

Development of analytical methods for low molecular weight isocyanates in workplace air

Part 2 – Isocyanic Acid and Methyl Isocyanate

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Monoisocyanates cause irritation to the eyes, skin and respiratory system. Existing methods for the determination of isocyanates were developed primarily to detect large di-isocyanate molecules and the analytical techniques employed are such that low molecular weight mono-isocyanates are not detected. The current work describes a modified detection method that enables separation, and therefore quantification, of mono isocyanates.

This modified method can be applied to suitable samples to enable an assessment of the contribution of mono-isocyanates (isocyanic acid and methyl isocyanate) to the total concentration of isocyanates in workplace air.

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EXECUTIVE SUMMARY

Objectives

The objective of this study was to develop methods for the determination of the two low molecular weight isocyanates (NCO): isocyanic acid (ICA) and methyl isocyanate (MIC). These species are produced by thermal degradation of isocyanate-derived polyurethanes at high temperatures and may be produced during machining of polyurethane painted parts e.g. in motor vehicle repair (MVR) shops or during flame bonding of polyurethane foams. They can also be produced by other processes e.g. by thermal decomposition of urea.

Main Findings

- The Hypercarb and C18 methods have been successfully developed from those in the earlier work (White, 2007).
- Both methods have been shown to give equivalent results and to be suitable for the determination of ICA and MIC in workplace air.
- The following Qualitative and Quantitative Detection Limits as defined by the International Standards Organisation (ISO) were found (ng NCO/filter);

Method	Isocyanate	Qualitative DL	Quantitative DL
Hypercarb Method	ICA-MP	18	60
	MIC-MP	48	160
C18	ICA-MP	15	50
	MIC-MP	21	70

- An alternative calculation of estimated Limit of Detection (est. LOD) using the mass spectrometer system software and based on the definition, est. LOD = 3x signal to noise ratio gave the following (ng NCO/filter);

Method	Isocyanate	Est. LOD
Hypercarb Method	ICA-MP	43
	MIC-MP	10
C18	ICA-MP	6
	MIC-MP	6

- The C18 method is the preferred method because of the easier sample work-up (i.e. no addition of acetic/hexanoic anhydride is required), slightly better method performance

and ease of integration into MDHS 25/3 which already specifies the use of a C18 column.

- All the glass fibre filter pre-treatments were found to give acceptable results for the C18 method i.e. no anhydride, hexanoic anhydride and acetic anhydride.
- The unknown interferent peak discussed in AS/2008/07 (White, 2007) has been identified as acetylated MP reagent.
- The dibutylamine method has been implemented on the HSL triple quadrupole.
- A novel application of the BSTFA derivatising reagent for the determination of ICA by GC/MS has been developed and a limited evaluation has taken place.
- The dibutylamine and BSTFA methods are useful for confirmation purposes i.e. for forensic and enforcement work.

Recommendations

These methods should be applied to suitable samples e.g. from “hot-working” processes, to enable HSE to better assess the contribution of isocyanic acid and methyl isocyanate to the workplace total isocyanate concentration.

1 INTRODUCTION

Isocyanates are potent respiratory sensitizers and a major cause of occupational asthma and work-related asthma in the UK (HSE, 2009). It has not been possible to establish a no-adverse-effect level for isocyanates. Isocyanates also cause irritation to the eyes, skin and respiratory system. The Health and Safety Executive (HSE) have set a long-term workplace exposure limit (WEL, 8 hr Time Weighted Average reference period) of $20 \mu\text{g}/\text{m}^3$ (total isocyanate (NCO) group) and a short-term limit (15 minutes) of $70 \mu\text{g}/\text{m}^3$ for workplace air (HSE, 2007).

HSE has published the method MDHS 25/3, developed by the Health and Safety Laboratory (HSL), which describes how airborne isocyanate exposure can be quantified (HSE, 1999). This method was developed primarily for the determination of the di-isocyanate monomers and oligo-isocyanates commonly used in industry and as routinely used at HSL is not suitable for the quantification of the low molecular mass isocyanates because of interference by the excess 1-(2-methoxyphenyl)piperazine (MP) reagent peak. The early eluting mono-isocyanate MP peaks will probably elute under the acetylated MP peak using the liquid chromatography (LC) conditions described in MDHS 25/3 and so will not be detectable by the ultra-violet/visible (UV/vis) or electro-chemical (EC) detectors described in this method.

Previous work (White, 2007) describes the successful extension of MDHS 25/3 for application to low molecular weight isocyanates by modification of the analytical part of the method. The sampling part of MDHS 25/3 as stated for vapour phase isocyanates is used unchanged i.e. sampling is carried out using an MP coated filter, in an IOM (Institute of Occupational Medicine, UK) sampling head with a 2 l/minute sampling flow rate.

The main modification to the analytical part of the method involves using a mass spectrometer in positive electrospray mode (ES+) as a detector. This report (White, 2007) found that a method using liquid chromatography (LC) with either an octadecylsilane column (C18 – as stated in MDHS 25/3), a modified mobile phase and LC gradient or a method using a Hypercarb column (graphitised carbon), a modified mobile phase and LC gradient coupled to selected ion monitoring (SIM) MS detection gave acceptable performance for a variety of mono-isocyanates. For the two lightest isocyanates, isocyanic acid (ICA - chemical formula H-NCO) and methyl isocyanate (MIC – chemical formula $\text{CH}_3\text{-NCO}$) recovery and interferent problems were initially observed but these were eventually resolved and acceptable methods developed (White, 2007). The method developed for ICA and MIC uses multiple reaction monitoring (MRM) mass spectrometry (MS) mode method to determine the MP derivatives of these two mono-isocyanates. This method monitors the daughter ions of specific fragmentations of the target compounds and so is more specific and less susceptible to interferences than the standard MS selected ion monitoring (SIM) methods. As isocyanic acid and methyl isocyanate are probably the most commonly encountered workplace mono-isocyanates it was suggested that further development work be carried out concentrating on these two isocyanate species. This report describes that work.

ICA (H-NCO) is chemically the simplest isocyanate. It can be formed by the breakdown of urea and by thermal decomposition of polyurethanes (Aigner et al, 1995; Paorici et al, 1999; Schaber et al, 2004; Koebel and Elsener, 1995; Blomquist et al, 2003 and Karlsson et al, 2001). It has also been synthesized in the laboratory by the reaction of sodium or potassium cyanate with stearic or oxalic acid (Fischer et al, 2002). A formal chemical analogy exists between ICA (H-NCO) and the tautomeric form cyanic acid (HO-CN). Of these two forms ICA is the most stable in dilute solution and is the only species present in the vapour phase at room temperature (Andrawes, 1984). Isocyanic acid is a gas at room temperature (b.p. 23.5°C) and exists as the monomeric species in the vapour phase (Fischer et al, 2002). The health effects of ICA have not been thoroughly studied and are usually estimated by analogy to MIC and the other isocyanates.

MIC is a liquid at room temperature (b.p. 39.1°C). Methyl isocyanate is used as chemical intermediate in the production of carbamate pesticides and some rubbers and adhesives. It has been detected as a product of the thermal breakdown of polyurethanes (Boutin et al, 2004; Boutin et al, 2005, Karlsson et al, 2001; Henricks-Eckerman et al, 2000; Westberg et al, 2005; Sennbro et al, 2004; White, 2003 and White, 2007). It is a highly toxic and irritating material, is hazardous to human health, and was involved in the Bhopal industrial disaster of 1984.

2 EXPERIMENTAL

2.1 MATERIALS AND INSTRUMENTATION

Ammonium formate, ammonium acetate, acetic acid, dibutylamine, formic acid, hexanoic anhydride and acetic anhydride were purchased from Aldrich, UK. Trimethylsilyl isocyanate and N,O-bis(trimethylsilyl)trifluoroacetamide solution were purchased from Fluka, UK. LC solvents (acetonitrile and methanol) were purchased from Rathburns, UK. LC grade water was provided by a Millipore reverse osmosis system. Methyl isocyanate (MIC) and isocyanic acid (ICA), the 1-(2-methoxyphenyl)piperazine (MP) derivatives and deuterated MP derivatives (d^3 -MP) were purchased from Synthelec, Sweden. The d^3 -MP derivatives were used as internal standards. ICA-DBA and MIC-DBA stock solutions were kindly supplied by Daniel Karlsson (Work Environment Chemistry, Stockholm University, Håssleholm, Sweden). Polyurethane and mineral fibre samples were taken by HSE inspectors during routine monitoring and enforcement activities. The LC/MS system used in this work consisted of an Applied Biosystems API2000 triple quadrupole MS and an Agilent 1100 LC pump, degasser and autosampler.

2.2 DEVELOPMENT OF HYPERCARB METHOD

The MRM method using a Hypercarb column (graphitised carbon – Thermo-Finnegan) was developed. Initial work looked at optimising the instrument tuning settings for ICA and MIC. Deuterated (d^3) ICA and MIC were used as internal standards. The instrumental conditions are given in Appendix 1.

The Hypercarb column was chosen as it is stated to give better retention than the more commonly used C18 for organic compounds. It was believed this would assist in removing the interferent problems seen initially in the previous work (White, 2007). To further increase the retention of the ICA-MP and MIC-MP derivatives a methanol/5 mM ammonium formate in water (0.1% formic acid) LC gradient was used. Methanol is a weaker LC solvent for the MP derivatives than the acetonitrile specified in MDHS 25/3.

Pre-treatment of the filters was suggested in the earlier study (White, 2007). Oven baking the filters at 400 °C prior to spiking with clean (re-crystallised) MP reagent was found to decrease the background signal, especially for protonated ICA-MP signal (mass to charge ratio – (m/z^+) of 236). Pre-treating the filters with hexanoic acid, prior to solvent desorption, instead of the acetic anhydride stated in MDHS 25/3 was suggested by the earlier study (White, 2007) as a means of removing mass spectrometric (isobaric) and chromatographic (retention time) interferences caused by the excess MP reagent desorbed from the filter. Hexanoylation of the excess MP reagent peak alters its retention time and changes its mass, thereby eliminating any interference with the ICA-MP peak. The hexanoyl group ($CH_3(CH_2)_4CO-$) with an m/z^+ of 99 reacts with MP to give the hexanoyl-MP peak with an m/z^+ of 292. Acetic anhydride adds the acetyl group (CH_3CO-) with an m/z^+ of 43 to give acetylated MP with an m/z^+ of 236. Hexanoyl-MP will be more strongly retained than acetyl MP on the Hypercarb LC column because of the longer alkyl chain on the hexanoyl group compared to the acetyl group and so will elute later. These modifications (methanol containing mobile phase, oven baking and hexanoic acid pre-treatment of the filters) were used in all the experiments using the Hypercarb method. The effect of hexanoylation on the excess MP reagent peak can clearly be seen in Figure 1.

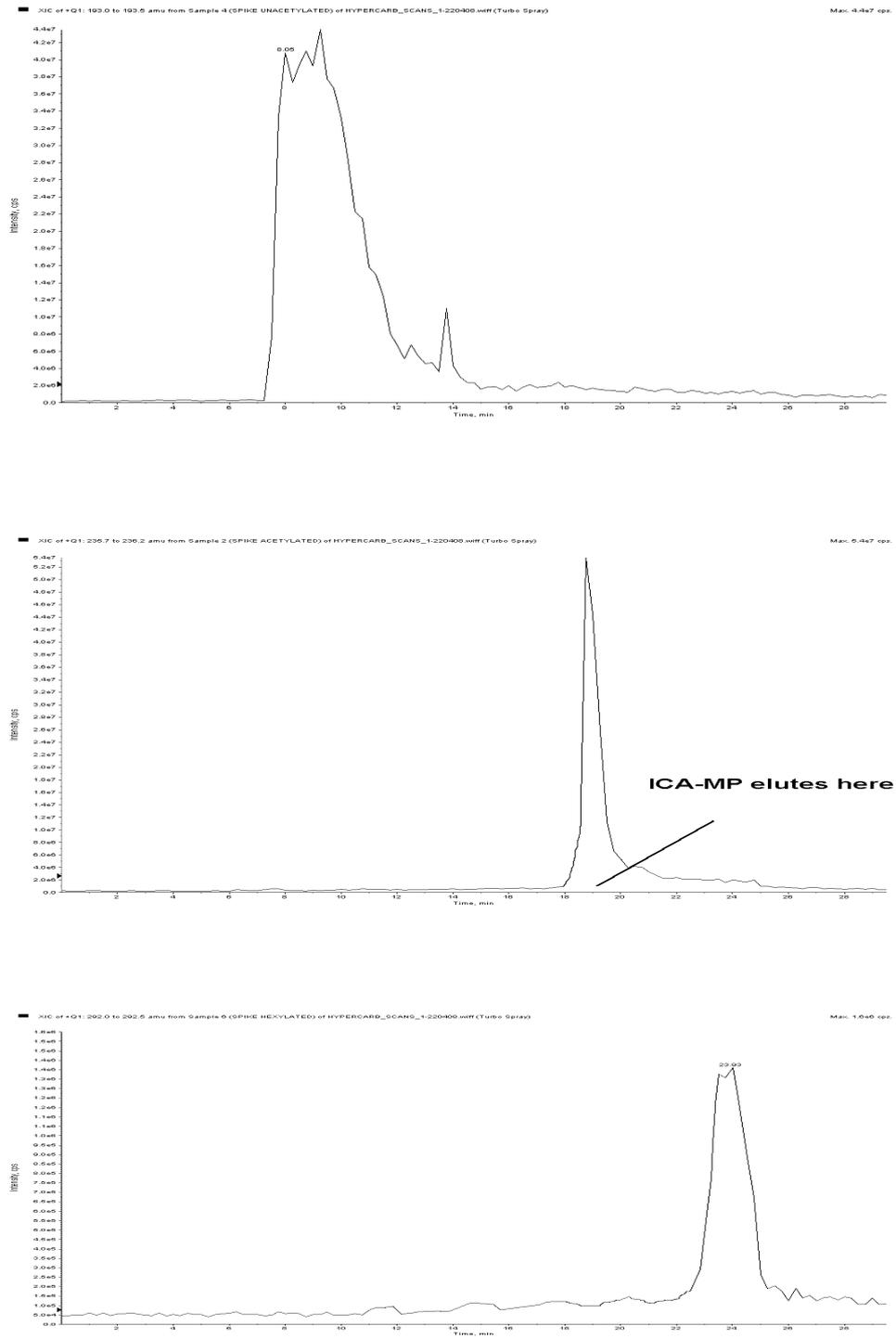
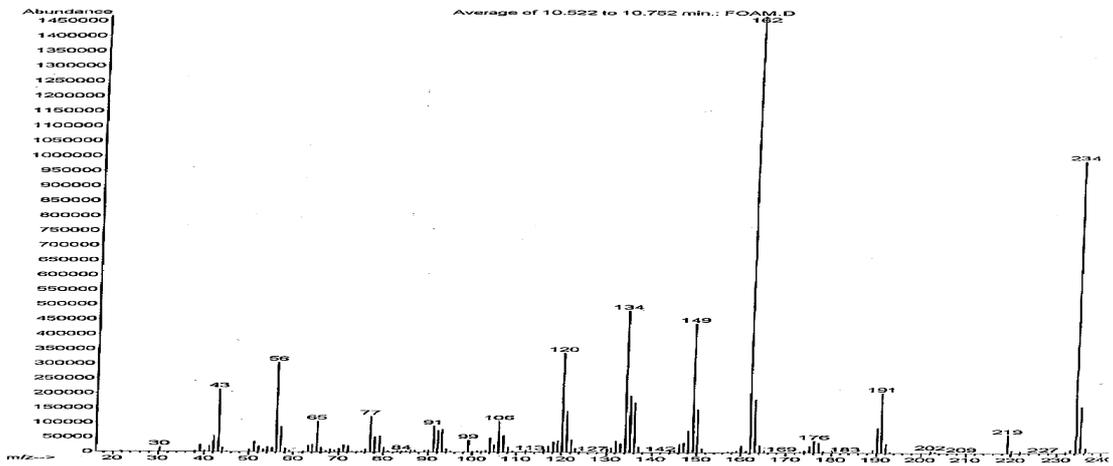


Figure 1. Example LC/MS Chromatograms for Untreated (upper, m/z+ 193.0 to 193.5), Acetylated (middle, m/z+ 235.7 to 236.2) and Hexanoylated (lower, m/z+ 292.0 to 292.5) MP reagent using the Hypercarb method.

Scan mode LC/MS and gas chromatography/mass spectrometry (GC/MS) was carried out to try to determine the identity of the unknown interferent peak identified previously (White, 2007). This work has identified the unknown peak as acetylated MP. It is suggested that the MP in these samples (White, 2007) had been acetylated prior to analysis as stated in MDHS 25/3 or, less likely, had been acetylated in the workplace by some chemical in the environment. Figure 2 shows a comparison of the MS spectra obtained for the GC/MS analysis of acetylated MP and the spectra obtained previously (White, 2007).



```

File       : C:\HPCHEM\1\DATA\JWNCO\ACMP.D
Operator   : JW
Acquired   : 19 Nov 2007  22:35      using AcqMethod JWSCAN
Instrument  : GC/MS Ins
Sample Name: acetyl MP
Misc Info  :
Vial Number: 6
  
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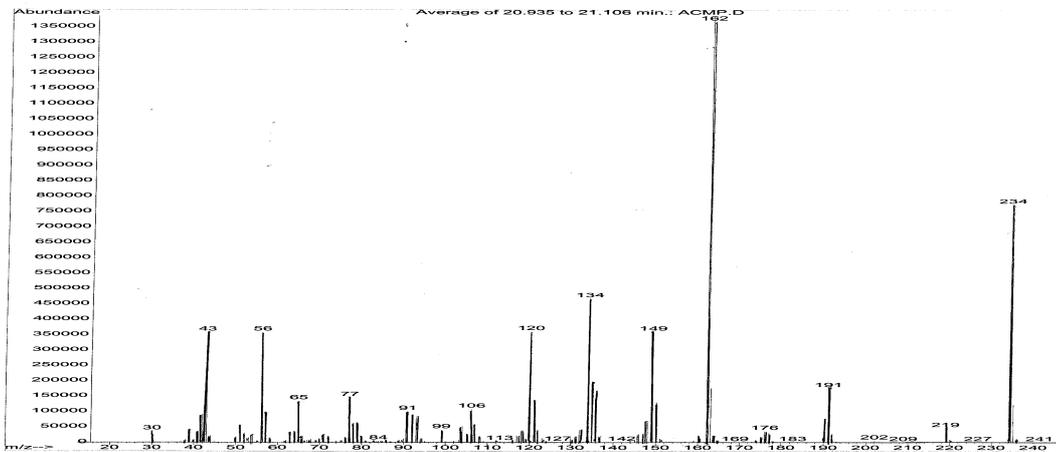


Figure 2. Comparison of 70 eV Electron Impact MS for Acetylated MP and Unknown Interferent

The different retention times for these peaks are because different GC methods, instruments and columns were used for operational reasons.

2.3 DEVELOPMENT OF MODIFIED MDHS 25/3 METHOD (C18 LC COLUMN)

MDHS 25/3 (HSE, 1999; White, 2006a) specifies the use of an octyldecylsilane (C18) column with an isocratic LC mobile phase run of ~ 50% acetonitrile/~50% sodium acetate buffer. An isocratic run is required because the electrochemical detector used in MDHS 25/3 cannot tolerate an LC gradient. The use of MS as the detector allows the use of an LC gradient as this detector is relatively unaffected by changing solvent compositions through the run. The MS was used in MRM mode. Involatile buffers such as sodium acetate are not recommended for use with MS as they precipitate out and clog up the MS skimmer stack. Optimizing the pH of the mobile phase can assist ion formation in the MS. For these reasons an LC gradient based on acetonitrile (+ 0.1% formic acid) and ammonium formate (5 mM in 0.1% formic acid) was used.

LC/MS methods for the diisocyanates using C18 columns have been published previously and were used as the basis for this work (White, 2006b; Östin et al, 2002) Initial work looked at optimising the instrument tuning settings for ICA and MIC. Deuterated (d^3) ICA and MIC were used as internal standards. The instrumental conditions are given in Appendix 2.

2.4 COMPARISON OF HSL METHODS

To examine the effect hexanoic anhydride pre-treatment on the two methods described above a series of linear calibration curves were prepared for ICA and MIC using spiked MP doped GF/A filters and in solution (acetonitrile for C18 method, methanol for Hypercarb method). The results of this work are given in Table 1.

All of the methods and treatments gave calibration curves with acceptable ($r^2 > 0.95$) linearity. Examining the gradients, it appears that the curves from the spiked MP coated GF/A usually gave slightly higher gradients than the curves from the solution calibration curves. This suggests there may be an ionisation enhancement caused by some compound that is desorbed from the MP doped GF/A. For this reason it is recommended that calibrations are carried out using ICA-MP and MIC-MP spiked MP doped GF/A filters i.e. a matrix matched calibration curve.

One comparison of particular interest is that between the ICA-MP on MP doped GF/A result for the “C18 –no anhydride pre-treatment experiment” and the analogous “Hypercarb – hexanoic acid pre-treatment” experiment. The gradients seen for these two results are very similar (0.252 vs. 0.262) suggesting that the untreated MP peak did not interfere with the C18 analysis. Scan mode LC/MS experiments similar to that described in section 2.2 and depicted in Figure 1 were carried out to compare the behaviour of untreated MP and acetylated MP on the C18 column. These experiments showed that although the untreated MP eluted as a broad (> 6 minutes across) peak and co-eluted with the ICA-MP and MIC-MP analyte peaks, it did not interfere with the MS detection. This is presumably because the MRM method filters out the untreated MP reagent in the Q1 quadrupole. However, it is surprising that the untreated MP reagent, which is present in great excess compared to the analytes, does not interfere with the ionisation process in the ES nebuliser and so cause ion suppression or enhancement. This finding suggests that the anhydride pre-treatment of the filters, specified by MDHS 25/3 to improve the chromatography, is superfluous if an MS detector is used. Previous work appears to agree with this conclusion (Boutin et al, 2004). Further work is recommended to test this suggestion for the di-isocyanates and oligo-isocyanates.

Table 1. Comparison of Calibration Curves for C18 and Hypercarb Methods**a) C18 – no anhydride pre-treatment**

Sample	Isocyanic acid -MP			Methyl Isocyanate-MP		
	A [†]	B [†]	r ^{2†}	A [†]	B [†]	r ^{2†}
MP doped GF/A	0.252	0.0161	0.9991	0.147	0.0322	0.9994
Solution	0.179	0.0181	0.9997	0.135	0.3256	0.9938

b) C18 – hexanoic anhydride pre-treatment

Sample	Isocyanic acid -MP			Methyl Isocyanate-MP		
	A [†]	B [†]	r ^{2†}	A [†]	B [†]	r ^{2†}
MP doped GF/A	0.276	0.0179	0.9983	0.164	-0.0431	0.9938
Solution	0.247	0.0007	0.9565	0.135	-0.0138	0.9959

c) Hypercarb - no anhydride pre-treatment

Sample	Isocyanic acid -MP			Methyl Isocyanate-MP		
	A [†]	B [†]	r ^{2†}	A [†]	B [†]	r ^{2†}
MP doped GF/A	0.254	0.0190	0.9851	0.123	0.0621	0.9685
Solution	0.248	-0.0072	0.9729	0.125	0.0150	0.9984

d) Hypercarb - hexanoic anhydride pre-treatment

Sample	Isocyanic acid -MP			Methyl Isocyanate-MP		
	A [†]	B [†]	r ^{2†}	A [†]	B [†]	r ^{2†}
MP doped GF/A	0.262	0.0228	0.9991	0.159	-0.0313	0.9985
Solution	0.269	-0.0121	0.9598	0.139	0.0131	0.9999

† A = Gradient; B = Intercept; r² = (Correlation Coefficient)²

Range of Calibration Curves

ICA-MP 0 – 5.5 µg NCO/filter

MIC-MP 0 – 17.8 µg NCO/filter

Workplace samples were taken during an HSE enforcement action at a mineral-fibre (stone wool) producing factory. Part of the manufacturing process involved heating urea to ~ 200 °C and so the production of ICA and MIC was considered likely. These samples were analysed using the Hypercarb method (see Appendix 1) and the C18 method (see Appendix 2). Figures 3 and 4 show the comparison for the MIC-MP and ICA-MP results respectively using these two methods.

The MIC-MP results shows a correlation exists between the results obtained by the Hypercarb and C18 methods. The low (< 0.9) r^2 value is probably because of the low (< 500 ng NCO/filter) amounts of MIC-MP seen in these samples. The ICA-MP results show a good correlation between the Hypercarb and C18 methods suggesting these two methods are giving equivalent results. Both methods detected large amounts of ICA-MP in the workplace air but relatively small amounts of MIC-MP. This is in agreement with the schemes for thermal decomposition of urea given in the references cited in the introduction.

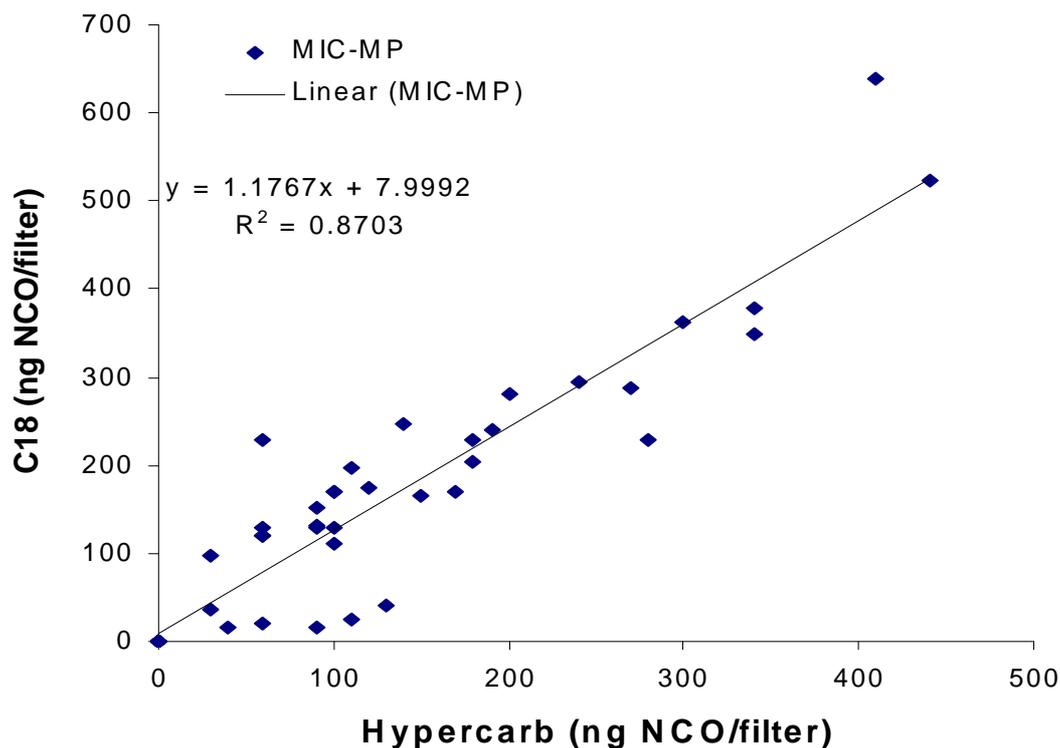


Figure 3. Comparison of MIC-MP Results for Analysis of Workplace Samples using the Hypercarb and C18 Methods

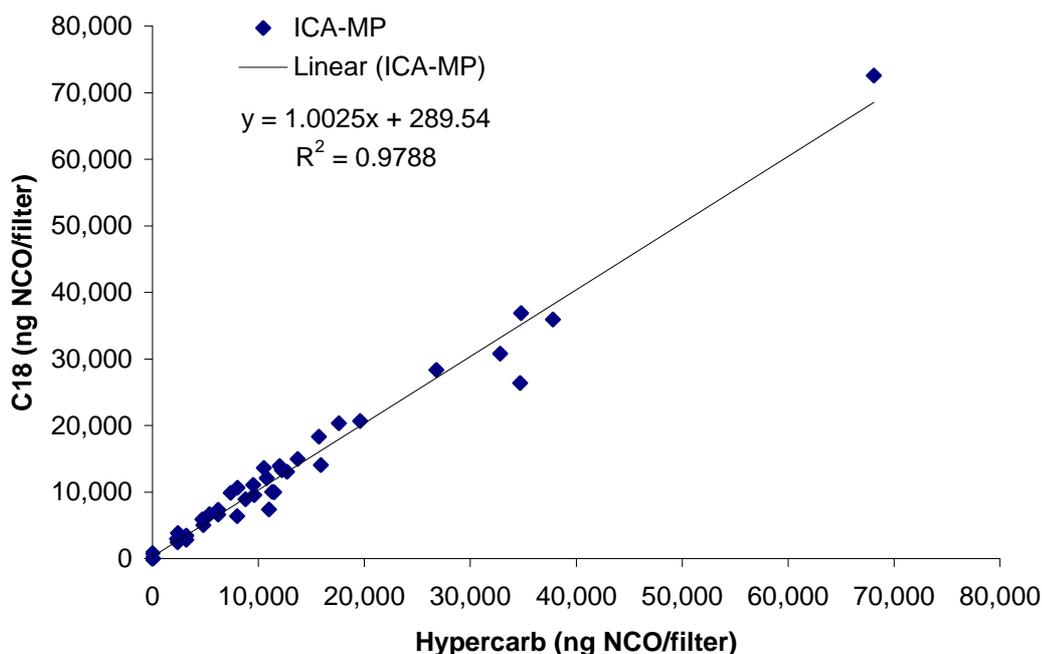


Figure 4. Comparison of ICA-MP Results for Analysis of Workplace Samples using the Hypercarb and C18 Methods

To enable a calculation of estimated limit of detection (est. LOD) for the two methods a number of blank MP doped filters were analysed. The filters were oven baked as suggested in the previous work (White, 2007). To provide an estimate of % recovery MP doped filters were spiked with low (88 ng NCO/filter ICA-MP and 382 ng NCO/filter MIC-MP) and high (879 ng NCO/filter ICA-MP and 3822 ng NCO/filter MIC-MP) levels of analyte. The results of this work are given in Table 2. Both methods gave acceptable recoveries ($\pm 25\%$) for both analytes at the levels spiked. The Hypercarb method (see Appendix 1) appeared to give slightly lower than 100% recovery whereas the C18 method (see Appendix 2) gave slightly above 100%. The blank filter values were below 20 ng NCO for both analytes and both methods with high % RSD values signifying the unreliability of the results at these low levels.

Table 2. % Recovery and Blank Filter Data for ICA-MP and MIC-MP spiked MP coated glass fibre filters using the Hypercarb and C18 Methods

a) Hypercarb Method

	Found (ng NCO)	SD (σ_{n-1})	RSD (%)	N	Recovery (%)
ICA-MP (ng NCO/filter)					
Blank	10	6	60	6	---
Low	75	9	12	6	85
High	868	45	5	6	99
MIC-MP (ng NCO/filter)					
Blank	15	16	107	6	---
Low	312	9	3	6	82
High	3,457	92	3	6	90

b) C18 Method

	Found (ng NCO)	SD (σ_{n-1})	RSD (%)	N	Recovery (%)
ICA-MP (ng NCO/filter)					
Blank	5	1	20	6	---
Low	82	19	23	6	107
High	907	24	3	6	103
MIC-MP (ng NCO/filter)					
Blank	7	7	100	6	---
Low	463	14	3	6	121
High	3,885	93	2	6	102

The qualitative and quantitative detection limits for isocyanate (as stated by the International Standards Organisation (ISO, 2007) are defined as three times and ten times the standard deviation of six blank determinations. Using these definitions the following qualitative and quantitative detection limits were calculated (see Table 3);

Table 3. Quantitative and Qualitative Detection Limits (as defined by ISO) for ICA-MP and MIC-MP using the Hypercarb and C18 Methods

Method	Isocyanate	Qualitative DL	Quantitative DL
Hypercarb Method	ICA-MP	18	60
	MIC-MP	48	160
C18	ICA-MP	15	50
	MIC-MP	21	70

An alternative calculation of est. LOD using the MS system software and based on the definition, est. LOD = 3x signal to noise ratio gave the following (ng NCO/filter);

Table 4. Estimated Limit of Detection (3x signal:noise ratio) for ICA-MP and MIC-MP using the Hypercarb and C18 Methods

Method	Isocyanate	Est. LOD
Hypercarb Method	ICA-MP	43
	MIC-MP	10
C18	ICA-MP	6
	MIC-MP	6

The C18 method appears to be giving slightly better performance i.e. lower qualitative and quantitative detection limits and estimated limits of detection. Even the “worst case” quantitative detection limit of ~ 160 ng NCO/filter, for a 15 l air sample, corresponds to ~ 11 µg NCO/m³ or ~ 1/6th of the current UK STEL.

2.5 WORKPLACE SAMPLES – POLYURETHANE PAINTED METAL

AS/2007/08 (White, 2007) described the analysis of ICA-MP and MIC-MP samples from welding and laboratory-based heating of polyurethanes.

Samples to determine workplace exposure to isocyanates were taken as described in MDHS 25/3 during routine exposure control sampling at a steel works. These samples were analysed firstly for MP derivatised hexamethylene diisocyanate (HDI) using the LC/MS/MS modification to the analytical procedure of MDHS 25/3 developed at HSL (Pengelly et al, 2008). The results of this analysis are given in Table 5.

The industrial process involved painting the metal with a blocked (stoved) isocyanate based paint. A blocked or stoved isocyanate is one in which the NCO group has been temporarily masked by reaction with a group, such as, phenol or tertiary alcohol. This forms a relatively weak urethane link. The blocked isocyanate can then be processed without fear of further reaction because no

unreacted isocyanate remains. When processing of the blocked isocyanate is complete, heat is applied which cleaves of the blocking group, freeing the isocyanate group that can then fully cure to the polyurethane. A temperature of ~200°C is often required to unblock a blocked isocyanate i.e. heating in a stove, from which the term stoved isocyanate is derived. It was considered that this heating could give rise to ICA and MIC by thermal breakdown of the cured polyurethane.

These samples were analysed using the C18 method developed in Section 2.3. Prior to the HDI analysis the samples had been treated with acetic anhydride as described in MDHS 25/3. The C18 method (see Appendix 2) was used to see if it gave acceptable performance for samples so treated. The results of this work are given in Table 5.

Analysis of the bulk paints by MDHS 25/3 found no isocyanates as expected because the paints contain blocked isocyanates. Pyrolysis GC/MS (Pengelly, 2002 and Pengelly et al, 2008) has been found to be extremely useful for identifying the parent isocyanate for blocked isocyanates and isocyanates produced by thermal degradation. Analysis of the bulks after heating at 200°C for five minutes and sampling onto MP coated GF/A found varying amounts of ICA (as the MP derivative) and very low amounts of MIC (as the MP derivative). Generally low levels or no isocyanate was found. However for sample 01686/08 the amount of ICA detected contributed significantly to the total isocyanate value.

One interesting analytical finding was that the acetylated MP peak was well separated from the analyte-MP peaks for the LC system used – see Figure 5. The upper trace shows the 236 > 193 transition, the ICA-MP peak with a retention time of 4.85 minutes is baseline resolved from the much larger, isobaric, acetylated-MP peak at 5.97 minutes. A useful confirmation that the smaller peak has been identified correctly is the retention time (4.76 min.) of the deuterated (d³) ICA-MP internal standard (MRM transition 239 > 196). For chemical reasons, deuterated ICA-MP should elute just before the ICA-MP peak and so the large 236 > 193 peak cannot be ICA-MP. In comparison, for the Hypercarb method the protonated hexanoyl-MP peak has an m/z+ of 292 and so is “invisible” to the 236 > 193 [ICA-MP-H]⁺ > [MP-H]⁺ transition i.e. is filtered out by the MRM method. For the C18 method, with no anhydride pre-treatment, the protonated MP peak has an m/z+ of 193 and is filtered out by the MRM method as just discussed for protonated hexanoyl-MP.

These results show that the C18 method can be used for the quantification of ICA and MIC from thermal degradation of heated polyurethanes. It is suggested that further monitoring of various “hot-working” processes involving polyurethanes and isocyanates is undertaken to assess the contribution of ICA and MIC to the total isocyanate value for these workplace activities.

Table 5. HDI-MP₂, ICA-MP and MIC-MP Results for Workplace Samples taken During Heating (200°C) of Metal Coated with Blocked Isocyanate-Based Paints

HSL Sample #	[HDI-MP ₂] ng NCO/filter	[ICA-MP] ng NCO/filter	[MIC-MP] ng NCO/filter
Bulk A Yellow Primer	HDI detected (by pyrolysis GC/MS) no HDI-MP ₂ detected for MP derivatised paint	12,100 5 minute sample @ 2l/minute. Paint heated to 200°C	~70 semi- quantitative
Bulk B White Topcoat	HDI detected (by pyrolysis GC/MS) no HDI-MP ₂ detected for MP derivatised paint	2,330 5 minute sample @ 2l/minute. Paint heated to 200°C	~10 semi- quantitative
Bulk C Black Primer	HDI detected (by pyrolysis GC/MS) no HDI-MP ₂ detected for MP derivatised paint	60 5 minute sample @ 2l/minute. Paint heated to 200°C	N.D.
01664/08 to 01665/08	N.D.	N.D.	N.D.
01666/08	6	N.D.	N.D.
01667/08 to 01670/08	N.D.	N.D.	N.D.
01671/08	7	N.D.	N.D.
01672/08	75	N.D.	N.D.
01673/08 to 01679/08	N.D.	N.D.	N.D.
01680/08	7	N.D.	N.D.
01681/08 to 01684/08	N.D.	N.D.	N.D.
01685/08	40	36	N.D.
01686/08	1,100	3,750	N.D.
01687/08 to 01691/08	N.D.	N.D.	N.D.
01692/08 to 01694/08	Blanks – The MIC-MP results have been blank corrected for small peaks seen in the blanks.		

Notes

N.D. = not detected i.e. below Est. LOD;

HDI-MP₂ ~5 ng NCO/filter

ICA-MP ~6 ng NCO/filter

MIC-MP ~6 ng NCO/filter

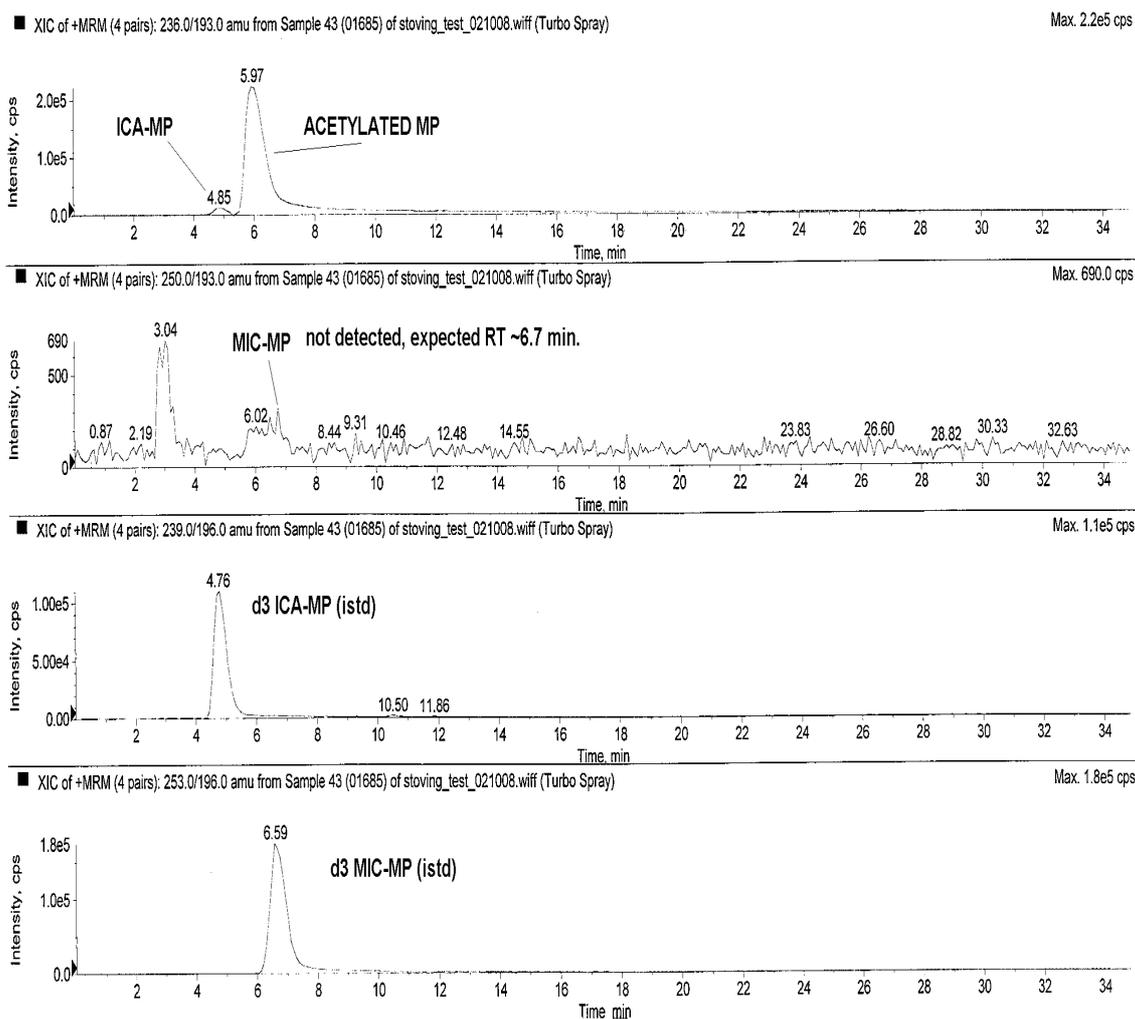


Figure 5. Analyte MRM Chromatograms (C18 Method) for Workplace Sample taken During Heating (200°C) of Metal Coated with Blocked Isocyanate-Based Paints

2.6 LABORATORY SAMPLES – HEATING OF POLYURETHANES

Using the techniques described in the earlier study (White, 2007) a variety of isocyanate based materials were heated at 250°C for 15 minutes. Any isocyanate containing fume or vapour emitted from these materials during heating was sampled via a glass funnel onto MP doped glass fibre filters at a flow rate of 2 l/min. These filters were then analysed by the Hypercarb method (Appendix 1) developed in Section 2.2. These results are given in Table 6.

Table 6. Determination of ICA and MIC (as MP derivatives) for Heated Polyurethane Products

Sample Type	[ICA-MP] ng NCO/filter	[MIC-MP] ng NCO/filter
Spray foam – aerosol can	1,300	N.D.
Flexible foam – car seat	11,700	N.D.
MVR Topcoat – cured film	39,000	~100
Rigid foam - packaging	N.D.	~100
Polyurethane Rod - sealant	1,420	N.D.

These results show that the Hypercarb method can be used for the quantification of ICA and MIC from thermal degradation of heated polyurethanes. They suggest that for the heating of polyurethanes, of the two isocyanate species, the most likely to be encountered is ICA. The experimental set-up of this work was, for operational reasons, different to that in the earlier work (White, 2007) so it is not possible to meaningfully compare the two result sets.

2.7 CONFIRMATORY METHODS

As ICA and MIC are low molecular weight molecules, their determination by MS can potentially be interfered with by a large number of compounds and breakdown products. For analysis carried out for enforcement and forensic purposes it is therefore useful to have methods to confirm the analyst's identification of a peak as being ICA or MIC derived. This section describes work carried out on methods to confirm the identity of ICA and MIC derived peaks.

2.7.1 LC/MS method with Dibutylamine Derivatisation

In addition to the methods already cited in this report, several other methods for ICA or MIC have been published e.g. Zwiegberk et al, 2002; Henriks-Eckerman et al, 2002 and McClure et al, 1984). Probably the most thoroughly researched method is that of Karlsson et al. (Karlsson et al., 2001) which uses dibutylamine (DBA) as derivatising agent. This method was implemented on the HSL triple quadrupole MS system. The instrumental conditions used are given in Appendix 3. Calibration curves were produced for ICA-DBA and MIC-DBA using stock solutions kindly supplied by Daniel Karlsson (Work Environment Chemistry, Stockholm University, Håssleholm, Sweden).

A beaker containing 10 to 20 g of urea was heated on a hotplate at 200°C for 5 to 30 minutes. Ten experiments (different amounts of urea and heating times) were carried out. Any isocyanate containing fume or vapour emitted from the urea during heating was sampled via a glass funnel connected to a plastic t-piece simultaneously onto MP doped glass fibre filters at a flow rate of 2 l/minute and into a midjet impinger containing 10 ml of 0.01 mol/l dibutylamine in toluene solution at a flow rate of 1 l/minute. These solutions were then analysed by the dibutylamine (see Appendix 3) and the HSL C18 method (see Appendix 2), the same LC column was used for both methods.

Both methods confirmed the presence of ICA in the sampled air. Neither method detected MIC. The DBA derivatised ICA and MIC gave slightly longer retention times (6.8 and 9.3 minutes for ICA-DBA and MIC-DBA respectively against 4.1 and 5.4 minutes for ICA-MP and MIC-MP) retention times on the C18 column used for both methods than the MP derivatised ICA and MIC. A meaningful comparison of the results given by the methods could not be carried out as both

methods gave extremely high results for all the ten different experiments (equivalent to 10,000s $\mu\text{g}/\text{m}^3$ of ICA as NCO for all the samples) and had overloaded both of the samplers. The results obtained for this work show the usefulness of the DBA method for confirmation i.e. it was confirmed that ICA is produced on heating of urea, and has resulted in the method being implemented on the HSL triple quadrupole and so made available if required. Repeat experiments using lower amounts of urea e.g. mg instead g, to give results for that two methods that could be numerically compared were not carried out because of time constraints.

2.7.2 Pyrolysis GC/MS

Pyrolysis gas chromatography/mass spectrometry (GC/MS) has been found to be a useful confirmatory technique for identifying the parent isocyanate for blocked isocyanates and isocyanates produced by thermal degradation. This work is reported elsewhere (Pengelly, 2002 and Pengelly et al, 2008).

2.7.3 GC/MS Method for Isocyanic Acid Using the Derivatising Reagent N,O-bis(trimethylsilyl)trifluoroacetamide (BSTFA)

2.7.3.1 Preparation of TMSI Standard

Trimethylsilyl isocyanate (TMSI) (5 μl , 4.26 mg) was added to 995 μl of toluene to give Standard A (4260 $\mu\text{g}/\text{ml}$). Standard A was serially diluted to give Standards B and C i.e. diluted 100 μl of Standard A to 1 ml with toluene to give Standard B (426 $\mu\text{g}/\text{ml}$) and diluted 100 μl of Standard B to 1 ml with toluene to give Standard C (42.6 $\mu\text{g}/\text{ml}$).

Standard C was analysed by GC-MS (see Appendix 4) using a scan mode (SCAN) MS method and a chromatogram with a peak at around 2.2 minutes (see Figure 6) with a mass spectrum (see Figure 7) matching that of the NIST library spectrum of TMSI was obtained. A selected ion monitoring (SIM) mode MS method using mass ions (m/z) 70, 72 and 100 was also used to monitor these methods. The SCAN peak area (at m/z 100) was approximately 24.5 million counts and the SIM peak area was approximately 38.4 million counts.

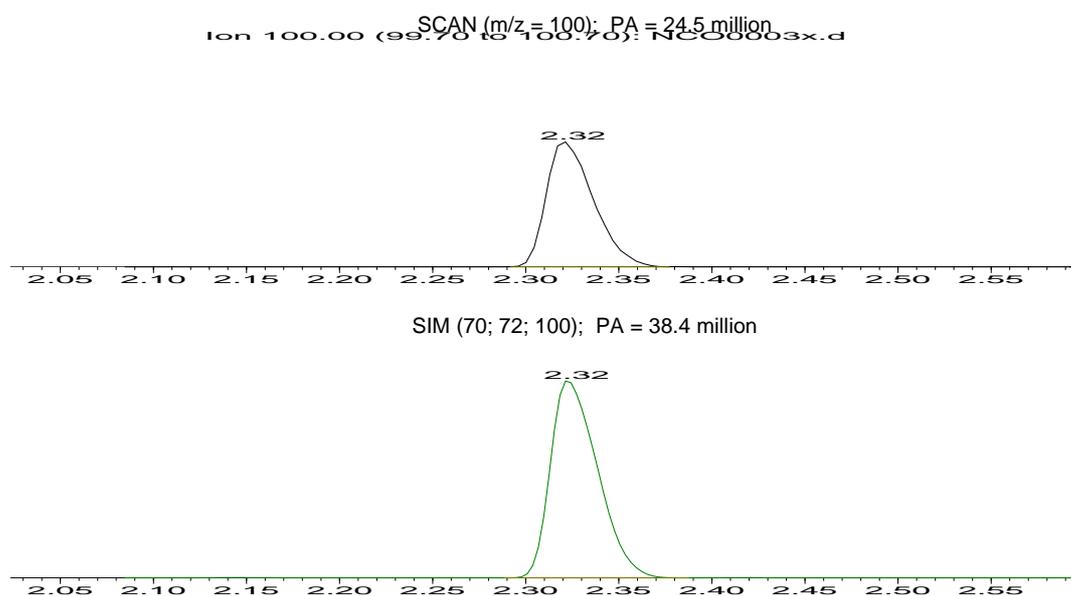


Figure 6. TMSI Standard – SCAN & SIM Chromatograms

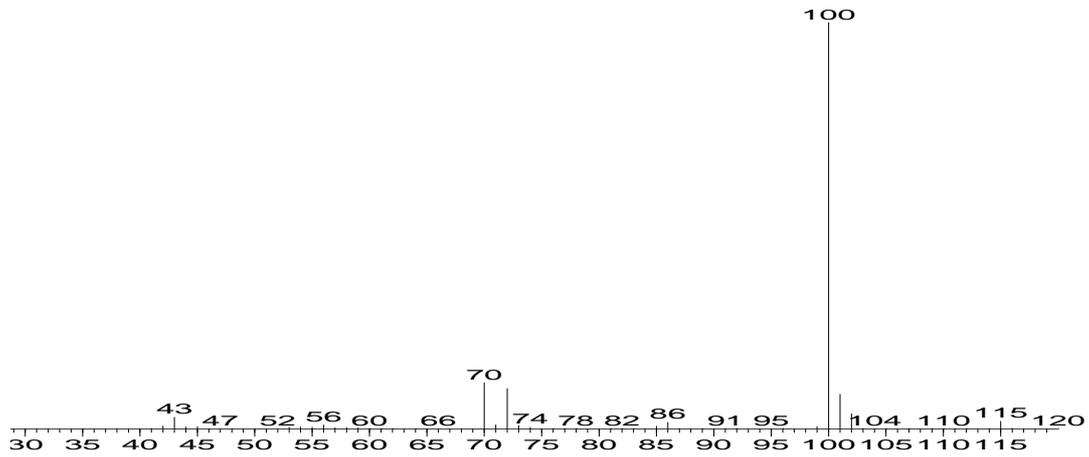


Figure 7. Mass Spectrum of TMSI Peak

2.7.3.2 Mineral-Fibre (Stone Wool) Tests

a) Experiment 1

A sample of uncured mineral-fibre was placed into 4 ml LC vial, capped with a Teflon-silicone septum and heated in a heating block at 150°C for approximately 15 minutes. The sample was removed from the heating block and left to cool to room temperature (ca. 5 minutes). Two ml of N,O-bis(trimethylsilyl)trifluoroacetamide (BSTFA) reagent (4% BSTFA solution/96% toluene – by volume) was added and the mixture left to stand for 30 minutes before being analysed by GC-MS in SIM and SCAN modes. A TMSI signal with SCAN peak area (m/z = 100) of approximately 0.24 million and SIM peak area of approximately 0.37 million counts was obtained (see Figure 8). The MS peak obtained for the heated mineral-fibre sample in scan mode gave an MS spectrum that exactly matched that of the TMSI standard (given in Figure 7). The sample peaks were approximately 100 times smaller than the TMSI standard giving a concentration of around 0.4 µg/ml, this equates to around 0.8 µg of TMSI (or 0.3 µg of ICA) in the sample.

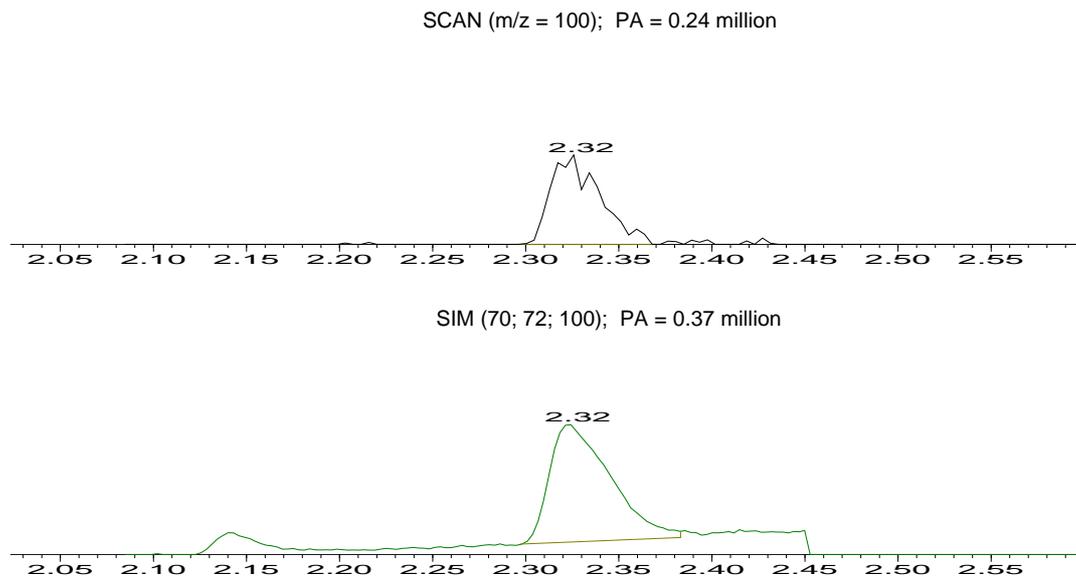


Figure 8. Experiment 1 – SCAN & SIM Chromatograms for BSTFA derivatised Heated Mineral-Fibre

b) Experiment 2

A larger sample of the uncured mineral-fibre was placed in a 50 ml flask sealed with a teflon-silicone septum. The sample was heated on a hot plate to 200°C for approximately 30 minutes during which time misting of walls of flask was observed. A 4 ml air sample was taken from the flask using a fine needle gas syringe and bubbled through 1 ml of BSTFA reagent. The reagent solution was then left to stand for 30 minutes before analysis by GC/MS in SIM and SCAN modes. A TMSI signal with SCAN peak area ($m/z = 100$) of approximately 0.1 million counts and SIM peak area of approximately 0.17 million counts (see Figure 9) was obtained. These peaks were approximately 200 times smaller than the TMSI standard giving a concentration of around 0.2 $\mu\text{g}/\text{ml}$, this equates to around 0.2 μg of TMSI (or 0.08 μg of ICA) in the sample.

c) Experiment 3

The mineral-fibre sample from Experiment 2 was heated for a further 60 minutes or so, then removed from the heater and placed in the freezer for 30 minutes in order to condense out any ICA present. The sample was then removed from the freezer, opened and the remaining solid mineral-fibre plug removed. One ml of BSTFA reagent was added and the mixture was left to stand for 30 minutes before analysis by GC-MS in SIM and SCAN modes. A TMSI signal with SCAN peak area ($m/z = 100$) of approximately 4.0 million counts and SIM peak area of approximately 7.5 million counts was obtained (see Figure 10). These peaks were 5 - 6 times smaller than the TMSI standard giving a concentration of around 7.5 $\mu\text{g}/\text{ml}$, this equates to around 7.5 μg of TMSI (or 3 μg of ICA) in the sample.

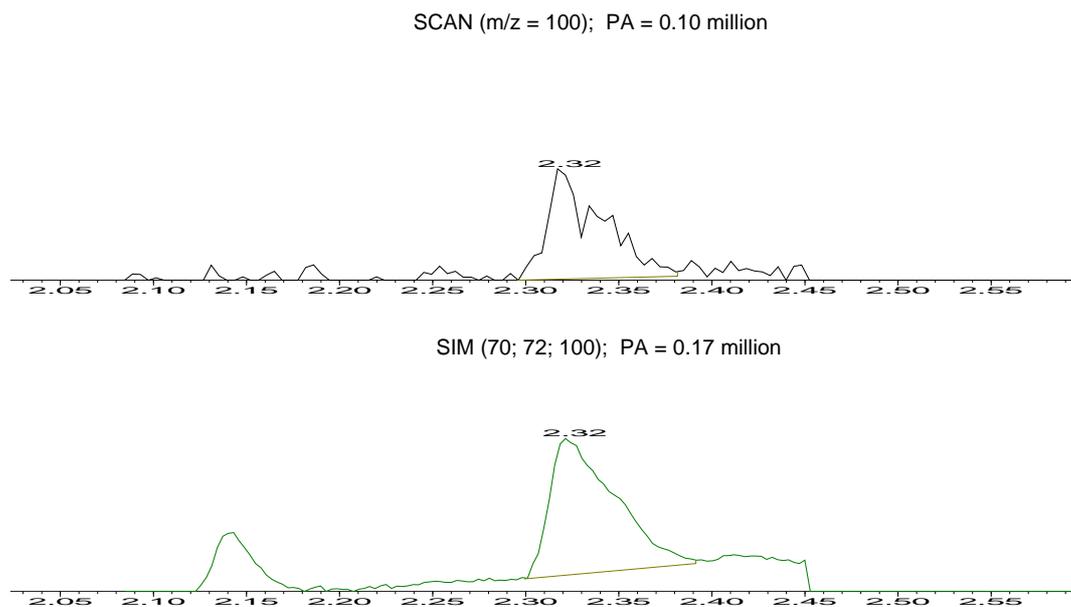
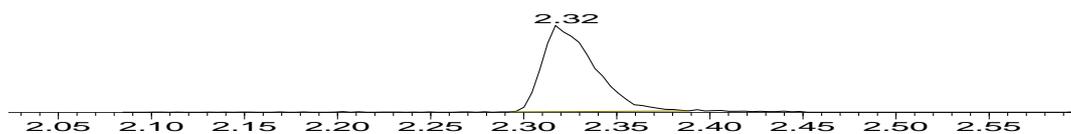


Figure 9. Experiment 2 – SCAN & SIM Chromatograms for BSTFA derivatised Heated Mineral-Fibre

SCAN (m/z = 100); PA = 4.0 million



SIM (70; 72; 100); PA = 7.5 million

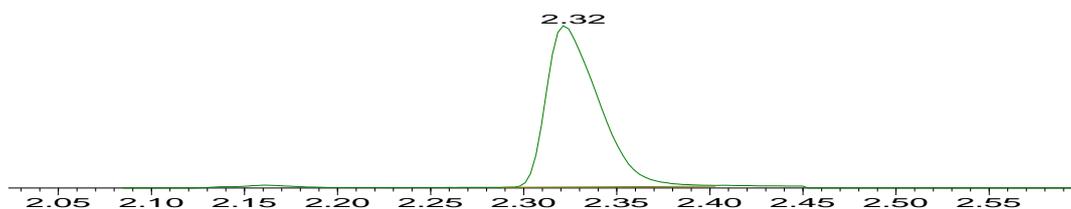


Figure 10. Experiment 3 – SCAN & SIM Chromatograms for BSTFA derivatised Heated Mineral-Fibre

This work has shown that BSTFA can be used to determine ICA produced by the heating of mineral-fibre. This is a novel application of the BSTFA derivatisation procedure and provides a useful confirmatory method, especially as the TMSI standard is commercially available. This method can be applied to ICA produced by heating polyurethanes and other materials.

3 CONCLUSIONS

The Hypercarb and C18 methods have both been shown to be suitable for the determination of ICA and MIC in workplace air. The C18 method (Appendix 2) is the preferred method because of the easier sample work-up (i.e. no addition of acetic/hexanoic anhydride is required), slightly better method performance (Table 2) and ease of integration into MDHS 25/3 which already specifies the use of a C18 column. In fact, all the glass fibre filter pre-treatments were found to give acceptable results for the C18 method i.e. no anhydride (Section 2.3), hexanoic anhydride (Section 2.4) and acetic anhydride (Section 2.5).

The unknown interferant peak discussed in AS/2008/07 (White, 2007) has been identified as acetylated MP reagent.

The dibutylamine method has been implemented on the HSL triple quadrupole. A novel application of the BSTFA derivatising reagent for the determination of ICA by GC/MS has been developed and a limited evaluation has taken place. These methods are useful for confirmation purposes i.e. for forensic and enforcement work.

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5 APPENDICES

Appendix 1. Hypercarb Method – “Hypercarb_2_B.dam”

a) Sampling conditions

Sampling onto an MP coated GF/A using a pumped sampler @ 2 l/minute. Pre-treatment of filters with 200 µl of hexanoic anhydride, dry down under N₂, re-suspend in methanol

b) LC conditions

LC column – Hypercarb, 5 µm, 100 x 3 mm, Thermo-Finnegan and Phenomenex Sentry-Guard C18 guard disc.

Injection volume 5 µl.

Gradient elution, 300 µl/min

Equilibrate at initial conditions for 5 min.

T (min.)	0	3	8	20	21	35
%B	65	65	90	90	65	65

%A = 5 mM ammonium formate/ 0.1% formic acid pH ~ 3.8

%B = methanol/ 0.1% formic acid

c) MS conditions

MS – ES+ mode, MRM

236 > 193	protonated ICA-MP > protonated MP transition	dwel 5,000
250 > 193	protonated MIC-MP > protonated MP transition	dwel 100 ms
239 > 196	protonated d ³ -ICA-MP > protonated d ³ -MP transition	dwel 100 ms
253 > 196	protonated d ³ -MIC-MP > protonated d ³ -MP transition	dwel 100 ms

d) MS settings

Declustering Potential – orifice plate (DP)	30 V
Focussing ring Potential (FP)	350 V
Entrance Potential – Q ₀ lens (EP)	5 V
Curtain gas (CUR)	30 psi
Electrospray needle Potential (IS)	5200 V
Source Temperature (TEM)	550 °C
Nebulizer gas (GSG1)	25 psi
Nebulizer gas (GSG2)	25 psi

Collision cell (Q2) Gas setting (CAD)	6	
Collision cell (Q2) Entrance Potential (CE)	20 V	
Collision cell (Q2) Exit Potential (CXP)	20 V	
Quadrupole Resolution	Q1 unit	Q3 low

Appendix 2. C18 Method – Modified MDHS 25/3 - “Ostin_Gromsil_2B.dam”

a) *Sampling conditions*

Sampling onto an MP coated GF/A using a pumped sampler @ 2 l/minute. No pre-treatment of filters with acid anhydrides required, dry down under N₂, re-suspend in acetonitrile

b) *LC conditions*

LC column - Grace Chromatography, 4 µm, Grom-sil 80 ODS 7PH, 150 x 3mm + 40 x 2 mm guard column of same packing

Injection volume 5 µl

Gradient elution, 250 µl/min

Equilibrate at initial conditions for 5 min.

T (min.)	0	4	14	20	21	30
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%B	40	40	90	90	40	40
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%A = 5 mM ammonium formate/ 0.1% formic acid pH ~ 3.8

%B = acetonitrile/ 0.1% formic acid

c) *MS conditions*

MS – ES+ mode, MRM

236 > 193	protonated ICA-MP > protonated MP transition	dwell 5,000
250 > 193	protonated MIC-MP > protonated MP transition	dwell 100 ms
239 > 196	protonated d ³ -ICA-MP > protonated d ³ -MP transition	dwell 100 ms
253 > 196	protonated d ³ -MIC-MP > protonated d ³ -MP transition	dwell 100 ms

d) *MS settings*

Declustering Potential – orifice plate (DP)	30 V
Focussing ring Potential (FP)	50 V
Entrance Potential – Q ₀ lens (EP)	10 V
Curtain gas (CUR)	30 psi
Electrospray needle Potential (IS)	5500 V
Source Temperature (TEM)	550 °C
Nebulizer gas (GSG1)	25 psi
Nebulizer gas (GSG2)	25 psi
Collision cell (Q2) Gas setting (CAD)	10
Collision cell (Q2) Entrance Potential (CE)	30 V

Collision cell (Q2) Exit Potential (CXP)

10 V

Quadrupole Resolution

Q1 unit

Q3 low

Appendix 3. HSL version of Karlsson's Dibutylamine derivatization Method – "Karlsson_dba_method.dam"

a) Sampling conditions

Sampling is into 10 ml of 0.01 mol/l dibutylamine in toluene solution in a midjet impinger. Samples are pumped air samples taken @ 1 l/minute. The samples were evaporated to dryness under a gentle stream of N₂ and re-suspended in acetonitrile prior to LC/MS analysis.

b) LC conditions

LC column - Grace Chromatography, 4 µm, Grom-sil 80 ODS 7PH, 150 x 3mm + 40 x 2 mm guard column of same packing

Injection volume 2 µl

Gradient elution, 250 µl/min

equilibrate at initial conditions for 1 minute – method is isocratic.

T (min.) 0 15

%B 50 50

%A = water/ 0.1% formic acid pH ~ 3.8

%B = acetonitrile/ 0.1% formic acid

c) MS conditions

MS – ES+ mode, MRM

173.3 > 130.3 protonated ICA-DBA > protonated DBA transition dwell 1,000 ms

187.3 > 130.3 protonated MIC-DBA > protonated DBA transition dwell 1,000 ms

d) MS settings

Declustering Potential – orifice plate (DP)	30 V
Focussing ring Potential (FP)	50 V
Entrance Potential – Q ₀ lens (EP)	10 V
Curtain gas (CUR)	30 psi
Electrospray needle Potential (IS)	5500 V
Source Temperature (TEM)	550 °C
Nebulizer gas (GSG1)	25 psi
Nebulizer gas (GSG2)	25 psi
Collision cell (Q2) Gas setting (CAD)	10
Collision cell (Q2) Entrance Potential (CE)	30 V
Collision cell (Q2) Exit Potential (CXP)	10 V

Quadrupole Resolution

Q1 unit

Q3 low

Appendix 4. GC/MS methods for ICA with BSTFA derivatization

a) Sampling conditions

Sample preparation as described in section 2.7.3

SCAN mode method – TMS_NCO_1

b) GC conditions

GC Column – Restek RX-5 Amine 30m x 0.25mm x 0.5 µm

Temperature Programme

Initial 50°C (for 30 s)

Ramp 1 @ 10 °C to 80°C (no hold time)

Ramp 2 @ 40 °C to 250°C (hold for 7.25 minutes)

Total run time 15 minutes

Solvent Delay 2 minutes

Detector off @ 2.45 minutes (this is to allow the toluene solvent peak to elute)

Detector on @ 5.50 minutes

Injection Volume 1 µl

Split 30:1

Column Flow 1 ml/minute

c) MS conditions

Mass range (m/z+) 40 – 400 (4 scans/s)

SIM method – TMS_NCO_2

Sample preparation, GC column and conditions as scan method

d) MS settings

Ions (m/z+) monitored - 70, 72, 100, 106

Optional - 298 (methyl stearate – internal standard)

Development of analytical methods for low molecular weight isocyanates in workplace air

Part 2 – Isocyanic Acid and Methyl Isocyanate

Monoisocyanates cause irritation to the eyes, skin and respiratory system. Existing methods for the determination of isocyanates were developed primarily to detect large di-isocyanate molecules and the analytical techniques employed are such that low molecular weight mono-isocyanates are not detected. The current work describes a modified detection method that enables separation, and therefore quantification, of mono isocyanates.

This modified method can be applied to suitable samples to enable an assessment of the contribution of mono-isocyanates (isocyanic acid and methyl isocyanate) to the total concentration of isocyanates in workplace air.

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