Biological monitoring of TDI-derived amines in polyurethane foam production

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Background  Toluene diisocyanate (TDI) is used in industry in the production of flexible polyurethane foam, commonly a mixture of the 2,4- and 2,6- isomers. The production process may lead to exposure to diisocyanates which are associated with respiratory disease. A method has been available for the determination of TDI biomarkers in urine for some years.

Aims  To explore the usefulness of urinary toluenediamine (uTDA) in assessing whether dermal absorption of diisocyanates makes a significant contribution to a worker's total exposure.

Methods  Twenty-six workers took part in the study. Thirteen workers whose duties brought them into physical contact with uncured polyurethane foam during their shift (handlers) were compared to a control group of 13 workers in the same block plant environment had no physical contact with uncured foam on the day that sampling took place (non-handlers). Creatinine-adjusted uTDA levels in the two groups were compared across a work shift.

Results  Both groups of workers were exposed to similar levels of airborne TDI. Ten handlers were found to have TDA in post-shift urine samples above detection limits compared with two non-handlers (P < 0.05). No clear relationship was found between the level of airborne TDI exposure and post-shift uTDA.

Conclusions  uTDA provides a useful indication of the contribution which skin absorption makes to total TDI exposure. The results suggest that skin protection when handling uncured polyurethane foam may not receive sufficient consideration.

Key words  Biological monitoring; Polyurethane; Toluene diamine; Toluene diisocyanate.

Introduction  Isocyanates are highly reactive chemicals used in industry in the production of polyurethane products, surface coatings, adhesives and paints. Toluene diisocyanate (TDI) reacts rapidly with polyols in the presence of amines in the manufacture of flexible polyurethane foam for the furniture, bedding and automotive industries. A mixture of the 2,4- and 2,6-TDI isomers are commonly used (Figure 1). The production process may lead to exposure to diisocyanates which are irritant to skin, mucous membranes and respiratory tract. They can also be associated with hypersensitivity reactions including contact dermatitis and hypersensitivity pneumonitis. The respiratory effects of isocyanates have been well studied [1]. Isocyanates were the most commonly cited agents causing occupational asthma in the UK in reporting schemes for industrial disease including Surveillance of work related and occupational respiratory disease and Occupational physicians reporting activity and the national Industrial Injuries Benefit schemes in the three years 1999–2001 [2].

Although the respiratory route of exposure is the one most commonly associated with the development of isocyanate asthma, it may not be the only route involved in the pathogenesis of isocyanate-induced sensitization.

The exposure pattern to isocyanates is complicated, and may not be fully characterized by air monitoring methods which give no indication whether dermal absorption may be occurring. Therefore, it has been suggested that biomarkers for isocyanate exposure may be valuable in the work environment [3]. A method has been available for the determination of biological markers for TDI in the urine for some years [4]. This relies on the detection of the amine corresponding to the isocyanate in hydrolysed urine, i.e. 2,4- and 2,6-toluenediamine (TDA). Urinary TDA (uTDA) offers the potential for use as a non-invasive measure of the total dose of diisocyanate absorbed into the body by all routes [5] and may therefore allow for more accurate assessment than airborne monitoring.
This study aimed to explore the value of uTDA at a polyurethane foam block production plant in assessing whether dermal absorption of diisocyanates made a significant contribution to a worker’s total exposure.

Methods

The study took place at a polyurethane block plant. The plant produced flexible polyurethane foam using an 80 : 20 mixture of 2,4- and 2,6-TDI. This was mixed with a polyol and other reagents including catalysts and blowing agents to volumize the foam and then poured via a foaming nozzle onto Kraft paper (a type of strong smooth brown wrapping paper) on a moving conveyor. The conveyor was enclosed within a ventilated curing tunnel. At the end of the tunnel, the Kraft paper was taken off and the foam slab cut into blocks which were then handled into a racking system to cool and complete the curing process. Foam production took place for between 2 and 6 h per day over the monitoring period.

Respiratory protection was used for short periods when performing tasks where exposure to TDI could be above occupational exposure limits. When not producing foam, workers were engaged in a variety of activities around the block plant. Gloves made of fabric and leather were worn by most of the workers when handling hot blocks of uncured foam but no other skin protection apart from general purpose work clothing was worn.

Twenty-six workers were included in the study. The study group comprised 13 workers whose duties brought them into direct skin contact with uncured polyurethane foam during their shift. Uncured foam was defined as foam within 24 h of being produced. The control group of 13 workers in the same block plant environment had no physical contact with uncured foam on the day that sampling took place but as they were working in the same environment had the potential for exposure by inhalation.

All were interviewed by an occupational physician (S.A.) about their length of employment, work tasks and smoking habits. Sampling started on the second day of the working week after a work stop at the weekend and was carried out over four consecutive days of polyurethane foam block production.

Personal and static sampling was undertaken to evaluate exposure to TDI using personal tape monitors manufactured by Mobay Chemical Corporation (supplied in the UK by MDA Scientific Chicago, IL, USA) worn on the chest of the worker. These comprise a chemically impregnated paper tape which is drawn continuously through a sampling aperture in the tape drive unit. A separate battery-operated sampling pump is used to draw the air sample through the tape at a flow rate of 200 ms/min. Where the sampled air contains isocyanate, a grey/purple stain develops on the tape. At the end of the monitoring period, the tape is inserted into a cassette protecting it from exposure to light and allowed to develop over a period of at least 6 h. The tape is then passed through an optical device which then converts the intensity of the stain into an electrical signal which is recorded on a chart as a ‘Datagram’.

In the case of one worker, it proved impractical to use a paper tape monitor in conjunction with the safety harness which he was required to wear at times during the shift. Consequently, the exposure of this worker was measured by a different technique using a diffusion badge (MDHS 25/3).

In addition to personal sampling, samplers were fixed at specific locations where work tasks were being performed on the plant in order to establish the level of isocyanate at that location.

A total of 30 air samples were analysed, of which 26 were personal samples and 4 were static samples. The sampling period ranged from 319 to 470 min (mean 409 min) depending upon the work task. The method of air monitoring used measured the total combined levels of the 2,4- and 2,6-TDI isomers present but not the individual level of each isomer.

Urine samples were collected at the beginning and the end of the work shift. Twenty-six samples were obtained from both the handlers and the non-handlers. A questionnaire was used by an observer (S.A.) through the shift to assess the work tasks completed during the shift for their manual handling content. A protocol was devised for taking urine samples for TDA analysis to avoid contamination of the sample by material from the skin or from clothing. The urine analysis was performed by the Health and Safety Laboratory, Buxton.

Results

Twenty-four of the workers were male and two female. Their mean age was 38 years (range 22–55 years). Their mean duration of potential TDI exposure in current employment was 15 years (range 1–37 years). Three of the handling group and five of the non-handlers were smokers. None of the workers reported work-related symptoms of skin or respiratory disorder.

There was no statistically significant difference in airborne TDI levels between the two groups (see Table 1). All the personal TDI exposures were below the exposure
limits being in the range of 18–42% of the Maximum Exposure Limit [20 µg NCO per m³, 8-h time-weighted average (equivalent to 5.7 ppb); 70 µg NCO per m³, 15-min time-weighted average (equivalent to 20 ppb)].

An increase in the total number of post-shift samples with detectable levels of uTDA compared to the total number of pre-shift samples was found (P < 0.05), see Table 1. Four handlers had detectable levels of uTDA present in pre-shift urine and in one of these the level was >1.0 µmol/mol creatinine (range 0.30–1.60 µmol/mol creatinine). In comparison, no uTDA (<0.05 µmol/mol creatinine) was detected in any of the pre-shift urine samples for non-handlers (P < 0.05). The mean pre-shift uTDA in the handlers was 0.24 µmol/mol creatinine. Only the less reactive 2,6-TDA was found in the pre-shift samples.

After shift, 10 out of 13 handlers had detectable uTDA with a mean level of 2.21 µmol/mol creatinine. In seven handlers, the level was >1.0 µmol/mol creatinine (range 0.30–1.60 µmol/mol creatinine). In comparison, only two non-handlers had detectable uTDA, this difference being significant (P < 0.01). The pre- and post-shift uTDA levels for each handler are shown in Figure 2.

No clear relationship was found between the level of TDI exposure and post-shift uTDA. The correlation coefficient was 0.027 between post-shift uTDA and the product of airborne TDI concentration and sampling time in those samples with levels above detection limits. Linear regression showed no correlation between post-shift uTDA and level of exposure to TDI. Smoking status showed no relation to post-shift uTDA level. There was no relation between the duration of employment of workers on the block plant and uTDA level. As uTDA levels are predominantly a marker of recent exposure, this is to be expected.

2,6-TDA was more frequently identified than 2,4-TDA in post-shift urine. The ratio of 2,4-:2,6-TDA in post-shift urine differed in the two groups with the level of the 2,6-TDA isomer in the handlers 36 times higher than that of the 2,4-TDA. In marked comparison, the ratio of the isomers in post-shift urine in non-handlers showed little increase in 2,6-TDA relative to 2,4-TDA (Table 2).

**Table 1.** TDI and uTDA levels in handlers and non-handlers

<table>
<thead>
<tr>
<th></th>
<th>Handlers</th>
<th>Non-handlers</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>13</td>
<td>13</td>
</tr>
<tr>
<td>Mean TDI</td>
<td>2.7 µg/m³ NCO</td>
<td>2.6 µg/m³ NCO</td>
</tr>
<tr>
<td>Range</td>
<td>&lt;3.5–8.4 µg/m³ NCO</td>
<td>&lt;3.8–8.4 µg/m³ NCO</td>
</tr>
<tr>
<td>uTDA detected before shift</td>
<td>4/13</td>
<td>0/13</td>
</tr>
<tr>
<td>uTDA detected after shift</td>
<td>10/13</td>
<td>2/13</td>
</tr>
<tr>
<td>Mean uTDA after shift</td>
<td>2.21 µmol/mol creatinine</td>
<td>0.11 µmol/mol creatinine</td>
</tr>
</tbody>
</table>

**Discussion**

This study suggests that manual handlers of uncured polyurethane foam are significantly more likely to have detectable uTDA than non-handlers working in similar air levels of TDI. The uTDA levels found in this study were comparable to those in similar studies in a workplace setting [3,6,7]. There are no previous data in the literature which indicate how dermal exposure to TDI will affect TDA levels in hydrolysed urine.

Urine samples mainly reflect only several hours of exposure due to the short half-life of uTDA. However, air samples reflect exposure throughout a shift. Therefore, the level of uTDA measured in post-shift samples in this study cannot be considered as a completely accurate comparison with TDI exposure.

Only the 2,6-TDA isomer was found in pre-shift urine and 2,6-TDA was more frequently identified than 2,4-TDA in post-shift urine (Table 2). This is a reversal of the ratio of the two isomers in the starting mix which constituted 2,4-TDI and 2,6-TDI in an 80:20 ratio. This ratio varies according to the stage of the production process with operatives working on the foam head at the forward end of the conveyor likely to be exposed to a relatively lower ratio of 2,6-TDI than those working further down the conveyor where the lower reactivity of the 2,6-TDI isomer allows greater release into the environment than the more reactive 2,4-TDI. Maitre et al. [7] also observed a greater proportion of 2,6-TDA relative to 2,4-TDA in urine of workers compared with the proportion of the two isomers of TDI in the workplace atmosphere, and this was suggested to reflect a contribution from dermal absorption. The marked difference in the ratio of the two isomers in post-shift urine of handlers and non-handlers in this study may also support the interpretation that 2,6-TDI is more readily absorbed through the skin. The differing reactivity of the two isomers and differences in their toxicokinetics may also contribute towards this finding. However, it is not possible to determine the precise contribution made by skin
absorption in this study. Further studies would be valuable, although the polyurethane block plant in which this study was carried out was one of the largest in the UK, and so it may be difficult to find a larger sample of workers for a similar study in an occupational setting.

Both handlers and non-handlers of uncured polyurethane foam were working in similar airborne TDI concentrations. However, the workload of handlers tends to be a more physically demanding one than that of non-handlers. Physical work, with its higher respiratory rate, will result in a higher volume of air inhaled during the shift and therefore handlers may thus be subject to a greater TDI exposure during a shift in the same environment than non-handlers. This makes difficult any accurate assessment of the contribution which skin absorption may play in uTDA levels found in the handling group. However, the magnitude of the difference in post-shift uTDA levels between handlers (mean uTDA = 2.21 μmol/mol creatinine) and non-handlers (mean uTDA = 0.11 μmol/mol creatinine) shows a 20-fold difference which would be difficult to account for simply by differences in respiratory rate (Table 2).

The personal protective equipment worn by handlers included gloves in most cases although gloves worn were made of fabric and leather and not designed for chemical resistance, so that there was a possibility of TDI exposure through the glove. However, the clothing worn was otherwise variable, although most workers wore a short-sleeved work shirt and work trousers. These left the possibility of absorption of TDI through the skin of the forearms and through a single layer of clothing. The blocks of uncured polyurethane foam produced by the block plant were typically of the order 2 m³ and workers required close contact in order to manoeuvre them into the racking system. Such close contact also brings the uncured foam to within 30 cm of the breathing zone with the potential for respiratory exposure. Skin absorption in handlers may also be affected by the more physically demanding nature of the tasks which they perform and which may lead to increased skin blood flow or sweat rate.

This study attempted to avoid contamination of the urine samples taken with material containing TDI using a simple decontamination protocol. Previously published studies have given no indication of whether a urine-sampling protocol has been applied. This is necessary in view of the potential for transfer of contamination from the skin (hands and genital area) and clothing into the urine sample. Even low levels of contamination would potentially influence the urine results greatly.

In protecting workers from the potential effects of isocyanate exposure, much effort has been made to avoid inhalation or to otherwise reduce airborne isocyanate levels as far as reasonably practicable by means of closed systems and ventilation [8]. When other methods of controlling worker exposures are insufficient, a variety of respirators are available. These may be used during situations such as the implementation of engineering controls, short duration maintenance procedures and emergency situations. However, the issue of appropriate skin protection may not receive sufficient consideration at times. This study suggests that uTDA is a useful and practical method of assessing the contribution which dermal absorption of diisocyanates makes to a worker’s total exposure. The results indicate that dermal absorption can occur in workers handling uncured polyurethane foam. Non-contact work practices should perhaps be given more consideration and when avoidance of physical contact is impracticable, such workers should be provided with and required to use appropriate skin protection such as impermeable overalls, aprons, chemically resistant gloves or gauntlets, goggles or face shields in addition to suitable respiratory protection.

Conflicts of interest
None declared.

References
3. Dalene M, Skarping G, Lind P. Workers exposed to thermal degradation products of TDI- and MDI-based

Table 2. Ratio of the isomers 2,4- and 2,6-TDA in post-shift urine

<table>
<thead>
<tr>
<th></th>
<th>Mean post-shift 2,4-TDA μmol/mol creatinine</th>
<th>Mean post-shift 2,6-TDA μmol/mol creatinine</th>
<th>Mean post-shift total TDA μmol/mol creatinine</th>
<th>Ratio 2,4- : 2,6-TDA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Handlers</td>
<td>0.06</td>
<td>2.15</td>
<td>2.21</td>
<td>1 : 36</td>
</tr>
<tr>
<td>Non-handlers</td>
<td>0.05</td>
<td>0.06</td>
<td>0.11</td>
<td>1 : 1.2</td>
</tr>
</tbody>
</table>

S. AUSTIN: TDI-DERIVED AMINES IN POLYURETHANE FOAM PRODUCTION 447
polyurethane: biomonitoring of 2,4-TDA, 2,6-TDA and 4,4-MDA in hydrolysed urine and plasma. *Am Ind Hyg Assoc J* 1997;58:587–591.


