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NIOSH Method 5505 for estimating isocyanate in workplace air is based on sampling air with an impinger containing a standard solution of 1-(2-methoxyphenyl)piperazine in toluene and relating the measured loss of reagent from the sample to the total quantity of isocyanate trapped from the air. An experiment, in which 0–740 L of isocyanate-free air was sampled at 0.4–1.6 L/min and analyzed following Method 5505, demonstrated a loss of reagent which increased with the volume of air sampled. Entrainment of reagent in the exit stream was shown to be at least a minor cause of this loss. The results dictate against further use of Method 5505. Seymour, M.J.; O'Connor, P.F.; Teass, A.W.: Investigation of Inaccuracy of NIOSH Method 5505 for Estimating the Concentration of Isocyanate in Air. Appl. Occup. Environ. Hyg. 5:115–122; 1990.

Introduction

Organic polyisocyanates, such as may be found in the droplets of spray of a two-component polyurethane paint, are suspected of posing the same hazard as diisocyanates.[1,2] Support for this suspicion is found in the report that the commonly used biuret derived from 1,6-hexamethylene diisocyanate is a respiratory irritant.[3] In a field investigation conducted by scientists at the National Institute for Occupational Safety and Health (NIOSH), this biuret was the major isocyanate found in a work area where workers exhibited symptoms of respiratory irritation.[4] To better study the relationship between the symptoms and the levels of polyisocyanates, NIOSH investigators needed a method for analyzing the work site air for all polyisocyanates.

NIOSH Method 5505 for estimating the concentration of isocyanate in air[5] was developed in response to this need to assess worker exposure to organic polyisocyanates of unknown specific identities. Such substances include isocyanate-terminated prepolymers, usually the product of reaction of polyol with a stoichiometric excess of diisocyanate monomer;[6] polyisocyanates, such as those derived from toluene diisocyanate and hexamethylene diisocyanate through isocyanurate and biuret formation;[6] isocyanate-bearing polyurethanes, formed as intermediates during polyurethane synthesis; and isocyanates formed during thermal breakdown of polyurethane.[7–9] Although frequently represented by idealized chemical formulas, polyisocyanate prepolymers are usually mixtures of compounds.[10] The estimate of the air concentration of isocyanate would include those compounds, providing data which would complement the determination of specific diisocyanates at the same worksite.

In developing the method, we took advantage of technology published by Warwick and co-workers,[11] who used a solution of 1-(2-methoxyphenyl)piperazine in toluene to sample air for isocyanates. The ureas which formed in the reaction of the reagent with the isocyanate were then quantified by high-performance liquid chromatography (HPLC). Method 5505 used the same sampling medium but quantified the unreacted 1-(2-methoxyphenyl)piperazine. The quantity of isocyanate group in the air was computed from the quantity of 1-(2-methoxyphenyl)piperazine lost. Thus, the method estimated the air concentration in terms of the number of isocyanate groups, or the equivalents of isocyanate, not the number or mass of molecules containing isocyanate groups.

Method 5505 had two major limitations. First, in using the method, one assumed urea formation to be the only cause of loss of reagent. This assumption was valid only if the air sampled contained no other compounds which would react with secondary amines, specifically the reagent. Second, the limits of detection for Method 5505 (0.4–0.5 μmol per sample) were above the levels at which specific diisocyanates might be found (0.01–0.5 μmol per sample of 300 L of air). This restriction, the result of trying

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to determine a small difference between two large measurements, was acceptable, since the method was a complement to, not a replacement for, methods which analyzed air for the specific diisocyanates.

Field use of the method between 1983 and 1986 and additional experimentation revealed several problems with the procedure.

1. The handling of the sampling medium in the field was exceptionally critical since accurate estimates depended upon the initial and final quantities of reagent being those contained in exactly 15 ml of sampling medium.

2. When, during sampling, sufficient water was trapped in the sampling medium to give two phases, a significant fraction of the 1-(2-methoxyphenyl)piperazine was extracted into the water, in which it is about 4 times more soluble than in toluene. This caused a positive bias, unless all of both the toluene and aqueous phases were included in the analysis.

3. The source and timing of the preparation of the blank samples used for determining the initial quantity of reagent were critical since toluene diffused through the walls of some containers, such as polyethylene bottles, used in the field for safety considerations.

4. The most serious problem was the loss of 1-(2-methoxyphenyl)piperazine during sampling by mechanisms other than reaction with isocyanate. While the first three problems could be solved by making minor modifications to the procedure, this last could not.

The existence of the problem of the loss of 1-(2-methoxyphenyl)piperazine was suggested by field samples which gave inexplicably high estimates of isocyanate in the air sampled. Two possible causes of this positive bias were reaction of the reagent with nonisocyanate compounds in the sample and mechanical removal of the reagent from the impinger. In laboratory experiments, we tested 12 non-isocyanate components of polyurethane systems as interferences with essentially negative results. Three catalysts, 2-butanone (representative ketone solvent), two polyester polyols (alkyd resins), and four polyol-pigment paint components did not consume measurable levels of 1-(2-methoxyphenyl)piperazine. Two other polyol-pigment paint components consumed in 25 days an amount of the reagent equivalent to the limit of detection for many field samples. In 1983, we tested the hypothesis that reagent was lost during sampling through entrainment as aerosol particles in the stream exiting the impinger. Nine samples of laboratory air (41–363 L), assumed to be isocyanate free, were taken at 0.6–1.1 L/min and analyzed for isocyanate by Method 5505. Only three of the samples showed detectable levels of reagent loss (0.32–0.39 μmol). As these levels were close to or below limits of detection reported for field samples, the loss was considered no more serious than extra uncertainty in the estimate. In 1986, V. Dharmarajan of Mobay Chemical Corporation sent NIOSH an internal report of their evaluation of Method 5505.[12] Their experimental results also demonstrated a loss of reagent dur-

ing sampling isocyanate-free air.

At best, Method 5505 required modification to reduce the error introduced during sampling in the field. However, we first needed to understand better the problem of reagent loss since this caused a positive error not readily eliminated. The experiments were designed to demonstrate the hypothesis that the loss of 1-(2-methoxyphenyl)piperazine during sampling was due to mechanical transfer of the reagent from the impinger. The results, presented herein, convinced NIOSH that Method 5505 was too inaccurate to use and prompted the recommendation against its further use to be published.[13]

Experimental

Reagents

Acetonitrile, methanol, dimethyl sulfoxide, and toluene were HPLC-grade solvents from Burdick & Jackson Laboratories. 1-(2-Methoxyphenyl)piperazine and 4,4'-methylenediphenyl isocyanate were from Aldrich Chemical Company. The 2,4-toluene diisocyanate was Hylene T from DuPont. Glacial acetic acid, hydrochloric acid, sodium hydroxide, sodium acetate trihydrate, and acetic anhydride, all reagent grade, were from Fisher Scientific. The distilled–deionized water was prepared by passing laboratory deionized water through a Millipore Milli Q system and distilling the effluent in a Corning Mega-pure 3-L automatic still.

The 92-mM sodium acetate buffer for the HPLC mobile phase was prepared by dissolving 25 g of sodium acetate trihydrate in 1 L of methanol and 1 L of distilled–deionized water. The pH of the solution was adjusted to 6.0 with glacial acetic acid.

Urea Derivatives

The 1-(2-methoxyphenyl)piperazine derivative of 2,4-toluene diisocyanate (TDI), N,N'-bis[4-(2-methoxyphenyl)piperazine-1-carbonyl]-2,4-toluenediamine (TDIU), was synthesized as follows: a solution of TDI (1.2 g., 6.9 mmol) in toluene (20 ml) was added to a stirred solution of 1-(2-methoxyphenyl)piperazine (3.5 g, 18 mmol) in toluene (70 ml). After about 2 hours, the resulting white precipitate was collected by suction filtration, rinsed with toluene, and recrystallized. Recrystallization was accomplished by suspending the solid in toluene at about 60°C, adding just enough methanol to effect dissolution, and storing the solution at room temperature until precipitation was complete. The melting point was 212°–213°C; field-desorption mass spectrum, m/e 558 (M+, $C_{31}H_{38}N_6O_4$); desorption chemical–ionization mass spectrum (ammonia), m/e 559 ([M + 1]+).

N,N'-bis[4-(2-methoxyphenyl)piperazine-1-carbonyl]-4,4'-methylenedianiline (MDIU), the 1-(2-methoxyphenyl)piperazine derivative of 4,4'-methylenediphenyl isocyanate (MDI), was synthesized by adding a solution of MDI (0.68 G, 2.7 mmol) in dimethyl sulfoxide (15 ml) to a stirred solution of 1-(2-methoxyphenyl)piperazine (1.3 g, 6.8 mmol) in dimethyl sulfoxide (45 ml). After 30 minutes,

the stirred solution was diluted with water (200 ml) and allowed to stand about 2 hours while the product precipitated. The white precipitate was collected by suction filtration, dried in a vacuum oven at about 60°C to remove the residual water, and recrystallized by the procedure described for TDIU. The melting point was 209°–210°C; field desorption mass spectrum, m/e 634 (M^+, $C_{37}H_{42}N_6O_4$); desorption chemical–ionization mass spectrum (methane), m/e 635 ($[M+1]^+$).

Mass Spectrometry

Mass spectra were obtained using a VG Instruments Model 7070HS mass spectrometer. For field-desorption mass spectra, the extraction potential was 11 kV, and the emitter current was 3 mA. For desorption chemical–ionization mass spectra, the emitter current was 1 A, and the reagent gas was methane or ammonia.

High-Performance Liquid Chromatography (HPLC)

The liquid chromatograph consisted of two Waters Model 6000A reciprocating pumps, a Waters Model 680 gradient controller, a Waters Model 710B autosampler, a Waters Model 440 ultraviolet absorbance detector equipped with a 254-nm filter, and an ESA Model 5100A electrochemical detector with an ESA Model 5010 standard analytical cell and an ESA Model 5020 guard cell. Both electrochemical cells contained high-surface area, porous graphite coulometric electrodes. The two detectors were serially connected, with the ultraviolet detector first in line. The electrochemical detector operated in the oxidation mode with a potential of +0.80 V at the analytical cell and +0.85 V at the guard cell, which was in line before the autosampler. Since the electrochemical detector had a limited linear range at any gain setting, the gain was adjusted to provide the amount of sensitivity required for the particular samples being analyzed. Signals from the detectors were monitored with a dual-pen Soltec recorder and integrated with a Hewlett-Packard Model 3357 laboratory automation system.

The column contained 3-μm particles of Supelcosil® LC-8DB, an octyldimethylsilyl-bonded silica with a reduced residual surface activity toward basic compounds. The column was 7.5 cm long and was preceded by a 2-cm long guard column containing 10-μm particles of the same packing. The internal diameter of both columns was 4.6 mm. Chromatography was isocratic with a mobile phase of 3:1 by volume acetonitrile-92 mM sodium acetate buffer flowing at 1 ml/min at ambient temperature. The injection volume was 10 μL. The mobile phase was degassed with a helium purge.

Sampling

Air or nitrogen was sampled using the following apparatus, alone or in combination as dictated by the design of the experiment: midget impingers containing toluene solutions of 1-(2-methoxyphenyl)piperazine (40–45 μg/ml) and midget bubblers containing solutions in 10 mM aqueous HCl. The exact contents of the solutions in the impingers and bubblers depended on the design of the experiment. When ambient laboratory air (about 40% relative humidity) was sampled, flow through the samplers was maintained with the house vacuum system and set by critical orifices constructed from 2.54-cm disposable syringe needles—23 gauge for 0.44–0.50 L/min, 21 gauge for 1.0–1.2 L/min, and 20 gauge for 1.5–1.6 L/min. Compressed air (dry, prepurified) and nitrogen (99.995%), both used without further purification, were sampled from a glass manifold with 10 or 12 ports, which were doubled, when necessary, using plastic Y-connectors. Samplers were connected to the manifold with rubber tubing. Flow was maintained at 1.3–1.4 L/min with the house vacuum using 1.3-cm, 26-gauge syringe needles as critical orifices. The volume of sampling medium in the impingers and bubblers dropped during sampling and was periodically restored to the original level by addition of toluene or 10 mM HCl, as appropriate.

After sampling was complete, the contents of each impinger and bubbler were transferred to a 20-ml glass scintillation vial for storage. In the experiment in which laboratory air was sampled using solutions of 1-(2-methoxyphenyl)piperazine in 10mM HCl, the volume of the contents was restored to 10 ml before transfer to the vial. Blank samples were prepared by delivering 15 ml of the toluene sampling medium or 10 ml of the 10-mM HCl sampling medium to scintillation vials.

TABLE I. Box–Behnken Experiment to Evaluate Loss of 1-(2-Methoxyphenyl)piperazine During Sampling

	Factor				Factor		
Run	Time (hr)	Flow Rate (L/min)	Impinger Jet-to-Base Distance (mm)	Run	Time (hr)	Flow Rate (L/min)	Impinger Jet-to-Base Distance (mm)
1	8	1.5–1.6	5	9	4.5	1.5–1.6	7–8
2	8	0.4–0.5	5	10	4.5	1.5–1.6	2–3
3	1	1.5–1.6	5	11	4.5	0.4–0.5	7–8
4	1	0.4–0.5	5	12	4.5	0.4–0.5	2–3
5	8	1.0–1.2	7–8	13	4.5	1.0–1.2	5
6	8	1.0–1.2	2–3	14	4.5	1.0–1.2	5
7	1	1.0–1.2	7–8	15	4.5	1.0–1.2	5
8	1	1.0–1.2	2–3				

Analysis

Samples in toluene solution were treated with 10 μL acetic anhydride [to acetylate the 1-(2-methoxyphenyl)piperazine] and taken to dryness under a stream of nitrogen with warming of the vials on a 60-°C surface. The residues were then dissolved in 15 ml of methanol with agitation for 15 minutes in an ultrasonic water bath and analyzed by HPLC. Samles in 10 mM HCl were made basic to at least pH 9 with 1 M aqueous NaOH (4–6 drops) before addition of the acetic anhydride and then treated as above.

Samples for the experiment in which compressed air was sampled using solutions of 1-(2-methoxyphenyl)piperazine in 10 mM HCl were made basic to at least pH 9 with 1 M NaOH (4–6 drops) and treated with 10 μL of acetic anhydride. These solutions, the final pH of which was 3 to 5, were analyzed by HPLC without further workup.

The HPLC procedure was calibrated with four to seven standard solutions containing 0.04–45 μg/ml each of MDIU, TDIU, and 1-(2-methoxyphenyl)piperazine (as 1-acetyl-4-(2-methoxyphenyl)piperazine) in methanol. These were prepared from separate stock solutions of approximately 0.5 mg/ml of each compound in methanol, the combined aliquots from which were treated with 10 μL of acetic anhydride before dilution with methanol. The MDIU and TDIU where quantified based on their electrochemical response, while the 1-(2-methoxyphenyl)piperazine was quantitiated with the ultraviolet detector.

Procedures of the Three Experiments

The entrainment experiment, aimed at demonstrting the loss of 1-(2-methoxyphenyl)piperazine caused by the mere passage of air through the sampling medium in the impinger, followed the Box–Behnken design outlined in Table I. The control factors chosen were sampling time, flow rate, and match of impinger parts. Impingers with matched parts have a jet-to-base distance of 5 mm. For each run, ambient laboratory air was drawn through a single sampling system consisting of an impinger containing 15 ml of a toluene solution of 606 μg of 1-(2-methoxyphenyl)piperazine, 37.3 μg of TDIU, and 34.8 μg of MDIU, followed by a bubbler containing 10 ml of 10 mM HCl. All runs were made concurrently and in duplicate. For each of the two sets of 15 samples, 3 blank samples of each sampling medium were prepared, giving 4 groups of 18 samples—2 of impinger samples and 2 of bubbler samples. The 72 samples, grouped by set and sample type, were worked up and analyzed at the same time. Within the four groups, the samples were randomized as to position during evaporation and to order during analysis. All samples were analyzed for 1-(2-methoxyphenyl)piperazine, MDIU, and TDIU. The average quantity of reagent in the six blank impinger samples was taken as the initial quantity of reagent.

For the study of the stability of 1-(2-methoxyphenyl)piperazine in the aqueous acid during sampling, air was drawn at 1.3–1.4 L/min through midget bubblers containing solutions of 0.0, 17.6, 88.2, 176, or 265 μg of 1-(2-methoxyphenyl)piperazine in 10 ml of 10 mM HCl. Quadruplicate samples were prepared at each level, half with a sampling period of 208 minutes and the other half 403 minutes. Two samples at the 265-μg level with 0 L of air sampled were also prepared. All samples were analyzed for 1-(2-methoxyphenyl)piperazine.

Reagent loss under conditions where the possibility for air oxidation was reduced considerably was tested by draw-
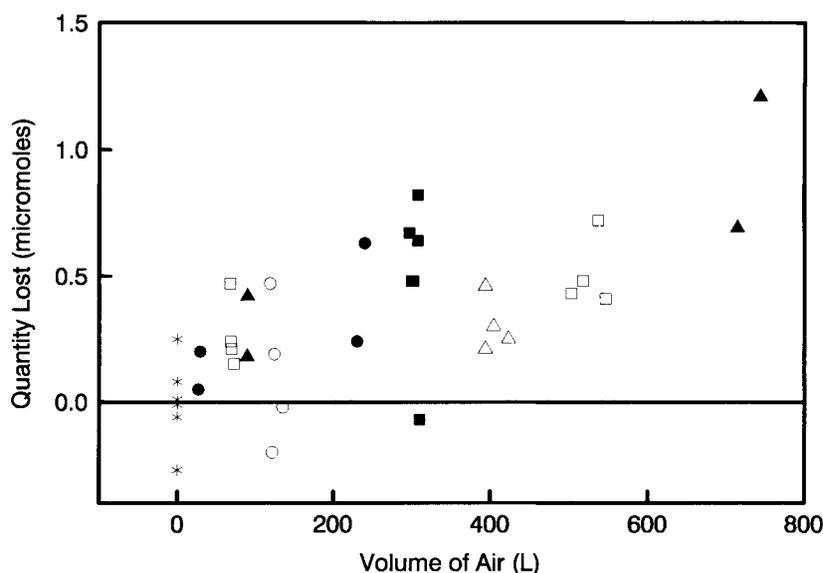
FIGURE 1. Volume dependency of the loss of 1-(2-methoxyphenyl)piperazine during impinger sampling of laboratory air using Method 5505. The flow rates and match of impinger parts were 0.4–0.5 L/min matched (●), 0.4–0.5 L/min unmatched (o), 1.0–1.2 L/min matched (■), 1.0–1.2 L/min unmatched (□), 1.5–1.6 L/min matched (▲), or 1.5–1.6 L/min unmatched (△). The six blank samples are at 0 L (*).
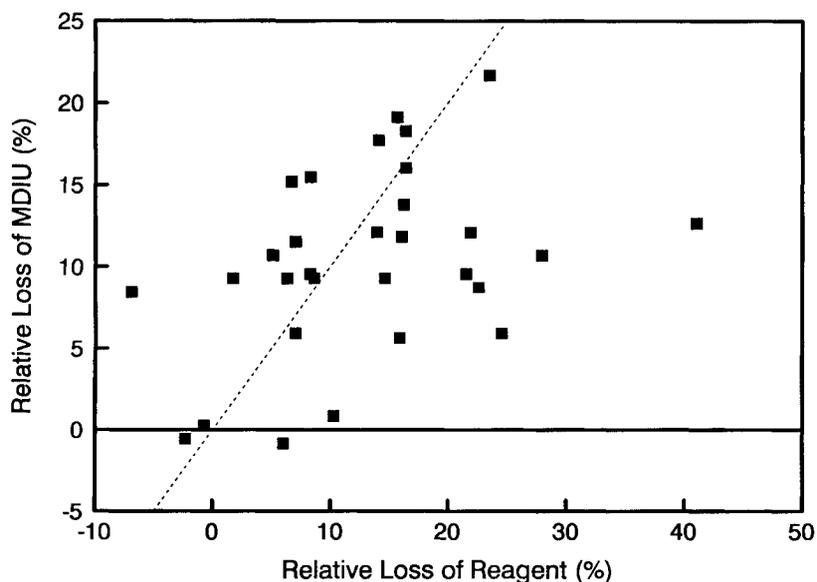
FIGURE 2. Relationship between the loss of 1-(2-methoxyphenyl)piperazine and the loss of MDIU during impinger sampling of laboratory air. The dotted line represents a 1:1 correlation between the losses of the two compounds.

ing nitrogen through ten impingers, each containing 15 ml of 44.8 μg/ml 1-(2-methoxyphenyl)piperazine in toluene. All impingers had matched parts. Nitrogen was sampled for 329 minutes at 1.3–1.4 L/min. These samples and ten blank samples were analyzed for 1-(2-methoxyphenyl)piperazine.

Results and Discussion

The major purpose of this investigation was to test the hypothesis that Method 5505 gave high estimates of isocyanate in air due to loss of 1-(2-methoxyphenyl)piperazine during sampling through entrainment of droplets of the reagent solution in the air stream exiting the impinger. This hypothesis was tested by the entrainment experiment in which 27–744 L of laboratory air, assumed to be free of isocyanate, was sampled per the procedure of Method 5505. The Box–Behnken design of the experiment allowed determination of the significance of sampling time, flow rate, and match of the impinger parts. The backup bubblers containing 10 mM hydrochloric acid were to trap the 1-(2-methoxyphenyl)piperazine which escaped the preceding impinger, thus providing positive evidence of the loss. Bubblers, rather than impingers, were chosen as backup samplers because in a similarly designed experiment, ruined by an error in the analysis of the toluene solutions, impingers containing 10 mM hydrochloric acid appeared to trap very little reagent. The MDIU and TDIU added to the toluene solution would be lost from the impinger at the same rate as the reagent if loss was due to aerosol formation and entrainment in the exit stream. The impinger samples and the bubbler samples were analyzed for 1-(2-methoxyphenyl)piperazine, MDIU, and TDIU.

The measured loss of 1-(2-methoxyphenyl)piperazine from the impinger samples showed a notable correlation

with the volume of air sampled (linear-regression correlation coefficient, 0.69), as shown in Figure 1. The scatter shown by the data could have at least three sources: the imprecision of the method, demonstrated by the data for the six blank samples (shown in Figure 1 at 0 L of air sampled); the variations of flow rate and match of impinger parts; and the change in rate of loss during the sampling period as the solutions became more concentrated with the evaporation of toluene and more dilute after addition of toluene. The quantity of reagent lost, ranging as high as 42 percent of the initial quantity, normally is assumed to be equivalent to the quantity of isocyanate present in the air sample. Therefore, had these samples been from an industrial hygiene survey, 7 would have been reported as containing 0.6–1.2 μmol of isocyanate and 23 would have been reported as containing less than 0.5 μmol. This latter quantity is the limit of detection, equal to three times the standard deviation for the six blank samples. Overall, these results support the hypothesis of mechanical loss of reagent.

The results from the quantification of TDIU in the impinger samples were rendered useless by the presence of an interference in 11 of the 18 samples for which the air volume was greater than 200 L. However, as shown in Figure 2, the data for the levels of MDIU lost from the samples reflected roughly the behavior of the data for the loss of 1-(2-methoxyphenyl)piperazine (linear-regression correlation coefficient, 0.40). These results are consistent with the hypothesis of mechanical loss of sampling medium during flow of air through the impinger.

The data from the analyses of the backup bubblers provided little proof that mechanical loss of reagent from the impingers was the major mechanism for the loss. As can be seen in Figure 3, with the exception of the sample containing 13 percent, less than 10 percent of the 1-(2-
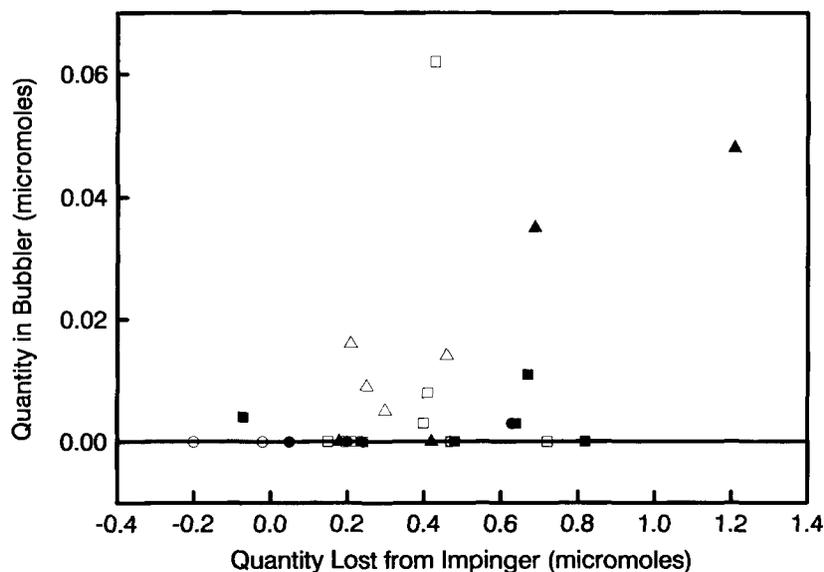
FIGURE 3. Relationship between the loss of 1-(2-methoxyphenyl)piperazine from the front impinger and quantity of 1-(2-methoxyphenyl)piperazine found in the backup bubbler after impinger sampling of laboratory air. The flow rates and match of impinger parts were 0.4–0.5 L/min matched (●), 0.4–0.5 L/min unmatched (o), 1.0–1.2 L/min matched (■), 1.0–1.2 L/min unmatched (□), 1.5–1.6 L/min matched (▲), or 1.5–1.6 L/min unnmatched (△).

methoxyphenyl)piperazine lost from the front impingers was found in the backup bubblers. Over half of the bubblers contained no detectable quantities of the reagent (detection limit 0.0003 µmol per sample). In addition, no MDIU or TDIU was detected in any of the backup bubblers (detection limit 0.3 µg per sample).

As higher levels of reagent were expected in the backup bubblers, the question of the reagent being trapped and then lost arose. Thus, the stability of 0.09–1.4 µmol of 1-(2-methoxyphenyl)piperazine in 10 mM hydrochloric acid during sampling was investigated, as described above. An average of 69 percent (range, 40–88%) of the 1-(2-methoxyphenyl)piperazine was recovered from the 16 samples. The variation in recovery, for which no explanation could be found, was independent of volume of air sampled and level of reagent. Recoveries of 89 and 99 percent were obtained for the two control samples, which contained 1.4 µmol of 1-(2-methoxyphenyl)piperazine and through which no air was sampled. Even with recoveries for the backup bubblers of only 40 percent, had most of the reagent lost from the impingers been present in the bubblers, it would have been measured.

To gain additional evidence that loss of 1-(2-methoxyphenyl)piperazine from the front impingers could occur through entrainment, 434–467 L of nitrogen was drawn at 1.3–1.4 L/min through the sampling medium— 45 µg/ml 1-(2-methoxyphenyl)piperazine in toluene. The ten samples lost 17–42 percent of the reagent, an observation consistent with the hypothesis that the loss of reagent when sampling isocyanate-free air was due primarily to entrainment. Although the flow rates and sampling periods were nearly the same for all of the samples, two impingers, which appeared to sample air more vigorously, lost the greater amounts of reagent. That a substantial loss

resulted in sampling pure nitrogen further suggests that reagent can be lost through entrainment. However, it does not eliminate the possibility of additional loss through reaction of the reagent with atmospheric oxygen or some airborne contaminant when laboratory air is sampled.

At this point, the evidence indirectly suggested the mechanism of reagent loss to be entrainment. The low recovery of the lost 1-(2-methoxyphenyl)piperazine from the backup bubblers could be attributed to inefficient trapping of the reagent-containing aerosol particles by the bubblers. Direct evidence for the entrainment mechanism was sought through experimentation in which the impinges were followed by Gelman type A/E glass fiber filters backed up with Tenax sampling tubes. The filters are known to be efficient samplers of particles of the size not readily trapped by impingers or bubblers.[14] If the reagent sublimed from the filters or dry aerosol particles, or if reagent vapor escaped the impingers, the vapor should be trapped by the Tenax, a sorbent shown suitable for sampling aromatic amines.[15] The results of a series of experiments suggested that the 1-(2-methoxyphenyl)piperazine sublimed readily from the filters and could be trapped by and recovered from the Tenax beds. However, less than 10 percent of the 1-(2-methoxyphenyl)piperazine lost from the impingers was found on the backup samplers. Thus, loss of 1-(2-methoxyphenyl)piperazine from the sampling system through some other mechanism, probably chemical change, seems a real possibility.

To test the reproducibility of the entrainment experiment, the results reported above were combined on the same graph with those obtained in 1983 and those reported to us by Dharmarajan.[12] Since the initial concentration of reagent was different in each experiment, the data were normalized to percent relative loss. As shown in Figure 4, the results of each

experiment are consistent. Together all of the experiments present a convincing picture of the loss of 1-(2-methoxyphenyl)piperazine during sampling isocyanate-free air.

The plot in Figure 4 has been used to reevaluate industrial hygiene data previously obtained using Method 5505. Those data which, when added to the plot, fall near or below the upper 95 percent confidence limit are considered to be simply a measure of the loss of reagent due to the sampling process. On the other hand, data which fall significantly above the upper 95 percent confidence limit may reflect the presence of isocyanate in the air sampled. In such cases, the workplace should be studied further using a method more specific and accurate for isocyanate. The spread of the data in Figure 4 suggests that results yielded by Method 5505 are too imprecise for any corrected quantitative estimate to be made.

Conclusions and Recommendations

The results of the experiments reported herein show that NIOSH Method 5505 for estimating isocyanate in air suffers from loss of the critical reagent, 1-(2-methoxyphenyl)piperazine, during the sampling of uncontaminated atmospheres. Method 5505 is basically the titration of an air sample with a standard solution of 1-(2-methoxyphenyl)piperazine in toluene, using HPLC to measure the quantity of reagent consumed. As the estimation of isocyanate depends upon the consumption of 1-(2-methoxyphenyl)piperazine through reaction with isocyanate and on the measurement of the quantity of reagent consumed, this loss causes an unacceptable high bias in the estimate. Therefore, it is recommended that use of the method be

discontinued.[13] Method 5505 has been removed from the *NIOSH Manual of Analytical Methods*.[16]

The loss of 1-(2-methoxyphenyl)piperazine during sampling was clearly related to the volume of air sampled, as shown in Figures 1 and 4. Mechanical entrainment of the sampling medium as aerosol particles in the stream exiting the impinger was shown to be at least a minor contributor to this loss, as 1-(2-methoxyphenyl)piperazine was found on samplers downstream from the impingers. Experimental attempts to prove definitively that this mechanism was the major factor in the loss were unsuccessful, leaving open the possibility that the 1-(2-methoxyphenyl)piperazine was undergoing a chemical change.

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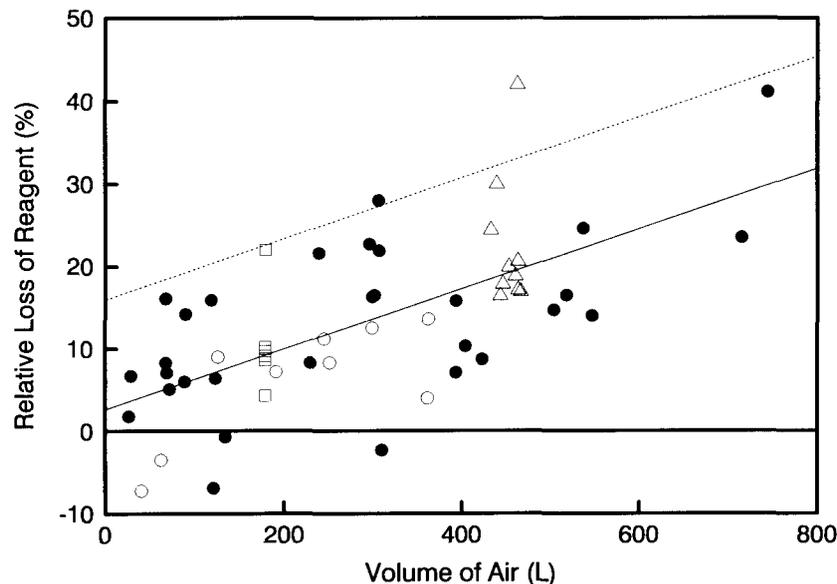
FIGURE 4. Volume dependency of the loss of 1-(2-methoxyphenyl)piperazine in four experiments using Method 5505 to sample laboratory air or nitrogen. The data presented are from the Box–Behnken entrainment experiment (●), the experiment with nitrogen (△), our 1983 experiment (○), and the experiment reported by Dharmarajan[12] (□). The solid and dotted lines represent, respectively, the linear least-squares regression of the data and its upper 95% confidence limit.

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