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Exposure to 2,4- and 2,6-toluene diisocyanate (TDI) during production of flexible foam: determination of airborne TDI and urinary 2,4- and 2,6-toluenediamine (TDA)

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Occupational exposure to 2,4- and 2,6-toluene diisocyanate (2,4- and 2,6-TDI) was measured during the production of flexible foam. The usefulness of urinalysis of the TDI-derived amines, 2,4- and 2,6-toluenediamine (2,4- and 2,6-TDA), for exposure assessment was compared with air monitoring. Urine samples were collected from 17 employees at two plants. The workers' personal exposure was measured using 1-(2-methoxyphenyl)-piperazine (2MP)-impregnated glass fibre filters for sampling and high-performance liquid chromatography (HPLC) with ultraviolet (UV) and electrochemical (EC) detection for quantification. The limit of detection (LOD) of 2,4- and 2,6-TDI was 0.01 μg ml^{-1} for a 20 μl injection. The precision of sample preparation, expressed as the relative standard deviation (RSD), was 0.6% with UV detection and 0.8% with EC detection at a 2,4-TDI concentration of 0.2 μg ml^{-1} (n = 6). For 2,6-TDI, the corresponding RSDs were 0.5% and 0.8%. The urinary 2,4- and 2,6-TDA metabolites were determined after acid hydrolysis as heptafluorobutyric anhydride derivatives by gas chromatography-mass spectrometry. The LOD in urine was 0.35 nmol l^{-1} for 2,4-TDA and 0.04 nmol l^{-1} for 2,6-TDA. The precision (RSD) of six analyses of human urine spiked to a concentration of 100 nmol l^{-1} was 3.7% for 2,4-TDA and 3.6% for 2,6-TDA. There was a trend for linear correlation between urinary TDA concentration and the product of airborne TDI concentration and sampling time. Urinalysis of TDA is proposed as a practical method for assessing personal exposures in workers exposed intermittently to TDI.

Introduction

Diisocyanates are reactive molecules containing two NCO functional groups. They are used in the manufacture of polyurethane products, such as flexible and rigid foams, elastomers, coatings, paints and adhesives. The aromatic toluene diisocyanate (TDI) is one of the commonest industrial isocyanates and is mainly used in the production of flexible foam for furniture, bedding and car upholstery.[1] Diisocyanates are irritating to the skin, mucous membranes, eyes and respiratory tract. Because of their wide range of applications in many workplaces, diisocyanates have become one of the main chemical causes of occupational asthma. Other health disorders include contact dermatitis and hypersensitivity pneumonitis.[2–5]

Diisocyanates undergo hydrolysis in the body,[6] resulting in diamines which are excreted in the urine. Toluenediamine (TDA) was detected in the urine of volunteers exposed to TDI in a test chamber.[7] TDA has also been found in the urine of workers occupationally exposed to TDI during foam production,[8–12] or in work environments where TDI-based foam or glue may be thermally degraded.[13–16]

The identification and quantification of isocyanates in air have been intensively investigated for many years.[17–22] A derivatisation reagent is required to stabilise the isocyanate moiety during sampling. Air is usually sampled either by bubbling it through an absorbent solution or by filtering it through a reagent-impregnated solid sorbent medium or glass fibre filter. The derivatives are separated by high-performance liquid chromatography (HPLC) combined with ultraviolet (UV), fluorescence, electrochemical (EC) or mass spectrometric (MS) detection.

Our previous findings suggested that worker exposure to 4,4′-methylenediphenyl diisocyanate (MDI) during rigid polyurethane foam production can be assessed by the determination of urinary methylenedianiline (MDA), but a poor correlation was found between airborne MDI and urinary MDA.[23] Here we extend our study to worker exposure to TDI during the manufacture of flexible slab foam. The usefulness of urinary TDA analysis for exposure assessment was evaluated by comparison with air monitoring. The workers' exposure profiles were utilised in a supplementary study of cytogenetic effects and genetic polymorphisms in isocyanate-metabolising enzymes in relation to individual susceptibility for the development of occupational asthma.

Experimental

Chemicals

Acetonitrile (HPLC grade) and ethyl acetate (SupraSolv) were purchased from Merck (Darmstadt, Germany), dichloromethane from Rathburn (Walkerburn, UK) and toluene from J.T.

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Baker (Deventer, The Netherlands). Acetic acid, acetic acid anhydride, sodium sulfate, methanol, sulfuric acid, sodium hydroxide, sodium chloride, sodium acetate, potassium dihydrogen phosphate (KH_2PO_4), all p.a. grade, were obtained from Merck. Heptafluorobutyric anhydride (HFBA) and 1-(2-methoxyphenyl)-piperazine (2MP) were purchased from Fluka Chemie (Buchs, Switzerland). 2,4- and 2,6-TDI ($C_9H_6N_2O_2$; M_r 174.2; CAS nos. 584-84-9 and 91-08-7) and 2,4- and 2,6-TDA ($C_7H_{10}N_2$; M_r 122.2; CAS nos. 95-80-7 and 823-40-5) were obtained from Aldrich (Steinheim, Germany). Trideuterated 2,4- and 2,6-TDA (2,4-d_3- and 2,6-d_3-TDA) were obtained from Synthelec (Lund, Sweden) and deuterated aniline (d_5) from Cambridge Isotope Laboratories (Andover, MA, USA).

Instrumentation

HPLC. TDI–2MP derivatives were determined using an HPLC system consisting of two Waters 510 pump units, a Waters 717 plus autosampler, a Waters 996 photodiode array (PDA) detector and a Waters 464 pulsed EC detector (Waters, Milford, MA, USA). The system was equipped with Millennium software. The compounds were separated at ambient temperature on a Sphereclone ODS (2) (4.6 × 150 mm, 3.0 μm) column preceded by a C_{18} guard column. The mobile phase consisted of acetonitrile–water (0.45 + 0.55) with 2.2 g sodium acetate per litre at pH 6, pumped at a flow rate of 1 ml min^{-1}. The injection volume was 20 μl. During the chromatographic run, UV spectra in the range 232–264 nm were monitored. The peak at 242 nm was extracted for quantification (Fig. 1). The EC detector was operated at +800 mV at ambient temperature in the 100 nA range (Fig. 2). The 2,4- and 2,6-TDI–2MP derivatives eluted at 11.4 and 8.1 min, respectively. The instrumental limit of detection (LOD) was 0.01 μg ml^{-1} for a 20 μl injection for both isomers. The response was linear over the range 0.01–50 μg ml^{-1} with the PDA detector and 0.01–1 μg ml^{-1} with the EC detector.

Gas chromatography-mass spectrometry. The gas chromatographic-mass spectrometric (GC-MS) apparatus consisted of a Hewlett-Packard 5989A mass spectrometer (Palo Alto, CA, USA) connected to a Hewlett-Packard 5890 Series II chromatograph equipped with a Hewlett-Packard 7673 autosampler (Little Falls, DE, USA). The HFBA derivatives of the amines were separated on a fused silica capillary column (HP-5, 25 m × 0.32 mm × 0.17 μm). Helium was used as the carrier gas at a flow rate of 1.5 ml min^{-1}. Samples (1 μl) were injected in the splitless mode at an inlet temperature of 260 °C and with a splitless time of 30 s. The column temperature program was as follows: 50 °C for 1.0 min, increase at 10 °C min^{-1} to 150 °C, increase at 20 °C min^{-1} to 230 °C, increase at 30 °C min^{-1} to 300 °C. The following parameter settings were used when the mass spectrometer was operated in the electron impact (EI) ionisation mode: interface temperature 260 °C, ion source temperature 300 °C, quadrupole temperature 100 °C, electron energy 70 eV. 2,4-d_3-TDA and 2,6-d_3-TDA were used as

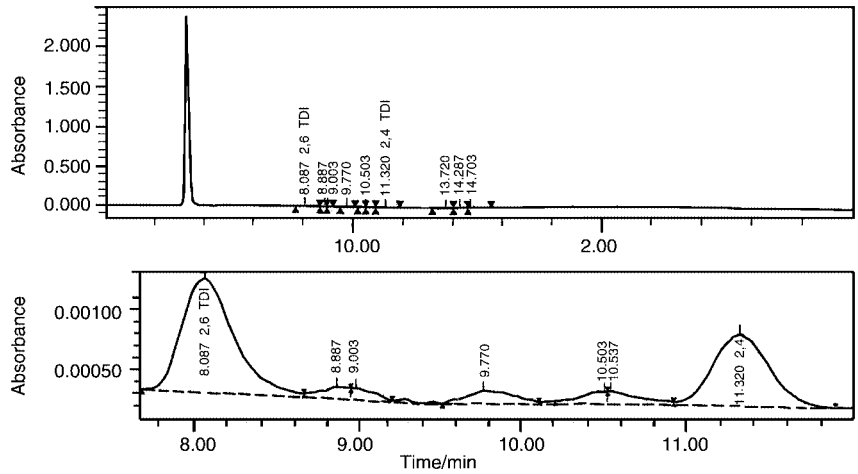

Fig. 1 HPLC-UV (at 242 nm) chromatogram of 2MP derivatives of TDI in an extract from a filter of a workplace air sample, showing 0.11 μg of 2,6-TDI (8.1 min) and 0.046 μg of 2,4-TDI (11.4 min).

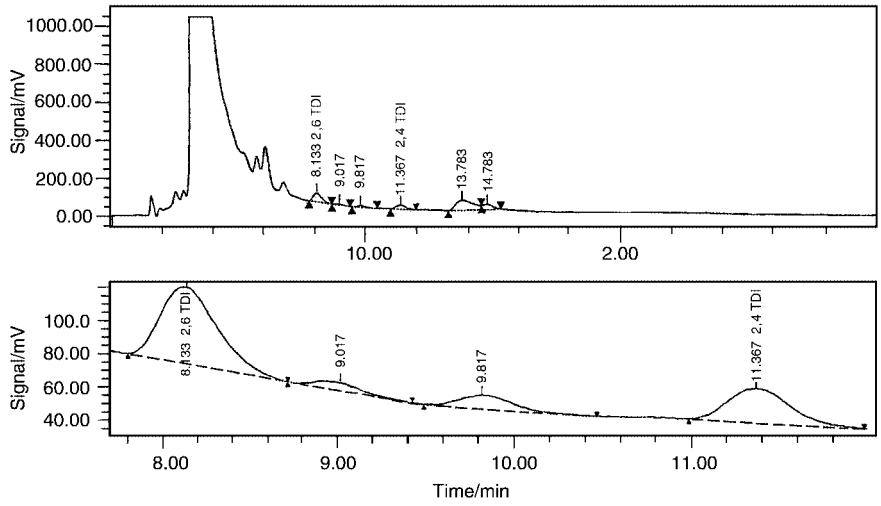

Fig. 2 HPLC-EC chromatogram of the sample shown in Fig. 1.

internal standards. The retention times of the 2,4- and 2,6-TDA derivatives were 12.2 and 12.0 min, respectively (Fig. 3). The following mass fragments were monitored with a dwell time of 60 ms: *m*/*z* 345 (M-C_3F_7) and *m*/*z* 514 (molecular ion) for di-HFBA derivatives of 2,4- and 2,6-TDA. The corresponding ions for the di-HFBA-d_3 derivatives were *m*/*z* 348 and *m*/*z* 517. Aniline-d_5 was used as recovery standard and the HFBA derivative was monitored with a dwell time of 80 ms: *m*/*z* 125 (M-C_3F_7) and *m*/*z* 294 (molecular ion). Low concentrations were analysed by operating the mass spectrometer in the negative chemical ionisation (NCI) mode with methane as reagent gas (≈ 1.4 Torr). The MS instrument parameter settings in the NCI mode were as follows: interface temperature 260 °C, ion source temperature 170 °C, quadrupole temperature 100 °C, electron energy 230 eV. The following mass fragments, corresponding to the M-20 ions, were monitored with a dwell time of 100 ms: *m*/*z* 274 for HFBA-d_5-aniline, *m*/*z* 494 for di-HFBA derivatives of 2,4- and 2,6-TDA, *m*/*z* 497 for di-HFBA derivatives of 2,4-d_3- and 2,6-d_3-TDA. The instrumental LOD was 200 fg μl^{-1}. The response was linear up to 200 pg μl^{-1}.

Subjects

This study was performed at two factories in southern and western Finland in 1996–1997. Seventeen workers (three women, 14 men) were interviewed about their work tasks, employment time, subjective airways or skin symptoms and smoking habits. The mean age of the workers was 42 years (range, 25–55 years), and the mean duration of potential exposure was 16 years (range, 1–35 years). Twelve of the workers were non-smokers and five were current smokers. Two of the workers reported perennial or seasonal rhinitis and two workers (including one current smoker) reported prolonged cough. Three workers experienced dyspnoea and two workers reported wheezing. Both workers who reported wheezing had a personal and family history of atopy. None of the aforementioned symptoms were reported as work related. Three workers (including one current smoker) suffered from phlegm production; two (including one current smoker) associated these symptoms with work. No-one reported having work-related eczema.

Description of the manufacturing process and exposure assessment

The two plants manufactured flexible polyurethane foam in a continuous slab stock process using an 80:20 mixture of 2,4- and 2,6-TDI as starting monomer. Plant 1 applied high-pressure moulding whereby the TDI and the polyol components were pumped from tanks and mixed together in a foaming nozzle and poured onto the foam conveyor. Plant 2 applied low-pressure moulding whereby the components were mixed together before entering the foaming nozzle. In both plants, the foam slab was cured on a conveyor belt lined with kraft paper. The conveyor was enclosed in a ventilated tunnel. At the end of the tunnel, the kraft paper was stripped off, and the slab was cut into blocks and moved to a maturing room for final curing. The foam was usually processed further after 3 days of storage. Stationary samples and personal breathing zone samples of air were taken at various stages of the process: preparation for moulding, pouring of the mixture onto the conveyor (forward end of the moulding line), paper stripping, transportation of blocks to the maturing room and cutting of matured foam into final products. Plant 1 had a 'crush room' in addition to the moulding line. In the crush room, waste foam from the cutting room was crushed into small pieces in a crush mill and then glued and pressed into blocks in a crush press. The glue contained 16% TDI, and polymerisation was achieved with water vapour.

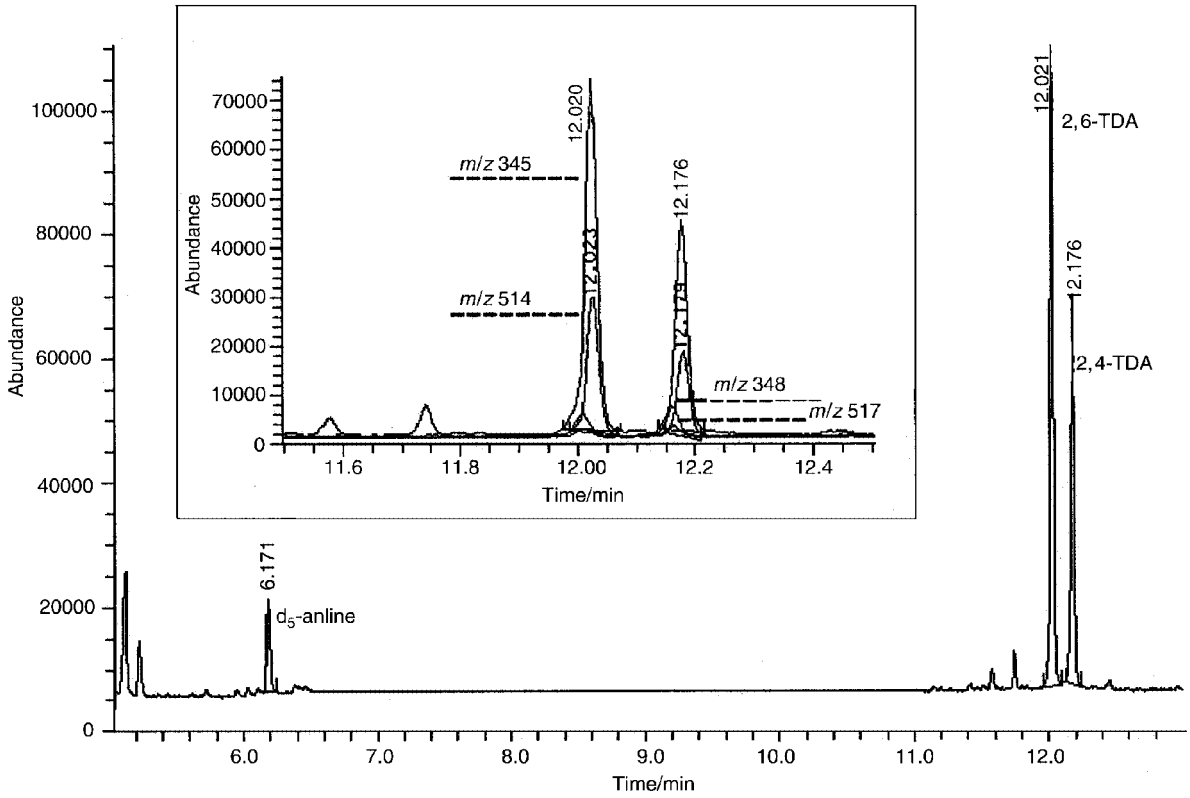

Fig. 3 GC-MS-EI total ion chromatogram of hydrolysed urine from a TDI-exposed worker. The inset shows the extracted ions *m*/*z* 514 and 345 (native TDA) and *m*/*z* 517 and 348 (d_3-TDA) of HFBA-acylated TDA. The 2,6-isomer (152 nmol l^{-1}) elutes at 12.0 min and the 2,4-isomer (67 nmol l^{-1}) at 12.2 min.

Air was sampled during one work shift on two consecutive days. Sampling was started on the second day of the working week after a production stop during the weekend. Altogether 133 air samples were analysed, of which 96 were personal samples from a worker's breathing zone and 37 were stationary samples. The sampling periods ranged from 5 to 250 min depending on the work task.

Urine samples were collected before, in the middle and at the end of the work shift. The samples were correspondingly labelled as A, B and C for the first sampling day and D, E and F for the second sampling day. Altogether, 100 urine samples were obtained from potentially exposed workers. Additionally, 12 urine samples were obtained from non-exposed workers. Written informed consent was obtained from the workers for the urine analyses.

Sampling and work-up procedure

Air samples. Workers' exposures to airborne 2,4- and 2,6-TDI were determined by drawing air through a reagent-impregnated glass fibre filter (Millipore Cat. no. AP4002405; Millipore, Bedford, MA, USA) placed in a filter holder (Millipore Cat. no. Swinnex SX00 02500) at a flow rate of 1 l min^{-1}. The filters were impregnated with 200 μl of 0.052 M 2MP in toluene.[24] Immediately after sampling, the filters were removed from the holders and placed in a glass tube containing 2 ml of 260 μM 2MP absorption solution in toluene. The samples were stored at +4 °C until further preparation. Before analysis, excess derivatisation reagent was removed by the addition of 100 μl acetic acid anhydride. The toluene was evaporated to dryness under a gentle stream of nitrogen. The residue was dissolved in 2 ml of acetonitrile, and the tube was placed in an ultrasonic bath for 10 min followed by centrifugation (10 min, 2500 rpm) before injection into the liquid chromatograph.

The reproducibility of the chromatographic method was examined by including a control sample as every sixth sample in the series. Follow-up reports for response and retention time were created. The precision (expressed as the relative standard deviation, RSD) was 0.6% for 2,4-TDI and 0.5% for 2,6-TDI at a concentration of 0.2 μg ml^{-1} (n = 6) with the PDA detector. The RSD was 0.8% for both isomers with the EC detector. The recovery of 2,4-TDI spiked on the filter at a concentration of 0.5 μg ml^{-1} was 88% with UV detection and 73% with EC detection. The corresponding recoveries of 2,6-TDI were 94% and 69% with UV and EC detection, respectively. The limit of quantification was 0.2 μg m^{-3} for a 200 l air sample.

Urine samples. The urine samples were made acidic (pH 4–5) with dilute sulfuric acid immediately after collection. The samples were stored at −20 °C until further preparation. Concentrated sulfuric acid (100 μl) and an internal standard (1800 pg of 2,4-d_3-TDA and 2,6-d_3-TDA in 60 μl of 1 M sulfuric acid) were added to a 1 ml portion of each sample. The sample was allowed to hydrolyse at 100 °C for 16 h. Sodium chloride (0.5 g) and 4 ml of 10 M sodium hydroxide were then added to the sample. The amines were extracted with dichloromethane (2 × 3 ml). The dichloromethane layer was recovered, and 20 μl of HFBA was added to derivatise the amines. The organic phase was washed with phosphate buffer solution (1 M KH_2PO_4, pH 7) and dried with sodium sulfate.[8] The sample was evaporated to dryness under a gentle stream of nitrogen and reconstituted to 60 μl with 300 pg of derivatised d_5-aniline in ethyl acetate. Two blanks and two control samples were prepared in conjunction with every set of actual samples. The precision (RSD) of the work-up and analysis was 3.7% for 2,4-TDA and 3.5% for 2,6-TDA when human urine was spiked to a concentration of 100 nmol l^{-1} (n = 6). The LOD in urine was 0.35 nmol l^{-1} for 2,4-TDA and 0.04 nmol l^{-1} for 2,6-TDA. The urinary concentrations of TDA in exposed workers were corrected for the excretion of creatinine determined by the alkaline picric acid method.[25]

Results and discussion

Airborne TDI

In our previous study,[23] we investigated the stability of a 2MP derivative of MDI stored on dry filters, in the absorbent solution or as a processed sample in acetonitrile for up to 8 weeks. The MDI–2MP derivative proved to be stable irrespective of the storage matrix during the test period. A similar stability test was performed with TDI. The TDI–2MP samples were stored for up to 6 weeks. The 2,4-TDI–2MP derivative was stable in all environments tested for up to 2.5 weeks. No degradation was observed after the 6 week study period in the solutions, whereas on the dry filters 15% of the derivative had degraded. The 2,6-TDI–2MP derivative was stable in an absorbent solution and in an acetonitrile solution for 3 days, but on dry filters a degradation of 20% was observed. A 10% reduction was observed after 2.5 weeks of storage in solutions. Because of the apparent instability of the 2,6-TDI–2MP derivative on the dry filter, samples should be dissolved immediately and analysed within 2.5 weeks.[26,27]

The Finnish occupational exposure limit (OEL) for isocyanates is 35 μg m^{-3} expressed as NCO groups (15 min short-term limit).[28] This value corresponds to 72 μg m^{-3} calculated as TDI. In the factories studied, the exposure levels ranged from less than 0.3% of the OEL to three times the OEL.

In Plant 1, the total TDI concentrations ranged from 'not detected' (< 0.2 μg m^{-3}) to 230 μg m^{-3}. The moulders' mean personal exposure was 76 μg m^{-3} during moulding. Assistants moving fresh slabs to the storage room, stripping the paper and cutting the slab were exposed to a mean TDI concentration of 12 μg m^{-3}. After 3 days, when the matured slab was transported to a workstation where it was form-cut for further processing, concentrations around 1.6 μg m^{-3} were detected in the storage room. However, no TDI was detected in the workers' breathing zone during actual form-cutting. The workers in the crush room were exposed to TDI during the whole work shift. The mean personal exposure level was 11 μg m^{-3} at the crush mill and 29 μg m^{-3} at the crush press.

In Plant 2, the exposures ranged from 'not detected' (< 0.2 μg m^{-3}) to 41 μg m^{-3}. The mean concentration of TDI in the moulders' breathing zone was 16 μg m^{-3} during moulding, but only 1.0 μg m^{-3} during pre-moulding operations. In this plant, the electricians and technicians who occasionally worked in the moulding area were exposed to mean TDI concentrations of 5.6 μg m^{-3} and 1.7 μg m^{-3}, respectively. No TDI was detected at the workstation where matured foam was form-cut for further processing. The mean exposures in Plant 1 and Pant 2 are presented in Table 1. The concentrations detected were similar by stationary sampling and breathing zone sampling.

The proportions of 2,4-TDI and 2,6-TDI in the total exposure varied according to the stage of the production process. In general, 2,6-TDI dominated the samples, constituting about 75% of all TDI detected. At the forward end of the conveyor, where the isocyanate–polyol mixture was poured onto the kraft paper, about 60% of the total airborne TDI was composed of the 2,6-isomer. At the far end of the conveyor, where the slab was cut and the paper stripped, 80% of the detected TDI consisted of the 2,6-isomer. In samples taken from the storage room, where the slabs were held for maturing, only 2,6-TDI was detected. The personal exposures of the technicians consisted solely of 2,6-TDI. In the crush room, the proportions of 2,4- and 2,6-TDI

were 75:25 at the crush press and 50:50 at the crush mill situated a couple of metres from the press. These isomeric ratios remained unchanged over the whole work shift in the crush room.

Our results corroborate previous studies indicating that, during foam production, the 2,6-isomer is more prevalent than the 2,4-isomer.[8,29–31] Although the starting mixture contained only 20% of 2,6-TDI, the lesser reactivity of this isomer allows more of it to be released into the work environment.[32] However, the crush room was an exception in this respect. In the crush room, more or as much 2,4-TDI was detected in the air compared with 2,6-TDI. Thus polymerisation with water vapour seems to alter the relative reactivities of the isomers.

Urinary TDA

All analyses were performed after acid hydrolysis of the urine samples. The amounts given as 2,4- and 2,6-TDA therefore denote the sum of free and hydrolysable compounds.[33] Fig. 4 shows the mean concentrations and ranges of total TDA in urine samples collected before, in the middle and at the end of working hours during two consecutive days. In all, the total TDA concentrations (2,4-TDA and 2,6-TDA) in individual samples were in the range 0.11–39 nmol mmol^{-1} creatinine in Plant 1 and < 0.05–7.1 nmol mmol^{-1} creatinine in Plant 2. The fivefold difference in urinary TDA concentrations between the two plants reflects the different TDI concentration levels between the plants. The high-pressure moulding technique (Plant 1) releases more TDI into the air compared with the low-pressure technique. The mean TDA concentrations in urine were higher in the middle of the work shift than before work, and peaked at the end of the work shift. It is notable that the mean concentrations in samples collected before work were higher than those in non-exposed workers (mean total TDA, 0.05 nmol mmol^{-1} creatinine; range, 0.02–0.1 nmol mmol^{-1} creatinine; n = 12), although the half-life of TDA is relatively short. TDA undergoes biphasic elimination from the body. The half-life is 1.9 h for 2,4-TDA and 1.6 h for 2,6-TDA in the first phase and 5 h for both isomers in the second phase.[34]

The mean TDA concentrations in urine from workers with different job descriptions are presented in Table 1. Generally, the ratio of 2,4- to 2,6-TDA in urine followed the pattern observed in the air samples. Although air analysis indicated exposure to only 2,6-TDI among the technicians in Plant 2, elevated 2,4-TDA concentrations were detected in seven out of 12 urine samples, compared with those in non-exposed workers (mean 2,4-TDA, 0.05 nmol mmol^{-1} creatinine; range, 0.02–0.1 nmol mmol^{-1} creatinine; n = 12). Similarly, TDI concentrations in the breathing zone of the form-cutters were below the detection limit, but still the urinary 2,4-TDA concentrations in five samples out of 18 exceeded the base level found in non-exposed workers. Moreover, the 2,6-TDA concentrations were about ten times those measured in non-exposed workers (mean 2,6-TDA, 0.01 nmol mmol^{-1} creatinine; range, 0.003–0.05 nmol mmol^{-1} creatinine; n = 12). The total TDA concentration was below the detection limit in one urine sample, voided before work.

Urinary metabolites are considered to mark recent exposure, and therefore the mean duration of employment at the workplace does not affect the urinary TDA levels. Nor was smoking related to the TDA levels in urine. For instance, in Plant 1, two of the three smokers were moulding operators and their urinary TDA concentrations were comparable to those of the two non-smoking operators and the two non-smoking crush press operators. Correspondingly, in Plant 2, the two smokers, both of whom were moulding operators, had urinary TDA levels similar to those of the two non-smoking operators. The TDA concentrations in urine were related foremost to the method of

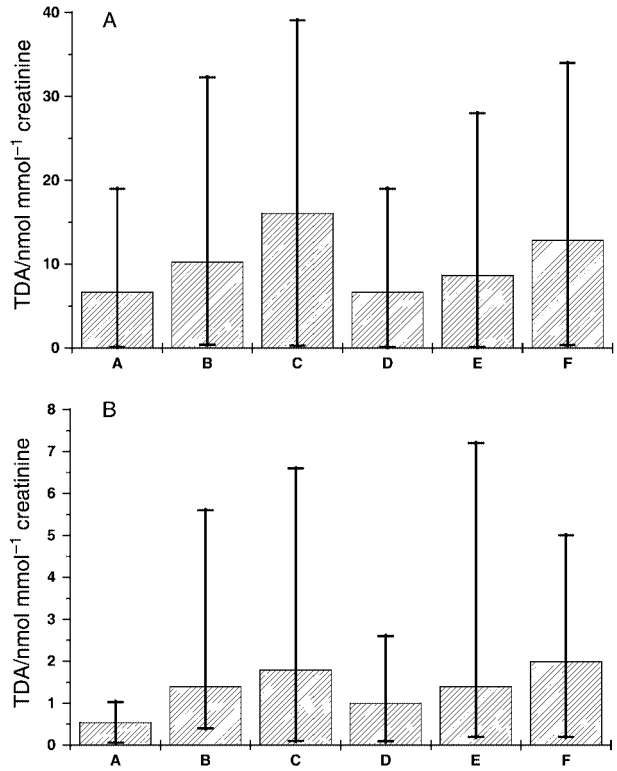

Fig. 4 Mean concentrations and ranges of urinary TDA during two consecutive days in Plant 1 (A) and Plant 2 (B) before work (A and D), in the middle of the work shift (B and E) and at the end of the work shift (C and F).

Table 1 Mean concentrations of airborne TDI (μg m^{-3}) in the flexible foam plants and mean concentrations of TDA (nmol mmol^{-1} creatinine) in the urine of workers during two consecutive days before work (A and D), in the middle (B and E) and at the end (C and F) of the work shift

Job description	Number of workers	TDI/μg m^{-3}	TDA/nmol mmol^{-1} creatinine					
			A	B	C	D	E	F
Plant 1								
Moulding operators	4	32	7.8	9.3	17.6	7.9	8.2	10.7
Crush press operators	2	20	11	23	29	11	28	30
Plant 2								
Moulding operators	4	16	0.89	1.4	0.98	1.4	2.3	2.8
Electricians	2	5.6	0.21	0.58	2.8	0.45	0.36	2.3
Technicians	2	1.7	0.17	3.0	3.4	1.4	1.0	0.97
Plants 1 and 2								
Form-cutters	3	nd[a]	0.27	0.28	0.21	0.14	0.22	0.35

[a] nd, not detected: < 0.2 μg m^{-3}.

moulding, *i.e.* high-pressure *vs.* low-pressure, and to work tasks and thereby to personal exposures to airborne TDI.

Because the exposure was intermittent, except in the crush room, with several peaks during the shift, averaging over time may not be justified when correlating airborne TDI and urinary TDA concentrations. To characterise the exposure accurately, we multiplied the sampling times by the concentrations detected. In this way, a good correlation was obtained between airborne TDI and urinary TDA in samples voided at the end of the work shift in both plants. In Plant 1, the correlation coefficient was 0.91 both for the sum of the isomers and for the 2,6-isomer only (Fig. 5). In Plant 2, the correlation coefficient was 0.86 for the sum of the isomers and 0.89 for the 2,6-isomer only (Fig. 6). The results show that urinary TDA is a good measure of airborne TDI exposure during flexible foam production.

In a Swedish study of flexible foam workers, comparable results to ours were obtained, although no clear correlation between airborne TDI and urinary TDA concentrations was found.[35] The mean concentration of TDI in air was 29.8 μg m^{-3} and the TDA concentrations in urine were in the range 0.2–4 μg $mmol^{-1}$ creatinine (1.6–30 nmol $mmol^{-1}$ creatinine). In a Belgian study,[11] urinary TDA concentrations of 1.6–9.1 μg l^{-1} were found in TDI-exposed workers. These values correspond to 1.1–5.7 nmol $mmol^{-1}$ creatinine using a mean urinary creatinine concentration of 13 mmol l^{-1}.[36] The study did not, however, report any airborne TDI concentrations to support a correlation between respiratory exposure and urinary TDA. A preliminary Finnish study of flexible foam workers in the mid-1980s showed a good correlation between airborne 2,6-TDI and urinary 2,6-TDA.[6]

There is no biological exposure index in Finland for isocyanate-derived amines in the urine after isocyanate exposure. In Germany, the maximum permissible level of 10 μg MDA g^{-1} creatinine (5.7 nmol $mmol^{-1}$ creatinine) is applied to MDI-exposed workers.[37] However, no corresponding limit for urinary TDA has been issued. In a study of Swiss workers, Maitre *et al.*[9] inferred that a biological exposure index of 21 μg TDA g^{-1} creatinine (19.5 nmol $mmol^{-1}$ creatinine) could be used at airborne TDI concentrations close to 40 μg m^{-3}, which is the Swiss limit value for airborne TDI. In another study,[38] the same authors proposed a biological exposure index for hexamethylene diisocyanate (HDI)-exposed workers of 19 μg hexamethylenediamine (HDA) g^{-1} creatinine (18.5 nmol $mmol^{-1}$ creatinine).

The mean TDA concentrations (Fig. 4) found in the present study did not exceed the above proposed limit value for TDA (19.5 nmol $mmol^{-1}$ creatinine), but some of the individual measurements did. In the present series, all subjects tested negative for isocyanate-specific immunoglobulin E (IgE) antibodies. However, this was also true in all cases of occupational diisocyanate-induced asthma (diagnosed earlier at the same factories).[39] It should also be emphasised that a biological exposure index cannot be used to predict work-related symptoms.[16]

In conclusion, the product of airborne TDI concentration and sampling time accurately reflects the urinary excretion of TDA. Urinalysis of TDA in post-shift samples is proposed as a practical means for assessing personal exposures in workers exposed intermittently to TDI during flexible foam production. The determination of either the 2,6-isomer alone or total TDA is applicable for exposure assessment.

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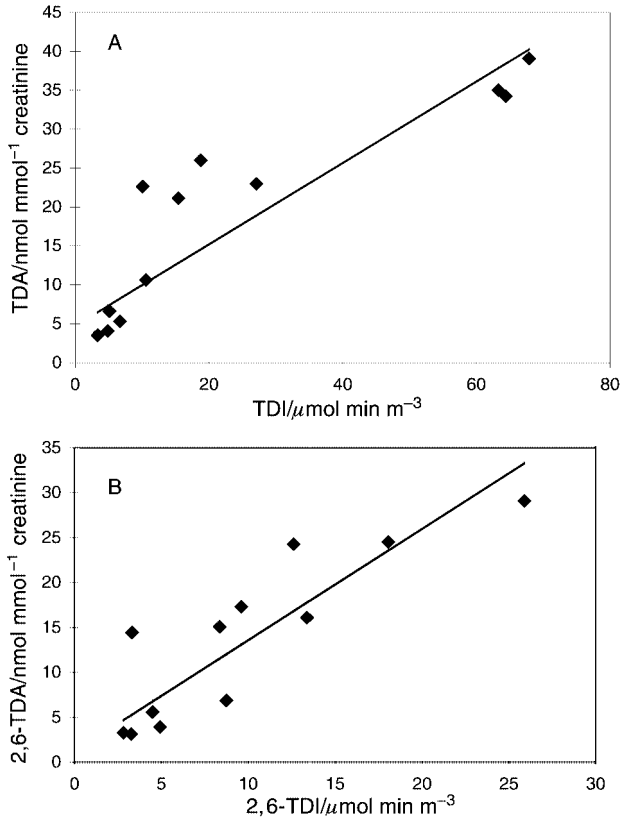

Fig. 5 Correlation between urinary TDA (A, total TDA; B, 2,6-isomer) concentration in post-shift samples and the product of airborne TDI concentration and sampling time in workers at Plant 1.

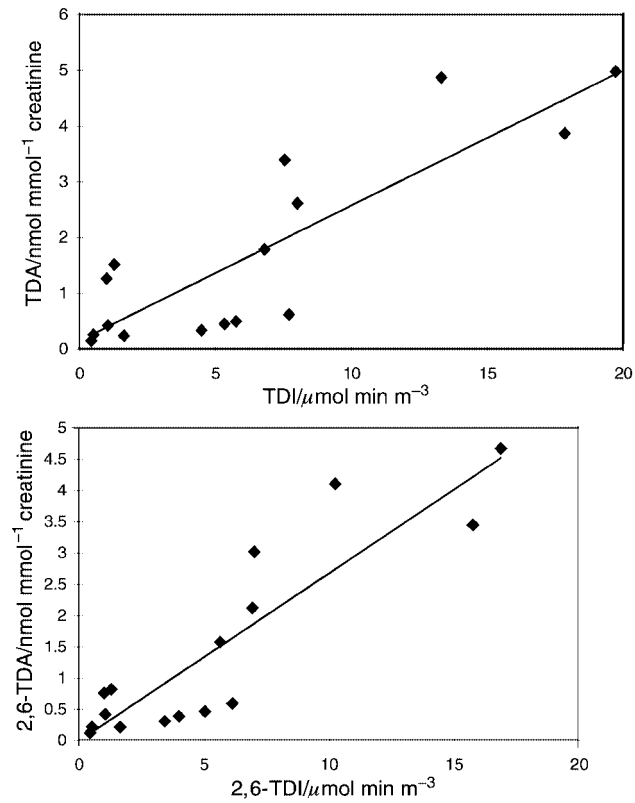

Fig. 6 Correlation between urinary TDA (A, total TDA; B, 2,6-isomer) concentration in post-shift samples and the product of airborne TDI concentration and sampling time in workers at Plant 2.

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