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Assessment and control of exposures to polymeric methylene diphenyl diisocyanate (pMDI) in spray polyurethane foam applicators

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ABSTRACT

In this work we characterize personal inhalation and dermal exposures to diphenyl methane diisocyanate (MDI) and other species in polymeric MDI (pMDI) formulations during spray polyurethane foam (SPF) insulation at 14 sites in New England. We further assess the adequacy of current workplace practices and exposure controls via comparative urinary biomonitoring of the corresponding methylene diphenyl diamine (MDA) pre- and post-shift. MDI and pMDI are potent dermal and respiratory sensitizers and asthmagens, strong irritants of the skin, eyes, and the respiratory tract, and may cause skin burns. This study is the first comprehensive report to-date on the work practices, inhalation and dermal exposures to isocyanates and effectiveness of existing controls during SPF applications.

Breathing zone exposures to 4,4′ MDI (n = 31; 24 sprayers, 7 helpers) ranged from 0.9 to 123.0 μg/m3 and had a geometric mean (GM) of 13.8 μg/m3 and geometric standard deviation (GSD) of 4.8. Stationary near field area samples (n = 15) were higher than personal exposures: GM, 40.9 (GSD, 3.9) μg/m3, range 1.4–240.8 μg/m3. Sixteen percent of personal air samples and 35% of area samples exceeded the National Institute for Occupational Health and Safety's (NIOSH) full shift recommended exposure limit (REL) of 50 μg/m3, assuming zero exposure for the unsampled time. 4,4′ MDI load on the glove dosimeters had a GM of 11.4 (GSD 2.9) μg/glove pair/min, suggesting high potential for dermal exposures. Urinary MDA had a GM of 0.7 (GSD, 3.0) μmol MDA/mol creatinine (range, nd-14.5 μmol MDA/mol creatinine). Twenty-five % of urine samples exceeded the Health and Safety Executive (HSE) biological monitoring guidance value (BMGV) of 1 μmol MDA/mol creatinine. We further report on field observations regarding current exposure controls, discuss implications of these findings and opportunities for improving work practices to prevent isocyanate exposures during SPF insulation.

1. Introduction

Spray polyurethane foam (SPF) is a highly effective thermal insulation material used in numerous applications in residential and commercial construction, including internal and external wall insulation, basement and ceiling insulation, as well as flat roofing insulation. Energy conservation efforts and green building initiatives have increased the market for SPF products, which is projected to double in the next decade to reach $2.5 B globally by 2024, with the highest share (40% of total) in North America (Global Markets Insights Inc, 2017). The SPF foam is produced from the chemical reaction of two components, commonly referred as part A and part B, which are supplied at an approximate ratio of 1:1 to a spray gun nozzle. Part A is comprised of polymeric methylene diphenyl diisocyanate (pMDI), a mixture of the 4,4′-methylene diphenyl diisocyanate (4,4′-MDI), other MDI isomers (2,4′- and 2,2′-MDI) and higher oligomers of MDI (such as three ring, and four ring structures). Part B is a mixture of polyols, amine catalysts, blowing agents, flame retardants, solvents, and other proprietary additives (Bello et al., 2018; Marlow et al., 2014; Lesage et al., 2007). The exothermic reaction between the isocyanates in part A and polyols in part B is accelerated by the amine catalysts and other additives in part B. Polymerization reaction starts immediately upon mixing of the two components. The foam expands, solidifies and cures within 2–48 h post-application, depending on the product type. In this paper, the term isocyanates has been used exclusively to mean pMDI or any of its components, such as MDI isomers, unless otherwise specified.

The growing use of SPF for insulation has been associated with growing concerns related to the adverse health effects of ingredients comprising these mixtures, including isocyanates (Huang and Tsuang, 2014; NIOSH, 2004) (Redlich, 2013). Isocyanates are well-known

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Table 1
Summary description of spray polyurethane foam (SPF) sampling sites, personal protective equipment used, and samples collected.

Sites	Number of sampling sites	Activity	Tasks performed	Type of foam	PPE used	Number of samples			
						Area, air	Personal, air	Gloves[a]	Urine[b]
New construction (Single family homes and new additions)	3	SPF insulation of walls, ceilings, and basements	SPF spraying with a spray gun; foam shaving against studs with a powered blade saw; spray gun cleaning; site cleaning	Open and closed cell	SAR[3] 3mil thin nitrile gloves Disposable coveralls	6	7	7	14
Existing construction (Single family homes and a nursing home)	7	SPF insulation of basements, attics, & ceilings of existing homes; attic in a nursing home	SPF spraying, foam cutting or trimming was not performed; gun cleaning; site cleaning (removal and disposal of foam waste)	Open and closed cell	Full face OVC[4] SARs were used at the nursing home Nitrile, nitrile covered cotton, latex gloves Disposable coveralls	8	15	13	34
Training Center Demo SPF application on a new outdoor garage	3[5]	SPF insulation of walls and floor of a new garage	SPF spraying with a spray gun; Foam cutting or trimming was not done	Closed cell foam/ walls; roofing SPF product/floor	Sprayers: SAR, coveralls, nitrile gloves Trainees/Bystanders: ½-face piece with OVC cartridge	6	10	16	42
One bedroom apartment at an elderly housing complex	1	Foam Injection	Drill holes on the wall; SPF injection on the window walls of two bedrooms; excess foam removal; gun cleaning	Closed cell	Full face OVC Nitrile gloves Disposable coverall	2	1	1	2
Total	14	*53% of participants used SAR; 45% OVC (full and 1/2 face); 82% nitrile gloves; 12% nitrile coated cotton gloves; 4% latex gloves; 98% coveralls; 100% goggles* [6]				22	33	37	92

[a] Each sample includes a pair of gloves.
[b] Pre- and post-shift urine samples; [3]SAR, supplied air respirator;[4] OVC, organic vapor cartridge without particulate filters;[5] Three trips at the training center, each demonstrating a different product with different groups of trainees. For all other field trips, one trip corresponds to one site.[6] Bystanders (n = 4) are excluded from the PPE statistics.

potent respiratory sensitizers and have one of the lowest occupational exposure limits ever established (5 parts per billion or ppb; 50 μg/m^3). They continue to be a leading cause of occupational asthma in industrial countries (Malo J-L and M. 2009; Redlich et al., 2007; Lockey et al., 2015). Once sensitized, individuals could respond to extremely low levels of airborne isocyanates. Workers with isocyanate asthma often have to give up their jobs, their prognosis of recovery remains poor, and they suffer economically due to limited reemployment options. Skin exposure to isocyanates causes irritant and allergic contact dermatitis, skin burns, and skin irritation (Geier et al., 2018; Goossens et al., 2002). A number of studies have shown that skin exposure to isocyanates is an effective route for inducing systemic sensitization in animals, and this pathway is considered plausible in humans (Bello et al., 2007; Redlich, 2010; Wisnewski et al., 2011; Henriks-Eckerman et al., 2015). Other health concerns of isocyanate exposures relate to upper airway irritation, burning eyes, and hypersensitivity pneumonitis, an inflammatory condition of the deep airways (Lockey et al., 2015; Wisnewski et al., 2006).

Spray foam insulation workers are exposed to pMDI ingredients, including 4,4′-MDI, its isomers (2,4′-MDI, and 2,2′-MDI), and other isocyanate species through inhalation of aerosols and, to a lesser extent, inhalation of vapors. Although MDI has a low vapor pressure at room temperature (5×10^{-6} mm Hg at 25 °C), heat produced during the exothermic reaction can enhance evaporation of free, unbound MDI species, and the potential for exposure to their vapors and condensation aerosols. Dermal exposure has been shown to be an important exposure pathway for MDI in the workplace (Jones et al., 2017; Liljelind et al., 2010). For chemicals that can enter the body via multiple pathways such as isocyanates, biomonitoring is particularly helpful in assessing exposure levels in the workplace because it takes into account all exposure pathways. Biomonitoring is also important in evaluating the effectiveness of protective clothing and respirators used in the workplace. The diamine 4,4′-methylenedianiline (4,4′-MDA), the only established urinary biomarker for MDI/pMDI to-date, has been shown in previous studies to be a sufficiently sensitive urinary biomarker for documenting cross-shift changes in urinary MDI exposure levels (Budnik et al., 2011; Creely et al., 2006; Sabbioni et al., 2007).

Currently, there are an estimated 60,000 insulation workers in the US (U.S. Bureau of Labor Statistics, 2018). A large number of insulation workers using the resin systems are self-employed or work for small contractors. During the construction slowdown period (2009–2012), carpenters, electricians, and workers from other trades, became SPF applicators with little training (Kavanaugh, 2016). Self-employed workers and small contractors often lack dedicated health and safety expertise and resources and may experience higher occupational exposures and disease risk. Despite these well-known risks associated with isocyanates, there are limited published quantitative data on personal airborne isocyanate exposures among SPF insulation workers, no quantitative data on dermal exposures during SPF, and little quantitative information on the adequacy of work practices and controls employed to reduce these exposures. The main objectives of this study were to (i) conduct a comprehensive evaluation of work practices among the SPF applicators; (ii) assess their inhalation and dermal exposures to pMDI; and (iii) assess effectiveness of controls via comparative pre- and post-shift urinary biomonitoring. Results of this work can help guide health and safety practitioners and workers on improving work practices and implementing more effective exposure controls.

2. Methods

2.1. Sampling sites and participants

Workplace sampling was performed during a two-year period in 2015 and 2016. During the course of the study we conducted sampling during 14 trips at 12 distinct SPF insulation sites in New England, which included one major training and distribution center. We recruited a total of 54 study participants, 41 of whom were sprayers, 9 helpers, and 4 bystanders. The majority of study participants were white males, 25% were Hispanics, and 3% were from the Pacific Islands. Everyone signed an informed consent form describing the study, which was approved by the Institutional Review Board of UMASS Lowell.

Workplace observations recorded contextual information on tasks/activities and their duration, type of products and manufacturer, number of workers, location, ventilation status, dimensions of the rooms, types of personal protective equipment for inhalation and dermal exposure and their use, and any other engineering controls. Our partner contractors were grouped into two categories: a) large contractors performing SPF insulation in new construction projects; and b) small contractors working on insulation of existing homes (Table 1).

The large insulation contractors employed an environmental health and safety professional (sometime a team of two specialists) and all study participants reported that they had completed SPF-specific health and safety trainings, consistently relied on supplied air respirators (SAR), high density polypropylene or Tyvek coveralls and thin nitrile gloves, and were particularly attentive to avoid having exposed skin during spraying. Dimensions of the rooms at study sites varied from one site to another, but in general they were large spaces and often without any installed doors. Windows were sealed with plastic covers and forced ventilation was applied at every site using sets of fans that supplied fresh outside air in from one side and exhausted the indoor air out on the other side (Fig. 1 A).

Small contractors were crews of 2–3 workers, mostly immigrants who spoke little English, and who had not received formal health and safety training. During SPF spraying they used organic vapor cartridge (OVC) respirators without particulate filters, breathable polypropylene coveralls, and a variety of glove types, such as thin nitrile, nitrile covered cotton gloves, or latex gloves. Retrofit insulation of the existing homes was done on attic walls, ceilings, basements, and garages. Dimensions of rooms were in general smaller compared to the new construction projects. At one site, workers performed basement ceiling insulation in very tight spaces. Ventilation was performed with exhaust fans, which were used at most sites (Fig. 1 C, D).

At the training center we conducted three trips, each demonstrating a different product/process (e.g. roofing and general insulation of walls) with different groups of study participants. The apprentice workers

Fig. 1. Representative, illustrative pictures of insulation workers investigated in this study. A: SPF spraying (sprayer and helper) of a new construction home by a large contractor; B: Training on SPF application at a training center (new garage); C: Insulation of the 1st floor of an existing home by a small contractor; D: Insulation of the basement of an existing home by another small contractor.

participated in hands-on practice training that involved spraying of the side walls or the floor of a new garage (Fig. 1 B). Training was led by experienced applicators who demonstrated best practices to apprentices, supervised each sprayer for a period of 15–30 min and provided feedback to them on improving their spraying techniques. The rest of the apprentice group observed about 2–3 m away from the sprayer. During SPF spraying, both the trainer and the sprayer used SAR respirators, while the apprentices used half-face OVC without particular filters. Everyone wore Tyvek coveralls and nitrile gloves.

Exposure measurements were also conducted during foam injection at a one-bedroom apartment inside an elderly residential complex. The foam injection technique differed considerably from spraying in that the foam was injected inside existing drywall through pre-drilled 1 cm diameter holes without tearing down the walls or disturbing existing drywall structure. To prepare the site, the worker opened a number holes at predetermined locations on the wall. The product was then injected inside the holes and small amounts of excess foam resulting after injection were cut and removed. The room was not ventilated but the windows were kept slightly open. The worker wore a half-face OVC without particulate filters, tyvek coveralls, and nitrile gloves.

2.2. SPF activities and products

Insulation at each site was performed mostly by a crew of 2 workers (a sprayer and a helper). Bigger spray jobs sometimes involved a second crew. The main SPF insulation tasks consisted of site preparation (establishing a tarp containment, sealing windows, doors, establishing active space ventilation, setting up the compressed air lines for SARs and SPF hoses, assembling spray guns), spraying of SPF, shaving/cutting of excess foam, and site cleanup, including removal of foam debris. Sprayers performed spraying of the product using spray guns, often stopping to re-position the hoses or unclog and clean the gun. Helpers were responsible for cutting the excess foam flat against the studs using saw blades and assisting the sprayer in a variety of ways (checking drums of raw materials, relocating supply foam lines and supplied air hoses, repositioning the ladder, etc.). Site preparation activities constituted a large part of the workday in most sites. On average, spraying of a full drum of part A and part B lasted around 2 h. In most sites, including retrofits and new add-on construction, active spraying lasted no longer than 2 h. In one large construction project, a three-story tall mansion, spraying continued for several days with six to 8 h/day of active spraying.

Products used at the SPF sites consisted of open and/or closed cell SPF foam. At the training center, a roofing formulation was used to demonstrate roofing applications. Composition of Part A was always based on pMDI, whereas part B was much more variable across the three types of foams (supplementary material, Table S2).

2.3. Exposure measurements

Exposure assessment strategy was based on simultaneous personal airborne and dermal exposure sampling, with concomitant pre- and post-shift shift urine biomonitoring. Air monitoring targeted personal breathing zone exposures (PBZ) of sprayers and helpers outside their respirators. Potential bystander exposures were assessed through stationary area samples located in the near field (3–6 m distance from sprayers depending on site geometry and with input from the safety engineer, site manager or the sprayer).

2.3.1. Personal breathing zone (PBZ) exposures

For personal sampling of isocyanates, we used a recently developed personal sampler CIP10MI (Arelco, Fontenay-Sous-Bios Cedex, France) which has been validated for measuring isocyanate aerosols during SPF applications (Puscasu et al. 2014, 2015). The CIP10MI collects the aerosol inside a sampling cup that rotates at ~6700 rpm inducing an air flow of 10 L/min. The rotation speed of the CIP10MI was measured prior to sampling in the field using a 6236 SI tachometer. Prior to sampling, the cup was filled with 2 mL of 1 mM MAP in butyl benzoate. The liquid media inside the cup is distributed into a thin film as a result of the high centrifugal force, which prevents the solvent from spilling, even when the sampler is turned upside down. This sampling method enables workers to move freely when performing daily tasks (Fig. 1). Personal sampling times for all PBZ samples collected (n = 31) had a median of 70 min (range 10–231 min), depending on task duration and workers' preference, and in all cases lasted either for the duration of spraying tasks or until the first set of drums was finished. Of all PBZ samples, 31 were collected among helpers and sprayers, one on a bystander at the nursing home, and one on the worker performing the foam injection. At the end of the sampling period, the liquid media was transferred into clean amber glass vials with disposable lab grade polypropylene pipettes and stored and transported to the lab in coolers with ice packs. In the lab, samples were stored at −20 °C until they were ready for processing and analysis (please refer to the chemical analysis details in the supplementary material section).

2.3.2. Area sampling

Stationary area sampling was conducted using a spill proof impinger-filter sampling train, the gold standard for aromatic isocyanate systems, according to the standard National Institute for Occupational Safety and Health (NIOSH, 2003). Impingers were filled with 15 mL of 0.1 mM MAP in butyl benzoate followed by a 13-mm MAP-impregnated glass fiber filter (500 μg MAP/filter), to collect any smaller particles that would break through the impinger. The backup filters were assembled inside a pre-cleaned delrin cassette connected in line with an impinger and pump, and pre-calibrated at 1 L/min. The backup filter was transferred in the field inside the impinger solution for a single sample and transported in the laboratory for further processing. Near field stationary area samples (n = 15) were placed in tripods at breathing zone height (~1.7 m above the floor level) inside the room. The distance of spraying from the near field area samples changed (range 3–6 m) as sprayers moved around the room. Additional outdoor area samples (n = 5) were collected at different points outside the spraying room such as at the end of exhaust vent line, outside the basement window, and inside the truck with SPF products. The duration of stationary area samples had a median of 114 min, and a range of 36–247 min. At the end of sampling, the liquid sampling media was transferred into a 20 mL pre-cleaned glass vial, sealed, stored and transported as the other PBZ samples described above (please refer to the chemical analysis details in the supplementary material section).

2.3.3. Dermal exposure sampling

Potential skin exposure was measured for both hands with a validated interception method that consisted of thin medical grade cotton gloves impregnated with the derivatizing MAP reagent, worn over a thin nitrile glove, as previously described by our group (Harari et al., 2016). The glove dosimeter (the pair of MAP-impregnated cotton glove and thin nitrile glove) was worn by the workers during sampling instead of their normal gloves. For the remainder of their workday, workers would continue to wear their own gloves, as summarized in later sections. At the end of sampling, both cotton glove dosimeters were transferred into a 100 mL capacity glass jar containing 50 mL of 50 mM MAP in ethyl acetate and shaken to ensure gloves were soaked in the solvent. Ethyl acetate was used as a solvent substitute for the more toxic acetonitrile (or methylene chloride). The jars, capped with a PTFE lid, were stored and transported to the lab in coolers with ice packs. When in the lab, another 50 mL ethyl acetate was added to the jar to improve extraction efficiency and jars were stored at −20 °C until ready for chemical analysis. Among all participants, 37 consented to wearing the glove dosimeter. Duration of glove sampling had a median of 40 min (range of 8–123 min) depending on the task duration and workers' preference for using the gloves. For the majority of samples, gloves were collected at the end of the spraying task.

2.3.4. Urine specimen collection

Spot urine samples were collected in sterile urine specimen collection cups at the beginning of the work shift and at the end of the task or work shift, with exact times depending on work schedules and worker availability. A total of 92 urine samples were collected: 45 were pre-shift and 47 post-shift. The time interval between pre- and post-shift urine collection had a median of 190 min (range 70–330 min). The shorter pre-to post-shift time intervals belonged to a small SPF job (outside garage sealing) at one site where workers left shortly after the end of spraying. After collection, urine samples were stored inside coolers with ice packs and, at the end of sampling, were transported to the lab and stored at −80 °C until further processing.

Among the 54 study participants, 33 consented to and wore personal air samplers (31 sprayers and helpers, one bystander and one foam injection worker); 37 wore the glove dosimeters; 45 provided pre-shift urine samples; and 47 provided post-shift urine. There were 43 matched pairs of pre- and post-shift urine samples for analysis. Twenty-six workers provided matched air, glove, and urine samples.

2.4. Sample processing and chemical analysis

Air samples: Samples were allowed to warm to room temperature, vortexed for 1 min, diluted 100–1000 times in acetonitrile, spiked with 10 µL of the corresponding internal standard (IS) cocktail (d8-MAP derivatives of 4,4′-MDI and phenyl isocyanate, PhI, final 100 ng/mL each), filtered through a 0.45 µm Acrodisc® filter, and analyzed by liquid chromatography-electrospray ionization-tandem mass spectrometry in the positive electrospray ionization mode (LC-ESI-MS/MS) as described in our previous work (Bello and R.P. Streicher, 2013; Mellette et al., 2018).

Glove samples: Jars containing gloves were shaken for 5 min to homogenize the sample and then sonicated for 30 min in a water bath. Then a 1 mL sample aliquot was taken from the jar, diluted 100–1000 times in acetonitrile, spiked with the internal standard (IS) cocktail as with the air samples, and filtered through two consecutive 0.25 µm filters into a 2 mL amber LC vial to remove cotton fibers and foam particles, followed by LC-ESI-MS/MS analysis. Further information about sample analysis (chromatographic conditions, MRMs, and MS optimization parameters) are provided in the methods section of the supplementary material and Table S1. The limit of detection for isocyanate species was (ng/mL): PhI, 0.025; 4,4′-MDI, 0.025; 2,4′- and 2,2′-MDI, 0.003; and MDI trimer, 0.2 ng/mL. These LODs are nearly identical to those reported in Harari et al. (2016), except for the MDI trimer, which has much better sensitivity due to further optimization of source parameters and instrument tuning.

Urine samples: After thawing in a temperature controlled water bath at 37 °C, the urine was centrifuged at 1000 rpm for 10 min to remove any cellular debris. Urine specific gravity was measured with a hand held digital pocket refractometer (PAL -10S Atago, Japan). Urine creatinine concentration was measured with LC-ESI-MS/MS according to the method of (Hou et al., 2012) with d_3-creatinine (25 ng/mL final concentration) as the internal standard, described in details in the supplementary material section.

For MDA analysis, 1 mL urine was acid hydrolyzed with sulfuric acid and processed according to a previously published method (Marand et al., 2004) with d_2-MDA as the internal standard (IS, 100 ng/mL) and 1,7-heptanediamine a s secondary IS, with the only modification that pentafluoropropionic acid anhydride (PFPA) was substituted with 0.1% benzoyl anhydride in toluene to improve extraction efficiency, analyte chromatographic retention, and sensitivity in MRM (supplemental material, Figs. S2 and S3). The final sample volume of 250 µL in methanol was analyzed by LC-ESI-MS/MS, monitoring the MRM transitions of the N,N'-(methylenebis(4,1-phenylene) dibenzamide and its corresponding IS (with d2-MDA), respectively (407.4 → 105.4; IS, 409.4 → 105.2; supplementary material, Table S1 and Fig. S3).

Quality control measures included running urine blanks, spikes, blind samples, replicates, conducting recovery studies, and secondary blind analyses of subsets of samples. The absolute recovery of MDA (without IS correction) over the 1–100 ng/mL spike range (1, 10, 100 ng/mL; n = 3 each level) in urine blanks with no detectable MDA in it, was 75.9%, 82.1% and 86.6% (standard deviation 7.4, 5.9, 4.6%), respectively. Recovery, corrected with the IS, varied between 87.2% and 96.5%. The limit of detection for N,N'-(methylenebis(4,1-phenylene) dibenzamide was 125 pg/mL urine. Calibration curve was linear over the 1–500 ng/mL, with an R^2 of 0.999. Reproducibility from independent urine aliquots was satisfactory, with a relative standard deviation (RSD) of 5–7% (Fig. S1). Agreement between two sets of independent runs (n = 19, yielded a slope coefficient of 0.99, R^2 = 0.80) and an average RSD of 20%. Detailed information about the LC-ESI-MS/MS method setup, including multiple reaction monitoring (MRM) transitions, is provided in the supplementary material section (supplementary material, Table S1).

2.5. Statistical analysis

Statistical analyses were performed using the SAS software (9.4 SAS Institute Inc. Cary, NC). Isocyanate concentrations in air, gloves, and urinary MDA biomarker data were examined for the underlying distribution using the Shapiro-Wilks statistic and by graphing probability plots and histograms. Log transformed data were used for statistical tests. Descriptive statistics, including geometric mean (GM), geometric standard deviations (GSD), range, median, and inter-quartiles, were generated for all isocyanate species measured in PBZ and gloves samples, as well as for pre- and post-shift urinary biomarker. Isocyanate loading on gloves, measured as µg isocyanate/pair, was standardized to a 1 min duration to account for different sampling times across samples. All air and dermal samples were above the limit of detection of the method for three MDI isomers and phenyl isocyanate, primarily because of the high sensitivity of the analytical method. Only three samples (one personal air and two gloves) had undetectable levels of the MDI trimer. In addition, urinary MDA was detectable in all but three urine samples. The undetectable MDA levels correspond to one sprayer at the training center (pre- and post-shift) who had less than one-month experience in the industry and one pre-shift sample collected from a helper who had just started working as an insulation worker. Due to the small percentage of non-detectable samples (< 3%), for statistical analysis samples below LOD were substituted with the LOD/√2 (Croghan and Egeghy, 2003). Personal 4,4′-MDI exposures were compared with the NIOSH REL of 50 µg/m^3 by calculating the 10-h TWA concentrations assuming zero exposures for the unsampled time and a ceiling limit of 200 µg/m^3 (NIOSH and OSHA). Similarity, TNCO exposures were compared with the Health and Safety Executive (UK HSE) 8-h TWA standard of 20 µg NCO/m^3 (Cocker et al., 2011; Bello et al., 2004), assuming zero exposures for the unsampled time.

Linear mixed effects models were used to investigate the PBZ and dermal exposure difference among sprayers and helpers, using site ID as a random effect. For the purpose of exposure data analysis, the worker was classified as a 'sprayer' even if he performed spraying for a small portion of the day. In the paper, variables 'task' and 'job' are used interchangeably. Results of SPF spraying and injection were not compared statistically due to the limited number of samples collected during foam injection. Similarity, we investigated the association of exposures by the type of foam product used (open cell, closed cell and roofing formulation), and site activity (training center, new homes, retrofit homes).

Concentrations of MDA in urine were normalized to both creatinine and specific gravity (SG) to adjust for different hydration rates of individual workers. Paired t-tests on log-transformed data were used to examine the pre- and post -shift differences on urinary MDA normalized to creatinine (µmol MDA/mol creatinine) and specific gravity (ng/mL). In addition, univariate and multivariate linear regression models were

run to investigate the effect of inhalation and dermal exposures (26 workers provided matched air, glove and post-shift urine samples) on the post-shift urinary MDA levels (dependent variable). Three different models were run: (i) MDA was normalized to creatinine; (ii) MDA was normalized to specific gravity; and (iii) creatinine was included in the model as a separate independent variable (Barr et al., 2005). We further investigated the influence of task (sprayer, helper), type of SPF foam (open cell, closed cell and roofing formulation) and respirator (SAR, OVC) on post-shift urinary MDA levels.

3. Results

3.1. Personal protective equipment

Field observation data summarized in Table 1 indicate that during spraying insulation tasks 53% of SPF applicators (the large contractors) wore air purifying supplied air respirators (SARs); 45% (the small contractors) wore full-face and half-face OVC respirators without particulate filters. The bystanders, including on site safety engineers and EHS personnel, would occasionally wear an OVC respirator without particulate filters when entering the site. All workers removed the respirators during lunch breaks and at the end of spraying, while still inside the spray space. Among all participants, 82% wore disposable thin blue nitrile gloves, 12% wore nitrile coated cotton gloves and 4% used latex gloves. One helper did not wear a respirator and another one did not wear gloves at the retrofitting sites. All but one wore disposable coveralls and all wore goggles to protect against SPF overspray particles and dust.

3.2. Personal breathing zone (PBZ) exposures

Results from PBZ samples among sprayers and helpers (n = 31) indicate high exposure variability among workers at different sites (Table 2). The highest airborne concentrations were found for 4,4′-MDI, with an overall GM of 13.8 (GSD 4.8) μg/m^3. The MDI trimer exposure distribution had a GM 6.6 (GSD 8.4) μg/m^3. The lowest exposure levels were measured, as expected, for 2,4′-MDI, 2,2′-MDI, and phenyl isocyanate (PhI). Sprayers had higher 4,4′-MDI exposures compared to helpers (GM 19.6 vs. 7.5 μg/m^3, respectively), although the difference was not statistically significant (p = 0.08) (Supplementary Material Fig. S4). We did not find a statistically significant difference on PBZ breathing zone concentration by activity and foam type (p = 0.48 and 0.89, respectively). All PBZ samples were below the OSHA ceiling limit of 200 μg/m^3 for 4,4′-MDI. However, 16% of samples exceeded the NIOSH 10-hr time weighted average (TWA) recommended exposure limit (REL) of 50 μg/m^3, assuming zero exposure for the unsampled time. The highest measured 4,4′-MDI concentration of 123 μg/m^3 was 2.5 fold higher than the NIOSH REL and it corresponds to a sprayer during SPF insulation in the basement of a new home with a closed cell foam product. It should be noted that personal exposures reported here represent exposures measured outside the respirators. The estimated total isocyanate group (TNCO) concentrations, calculated based on the measured isocyanate species, not the true total NCO (Bello and Streicher, 2013; Streicher et al., 2006; Bello et al., 2004; Puscasu et al., 2016), were higher among the sprayers compared to helpers (GM 16.4 vs. 6.9 μg NCO/m^3). Overall, TNCO exposures were higher than the United Kingdom Health and Safety Executive (UK HSE) 8 h TWA standard of 20 μg NCO/m^3 (Bello et al., 2004) for 36% of the samples and higher than the 10 min Ceiling limit of 70 μg NCO/m^3 for 13% of the samples. The PBZ sample collected on the bystander (EHS manager) at the nursing home showed non-detectable levels for all isocyanate species. This sample was collected for 45 min, however the manager was present in the attic during SPF application for only 5 min.

3.3. Stationary area sampling results

Area samples collected indoors (n = 15, near field) and outdoors (n = 5) are summarized in Table 3. Thirty-five % of area samples exceeded the NIOSH REL of 50 μg/m^3 for 4,4′-MDI, assuming zero exposure for the unsampled time. The highest 4,4′-MDI concentration of 240 μg/m^3 corresponds to a stationary sample inside the basement of a new home. This sample also relates to the highest phenyl isocyanate concentration of 1536 μg/m^3, an outlier value compared to all other samples (0.02–85.6 μg/m^3). Similarly, an unusually high MDI trimer concentration (437.3 μg/m^3) was measured at another new home. We have no clear explanation for these much higher values of phenyl isocyanate and MDI trimer, except that they may reflect the tight spaces and high volume spraying. All area samples had detectable levels of all isocyanate species. Near field isocyanate exposures varied across different sites with the highest levels measured at the training center (p = 0.05), followed by new homes and retrofit insulation of existing homes (Fig. 2). Outdoor samples located at different points (a sample near a basement window, a sample at the end of an exhaust vent line, a sample 4 m downwind of the outdoor garage at the training center and two samples inside two different trucks with SPF products) were all positive for isocyanates (Table 3). Such isocyanate emissions may present problems for sensitive members of the community.

3.4. Glove dosimeter results

Potential isocyanate dermal exposures, as measured with the glove dosimeters (n = 37), are summarized in Table 4. The amount of 4,4′-MDI deposited on glove samples varied from 2 to 152.5 μg/pair/min with a GM of 11.4 (GSD 2.9) μg/pair/min. Similar to air samples, concentrations of the other isocyanates species were much lower than those of 4,4′-MDI. Gloves of sprayers had statistically significant (p = 0.05) higher 4,4′-MDI loads compared to helpers (supplementary material, Fig. S5). However, glove loading did not change significantly between different foam types and activities (p = 0.7 and 0.11, respectively).

3.5. Biomonitoring results

Urinary MDA was detected in 97% (n = 92) of all urine samples of

Table 2
Personal breathing zone (PBZ) airborne concentrations of isocyanate species of spray polyurethane foam (SPF) insulation workers.

Isocyanate species	Personal air concentrations (μg/m^3)					
	All samples (n = 31)		Sprayers (n = 24)		Helpers (n = 7)	
	GM (GSD)	Range[2]	GM (GSD)	Range	GM (GSD)	Range
4,4′-MDI	13.8 (4.8)	0.80–123.0	19.6 (4.1)	0.90–123.0	7.5 (3.5)	0.80–42.2
2,4′-MDI	1.4 (5.0)	0.04–12.7	2.2 (3.4)	0.11–12.7	0.5 (4.8)	0.04–0.35
2,2′-MDI	0.1 (8.5)	< 0.01–180.2	0.2 (7.2)	< 0.01–180.2	0.1 (20.4)	0.01–79.5
MDI Trimer	6.6 (8.4)	< 0.01–672.9	8.5 (7.4)	< 0.01–672.9	5.8 (5.8)	0.16–32.6
Phenyl Isocyanate	0.7 (21)	< 0.01–465.9	0.7 (26.9)	< 0.01–465.9	1.3 (6.3)	0.05–17.3
Sum of species as total NCO	11.6 (6)	< 0.09–253.7	16.4 (5.0)	< 0.09–253.7	6.9 (4.7)	0.34–44.6

Table 3
Concentration of isocyanate species (μg/m^3) measured from stationary area samples at the SPF sampling sites.

Isocyanate species	Inside area (near field) exposures [a] (μg/m^3) (n = 15)		Outside area exposures [a] (μg/m^3) (n = 5)	
	GM (GSD)	Range	GM (GSD)	Range
4,4′-MDI	40.9 (3.9)	1.4–240.8	0.38 (16.5)	0.01–27.0
2,4′-MDI	4.2 (4.0)	0.2–28.4	0.08 (9.8)	0.02–4.2
2,2′-MDI	0.3 (3.8)	0.01–2.6	0.01 (6.0)	< 0.01–2.6
Phenyl Isocyanate	4.3 (15.5)	0.1–1536.4	0.14 (6.5)	0.02–2.4
Trimer	14.5 (6.3)	0.5–437.2	0.08 (14.2)	< 0.01–4.34
Sum of species as total NCO (TNCO)	38.9 (3.4)	3.2–579.1	0.57 (6.6)	0.09–12.0

[a] Samples (n = 15) were collected in the near field of sprayers (3–6 m away), inside the rooms where spraying took place.[2] Outdoor samples (n = 5) included a sample located near the basement window, a sample at the end of an exhaust vent line, a sample located 4 m downwind of the outdoor garage at the training center, and two samples inside two different SPF trucks. All area samples had detectable levels of isocyanate species, raising concerns over community exposures to MDI during SPF. Sampling duration ranged from 36 to 247 min (median = 114 min).

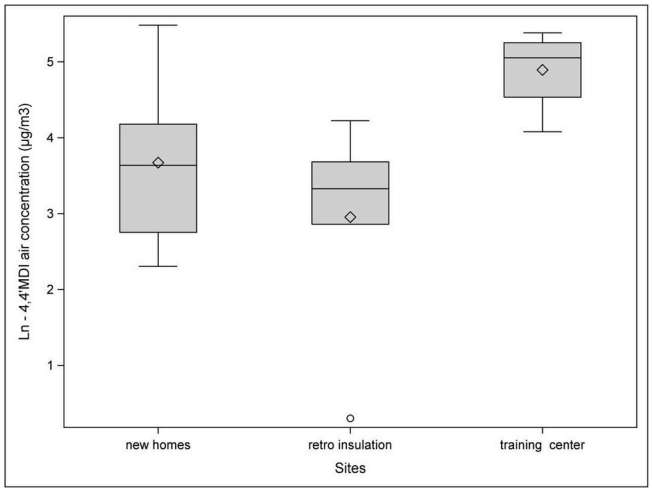

Fig. 2. Concentrations of 4,4′-MDI (μg/m^3) in stationary area samples collected indoors at different sites: new homes (n = 6); existing homes or retro insulation (n = 8); training center (n = 6)[1].[1]Concentrations of 4,4′-MDI in indoor area samples were significantly higher at the training center (p-value = 0.05), which we believe to be related to aerosol downwind drifting. Legend: Summary statistics presented by the boxplots: whiskers represent the 5th (lower) and 95th (upper) percentile of the distribution; box represents the 25th (lower edge), 50th (median, middle line), 75th (upper edge) percentile of the distribution; the diamond represents the arithmetic mean; circles represent outliers.

spray foam insulation workers collected pre-and post-shift. Descriptive statistics for urinary MDA normalized to creatinine and specific gravity (SG) are presented in Table 5. The UK Health and Safety Executive has established a Biological Monitoring Guidance Value (BMGV) for urinary MDA of 1 μmol MDA/mol creatinine (Jones et al., 2017). There is also a German Deutsche Forschungsgemeinschaft (DGF) biological tolerance value (BAT) of 10 μg/g creatinine (5.7 μmol MDA/mol creatinine) as well as a French BMGV of 5 μg/g creatinine (2.8 μmol MDA/mol creatinine) (Robert et al., 2007). Urinary MDA concentrations greater than the BMGV value reflect potential occupational exposures and inadequate hygiene practices. Overall, 25% of urine samples (pre- and post-shift) exceeded the HSE BMGV for MDI in urine (supplementary material, Figure S6), 5.4% of samples exceeded the French BMGV, and 2.2% were higher than German BAT value. The distributions of creatinine normalized urinary MDA concentrations were not significantly different between pre- and post-shift (p = 0.90) (supplementary material, Fig. S7). The highest MDA level of 14.5 μmol MDA/mol creatinine belonged to the post-shift urine sample of a trainee at the training center. This worker performed spraying for 15 min and was a bystander at the site for 2 h while other trainees were spraying nearby. In contrast, the post-shift *SG* normalized MDA were higher than pre-shift (GM 2.5 vs 2.0 ng/mL), although this difference was not statistically significant (p = 0.19). The dependence of urinary MDA distributions on the normalization procedure reflects the cross-shift increase in the urinary excretion rates of creatinine. Post-shift urinary creatinine concentrations were significantly higher (p = 0.03) than pre-shift values, while the SG values pre- and post-shift were not significantly different (p = 0.30). About 13% of pre-shift and 27% of post-shift urine samples (supplementary material, Fig. S8) had creatinine concentrations above the World Health Organization (WHO) upper normal guidance value of 300 mg/dL for workplace biomonitoring (World Health Organization, 1996).

Workers using OVC respirators (without particulate filters) had higher post-shift MDA compared to workers using SAR, although the difference was not statistically significant (p = 0.23) (Fig. 3). Moreover, post-shift urinary MDA levels among sprayers and helpers were not significantly different (p = 0.83) (Fig. 4). Trainees at the training

Table 4
Potential exposure of hands to isocyanate species in glove samples normalized per minute of spraying (μg/glove pair/min).

Isocyanate species	Glove concentrations (μg/glove pair/min)					
	All samples (n = 37)[a]		Sprayers (n = 31)		Helpers (n = 6)	
	GM (GSD)	Range	GM (GSD)	Range	GM (GSD)	Range
4,4′-MDI	11.4 (2.9)	2.0–152.5	13.3 (2.8)	2.1–152.5	4.8 (2.4)	2.0–19.7
2,4′-MDI	1.5 (4.5)	0.02–12.6	1.9 (3.6)	0.02–12.6	0.8 (1.9)	0.3–2.3
2,2′-MDI	0.3 (3.6)	0.03–14.6	0.3 (2.8)	0.03–2.6	0.2 (9.0)	0.4–14.6
MDI trimer	2.2 (7.4)	< 0.01–51.1	2.2 (8.6)	< 0.01–51.1	2.6 (3.2)	0.3–6.4
Phenyl isocyanate	0.1 (8.9)	0.01–17.1	0.1(9.7)	0.01–17.1	0.2 (5.2)	0.03–2.1
Sum of species as total NCO (TNCO)	6.7 (2.6)	1.0–72.5	7.2 (2.8)	1.0–72.5	4.4 (1.6)	2.1–8.3

[a] Samples include sprayers and helpers who provided their gloves at the end of the task. The foam injection site has been excluded from this analysis. The three MDI isomers and phenyl isocyanate were above the limit of detection for all glove samples. Only two samples collected at the training center had undetectable levels of the MDI trimer. Sampling duration ranged from 8 to 123 min (median 40 min).

Table 5
Changes in the urinary biomarker 4,4′-methylene diphenyl diamine ((MDA) normalized to creatinine and specific gravity, as well as creatinine and specific gravity, in spray polyuretheane foam (SPF) insulation workers (sprayers, helpers, and bystanders).

Urinary biomarkers	Pre-shift (n = 45)		Post-shift (n = 47)		Paired t -test for pre -and post-shift values
	GM (GSD)	Range [a]	GM (GSD)	Range	p-value
MDA normalized to creatinine (μmol MDA/mol creatinine)	0.7 (3.4)	nd - 7.1	0.7 (2.8)	nd-14.5	0.90
MDA normalized to specific gravity (ng/mL)	2.0 (3.3)	nd-8.2	2.5 (2.4)	nd-12.3	0.19
Creatinine (mmol/L)	15.2 (1.8)	2.5–36.8	19.8 (1.8)	3.3–57.5	0.02
Specific gravity (g/L)	1.02 (1.0)	1.00–1.03	1.02 (1.0)	1.00–1.04	0.30

[a] Nd, non-detectable. Urinary MDA was detectable in all (n = 92) but 3 urine samples. The undetectable MDA levels correspond to a sprayer at the training center (pre- and post-shift) who had less than one-month experience in the industry, and one pre-shift sample of a helper who had just started working as an insulation worker.

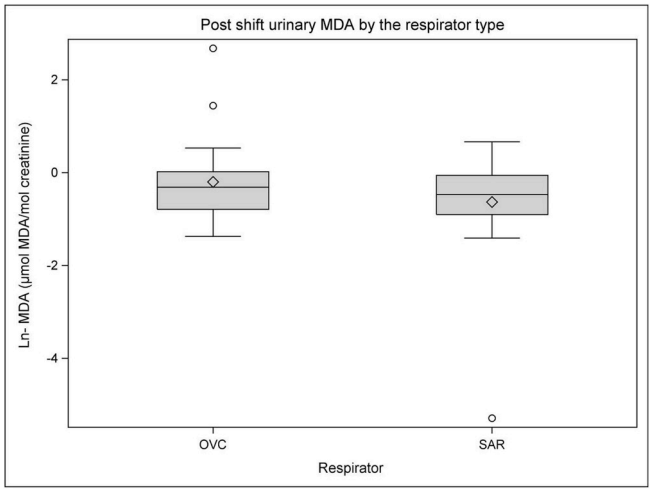

Fig. 3. Creatinine normalized post-shift urinary MDA concetrations (μmol MDA/mol creatinine), stratified by the respirator type: OVC (half or full face organic vapor cartridge without particulate filters; n = 21); SAR, supplied air respirators (n = 26)[1].
[1] The difference on the urinary MDA levels among workers wearing OVC and SAR was not statistically significant (p-value = 0.23). Urinary biomarker data for bystanders and the foam injection sprayer are excluded from this analysis.
Legend: Summary statistics presented by the boxplots: whiskers represent the 5th (lower) and 95th (upper) percentile of the distribution; box represents the 25th (lower edge), 50th (median, middle line), 75th (upper edge) percentile of the distribution; the diamond represents the arithmetic mean; circles represent outliers.

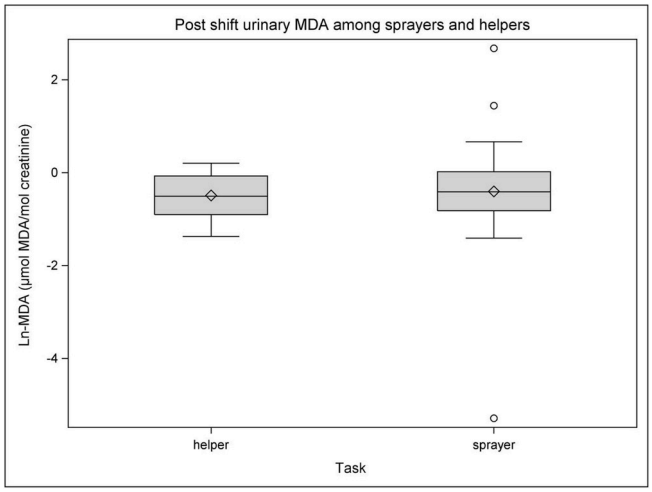

Fig. 4. Distribution of post-shift urinary MDA concentrations among sprayers (n = 33) and helpers (n = 9) (p-value = 0.83).

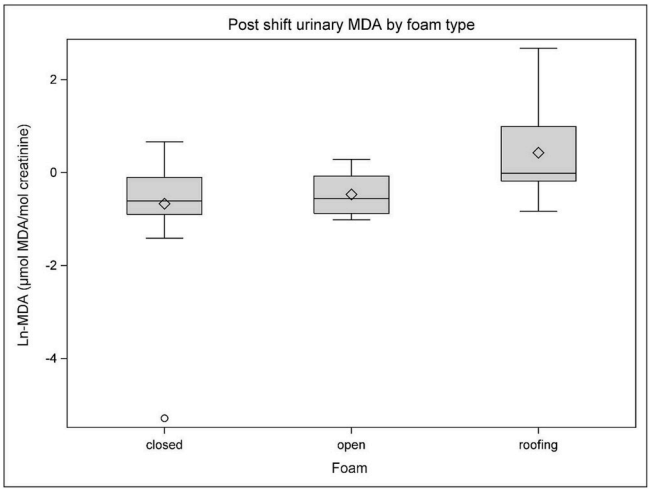

Fig. 5. Distribution of post-shift urinary MDA concentrations for different types of foam products:[1] closed (n = 27), open (n = 8), roofing (n = 9) (p-value = 0.04)
[1] The urinary biomarker levels for bystanders and the foam injection sprayer are not included here.
Legend: Summary statistics presented by the boxplots: whiskers represent the 5th (lower) and 95th (upper) percentile of the distribution; box represents the 25th (lower edge), 50th (median, middle line), 75th (upper edge) percentile of the distribution; the diamond represents the arithmetic mean; circles represent outliers.

center using roofing formulation (downward spraying) had higher urinary MDA levels (p = 0.04) compared to workers in sites using open and closed cell foam (Fig. 5). Overall, neither 4,4′-MDI air exposures nor glove loading were associated with urinary biomarkers in univariate analysis (p, 0.68 and 0.18 respectively). The results of multivariate regression models indicate that urinary MDA normalized for SG was strongly (but inversely) associated with personal airborne exposures (p = 0.03), but not with glove loading (p = 0.98). In the models with MDA as dependent variable normalized to creatinine and creatinine as a separate independent variable, neither PBZ nor dermal exposures were significant predictors of the urinary biomarker (supplementary material, Table S3). We have no explanation for this negative association of biomonitoring data with airborne MDI levels.

3.6. Foam injection exposures

Foam injection is an emerging technique for improving insulation of existing wall structures without taking the walls down and displacing the building occupants for long periods of time. This technique uses a two-pack low pressure insulation kit. Both area and personal sampling results revealed very low airborne exposures to 4,4′-MDI (non-detectable, and 0.24 μg/m^3, respectively) at the injection foam site. The glove sample collected from the applicator yielded 26.1 μg/pair/min for 4,4′-

MDI and lower or non-detectable levels for other isocyanate species (supplementary material, Table S4). Although airborne exposures to isocyanates are practically negligible during injection foam, there is still moderate opportunity for exposure to isocyanates through skin, indicated by the increase in the urinary MDA of this applicator from 0.44 μmol MDA/mol creatinine pre-shift to 0.77 post-shift.

4. Discussion

We present herein the results of a quantitative characterization of inhalation, dermal and urinary biomarkers of aromatic pMDI isocyanates among spray foam insulation workers. This study of SPF insulation workers provides a comprehensive view of work practices, PPEs, quantitative inhalation, and dermal exposures, complemented by urinary biomonitoring results pre- and post-shift. This is also the first study to report on numerous aromatic isocyanate species during SPF applications, including phenyl isocyanate, the two secondary MDI isomers, 2,4' - and 2,2′-MDI, and the MDI trimer. All quantitative data rely on advanced mass spectrometry techniques (LC-UV-ESI-MS/MS) for quantitation of isocyanates in complex media, in particular for dermal exposures. The high sensitivity and specificity of the analytical methods employed in this study, from the quantitation of isocyanates in air to the quantitation of urinary biomarkers, is an important consideration, reflected in negligible non-detect samples across all sample types.

4.1. Airborne pMDI concentrations and implications

Personal 4,4′-MDI exposures of spray foam insulation workers we report here (GM 13.8 μg/m^3 and range 0.9–123.0 μg/m^3) are lower than those previously reported in the literature. Sprayers had higher exposures than helpers, likely due to their proximity to the exposure source. One of the earliest studies on spray foam insulation work was published in 1962 and reports on TDI (toluene diisocyanate) exposures among spray foam applicators (Peterson et al., 1962). In 1981, Hosein and Farkas, (1981) investigated TDI-based foam exposures and reported inadequate protection of workers, who often voluntarily used plastic bags to protect head, eyes and neck during spray foam insulation. At that time, TDI was the main active ingredient in part A foams, but over the years TDI in spray foam formulations has been substituted with the much less volatile pMDI (EPA, 2011). Exposures to MDI among SPF workers were first reported by Bilan and Haflidson in 1989. These authors reported exposures frequently above the ceiling limit of 200 μg/m^3, and as high as 1290 μg/m^3. A study by Crespo and Galan in Spain (Crespo and Galan, 1999) found that sprayers and helpers had higher exposures than the ACGIH 8hr-TWA limit for MDI (51 μg/m^3). Exposure levels among sprayers in Crespo and Galan's study were in the range of 12–570 μg/m^3, whereas among helpers they ranged from 6 to 408 μg/m^3. These concentrations are at least 4 times higher than those found in this study. In addition (Lesage et al., 2007), reported MDI concentrations of 0.07–2050 μg/m^3 during SPF installation in residential homes in Canada. The majority of their samples exceeded the OSHA PEL Ceiling of 200 μg/m^3, in some cases by a factor of 10. Comparable exposure levels with the results of our study were reported in 2014 by a NIOSH survey pertaining to spray foam applicators. Personal air samples for sprayers had a GM of 10.1 (range 4.9–18.7) μg/m^3 whereas for helpers, the GM was 2.9 (range 0.2–7.9) μg/m^3 (Marlow et al., 2014). However, exposures levels measured as part of this NIOSH report could have been underestimated (by a factor of two) because of insufficient isocyanate derivatization on solventless glass fiber filters (Lesage et al., 2007). Overall, the historical trend appears to be that airborne exposures to pMDI in SPF applications have been decreasing, whereas awareness to workplace hazards and work practices continue to improve. This significant progress should not be overlooked and can be attributed in part to product formulation for much faster curing (tack-free touch in a few minutes), as well as development of newer pumping and proportioning systems.

Air sampling of reactive fast curing isocyanates continues to present unique challenges. The CIP10MI sampler was used as a desirable substitute for impinger sampling. This unit has a collection efficiency of > 95% for aerosol particles with aerodynamic diameter (AD) of > 2.8 μm, > 50% collection efficiency for AD 1.8 μm and only 20% for aerosols with AD < 1 μm (Simon et al., 2016). In a field study, CIP10MI compared favorably with impingers and, although it did underestimate exposures slightly, it was considered a desirable alternative to impingers (Puscasu et al., 2015). The collection efficiency curve of CIP10MI may have contributed in part to the higher (stationary) near field MDI concentrations of the impinger-filters train. However, aerosol drifting away from the spray surface is a more likely explanation.

This is the first study to report on exposures to other pMDI species in SPF formulations, especially 2,4'-, 2,2′-MDI and PhI. The ratio of GM concentrations of 4,4'-/2,4′-MDI for sprayers, helpers and bystanders (near field) was: 8.9, 15, and 9.7, respectively. The concentrations of 4,4′-MDI were approximately an order of magnitude higher than of 2,4′-MDI. There is no clear enrichment of airborne aerosols with the less reactive 2,4′-MDI isomer. The concentrations of the 2,2′-MDI isomer were roughly 10 times lower than the 2,4′-MDI. PhI, a highly volatile monoisocyanate (vapor pressure, 1.4 mm Hg at 20 °C), is found in trace quantities in pMDI products. In the air, PhI is expected to be distributed in both the vapor phase and aerosol. The CIP10MI sampler is not expected to collect PhI vapors. Therefore, personal PhI results likely reflect the aerosol portion and are underestimates of true PhI concentrations. Compared to the much higher PhI bystander concentrations measured with the impingers (4.3 vs 0.7 μg/m^3), PhI in PBZ samples may have been underestimated by as much as 6 times.

The much higher near field (area) airborne exposures compared to personal samples (GM of 40.9 vs 13.8 μg/m^3 for PBZ) should be noted. In one area sample (240.8 μg/m^3), exposures exceeded the OSHA ceiling of 200 μg/m^3, indicating high exposure risks for bystanders. These results have practical implications for respirator use by bystanders such as field engineers, EHS supervisors, service crews (e.g. electricians, carpenters) or homeowners entering the indoor space during spraying. In the majority of our observations at the study sites, managers and other bystanders present at the site were wearing half-facepiece cartridge respirators. Previous studies have reported concentrations as high as 840 μg/m^3 in area samples collected 3–6 m away from spraying (Lesage et al., 2007). Lower area MDI exposures (max of 83.3 μg/m^3) have been reported by NIOSH from impinger samples located 3–15 m away from the sprayers. Limited data show that exposures decline at distances 6–12 m and are not detectable at distances ~15 m from spraying (Lesage et al., 2007; Marlow et al., 2014). Although area exposures in our study, similar to personal exposures, were lower than those reported in earlier studies, they still could be quite high. Overall, results of our study warrant the need for respiratory protection for everyone entering the indoor space adjacent to SPF. Furthermore, it is necessary to consider restricted access to active SPF sites of non-essential personnel.

The total isocyanate group (TNCO) calculated from the individual pMDI species is not a true total NCO because the analytical method misses multiple non-chromatographable species (such as large pre-polymeric molecules, and airborne foam particles) and numerous new isocyanate species that are formed as a result of the polymerization chemistry (Streicher et al., 2006). In fact, the true TNCO measured with an alternative method based on 1,8-diaminonaphathelene (or DAN method), designed for such purposes, yielded ~ 10 times higher values than the MAP method in controlled simulated SPF applications (Bello and R.P. Streicher, 2013), as well as in independent validation of our DAN method by another research group (Puscasu et al., 2017). Our data indicate that if the true TNCO is used as a reference value, all samples would exceed the HSE 8-h TWA standard of 20 μg NCO/m^3. It is therefore, important to avoid entering SPF sites without respirators or remove respirators prematurely while still in the spray area.

4.2. Potential for dermal exposure and implications

The high loadings of isocyanates on glove samples indicate high potential for dermal exposures through hands. The interception method we used for isocyanate sampling is preferable over removal techniques because it measures more accurately the amount of isocyanate that reaches the skin. For the fast curing aromatic isocyanates, as in SPF applications, removal techniques result in substantial isocyanate losses due to isocyanate reaction with the skin, continued curing reactions with themselves, reactions with the tape strip and wipe material, water and sweat (Harari et al., 2016). Detailed kinetic studies of pure MDI losses on skin have revealed that up to 80% of MDI is lost to these reactions within the first 5 min (Bello et al., 2007). The reasons why sprayers had significantly higher dermal exposure to hands compared to helpers ($p = 0.05$) is only partly related to proximity to the spray gun. Sprayers frequently insert their gloved hands inside the freshly sprayed foam to test foam quality, release any buildup pressure, or clean up a clogged gun.

High potential for dermal exposures are not limited to hands only. In fact, we have looked at the deposition of isocyanates on different body parts using reagent impregnated patches on protective suits and have found that much higher deposition than in hands occurs on the neck and head region (unpublished results). In a separate study we investigated permeation rate of SPF components through various gloves and garment materials (Mellette et al., 2018). The MDI loads on the gloves and other garments were on average 4.9 μg MDI/cm^2 (maximum 16.2 μg/cm^2). MDI and PhI penetrated all garments in a linear fashion with time over the 20 min testing interval. Based on these permeation panel data of 0.55 ng MDI/cm^2/min up to 550 ng MDI could permeate the thin nitrile gloves to reach the hands of SPF sprayers over a 20-min period. Exposures can reach bare skin areas (wrists, forearms, forehead), seen often in SFP applicators in the field. Dermal 4,4′-MDI doses in the range of concentrations measured with the dosimeter in our study (range 2–152 ng/cm^2/min, or 59–4575 ng/cm^2) can be delivered to the exposed skin. Liljelind et al. (2010) used a tape strip method to measure MDI skin exposures among iron foundry workers in different anatomic sites and found an equivalent of 13–34 ng MDI/cm^2 skin, which are lower than the SPF loading we report here (Liljelind et al., 2010). Jones et al., (2017) measured MDI on gloves using a glove interception technique consisting of thin cotton glove (without a derivatizing reagent) during casting, grouting and floor screeding operations in construction and found, < 0.05–20.5, 230, and < 0.05–1091 μg MDI/glove, respectively (or ~0.002–0.04, 0.4, and 2.0 μg/cm^2). These dermal loading results are comparable to our findings, not adjusted for the sampling time (supplementary material, Table S5).

Sensitization and allergic contact dermatitis have been reported in workers exposed to MDI in various trades even in the presence of gloves and sleeves, with hands and forearms being the two main anatomical sites (Burrows et al., 2015). MDI in particular is a very potent, class 1A skin sensitizer (Hamada et al., 2017). In patch testing, nominal concentrations varying from 0.1% to 2% MDI in different vehicles are used, although 1–2% in petrolatum are more common (DeGroot AC, 2008). Nominal MDI surface densities of 31.2 μg/cm^2 are applied during the sensitization phase (1% or 40 mM MDI, 100 μL, 4 × 8 cm^2) (Hamada et al., 2017). At the lowest test doses of 0.1% MDI, 3.1 μg MDI/cm^2 is being applied to the skin during patch testing. The maximum loading values of 4.6 μg MDI/cm^2 measured in the gloves of SPF applicators are comparable to those employed during patch testing. Sensitization doses can be easily achieved during contact with MDI (part A) in directly exposed skin. Furthermore, the presence of other irritants, sensitizers (MDA for example), and stronger solvents, may lower the sensitization threshold. In our observations, 2% of SPF workers did not wear any gloves, and 4% wore latex gloves which had the highest permeation rate in our permeation panel study. Exposed skin around wrists was relatively common. Furthermore, dermal exposures could be happening after spraying when the workers remove the gloves and expose skin during foam inspection and by touching work tools.

4.3. Urinary biomonitoring and implications

Twenty-five percent of all urine samples were above the biological monitoring guidance value of 1 μmol MDA/mol creatinine, 5.4% exceeded the French BMGV of 2.8 μmol MDA/mol creatinine and 2.2% were higher than the German BAT value of 5.7 μmoL/mol creatinine. The post-shift urinary MDA concentrations normalized to creatinine were not statistically different from the pre-shift values. There are several possible factors leading to this overall finding. First, PPEs are playing an important role in protecting against inhalation and dermal exposures and elevated urinary MDA indicate that exposures could be happening during intermediate tasks. Another important factor to consider is the clearance half-life of MDA. MDA, the corresponding diamine of MDI, is considered a reasonably good exposure biomarker of MDI (Jones et al., 2017; Robert et al., 2007) since MDI constitutes a significant portion of the total NCO group in pMDI (~54% in pMDI and ~100% in MDI products). The half-life of MDA in hydrolyzed urine is between 2 and 10 h (Gaines et al., 2010). The source of this variability in the half-life estimates of MDA is unclear. For a half-life of 2 h, which is close to the average task duration, one would expect fast changes in urinary MDA cross-shift, and little carry over from the prior shifts. For a clearance half-life of 10 h (upper end of the estimates), 25–50% of the exposures from the end of previous shift would be carried forward to the next day. Therefore, cross-shift changes would be less prominent. A third important consideration relates to specificity of this hydrolysis biomarker. Although MDA reflects the total pool of MDI-adducts in urine, at present it is not clear yet what exactly these MDI-adducts excreted in urine are, and how their relative abundance impacts the half-life of MDA. We hypothesize that MDA in hydrolyzed urine reflects two distinct clearance phases – one fast clearance of non-protein derived adducts (possibly adducts with glutathione, Wisnewski et al., 2019), and one slow clearance of MDI adducts with proteins- or protein fragments following their recycling in the liver. Elevated levels of MDA in pre-shift urine observed in our cohort of workers likely reflect the slower clearance of MDI-protein adducts, such as those with lysine terminals in albumin, and therefore they reflect exposures on previous days, or slower MDI skin absorption from previous day exposures (Jones et al., 2017). Although the MDA hydrolysis method cannot distinguish between these two excretion phases, the cross-shift increases in MDA levels likely reflect primarily the fast clearance phase, and hence the most recent exposures. Future work on the new generation of MDI specific-adducts will likely shed more light on the urinary clearance kinetics of MDI-adducts.

Our data raise questions regarding the suitability of urinary MDA normalization to creatinine, because significant cross-shift changes in creatinine that parallel MDA changes would induce a negative bias towards the null. In mixed linear models with urinary MDA normalized to SG, air levels were significant predictors of urinary MDA, although inversely associated. In a recent study of the flame retardant Tris 1-Chloro 2-Propyl Phosphate (TCIPP) among the subset of SPF applicators who wore SAR, we found high pre-shift concentrations for two biomarkers of TCIPP, namely bis (2-chloropropyl) phosphate (BCIPP) and bis (1-chloro-2-propyl) 1-hydroxy-2-propyl phosphate (BCIPHIPP), which increased significantly post-shift, during the same time frame as the MDA biomarker. Dermal exposure was strongly associated with these TCIPP urinary biomarkers (BCIPP and BCIPHIPP) when they were normalized to specific gravity, but not for creatinine (Bello et al., 2018). Further investigations on the suitability of urinary MDA normalization to SG are warranted.

Another important consideration in interpretation of urinary MDI biomonitoring via MDA is possible confounding by co-exposures to MDA arising from partial hydrolysis of MDI in the air and skin, which is also monitored in urine as MDA (Jones et al., 2017). We did perform exploratory analysis on 14 personal air and glove samples across

multiple sites by analyzing for free MDA using LC-ESI-MS/MS (MRM, 119.6 → 106.2; d_2-MDA, IS; Supplementary material, Tables S1 and S6). Seven of the 11 personal air samples from seven sites had no detectable MDA (limit of detection, 0.060 ng/mL). In the remainder four air samples, MDA had a mean of 2.9 ng/sample (range, 0.02–12 ng/sample) and represented a mean of 0.02% (range 0.005–8.4%) of the airborne 4,4′-MDI in those samples. No MDA was found in one of the two MAP-impregnated glove samples. In the other two glove samples, MDA was found at 1.65 ng/sample (range 1.1–2.2 ng/sample) and comprised 0.8–1.2% of the MDI content in the glove samples. These findings of limited presence of MDA in air and glove samples are similar to the findings of Jones et al. (2017) for MDI grouting and floor screeding applications. Therefore, it is reasonable to conclude that urinary MDA results reflect predominantly exposures to MDI. It is also important to note that Jones et al. (2017) found significant association of urinary MDA with MDI skin exposure, whereas we did not. This may be due to better exposure controls during SPF operations.

4.4. Exposure controls

To prevent inhalation exposures to isocyanates, OSHA and NIOSH recommend that workers wear supplied air respirators (SAR) during spraying. Although urinary biomonitoring data did not indicate any significant differences between SAR and OVC respirators, we encourage the use of Powered Air Purified Respirators (PAPR) with a higher assigned protection factor (APF = 25), instead of the OVC half-face piece respirator (APF = 10). We recommend that workers do not remove the respirators while still in the SPF space. Furthermore, bystanders should not enter active SPF spraying without a respirator. Dermal exposure is a serious problem amongst SPF workers as documented by quantitative measurements and field observations.

We recommend the use of thick nitrile gloves instead of the more common thin nitrile gloves which tear easily, discontinuation of latex gloves and thick cotton gloves with polymer coating only on the palmar side, tool decontamination, full coverage of exposed skin, hand cleaning at the end of the spray task, and avoiding contact of the recent foam with bare hands. Furthermore, access to active SPF sites should be restricted to only the necessary personnel and by posting adequate warning signs and establishing safe perimeter areas.

5. Conclusions

The big picture emerging from this study is that inhalation exposures for 4,4′-MDI were generally lower than in earlier studies suggesting a historical trend of exposure reduction during SPF applications. These improvements are driven primarily by product reformulations in favor of faster foam curing rates, improvements in spray proportioning systems, and better exposure controls. Yet, 36% of personal air samples were higher than the (UK HSE) 8-hr TWA total NCO standard of 20 μg NCO/m^3 and 13% were higher than the 10 min Ceiling of 70 μg NCO/m^3. Similarly, 16% of personal air samples exceeded the NIOSH 10-hr TWA REL for MDI of 50 μg/m^3. Exposures to bystanders may be significant, as documented by high near field exposures. Furthermore, there is high potential for dermal exposure among SPF insulation workers. Twenty-five % of all urine samples were above the HSE biological monitoring guidance value (BMGV) for good hygiene practice of 1 μmol MDA/mol creatinine. Abnormal creatinine concentrations in the urine of SPF workers (> 300 mg/dL), which doubled from 13% at the beginning of the shift to 27% in post-shift samples, indicate possible nephrotoxicity or reduced blood flow to the kidneys, which can be a result of a combination of work-related factors - hot environments, dehydration, and chemical exposures. For these reasons, suitability of creatinine adjustments of urinary MDA in SPF applications should be verified with independent measures of a panel of biomarkers of kidney injury.

Conflicts of interest

The authors have not any conflict of interest to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijheh.2019.04.014.

The highest MDA level of 14.5 μmol MDA/mol creatinine correspond to the post-shift urine sample of one of the trainees at the training center. The lowest levels were also measured among one of the trainees at the traning center who had less than one-month experience as an SPF insulator.Legend: Summary statistics presented by the boxplots: whiskers represent the 5th (lower) and 95th (upper) percentile of the distribution; box represents the 25th (lower edge), 50^{th} (median, middle line), 75th (upper edge) percentile of the distribution; the diamond represents the arithmetic mean; circles represent outliers.

Samples include sprayers and helpers at all insulation sites (excluding foam injection site). The PBZ samples were above the limit of detection for all isocyanate species with the exception of one sample collected at the training center that had undetectable levels of the MDI trimer. Sampling duration ranged from 10 to 231 min (median 70 min).

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