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SHORT COMMUNICATION

MEASUREMENT OF TISSUE DISTRIBUTION OF *m*-XYLENE IN RAT TISSUES BY HEAD SPACE GAS CHROMATOGRAPHY

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An automated head space-gas chromatography (HS-GC) method was developed and evaluated for reliability in measurement of *m*-xylene in rat tissues. For tissue samples spiked with *m*-xylene (n=2), the analytical precision was better than 12% relative standard deviation (RSD) over the concentration range of 0.1 to ca 100 µg/g for liver and kidney, 0.1 to 170 µg/g for brain, 1.2 to 250 µg/g for fat, and 0.006 to 50 µg/mL for blood. For rats sacrificed immediately after an acute exposure to 1100 ppm of *m*-xylene, the relative tissue *m*-xylene concentrations were in the ascending order as follows: brain ≤ blood ≤ kidney < liver << fat. A precision of < 13% RSD was generally obtained for duplicate tissue samples from exposed animals, with *m*-xylene concentrations of about 10 µg/g of tissue.

Key words:
automated HS-GC method, blood, distribution, inhalation exposure, *m*-xylene, tissue

There have been reports on neurological effects in humans (1) and renal toxic effects in rats (2) after exposure to airborne xylenes for a long period of time. The widespread use and occurrence of xylenes (3) may result in exposures of some population groups to hazardous levels of these compounds. To better understand the nature of the impact of these compounds on biological systems, accurate information on the relationship between exposure levels, tissue concentrations, and consequent health effects are required.

Both direct chemical analysis of tissues such as biomonitoring, and physiologically based pharmacokinetic modelling (4) have been used to estimate concentrations of the test substances in the biological system, and to provide information for health risk assessment (5–7). Although various analytical methods have been used to determine the levels of aromatic hydrocarbons in tissues as well as to estimate tissue:blood partition (distribution) coefficients (K_D) for use in physiologically based pharmacokinetic modelling (PBPK), they were found to be cumbersome and labour intensive (8, 9).

The objective of the present study was to develop a facile and reliable method which could be used for the determination of volatile organic compounds (VOCs), namely, *m*-xylene and perhaps other chemicals in animal tissues.

MATERIALS AND METHODS

Materials

m-Xylene, ethylbenzene and chlorobenzene were obtained from Aldrich Chemicals Company Inc. (Milwaukee, WI); *o*-xylene and *p*-xylene were purchased from Eastman Kodak Company (Rochester, NY). The sodium salt of ethylene diamine tetraacetic acid (EDTA) was of ACS reagent grade purity, and was purchased from Sigma Chemical Company (St Louis, MO). Glass distilled acetone was supplied by Caledon Laboratories Ltd., (Georgetown, Ont.). Somnotol (sodium pentobarbital) was obtained from Canada Packers Inc. (Cambridge, Ont.). Deionized water was obtained from a Super-Q Plus High Purity Water System (Millipore Corporation, Bedford, MA), and was degassed with nitrogen gas. All gases were supplied by Matheson Gas Products, Canada (Whitby, Ont.). The compressed air was of zero grade, and helium, hydrogen, nitrogen and oxygen were of UHP grade quality. A standard gas mixture (10 ppm, of each *m*-, *o*-, *p*-xylenes and ethylbenzene in air) was custom-made by Matheson Gas Products. Amber glass vials (40, 14 and 1.5 mL), the open top screw caps, Tuf-Bond Teflon/Silicone (TBTS) discs, and the Hamilton gas tight syringes were purchased from Chromatographic Specialities Inc., (Brockville, Ont.). The discs for the open top screw caps of 1.5 mL autosampler vials were purchased from Chromacol Ltd. (Montreal, Quebec).

A composite stock solution of *m*-, *o*-, *p*-xylene isomers and ethylbenzene (ca 62 mg/mL, each) was made by transferring 2.0 mL of each of the compounds into 20 mL of acetone containing chlorobenzene (55.4 μg/mL), the internal standard. Similarly, a stock solution of *m*-xylene (64.3 mg/mL) was prepared by the addition of 2.0 mL of *m*-xylene into 25 mL of acetone containing chlorobenzene (55.4 μg/mL). Single component and composite working standard solutions were prepared in 40 mL vials by serial dilution of the appropriate stock solutions with acetone spiked with chlorobenzene (55.4 μg/mL) to contain each of the target compounds at nominal concentrations of 0.04, 0.22, 1.3, 8.0, 48, 290, 1700, and 10000 ng/μL. The vials were sealed with open top screw caps and TBTS discs, and then with Teflon tape.

Apparatus

A Hewlett-Packard (HP; Avondale, PA) Model 5890 gas chromatograph (GC) equipped with a HP-20M wide bore capillary column (Carbowax-20M; 30 m long, 0.53 mm i.d., 1.33 μm film thickness), and a flame ionization detector (FID) was operated as previously described (10). Aliquots of liquid samples (1 μL), head space gas (1 mL), and chamber air (0.5 mL), respectively, were injected into the GC by means of a HP model 7673 autosampler, a HP model 19395A automated head space sampler, and a Carle mini MK II valve connected to a timer (11). The GC-FID was calibrated by

analysis of 1 μL aliquots (automated injections) of working standard solutions of xylene isomers and ethyl benzene in acetone, and manually injected, 0.5 mL and 1.0 mL samples of the standard gas mixture of xylenes and ethylbenzene in air. The head space (HS) method for blood analyses, and the Carle valve performance were also calibrated as previously described (10, 11).

Generation of m-xylene vapour

The vapour generating system for *m*-xylene used in the exposure experiment is described in detail elsewhere (11). Briefly, the system consisted of the following components: 1. *solvent delivery system*, *m*-xylene delivered by a syringe at a rate of 1.2 mL/h; 2. *vaporizing system*, heated block injector at 165 °C; 3. *gas supply*, composed of nitrogen carrier gas (800 mL/min), air (3.5 L/min), and oxygen for make up gas (200 mL/min, to compensate for the addition of nitrogen); 4. *mixing chamber*, a 2 L capacity glass jar equipped with an inlet for the combined stream of the three gases, and an outlet to the exposure chamber; 5. *exposure chamber*, a 27.5 L glass exposure chamber (11) with an inlet from the mixing chamber, and two outlets, of which one connected to the vent (flow of 3.5 L/min) and the other to the GC-FID (flow of 100 mL/min) for sampling of test atmosphere. The test atmosphere was sampled at 5 min intervals by the Carle valve system controlled by a timer, and monitored by the GC-FID.

Animals

Adult, male, Sprague-Dawley rats were obtained from Charles River Laboratories, Montreal, and were fed standard laboratory chow. Rats weighing 325±25 g were anesthetized with intraperitoneal injection of Somnotol (0.3 mL/rat) and were exsanguinated from the abdominal aorta. The blood was treated with EDTA (2.3 mg/mL) and stored at room temperature in sealed vials. Brain, kidney, liver and fat tissues were excised and kept frozen until analysis.

Spiked tissue tests

Spiked blood samples were prepared for HS analysis according to the procedure described by *Otson* and *Kumarathasan* (10). Organs were trimmed to remove connective tissues for the preparation of HS samples of brain, kidney, liver and fat. Duplicate samples of the same tissue type of approximately equal weights were transferred into individual amber glass vials (14 mL). Tissue samples were spiked (5 μL) with working standard solutions containing *m*-xylene alone or a mixture of xylene isomers and ethylbenzene. To minimize losses of the aromatic compounds, the syringe needle was inserted ca 3 mm into the sample before delivery of the solution. Vials were capped immediately, sealed with Teflon tape, agitated for 10 sec, and equilibrated at room temperature (21±1 °C). Equilibrated HS samples were then left in the HS sampler bath (55 °C) for 60 min prior to the injection of head space vapour into the GC. The amounts of reagents used in all preparations were confirmed by weighing. A comparison of analysis results for head space samples prepared from spiked liver at room temperature and liver that underwent heat treatment (55 °C; 1 h)

suggested no enzymatic influence on analysis, permitting a sample preparation procedure as for other tissues.

Spiked brain, kidney, liver and fat samples (ca 8.6 μg/tissue, of each VOC) were allowed to equilibrate at room temperature prior to HS-GC-FID analysis, to determine suitable sample storage conditions. Storage at 0, 4 h, 1 day, or 2 days was tested. Both stored and freshly spiked (for comparison) tissue samples were equilibrated for 1 day at room temperature, prior to HS-GC analysis.

Control animal tissues such as brain, kidney, liver and fat with weights of ca 0.3, 0.6, 0.5, and 0.2 g, respectively and 1 mL of blood were transferred into separate vials (14 mL) for calibration of the HS-GC-FID. These samples were then spiked to contain *m*-xylene (and each of its isomer) at levels of 0.00003, 0.0001, 0.006, 0.04, 0.24, 1.4, 8.6, and 50 μg/tissue sample. Vials were capped immediately and sealed with Teflon tape. Sealed sample vials were agitated, equilibrated at room temperature for 1 day, and placed in the head space sampler bath (55 °C) for 1 h prior to HS-GC analysis. Blank blood and water samples were prepared by spiking 1 mL each of control blood and degassed Super-Q water separately with 5 μL aliquots of acetone containing chlorobenzene (55.4 μg/mL). Similarly, blank tissue samples were prepared by spiking tissues of weights similar to those of the spiked samples, with 5 μL aliquots of acetone containing chlorobenzene. Empty sampling vials were also tested by HS-GC analysis. All samples were prepared in duplicate.

Animal exposure experiments

At the beginning of the exposure experiment, the gas flows for the vapour generating system were started, and the vaporizing unit was heated to reach a stable operating temperature (165–167 °C). *m*-Xylene delivery and test atmosphere monitoring were then started. Three male Sprague Dawley rats were placed in the inhalation chamber when ca 95% of the desired *m*-xylene level was reached. At the end of the 2-hour exposure, the rats were removed from the inhalation chamber, and were anesthetized by intraperitoneal injections of Somnotol (0.3 mL/rat). The rats were immediately placed back in the exposure chamber until dissection to avoid any loss of xylene. After the anaesthetic had taken effect, the animals were removed from the chamber and dissected immediately. Dissection and preparation of head space samples involved a short time period (10 min/rat).

Blood withdrawn from the abdominal aorta was transferred into amber glass vials containing EDTA (2.3 mg/mL blood), and the vials were shaken briefly. Brain, liver, kidney, and fat were then harvested in a random order to minimize the bias in m-xylene concentrations due to time dependent analyte loss. As one analyst harvested tissues, the other immediately weighed and transferred (0.2–0.6 g) the tissue samples into 14 mL amber glass vials. Measured aliquots of blood (1 mL) and the weighed portions of tissue samples from exposed animals in vials were spiked with 5 μL of acetone containing chlorobenzene (55.4 μg/mL). In order to maintain matrix compositions similar to those of the spiked controls used to generate calibration curves, blood and tissue samples from the exposed animals were spiked with acetone containing the internal standard. Aliquots (1 mL) of blood samples obtained from control animals were spiked with 5 μL of working standard solutions containing *m*-xylene

(1.4, 8.6 μg/mL blood), and were analyzed along with the exposed samples using the HS-GC-FID method. Blank tissue, blood and water samples were also analyzed.

RESULTS AND DISCUSSION

A reliable method which provides accurate determination of VOC concentrations was necessary for PBPK modelling studies. The ease of use, reliability and enhanced precision of analytical results of the automated head space-GC (HS-GC) method was previously demonstrated (10) for analysis of VOCs in water and blood, but not in tissues. The present study explored the application of the HS-GC method to the analysis of tissue samples containing *m*-xylene and its isomers. Since the isomers of *m*-xylene coexist in environmental samples, they were included in the method development for analysis of tissue samples containing these VOCs. However, as this HS-GC method was applied to analyze real tissue samples obtained from rats exposed *m*-xylene vapour, the results are discussed mainly in terms of *m*-xylene.

Initially, the GC-FID performance was optimized for determination of xylene isomers and ethylbenzene as described in our previous work (10). The head space GC method was then examined for its suitability in the analysis of tissue samples containing VOCs. The method commonly used for sample preparation which involved homogenization of tissue in 0.9% saline (5) had a potential for loss of VOCs. A separate study conducted with homogenates of spiked tissues in saline confirmed the loss of xylene isomers, making this procedure less suitable for VOC containing tissue analysis. Sample preparation method was therefore developed to minimize VOC loss.

HS-GC Method

Various methods were tried with unhomogenized tissue samples spiked with *m*-xylene and its three isomers to characterize and optimize the procedure. As a result, weights of ca 0.3, 0.6, 0.5 and 0.2 g for brain, kidney, liver and fat, respectively, were selected for the preparation of spiked tissue samples. The optimum storage time at room temperature (21±1 °C) for equilibration of VOCs in tissue and the head space above it was 2 days for brain, kidney and liver, and 1 day for fat, based on better analytical precision values. However, one day of equilibration was used because it provided earlier analyses and better sample integrity. For optimum analytical sensitivity, the head space above the spiked tissue samples was analyzed 60 min after the vials were placed in the HS sampler bath at 55 °C, to reduce interference by VOCs other than the analytes of interest.

To evaluate and characterize the HS-GC method, a series of spiked tissue samples were analyzed under the above mentioned experimental conditions. Although Table 1 only summarizes salient characteristics of the method for *m*-xylene, it was evident that similar results were obtained for the other xylene isomers and ethylbenzene. Method detection limits (MDL) for the analysis of *m*-xylene spiked tissues of approximately (0.4±0.2)g and 1 ml of blood were based on a 3:1 signal to noise ratio

(Table 1). Practical quantitation limit (PQL) values and MDLs were higher for fat and kidney compared to other tissues presumably due to increased solubility of *m*-xylene in these tissues. PQL was defined based on this value being within 95% confidence interval about the regression line with an analytical precision better than ±12%. The analytical precision values for duplicate tissue samples wereimproved by normalization of analyte peak areas to a representative internal standard (chlorobenzene) peak area. Application of the normalization procedure resulted in an improvement of relative standard deviation (RSD) percentage for all tissues.

Table 1 *Analytical method characteristics*[A]

Parameters	Blood	Brain	Kidney	Liver	Fat
Weight of sample (g)	1.0	0.4	0.6	0.5	0.2
Blank (μg/g)	<MDL	<MDL	<MDL	<MDL	<MDL
MDL (μg/g)	0.006	0.015	0.066	0.012	0.2
PQL (μg/g)	0.04	0.1	0.07	0.08	1.2
Maximum Range (μg/g)	50	170	85	100	250
%RSD (overall, N =8-10)	<4	<5	<12	<10	<5

A. Using spiked tissue samples. MDL: Method detection limit; PQL: Practical quantitation limit; RSD: Relative standard deviation.

There was a linear relationship ($r^2 > 0.99$) between GC-FID responses and analyte concentrations in tissue for *m*-xylene concentration ranges as follows: liver, brain and kidney at 0.04 μg to 50 μg/tissue sample; fat at 0.24 μg to 50 μg/tissue sample; and blood at 0.006 μg to 50 μg/mL. These ranges correspond to the μg/g values reported for tissues in Table 1. Overall normalized precision values for duplicate spiked tissue and blood samples were better than ±12% over the whole quantitation range (Table 1). When care was taken to establish operating conditions of the instruments, the characteristics of the calibration curves for the head space blood as well as tissue samples remained consistent over long time periods (e.g. 4 months). For example, the parameters of calibration curves for *m*-xylene in blood were as follows: $r^2 = 0.99$ and >0.999; the slopes (a), 9.648 and 9.647; the intercepts (b), 76.4 and 103.0, for analyses made 3 months apart.

Blank tissue and blood samples were analyzed to check for interfering contaminants. Blank water samples were analyzed for cross contamination during sample analyses, and for the effectiveness of the system cleaning. In general, potentially interfering peaks with retention times corresponding to those for the four analytes were not detected (<MDL) in the blank samples. Water blanks were analyzed after each set of 4 samples as a part of the normal analytical procedure.

To obtain accurate quantitative data, three types of measurements were necessary to calibrate the analytical system for use in the animal exposure tests. The calibration of GC-FID by analysis of working standard solutions resulted in a linear relationship ($r^2 > 0.9999$) for the FID response and concentrations of *m*-xylene ranging from 0.22 to 290 ng/μL. Normalization of analyte peak areas to the peak area of

chlorobenzene was beneficial in terms of improved analytical precision. The analytical precision for triplicate samples was better than 5% RSD after normalization, for *m*-xylene concentrations ≥ 0.22 ng/μL (10). For head space and exposure chamber air analyses, calibration of the GC-FID response with the certified standard gas mixture containing xylene isomers and ethylbenzene (10 ppm, each compound in air) by manual sampling and injection gave an analytical precision better than 2% RSD for triplicate samples. The volume of the Carle valve system was then determined to be 0.5 mL by comparison of results from the analysis of the standard gas mixture by valve system injection and manual injection (0.5 mL). The average *m*-xylene peak area value for manual injection was within ±3% of that obtained with the Carle valve system.

Exposure experiments

The target *m*-xylene concentration in the experimental atmosphere was 1125 ppm. The *m*-xylene flow for the syringe pump was calculated to be 1.2 mL/h from the equation given below, for a total flow of 3.5 L/min through the exposure chamber, to achieve the target concentration.

$$V_1 = \frac{C_n\ (\text{ppm}) * MW * V_2 * 273\ ^\circ\text{C} * 760\ \text{mm Hg}}{22.4\ \text{L/mole} * 10^6 * d * 293\ ^\circ\text{C} * 760\ \text{mm Hg}}$$

where, V_1 is the flow (mL/min) of chemical (*m*-xylene) for the exposure experiment; V_2 is the total flow through the chamber in L/min; C_n is the concentration of the chemical in ppm; MW is the molecular weight of the chemical in g/mole; d is the density of the chemical in g/mL. The average *m*-xylene concentration during the period of exposure was 1100 ppm based on the calibration of GC-FID performance. This was in good agreement with the target value.

Tissue samples from the exposed animals were equilibrated for 4 h, 1 day and 2 days at room temperature to assess the effect of storage time on the equilibration of *m*-xylene with the head space above. Although the head space xylene concentrations above the tissue samples stored for 4 h, 1 day and 2 days were of similar magnitude within sample variation, the analytical precision between duplicate samples was the best for 1 day of storage indicating optimal equilibration. For example, the analytical precision for liver samples were, 4 h: ±16%; 1 day: ±4%; 2 days: ±11%. Comparing these results with those for the spiked tissue samples, the analytical precision values were better at 2 d for spiked tissue samples, except for fat and blood (1 day). This discrepancy between real and spiked samples could be attributed to the fact that the organics were already homogeneously distributed in the exposed tissue samples, unlike in spiked tissue samples. The optimum period of 1 day of storage was selected as it permitted sufficient time to acquire samples at different time points of the exposure experiment and to analyze without any loss of sample integrity.

Table 2 illustrates the *m*-xylene concentrations in rat tissue samples immediately after exposure (n=3). The increase in head space analyte concentrations due to matrix modification by high concentrations of coexisting VOCs other than the analyte of interest is attributed to co-pollutant effect (10). The *m*-xylene concentrations in

Table 2 *Distribution of m-xylene in tissues (ng/g)*

Rat^ #	Blood	Brain	Kidney	Liver	Fat
1	3932	3062	3461	4986	11960
2	7488	6552	7003	6257	15670
3	6604	5438	6408	6705	39707

A. Exposed animals.

exposed tissues determined by the use of calibration curves generated by analysis of composite VOCs spiked tissues were not subjected to co-pollutant effect at these VOC concentrations. For instance, the *m*-xylene concentrations in the exposed blood samples obtained on the basis of concentrations in the control blood samples with *m*-xylene alone and with xylene isomers and ethyl benzene were in the same order of magnitude. Based on our previous study (10), it is also known that co-pollutant effect would be negligible for these exposed blood levels (5 μg/mL). Although the overall analytical precision for duplicate samples was better than ±13%, the inter-animal variations were greater. The distribution of *m*-xylene expressed in terms of tissue: blood ratio at the end of exposure, exhibited the fat: blood value to be the highest compared to the other tissues, as expected. Inter-animal variations in tissue:blood values were ca ±6% for brain and kidney, and ca ±20% for liver, and the highest variation was seen for fat. The higher inter-animal variations could be attributed to the difference in metabolic activities and body fat contents. Previous studies have shown an association between body fat content and organic levels in fat tissues following exposure (12).

Table 3 *Tissue:blood distribution ratios for m-xylene*

Rat^ #	Brain:Blood	Kidney:Blood	Liver:Blood	Fat:Blood
1	0.78	0.88	1.27	3.04
2	0.88	0.94	0.84	2.09
3	0.82	0.97	1.02	6.01

A. Exposed animals.

A comparison of tissue: blood distribution values in the exposed animals (Table 3) with the partition coefficient (K_d) values obtained by HS-GC analysis of *m*-xylene spiked unhomogenized tissues from a separate study indicated major differences for fat: blood values. The tissue: blood partition coefficient values for *m*-xylene from spiked tissue analysis were, 1.9, 2.1, 4.2 and 54 for brain, kidney, liver, and fat, respectively. In general, K_d values from spiked tissues were higher than tissue: blood values for the exposed tissues, and showed similar pattern of differences among tissues. In this study, the amounts of *m*-xylene retained in fat tissues of the exposed

animals were not large despite the fact that tissue: blood K_d values for spiked tissues were high, probably because it was an acute exposure. The difference in tissue:blood distribution values obtained from spiked and exposed tissue analyses could be attributed to the dynamic nature of VOC equilibration in the exposed animals, brought about by metabolism, exhalation, and excretion, in addition to partitioning between tissues. The HS-GC method thus permits accurate measurement of the actual internal doses of VOCs in tissues, which would have direct relevance to the biological effects caused by inhalation exposure in animals and humans.

CONCLUSION

A sensitive, reliable and precise HS-GC-FID method was developed for the determination of xylene isomers and ethylbenzene in tissues. The loss of VOCs was minimized in this method by reduced sample handling and residence time in air. As the matrix and physical characteristics of the spiked and real samples were kept the same, the determination of *m*-xylene concentrations in real samples based on spiked sample analysis results would be more reliable compared to the use of homogenized tissues. The improved accuracy of these tissue analysis results has a significant contribution in forming the basis for biomonitoring. The extension of this HS-GC-FID method for tissue sampling at different time periods of exposure, and partition coefficient determination would be useful in conducting PBPK modelling studies with improved accuracy.

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Summary

MJERENJE RASPODJELE *m*-KSILENA U TKIVIMA ŠTAKORA PLINSKOKROMATOGRAFSKOM ANALIZOM PARA IZNAD UZORKA (HEAD SPACE GAS CHROMATOGRAPHY)

Razvijena je automatizirana metoda plinske *head space* kromatografije (izvorno: HS-GC), pouzdanost koje je provjerena mjerenjem *m*-ksilena u tkivima štakora. Analitička preciznost za uzorke tkiva (n=2) kojima je dodan *m*-ksilen u rasponu koncentracija od 0,1 do gotovo 100 µg/g za jetru i bubreg, od 0,1 do 170 µg/g za mozak, od 1,2 do 250 µg/g za masno tkivo te od 0,006 do 50 µg/g za krv, pokazala se boljom od 12-postotne relativne standardne devijacije (RSD). Relativne koncentracije *m*-ksilena u tkivu štakora žrtvovanih odmah nakon akutne izloženosti *m*-ksilenu od 1100 ppm kretale su se ovim uzlaznim slijedom: mozak ≤ krv ≤ bubreg < jetra << masno tkivo. Sveukupna preciznost iznosila je < 13% RSD u paralelnim uzorcima izloženih životinja kod koncentracije *m*-ksilena u tkivu od oko 10 µg/g.

Ključne riječi:
automatska HS-CG metoda, inhalacijska izloženost, krv, *m*-ksilen, raspodjela, tkivo

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