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**Underestimation of toluene diisocyanate concentration using long-term sampling
with 1-(2-methoxyphenyl) piperazine impregnated filters**

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Abstract

Occupational exposure to toluene diisocyanate (TDI) is a known occupational hazard and the occupational exposure limits in air are very low. One of the most common methods to monitor exposure to isocyanates is to sample air through filters impregnated with 1-(2-methoxyphenyl) piperazine (2MP). In one earlier field study it was found that long-term sampling with 2MP-filters underestimated the exposure compared with consecutive short term samples of TDI. The aim of this study was to confirm that finding in a controlled atmosphere in the laboratory. A test atmosphere of 2,4-TDI or 2,6-TDI was generated in a small test chamber and parallel long-term samples and consecutive short-term samples were collected. A total of 159 filters were exposed. The long-term samples collected significant lower amounts of TDI than the sum of the short-term samples. For a 4-hour sampling, the air levels were calculated to underestimate the exposure for 2,4-TDI by a factor 1.4 and for 2,6-TDI by a factor 1.3. The calculated underestimation was lower than earlier reported.

Keywords: Diisocyanates, isocyanate, exposure, TDI, determination, air.

Introduction

Toluene diisocyanate (TDI) commercially exists as a mixture of 2,4 and 2,6 isomers and are mainly used in the manufacture of polyurethane (PUR). Occupational exposure to TDI can occur during production of TDI (Dharmarajan et al., 1978) or PUR based on TDI or refining of PUR (Sennbro et al 2004b) for example by thermal decomposition. Exposure to isocyanates is associated with respiratory disorders such as occupational asthma (Vandenplas et al., 1993, Baur et al., 1994).

The most common way to control exposure for isocyanates is to perform air sampling with subsequent determination of the isocyanates at the laboratory. As isocyanates are very reactive compounds they need to be derivatised during the sampling step. One way to sample isocyanates is to use filters impregnated with 1-(2-methoxyphenyl) piperazine (2MP) as first shown by Warwick et al. (1981). This method has been further developed in several steps (Health and Safety Laboratory 1999, Östin et al., 2002). Henriks-Eckerman et al. (2000) introduced a method for sampling methylisocyanate and isocyanic acid using two filters impregnated with 2MP (FINMP-method). In earlier studies the formed 2MP-isocyanate derivative has been shown to have limited stability (NIOSH 1994) and the long-term performance has been insufficiently described. In an evaluation of the long-term field performance of the 2MP-method Sennbro et al. (2004a) showed that significant lower levels of TDI were found for long-term samplings compared to parallel consecutive short time samplings. Sennbro et al. introduced a correction factor for long-term sampling of TDI with the 2MP-method:

$$C_{(\text{TRUE})} = C_{(\text{OBS})} \cdot \frac{k \cdot t}{1 - e^{-k \cdot t}}$$

$C_{(TRUE)}$ is the air concentration measured with consecutive short-term samples of TDI, $C_{(OBS)}$ is the observed air concentration of TDI and $(kt)/(1-e^{-kt})$ is a time dependent correction factor where t is the sampling time in hours and k is the first order constant for the losses of TDI.

The aim of this study was to evaluate the long-term sampling performance of TDI using both the 2MP-method and the FINMP-method in an exposure chamber.

Material and method

Chemicals

2,4-toluene diisocyanate (2,4-TDI) (96%) from Aldrich (Milwaukee, WI, USA). 2,6-toluene diisocyanate (2,6-TDI) (97%) and 1(2-methoxyphenyl) piperazine (2MP) (98%) from Sigma Aldrich (Steinheim, Germany). Trideuterated 2(1-methoxyphenyl) piperazine (d_3 -2MP) from Synthelec (Lund Sweden). Ammonium acetate (p.a) from Merck (Darmstadt, Germany). Toluene and acetonitrile, both HPLC-grade from Lab Scan (Dublin, Ireland).

Preparation of filters

For the 2MP-method (Health and Safety Laboratory 1999 and Östin *et al.* 2002) a single glass fiber filter (25 mm diameter and 1.0 μ m pore size, Omega Specialty Instrument Co Chelmsford, MA, USA) was impregnated with 10.4 μ mol 2MP.

For the FINMP-method (Henriks-Eckerman *et al.* 2000) two glass fiber filters (GF/B 25 mm diameter and 1.0 μ m pore size, Whatman International Ltd Maidstone, UK) were each impregnated with 20.8 μ mol 2MP.

Generation of a TDI atmosphere and sampling

A small test chamber (60 l) of glass was used for generation of a standard atmosphere of 2,4-TDI and 2,6-TDI. A similar generation technique as in Tinnerberg et al. (1995) was used. The generation was based on gas-phase permeation through a silicone rubber tube with an inner diameter of 8 mm and a thickness of 2 mm (Saint-Gobain, Charny, France). The isocyanates were placed in a glass vial connected with the silicone tube and a plug. The vial was placed in a vessel in a water bath (Grant W14, Kebo Lab AB, Sweden) and the formed vapor was transported into the test chamber by the airflow. The concentrations of TDI could be varied by changing the temperature in the water bath between 20 and 60 °C. Mass flow regulators and flow meters (Norgren, Max sec 2 bars 30 PSI, Staffordshire, UK and Platon A10D, Platon Park. Viabes, Basingstoke Hunts, UK) were used for controlling the airflows. All tubing was made of glass or Teflon. To prevent a concentration gradient inside the chamber, a small fan was used for mixing the air.

Long-term sampling

The sampling performance of the 2MP- and the FINMP-method was studied by comparing the amount of collected isocyanate for long-term sampling with the sum of the amount with parallel consecutive short-term samplings. Sampling were performed inside the chamber where eight to ten filters were connected to a critical nozzle (about 1 l/min) and a pump (Gast, Model DOA-P109-FD, MFG. Corp. Benton Harbor, MI, USA). A flow meter (DryCal, DC-lite, Scantec Lab. Sävedalen, Sweden) was used for controlling each filter flow before and after the sampling. Immediately after sampling the filters were transferred to glass vials containing acetonitrile. When changing filters for consecutive short term sampling the isocyanate flow was turned off and the ventilation air was used. The sampling times varied between 20 and 180 minutes. Totally 159 filters were sampled and the sample sets consisted of long-term samples

(L₁-L₆), short-term samples (S₁-S₃₆) and both long- and short-term samples (LS₁-LS₁₁) (Table 1 and 2). The total airborne TDI concentration in the standard atmosphere was between 6 and 104 µg/m³ (6 and 51 µg/m³ and 0.5 and 53 µg/m³ for 2,4- TDI and 2,6-TDI, respectively) which is relevant exposure levels in comparison with common occupational exposure limits.

The amount of TDI collected by long-term sampling and the sum of amounts collected for short-term sampling was compared by paired t-test and Wilcoxon signed rank test. The constant k in the correction factor introduced by Sennbro et al. (2004) was calculated for each sample set.

Analysis and quantification

Standards for quantification were prepared according to the procedure described in MDHS 25/3 (Health and Safety Laboratory 1999). As internal standard 2,6-TDI was synthesized with d₃-2MP. The 2MP- and FINMP-samples were analyzed using a liquid chromatography system (Perkin-Elmer Biosystems, Foster City, CA, USA) equipped with a PE 200 autosampler and two PE LC-200 Micro Pumps. The injected volume was 5 µl and the column was a HypurityTM Advance 150x3 mm, 5 µm particles, from Thermo Electron Corporation (ChromTech AB Hägersten Sweden). The mobile phase was (A) 10 mM ammonium acetate and (B) acetonitrile. A gradient from 95 to 0 % A was applied for ten minutes followed by 95 % A for three minutes. Quantification was performed using a triple quadrupole mass spectrometer equipped with electrospray ionisation (ESI) on a turbo ionspray source (API 3000, Perkin-Elmer Biosystem, Foster City, CA, USA). The temperature of the auxiliary gas was set to 350°C and the ion spray voltage was 5000 V. The MS analyses were carried out using selected reaction monitoring (SRM) in the positive ion mode. The SRM transition used for TDI with 2MP was m/z 559.3/192.9 with a declustering potential

(DP) 40 and collision energy (CE) 40 volts. For TDI with d_3 -2MP the transition m/z 565.5/196.0 with DP 35 and CE 40 volts was monitored. The limit of detection was 2 ng/sample for both 2,4-TDI and 2,6-TDI.

Results

Table 3 and 4 shows the results in μg TDI/sample of the long-term sampling performance of the 2MP- and the FINMP-method. Each filter amount is corrected for the filter airflow and the results are shown as the mean value of 2-5 filters. The average relative standard deviation (RSD %) is showed for each sample set ($n = 2-5$).

There was no difference between the calculated values of k for the 2MP-method and the FINMP-method. Wilcoxon signed rank test of k between the methods gave $p=0.59$ for 2,4-TDI and $p=0.86$ for 2,6-TDI. Due to these findings the results from the two methods are treated together.

Paired t-test and Wilcoxon signed rank test showed that lower amounts were sampled with long-term sampling than with the sum of short-term samplings for both 2,4-TDI ($p=0.012$ and $p<0.001$) and 2,6-TDI ($p=0.002$ and $p=0.001$).

The calculated first order constant k was on average 0.18 h^{-1} for 2,4-TDI and 0.12 h^{-1} for 2,6-TDI. For a 4-hour sampling, the air levels are underestimated by a factor 1.4 for 2,4-TDI and by a factor 1.3 for 2,6-TDI.

Discussion

The aim of this study was to confirm the underestimation of TDI air levels using the 2MP method for long-term sampling as shown by Sennbro et al. (2004a). In that study a limited number of samples in real work environment were sampled and there was a rather large standard deviation, but the trend was clear that with longer sampling times the true air levels were underestimated. We have in this study with higher

accuracy confirmed that the 2MP-method underestimate the true concentration of TDI in air when using it for longer sampling times. However we found that the underestimation of TDI was smaller than calculated by Sennbro. When using the 2MP- and FINMP-filters for 4 hours 2,4-TDI was underestimated by a factor 1,4 and 2,6-TDI by a factor of 1,3. Sennbro et al (2004a) calculated these values to be 1.7 for the 2,4-TDI and 1.5 for the 2,6-TDI.

The reasons for the found underestimation of TDI in long-term sampling with the 2MP-method is however still not clear. One possibility is that the isocyanates does not reach to the reagent fast enough and reacts with something else before it reaches the reagent. If that would be the case it would be a concentration dependent and not time dependent underestimation, and we have not seen that. Further if that would be the case the amount of reagent on the filters could possible enhance the possibility for the isocyanates to reach the reagent, that means that by using the FINMP method the losses would be less than using the original method as the FINMP has much more reagent on the filter. However we did not see any differences in the underestimation with the two methods. Further, in a few experiments we separately analysed the two filters when using the FINMP method, but we did not found any break trough.

Another possibility is that the formed 2MP-derivative degrades on the filters. In some earlier studies it is shown that the isocyanate-2MP derivative can degrade (NIOSH 1994, Kääriä *et al.* 2001, Henricks-Eckermann *et al.* 2000). To investigate that further we performed a small experiment were we spiked filters with TDI-2MP derivative and pumped air trough the filter. Afterwards we performed qualitative analysis with LC-MS/MS and compared the spiked sampled filters with spiked unsampled filters. We found several extra peaks on the sampled filters but we could not identify the structure. When the same experiment was repeated other unidentified extra peaks

were found. We interpret this as there in fact is a degradation of the derivative or of the reagent but it was not reproducible. To test that the decrease of derivative is not due to breakthrough on the filter, back-up filters were placed in series with the spiked filters and the filter cassettes were rinsed with acetonitrile. Neither the back-up filter nor the acetonitrile contained any substantial amounts and this verifies that no derivative was detached from the filters during sampling that could explain the degradation.

In the work environment the exposure to isocyanates are typically intermittent. This means that the underestimation of the exposure will be different for different exposure scenarios. If collecting TDI during 4 hours and there are high exposure during the first hour the underestimation will be larger than if there are high exposures during the last hour. The only safe way to handle this is to shorten the sampling time, but then the cost will rise. A more reasonable way to handle this is to change filters if the workers during sampling are performing tasks with known high exposure during the first part of the sampling.

Is this underestimation of the true isocyanate air levels important? If you want to compare one or a few measurements with the occupational exposure levels (OEL) of course a systematic underestimation of the measured exposure makes exceedance less plausible. On the other hand we know that the variation of exposure in the industry varies considerably between days and workers and that the calculated underestimation for four hour sampling time is in this context small. Another problem can arise if dose-response calculations are performed where the dose is calculated from air measurements performed with the 2MP-method. If only such studies are used as background for developing OELs the calculated OELs will be too low which will lead

to overprotection of the workers. Further if the method is used for a longer time than four hours, i e for a whole day, the underestimation is considerable.

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Tables

Table 1. Description of the parallel sample sets with the 2MP-method

Sample set	Long-term sampling			Short-term sampling		
	Sample ID	Sampling time (min)	Number of filters	Sample ID	Sampling times (min)	Number of filters
1	L ₁	120	5	S ₁ , S ₂ , S ₃ , S ₄ , S ₅ , S ₆	6*20	6*3
2	L ₂	120	4	S ₇ , S ₈ , S ₉ , S ₁₀ , S ₁₁ , S ₁₂	6*20	6*3
3	L ₃	120	4	S ₁₃ , S ₁₄ , S ₁₅ , S ₁₆ , S ₁₇ , S ₁₈	6*20	6*3
4	L ₄	120	4	S ₁₉ , S ₂₀ , S ₂₁ , S ₂₂ , S ₂₃ , S ₂₄	6*20	6*3
5	LS ₁	60	3	S ₇ , S ₈ , S ₉	3*20	3*3
6	LS ₂	60	3	S ₁₀ , S ₁₁ , S ₁₂	3*20	3*3
7	LS ₃	60	3	S ₁₃ , S ₁₄ , S ₁₅	3*20	3*3
8	LS ₄	60	3	S ₁₆ , S ₁₇ , S ₁₈	3*20	3*3
9	LS ₅	60	3	S ₁₉ , S ₂₀ , S ₂₁	3*20	3*3
10	LS ₆	60	3	S ₂₂ , S ₂₃ , S ₂₄	3*20	3*3
11	L ₂	120	4	LS ₁ , LS ₂	2*60	2*3
12	L ₃	120	4	LS ₃ , LS ₄	2*60	2*3
13	L ₄	120	4	LS ₅ , LS ₆	2*60	2*3

Table 2. Description of the parallel sample sets with the FINMP-method

Sample set	Long-term sampling			Short-term sampling		
	Sample ID	Sampling time (min)	Number of filters	Sample ID	Sampling times (min)	Number of filters
1	L ₅	120	5	S ₂₅ , S ₂₆ , S ₂₇ , S ₂₈ , S ₂₉ , S ₃₀	6*20	6*2
2	L ₆	180	4	S ₃₁ , S ₃₂ , S ₃₃ , S ₃₄ , S ₃₅ , S ₃₆	6*30	6*3
3	LS ₈	60	2	S ₂₈ , S ₂₉ , S ₃₀	3*20	3*2
4	LS ₉	60	3	S ₃₁ , S ₃₂	2*30	2*3
5	LS ₁₀	60	3	S ₃₃ , S ₃₄	2*30	2*3
6	LS ₁₁	60	3	S ₃₅ , S ₃₆	2*30	2*3
7	L ₅	120	5	LS ₇ , LS ₈	2*60	2*2
8	L ₆	180	4	LS ₉ , LS ₁₀ , LS ₁₁	3*60	3*3

Table 3. Results of the long-term sampling performance of the 2MP-method

Sample set	2,4-TDI (μg)				2,6-TDI (μg)			
	Long-term sampling	Sum of short-term samplings	Average RSD (%)	k (h^{-1})	Long-term sampling	Sum of short-term samplings	Average RSD (%)	k (h^{-1})
1	0.68	0.74	12	0.130	0.06	0.06	10	0.040
2	0.93	1.10	5	0.203	2.45	2.79	6	0.164
3	0.73	0.89	6	0.238	2.61	2.81	6	0.086
4	0.86	0.92	4	0.074	0.30	0.32	4	0.105
5	0.51	0.57	5	0.341	1.28	1.39	7	0.267
6	0.51	0.53	5	0.116	1.37	1.40	5	0.070
7	0.42	0.45	4	0.250	1.50	1.49	4	-0.018
8	0.37	0.43	6	0.521	1.26	1.32	7	0.132
9	0.46	0.47	3	0.082	0.16	0.17	3	0.083
10	0.45	0.44	2	-0.080	0.15	0.16	3	0.112
11	0.93	1.02	5	0.190	2.45	2.65	7	0.169
12	0.73	0.79	4	0.139	2.61	2.76	5	0.106
13	0.86	0.92	5	0.128	0.30	0.31	5	0.109

Table 4. Results of the long-term sampling performance of the FINMP-method

Sample set	2,4-TDI (μg)				2,6-TDI (μg)			
	Long-term sampling	Sum of short-term samplings	Average RSD (%)	k (h^{-1})	Long-term sampling	Sum of short-term samplings	Average RSD (%)	k (h^{-1})
1	0.93	1.09	7	0.243	0.50	0.59	4	0.294
2	9.17	10.28	6	0.086	9.55	9.76	5	0.016
3	0.55	0.63	7	0.466	0.35	0.38	3	0.250
4	3.95	4.06	6	0.102	3.82	3.78	6	-0.042
5	3.25	3.28	5	0.039	3.24	3.16	3	-0.106
6	2.68	2.94	4	0.395	2.71	2.82	3	0.155
7	0.93	0.97	5	0.114	0.50	0.53	5	0.183
8	9.17	9.87	2	0.067	9.55	9.77	1	0.021