

## Biological monitoring for isocyanates

### Annex 1

#### Summary

Isocyanates are respiratory sensitisers, the major cause of occupational asthma in Great Britain. Occupational exposure to isocyanates must be well controlled. In the case of spray painting, the controls normally needed are a spray booth and respiratory protective equipment (RPE). COSHH requires the assessment of exposure control efficacy. This paper proposes the use of biological monitoring as an essential element of assessing the control of exposure. As biological monitoring is the only practical method for measuring exposure when RPE is part of the control measures, it also suggests a biological monitoring guidance value.

Isocyanates are absorbed by inhalation, and converted to amine-protein or amine-haemoglobin adducts. Urinary elimination of protein adducts is swift (a few hours). The measurement of isocyanate-derived diamines in urine provides a sensitive means of assessing exposure. This approach has been applied in both field studies of occupational exposure to reacting isocyanate mixtures and in volunteer studies involving the more commonly used pure diisocyanates. The peer-reviewed literature is briefly summarised, within more detail in Annex A. There is a clear relationship between inhalation exposure to pure HDI, TDI and IPDI and the elimination of the respective diamines released by hydrolysis from protein adducts in urine. Field studies show that analysis of urine samples for these diamines has sufficient sensitivity to help assess occupational exposure and the adequacy of controls. Studies by HSE have shown that where good control practice measures are in place, the levels of isocyanate-derived diamines are below 0.5  $\mu\text{mol/mol}$  creatinine and this is proposed as a biological monitoring guidance value.

#### Introduction

1 For regulatory purposes, all isocyanates are regarded as respiratory sensitisers. The publication "Occupational Exposure Limits" EH40 lists Maximum Exposure Limits (MELs) for total isocyanate at  $0.02\text{mg/m}^3$  (8-hour TWA) and  $0.07\text{ mg/m}^3$  (15 minute short-term exposure limit), accompanied with a "Sen" notation. These are not health-based limits – it is not possible to identify a no-effect threshold.

2 The more commonly used isocyanates are:

- Hexamethylene diisocyanate (HDI) and polymers, used in paints and coatings;
- Toluene diisocyanate (TDI), eg used for flexible polyurethane foam;
- Methylenediphenyl diisocyanate (MDI), used for rigid foam and adhesives; and
- Isophorone diisocyanate (IPDI), also used with HDI in 2 pack isocyanate based paints.

While there are uses for naphthalene diisocyanate (NDI) and tosyl isocyanate (TsI), these are less common.

3 Exposure to isocyanate by inhalation is most likely for HDI and IPDI due both to their volatility, and to application by spraying. Polymeric paint preparations are based on dimers, trimers or short-chain polymers based on HDI and IPDI, with isocyanate terminal groups: these polymeric forms have much lower volatility than the monomers. Such preparations are common, but contain small amounts of monomeric diisocyanate. However, spraying creates inhalable aerosols.

TDI and MDI are less volatile. Isocyanate can also be released by cutting or heating cured polyurethane foams, films, etc.

## Metabolism

4 The metabolism of isocyanates in humans is poorly understood. Isocyanates are very reactive with compounds containing active hydrogen, eg hydroxyl, sulphhydryl and amino groups in proteins. It is likely that isocyanates react with tissues with which they come into contact, rather than being absorbed and distributed as free isocyanate molecules.

5 No free amines have been reported in plasma or urine after exposure to diisocyanate compounds. However, toluene diamine (TDA), methylenediamine (MDA), hexamethylene diamine (HDA) and isophorone diamine (IPDA) have been released from adducts after acid or alkaline hydrolysis.

6 Several authors report TDI - protein adducts in plasma and urine in volunteer studies (Skarping et al 1991, Persson et al 1993, Lind et al 1996 & 1997) and of MDI (Dalene et al 1996, Sepai et al 1996).

Haemoglobin adducts of TDI have been reported in plasma from workers (Lind et al 1997) or of MDI (Schutze et al 1995, Sepai et al 1995), but no such adducts were found in volunteers exposed to HDI or to IPDI (Brorson et al 1990, Tinnerberg 1995).

## Absorption by inhalation

7 Analysis of the isocyanate-derived diamines after hydrolysis of urine from volunteers inhaling known concentrations to isocyanate showed that for TDI, 15 to 20% of the dose of 2,4-TDA and 17 to 23% of the dose of 2,6-TDA is absorbed and excreted as adducts in urine (Brorson et al 1991).

Skarping et al (1991) found similar values – 8 to 14% of the inhaled dose of 2,4-TDI and 14 to 18% of 2,6-TDI.

Tinnerberg et al (1995) found 39% (range 9 to 94%) of an inhaled dose of HDI and 27% (range 19 to 46%) of a dose of IPDI to be excreted in urine as hydrolysable adducts.

8 Isocyanates do not carry a skin notation in EH40, though they are capable of skin sensitisation. Being reactive, they are expected to bind to skin. However, direct skin contact with spray products is limited to a few percent of the total deposition on the sprayer's coverall (HSE, 2002), and by using disposable protective gloves.

## Elimination

9 The initial elimination half-life of TDI-adducts in urine is 1.9 hours for 2,4-TDA and 1.6 hours for 2,6-TDA, with both isomers having a second half-life around 5 hours (Brorson et al 1991, Skarping et al 1991). The half-life for the elimination of TDI – adducts in plasma is around 10 days and 21 days (Lind et al 1996 & 1997).

The half-life for elimination of HDI-adducts in urine is 2.5 hours (range 1 to 4.3) and for IPDI-adducts in urine is 2.8 hours (range 1.7 to 4.7 hours) (Tinnerberg et al 1995).

## Biological Monitoring

10 Several volunteer and occupational studies show a good correlation between airborne concentrations of TDI and their hydrolysable adducts in urine (Rosenberg & Saviolainen 1986b, Brorson et al 1991, Maitre et al 1993, Persson et al 1993, Kaaria et al 2001) HDI (Maitre et al 1996, Tinnerberg 1995) and IPDI (Tinnerberg 1995).

Peak excretion occurs at the end of exposure for TDI (Skarping et al 1991, Brorson et al 1991), and for HDI and IPDI (Tinnerberg 1995). Coupled with the short half-life, this suggests sample collection at the end of work/shift.

11 Field studies have shown the utility of biological monitoring for detecting low-level exposure to isocyanates (including polymeric isocyanates). Persson et al 1993 was able to detect exposure to TDI based on measurements of TDA hydrolysable adducts in urine, for workers exposed to concentrations at 1 to 10% of the Swedish exposure limit ( $40 \mu\text{g}/\text{m}^3$ ).

A series of studies have shown that measurement of MDA in hydrolysed urine can detect exposure to MDI at levels below the detection limit for air monitoring (Skarping et al 1996, Schutze et al 1995, Sepai et al 1995, Kaaria et al 2001).

Rosenberg & Saviolainen (1986a) showed that 15-minute exposures to  $2.8 \mu\text{mol}/\text{m}^3$  of functional isocyanate groups [equivalent to  $118 \mu\text{g}/\text{m}^3$ ] could produce  $63 \mu\text{mol}$  HDA/mol creatinine in urine collected 30 minutes after exposure. That is about 100 times greater than the detection limit for HDA in urine.

12 Poor controls can result in detectable levels of TDI-adducts in urine (Maitre et al 1993) and HDI-adducts in urine (Williams et al 1999). However, biological monitoring has shown there to be no HDI-adducts detectable in urine when exposure was properly controlled (Rosenberg & Saviolainen 1986a, Williams et al 1999).

13 Urinary diamine adducts do not occur in populations that are not exposed to diisocyanates or diamines (eg in epoxy adhesives). Table 1 summarises the urinary concentrations related to 'MEL equivalent' inhaled concentrations.

Table 1 Summary of urinary diamine concentrations following inhalation exposure to isocyanate monomer

Isocyanate monomer	Mol. Wt	MEL $\equiv$ * $\mu\text{g}/\text{m}^3$	Analyte (after hydrolysis)	Mol. Wt	Approx. value in urine** after exposure at MEL		Reference (Duration of exposure)
					$\mu\text{mol}/\text{mol}$	$\mu\text{g}/\text{g}$	
HDI	168	40	HDA	116	14	15	Maitre et al 1996 (8h) Brorson et al 1990 (8h)
					32	33	
IPDI	222	53	IPDA	170	16	24	Tinnerberg 1995 (2h)
TDI (total)	174	41	TDA	122	18	19	Maitre et al 1993 (8h)
2,4 TDI	174	41	2,4-TDA	122	23	25	Brorson et al 1991 (4h)
					18	19	
2,6 TDI	174	41	2,6-TDA	122	29	31	
					27	29	
MDI	250	60	MDA	198	6	10	DFG 2003

\* The MEL ( $20 \mu\text{g}/\text{m}^3$  total isocyanate) is adjusted by Mol.Wt / 84 to convert to the parent substance's MEL equivalent value.

\*\* Collected at the end of shift

## Analytical method

14 All the reported analytical methods begin with hydrolysis to liberate amines from urinary conjugates.

Sulphuric acid hydrolysis is frequently used to generate HDA, TDA, MDA and IPDA (Skarping & Dalene 1995, Rosenberg & Saviolainen 1996a, Tinnerberg et al 1997, Williams et al 1999, Sakai et al 2002). Hydrochloric acid hydrolysis is also reported (Tiljander et al 1989, Sandstrom 1989, Dalene et al 1990, Dalene et al 1994b, Sepai et al 1995, Kaaria et al 2001, Skarping et al 1991 Maitre et al 1993).

Three authors report using alkaline hydrolysis to HDA and IPDA, followed by HPLC-MS (Skarping et al 1994b, Dalene et al 1994, Tinnerberg 1995), to TDA followed by HPLC with electrochemical detection (Carbonnelle 1996) and to TDA followed by GC-MS (Sennbro et al 2003).

Unpublished work by the Health and Safety Laboratory (HSL) has shown interfering / artefact peaks when alkaline hydrolysis to HDA was used with GC-MS.

15 Acid hydrolysates are made alkaline, extracted into an organic solvent and derivatised with pentafluoropropionic (PFP) anhydride (Skarping et al 1991, 1994b & 1994c, 1995, Tiljander et al 1989, Marand et al 2004) or heptafluorobutyric anhydride (Dalene et al 1990, Maitre et al 1993, Rosenberg & Saviolainen 1996a, Kaaria 2001, Williams et al 1999). This is followed by separation and detection by GC-MS with selected ion monitoring in either the electron impact or negative ion chemical ionisation. Detection limits are in the range 0.5 to 5 nmol/l and coefficients of variation are typically <5% for within day and <10% day to day.

16 A few methods are based on HPLC with either electrochemical detection (Carbonnelle et al 1996) or LC-MS of the PFP derivatives of HDA and IPDA (Skarping et al 1994b, Tinnerberg 1995, Marand et al 2004) or trifluoroethylformate derivatives (Dalene et al 1994). One report concerned analysis of TDA by atmospheric ionisation LC-MS without derivatisation (Sakai et al 2002).

17 The method used by HSL involves acid hydrolysis followed by solvent extraction of the basified solution and formation of the heptafluorobutyryl derivatives. Separation and detection is by negative ion chemical ionisation mass spectrometry. The limit of quantitation is 5nmol/l (approximately 0.5  $\mu$ mol/mol creatinine) and the reproducibility (CV) is 5% within day and 10% from day to day (Williams et al 1999).

### Note

The limit of detection (LoD) for the method is 1 nmol/l – approximately 1  $\mu$ mol/mol creatinine, based on 3x background noise. The Limit of Quantitation (LoQ) is 5 nmol/l

(0.5 µmol/mol creatinine) based on 5xLoD. The analytical precision of the method, expressed as the coefficient of variation, is <10% at 100 nmol/l.

18 The short half lives of the metabolites in urine means that samples should be collected at the end of a work shift. Unpublished work at HSL showed a decline in detectable levels of TDA in spiked urine samples if these are not acidified. Samples from exposed workers containing TDA adducts may be more stable than the free amine; however, HSL considers it prudent to acidify the samples with citric acid after collection, to keep them refrigerated, and to analyse them as soon as possible.

## **Studies by HSE & HSL**

19 HSL has analysed urine samples for diisocyanate metabolites since 1997, storing the results in the Biological Monitoring Database (BMDB). Samples were taken in HSE investigations, though increasingly these come directly from occupational health providers and small firms.

Most samples have no contextual occupational hygiene or control information. Many samples have no specific indication of the type of diisocyanate, so all samples are analysed for all four diamines. So, for example, while the database records 722 samples analysed for IPDA this does not indicate 722 workers exposed to IPDA.

20 Table 2 summarises data from the BMDB where HSL has contextual data, either because the samples were part of a HSE study or through information supplied with samples. The mean and 90% values show that compared with reported studies in the literature, occupational exposure to diisocyanate in the UK appears to be low.

However, the table includes data from workplaces with poor control. There is widespread poor compliance with good control practice in motor vehicle repair using HDI (see para.21). All the samples for IPDA are from a single company with poor control, and for MDA, the data include a site recycling rubber using an MDI based glue with poor control –(HSE investigation, Baldwin 2003).

Table 2 Summary of biological monitoring data for known diisocyanates,  $\mu\text{mol/mol}$  creatinine (all industries, including those with poor control)

Analyte	No of samples	Mean value ( $\mu\text{mol/mol}$ )	90% value ( $\mu\text{mol/mol}$ )	Max. Value ( $\mu\text{mol/mol}$ )
2,6-TDA	383	<0.5	<0.5	7
2,4-TDA	383	<0.5	<0.5	10
HDA	752	0.8	1.8	78
IPDA	7	55.4	123 *	140 *
MDA	279	0.7	1	50

\* All from one company

Where controls were judged to be 'adequate', most samples were close to or below 0.5  $\mu\text{mol/mol}$  creatinine. It is proposed to revise this table in 2007, when many more data will be available.

21 From the following work, HSE's occupational hygienists observed that where exposure controls were deficient, urinary diamine would normally be detected and this would prompt an investigation of the cause. But where all controls were working correctly, including behavioural controls, no significant urinary diamine would be found (ie <0.5  $\mu\text{mol}$  urinary diamine / mol creatinine).

22 Recent occupational hygiene studies and investigations by HSE concern exposure to HDI during spray painting of vehicles (Piney 2000, Bagon and Sandys 2003). While air monitoring has an important role in assessing the effectiveness of control measures (such as an enclosed spray booth) and the spread of airborne contamination, the only practicable way of measuring personal exposure to isocyanates is biological monitoring, indicating the efficacy of respiratory protective equipment (RPE) and behavioural controls. The results of biological monitoring showed that control of exposure to diisocyanates was often poor, both for escape of contamination from the spray booth, and for sprayer behaviour.

In this study (195 samples), 21% of the samples exceeded 0.5  $\mu\text{mol}$  HDA /mol creatinine and 9% exceeded 1.0  $\mu\text{mol/mol}$ . For IPDA, 13 samples were above the limit of detection, with 5 samples exceeding 0.5  $\mu\text{mol}$  HDA /mol creatinine. The 50<sup>th</sup> percentile value of the whole dataset was below the limit of detection; and the 90<sup>th</sup> percentile was at 0.8  $\mu\text{mol/mol}$  creatinine.

23 A value of 0.5  $\mu\text{mol}$  urinary diamine / mol creatinine is approximately equivalent to inhaling <5% of the MEL for the parent isocyanate monomer. Although this is around the limit of quantitation, the amount is proposed as a biological monitoring benchmark value. The detection of urinary diamine above 0.5  $\mu\text{mol}$  urinary diamine / mol creatinine

is a prompt for further investigation into the reasons for exposure. Two case studies (Annex B) help illustrate the point.

## Proposal

24 Biological monitoring, based on the analysis of diamines in urine after hydrolysis of isocyanate-protein adducts, is a useful tool for assessing the efficacy of exposure controls for isocyanates. It is particularly relevant where control of exposure includes respiratory protective equipment. Biological monitoring based on collection of urine samples at the end of work is a simple way for employers and workers to assess the efficacy of control measures and should be promoted.

25 A guidance value is critical to the interpretation of the results of biological monitoring. Volunteer and occupational hygiene studies show a good relationship between inhalation exposure and isocyanate adducts in urine. But for substances like isocyanates that do not have health-based exposure limits, a proposal of a biological monitoring value equivalent to inhalation exposure at the MEL is not appropriate. A biological monitoring guidance value based on a relationship with good occupational hygiene practice is more appropriate. This does not remove the requirement for health surveillance for the development of asthma.

The urinary diamine concentrations reported in Table 2, while indicative of current exposure in many UK workplaces, reflect concentrations that have been found in recent surveys where good control practice was generally not observed. A biological monitoring guidance value lower than the 90% values reported in Table 2 is both desirable and possible. HSE's occupational hygienists have found that in workplaces observing good occupational hygiene practice, urinary concentrations below 0.5  $\mu\text{mol}$  amine /mol creatinine are achieved.

26 A Biological Monitoring Guidance Value (BMGV) is proposed, based on the release of diamines after hydrolysis from HDI, TDI, MDI or IPDI protein conjugates, at a level of 0.5  $\mu\text{mol}$  diamines/mol creatinine, in urine samples collected at the end of exposure. The purpose of this guidance value is to prompt an investigation of the reason for exposure, and to remedy defects.

27 The draft Control Guidance Sheet at Annex C is simply an illustration of the format that guidance might take. The ACTS COSHH Essential Working Group is responsible for endorsing such guidance. The only known UK service provider is, at present, the Health and Safety Laboratory (HSL). HSE would like to encourage other analytical laboratories to offer services to the market.

The slide reproduced in Annex D is used in Safety and Health Awareness Days (SHAD) for motor vehicle repairers engaged in spraying isocyanate-based paints.

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## Annex A Reported studies

### *TDI*

#### Occupational studies

Rosenberg & Saviolainen (1986b) looked at workers exposed to an 80:20 mixture of 2,4 and 2,6 TDI in the manufacture of polyurethane foam. Air monitoring showed the 2,6 TDI isomer was in the range 9 – 78  $\mu\text{g}/\text{m}^3$  during various tasks and was present in greater amounts than the 2,4 isomer and so urine was analysed for 2,6 TDA only. No individual urine values were reported but the authors describe a good correlation between the product of 2,6-TDI in personal air samples x 'sampling time' (not explained) and TDA in urine ( $y(\text{nmol}/\text{mol}) = 2.18 \times (\mu\text{mol} \times \text{min} \times \text{m}^{-3}) - 6.25$ ,  $r = 0.9$ ,  $n=10$ ). Because the authors did not elaborate on 'sampling time' the relationship cannot be used to predict exposures for 8h TWA.

Maitre et al (1993) also looked at 9 polyurethane foam workers exposed to a 2,4 and 2,6 TDI mixture in an 80:20 ratio. There was no ventilation system and the workers wore no personal protective equipment. Their exposure levels varied from 9.5 to 94  $\mu\text{g}/\text{m}^3$  (8h TWA) and their end of shift urine samples had a mean 'total' TDA concentration of 15.7 (+/- 8.3)  $\mu\text{g}/\text{g}$  (range 6.5 to 31.7  $\mu\text{g}/\text{g}$  creatinine with a linear relationship to airborne TDI levels ( $\log(y) = 0.5795\text{Log}(x) + 3.278$   $r = 0.91$  of the log transformed data). This suggests inhalation for 8h of 38  $\mu\text{g}/\text{m}^3$  would give an end of shift TDA value of 18  $\mu\text{g}/\text{g}$ .

Persson et al (1993) studied exposure to TDI over 48h in a factory producing polyurethane foam. Five exposed workers, 2 supervisors (laboratory worker and a manager) and 2 'volunteers' provided several urine and blood samples that were analysed for 2,4 and 2,6 toluenediamine by GC-MS. Workers only wore RPE when they expected high concentrations of TDI (eg in the curing tunnel). Air monitoring showed inhalation concentrations between 1% and 10% of the Swedish TLV of 40  $\mu\text{g}/\text{m}^3$ . The 5 workers showed the highest urinary elimination rate of TDA. Two workers and two supervisors had elimination rates of 20 – 70 ng/h (sum of 2,4 and 2,6 TDA assuming a creatinine excretion rate of 67 mg/h this is 0.3 to 1  $\mu\text{g}/\text{g}$ ) and 3 production workers had an average of 100 – 300 ng/h (1.5 to 4.5  $\mu\text{g}/\text{g}$ ). The elimination rate curves for all subjects had a linear relationship to exposure to TDI.

Lind et al (1996) Looked at exposure of 11 workers to 2,4 and 2,6 TDI in two polyurethane foam plants. Airborne TDA exposures ranged from 0.4 to 4  $\mu\text{g}/\text{m}^3$  in one plant and 10 to 120  $\mu\text{g}/\text{m}^3$  in the second plant. Air sampling was carried out several days before the biological monitoring. Urine excretion of 2,4 TDA before the holiday ranged from 0.04 to 0.54  $\mu\text{g}/\text{h}$  (0.5 to 7.4  $\mu\text{mol}/\text{mol}$ ) and 0.02 to 0.18  $\mu\text{g}/\text{h}$  (0.3 to 2.5  $\mu\text{mol}/\text{mol}$ ) afterwards. The concentrations of 2,6 TDA were 0.18 to 0.76  $\mu\text{g}/\text{h}$  (2.5 to 10.5  $\mu\text{mol}/\text{mol}$ ) before and 0.09 – 0.27 (1.2 to 3.7  $\mu\text{mol}/\text{mol}$ ) after the holiday. The half- time for urinary TDA ranged from 5.8 to 11 days.

Tinnerberg et al (1997) studied 4 exposed workers (and one 'volunteer') in a TDI foaming plant – the average air concentration was  $29.8 \mu\text{g}/\text{m}^3$  ( $12.5 - 79.9$  n=12). The highest concentration was around  $3\text{mg}/\text{m}^3$ . Exposure durations were typically 2-3h per day and workers used RPE only when occupied with preparation of the foaming apparatus that occasionally caused high exposures. 2,4 and 2,6 TDA were measured in urine and plasma after strong acid hydrolysis using GC-MS. Urinary TDA values ranged from none detected to  $2 \mu\text{g}/\text{mmol}$  ( $18 \mu\text{g}/\text{g}$  or  $16 \mu\text{mol}/\text{mol}$ ) and varied greatly with time and exposure. Peak urinary TDA values were found shortly after exposure.

Kaaria et al (2001) in a method development paper looked at occupational exposure to TDI in 17 employees in 2 plants making flexible foam and found a trend for a linear correlation ( $r = 0.86$ ) between urinary TDA and the product of the airborne TDI concentration and time. Urinary TDA in plant 1 ranged from 0.11 to 39 nmol/mmol and in plant 2, <0.05 to 7.1 nmol/mmol. Plant 1 had a high pressure moulding technique that released more TDI into the air. The ratio of 2,4 to 2,6 TDA in urine followed the pattern observed in air samples. 2,6 TDA was reported in non-occupationally exposed people (n=12, mean  $0.01 \mu\text{mol}/\text{mol}$  range 0.003 to  $0.05 \mu\text{mol}/\text{mol}$ )

Sakai et al (2002) in a method development paper described a small study of 13 workers exposed to TDI (a mixture of 2,4- and 2,6-TDI) during polymerisation of foam and 20 non-exposed subjects. TDA was not detected in urine ( $<1 \mu\text{g}/\text{l}$ ,  $8 \text{nmol}/\text{l}$ ) of non-exposed subjects but exposed workers had TDA levels up to  $250 \mu\text{g}/\text{l}$  and  $63 \mu\text{g}/\text{l}$  for 2,6 and 2,4 TDA respectively.

### **Volunteer studies with TDI**

Brorson et al (1991) exposed two volunteers to 3 concentrations of TDI (a mixture of 2,4- and 2,6 TDI in a 30:70 ratio) for 4 hours on separate occasions to  $25 \mu\text{g}/\text{m}^3$ ,  $50 \mu\text{g}/\text{m}^3$  and  $70 \mu\text{g}/\text{m}^3$ . TDA was measured in urine after hydrolysis and the accumulated amount excreted over 24h accounted for 15-19% of the dose of 2,4-TDI and 17-23% of the dose of 2,6-TDA. TDA was rapidly eliminated from urine with a mean initial half-life for 2,4-TDA of 1.9h and 1.6h for 2,6-TDA. The second phase the half-life was about 5 hours for both isomers. There was a linear relationship ( $r = 0.98$ ) between inhalation concentration and cumulative urinary excretion. The excretion of 2,4- and 2,6-TDA after exposure to  $20 \mu\text{g}/\text{m}^3$  2,4- and 2,6-TDA is estimated (from a figure) to be 0.8 and  $1 \mu\text{g}/\text{h}$ . If a creatinine excretion rate of  $67\text{mg}/\text{h}$  is used this would give a urinary concentration of 2,4 TDA of  $12 \mu\text{g}/\text{g}$  and of 2,6-TDA of  $15 \mu\text{g}/\text{g}$  (or  $11 \mu\text{mol}/\text{mol}$  and  $14 \mu\text{mol}/\text{mol}$  respectively). So after exposure to  $40 \mu\text{g}/\text{m}^3$  2,4 and 2,6 TDA the urinary 2,4 and 2,6 TDA values would be  $25 \mu\text{g}/\text{g}$  and  $31 \mu\text{g}/\text{g}$  respectively. Using the table of urine TDA found in end of exposure samples with their corresponding inhalation concentrations and using a linear regression gives an alternative approach to predicting concentrations of TDA. Using this method after exposure for 4h to  $20 \mu\text{g}/\text{m}^3$  2,4- and 2,6-TDA the

calculated 2,4- and 2,6 TDA concentrations are 9 and 13  $\mu\text{mol/mol}$  creatinine respectively. After exposure to  $40 \mu\text{g}/\text{m}^3$  the urinary TDA values would be 18 and 27  $\mu\text{g}/\text{mol}$  for 2,4 and 2,6 TDA respectively.

Skarping et al (1991) exposed five men to a mean air concentration of 40 (range 36 – 43)  $\mu\text{g}/\text{m}^3$  total TDI for 7.5h. The isomeric composition was ca 48% 2,4-TDI and 52% 2,6-TDI (no amines formed by hydrolysis of TDI were detected in the air). The inhaled dose (pulmonary ventilation x exposure concentration x duration of exposure) of 2,4- and 2,6-TDI were ca.120  $\mu\text{g}$ . Urine and blood samples were collected from the volunteers and after hydrolysis were analysed for 2,4- and 2,6-TDA by GCMS. The peak of excretion was in the 6 – 8h sample (end of exposure) with the rate of excretion for 2,4- TDA averaging 0.6  $\mu\text{g}/\text{h}$  and that for 2,6-TDA averaging 1.0  $\mu\text{g}/\text{h}$ . The average 2,4-TDA concentration in the 6-8h sample was 5  $\mu\text{g}/\text{l}$  (range 2.8 – 9.6) and the values for 2,6-TDA were 8.6  $\mu\text{g}/\text{l}$  (range 5.6 – 16.6). Only traces of 2,4- and 2,6-TDA were found in the samples collected after 24 h. The urinary elimination of TDAs showed a possible biphasic pattern with the initial rapid phase half-lives of 1.9h (range 1.1 – 2.5) for 2,4-TDA and 1.6h (range 1.1 – 2.2) for 2,6-TDA. The approximate half time for the second phase was ca. 5h for both compounds. The cumulative elimination of 2,4-TDA within 28h ranged from 8 to 14% of the estimated dose and for 2,6-TDA was 14-18%. No correlation was found between acetylator phenotype and 2,4- or 2,6- TDA in hydrolysed urine.

## **MDI**

### **Occupational studies**

Skarping et al (1996) studied exposure to MDI in a factory using isocyanate-based polyurethane glue. Isocyanate concentrations were measured in air and samples from 174 workers were analysed after hydrolysis by GCMS for MDA in urine and plasma. Employees were screened for work related respiratory symptoms and tested for specific immunoglobulin E (IgE) and IgG antibodies directed against conjugated human serum albumin. TWA concentrations of isocyanate in workers' breathing zones were low (MDI  $< 0.2 - 7$ ; HDI  $0.1 - 7$ ; 2,6-TDI  $0 - 1 \mu\text{g}/\text{m}^3$ ). All subjects had detectable levels of MDA in plasma and urine and there were significant associations between estimates of exposure to thermal degradation products of MDI based glue and MDA in plasma ( $0.1 - 5.5 \mu\text{g}/\text{l}$ ) and MDA in urine ( $0.04 - 5 \mu\text{g}/\text{l}$ ). In cases of heavy exposure plasma MDA and urine MDA were associated with each other ( $r=0.64$   $p=0.0001$ ), with work related symptoms (plasma MDA –  $P=0.03$  Mann-Whitney U test), and serum concentrations of MDI specific IgG antibodies ( $r=0.26$   $p=0.0007$ ). Unexpectedly high plasma and urine MDA concentrations were also seen in workers cutting textile – no reason given. MDA was only seen in plasma and urine after hydrolysis, there was no free MDA.

Skarping & Dalene 1995 in a method development paper reported a concentration of 2.3  $\mu\text{g}/\text{l}$  MDA in a pooled urine sample from 10 workers exposed to MDI (details not given)

Schutze et al (1995) developed analytical methods for MDA in urine and from haemoglobin adducts. Although workers were exposed only to low levels of MDI (only 3 samples above the detection limit of  $3 \mu\text{g}/\text{m}^3$ ) MDA could be detected in most urine samples after hydrolysis (range 0.7 to  $10 \text{ nmol}/\text{l}$ ). MDI exposure could be detected in more workers by measurement of urine metabolites than by haemoglobin adducts or air monitoring.

Sepai et al (1995) studied twenty workers exposed to MDI during the manufacture of polyurethane products. Air levels were measured by personal and workroom samplers and were mostly below detection limits. Blood and urine samples were analysed for the presence of adducts and metabolites by GC-MS. The amount of MDA released after acid hydrolysis was 6.5 times greater than the sum of free MDA and acetyl-MDA suggesting the presence of other adducts/conjugates. MDA was detected as haemoglobin adduct in all of the 20 exposed workers. The levels ranged from 70 to  $710 \text{ fmol}/\text{g Hb}$ . Plasma protein adducts of MDA ranged from 0.25 to  $5.4 \text{ pmol}/\text{ml}$ .

Dalene et al (1996) found MDA in urine of 4 workers (0.1, 0.6, 2.05,  $1.25 \mu\text{g}/\text{l}$ ) exposed to thermal degradation products of MDI-based polyurethane during welding of pipes. This study also looked at plasma levels of MDA (after hydrolysis) and found MDA in 18 of 30 pipe layers who had been welding pipe during the 3 months prior to the study. They also reported no association between acetylator genotype and levels of MDA in plasma.

Kaaria et al (2001) in a method development paper reports detecting MDA in urine from 97% of workers ( $n=57$ ) exposed to MDI moulding rigid polyurethane foam even though MDI in air was below the detection limit for the air method for 67% of the workers.

### **Volunteer studies with MDI**

There are no reported volunteer studies with MDI

## ***HDI***

### **Occupational studies**

Maitre et al (1996) studied 19 men exposed to HDI during monomer production. Airborne concentrations ranged from 0.3 to  $97.7 \mu\text{g}/\text{m}^3$ . Urine HDA was measured in post shift samples after acid hydrolysis and values ranged from  $1.36 \mu\text{g}/\text{g}$  to  $27.7 \mu\text{g}/\text{g}$  and there was a linear association between HDI in air and urinary HDA ( $\log(y) \mu\text{g}/\text{g} = 0.4396 \log(x) \mu\text{g}/\text{m}^3 + 0.4612$  ( $r=0.698$ ,  $p=0.001$ ,  $n=19$ ). The authors proposed a biological exposure index value of  $19 \mu\text{g}/\text{g}$  in post-shift urine samples as an indicator of exposure to HDI monomer at an 8h TWA of  $75 \mu\text{g}/\text{m}^3$ .

Williams et al (1999) looked at occupational exposure to HDI in sprayers employed in motor vehicle repair. Urine samples were collected at the beginning, middle and end of shift from 22 workers (11 sprayers, 4 bystanders and 8 unexposed) and analysed for HDA by GC-MS. HDI monomer was probably a small proportion of the total isocyanate: nevertheless HDA was found in the urine of 4 sprayers (maximum concentrations 11, 1, 1 & 3  $\mu\text{mol/mol}$ ) and one bystander (12  $\mu\text{mol/mol}$ ) but not other potentially exposed workers. The study concluded that exposure to HDI could still occur in workers wearing full face air-fed personal protective equipment and working in a ventilated space probably due to poor fit of the RPE and/or removing the RPE at the end of spraying but while a significant concentration of HDI remained in the spray booth. Bystander exposure was thought to be due to the bystander going into the spray booth to talk to the sprayer. No HDA was found in any sample taken before shift or in unexposed subjects and the half-life of elimination was thought to be consistent with 1.5 to 2 hours.

### **Volunteer studies with HDI**

Rosenberg & Saviolainen (1986a) looked at car painters exposed to HDI polymer-based paint in an exposure chamber. The average concentration of the HDI polymer was 34% and that of the monomer was 0.24% in the hardener. The concentration of inhaled functional NCO groups during a 15 minute exposure was  $2.8 \pm 0.8 \mu\text{mol/m}^3$  and the HDA concentration in urine was  $63 \pm 33 \text{ nmol/mmol creatinine}$  ( $65 \mu\text{g/g}$ ) in samples collected 30 minutes after the end of exposure. This value is higher than might be expected from the concentration of HDI monomer alone and suggests that HDA may be coming from both monomeric and polymeric HDI. This study also reported a single occupational exposure where no HDA was found in the urine of a car painter spraying wearing an air-fed hood – the spray booth had an isocyanate monomer concentration of  $0.2 \mu\text{mol/m}^3$  but no isocyanate was detected inside the hood.

Brorson et al (1990) exposed 5 volunteers to 1,6 hexamethylene diisocyanate ( $25 \mu\text{g/m}^3$ ) for 7.5h and the inhaled dose was estimated to be around 100  $\mu\text{g}$ . After acid hydrolysis 1,6 HDA was determined in plasma and urine by GC-MS (CI+) of the HFB derivatives. The cumulative urinary excretion of HDA accounted for 11 to 21% of the estimated inhaled dose. Urine samples collected at the end of exposure had an average HDA concentration of 0.02 mmol/mol creatinine (range 0.01 to 0.03 mmol/mol or 10 to 30  $\mu\text{g/g}$ ) and the peak excretion rate was 1.1 to 1.4  $\mu\text{g/h}$ . The half time for elimination of HDA in urine was 1.1 to 1.4h. No specific IgE or IgG antibodies to HDI were detected before or after provocation. Assuming a linear response to the MEL of  $40 \mu\text{g/m}^3$  this could result in urinary HDA of 32  $\mu\text{mol/mol}$ .

Tinnerberg (1995) exposed 3 volunteers at rest to 3 concentrations of HDI (11.9, 20.5, 22.1  $\mu\text{g/m}^3$ ) and IPDI (12.1, 17.7, 50.7  $\mu\text{g/m}^3$ ) on separate occasions for 2h in an exposure chamber. Inhaled doses were estimated from pulmonary ventilation x dose level x duration. All urine was collected and blood samples were taken before and half an hour after exposure and again the next day. HDA and IPDA were not found 'free'

(before hydrolysis). After hydrolysis an average of 39% of the estimated dose of HDI was found in urine (range 9 – 94%) over 48h. The maximum urine concentration of HDA was in samples collected at the end of exposure (but no values were reported). The average elimination half-life of HDA in urine was 2.5h (range 1.0 – 4.3). No HDA was found in hydrolysed plasma.

### **Mixed exposures**

Dalene et al (1997) investigated exposure to TDI and MDI in 15 female workers as a consequence of exposure to thermal degradation products of polyurethane based foam and glue respectively. The workers made parts for passenger areas of cars using textile, polyurethane foam and MDI-based glues. During spraying of the glue workers wore respiratory protection (type not specified) and rubber gloves. After the solvents evaporated the parts were heated under infra red lamps for 10-20 sec or with heat guns. No air monitoring was done. Urinary elimination rates were in the range <0.1 to 5.7 µg/h of 2,4 TDA and <0.01 to 3.5 µg/h of 2,6 TDA and <0.1 to 1.6 µg/h of MDA.

Littorin et al 2000 looked at respiratory symptoms in a cross sectional study of 152 workers exposed to TDI and MDI while gluing and heating polyurethanes. After hydrolysis MDA was found in plasma from 65% of workers. TDA was found in urine from 47% of workers. Urinary MDA was associated with work related symptoms from the airways (OR = 3.7) and plasma TDA with work related symptoms from the lower airways (OR=6.6). Nine women making arm-rests had higher exposure than other workers and had median urine MDA values of 3.3µg/l, 2,4-TDA 0.6µg/l and 2,6-TDA of 0.5µg/l. Five of the arm-rest workers had work related symptoms.

Rosenberg et al (2002) studied workers in 5 different polyurethane processing environments – grinding and welding in car repair shops, milling and turning polyurethane coated metal cylinders, injection moulding thermoplastic polyurethanes, welding and cutting polyurethane insulated heating pipes, jointing and welding and heat flexing of polyurethane floor covering. TDA and MDA were detected in urine samples from car repair shops and MDA from workers welding heating pipes. The 2,4-TDA isomer accounted for 80% of the TDA detected. The highest TDA and MDA concentrations were 0.79 and 3.1 nmol/mmol creatinine respectively. Low levels of the amines were found in non-occupationally exposed workers – 0.08 and 0.05 nmol/mmol (arithmetic means) for MDA and TDA respectively. Exposure to thermal degradation products of polyurethanes are often intermittent and short duration but can be detected by analysis of diisocyanate derived material in urine.

## ***IPDI***

### **Volunteer studies**

Tinnerberg (1995) exposed 3 volunteers at rest to 3 concentrations of IPDI (12.1, 17.7, 50.7  $\mu\text{g}/\text{m}^3$ ) on separate occasions for 2h in an exposure chamber. Inhaled doses were estimated from pulmonary ventilation x dose level x duration. All urine was collected and blood samples were taken before and half an hour after exposure and again the next day. IPDA was not found 'free' (before hydrolysis). After hydrolysis an average of 27% of the estimated dose of IPDI was found in urine (range 19 – 46%) over 48h. The maximum urine concentration of IPDA was in samples collected at the end of exposure. A figure gave values for a single volunteer exposed to each of the 3 IPDI levels and reported excretion rates (read from the figure) of approximately 420, 780 and 720 ng/h. Using an average excretion of creatinine of 67 mg/h this would give urinary IPDA concentrations of roughly 6, 12, & 11  $\mu\text{g}/\text{g}$  (or 4, 8 and 7  $\mu\text{mol}/\text{mol}$ ) after each inhalation concentration. Taking a simple average of all three values extrapolated to 53  $\mu\text{g}/\text{m}^3$  gives an average urinary IPDA of 24  $\mu\text{g}/\text{g}$  (16  $\mu\text{mol}/\text{mol}$ ). The average elimination half-life of IPDA in urine was 2.8h (range 1.7 – 4.7)

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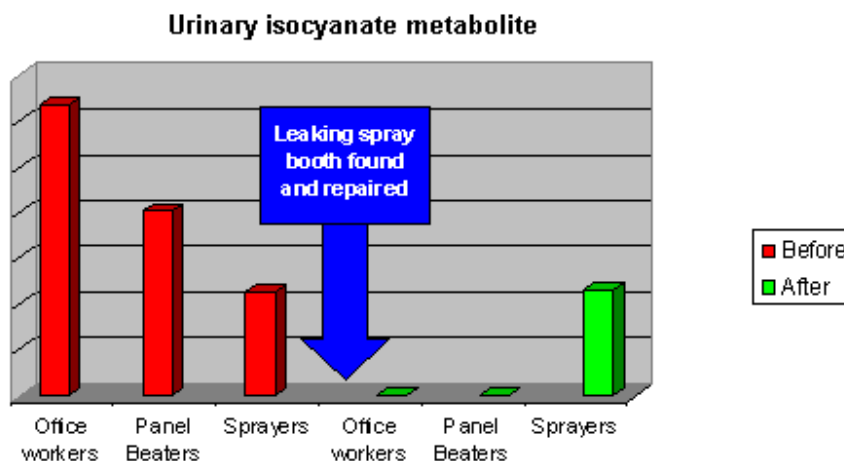
## Annex B Case Studies

### Case Study A

An MVR site was investigated because there were reports of occupational ill health amongst workers. Biological monitoring (BM) showed that all staff, including administrative staff that never did any painting, had been exposed to isocyanates from the spray paints in use at the factory.

Investigation showed that the spray booth was leaking. Isocyanates from the booth were able to spread throughout the building, so everybody who worked there was exposed to them. This was an unexpected finding because the spray booth had been recently serviced, inspected and tested, and was thought to be working properly.

The leaking spray booth was repaired. Further BM showed that the spray booth was working properly, but one of the paint sprayers was still exposed to isocyanates because he had not received proper instructions and was not using his air-fed RPE correctly. His exposure was not as low as it should have been.

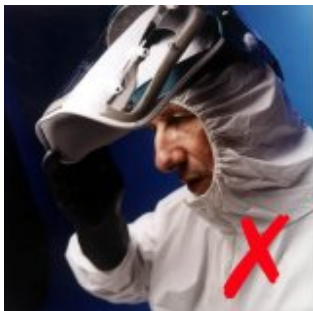


## Case Study B

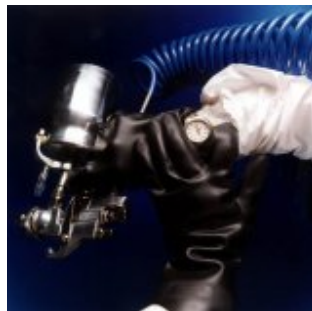
A biological monitoring survey was undertaken in a variety of motor vehicle repairers ranged from national dealerships to 'one man' operations. Factors that might lead to isocyanates exposure were identified. These included:

- Spraying above head height. Respiratory protective equipment sometimes does not fit properly when people tilt the head upwards;
- Lifting visors to take a closer look at the job quality. Wearers are then not protected;
- Entering a spray booth unprotected, before the correct 'clearance time' had elapsed;
- Unprotected workers entering spray areas to speak to protected colleagues during spraying.

Biological Monitoring allowed these risk factors to be identified. They might otherwise have gone unnoticed. It highlighted areas where improved health and safety procedures were needed.



**Sprayers should not lift their visor to check on the job**



**Sprayers should always know and observe clearance times for booths and ventilated spaces**



**Never allow an unprotected person to approach a sprayer while spraying**

<p style="text-align: center;"><b>ANNEX C</b></p> <p style="text-align: center;"><b>4</b></p> <p style="text-align: center;"><b>SPECIAL</b></p>	<p style="text-align: right;"><b>DRAFT</b></p> <p style="text-align: center;"><b>Special advice</b></p> <p style="text-align: center;"><b>Measuring exposure to isocyanates by Biological Monitoring</b></p> <p style="text-align: center;"><b>40X</b></p>
<p><b>Essentials Logo</b></p> <p>This guidance sheet is for <b>employers</b>. It will help them comply with the requirements of the Control of Substances Hazardous to Health Regulations 2002 (COSHH) by helping them check on the effectiveness of the controls that protect workers' health.</p> <p>This sheet covers the points you need to have clear when using biological monitoring to measure isocyanate exposure.</p> <p><b>Reference</b></p> <p>Williams N, Jones K, Cocker J (1999). Biological monitoring to assess exposure from isocyanate use in motor vehicle repair. Occup. Environ. Med. 56 pp. 598 - 601.</p>	<p><b>Introduction</b></p> <p>This control sheet provides general advice on the points to consider when measuring exposure to isocyanates by biological monitoring.</p> <p>Isocyanates often occur in:</p> <ul style="list-style-type: none"> <li>▪ 2-pack spray paint, lacquer, underseal and varnish.</li> <li>▪ Some glues and adhesives.</li> <li>▪ Foam and plastic production.</li> <li>▪ Hot work on polyurethane foam, cured paint or plastic.</li> </ul> <p>Relatively low levels of exposure to isocyanate may cause asthma. Exposure should be as low as is reasonably practicable. Even people working nearby can be affected. Biological monitoring is one practical way to assess exposure, and the effectiveness of control measures which include respiratory protective equipment (RPE).</p> <p><b>Biological Monitoring</b></p> <p>Measuring exposure by biological monitoring is a sure way to know if exposures are properly controlled. Companies that set-up their control measures properly (including proper training and instruction of workers directly involved) can get isocyanate exposures down to low levels.</p> <p>Biological monitoring works by measuring the breakdown products of isocyanate in urine. This means taking samples of urine from people who may be exposed.</p> <p>Control of exposure includes:</p> <ul style="list-style-type: none"> <li>▪ Work process, work organisation and worker behaviour to minimise exposure.</li> <li>▪ Engineering controls such as spray booths and enclosed systems.</li> <li>▪ Air-fed respiratory protective equipment (RPE).</li> <li>▪ Excluding other people from areas where isocyanates are used.</li> </ul> <p>Biological monitoring will tell if people have breathed in isocyanate - if so, the control measures are not working properly.</p> <p><b>Urine sampling</b></p> <p><i>The Health and Safety Laboratory (HSL) offers a commercial service to measure isocyanate breakdown products in urine. HSL charges about £50 per sample, which includes collection kit, packing and instructions. Other laboratories may be able to offer equivalent services.</i></p> <ul style="list-style-type: none"> <li>▪ Urine samples should be collected immediately the task or shift has finished.</li> </ul>
<p><b>Useful Addresses</b></p> <p>Business Development Unit Health &amp; Safety Laboratory Harpur Hill Buxton SK17 9JN</p> <p>☎ 0129 821 8800 email hslinfo@hsl.gov.uk</p>	<p><b>Interpreting results</b></p> <p>Biological monitoring gives no information about health – it is simply a measure of exposure. You need to explain this clearly to everyone taking part, and get their informed consent.</p> <p>Why are the results high? Results need interpreting. HSL can advise on simple practical ways of setting up a biological monitoring programme, and can help in interpreting the results.</p> <p><b>Quality assurance</b></p> <p>Any laboratory offering a service should participate in a relevant Quality Assurance scheme.</p>

**ANNEX D**

**Slide used in Safety and Health Awareness Days - Motor Vehicle Repair and 2 pack paints.**

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## The law on exposure measurement

COSHH (Control of Substance Hazardous to Health Regulations 2002), Regulation 10

*(1) Where the risk assessment (Reg 6) indicates that –*

*(a) It is requisite for ensuring the maintenance of adequate control...the employer shall ensure that the exposure of employees ...is monitored in accordance with a suitable procedure.”*

Currently, for MVR bodyshops the only “suitable procedure” for measuring exposure is via biological monitoring



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