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Isocyanate Exposure Assessment Combining Industrial Hygiene Methods with Biomonitoring for End Users of Orthopedic Casting Products

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Previous studies have suggested a potential risk to healthcare workers applying isocyanate-containing casts, but the authors reached their conclusions based on immunological or clinical pulmonology test results alone. We designed a study to assess potential exposure to methylene diphenyl diisocyanate (MDI) among medical personnel applying orthopedic casts using two different application methods. Air, dermal, surface, and glove permeation sampling methods were combined with urinary biomonitoring to assess the overall risk of occupational asthma to workers handling these materials. No MDI was detected in any of the personal and area air samples obtained. No glove permeation of MDI was detected. A small proportion of surface (3/45) and dermal wipe (1/60) samples were positive for MDI, but were all from inexperienced technicians. Urinary metabolites of MDI [methylenedianiline (MDA)] were detected in three of six study participants prior to both a 'dry' and 'wet' application method, five of six after the dry method, and three of six after the wet method. All MDA results were below levels noted in worker or general populations. Our conclusion is that the risk of MDI exposure is small, but unquantifiable. Because there is some potential risk of dermal exposure, medical personnel are instructed to wear a minimum of 5-mil-thick (5 mil = 0.005 inches) nitrile gloves and avoid contact to unprotected skin. This could include gauntlets, long sleeves, and/or a laboratory coat.

Keywords: air; biomonitoring; casts; dermal; gloves; isocyanate; MDI, orthopedic

INTRODUCTION

Detailed information on potential exposures is necessary to define acceptable risk management measures (e.g. personal protective equipment, local exhaust ventilation, and usage instructions) for use of products containing potentially hazardous chemicals. Studies involving chemical exposure assessment during product use have historically focused on the inhalation route of exposure. Occasionally, the dermal route of exposure may be assessed to supplement inhalation exposure data for chemicals that may be absorbed dermally or pose a risk of sensitization. Comprehensive studies that assess inhalation and dermal exposures concurrently with biomonitoring for the same worker population are infrequent, but increasing (Paustenbach and Galbraith, 2006). For materials such as methylene diphenyl diisocyanate (MDI), this type of comprehensive study will likely become more important because exposure to isocyanates is thought to be one of the leading causes of occupational asthma internationally (Stenton, 2010) and

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because recent studies suggest inhalation may not be the sole, or even primary, route of isocyanate exposure that leads to asthma (Bello *et al.*, 2007; Wisniewski and Jones, 2010; Wisniewski *et al.*, 2011). We found three case reports suggesting that respiratory sensitization occurred after exposure to MDI-containing casting materials, but none of these reports provided any industrial hygiene or exposure assessment data to support their conclusions (Tanaka *et al.*, 1994; Sommer *et al.*, 2000; Donnelly *et al.*, 2003).

Thousands of workers internationally use these types of products on a daily basis in surgery departments, emergency departments, and urgent care centers. The casting products are used to treat patients of all ages with orthopedic injuries. The goal of this study was to evaluate inhalation and skin exposures typically encountered by end users of three varieties of 3M Company Scotchcast™ orthopedic casting/immobilization products. The 3M Company products studied (Scotchcast Plus™, Scotchcast Premium™, and Soft Cast™) are fabric materials impregnated with an isocyanate-containing resin, which cures quickly in contact with water to form a hard cast for medical use. The isocyanate used in the products is a carbodiimide-modified isocyanate to maintain a liquid state. MDI used in these products is a mixture of 2,2′-MDI, 2,4′-MDI, and 4,4′-MDI.

It should be noted that this study was conducted as a simulation rather than in an actual clinical setting due to reduced time requirements and cost concerns. Instructions for use that are provided to end-use customers were carefully followed to ensure that the simulation reflected as closely as possible actual customer use.

METHODS

Use and environmental factors

To determine the most representative casting application methods, interviews were conducted with 3M Company employees with extensive experience in the use of the casting products. Based on these interviews, the two types of subjects whose exposure to MDI were to be evaluated were 'Application Techs' (who apply the immobilization products) and 'Limb Holders' (who assist the Application Tech, while holding and repositioning the patient's limb during product application). Each of the three types of Scotchcast products were evaluated in separate study rooms. Study rooms were chosen to represent a range of environmental conditions (size and air exchange rates) typical of a medical clinic or hospital environment.

The study procedures were conducted on two separate days to assess any differences in exposure attributable to the application method. A 2-week gap was scheduled between study days to allow 'washout' of any residual urinary methylenedianiline (MDA) because of toxicokinetic considerations. The first study day was a 'dry' application of five repeated cast applications, meaning that the product was not immersed in water before being applied and was sprayed with water after being applied. The second study day was a 'wet' application, again, of five repeated cast applications, meaning the product was immersed in water before being applied. There were five casts of the same product applied in succession to each 'Patient' on each of the study procedure days, and all five casts of the same product were removed soon after completion of each curing cycle. Removal was performed using an oscillating saw, which is typically used to remove casts.

Application Techs and Limb Holders both wore 5-mil-thick (5 mil = 0.005 inches) nitrile examination gloves (manufactured by Kimberly Clark). Neither latex nor vinyl (polyvinylchloride) gloves were chosen for this assessment because both have been demonstrated to have high leakage rates (Korniewicz *et al.*, 1993). Latex gloves have also been demonstrated to have significant permeation by other isocyanate monomers (Liu *et al.*, 2007). Heavier chemical-protective gloves such as butyl rubber or neoprene would not provide adequate dexterity for application of the casting products. Nitrile gloves were chosen because of their wide use in clinical settings and their ability to provide good dexterity. No respiratory protection was worn by either type of subject. Figure 1 shows the personnel and procedure during application of one of the Scotchcast products.

Table 1 presents summary information on the rooms, products, and environmental factors of our study.

Temperature and relative humidity were continuously tracked with a TSI Q-Trak.

Air quality monitoring

Three area air samples (one in each study room) were collected the day prior to work commencing to rule out background air contamination by MDI. One area air sample was obtained during product application over the time required for three successive product applications (castings). Two personal/breathing zone air samples were taken over the same time period—one each from the Application Tech and the Limb Holder.

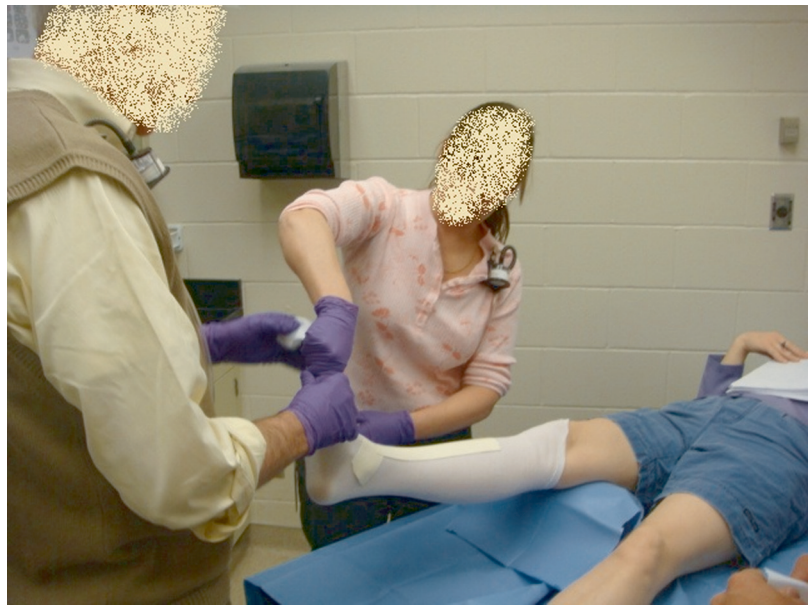

Fig. 1. Product application.

Table 1. Room/product/environment data.

Study room umber	Product applied	Room volume (m^3)	Air exchange rate (air changes per hour)	Temperature (°F/°C)	Relative humidity (%)
1	Scotchcast Plus	29.3	4.2	70.6/21.4	28.6
2	Softcast	31.1	2.2	72.6/22.6	34.3
3	Scotchcast Premium	35.8	0.4	72.5/22.5	30.4

Air sampling was conducted using 37-mm-diameter specialty glass fiber filters coated with 1.0 mg of 1-(2-pyridyl)piperazine (sampled open face), utilizing SKC AirChek XR5000 personal sampling pumps at a flow rate of 1 l min^{-1}, pre- and post-calibrated with a Bios Defender 520m DryCal calibrator. The filters were analyzed by Occupational Safety and Health Administration Method 47 using high-pressure liquid chromatography by an independent laboratory accredited by American Industrial Hygiene Association. The method limit of quantitation was 0.1 µg. With a sampling airflow rate of 1 l min^{-1}, our sampling period resulted in an MDI reporting limit ranging from 0.00006 to 0.00010 p.p.m., which is approximately 2% of the occupational exposure limit chosen for comparison in this study. Air sampling times ranged from 90 to 135 min.

The air sampling data were analyzed with Bayesian statistical methods, using the software package 'IHDataAnalyst' v. 1.01 (Exposure Assessment Solutions, Inc.). Since all of the results were below detection limits, the data were not log-normally distributed, and the results were treated as a 'highly censored data set' (Hewett and Ganser, 2007).

Dermal/surface monitoring

A variety of skin and surface samples were taken during use of the Scotchcast products. Two Skin Swype™ (Colorimetric Laboratories, Inc., Des Plaines, IL, USA) samples of unprotected skin were taken of each Application Tech and Limb Holder [one from the right (dominant hand) wrist, immediately above the top edge of the glove on the forearm, in a continuous circumference around the wrist over the width of the Swype]. Three Surface Swype™ (Colorimetric Laboratories, Inc., Des Plaines, IL, USA) samples of working surfaces (one of the patient table, one of the knee support, and one of the Scotchcast kit table) were taken over a 100-cm^2 surface area for each application/location. We conducted surface Swype sampling to demonstrate the presence of reactive NC=O groups on the surface of the three Scotchcast materials during and after the cure

cycle, as well as on a secondary surface through contact transfer from the cast rolls as a positive check. The published limit of detection for the Colorimetric Laboratories, Inc products is 5 µg.

Glove permeation monitoring

Three Permea-Tec Sensor™ (for additional details, see www.clilabs.com; Colorimetric Laboratories, Inc.) samples were taken on the underside surface of the dominant hand for each Application Tech and Limb Holder beneath nitrile gloves (essentially double gloving), to assess potential glove breakthrough by MDI. The detection limit for the Permea-Tec Sensors is also 5 µg. Figure 2 shows the locations of sensors. A second glove was worn over the sensors.

Biomonitoring

Urine samples were obtained from three Application Techs and three Limb Holders, for a total of six subjects. A one-time (single voiding) urinary collection was performed to assess background levels of MDA (which MDI is metabolized to *in vivo*) on the first of the two study days just before the application procedures began, and prior to handling of any Scotchcast products. A second urine sample was taken as a 12-h collection immediately after the product application to assess MDI exposure that may have occurred during product use. A 2-week gap was scheduled between runs to allow 'washout' of any residual urinary MDA, at which time the subjects' urine was sampled again. The samples were frozen and sent by air transport to NMS Labs (Willow Grove, PA), where they were analyzed for MDA by NMS Method 2986U. This test is a qualitative identification and a quantitative measurement of 4,4′-methylene dianiline (4,4′-MDA) in urine. The samples are hydrolyzed with sodium hydroxide at 80°C for 2 h. Sample preparation includes a pH-adjusted extraction into organic solvents followed by derivatization with pentafluoropropionic anhydride. The derivative is then washed with a neutral buffer and concentrated by evaporation. Analysis is performed by capillary gas chromatography–mass spectrometry and selective ion monitoring.

Application Techs with potential exposure to casting products during the 2-week period in-between the two study days were asked to document their activities, and this information was reviewed by investigators to determine if this could have affected their MDA results from the second study day. Limb Holders had no exposure to casting products in the course of their normal employment. The same is true of Application Techs, with the exception of Subject #3, who is a current immobilization tech service engineer and did conduct non-study-related casting applications within 48 h of the study procedures.

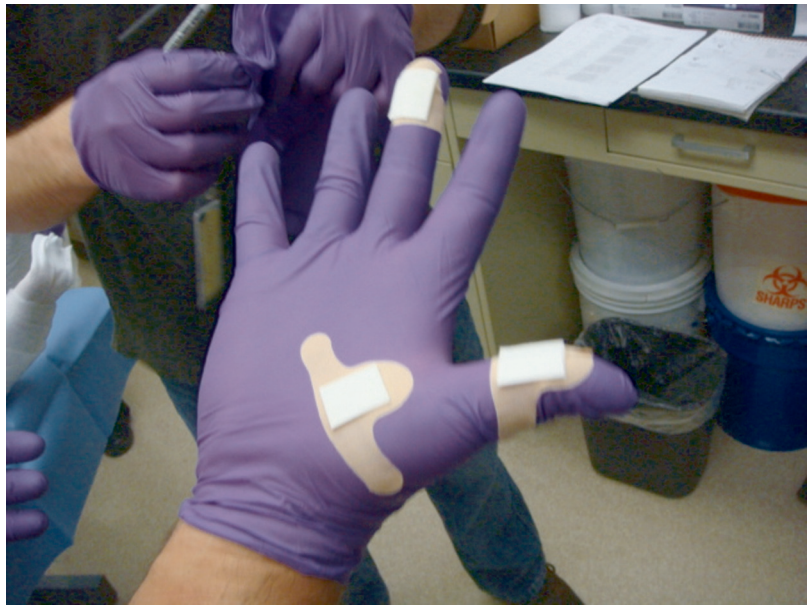

Fig. 2. Permea-Tec sensor locations.

Subject recruitment

Since this study involved human subjects, a 3M Company Institutional Review Board reviewed and approved the study prior to initiation of the study, per requirements of US 21 CFR (Code of Federal Regulations) 56. Because subject technical skills were required for this study including casting procedures (Application Tech subjects) and experience with physical contact with other subjects (Limb Holders), subjects were recruited based on their background and experience. The Institutional Research Board approved this recruitment method for this study only. For typical internal 3M studies as well as 'patient' subjects in this study on whom casts were applied, subjects are/were recruited by sending blind copy emails to a large number of 3M Company employees as potential subjects whose contact information was maintained in a confidential database. External experts are also included on the IRB, and 3M Company has an external audit procedure.

RESULTS

Air quality monitoring

Air sampling and analyses revealed no detectable MDI (at a reporting limit ranging from 0.00006 to 0.00010 p.p.m.) in any of nine samples (six personal and three area) taken during the dry application or in any of nine samples (six personal and three area) during the wet application.

Dermal/surface monitoring

Skin Swype samples revealed detectable MDI on only 1 of 60 samples (1.7%) taken during the dry application, and none of 60 samples (0%) during the wet application. Surface Swype samples revealed detectable MDI on 4 of 45 samples (8.9%) taken during the dry application and 3 of 45 samples (6.7%) during the wet application. All of the positive results were from the room where an inexperienced technician was applying the casting materials. A color change was evident in the Swypes (additional details regarding Skin SWYPES™ and Surface SWYPES™ used in the study can be found at www.clilabs.com) taken from the surface of all three casting materials 5 min after application, but no color change was seen at 20 min in any of the three products. Figure 3 shows the results of surface Swype sampling with the curing time progression.

Glove permeation monitoring

Permea-Tec samples taken from under the outer nitrile gloves revealed no detectable MDI on any of 90 samples (0%) taken during the dry application or in any of 90 samples (0%) taken during the wet application.

Biomonitoring

Urine samples revealed MDA concentrations ranging from 0.22 to 0.34 µmol MDA per mole creatinine taken from six subjects, on two separate study days ('dry' and 'wet' applications, 14 days apart). The limit of detection was 0.11 µmol MDA per mole creatinine (at an average creatinine level of 1000 mg day^{-1}).

For the dry application method, MDA was detected in 8 of 12 urine samples (67%). Three detectable MDA results were before applications, and five were after applications. Three subjects' results were lower after application, two were higher, and one was the same.

For the wet application method, MDA was detected in 6 of 12 urine samples (50%). Three detectable MDA results were before applications, and three were after applications. Two subjects' results were lower after application, one was higher, and three were the same.

DISCUSSION

Air monitoring

Air monitoring results were compared to the American Conference of Governmental Industrial Hygienists threshold limit value (TLV) of 0.005 p.p.m., for MDI, as a TWA (8-h time-weighted average). The reporting limits for our sampling, based on the limit of detection for the analytical method used, ranged from 0.00006 to 0.00010 p.p.m., which is approximately 2% of the TLV. Due to the extremely low vapor pressure of MDI monomer (0.000005 mm Hg at 25°C), these results were not surprising. No aerosolization of uncured isocyanate was expected, as the materials were only manipulated by hand pressure, and the MDI-containing resin is impregnated into the base fabric. Any particulate generated during removal of the casts with the oscillating saw were expected to contain only fully cured polymeric isocyanates, as the casts were allowed to cure for approximately 20 min before removal. It is possible that some thermal degradation products of MDI could be generated during high-speed cutting during cast removal, but an assessment of these was

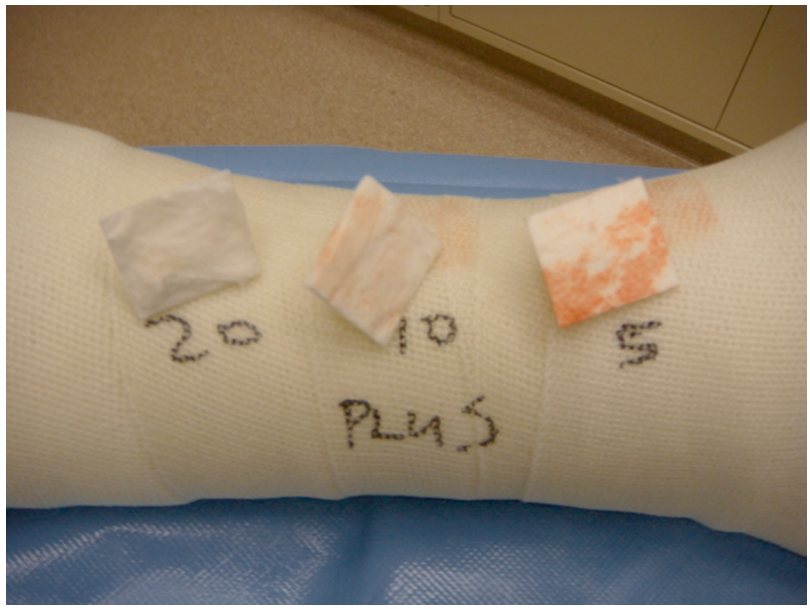

Fig. 3. Surface Swype sampling results over curing time range.

beyond the scope of our study. The results of the air sampling are summarized in supplementary data at *Annals of Occupational Hygiene* online.

The results of statistical analysis predicted a maximum likelihood estimate of 95% that all results were <1% of the TLV. In other words, 95% of the time, the actual results would be <0.005 p.p.m.

We did not assess the effect of different air exchange rates between rooms, and the product types used in each. We felt that it was unlikely we would find any detectable airborne MDI, and that it was more important (within the study budget available) to perform replicate samples to allow statistical confidence in the readings within each application room.

The results of air sampling are summarized in supplementary data at *Annals of Occupational Hygiene* online.

Dermal/surface monitoring

The results of dermal Swypes suggest that there is a small, but unquantifiable risk of exposure to MDI on unprotected skin. The Swype methods used have a detection limit of 5 µg per surface area wiped and should be considered qualitative since the amount of MDI found to induce immune sensitization by dermal exposure has not been precisely quantified in the scientific literature. Since the isocyanate is in a resinous rather than liquid form, droplet formation is unlikely. Unless accidental and direct contact between unprotected skin and uncured Scotchcast fabric was to occur (which would be a very infrequent occurrence), exposure potential appears to be very unlikely. As noted above, the small proportion of positive dermal/surface results were primarily from an inexperienced technician. This may be attributable to the fact that inexperienced technicians would not be as precise in handling the fabric (resulting in inadvertent contact on surfaces and/or skin) and generally would require more time in the casting process. New technicians will undergo a period of in-depth training and practice before being allowed to apply casting products to patients.

There are more sensitive methods available for dermal monitoring such as high-performance liquid chromatography (HPLC) assays; however, the CLI products have undergone extensive validation (Ceballos, 2007; Liu *et al.*, 2007) and we chose to use them as a practical, albeit qualitative, means of assessing potential dermal exposure.

Based on the data obtained from surface Swypes of the casting materials during curing, it appears that a full cure is achieved in 20–30 min, after which there is little if any chance of dermal exposure to reactive NC=O groups. Product application information instructs users to 'smooth and mold' the surface of the casting materials after application, which further enhances curing.

The results of the dermal/surface sampling are summarized in supplementary data at *Annals of Occupational Hygiene* online.

Glove permeation monitoring

No detection of MDI was revealed in any of 90 sensors placed on the subjects from beneath the outer nitrile gloves used. Nitrile appears to be a good choice for disposable gloves based on these factors. As with the dermal monitoring we conducted, HPLC methods would provide greater sensitivity, but they have been used in other studies with monomeric isocyanates, and we chose to also use them as a practical means of assessing potential glove permeation. It should also be noted that the Application Techs and Limb Holders kept the same gloves on from application No. 3 to No. 4 in an effort to assess if application of more than one cast at any given time would lead to glove degradation/abrasion and breakthrough.

The results of the glove permeation sampling are summarized in supplementary data at *Annals of Occupational Hygiene* online.

Biomonitoring

The two study days were planned at a 2-week interval to allow adequate 'washout' of MDA from the employee subjects, which would ensure they had returned to background MDA concentrations in urine. This time interval was based on literature data suggesting that the biological half-life of MDA in humans ranges from 50 to 70 h (Dalene, 1995). The biomonitoring analytical method used in this study had an MDA reporting limit of 0.2 ng ml^{-1} urine (equivalent to 0.11 µmol MDA per mole creatinine, with an average creatinine level of 1000 mg day^{-1}).

We believe that the data represent actual concentrations of MDA in the employees' urine; however, we also feel that they do not reflect any significant exposure from Scotchcast use. Other investigators have calculated an upper reference level of 0.31 µmol MDA per mole creatinine (Sennbro, 2005) derived from extensive populations of non-exposed individuals. In the Sennbro study, they also found that 97% of the subjects in the reference group had detectable levels of MDI as a biomarker. The most likely explanation of positive results in some of our samples is that a low level of bioburden was present in our worker population that is unrelated to use of MDI. Other investigators have researched other potential sources of isocyanates that members of the public may be exposed to such as foodstuffs with epoxy-based resins (Damant *et al.*, 1995; Lambert, 1997), cooking utensils (Mortensen *et al.*, 2005), and polyurethane foams (Krone and Klingner, 2005) but none provide a conclusive link between such exposures and the presence of MDA *in vivo*.

We felt that the most definitive value for comparison of the biomonitoring results is the UK biological guidance value (BGV) of 1.0 µmol isocyanate-derived diamine per mole creatinine. The values found for the dry application were 0.120–0.222 µmol MDA per mole creatinine (mean = 0.169), and the values for the wet application ranged from 0.147 to 0.341 µmol MDA per mole creatinine (mean = 0.170). There are non-parametric methods to evaluate data such as this, but the sample size was too small to detect a difference. Based on our application of the Wilcoxon ranked sums test, there appears to be no statistically significant difference in MDI exposures between the dry and wet application methods, and before and after the use of the Scotchcast products. We also conducted a *t*-test to compare the data from Limb Holders versus Application Techs. There appeared to be a difference in means, which could be due to the experience levels of Limb Holders versus Application Techs, but not at the 95% confidence level. Regardless, all of the values were well below the BGV. It should be emphasized that the BGV is not a health-based value, but rather a control guideline. The UK HSE states 'If a result is greater than a BGV it does not necessarily mean that ill health will occur, but it does mean that exposure is not being adequately controlled'. It is generally accepted that it is not possible to set a health-based exposure limit for prevention of a 'non-threshold' toxic effect such as sensitization leading to asthma. The UK documentation states that if the values are below the BGV, then 'they show either no exposure or well-controlled exposure' (UK HSE, 2005). It also appears that this value takes into consideration typical background levels as it relates to the general population.

The results of the biomonitoring data are summarized in supplementary data at *Annals of Occupational Hygiene* online.

CONCLUSIONS

The results indicated with a high level of confidence that >95% of all air samples would be <10% of the TLV for MDI. Biological monitoring samples indicate that any exposure that may

have occurred during the Scotchcast applications in this study is well controlled. Surface sampling indicates that direct contact with the cast surface without the use of gloves should be avoided until curing has completed. This study indicated that the cast surface should be free of monomer and polymer isocyanate within 20 min when proper wetting techniques are used. Application specialists who are properly trained and follow good practice recommendations, including the use of 5-mil thickness nitrile gloves (as outlined in product instructions), should be adequately protected. Additional skin Personal Protective Equipment may be needed as a result of a user exposure assessment, such as gauntlets, long-sleeve shirts, or lab coats. We also recommended that users be instructed on proper methods to clean skin known to be exposed to uncured resin or droplets, by use of commercially available cleaning solutions. We do not feel that biomonitoring would be justified as a routine assessment tool in the clinical setting, based on the exposure potential seen in this study. It should also be noted that manufacturers of similar products may have different properties and caution should be exercised when inferring potential exposures to users of those products from this study.

SUPPLEMENTARY DATA

Supplementary data can be found at http://annhyg.oxfordjournals.org/.

FUNDING

3M Company, St Paul, MN, USA.

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