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Comparison between the ASSET EZ4 NCO and Impinger Sampling Devices for Aerosol Sampling of 4,4′-Methylene Diphenyl Diisocyanate in Spray Foam Application

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ABSTRACT

4,4′-methylene diphenyl diisocyanate (MDI) aerosol exposure evaluation in spray foam insulation application is known to be a challenge. Current available techniques are either not user-friendly or are inaccurate or are not validated for this application. A new sampler has recently been developed to address the user-friendliness issues with other samplers: the ASSET EZ4-NCO, but the use of this sampler in spray foam insulation applications has not been demonstrated or validated. Because of this, the current work was undertaken to provide a comparison of the ASSET sampler with an impinger method, considered to be the best available method in the context of spray foam insulation, and hence the pertinence of comparing this sampler to an impinger method, considered to be the best available method for measuring MDI monomer and oligomers for this particular application. Liquid chromatography coupled with tandem mass spectrometry method for MDI monomer and oligomer analysis was implemented based on the Supelco literature. It allows the analysis of MDI–dibutylamine (DBA) and MDI 3-ring-DBA with a minimum reported value of 5 ng ml^{-1}, a dynamic range of 5–140 ng ml^{-1}, precision <15% and accuracy >80%. This method was used to quantify MDI aerosols collected with the ASSET sampler in an MDI spray foam environment in parallel with the toluene/MOPIP impinger reference method. The ASSET sampler significantly underestimated the levels of MDI monomer and oligomers when compared to the reference method. The estimated bias was 72% (95% confidence interval [CI] 54–89%) for the monomer and 96% (95% CI 76–115%) for the oligomers. These results demonstrate the importance of evaluating each new sampler for each isocyanate application prior to a formal worker exposure evaluation.

KEYWORDS: ASSET EZ4-NCO sampler; denuder; impinger; isocyanate; MDI

INTRODUCTION

Polyurethanes are used worldwide in various applications. One application is for insulation foam which involves the polymerization of an isocyanate, namely 4,4′-methylene diphenyl diisocyanate (MDI) and its oligomers with a polyol. It is well established that

MDI is a respiratory and cutaneous chemical irritant and a sensitizer causing occupational asthma as a major work-related illness (Malo *et al.*, 1983; Banks *et al.*, 1986; Mapp et al., 1988, 1999; Musk *et al.*, 1988; Vandenplas *et al.*, 1992). Airborne isocyanates are usually found in two different forms: vapor and liquid, and in MDI spray foam application, it is used in dispersed liquid droplets (liquid aerosols) (Roberge *et al.*, 2009). In order to protect workers using this chemical substance, an occupational exposure limit (OEL) has been set at 5 ppb for the monomer by most countries (OSHA, 1992; National Institute for Occupational Safety and Health Alert, 1996; Swedish National Board of Occupational Safety and Health, 2000; Québec (Province), 2012; American Conference of Governmental Industrial Hygienists, 2013). Even though most of the regulations throughout the world cover only the monomer, both the monomer and the oligomers must be measured in a context of worker protection as both forms can cause work-related illness (Bello *et al.*, 2004). It is also known that sensitized individuals can have symptoms at levels below the OEL (Baur *et al.*, 1984; Mapp *et al.*, 1999; Gagné *et al.*, 2003; Gagne *et al.*, 2005). Reliable and user-friendly sampling methods for MDI aerosol exposure evaluation in the fast-curing application of spray foam insulation have been lacking for several years and are much needed (Streicher *et al.*, 1998; Lesage *et al.*, 2007; Puscasu et al., 2014a,b).

The reference method for MDI aerosol sampling is the toluene/1-(2-methoxyphenyl)piperazine (MOPIP) impinger (Lesage *et al.*, 2007; Puscasu et al., 2014a,b). However, this approach is deficient in terms of user-friendliness in the field for personal sampling. Several alternative technologies have been tried to replace the impinger (Rudzinski *et al.*, 1998; Streicher *et al.*, 1998; Rando and Poovey, 1999; Marand *et al.*, 2005; Nordqvist *et al.*, 2005; Lesage *et al.*, 2007), with the filter cassette sampling method as the most common one. Unfortunately, filter cassette sampling approaches underestimate MDI levels in some situations (Lesage *et al.*, 2007), and researchers have been attempting to come up with new tactics. Recently, a CIP10M was optimized and used efficiently for MDI aerosol sampling (Puscasu et al., 2014a,b). The CIP10M method has been developed because commercially available technologies alternative to impinger and filter cassettes have not been extensively validated for MDI aerosol sampling in fast-curing applications. Some limitations linked to large particle size sampling have been suspected, but no data are available in the literature to invalidate or confirm these concerns.

Among the recently developed sampling devices, the ASSET EZ4 NCO was put on the market as a method of reference for measuring the air concentration of the most common isocyanates used in the workplace (Marand *et al.*, 2005; Nordqvist *et al.*, 2005). However, the validation data reported for the context of spray foam insulation were obtained with the prototype but not with the commercial version. The ASSET EZ4 NCO sampler is a small solvent-free device that can be better adapted than an impinger to personal sampling. The ASSET EZ4 NCO sampler is a tube with a length of 7 cm and an internal diameter of 0.8 cm, and sampling at a recommended airflow rate of 0.2 l min^{-1}. Its inner wall is covered with filter paper that is coated with a derivatization reagent. A filter with the same derivatization reagent is also added after the denuder to collect constituents that could have passed through the denuder. To increase the sampler's capacity and the system's collection efficiency, a third V-shaped filter was subsequently placed inside the denuder (Gylestam *et al.*, 2014). As the isocyanates are aspirated through the denuder, they are stabilized by the derivatization agent dibutylamine (DBA) that comes in contact with them and this allows sample analysis in laboratory. The combination denuder/filter impregnated with DBA used in the ASSET EZ4 NCO sampler provides the same collection efficiency range as the impinger/filter approach for several applications involving isocyanate vapor forms (Marand *et al.*, 2005; Nordqvist *et al.*, 2005). However, many uncertainties surround this approach for aerosol sampling mainly due to the fact that low sampling rates are required and a limited contact surface is available to completely dissolve and stabilize the aerosol, which is the main form of MDI in fast-curing processes. Stabilization is thought to be effective only at the aerosol surface, leaving the core of the liquid particles reactive because the sampler contact surface does not completely absorb the liquid aerosols. Moreover, the efficiency of the sampler's inlet can be affected, especially for large aerosol particles lost by inertia or overestimated by settling (Brockmann, 2011). Unfortunately, all of the above have not been studied for fast-curing applications.

However, a direct side-by-side comparison between the reference method and the ASSET EZ4-NCO approach can be easily achieved. Comparisons have also been made, usually with methods using DBA as the derivatization agent, and this agent is not the one used in the reference method (Marand *et al.*, 2005). Furthermore, no complete analytical methods by liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS) have been investigated to analyze MDI-DBA oligomers collected with the ASSET sampler. The published methods target only MDI-DBA and MDI 3-ring-DBA (Marand *et al.*, 2005). The objectives of this study are:

- To develop an extended analytical method to quantify simultaneously MDI-DBA and as many MDI oligomers as possible by LC-MS/MS using commercially available MDI-DBA standards kits (Supelco).
- To compare the ASSET EZ4-NCO with the reference impinger method using toluene/MOPIP for sampling MDI aerosols in spray foam insulation application.

MATERIALS AND METHODS

Chemicals

4,4′-MDI (98% purity), 1-(2-methoxyphenyl)piperazine; MOPIP (98% purity), DBA (>99% purity), dimethylsulfoxide (DMSO; >99.9%) and acetic anhydride (AA; 98% purity) were obtained from Sigma–Aldrich (Milwaukee, WI, USA) and were used without any further purification. A DBA isocyanate standard kit, MDI-DBA oligomer standard, and MDI-DBA-d9 oligomer standard kits were obtained from Supelco (Bellefonte, PA, USA). Mondur 541 polymeric MDI (pMDI) was obtained from Bayer Material Science (Leverkusen, Germany). Acetonitrile (ACN), water (H_2O), formic acid (FA), all optima LC-MS grade, and sodium acetate (99.4% purity) were obtained from Fisher Scientific (Canada). Glacial acetic acid, sulfuric acid (96% purity) and methanol (MeOH; HPLC grade) were obtained from J.T. Baker. Toluene (99.9% purity) was obtained from EMD Millipore Corp. (Billerica, MA, USA). The in-house synthesis of MDI-MOPIP monomer derivative and the purity check were done using a known and reliable procedure (Puscasu et al., 2014a). The in-house synthesis of MDI-MOPIP oligomers was done using the same protocol as for the MDI-MOPIP monomer, except that the MDI monomer was replaced by pMDI (Puscasu *et al.*, 2014a).

Instruments and analytical conditions

The impinger samples were analyzed with the same instrument and conditions as in Puscasu *et al.* (2014b). The ASSET EZ4-NCO samples were analyzed on a UPLC-MS/MS system consisting of a Waters Acquity UPLC coupled with a Waters Xevo TQ triple quadrupole mass spectrometer (Beverly, MA, USA) equipped with an electrospray source. The analytical column used was an Acquity UPLC BEH C18 1.7 µm, 2.1 mm × 100 mm from Waters (Santry, Ireland). The software used to operate the system and analyze the data was Masslynx. Peak integration was done using the automatic feature for integrating the peak area. Manual adjustments were done on integrations not covering the entire peak. The regression calibration curve used linear fit.

The mobile phase was composed of ACN + 0.1% FA (eluent A), and water + 0.1% FA (eluent B). UPLC separation was achieved using a gradient of 70% eluent A held for 0.5 min, then ramped to 90% eluent A for 2.5 min, then held at 90% eluent A for 2 min, then ramped to 100% eluent A for 3 min, and finally equilibrated at 70% eluent A for 2 min. The flow rate was 0.6 ml min^{-1} and the column was kept at 50°C. The injection volume was 10 µl using the partial loop with needle overfill feature. The samples were kept at 15°C in the autosampler. The Xevo TQ was operated in positive mode, the capillary voltage was set at 2 kV, the source temperature at 150°C, the desolvation temperature at 500°C, the desolvation flow at 1000 l hr^{-1}, the collision gas flow at 0.15 ml min^{-1}, and the data were acquired in multiple reaction monitoring (MRM) mode. The MRM transition and conditions used for MDI-DBA analytes and internal standards are listed in Table 1.

Sample and standard preparation

The impinger samples and standards were prepared using a previously described protocol (Puscasu *et al.*, 2014b). The ASSET EZ4-NCO samples and standards were prepared following the protocol provided by Supelco (Halpenny and Brown, 2013). The ASSET EZ4-NCO dry samplers were supplied by Supelco.

Table 1. MRM transitions.

Substances	Calculated $[M+H]^+$	MRM transition	Cone (V)	Collision energy (eV)
MDI-DBA	509	509.3–130.2	35	20
MDI-DBA-d18	527	527.4–139.2	45	30
MDI 3-ring-DBA	769	769.6–130.2	45	45
MDI 3 ring-DBA-d27	796	796.8–139.2	50	35
MDI 4 ring-DBA	1030	1029.8–130.2	35	45
MDI 4 ring-DBA-d36	1066	1066.1–139.2	40	50
MDI 5-ring-DBA	1290	Not observed	10–60	n. a.

The shaker was from Eberbach Corporation (MI, USA). The ultrasonic bath was a model B-52 from Branson (Danbury, CT, USA). The Sorvall ST 40R centrifuge was from Thermo Scientific (Canada). The Zymark Turbovap LV-ZW700 evaporator was from Biotage (Charlotte, NC, USA).

Analytical performance evaluation

The impinger method (Puscasu *et al.*, 2014b) has been previously described. The MRM descriptors used for the MDI-DBA analytes and internal standards were optimized by infusion, at a flow rate of 10 µl min^{-1}. A solution of 10 µM prepared in 50% water/50% ACN + 0.1% FA was infused. The analytical method is described by Supelco (Halpenny and Brown, 2013) and its performance has already been established. As the method was implemented as is, no extended performance evaluation was performed. Some analytical parameters were verified to check the implementation. These parameters were the dynamic range, the minimum reported value (MRV) set over the limit of quantification (LOQ) based on signal-to-noise ratios of 10:1, the intra-day precision calculated from six separate measurements at five concentrations levels in the desired dynamic range on a single day, and the accuracy evaluated by analyzing a known concentration of MDI-DBA spiked in the ASSET EZ4-NCO sampler in the dynamic range, extracted and quantified using a standard curve.

Air sample collection

Impinger samples were collected as in Puscasu *et al.* (2014b). ASSET EZ4-NCO samples were collected at 0.2 l min^{-1} as recommended by Supelco in the booklet provided with the samplers. The workplace set-up was the same as in Puscasu *et al.* (2014b). The comparison study was done with the same jar used in Puscasu *et al.* (2014b). Two plywood panels (1.2 m × 2.4 m) were placed in the room and the sprayer applied 2 cm of foam on each plywood panel every 5 min, using exactly the same procedure as in a normal working day. Inside the room, the sampling jar containing the samplers was positioned near the sprayer. After each application, the sprayer was asked to leave the room. Each test consisted of this procedure repeated at least four or five times, which led to test durations of ~30 min. A total of nine tests were carried out over two days of sampling for a total of 27 samples (n = 3 for each test). The amount of MDI-based foam sprayed per test allowed the concentration of MDI in the jar to reach 50–150% of the typical OEL (0.051 mg m^{-3} MDI monomer). The ASSET samplers were oriented upward in accordance with the Supelco statement that all orientations are equivalent.

Statistics

The statistical treatment was done using the same method as in Puscasu *et al.* (2014b).

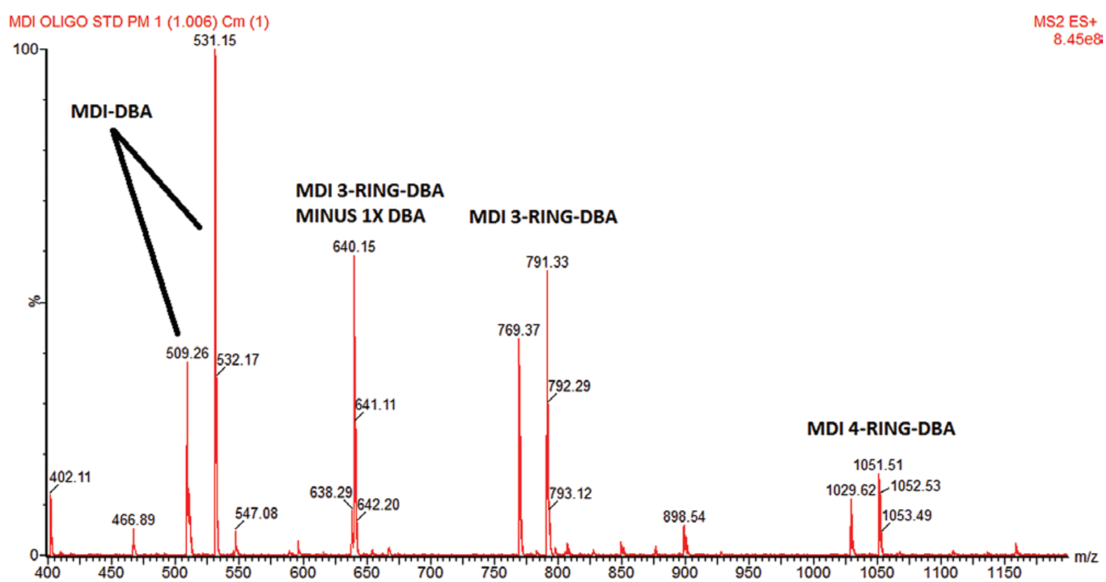
RESULTS AND DISCUSSION

Laboratory method development

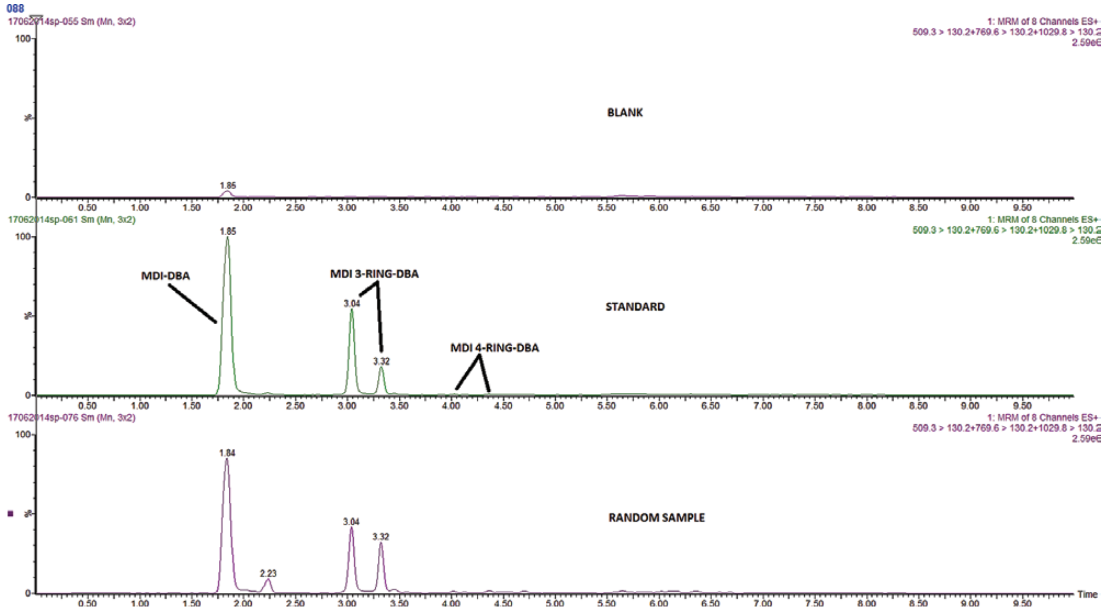
Many analytical methods by LC-MS/MS are described in the literature to quantify many types of isocyanates collected with the ASSET sampler (Marand *et al.*, 2005; Nordqvist *et al.*, 2005). Such a protocol is supplied by the company selling the ASSET samplers (Halpenny and Brown, 2013). It provides the information needed to implement the analytical method in a laboratory equipped with an LC-MS system. Standards are commercially available for the MDI-DBA monomer and MDI-DBA oligomers. However, no complete analytical method by LC-MS/MS has been published to quantify MDI-DBA, MDI 3-ring-DBA, MDI 4-ring-DBA and MDI 5-ring-DBA simultaneously. In order to suitably compare the results of the ASSET sampler and the impinger sampler for MDI aerosol sampling during spray foam application, a method by LC-MS/MS had to be developed using the commercially available MDI-DBA standard kits. This method would allow the quantitation of MDI-DBA and as many MDI oligomers as possible in order to compare both the MDI monomer and the MDI oligomers collected with the ASSET sampler with those collected with the toluene/MOPIP impinger.

Initially, the MDI-DBA oligomer standard was infused into the LC-MS/MS system to optimize the MRM transition for each compound. Figure 1 shows the mass spectra of the infused solution containing the MDI-DBA oligomer standards. As can be seen in this figure, $[M+H]^+$ and $[M+Na]^+$ ions were detected for MDI-DBA, MDI 3-ring-DBA and MDI 4-ring-DBA. No doubly-charged species were observed for MDI 4-ring-DBA. Moreover, no ions related to MDI 5-ring-DBA were observed considering the expected mass (Karlsson, 2001). An ion was observed at *m/z* of 640.2. It is the derivatized MDI 3-ring minus a molecule of DBA. This ion was not considered for further analysis. Also, no $[M+H]^+$ or multiple charged ions were observed for the MDI 5-ring-DBA at expected masses even though the solvents and the solution concentrations were changed, so no further development was done for this oligomer with the commercially available standard kit. Table 1 shows the MRM transitions and the MS/MS conditions that were used for the analysis for MDI-DBA, MDI 3-ring-DBA and MDI 4-ring-DBA.

The sample preparation protocol provided by Supelco was carried out as is. Typical LC-MS/MS chromatograms are shown in Fig. 2 for the blank, the standard, and a typical sample. As can be seen, MDI-DBA and MDI 3-ring-DBA are baseline separated. In the dynamic range of interest, MDI 4-ring-DBA was minimally detected at the mid-range up to the last point of the curve, so the measure of this oligomer is limited in the dynamic range of interest. Moreover, no suitable linear regression curve could be drawn for this oligomer. The MDI 4-ring-DBA oligomers have intensity negligible as compared to the other compounds as the MDI-DBA and the MDI 3-ring-DBA oligomers. To confirm the appropriate implementation for MDI-DBA and MDI 3-ring-DBA before comparing



1 MDI oligomer standard mass spectra.

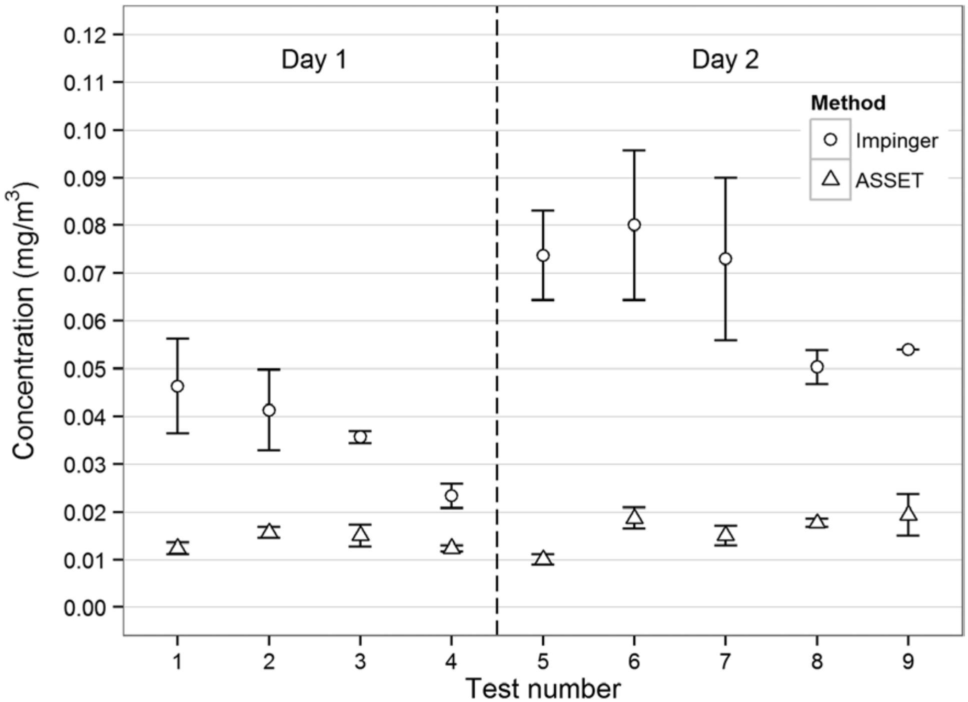


2 Representative chromatograms for MDI oligomers: blank, standard and typical sample.

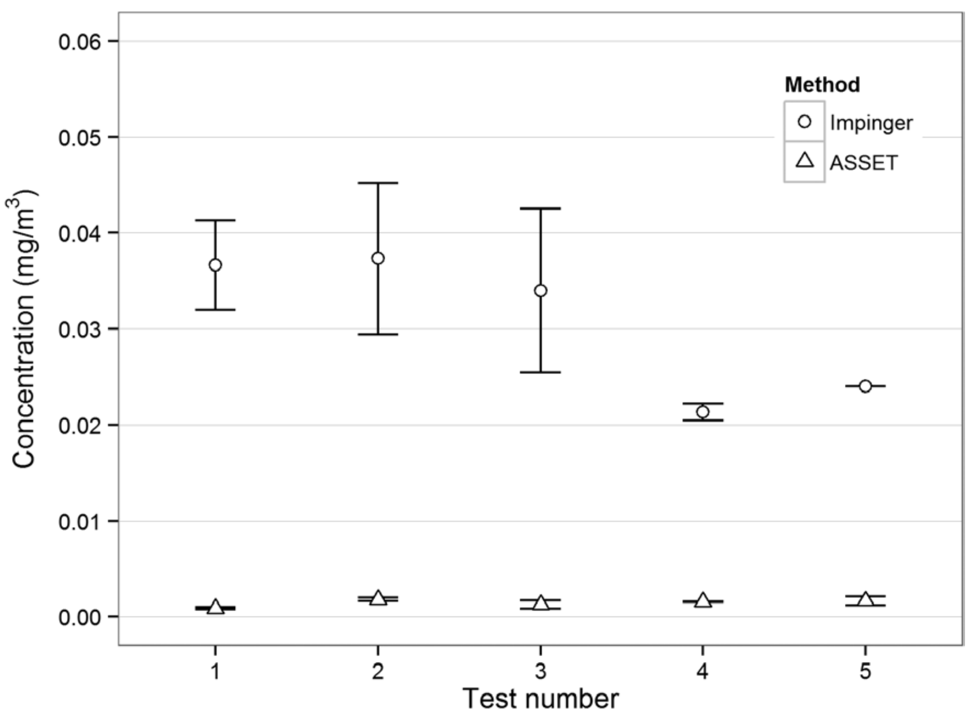
the ASSET sampler and the impinger sampler using toluene/MOPIP, the dynamic range, MRV, intra-day precision and accuracy were established. The internal standard MDI-DBA-d18 was used for all the analytes as it provided the best performance. The MRV of 5 ng ml^{-1} and the dynamic range between 5 and 140 ng ml^{-1} were equivalent to those proposed by Supelco for MDI-DBA and MDI 3-ring-DBA with R^2 >0.995. The intra-day precision <15% and accuracy >80% were both in an acceptable range. High internal standard variations were observed with standards spiked in the sampler and extracted. The use of an analyte/internal standard ratio is highly needed with this method as the extraction variability has to be corrected to obtain reproducible results. The analytical performance was judged acceptable for MDI-DBA and MDI 3-ring-DBA to conduct the direct field comparison between the ASSET sampler and the impinger sampler using toluene/MOPIP for MDI aerosol spray foam sampling.

Field comparison

The tests were conducted over two different days to obtain a sufficient number of samples in order to achieve statistical method reliability with a high level of confidence without overwhelming the workers. The datasets are presented in Figs 3 and 4. The results for the impingers showed higher variability than the ones for the ASSET EZ4-NCO. The explanation for the impinger variability could be the inlet orientation and the presence of large particles, as pointed out by the authors of a study involving different kinds of samplers for MDI and pMDI particles (Hext *et al.*, 2003). Since the ASSET samplers were oriented the same way, the presence of large particles would be the only remaining hypothesis. However, even by taking the variability into account, the ASSET EZ4-NCO still underestimated the concentration of MDI monomer in a statistically significant manner. The monomer concentrations provided by the ASSET sampler were 72% (95% confidence interval [CI] 54–89%) lower than the ones provided by the reference method. It is difficult to give an explanation for this significant underestimation based on inlet sampling efficiency. The ASSET sampler, due to its larger upward inlet, can allow larger particles to settle in it and therefore oversample them when compared to the impinger, assuming a still air environment. However, the data obtained in this study show an underestimation of the concentration. This led us to conclude that a mechanism other than the efficiency of inlet sampling is responsible for the underestimation observed for the ASSET sampler. Additionally, the lower air flow of the ASSET sampler could make it harder for the ASSET sampler



3 Comparison ASSET/impinger sampler for MDI monomer.



4 Comparison ASSET/impinger sampler for MDI oligomers (oligomer mass was determined as the sum of 3-ring results).

to capture some aerosols that are not heading directly for the inlet (Brockmann, 2011).

Furthermore, the low surface contact between the relatively large aerosols, mass median aerodynamic diameter (MMAD) of 13 µm (Puscasu *et al.*, 2014b), and the derivatization agent in the dry sampler could be an explanation. Only the aerosol peripheries would be stabilized and the aerosol cores would remain reactive. Moreover, the ASSET sampler seems to saturate at some point, always providing the same concentrations independently of the amount present when compared to the impinger sampler. These observations were made at concentrations typical of a spray foam environment and were the same as the ones obtained when the efficient range documented for the ASSET prototype was established (Marand *et al.*, 2005). From this perspective, the real exposure measurement is difficult to obtain with this sampling device for MDI aerosol in spray foam application. On the other hand, Fig. 4 shows the results for MDI oligomers for the impinger sampler and the ASSET sampler. It must be pointed out that the MDI oligomer standard kits were not available at the beginning of the investigation, so the results are provided only starting when the MDI oligomers standard kits were available. The oligomer mass was determined for the ASSET sampler as the sum of 3-ring results. As for the monomer, the oligomer concentrations provided by the ASSET sampler were 96% (95% CI 76–115%) lower than the ones provided by the reference method. One portion of this underestimation is due to the amount of oligomers detected by each method. The analytical method linked to the ASSET sampler detects only two MDI 3-ring-oligomers as opposed to the impinger analytical method that can detect up to six different oligomers. Even if only the main 3-ring oligomer, which accounts for 65% of the total oligomers, is compared between both methods, the underestimation is still of the same order of magnitude. This being said, the same explanations as presented previously for the MDI monomer could contribute to this underestimation for the oligomers. Under the current conditions, both MDI monomer and MDI oligomers are underestimated by the ASSET sampler in the sampling of MDI aerosols in spray foam insulation application as compared to the toluene/MOPIP impinger reference method.

CONCLUSION

The analytical method by LC-MS/MS suggested by Supelco for the analysis of ASSET EZ4-NCO samples has been implemented successfully using their literature and standard kits. The method allows the detection of MDI-DBA and MDI 3-ring-DBA, but no MDI 4-ring-DBA and MDI 5-ring-DBA in the dynamic range of interest using the standard kits commercially available. Using this analytical method to quantify MDI-DBA, the MDI monomer present in spray foam application was significantly underestimated by the ASSET sampler as compared to the impinger sampler reference method using toluene/MOPIP. A significant underestimation for MDI oligomers analyzed by the ASSET sampler was observed, compared to the reference method, even when the omission of 4- and 5-ring MDI oligomers was considered. Moreover, the ASSET sampler seemed to be saturated at some point and this could lead to the divergence obtained as compared to the reference method. Even though the prototype of the ASSET sampler performed well with vapor or slow-curing isocyanate applications in past studies (Marand *et al.*, 2005; Nordqvist *et al.*, 2005), the present study showed important limitations in the sampling and analysis of MDI aerosols from spray foam application. This emphasizes the need to evaluate each isocyanate application independently when a new sampling methodology is offered on the market, since isocyanates are complex mixtures of different chemical and physical forms involving different principles based on the application.

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DISCLAIMER

The article contents, including any opinions and/or conclusions expressed, are those of the authors.

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