

Role of dermal exposure in systemic intake of methylenediphenyl diisocyanate (MDI) among construction and boat building workers

Maj-Len Henriks-Eckerman^{a,*}, Erja A. Mäkelä^b, Juha Laitinen^c, Katriina Ylinen^b, Katri Suuronen^b, Aki Vuokko^b, Riitta Sauni^d

^a Finnish Institute of Occupational Health, Lemminkäisenkatu 14-18 B, FI-20520 Turku, Finland

^b Finnish Institute of Occupational Health, Helsinki, Finland

^c Finnish Institute of Occupational Health, Kuopio, Finland

^d Finnish Institute of Occupational Health, Tampere, Finland

HIGHLIGHTS

- Workers may be exposed to methylenedianiline (MDA) when handling one-component MDI-containing raw materials.
- It is important to minimize skin exposure to MDI in order to reduce the risk of allergic contact dermatitis and possibly also asthma.
- The use of chemical protective gloves lowered the skin exposure of the hands to MDI.
- Indication of dermal uptake of MDI can be detected in next morning urine samples.

ARTICLE INFO

Article history:

Received 7 November 2014

Received in revised form 19 December 2014

Accepted 19 December 2014

Available online 24 December 2014

Keywords:

MDI

Isocyanate

Dermal exposure

ABSTRACT

The causal relationship between inhalation exposure to methylenediphenyl diisocyanate (MDI) and the risk of occupational asthma is well known, but the role of dermal exposure and dermal uptake of MDI in this process is still unclear. The aims of this study were to measure dermal exposure to and the dermal uptake of MDI among workers ($n = 24$) who regularly handle MDI-urethanes. Dermal exposure was measured by the tape-strip technique from four sites on the dominant hand and arm. The workers with the highest exposure ($n = 5$) were biomonitored immediately after their work shift, in the evening and the next morning, using urinary 4-methylenedianiline (MDA) as a marker. Dermal uptake was evaluated by comparing workers' MDA excretions both when they were equipped with respiratory protective devices (RPDs) and when they did not use them. The measured amounts of MDI on their hands varied from below 0.1 to 17 $\mu\text{g}/10\text{cm}^2$ during the test. MDI concentrations were in the range of 0.08 to 27 $\mu\text{g m}^{-3}$ in the breathing zone outside the RPDs. MDA concentrations varied from 0.1 to 0.2 $\mu\text{mol mol}^{-1}$ creatinine during the test period. The decreasing effect of RPDs on inhalation exposure was absent in the next morning urine samples; this excretion pattern might be an indication of dermal uptake of MDI.

© 2014 Elsevier Ireland Ltd. All rights reserved.

1. Introduction

Isocyanates, a diverse group of reactive chemicals with the functional group NCO, are well-known causes of occupational asthma worldwide. Due to its low volatility, methylenediphenyl diisocyanate (MDI) has become the most commonly produced and technically used isocyanate. Commercial MDI or polymeric MDI (PMDI) is chemically a mixture of monomeric and oligomeric MDI.

MDI or pure MDI is a mixture of primarily 4,4'-MDI with small amounts of 2,4 and 2,2' isomers. PMDI typically contains 25–65% MDI monomers with the balance consisting of oligomeric polyisocyanate homologues of MDI. MDI monomers are classified as respiratory and skin sensitizing, and cases of allergic contact dermatitis to MDI have also been reported (Aalto-Korte et al., 2012; Engfeldt et al., 2013). Several cases of occupational asthma related to low levels of airborne MDI have been reported. A case report of two nurses' asthma due to MDI-containing orthopedic plaster casts has been published (Suojalehto et al., 2011). These nurses were exposed to airborne MDI concentrations of 0.11 $\mu\text{g NCO m}^{-3}$ during the casting, which is less than 3% of the Finnish 15-min

* Corresponding author. Tel.: +358 30 4747530; fax: +358 30 4747556.

E-mail address: maj-len.henriks-eckerman@ttl.fi (M.-L. Henriks-Eckerman).

occupational exposure limit (OEL), $35 \mu\text{g NCO m}^{-3}$. These and other similar cases have raised the question: can respiratory sensitization and the development of asthma be accelerated by skin contact with MDI (Bello et al., 2007; Redlich, 2010)?

A poor correlation was observed between airborne MDI levels and 4,4'-methylenedianiline (MDA) concentrations in urine during a moulding process (Kääriä et al., 2001), indicating possible dermal uptake of MDI, found as MDA in urine. Later, tape-strip methods were developed to determine dermal exposure to isocyanates (Fent et al., 2006; Liljelind et al., 2010). A study of total exposure to 1,6-hexamethylene diisocyanate (HDI) during spray painting indicated that both dermal and inhalation exposure to HDI contributed to the urine levels of its metabolite 1,6-hexamethylene diamine (HDA) (Gaines et al., 2010). Liljelind et al. (2010) studied dermal and inhalation exposure to MDI in iron foundry workers but did not carry out biological monitoring. Thus, there is a need to investigate dermal exposure to MDI and its relationship with the systemic dose, including the role of protective gloves. The target of such a study should be manual handling of MDI that results in a high risk of skin exposure.

The aims of this study were to evaluate the dermal exposure and dermal uptake of MDI. Dermal exposure was measured among workers mostly handling MDI manually in different processes in construction work and the boat building industry, using the tape-strip method. Workers showing the highest dermal exposure were selected for monitoring of urine MDA levels.

2. Materials and methods

2.1. Participating enterprises, participants and study design

We contacted approximately 15 enterprises, in which manual handling of MDI was common. Twelve of these participated in the study: they were small to medium sized enterprises, representing the boat building industry (5), construction work (6) and production of prefabricated units (1). In each enterprise, 2–4 workers regularly handled MDI formulations without respiratory protection. The processes included foaming, moulding, gluing, laminating, and coating with polyurethane, which is mixture of polyols and MDI hardener. The size of the mixed polyurethane batches varied from 200 g to 5 kg. Each batch process was repeated 2–20 times per shift, on 3–5 days of the working week.

Twenty-four workers were interviewed and observed in 27 different working situations in which MDI formulations were handled. Many workers wore T-shirts, exposing bare skin on the arms. Fourteen workers (58%) did not use gloves at all, or used gloves that were not intended for chemical protection. We used the tape-strip technique to determine the dermal exposure of these 24 workers to MDI during our first visit. On the basis of field observations and results from other studies (Liljelind et al., 2010), the dominant hand and arm of each worker were chosen as sampling sites for studying dermal exposure and to find workers with high dermal exposure.

The samples were taken once from each worker after the exposing job (15–60 min for the batch process) was finished. The tape-stripping is described in Section 2.3. The workers showing the highest dermal exposure in the tape-strip measurement were asked to participate in a biological monitoring study in order to determine if dermal exposure to MDI could be seen in their urine MDI metabolite level (urine MDA).

During our second visit to the workplaces, we carried out urine sampling, took tape-strip samples and collected air samples. The collection of urine samples started on the third working day (usually Wednesday) and the first sample was given after the exposing work was finished for the day. It continued during the fourth and fifth working day and over the weekend or days off. The

last urine sample was given on the morning before the next working week started. The urine sampling procedure is described in detail in Section 2.7. Air samples were also collected at the same time during the exposing job on day 4 and day 5, and tape-strip samples were taken immediately after the job was finished. Respiratory protective devices (RPD) were used when handling MDI on day 4 and day 5.

Of the 24 workers who gave their consent, only five were able to participate in the second part of the study, due to practical reasons. Four of these workers were provided with powered filtering RPDs with a hood (class TH3A2B2E2K2P), which should be efficient enough to minimize inhalation exposure when performing MDI work. The fifth worker used the RPD (TH2A2P) provided by his employer. Inhalation exposure to MDI was measured by sampling in the breathing zone and inside the hood during the exposing work. The condition of the RPDs was checked before and after the air measurements. In the spraying process, the RPD filters were changed daily and before the air measurements; in the gluing or laminating processes the filters were used for two days.

The field measurements were performed from December 2010 to May 2012. The Ethics Committee of the Hospital District of Helsinki and Uusimaa approved the study (reference number 298/13/03/00/2010). All participants gave their written informed consent.

2.2. Chemicals

The chemicals used in this study were acetonitrile (HPLC grade S, Rathburn), acetic anhydride, formic acid, sulphuric acid, toluene, potassium dihydrogenphosphate, sodium hydroxide and ethylacetate (all of analytical reagent grade or purer, Merck). Heptafluorobutyric anhydride (HFBA) was from Pierce Chemical. Solid derivatives of 2,4'-MDI and 4,4'-MDI with 1-(2-methoxyphenyl) piperazine (2MP, Aldrich) were used to quantify MDI monomers. They were prepared as described in the ISO 16702 standard (2007). The deuterated 4,4'-d₂-MDA (used as an internal standard in the biological monitoring analysis) and d₃-2MP (used to prepare an internal standard for MDI) were from Ramidus Ab (Lund, Sweden). The MDA was from Sigma and its internal standard ethylenedianiline (EDA, purity 95%) was from Acros Organics. PMDI (Merck Schuchardt) was used to determine recovery from the tapes. Citric acid (Fisher Scientific, general purpose grade) was used to stabilize the urine samples.

2.3. Determination of dermal exposure – field sampling and work-up procedure

MDI monomers on the skin of 24 workers were measured using the tape-strip technique described by Liljelind et al. (2010). The tape-strips ($2.5 \times 4 \text{ cm}^2$, Fixomull[®], BSN medical GmbH & Co., Hamburg, Germany) were applied to four different skin sites on the dominant hand and arm: forefinger, middle finger (palmar side of the fingertip), palm (middle) and wrist (palmar side on which bare skin was visible) or arm (where bare skin was visible). Whether wrist or arm was chosen depended on where bare skin was visible. Otherwise the sample was taken from the point at which the glove ended. Three consecutive tape-strip samples were collected from each skin site. The sum of these three collections was reported as the result. After collection, each tape was immediately placed in a clean glass vial containing 2MP (1 mg ml^{-1}) in dry acetonitrile (5 ml). Two blank tapes representing field blanks were also placed in 2MP containing vials during the collection. Samples were stored at room temperature for one day to allow complete derivatization. After this, the internal standard was added and with the use of 50 μl of acetic anhydride, the amines in the sample were acetylated for at least 4 h before analysis.

2.4. Recovery of MDI and MDA from tapes and stability study of MDI on the tapes

The tape-stripping method was evaluated by adding 200 ng and 1000 ng of PMDI to the tape in a glass vial. The spiked amounts represented two different exposure levels, 100 ng and 500 ng of MDI monomers. The addition of MDA was 100 ng and 1000 ng. Recovery of MDI was tested both with and without the MDA addition. After spiking, 5 ml of acetonitrile containing 1 mg ml⁻¹ of 2MP were added. The same amounts of MDI and MDA were also added to 2MP reagent solutions without tape. Following this, all solutions were treated in the same way as the field tape samples. Six replicates were made of each concentration. We also tested the stability of MDI monomers on the tape (end of March). 2000 ng of PMDI were spiked on the tape in a glass vial. Reagent solution was added immediately, after two hours, after 6 h, after 24 h and after 30 h to desorb the tape for analysis. The stability test was done in duplicate.

2.5. Determination of inhalation exposure – air sampling and work-up procedure

Glass fibre filters (Whatman GF/B, 25 mm) impregnated with 3.5 mg of 2MP per filter and placed in Swinnex 25 mm filter holders (Millipore) were used to collect air samples of MDI. Air was pumped through the filter by accurately calibrated pumps at a sampling rate of 2 l min⁻¹. Samples were collected from the breathing zone and from inside the hood. The sampling lasted the full duration of the exposing job, usually 15–60 min. After sampling, the filter was immediately placed in 2 ml of dry acetonitrile for desorption and to complete the derivatization.

2.6. Analysis of 2MP-derivatives and acetylated MDA

The urea derivatives of 2,4'-MDI and 4,4'-MDI and the acetylated 4,4'-MDA in acetonitrile were analysed using a liquid chromatograph (LC; Thermo Accela) coupled with a triple quadrupole mass spectrometer (MS/MS; Thermo TSQ Quantum Access). The spray voltage was 5000 V and the capillary temperature was 250 °C. Separation took place on a Symmetry C18 column (150 × 2.1 mm, Waters Corp.), using a gradient mobile phase of acetonitrile–water with 0.1% formic acid, giving retention times of 12–14 min for MDI and about 4 min for MDA. The flow rate was 0.2 ml min⁻¹. Positive ions were monitored in the electrospray mode. For MDI, the parent ion was the doubly charged molecular ion (M + 2H)²⁺. The daughter ion monitored was the 2MP fragment at *m/z* = 193. For MDA, the parent ion was 283 (M + H)¹⁺ and the daughter ions were 106 and 241, of which *m/z* = 241 corresponded to the loss of one acetyl group. The internal standard method and standard solutions containing the tape were used for quantification. The limit of detection (LOD) was 3 ng per tape and 2 ng per filter for MDI, and 5 ng per tape for MDA.

2.7. Biological monitoring – sampling and chemical analysis

Urine samples from five workers were collected before the work shift (usually in the morning), after the MDI work (usually in the afternoon on working days) and in the evening. Evening and morning samples were also given during the weekend or days off. The last urine sample was given on Monday morning, or on the first morning of the next working week. The samples were stabilized by adjusting the pH to ≤4 with citric acid. They were stored at –20 °C until further preparation. The 4,4'-MDA and other diamines were liberated from the amine conjugates by strong acidic hydrolysis.

This solution was then made alkaline and the amines were extracted into toluene, to which HFBA was added to derivatize them. The samples were concentrated and reconstituted into a small volume of ethyl acetate for gas chromatography–mass spectrometry (GC–MS) analysis in the negative chemical ionization (NCI) mode (Agilent 6890A GC and 5973N MSD). The detection limit was 0.1 µg/l or lower (0.04–0.1 µmol mol⁻¹ creatinine, depending on the amount of creatinine in the urine). The work-up procedure and analytical conditions are described in detail by Rosenberg et al. (2002).

3. Results

3.1. Collection on the tape and recovery from the tape

As the amount in the third collection was 5–15% of the summarized amounts, MDI was considered to be quantitatively collected from the skin by three consecutive tape-strip samples when the collected amount was below 1 µg/10 cm². For results over 1 µg/10 cm², the collection was incomplete, as the proportion of the third collection was over 20%. The recovery of MDA and MDI monomers from tapes using 2MP containing acetonitrile as the desorption solvent was over 95% for all tested concentration levels. The stability test revealed that about 5% of the 4,4'-MDI monomer, the main MDI component, had turned into the corresponding diamine, MDA after 6 h on the tape in contact with air and it's moist. The MDA concentration was at its highest 24 h after spiking the tape with PMDI. The 4,4'-MDI concentration decreased as a function of time, and after 30 h, less than 3% of the original concentration was detected on the tape.

3.2. Dermal exposure

Mean and median concentrations of MDI monomers on different skin sites of the hand and arm are presented in Table 1. The mean concentration for all workers was below 1 µg/10 cm² for all skin sites except the palm. The medians of the amounts of MDI on the skin of the workers using chemical protective gloves were below 0.1 µg/10 cm². The medians for the users of other types of gloves were usually higher than 0.1 µg/10 cm². The highest medians were observed on the skin of workers who did not use gloves. Visual observations supported the measured low skin exposure. In many cases, the work seemed fairly clean and was not in direct contact with the MDI formulation.

Three results from three different workers exceeded 2 µg/10 cm². A result of 17 µg/10 cm² was determined from the palm of a worker who had a habit of leaning on the plywood when laminating it. He usually changed his natural rubber gloves (thickness 0.45 mm) once a week or when they broke. On the sampling day, his gloves had been used for three days. A result of 15 µg/10 cm² was measured after an accident with an automatic polyurethane mixing tip. The damaged tip was handled using polyurethane gloves that were not water tight, and furthermore, the contaminated gloves were held in the naked palm after they were taken off. The worker with 8 µg/10 cm² of MDI on his forefinger spread 165 kg of polyurethane glue daily onto plastic sheets of 18 m² or more with his work partner. This task took most of the 8-h working day. The working tools were a 3-m long and about 12 cm-thick spatula and a smaller spatula with a shaft of about 1 m. The workers' gloves were made of leather.

MDA was detected on the skin of only one worker, namely a worker who insulated windows, using one-component MDI foam and no gloves. The amount of MDA was 0.25 µg/10 cm² on the forefinger and 0.40 µg/10 cm² on the middle finger. The

Table 1

Arithmetic mean and median concentrations of methylenediphenyl diisocyanate (MDI) measured on tape-strips from each skin site (skin area 10 cm², dominant hand) of 24 workers. MDI is reported as the sum of 2,4-MDI and 4,4'-MDI.

Protective gloves in use	MDI amount/skin site (μg)			
	Forefinger	Middle finger	Palm	Wrist or arm
All participants (<i>n</i> ^a = 24)				
Arithmetic mean	0.68	0.28	1.38	0.16
Standard deviation	1.67	0.46	4.64	0.36
Median	0.18	0.07	0.02	0.03
Chemical protective gloves ^b (<i>n</i> ^a = 10)				
Arithmetic mean	0.21	0.12	0.02	0.12
Standard deviation	0.39	0.30	0.02	0.18
Median	0.06	0.03	0.01	0.04
Gloves with a water-tight film ^c (<i>n</i> ^a = 5)				
Arithmetic mean	0.21	0.11	3.43	0.43
Standard deviation	0.16	0.09	7.59	0.69
Median	0.17	0.10	0.05	0.07
Leather gloves (<i>n</i> ^a = 3)				
Arithmetic mean	3.16	0.94	0.10	0.08
Standard deviation	4.15	0.93	0.13	0.12
Median	1.62	0.94	0.05	0.01
Textile and polyurethane coated gloves (<i>n</i> ^a = 3)				
Arithmetic mean	0.44	0.14	4.88	0.05
Standard deviation	0.61	0.15	8.33	0.06
Median	0.19	0.09	0.10	0.03
No gloves in use (<i>n</i> ^a = 3)				
Arithmetic mean	0.76	0.6	0.26	–
Standard deviation	0.38	0.46	0.44	
Median	0.78	0.52	<0.005	

–: no sample taken.

^a *n* = number of workers.

^b Materials: neoprene, nitrile rubber, natural rubber or vinyl (PVC).

^c Not chemical protective gloves, but thin vinyl, natural rubber, nitrile coated gloves or winter gloves with a thin polyurethane film.

corresponding MDI concentrations were 0.36 and 0.52 μg/10 cm², respectively.

3.3. Biological monitoring

The role of dermal exposure in the systemic intake of MDI was studied by measuring the MDI metabolite MDA in the urine of workers who used and did not use respiratory protection. For comparison, the excretion of MDA was also monitored during days off work. The combined results of five workers are presented in Fig. 1. During the work period, the MDA concentrations were in the range of 0.1–0.2 μmol mol^{−1} creatinine. During the days off, the MDA concentrations were below 0.1 μmol mol^{−1} creatinine. The difference between workers' MDA excretion at three time points (after the work shift, in the evening, next morning) and during working days were tested using the Kruskal–Wallis exact test. No statistical differences between the different time points were found among the group (*p*-values: 0.9838, 0.4070 and 0.6298). On the other hand, statistically significant differences were found between the working days and days off (*p*-values: 0.0013 (next morning), 0.007 (after work shift) and 0.0724 (in the evening)).

The tape-stripping was repeated on four of the workers who took part in the biological monitoring. All amounts of MDI on the skin were substantially lower than those in the skin exposure measurements during the first visit. The highest amount detected in the second measurement was 0.16 μg/10 cm² on the forefinger after laminating plywood. The corresponding amount during the first visit was 0.39 μg/10 cm².

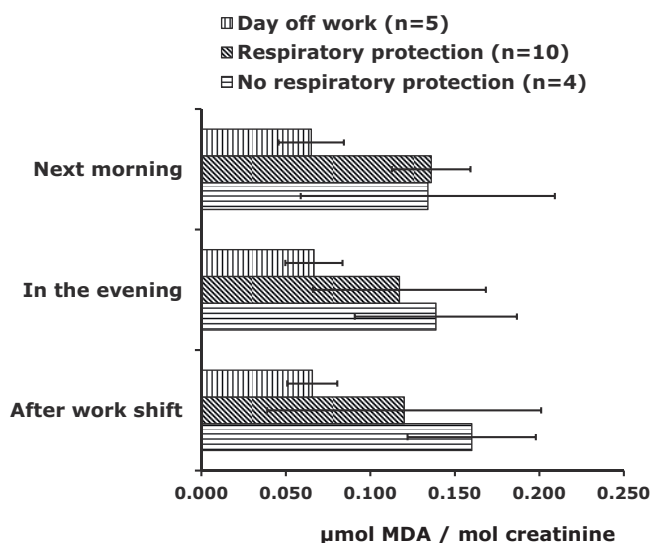


Fig. 1. Influence of the use of respiratory protection on the mean MDA concentration in the urine of five workers. Combined results of samples given after the work shift, in the evening and the next morning are compared to sample results from the days off work.

3.4. Inhalation exposure

The workers who took part in biological monitoring were exposed to MDI concentrations of 0.08–0.8 μg m^{−3} when they worked without respiratory protection. The use of a powered hood, RPD class THA2B2E2K2P, reduced the inhalable concentration of MDI by 60%. In a foaming process with a spray gun, the use of an RPD class of TH2A2P reduced the exposure from 27 μg m^{−3} to 0.50 μg m^{−3} (=98% reduction).

4. Discussion

4.1. Dermal exposure

The tape-strip measurement results from the skin of the hand and arms were below 2 μg/10 cm² for nearly all workers, although glove usage, mixing methods, glue and foam application methods, and the amount of MDI used at work varied greatly. This was lower than the 1 μg/cm² measured on the inside of the gloves, which our research group evaluated as most likely safe as regards skin sensitization. (Mäkelä et al., 2014). However, this safety limit cannot be strictly correlated to a tape-stripping result of 10 μg/10 cm², since it is not known how much MDI was on the skin surface, as MDI is part of a curing reaction and its amount decreases during work task. In addition, some of the MDI may be absorbed into or adhere to the skin so strongly that it cannot be stripped off.

Iron foundry workers' dermal exposure to MDI has previously been studied by Liljelind et al. (2010), using the same tape-strip technique. In their study, all results for hands, arms and wrists were below 0.6 μg/10 cm², except in the case of two wrist samples and one forehead sample. Thus, handling MDI in foundries seems to result in lower skin exposure than in construction work and the boat building industry. Although we did not measure skin exposure on the face, it should be kept in mind that the face, due to its large (500–600 cm²), usually uncovered skin area, may contribute to the majority of the total body burden from dermal exposure to MDI, especially when small splashes are spread during mixing and application.

The analysis of the statistical significance of differences between the skin exposure of different glove user groups turned

out to be unsuitable because of the high deviation in each group (Table 1). However, the efficiency of chemical protective gloves in reducing the skin exposure of the hands can be seen from the differences in median concentrations. High dermal exposure to MDI is less likely when using chemical protective gloves, which is a result that should motivate workers to use these instead of leather gloves or no gloves at all.

Detailed observation of the work was needed to find explanations for high exposures. Three exceptionally high results (8, 15 and 17 $\mu\text{g}/10\text{ cm}^2$) showed that high skin exposure may occur in accidental situations, when chemical protective gloves are not used, and contact with the chemical is not scrupulously avoided. In fact, in these three cases, the actual concentrations might have been much higher, as only three consecutive tape-strippings did not collect MDI quantitatively from the skin when the amount was over 1 $\mu\text{g}/10\text{ cm}^2$. It should also be kept in mind that these solitary results represent only one work situation and a small skin area. The removal of gloves may also result in contaminated fingertips if not done properly. Therefore, it is important to practice safe working habits and to avoid contamination throughout the work shift.

Small amounts of MDA were detected on the skin of one worker who insulated windows using one-component MDI foam and no gloves. To our knowledge, this is the first report on skin exposure to MDA when using MDI formulations. As one-component MDI foam hardens after some of the MDI molecules have turned into MDA molecules, exposure to MDA may be possible.

4.2. Biological monitoring

The MDA concentrations in urine during working days (0.1–0.2 $\mu\text{mol mol}^{-1}$ creatinine) were of the same level as earlier reported mean and median concentrations for moulders (Kääriä et al., 2001). The workers' urine MDA concentrations were significantly higher during working days than days off, although the workers were given respiratory protection after the collections of urine samples on the first day. This is not a surprising result, as according to airborne measurements, respiratory protection reduced the inhalable amount by only 60%. The air flow of the RPD was about 120 $\text{dm}^3\text{ min}^{-1}$, which may have been too low for the tasks of the workers, and therefore caused inward leakage.

The dominant elimination half-lives of the isocyanate-derived diamines in urine are relatively short (2–5 h) (Cocker, 2011). Therefore, in routine biomonitoring of diisocyanates, urine samples representing inhalation exposure are given within 2 h of after the exposing job is finished. The decreasing effect of RPDs on inhalation exposure was immediately noticed in the after-work shift urine samples. The difference started to gradually disappear in the evening and was totally absent in the next morning urine samples, although the levels remained significantly higher than the background samples taken during vacation (Fig. 1). This excretion pattern might be an indication of dermal MDI uptake. It is common that dermal exposure can cause a delay in the excretion pattern in comparison to pure inhalation exposure (Bentur et al., 1998; Laitinen et al., 2012). In addition to dermal exposure, the urinary levels may also indicate a two-phase elimination pattern of MDA and a longer half-life of a second phase metabolite, as half-lives of about 70 h have been reported for MDI (Dalene et al., 1997). Recently, Tinnerberg et al. (2014) have reported on another slow elimination pattern of MDI that was concluded to result from inhalation exposure. According to that study Monday morning urine samples may be used as a long-term biomarker of exposure instead of analyzing the protein adducts in the blood. In our study the MDA concentrations in the Monday morning samples were well below the reference limit, 0.5 $\mu\text{g}/\text{l}$, and cannot therefore be used as a long-term measure of exposure. However, the measured urinary concentrations during work days were on an expectable

level in comparison to the concentrations in the breathing zone and on different skin sites.

The studied group was too small to provide statistically significant results for the differences in mean concentrations caused by different exposure routes. The most efficient way to exclude inhalation exposure when studying the role of dermal exposure and the half-life of MDI via this exposure route would be to expose the skin of volunteers to MDI under strictly controlled conditions. The MDI amounts on the skin should be chosen so that they give rise to MDA concentrations in urine in the range of 0.2–1 $\mu\text{mol mol}^{-1}$ creatinine, but such exposures seldom occur anymore, and ethical issues need to be addressed. For example, a study by Hamada et al. (2012) showed that such experiments may lead to test sensitization of the skin.

4.3. Theoretical uptake calculations for MDI in different exposure scenarios

Previous studies have raised the question of whether respiratory sensitization and the development of asthma can be accelerated by skin contact with MDI (Suojalehto et al., 2011; Bello et al., 2007; Redlich, 2010). As the skin exposure to MDI in this study was too low to be reliably measured in urine after systemic intake, we calculated how high dermal exposure of MDI should be in order to significantly contribute to systemic intake, in comparison with inhalation exposure of MDI. We assumed an intake caused by inhalation of 0.7 $\mu\text{g m}^{-3}$ 4,4'-MDI, a common airborne concentration in this study and many other MDI workplaces. We also assumed 20 min of inhalation exposure and a breathing rate of 30 l min^{-1} , 70% uptake through the lungs and a half-life of 2–5 h, which would result in 0.2 μg MDI excreting into one litre of urine as MDA within two hours of exposure ending. This corresponds to a urine concentration of about 0.1 $\mu\text{mol mol}^{-1}$ creatinine, which is also supported by the biological monitoring results of this study (Fig. 1).

In order to distinguish skin exposure from inhalation exposure, we also assumed that the amount absorbed by the skin should produce a measurable systemic intake about ten times higher than that taken in by inhalation. Ten times the inhaled amount in this example is 2 μg MDI. The assumption that the dermal uptake is at most 1% of the applied amount (Hoffmann et al., 2010) would mean that at least 200 μg MDI is needed on the skin. A few splashes on bare arms or the face, or penetration through clothing may easily produce such an amount, as one small (20 μl) drop of MDI-polyol formulations contains about 5 mg of MDI (Henriks-Eckerman and Mäkelä, 2014). Thus, exposure situations in which dermal intake may easily exceed respiratory intake are possible.

5. Conclusions and recommendations

The MDA excretion pattern during working days and days off might be an indication of dermal uptake of MDI, as the decreasing effect of RPDs on inhalation exposure was absent in the next morning urine samples. Theoretical uptake calculations also indicated that dermal exposure to MDI may play a role in systemic intake. Conclusions regarding the role of dermal exposure in the development of asthma cannot be made on the basis of such a small amount of material and size of study setting. Nevertheless, it is important to minimize skin exposure in order to reduce the risk of allergic contact dermatitis and possibly also asthma. This is done by using chemical protective gloves correctly according to the recommended period of safe use, and by using proper protective clothing and face shields.

The workers' awareness of the risk of skin exposure increased during the study, resulting in considerably lower dermal exposure during the second visit, evidently due to improved working habits.

This study also demonstrated that the use of chemical protective gloves resulted in lower skin exposure of the hands to MDI than that of workers without gloves. These observations highlight the importance of training and information regarding risks and efficient skin protection.

We demonstrated for the first time by tape-stripping that workers' skin may be exposed to MDA when handling one-component MDI-containing raw materials.

Transparency document

The [Transparency document](#) associated with this article can be found in the online version.

Acknowledgements

This work was supported by The Finnish Work Environment Fund (project 110160). We also thank Maria Hirvonen for her help with the statistical analyses.

References

- Aalto-Korte, K., Suuronen, K., Kuuliala, O., Henriks-Eckerman, M.-L., Jolanki, R., 2012. Occupational contact allergy to monomeric isocyanates. *Contact Dermat.* 67, 78–88.
- Bello, D., Herrick, C., Smith, T., Woskie, S., Streicher, R., Cullen, M., Liu, Y., Redlich, C., 2007. Skin exposure to isocyanates: reasons for concern. *Environ. Health Perspect.* 115, 328–335.
- Bentur, Shoshani, O., Tabak, A., Bin-Nun, A., Ramon, Y., Ulman, Y., Berger, Y., Nachlieli, T., Peled, Y.J., 1998. Prolonged elimination half-life of phenol after dermal exposure. *J. Toxicol. Clin. Toxicol.* 36 (7), 707–711.
- Cocker, J., 2011. Biological monitoring for isocyanates. *Ann. Occup. Hyg.* 55, 127–131.
- Dalene, M., Skarping, G., Lind, P., 1997. Workers Exposed to thermal degradation products of TDI and MDI-based polyurethane: biomonitoring of 2,4-TDA 2, 6-TDA and 4,4'-MDA in hydrolyzed urine and plasma. *Am. Ind. Hyg. Assoc. J.* 58, 587–591.
- Engfeldt, M., Isaksson, M., Zimerson, E., Bruze, M., 2013. Several cases of work-related allergic contact dermatitis caused by isocyanates at a company manufacturing heat exchangers. *Contact Dermat.* 68, 175–180.
- Fent, K., Jayaraj, K., Gold, A., Ball, L., Nylander-French, L., 2006. Tape-strip sampling for measuring dermal exposure to 1,6-hexamethylene diisocyanate. *Scand. J. Work Environ. Health* 32, 225–231.
- Gaines, L., Fent, K., Flack, S., Thomasen, J., Ball, L., Richardson, D., Ding, K., Whittaker, S., Nylander-French, L., 2010. Urine 1,6-hexamethylenediamine (HAD) levels among workers exposed to 1,6-hexamethylene diisocyanate (HDI). *Ann. Occup. Hyg.* 54, 678–691.
- Hamada, H., Isaksson, M., Bruze, M., Engfeldt, M., Liljelind, L., Axelsson, S., Jönsson, B., Tinnerberg, H., Zimerson, E., 2012. Dermal uptake study with 4,4'-diphenylmethane diisocyanate led to active sensitization. *Contact Dermat.* 66, 101–105.
- Henriks-Eckerman, M.-L., Mäkelä, E., 2014. A new penetration test method: protection efficiency of glove and clothing materials against diphenylmethane diisocyanate (MDI). *Ann. Occup. Hyg.* doi:http://dx.doi.org/10.1093/annhyg/meu078.
- Hoffmann, H., Leibold, E., Ehnes, C., Fabian, E., Landsiedel, R., Poole, A., 2010. Dermal uptake and excretion of ¹⁴C-toluene diisocyanate (TDI) and ¹⁴C-methylene diphenyl diisocyanate (MDI) in male rats. Clinical signs and histopathology following dermal exposure of male rats to TDI. *Toxicol. Lett.* 199, 364–371.
- ISO 16702, 2007. Workplace air quality – determination of total isocyanate groups in air using 1-(2-methoxyphenyl) piperazine and liquid chromatography.
- Kääriä, K., Hirvonen, A., Norppa, H., Piirä, P., Vainio, H., Rosenberg, C., 2001. Exposure to 4,4'-methylenediphenyl diisocyanate (MDI) during moulding of rigid polyurethane foam: determination of airborne MDI and urinary 4,4'-methylenedianiline (MDA). *Analyst* 126, 476–479.
- Laitinen, J., Mäkelä, M., Mikkola, J., Huttu, I., 2012. Firefighters' multiple exposure assessments in practice. *Toxicol. Lett.* 213, 129–133.
- Liljelind, L., Norberg, C., Egelrud, L., Westberg, H., Eriksson, K., Nylander-French, L., 2010. Dermal and inhalation exposure to methylene bisphenyl isocyanate (MDI) in iron foundry workers. *Ann. Occup. Hyg.* 54, 31–40.
- Mäkelä, E.A., Henriks-Eckerman, M.-L., Ylinen, K., Vuokko, A., Suuronen, K., 2014. Permeation tests of glove and clothing materials against sensitizing chemicals using diphenylmethane diisocyanate as an example. *Ann. Occup. Hyg.* 58, 921–930.
- Redlich, C., 2010. Skin exposure and asthma: is there a connection? *Proc. Am. Thorac. Soc.* 7, 134–137.
- Rosenberg, C., Nikkilä, K., Henriks-Eckerman, M.-L., Peltonen, K., Engström, K., 2002. Biological monitoring of aromatic diisocyanates in workers exposed to thermal degradation products of polyurethanes. *J. Environ. Monit.* 4, 711–716.
- Suojalehto, H., Lindström, I., Henriks-Eckerman, M.-L., Jungewelter, S., Suuronen, K., 2011. Occupational asthma related to low levels of airborne methylenediphenyl diisocyanate (MDI) in orthopedic casting work. *Am. J. Ind. Med.* 54, 906–911.
- Tinnerberg, H., Broberg, K., Lindh, C.H., Jönsson, B.A.G., 2014. Biomarkers of exposure in Monday morning urine samples as a long-term measure of exposure to aromatic diisocyanates. *Int. Arch. Occup. Environ. Health* 87, 365–372.