin exposures

The development and performance evaluation of the MAP reagent-impregnated gloves used for assessing skin exposure to pMDI was previously described (Harari et al., 2016). The impregnated gloves were prepared 1–2 days prior to sampling, kept in a refrigerator at 4° C, and then transported to the field in a cooler with ice packs until use. Once at the factory, and prior the start of the shift, workers were provided with a new pair of nitrile gloves, over which the MAP reagent-impregnated gloves were worn. At least one pair of gloves was collected from each worker during an 8-h shift. In some cases where gloves looked dirty or damaged during the shift, they were removed and replaced with new impregnated gloves. Using two pairs of gloves for the whole 8-h shift would be desirable since workers tend to remove gloves at lunch and the thin cotton gloves were sometimes damaged over an 8-h shift. We could not apply this sampling approach consistently because of the complex sampling logistics needed for the overall study and occasional workers' hesitancy. The workers were observed throughout their 8-h shifts over the whole week (5 consecutive workdays). At the end of the work shift, the impregnated gloves from each hand were removed by researchers wearing clean nitrile gloves and placed into an individual 120 mL glass jar with a PTFE cap containing 50 mL of a $5x10^{-4}$ MAP solution in acetonitrile. The jars were placed in a cooler and transported at the end of the day to the laboratory for analysis. The glove dosimeter data are reported as 8-h averages.

Sample preparation and analysis

Area and personal breathing zone samples. Area and breathing zone samples were prepared following an adapted version of NIOSH Method 5525 (Bello et al., 2002). For area samples, a 5 mL aliquot of the sample was passed through a 6-mL LC-Si Supelclean™ tubes to exchange butyl benzoate with an LC-compatible solvent (acetonitrile). Once extracted, the solution was concentrated in a Visiprep™ SPE vacuum manifold (Sigma-Aldrich, St Louis, MO, USA) under vacuum with a stream of N_2 (Airgas, Billerica, MA, USA) and reconstituted with acetonitrile to a final volume of 1 mL. The remaining 1 mL was transferred into a 2 mL LC vial, and 10 µL of acetic anhydride was added and allowed to react overnight to consume excess MAP. For personal breathing zone samples, the 10 mL solution containing the impregnated filter was filtered under vacuum through a 0.45 µm PTFE membrane Acrodisc® filter and subsequently concentrated and prepared following the area sample procedures described above. Samples were then spiked with the internal standard (IS, MDI-MAP-d8) to give a final concentration of 10 ng/mL prior to analysis.

Skin exposure samples (interception glove sampler or glove dosimeters). The interception glove sampler for each hand was prepared as an individual sample. Each sample jar was brought up to 100 mL with acetonitrile, and 200 ng (200 µL of 1 µg/mL) of an internal

standard (MDI-MAP-d8) was added to the solution to give a final concentration of 2 ng/mL internal standard prior to analysis.

Jars were mechanically shaken for 5 min and then were placed in a sonication bath for 30 min to extract MDI-MAP derivatives from the fabric and homogenize the sample. After sonication, a 1 mL aliquot from the sample jar was filtered through a 0.20-µm PTFE membrane Acrodisc® filter directly into a 2 mL amber LC vial, and 10 µL of acetic anhydride was added and allowed to react overnight to consume the excess MAP.

Chemical analysis of MDI species was performed on a UPLC-UV-MS/MS system as described elsewhere (Bello et al., 2019; Harari et al., 2016). The method enabled quantitation of three MDI isomers, 4,4′-MDI, 2,4′-MDI, 2,2′-MDI, and the 3-ring oligomer (also referred to as 3-ring MDI) with limits of detection (pg/mL) of 25, 5, 5, and 1000, respectively.

Statistical data analysis

The 4,4′-MDI monomer, the 2,4′- and 2,2′-MDI isomers, and the 3-ring MDI were quantified individually. The data were also presented and analyzed for the total reactive isocyanate group (TRIG), or total NCO, as suggested in other studies (Pisaniello and Muriale, 1989; Bello et al., 2002, 2004). For samples below the limit of detection (LOD), a value of LOD/2 was used in the statistical analysis (Hornung and Reed, 1990). SAS statistical software version 9.4 (SAS Software, Cary, NC, USA) was used for statistical analysis. Since some of the MDI species were below the limit of detection (LOD) in a large number of samples, the median was reported for the species-specific data. However, for the total NCO, there were no samples below the LOD, so the sample distribution was examined graphically by Shapiro-Wilks, showing that the data were not normally distributed. Consequently log-transformed air and skin exposure data were used for all analyses, and exposures are reported as geometric mean (GM), geometric standard deviation (GSD), and range.

Personal 4′4′-MDI exposures were compared to the NIOSH REL of 50 µg MDI/m^3, and total NCO exposures were compared to the Health and Safety Executive (HSE) 8-h TWA standard of 20 µg NCO/m^3. A correlation analysis of air and skin exposure data by job group and by worker was conducted using Spearman's rank-order correlation. For each worker over a week's period and by job, all correlation coefficients were obtained using linear mixed-effects models (Hamlett et al., 2003; McClean et al., 2004). Job type as a fixed effect and the variability (between and within) jobs were analyzed using linear mixed-effects models for the inhalation and skin exposure data expressed as the natural logarithm of the total NCO concentration. Several covariance structures, including unstructured (UN) and compound symmetry (CS) covariance matrix, were evaluated using restricted maximum likelihood (REML) estimation (McClean et al., 2004). The overall model structure is presented in equation (1)

$$Y_{ijk} = \mathrm{Ln}\left(X_{ijk}\right) = \beta_0 + \beta_1 \mathrm{JOB} + b_i + \varepsilon_{ijk} \quad (1)$$

where X_{ijk} represents the total NCO exposure level of the ith worker on the jth day, and Y_{ijk} is the natural logarithm of $X_{ijk.}$ The β_0 represents the intercept, whereas β_1 represents the fixed effects for the covariate job group where k = {coating preparation worker, machine operator, material handler, mixing area worker, waste management worker}. The b_i term represents the random effect and ε_{ijk} is random error.

To examine the relative contribution of skin exposure and inhalation exposures, on each day, the total NCO amount measured on the glove pairs worn was compared to the total amount of NCO inhaled, which was estimated based on the workers personal breathing zone air concentration and the assumption that the worker had a reference light work breathing rate of 9.8 m^3 for the 8-h workday and 100% lung retention. The arithmetic mean total NCO skin and personal inhaled exposure for a job group was calculated by averaging the individual estimated values for each exposure pathway across all workers and days within each job group.

Results

Summary statistics of inhalation and skin exposures by MDI species are presented in Table 1. The dominant species detected in both inhalation and skin exposure samples was the monomer 4,4′-MDI, present in all 234 air and glove samples analyzed. The monomer 4,4′-MDI constituted a mean of 80% of the total NCO analyzed in all of the air samples (range 25–100%). The 2,4′-MDI monomer was the second most abundant species, contributing approximately 16%–21% of the total NCO in all the air samples. The concentration of 3-ring MDI in air was minimal—it was non-detectable

Table 1. Summary statistics of inhalation and glove dosimeter samples by aromatic isocyanate species.

Type of sample	% ≤ LOD[b]	GM	GSD	Range	Mean NCO %	Range NCO %
Area samples n = 71 (ng NCO/m^3)[a,c]						
4,4′-MDI	0	4.4	9.1	0.2–8483	78	53–100
2,4′-MDI	4	1.1	9.3	0.02–1798	21	0–46
2,2′-MDI	31	0.1	7.4	0.02–207.5	1	0–5
MDI-trimer[e]	100	-	-	-	-	-
Total NCO	-	6.4	8.4	0.4–10298	-	-
Personal breathing zone n = 88 (ng NCO/m^3)						
4,4′-MDI	0	5.1	3.3	0.5–1862	81	21–98
2,4′-MDI	0	0.9	3.9	0.02–67.5	16	2–27
2,2′-MDI	11	0.1	4.1	0.02–13.5	1	0–5
MDI-trimer	93	0.3	2.9	0.2–153.8	3	0–5
Total NCO	-	6.9	3.3	0.7–2096	-	-
Glove samples n = 112 (ng NCO/cm^2)[d]						
4,4′-MDI	0	10.6	20.0	0–294.7	80	25–99
2,4′-MDI	0	0.6	15.7	0–22.7	10	0–29
2,2′-MDI	0	0.2	10.4	0–61.5	5	0–50
MDI-trimer	33	0.7	10.4	0–34.9	5	0–16
Total NCO	-	13.7	16.1	0–349.6	-	-

[a]Total NCO = total reactive isocyanate group.
[b]LOD values were replaced with LOD/2. LOD, limit of detection.
[c]Conversion: 1 ng NCO/m^3 MDI = 2.98 ng MDI/m^3 = 0.3 parts per trillion (ppt).
[d]Glove surface area = 550 cm^2.
[e]MDI-trimer refers to 3-ring MDI.

in all area samples and detectable only in a few personal breathing samples (7%, 6 samples). The GM of the total NCO concentration in the area samples was 6.4 ng NCO/m^3 (GSD 8.4), comparable to the GM of the total NCO concentration in the personal samples of 6.9 ng NCO/m^3 (GSD 3.3).

The GM of the total NCO collected on the glove dosimeters was 13.7 ng NCO/cm^2 (GSD 16.1). With each glove having a surface area of 550 cm^2, the GM of the total NCO was 7535 ng per glove (or 15750 ng NCO per pair). The MDI isomers were detected in 100% of the glove samples, while 3-ring MDI could be quantified in 67% of the samples. MDI species with more than 3 rings were not detected in any of the air or glove samples.

Personal breathing zone samples

Air sampling from workers' personal breathing zones was performed to better characterize individual inhalation exposures. All personal air sampling results are presented as 8-h TWA. A total of 88 personal air samples were collected over 2 weeks from workers stationed in 5 different areas of the factory. The total NCO of all personal samples was less than the UK HSE standard (20 µg NCO/m^3), and the total 4,4′-MDI was less than the US NIOSH REL (50 µg MDI/m^3). As shown in Table 2, the highest total NCO levels were measured for fabric coating workers (GM 7.87 ng NCO/m^3, GSD 2.97) and waste management workers (GM 11.75 ng NCO/m^3, GSD 8.04).

Area sampling of airborne methylene diphenyl diisocyanate

A total of 72 area samples from eight different work areas of the factory where MDI was used were collected over the course of a 2-week data collection period. The areas sampled included the mixing area, coating preparation, waste management, and five different fabric coating machine areas. All area sampling results are presented as 8-h TWA. As shown in Table 2, the total NCO concentrations (ng/m^3 total NCO) varied by workplace location. The lowest levels were in the mixing area (GM 5.05 ng NCO/m^3, GSD 2.63), while the highest total NCO levels were found in the waste management area (GM 9.56 ng NCO/m^3; GSD 2.4). The fabric coating area (GM 6.48 ng NCO/m^3 total NCO, GSD 9.26) presented the widest range of concentrations (0.38–10298 ng NCO/m^3). There was a statistically significant difference between the area exposures related to the jobs ($p < 0.0001$), with the

Table 2. Personal breathing zone and area air sample concentrations of total NCO for each job group.

	Personal breathing zone[a]						Area samples			
Job groups	k	r	n	GM (ng/m³ total NCO)[b]	GSD (ng/m³ total NCO)	Range (ng/m³ total NCO)	n	GM (ng/m³ total NCO)	GSD (ng/m³ total NCO)	Range (ng/m³ total NCO)
Fabric coating	6	3–4	47	7.87	2.97	1.62–152	48	6.48	9.26	0.38–10298
Coating preparation	2	4–5	17	4.10	2.22	0.69–28.4	9	6.91	12.02	0.91–2609
Mixing area	1	4	8	7.77	2.67	1.79–36.8	8	5.05	2.63	1.51–15.12
Waste management	1	5	10	11.75	8.04	2.86–2096	6	9.56	2.39	1.58–24.5
Material handling	1	3	6	3.99	2.41	1.16–15.1	-	-	-	-
Total number	11		88				71			

k: number of workers sampled over the study period (1 week for personal breathing zone sampling; 2 weeks for area sampling); r: number of days workers were sampled during a week; n: the total number of samples collected for all workers in each job group; GM: geometric mean, GSD = geometric standard deviation.

[a]Personal air samples (n total = 88 samples) and area samples (n total = 71) were collected over two consecutive weeks (5 days/week, Monday–Friday).

[b]Total NCO = total reactive isocyanate groups; conversion: 1 ng NCO/m^3 MDI = 2.98 ng MDI/m^3 = 0.3 parts per trillion (ppt).

highest GM concentration measured in the waste management and coating preparation areas.

Higher area air concentrations in the coating preparation station relative to breathing zone values of coating preparation workers likely reflected worker mobility as these workers spent time away from the coating preparation stations.

Table 3. Skin exposure: Concentration of total NCO in MAP-impregnated gloves.

			Total NCO in MAP-impregnated glove[a] (ng/cm^2 total NCO)[b]		
Job groups	k	n	GM	GSD	Range
Fabric coating	6	35	15.1	25.5	0.5–349.6
Material handler	1	4	16.9	4.7	4.2–88.3
Mixing area	1	3	2.3	3.2	0.5–5.3
Coating preparation	1	4	3.8	1.8	2.1–7.1
Waste management	1	7	103.8	3.0	23.3–285.1
Total number	10	53			

k: number of workers sampled in each job group; n: the total number of glove pairs collected from all workers in that job group; GM: geometric mean, GSD: geometric standard deviation.
[a]A total of 53 glove pairs (106 gloves) were collected from ten workers over the course of 1 week (5 days/week).
[b]Total NCO = total reactive isocyanate group.

Potential skin exposure

The potential for skin exposure to 4,4′-MDI was assessed using the MAP-impregnated glove sampler or dosimeter (interception technique) developed in our lab (Harari et al., 2016). A total of 106 gloves (53 pairs) from ten workers were collected over a 5-day period. The highest potential for skin exposure (Table 3) was measured for the six fabric coating workers and one waste management worker, with individual glove samples containing up to 350 ng/cm^2 total NCO or 192.5 µg total NCO per glove.

Daily variability in air and potential skin exposures

There was a statistically significant difference in personal breathing zone exposures of workers between the different job groups ($p < 0.0001$), with the highest exposures measured for waste management workers, followed by fabric coating workers. The "job" variable explained 7% of the variance in exposure levels, while between-worker and within-worker (day to day) variability explained 2% and 91% of the total personal breathing zone exposure, respectively (Table 4).

The total NCO exposure level on each glove pair was similar throughout the week, except for Monday, when levels were 3- to 4-fold less, and Friday, when slightly greater skin exposures may reflect "end-of-

Table 4. Models for inhalation and skin exposures for polyurethane fabric coating workers.

Parameter	Total NCO exposure models[a]			
	Personal inhalation exposure		Skin exposure	
	Parameter estimates (SE)	*p*-value	Parameter estimates (SE)	*p*-value
Fixed effects				
Intercept	2.69 (0.44)		2.62 (0.60)	
Job		< 0.0001		< 0.0016
Coating preparation	−1.16 (0.46)		−1.82 (3.03)	
Machine operator	−0.52 (0.40)		−1.81 (2.26)	
Material handler	−1.14 (0.59)		−3.83 (2.95)	
Mixing area	−0.46 (0.52)		−3.31 (3.03)	
Waste management	0.0 (Ref)[b]		0.0 (Ref)	
Random effects	Variance		Variance	
Between groups	0.10 (0.15)		1.97 (1.72)	
Between workers	0.02 (0)		0.004 (0)	
Within same worker	1.29 (0.21)		5.9 (1.59)	

[a]Total NCO = total reactive isocyanate group.
[b]Ref: used as a reference group; SE = standard error.

the-week" specific tasks, including routine cleaning and maintenance. There was a statistically significant difference in potential skin exposures measured by glove dosimeters between different jobs ($p < 0.0016$). The "job" variable explained 25% of the variance in glove dosimeter exposures, while between-worker and within-worker (day to day) variance explained 0.1% and 74.9% of the total skin exposure variability, respectively (Table 4).

Lack of correlation between inhalation and dermal methylene diphenyl diisocyanate exposures

To evaluate the association between potential inhalation exposures and skin exposures to MDI, we plotted inhalation versus skin exposures by day, by subject, and by job. Correlation coefficients were all < 0.3 and not significantly different from zero, suggesting a weak association between air and skin exposures among these workers (data not shown).

Comparison of estimated total inhaled and skin methylene diphenyl diisocyanate exposures

The total full-shift NCO skin and inhalation exposures were estimated for each job group, as shown in Figure 2, taking into account the total surface glove area and estimated 9.8 m^3 inhaled per shift. Estimated potential skin exposure, assuming no glove use and complete absorption, was over 250-fold higher than inhalation exposure.

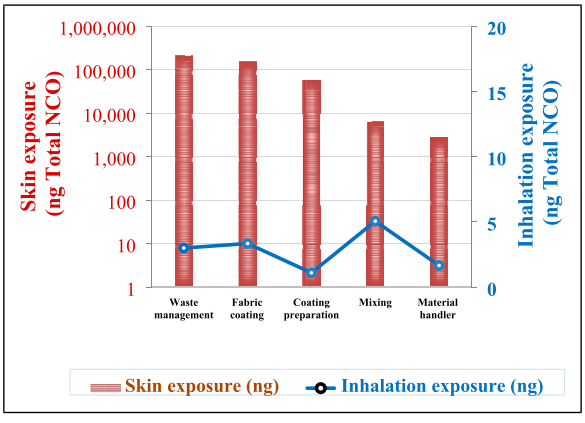

Figure 2. Estimated arithmetic mean full-shift skin and inhalation exposure to total NCO by job group. Skin and inhalation total NCO were averaged across all workers and days in the week for each job group. For inhalation exposure, 100% lung retention and 9.8 m^3 air inhaled per day were assumed. Total NCO = total reactive isocyanate group.

Discussion

In this work, we used highly sensitive and specific analytical methods to assess simultaneously inhalation and potential skin exposure to MDI isomers and higher-order oligomers in workers who produced polyurethane coated fabrics. Although both routes of exposure likely contributed to isocyanate sensitization, their relative contribution is poorly understood. The 4,4′-MDI monomer, the dominant isocyanate species identified, was identified in all personal and area airborne samples, but all values were low, well below the NIOSH 8-h TWA REL of 50 µg MDI/m^3 and the OSHA and NIOSH ceiling limits for 4,4′-MDI of 200 µg MDI/m^3 (100-fold less). Total NCO inhalational exposures were also well below the HSE 8-h TWA standard of 20 µg NCO/m^3. The 3-ring oligomer in polymeric MDI (3-ring MDI) was rarely detected in airborne samples. Using our previously validated MAP-impregnated cotton glove dosimeters, we found quantifiable levels of 4,4′-, 2,4′-, and 2,2′-MDI isomers in all glove samples, while 3-ring MDI (3-ring MDI) was detectable in 67% of the glove samples. Oligomers with more than 3 rings were not found in any of the glove or air samples. Exposures varied substantially with job groups. Estimated total NCO skin exposures were substantially greater than estimated inhalation exposures for all workers and could not be predicted based on airborne personal or area sampling.

The air sampling results in this investigation shared similarities with previous studies of MDI airborne levels in other industries that did not involve spraying of isocyanate products, such as orthopedic cast application (Pearson et al., 2013), iron foundry work (Liljelind et al., 2010), and boat building (Henriks-Eckerman et al., 2015). In the orthopedic cast applications, airborne MDI levels were below the detection limit of the method (estimated at under 0.1 ppb in air). In the study of iron foundry workers, the arithmetic mean airborne 4,4′-MDI concentration of the highest exposed group, core makers, was 0.77 µg/m^3 (GM 0.34 µg MDI/m^3 or 0.11 µg NCO/m^3), which is higher than in our study but well below the exposure limits. Airborne MDI concentrations of 0.08–0.8 µg MDI/m^3 reported for workers in boat building (Henriks-Eckerman et al., 2015) were comparable to MDI levels reported by Liljelind et al. (2010) for foundry

workers. Both were higher than our results of fabric coating workers.

The 4,4′-MDI monomer is an odorless solid with a low vapor pressure (5×10^{-6} mmHg at 25°C). MDI/pMDI formulations are dissolved in solvents and then applied to the fabric in the form of a thin liquid film, followed by fabric curing at variable temperatures on a conveyor belt that runs through an enclosed oven. Low airborne MDI concentrations in our study were presumed to be in the form of MDI vapors resulting from limited evaporation of MDI, primarily the abundant 4,4′-MDI isomer, from the fabric during curing and from handling liquid MDI. This conclusion was corroborated by comparable GMs for impingers and filters and the detection of 3-ring MDI in only 7% of personal air samples, even upon reanalysis with a more sensitive analytical method for 3-ring MDI. The greater GM of airborne total NCO for waste management relative to fabric coating workers likely reflects the practice that waste management workers frequently carried open buckets with residual materials.

Most notable, our findings demonstrated substantial potential for skin exposure given the large quantities of MDI detected on the interception glove dosimeters. The findings are consistent with our field observations of the potential for MDI exposures based on job duties/tasks. For example, the application of the liquid MDI solution by the fabric coating workers frequently involved direct hand contact with the fabric, tools, containers, and contaminated surfaces. Splashes were occasionally observed during product mixing and pouring. Waste management workers may have experienced frequent hand contact with residue MDI/pMDI formulations during the removal and disposal of such containers. The detection of 3-ring MDI in 67% of glove dosimeters, but in only 7% of air samples, is consistent with the hypothesis that skin exposure results from direct contact with the uncured liquid coating material.

To date, most studies of MDI-exposed workers have focused almost exclusively on airborne exposures. Limited studies have documented the potential for MDI skin exposure, most commonly based on qualitative assessments given the challenges of quantitating skin exposure. Petsonk et al. (2000) reported skin stains due to contact with MDI and found an association between skin stains and MDI asthma among workers in a wood production plant where air exposures were low, but the study did not include quantitative estimates of skin exposure. Liljelind et al. (2010) quantified MDI skin exposure in iron foundry workers using a tape stripping method to sample skin and reported arithmetic mean skin exposure to fingers, wrist, and forehead of core makers (the highest exposure group) ranging from 13 to 33 ng MDI/cm^2 (GM 7.6–15 ng MDI/cm^2). These values are approximately 3–10 times smaller than the values reported here for fabric coating workers, especially waste management personnel. Using the same glove dosimeter, we have documented a similarly high potential for skin exposure to MDI/pMDI in workers applying spray polyurethane foam for insulation (Bello et al., 2019).

We have previously compared side-by-side the MAP-impregnated glove dosimeter with tape striping in two MDI applications, one being in this fabric coating factory (Harari et al., 2016). The glove dosimeter, an interception technique, measured over 400 times greater isocyanate surface density (ng/cm^2) for machine operators than tape stripping, a removal technique (Harari et al., 2016). In earlier pilot work, we also found that skin wiping, another technique that has been used to sample skin, resulted in MDI levels that on average were 20 times smaller compared to tape stripping (unpublished data). These differences in sampler performance (glove dosimeter vs. tape stripping vs. wiping) most likely reflected the high chemical reactivity of MDI, which reacts quickly with skin (Bello et al., 2006; Henriks-Eckerman et al., 2015), water, and other chemicals in two-part polyurethane formulations. Thus, the use of tape stripping or wiping of skin would be expected to underestimate exposures to reactive chemicals such as MDI. These sampler comparisons illustrate the importance of considering the strengths and limitations of different approaches when selecting the optimal skin sampler and analytical technique for a particular isocyanate application.

The high levels of MDI/pMDI detected in this study using glove dosimeters should be interpreted in the context of skin protection used by the workers, such as gloves and other protective clothing. Glove dosimeter data represent actual skin exposure to hands if no gloves are worn and potential for skin exposure to hands when gloves are worn. Field observations in this workplace at the time of the study had noted bare skin, including hands, forearms, face/forehead, and neck areas for a number of workers, including material handlers. In addition to documenting hand skin exposure, the findings presented here also suggest potential

exposure of other body parts (forearms, neck, and face) to MDI.

In prior work on isocyanate permeation panel testing (Bello et al., 2019, 2020; Mellette et al., 2018) and industrial coatings in construction, we have demonstrated that thick cotton gloves provide little protection against isocyanate formulations, whereas rubber and thick nitrile gloves provide excellent protection. In addition, thick cotton gloves can act like a sponge, retaining large amounts of product trapped inside them, leading to increased potential for skin exposure. Thus, it is important to consider the personal protective equipment worn when using glove dosimeter data to assess the extent of skin exposure.

Glove dosimeter data were averaged over the whole hand. It is expected however that contaminant distribution on hands is uneven and is influenced by the task performed and other factors. In earlier work (Harari et al., 2016), we investigated the distribution of 4,4′-MDI across different anatomical parts of both hands by analyzing separately each finger, as well as the dorsal and planar side of each glove. The palmar side of the hand had more MDI contamination than the dorsal side, as did the dominant hand (often the right one) compared to the non-dominant hand, as would be expected.

Methylene diphenyl diisocyanate immune sensitization, as reflected in elevated levels of MDI-specific serum IgG (and less commonly MDI-specific IgE), has been noted in workers at this polyurethane fabric coating factory despite air levels that have been extremely low, well below regulatory limits (unpublished data). These findings, consistent with experimental findings in mice exposed to MDI via skin (Wisnewski et al., 2011), support the notion that skin exposure to MDI can contribute to sensitization. In animal studies, low level respiratory exposures following repeated skin exposure and sensitization can induce airway inflammation (Wisnewski et al., 1999, 2011). Similarly, once sensitized, individuals may have asthmatic responses at extremely low airborne exposure levels, below occupational exposure limits. Therefore, reliance on air sampling for exposure surveillance in workplaces that produce or use isocyanate products, as is the contemporary practice, may miss skin exposure and not protect workers from future disease. Isocyanate monitoring of skin exposures, in addition to airborne exposures, using LC-MS/MS quantitative methods, is warranted in work settings with potential for isocyanate skin exposure.

Methylene diphenyl diisocyanate is a very potent skin sensitizer (Hamada et al., 2017). However, quantitative relationships between the skin MDI dose and immune sensitization are poorly understood and are believed to be non-linear (Pauluhn, 2014; Pollaris et al., 2019; Wisnewski et al., 2011). In fact, higher (10%) vs lower (1%) concentrations of skin MDI exposure have been shown to induce less airway inflammation following the same airway challenge, and the degree of systemic sensitization (MDI-specific IgG) may not predict airway inflammatory responses (Wisnewski et al., 2011).

Predicting MDI immune dose-response relationships are further complicated by several uncertainties, including the extent MDI is absorbed by skin as well as the reactivity of MDI with proteins and other components of skin. Data on MDI skin absorption are very limited. MDI uptake by skin, measured via radioactive tracers, has been shown to be low in rats (Hoffmann et al., 2010). However, we are not aware of similar data in humans and other species, and there are substantial interspecies differences in skin structure and barrier function. In addition, the absorption of MDI is likely modified by the presence of solvents (such as toluene, methyl ethyl ketone, tetrahydrofuran, or N-methyl pyrrolidone), other workplace co-exposures such as irritants, and skin trauma.

Repeated MDI skin exposure is required to induce sensitization, as demonstrated in several animal models of isocyanate asthma (Hoffmann et al., 2010; Pollaris et al., 2021; Wisnewski et al., 2011). In addition to the concentration and total dose, the frequency and timing of exposure (interval between exposure) are also important determinants of sensitization, with greater number of exposures and longer intervals typically promoting stronger immune responses.

Hilton et al. (1995) have reported an EC3[1] potency of 7.5 μg MDI/cm^2 (corresponding to a 0.03% MDI formulation) based on local lymph node assays conducted in mice. In patch testing in humans, nominal concentrations of 0.1%–2% MDI in different vehicles (including petrolatum) are used (DeGroot AC, 2008), which correspond to a lower dose of 3.1 μg MDI/cm^2 skin. The maximum surface concentration of 4,4′-MDI measured on glove dosimeters in this study was at the 1 μg MDI/cm^2 surface loading, with the majority being less than the 3 μg MDI/cm^2. However, localized skin exposures to MDI at or above 3 μg MDI/cm^2, can be easily achieved in workplaces, as it has been argued in earlier work (Bello et al., 2007; Henriks-Eckerman

et al., 2015), even when the average glove concentration is less than 1 μg MDI/cm^2. A threshold of 1.0 μg MDI/cm^2 has been suggested as an acceptable MDI skin load in penetration tests based on clinical patch test data (Henriks-Eckerman et al., 2015; Mäkelä et al., 2014). Although important in providing a general guidance for establishing a benchmark for best hygiene practices, such recommendations should be interpreted with some caution and consider other important workplace variables that drive a worker's sensitization (total amount, dose/cm^2 skin, exposure frequency, timing between exposure intervals, vehicle solvent, other irritants, and skin barrier integrity). Ongoing work on this cohort of workers is assessing MDI-specific biomonitoring in plasma and urine, as well as investigating relationships between skin exposure to MDI, plasma MDI-adduct levels, and immune sensitization. In the meantime, the findings presented here, along with an extensive animal and human literature on isocyanate exposure, sensitization, and asthma, provide sufficient information to conclude that isocyanate skin exposure likely occurs in the workplace and that greater efforts are needed to minimize skin exposure.

Conclusion

Analysis of workplace samples from a modern polyurethane fabric coating production plant demonstrated the potential for substantial MDI skin exposure despite extremely low (< 1 ppb MDI) airborne levels. The study made use of a new interception-based approach for assessing skin exposure to reactive isocyanates. This approach combined a MAP-impregnated glove dosimeter, which captures and stabilizes MDI at the time of initial contact that would otherwise react with the workers' skin, with high sensitivity and specificity mass spectrometry analysis. The data demonstrated the feasibility of using the newly developed glove dosimeters to better assess the risk of skin exposure to MDI in a polyurethane fabric coating factory, which can be applied to other similar settings. These findings highlighted the potential for unrecognized dermal MDI exposures, which despite the regulation of air exposures, may result in the development of immune sensitization and asthma. The data also demonstrated the potential utility of using new interception glove dosimeters to improve workplace MDI surveillance and to evaluate the effectiveness of hygiene, safety engineering, or other exposure interventions.

Acknowledgments

Authors would like to thank Elyor Vidal, Eden Hok, and Anthony Federico for their help with sample collection and preparation. Special thanks go to Dr. Robert Streicher of NIOSH for his insightful discussions over the years on sample collection and analysis and his generous donation of important MAP and MAP-d8 reagents and MAP- and MAP-d8-isocyanate standards. Most importantly, we would like to thank all the workers that participated in the study and plant owners for granting access for this work.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical approval

Subject recruitment and consent followed procedures approved by the Institutional Review Board at Yale University and University of Massachusetts Lowell.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: The study was funded through NIOSH Grant RO1 OH009375-01.

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Note

1. EC3: concentration resulting in a stimulation index of 3 in the local lymph node assay.

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