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An Approach to Area Sampling and Analysis for Total Isocyanates in Workplace Air

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An approach to sampling and analysis for total isocyanates (monomer plus any associated oligomers of a given isocyanate) in workplace air has been developed and evaluated. Based on a method developed by the Occupational Health Laboratory, Ontario Ministry of Labour, Ontario, Canada, isocyanates present in air are derivatized with a fluorescent reagent, tryptamine, in an impinger and subsequently analyzed via high-performance liquid chromatography (HPLC) with fluorescence detection. Excitation and emission wavelengths are set at 275 and 320 nm, respectively. A modification to the Ontario method was made in the replacement of the recommended impinger solvents (acetonitrile and 2,2,4-trimethylpentane) with dimethyl sulfoxide (DMSO). DMSO has the advantages of being compatible with reversed-phase HPLC and not evaporating during sampling, as do the more volatile solvents used in the Ontario method. DMSO also may dissolve aerosol particles more efficiently during sampling than relatively nonpolar solvents. Several formulations containing diisocyanate prepolymers have been tested with this method in the laboratory. This method has been issued as National Institute for Occupational Safety and Health (NIOSH) Method 5522 in the first supplement to the fourth edition of the NIOSH *Manual of Analytical Methods.* This method is recommended for area sampling only due to possible hazards from contact with DMSO solutions containing isocyanate derivatives. The limits of detection are 0.1 μg/sample for 2,4-toluene diisocyanate, 0.2 μg/sample for 2,6-toluene diisocyanate, 0.3 μg/sample for methylene bisphenyl diisocyanate, and 0.2 μg/sample for 1,6-hexamethylene diisocyanate.

Keywords: isocyanates, sampling and analysis

Mention of company names and products does not constitute endorsement by the Centers for Disease Control and Prevention.

Health effects that are known to be due to monomeric diisocyanates are being observed also in applications that involve prepolymeric or oligomeric forms of diisocyanate compounds.[1–11] The majority of existing sampling and analytical methods for diisocyanates in air address only the monomeric compounds.[12,13] Although there are no existing national exposure limits in the United States to specific prepolymers or oligomeric isocyanates, the ability to detect the prepolymers and oligomeric compounds as well as the parent monomeric diisocyanate compounds would prove very useful in assessing health effects of workers exposed via a variety of exposure pathways. There is a wealth of ongoing research seeking to address the collection and analysis of the oligomeric forms of isocyanates as well as the monomers. Determination of total isocyanate involves the measurement of a given monomer and any associated oligomers of that monomer, e.g., hexamethylene diisocyanate monomer and any associated oligomers contained in the formulation or generated during the application process. The challenge of measuring total isocyanates is well known in the isocyanate community. Research efforts include industry methods developed by isocyanate producers, work in the area of calibrated real-time monitoring, innovative engineering research that seeks to address the physical challenges of collection of all isocyanate species present in the air, and modification of current methods and technology to include oligomeric species of isocyanates.[9,13–16] It is not the purpose

of this article to review this area of research, but rather to add an approach to this growing repertoire of methods developed for the measurement of total isocyanates.

Recently, National Institute for Occupational Safety and Health (NIOSH) *Manual of Analytical Methods* (NMAM) 5521 for total isocyanates,[17] adapted from *Methods for Determination of Hazardous Substances* (MDHS) 25,[18] has come into question concerning its ability to identify oligomers of aromatic diisocyanates due to the contribution of additional ultraviolet (UV) response from the aromatic rings in these compounds.[19–21] Contribution from parts of the molecule other than the derivatized isocyanate functionality can lead to variability in the detector response ratios, which are the basis of identification of isocyanate-based oligomers in NMAM 5521. This method can be used for the measurement of monomers and associated oligomers of aliphatic diisocyanates by the addition of a photodiode array (PDA) detector for confirmation of the isocyanate-derived oligomeric species by comparing the PDA UV spectra of the high-performance liquid chromatography (HPLC) peaks with an established PDA UV reference spectrum for the derivatized monomer.[20] In the NMAM, fourth edition, Method 5521 was restricted to monomers of the aromatic diisocyanates.[22]

In NMAM 5521 a sample of air is drawn through an impinger containing a toluene solution of the reagent 1-(2-methoxyphenyl)piperazine. Any isocyanate that is collected is derivatized to the corresponding urea in the reagent solution during sampling. The sample is analyzed by reversed-phase HPLC. For analysis of the monomers, two detectors are set up in series to measure the analyte: a UV detector (242 nm) and an electrochemical (EC) detector (+0.8 V versus Ag/AgCl). The more sensitive EC detector is used for quantification.

Wu et al. have developed an analytical method for total isocyanates that involves the use of fluorescence detection of tryptamine-derivatized isocyanates.[23] Although the method is sensitive, their selected sampling techniques appear to have disadvantages. (a) Air sampling with an impinger containing the reagent in a volatile solvent (toluene, acetonitrile, or 2,2,4-trimethylpentane) results in the need to replenish the solvent at short intervals (the interval can be as short as 15 minutes when the ambient temperature is about 35°C). (b) The volatile solvent may result in exposure to vapors that are toxic or a fire hazard.[24] (c) A solvent exchange must be performed on every sample in order to obtain a sample that is compatible with reversed-phase HPLC, resulting in a complex sample preparation step. (d) It has been noted that the collection efficiency of nonpolar solvents such as toluene and 2,2,4-trimethylpentane may not be as efficient for the sampling of isocyanate aerosols.[25] Aerosols are of importance when sampling for total isocyanates since isocyanate-based formulations are used commonly during aerosol-producing operations such as spray-painting or foam applications. In addition, air sampling of isocyanate aerosols with a reagent-coated solid support can lead to poor yields of the tryptamine derivatives because isocyanate groups trapped below the surfaces of aerosol particles may have no opportunity to react with the reagent.[26] The opportunity of reaction of the isocyanate groups with reagent must be immediate; otherwise, the isocyanate groups may take a different pathway for reaction, such as polymerization.

An appropriate sampler for total isocyanates and isocyanate aerosols appears to be an impinger containing tryptamine in solution with a nonvolatile solvent. The solvent must dissolve the isocyanate aerosol instantly to permit the trapped isocyanate groups to react immediately with reagent. Furthermore, the solubility of tryptamine in the sampling solvent is an important consideration. Tryptamine has shown limited solubility in otherwise suitable solvents. In this study, the development and evaluation of a sampling and analytical method for total isocyanates is reported that employs tryptamine dissolved in a nearly ideal solvent: i.e., dimethyl sulfoxide (DMSO). DMSO is an excellent solvent for tryptamine and its isocyanate derivatives, because DMSO solubilizes tryptamine, isocyanates, and the urea derivatives. Also, DMSO is nontoxic and relatively nonvolatile. Moreover, DMSO is compatible with reversed-phase HPLC; therefore, a complex solvent exchange step for field samples is eliminated. The ease with which DMSO transports dissolved substances through the skin precludes the use of DMSO for personal sampling when breakage of the impinger is a possibility. However, DMSO is recommended as a solvent for tryptamine in area sampling. NIOSH has issued this method as NMAM 5522 for area sampling for total isocyanates (monomer plus any associated oligomers of a given isocyanate).[27] This method is not recommended for mixtures of different isocyanates.

In NMAM 5522 a sample of air is drawn through an impinger containing a DMSO solution of the tryptamine reagent. Any isocyanate that is collected is derivatized to the corresponding urea in the reagent solution during sampling. Since DMSO is hygroscopic, the impinger solution may increase in volume over the sampling period. Therefore, the final volumes of field samples must be noted. The sample is analyzed by reversed-phase HPLC. A fluorescence detector is used to measure the analyte, with an electrochemical detector set up in series for confirmation of the identity of the analyte. The final data can be corrected for volume changes.

EXPERIMENTAL

Reagents and Materials

Acetonitrile, methanol, and DMSO were HPLC-grade solvents from Burdick and Jackson Laboratories (Muskegon, Mich.). Tryptamine, >99% pure, was obtained from Sigma (St. Louis, Mo.) and was further purified before use. For purification, 1.0 g of tryptamine was dissolved in 60 mL acetonitrile, heated to 60°C for 15 minutes, filtered, and allowed to cool to room temperature. The crystals were collected and dried in a vacuum oven at 37°C, with slight ventilation to remove vapors generated. Glacial acetic acid and sodium acetate trihydrate were reagent grade and were obtained from Fisher Scientific (Vienna, Va.). Heptane, tetrahydrofuran, and n-propanol were reagent grade and were obtained from Burdick and Jackson. Reagent grade n-butylamine was obtained from Aldrich (Milwaukee, Wis.). The double-deionized water was prepared by passing laboratory deionized water through a Peck Water Systems mixed bed ion-exchange column, carbon scavenger, and 0.2 μm polishing filter. The 0.1 N sodium acetate buffer for the HPLC mobile phase was prepared by dissolving 25 g of sodium acetate trihydrate in a solution containing 1 L of methanol and 1 L of double-deionized water. The pH of the solution was adjusted to 6.0 with glacial acetic acid. Neoprene latex gloves were obtained from Fisher Scientific.

Desmodur N-3300 was obtained from Bayer, Inc. (Pittsburgh, Pa.)[28] This formulation contains 100% isocyanurate trimer of 1,6-hexamethylene diisocyanate (HDI). PAPI 27 was obtained from Dow Chemical Company (Midland, Mich.).[29] This formulation contains a mixture of monomer and prepolymer of methylene bisphenyl diisocyanate (MDI). A titration was performed on each formulation as an independent method of determining the

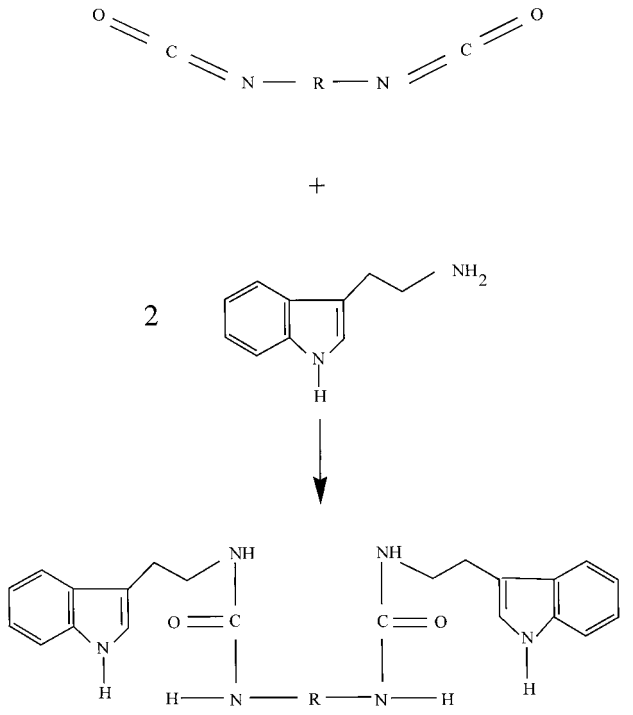

FIGURE 1. Reaction of tryptamine with diisocyanate

amount of NCO group contained in the respective formulations.[30] The titration involved dissolving a known amount of the formulation in tetrahydrofuran, adding a known amount of n-butylamine in excess, and allowing the isocyanate in the formulation to react with the n-butylamine. From the amount of standardized HC1 required to titrate the unreacted n-butylamine the amount of NCO group present in the sample can be calculated.

Urea Derivatives

Tryptamine is 2-(3-indolyl)ethylamine. The reaction of tryptamine with diisocyanate yields 2-(3-indolyl)ethyl urea as shown in Figure 1. The procedure for preparation of the urea derivatives is summarized in the flowchart shown in Figure 2. The urea derivatives of MDI, HDI, 2,4-toluene diisocyanate (2,4-TDI), and 2,6-toluene diisocyanate (2,6-TDI) were synthesized by dissolving 0.00250 mole (0.41 g) of tryptamine (>99% pure) in 300 mL of toluene, heating the solution to 60°C while stirring until much of the tryptamine was dissolved, and adding a solution of the respective diisocyanate (0.001 mole) in 20 mL of toluene. The urea derivative precipitated as a white gel and was collected in a fritted-glass funnel by suction filtration. For the urea derivatives of HDI and MDI, the precipitate was dissolved in 100 mL or 450 mL of hot n-propanol, respectively. The solution was filtered, allowed to cool, and the crystals were collected. For the urea derivatives of 2,4-TDI and 2,6-TDI, the precipitate was dissolved in 50 mL of hot n-propanol. The solution was filtered and allowed to cool. Next, heptane (175 mL for 2,4-TDI and 100 mL for 2,6-TDI) was added, and the precipitate was collected in a fritted-glass funnel by suction filtration. All urea derivatives were dried in a vacuum oven at 60°C. The melting points for the urea derivatives were 201–201.5°C for HDI, 270°C for MDI, 216–219°C for 2,4-TDI, and 298–310°C for 2,6-TDI. The urea derivatives are stable and can be stored for at least 6 months at ambient temperature.

HPLC

The liquid chromatograph for the analyses of samples consisted of two Waters Model 6000A reciprocating pumps, a Waters Model 600-MS controller, a Waters Model 710B autosampler, a Shimadzu RF-535 fluorescence detector set at 275 nm excitation and 320 nm emission, and an ESA Model 5100A electrochemical detector operated in the oxidative mode (+0.8 V versus Ag/AgCl). The analytical column was from Waters: 3.9 cm ID × 150 mm stainless steel packed with 10 μm μ-Bondapak C-18. The flow rate was 1.0 mL/minute, the injection volume was 25 μL. The mobile phase was 50:50 (for HDI, 2,4-, and 2,6-TDI) and 60:40 (for MDI) acetonitrile:buffer (0.1 N sodium acetate), isocratic.

HPLC conditions have been established for quantification of total isocyanates, i.e., monomer plus the associated oligomers of the specific monomer: (a) a mobile phase of 50:50 acetonitrile: buffer is used for the analysis of monomer and associated oligomers of HDI, (b) a mobile phase of 50:50 acetonitrile:buffer is used for the analysis of monomer and associated oligomers of 2,4- and 2,6-TDI, and (c) a mobile phase of 60:40 acetonitrile:buffer is used for the analysis of monomer and associated oligomers of MDI. An aliquot, 25 μL, of the field sample is directly injected into the HPLC; no sample preparation is required.

Calibration and Limits of Detection and Quantitation

Calibration curves were run for each analyte. The calibration curves were based on the fluorescent response of the synthesized urea derivatives of the diisocyanate monomers. The standard solutions were prepared in the sampling medium, 450 mg/L tryptamine in DMSO.

For each analyte, the limit of detection (LOD) was determined by preparing six low-level calibration standards covering a range from less than the expected LOD to 10 times the LOD.[31] A calibration curve was constructed for each analyte. In each case, the linear regression calculation yielded a calculated LOD value lower than the lowest standard. Thus, the LOD was reported as the lowest standard for each analyte. The limit of quantitation (LOQ) is 3.33 times the LOD and is used as the lower limit of the analytical range. The LODs and analytical ranges for the analytes are given in Table I.

Solvent Experiments

In a preliminary experiment conducted in a room with a steady humidity of 45%, it was found that 20 mL of DMSO (the recommended volume for impinger sampling) took on 17% (v/v) water (less than 4 mL) during 14 hours of continuous air sampling at a 1 L/min flow rate (see Figure 3). To investigate the potential interference of water, recovery studies were conducted for HDI and MDI in pure DMSO and in DMSO solutions of DMSO containing 17% water (v/v). This study was conducted at a tryptamine concentration of 45 mg/L. Vapor spikes were prepared for HDI by depositing a known amount of pure HDI in a u-tube attached to an impinger containing the reagent medium. Air was pulled through the impinger at a nominal flow rate of 1 L/min until no HDI remained, about 1 hour. Due to MDI's low vapor pressure, liquid spikes were prepared in these two reagent media. This study also was repeated for all four diisocyanates at a tryptamine concentration of 450 mg/L. For the two TDI monomers and HDI monomer, three levels of vapor spikes were prepared in the presence of no added water and one level with 17% water. Liquid spikes were prepared for MDI monomer in the two reagent media.

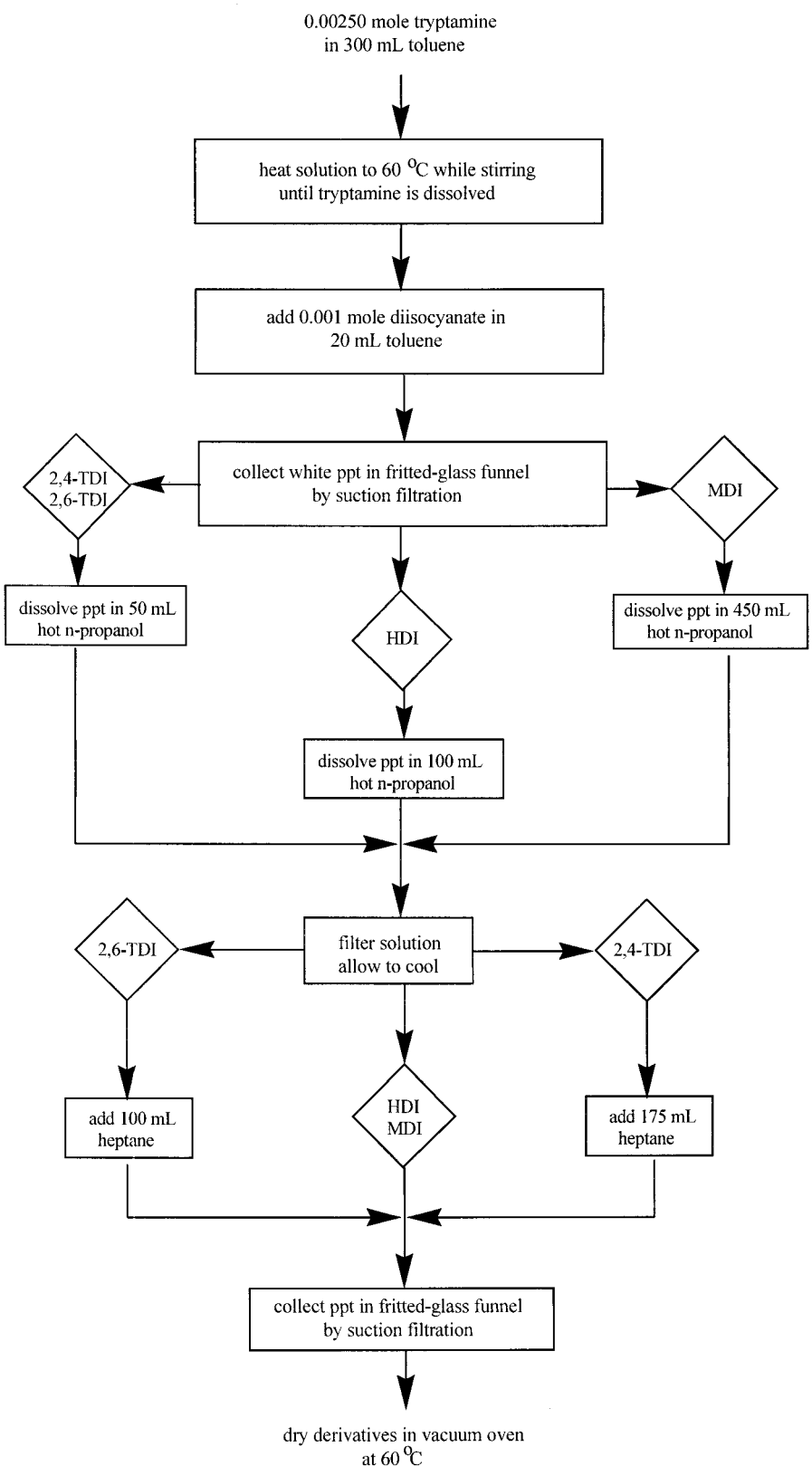

FIGURE 2. Preparation of tryptamine-diisocyanate derivatives

TABLE I. Limits of Detection and Analytical Ranges

Analyte	LOD μg/sample	LOD ppb (15-L air sample)	Analytical Range μg/sample
2,4-TDI	0.1	0.93	0.3–14.0
2,6-TDI	0.2	1.9	0.6–14.0
HDI	0.2	1.9	0.6–20.0
MDI	0.3	1.9	1.0–10.0

TABLE II. Recoveries at 45 mg/L Tryptamine Concentration

Analyte	Quantity (μg)	% Water	Average Recovery (%)
HDI	54.8	0	90.1
	54.8	17	76.9
MDI	71.4	0	89.7
	71.4	17	40.7

During the sampling, about 2% water was taken on by the sampling medium that contained no added water. In addition, storage stabilities of the analytes were run at low or zero water content and at 17% water content at a tryptamine concentration of 450 mg/L. Six samples of each isocyanate were stored at four levels at ambient temperature in the dark for a total of at least 28 days.

RESULTS AND DISCUSSION

Solvent Studies

There were several potential problems with the proposed use of DMSO. Investigation into the possible toxicity of DMSO yielded the following information.[32–34] The Occupational Safety and Health Administration (OSHA), NIOSH, and the American Conference of Governmental Industrial Hygienists have no exposure limits for DMSO. Skin irritations are reversible. DMSO is not mutagenic in the Ames test and has a low carcinogenic potency. The issue of most concern was the fact that DMSO is known to be absorbed readily into the skin and may carry into the body dissolved chemicals. Although DMSO itself is not known to be toxic, isocyanate derivatives dissolved in the impinger sampling medium may be transported into the body if the solution comes into contact with the skin. The literature indicated that neoprene latex gloves show no breakthrough of DMSO after more than 8 hours in contact with water on one side and DMSO on the other side.[35] Therefore, neoprene latex gloves were deemed to provide adequate skin protection in working with DMSO solutions. Because of time constraints, it was not possible to perform an exhaustive investigation of other solvents to find a solvent with similar desirable properties as DMSO that could be used during personal sampling.

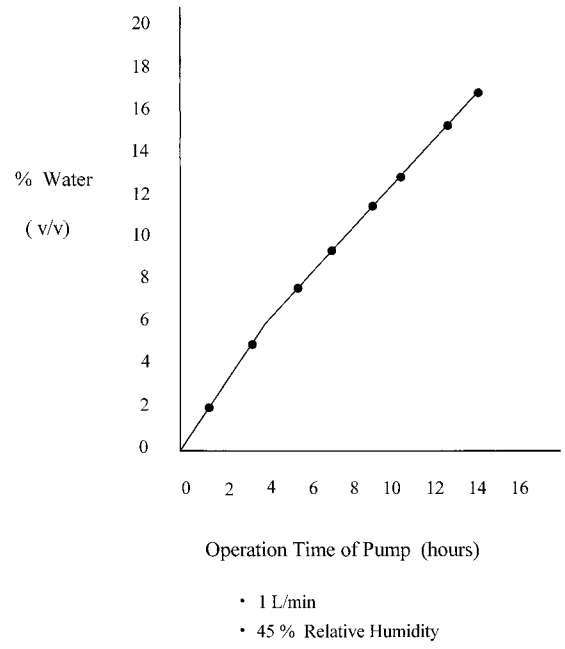

FIGURE 3. Absorption of water vapor by dimethyl sulfoxide during air sampling

The second potential problem requiring investigation was the hygroscopic nature of DMSO. As can be seen in Table II, at a reagent concentration of 45 mg/L, 17% water content in the sampling medium resulted in substantial loss of the analyte, with recoveries ranging as low as about 41%. Table III shows the recoveries obtained for a reagent concentration of 450 mg/L in the sampling medium. The recoveries were quite good at the higher reagent concentration in solutions with low water content and in solutions with 17% water content. Thus, the conclusion is that at a concentration of 450 mg/L of tryptamine in DMSO, the reaction rate of the isocyanate with the derivatizing reagent is much faster than the reaction rate with water; therefore, water does not significantly compete for the isocyanate. Results for 28-day storage stability studies gave recoveries above 90% for all of the urea derivatives.

The final potential problem with using DMSO as a sampling solvent is the relatively high freezing point. An example of environments where freezing could be a problem is mining environments in which the ambient temperature is about 13°C. MDI-based formulations are used to repair cracks in the walls of mine tunnels. The Mine Safety and Health Administration allowed testing of this method in a routine survey during repair operations.[36] It was observed that small crystals formed in the impingers, indicating that partial freezing did occur during sampling at 13°C

TABLE III. Recoveries at 450 mg/L Tryptamine Concentration

Analyte	Quantity (μg)	% Water	Average Recovery (%)
2,4-TDI	4.9	2	87.1
	15	2	98.2
	60	2	86.1
	60	17	93.6
2,6-TDI	6.0	2	100.2
	15	2	104.0
	60	17	104.1
HDI	5.0	2	87.3
	15	2	86.7
	60	2	94.5
	47	17	96.4
MDI	3.2	0	99.5
	16	0	97.9
	71	0	91.9
	71	17	93.6

in the impingers containing the DMSO-tryptamine sampling medium. The sampling medium was modified by adding acetonitrile. A solution containing tryptamine in 20:80 acetonitrile:DMSO freezes at −4°C. Samples then were collected for this survey using this modified solution and no freezing was observed during sampling. The recoveries of the four diisocyanate analytes were conducted in the 20:80 acetonitrile:DMSO sampling medium. Recoveries were above 90% and 28-day storage stability studies also gave recoveries above 90% for all the urea derivatives. The results indicate that this sampling medium is satisfactory for sampling in ambient temperatures less than 15°C.

Monomer Studies

The retention times for the diisocyanate monomers were 12.6 minutes for the urea derivative of 2,4-TDI, 9.6 minutes for the urea derivative of 2,6-TDI, 11.0 minutes for the urea derivative of HDI, and 7.3 minutes for the urea derivative of MDI. Each monomer was run separately.

Fluorescence studies were performed in an effort to investigate the correlation of fluorescence yields of different diisocyanates. Wu et al. stated that the fluorescence yields of the various tryptamine-derivatized diisocyanate monomers should have a high degree of correlation since the electronic structure of the tryptamine indolyl group Π-system is not perturbed upon derivatization.[37] Theoretically, one standard should be sufficient for quantification regardless of the specific diisocyanate being quantified. However, fluorescence measurements for each of the urea derivatives of the four diisocyanate monomers exhibited a fluorescence response variation of about 16%. Therefore, it is recommended that a calibration curve be determined for each diisocyanate analyte.

Oligomer Studies

For quantification of isocyanate-based oligomers, two protocols were considered. One approach is to make dilution standards of the formulations themselves and to quantitate based on the formulation. An advantage of this approach is that one can obtain the exposure to that particular formulation, which is very useful. A disadvantage is that the U.S. legal exposure limits are written for the monomeric diisocyanates, not for individual formulations. There is one exception: Oregon state OSHA has issued an exposure limit for Desmodur N-3300, which is used commonly in the autobody paint industry.[11] However, there are hundreds of different formulations with varying percentages of oligomers. It is virtually impossible to obtain pure standards of the major individual components of different formulations.[37] In addition, running dilution standards using formulations can take up to an hour or more for each standard, since the isocyanate-based oligomers elute much later than the parent monomer.

In the third edition NMAM, NIOSH Method 5521 used a monomer calibration curve for quantification of oligomers. This second approach was chosen in adapting the Ontario method. Advantages of using the monomer standards include the short runtime required to generate the calibration curve and the ease of availability of the standards. A disadvantage of this approach is the assumption that the fluorescent yield for the isocyanate functional group attached to oligomeric species is the same as the fluorescent yield for the isocyanate functional group attached to monomeric species. Electrochemical detection is used to confirm that the eluting species is an isocyanate-derived oligomer.

Chromatograms for the two formulations studied are given in Figures 4 and 5. Desmodur N-3300 (Figure 4), consists of 100% HDI isocyanurate trimer. Thus, only one peak is expected, and it will have a retention time greater than the HDI monomer urea derivative (11.0 minutes). One peak was seen at a retention time of 25.2 minutes, see Figure 4. PAPI 27 (Figure 5), consists of 50–60% by weight MDI oligomer and 40–50% of a component that contains MDI monomer. Thus, two peaks are expected, one at the retention time of the MDI monomer urea derivative (7.3 minutes) and a second peak at a retention time greater than the MDI monomer urea derivative. Two peaks were seen, one eluting at the retention time of the MDI monomer urea derivative (7.3 minutes), and the second peak eluting at a retention time of 13.5 minutes, see Figure 5.

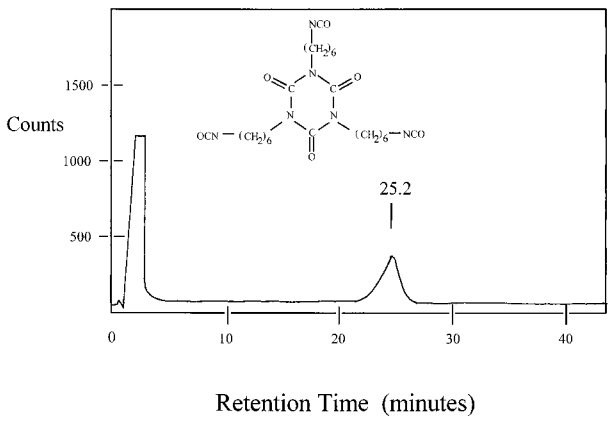

FIGURE 4. HPLC fluorescence chromatogram and structure of Desmodur N-3300

CONCLUSIONS

An approach to sampling and analysis for total isocyanates in workplace air has been adapted from the work by Wu et al.[23] The replacement of the impinger solvent with DMSO has several advantages: An aliquot of the field samples can be injected directly into the HPLC, no replenishment of the impinger solvent is necessary, and the samples can be stored at ambient temperature in the dark and exhibit a high degree of storage stability. It was found that at a reagent concentration of 450 mg/L of tryptamine, any

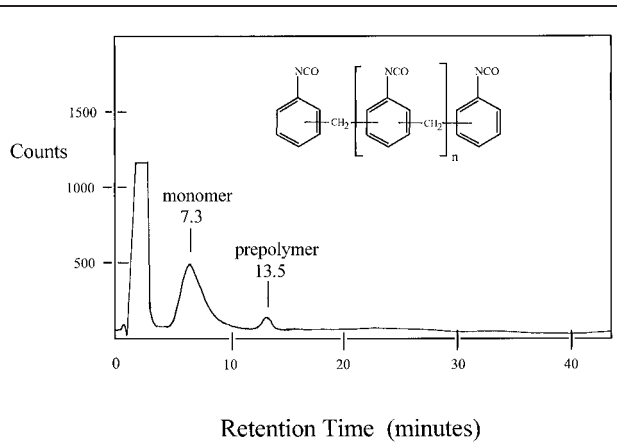

FIGURE 5. HPLC fluorescence chromatogram and structure of PAPI 27 (50% monomer, 50% prepolymer)

water present either in the solvent or in the sampling atmosphere did not significantly compete for the isocyanate. A solvent modification using the addition of acetonitrile extends the range of sampling temperatures to below 15°C. NMAM 5522 has been used during a number of field studies.[38–48] In the challenging field of isocyanate sampling and analysis, this method adaptation represents an approach that can be used to assess isocyanate monomers and associated oligomers in workplace air.

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