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Journal of Chromatography A, 1011 (2003) 135–142
JOURNAL OF CHROMATOGRAPHY A
www.elsevier.com/locate/chroma

Application of isotope dilution to the determination of methylmercury in fish tissue by solid-phase microextraction gas chromatography–mass spectrometry

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Received 2 May 2003; received in revised form 20 June 2003; accepted 20 June 2003

Abstract

Species-specific isotope dilution (ID) calibration using solid-phase microextraction (SPME) in combination with gas chromatography–mass spectrometry (GC–MS) for separation and detection of methylmercury (MeHg) in fish tissue is described. Samples were digested with methanolic potassium hydroxide. Analytes were propylated and headspace sampled with a polydimethylsiloxane-coated SPME fused-silica fiber. ID analysis was performed using a laboratory-synthesized ^{198}Hg-enriched methylmercury (Me^{198}Hg) spike. Using selective ion monitoring (SIM) mode, the intensities of Me^{202}HgPr^{+} at m/z 260 and Me^{198}HgPr^{+} at m/z 256 were used to calculate the m/z ratio at 260/256, which was used to quantify MeHg in NRCC CRM DORM-2 fish tissue. A MeHg concentration of 4.336±0.091 μg g^{-1} (one standard deviation, $n=4$) as Hg was obtained in DORM-2, in good agreement with the certified value of 4.47±0.32 μg g^{-1} (95% confidence interval). A concentration of 4.58±0.31 μg g^{-1} was determined by standard additions calibration using ethylmercury (EtHg) as an internal standard. The three-fold improvement in the precision of measured MeHg concentrations using ID highlights its superiority in providing more precise results compared to the method of standard additions. A method detection limit (3 S.D.) of 0.037 μg g^{-1} was estimated based on a 0.25 g subsample of DORM-2.

Keywords: Fish; Isotopic dilution; Organomercury compounds

1. Introduction

Mercury is a well-known environmental pollutant that exists in three major forms, elemental Hg^0, a common form in air, inorganic Hg^{2+} and organic Hg, in particular, methylmercury (MeHg) [1]. MeHg is the most toxic form of mercury present in the environment and its bioaccumulation in fish provides the major route of exposure for humans. As a result, many countries have set guidelines for fish consumption to safeguard human health and efforts have been devoted to the development of sensitive, accurate and rapid analytical methods for monitoring MeHg in biological and environmental samples during the last two decades.

Determination of methylmercury in solid samples generally involves several analytical steps, including extraction, derivatization (where gas chromatography [GC] separation is involved), separation and detection, each of which can contribute to the difficulty

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0021-9673/03/$ – see front matter
doi:10.1016/S0021-9673(03)01122-1

of analysis, degrading the accuracy and precision of the results. The most frequently used procedures for the extraction of mercury species from solid samples are based on alkaline [2–6] and acidic leaching [7,8], aqueous distillation [9–13], supercritical fluid extraction [14] and microwave-assisted extraction [15–17]. Grignard derivatization of mercury species [18–21] has been generally superceded by simpler approaches using sodium tetraethylborate ($NaBEt_4$) [17,22–26], sodium tetrapropylborate ($NaBPr_4$) [18,27,28] or sodium tetraphenylborate ($NaBPh_4$) [29–34]. Gas and liquid chromatography are two of the most common techniques used for the separation of mercury species and detection is often undertaken in combination with sensitive and selective instrumentation, such as inductively coupled plasma mass spectrometry (ICP–MS) [18,24,35–38].

Among the separation techniques, GC remains the most popular for speciation work due to its high resolution. On the other hand, sample preparation for GC analysis is usually time-consuming, and organic solvents used in the liquid–liquid extraction can be toxic. Solid-phase microextraction (SPME) was introduced by Pawliszyn and co-workers [39,40] in the early 1990s in an effort to simplify sample preparation while retaining the merits of GC. The drawback noted with this technique is its poor precision (typically 10% RSD). As the volume of the extraction phase provided by the fiber is extremely small, any irregularity/inhomogeneity in the polymer phase/surface may impart a significant effect on its extraction characteristics [41,42]. In addition, some degradation of the fiber coating generally occurs during repeated usage and, as a result, accuracy and precision achieved with the SPME technique can be compromised. Recently, SPME has been applied to the determination of MeHg as an elegant, solvent-free sample extraction technique [6,27,34,43–46]. The precision of results obtained is typically in the range of 2 to 10% RSD for MeHg.

Isotope dilution mass spectrometry (ID-MS) has been widely employed for trace element analysis in a variety of sample matrices as it serves to improve both accuracy and precision. This arises because a ratio, rather than an absolute intensity measurement, is used for quantitation of the analyte concentration [47]. Under appropriate conditions, the ID-MS technique is considered to be a primary method of analysis [48]. Applications of species specific ID determinations have been limited due to the need to synthesize species-specific spikes. If these are available and the equilibration of spike and endogenous analyte is achieved prior to ratio measurements, a number of advantages accrue, including: enhanced precision and accuracy in results as the species-specific spike serves as an ideal internal standard; matrix effects are accounted for since quantitation is done by ratio measurements; analyte loss during subsequent sample preparation does not impact on the final results; species alteration during sample work-up can be assessed [49]; and an alternative and comparative quantitation strategy is provided. However, despite advantages offered by this approach, few applications of ID for the determination of MeHg have been reported [23,24,50–57].

Gas chromatography–mass spectrometry (GC–MS) has been used as a powerful technique for characterizing organic molecules, including organometallic compounds in various sample matrices due to its capability for identification. Moreover, the cost for GC–MS instrumentation is much lower than that for GC–ICP-MS, one of the most popular techniques used in speciation. On the other hand, the spectra generated by GC–MS is complicated, due to contributions from organic ligands or solvents. Despite the advantages offered by GC–MS, isotope dilution calibration has rarely been applied due to the complex molecular spectrum generated and the need to calculate relative isotopic abundance of molecular ions. Only recently, Barshick et al. [58] reported an GC–ID-MS method for the quantitation of inorganic mercury by converting it to methylmercury iodide before sampling with SPME.

The objective of this study was to evaluate the application of isotope dilution with GC–MS detection for the determination of MeHg in biological samples using a $Me^{198}Hg$-enriched spike [57]. A reverse spike isotope dilution approach was performed to quantify the concentration of the enriched $Me^{198}Hg$ spike. The method was validated by the determination of MeHg in National Research Council of Canada dogfish muscle tissue CRM DORM-2. To the best of our knowledge, this is the first report of the application of the isotope dilution calibration for the determination of MeHg in biological samples using GC–MS.

2. Experimental

2.1. Instrumentation

A Hewlett-Packard HP 6890 GC–MS (Agilent Technologies Canada, Mississauga, Canada) fitted with a DB-5MS column (Iso-Mass Scientific, Calgary, Canada) was used for the separation and detection of the mercury species. The HP model 5973 mass-selective detector was used. Typical GC–MS operating conditions are summarized in Table 1.

A manual SPME device, equipped with a fused-silica fiber coated with a 100 μm film of polydimethylsiloxane (Supelco, Bellefonte, PA, USA), was used for the sampling of propylated MeHg from the headspace above the aqueous solutions. For convenience, SPME sampling was conducted in a regular fumehood.

2.2. Reagents and solutions

Methanolic potassium hydroxide solution, 25% (m/v), was prepared by dissolving KOH (Fisher Scientific, Nepean, Canada) in methanol. Acetic acid was purified in the laboratory prior to use by subboiling distillation of reagent grade feedstock in a quartz still. OmniSolv methanol (glass-distilled) was purchased from EM Science (Gibbstown, NJ, USA). High-purity deionized water (DIW) was obtained from a NanoPure mixed-bed ion-exchange system fed with reverse osmosis domestic feed water (Barnstead/Thermolyne, IA, USA). Sodium tetrapropylborate solution, 1% (m/v), was prepared by dissolving $NaBPr_4$ (GALAB, Geesthacht, Germany) in DIW. A 1 mol l^{-1} sodium acetate (NaAc) buffer was prepared by dissolving an appropriate amount of sodium acetate (Fisher Scientific) in water and adjusting the pH to 5 with acetic acid.

Methylmercury chloride and ethylmercury chloride were purchased from Alfa Aesar (Ward Hill, MA, USA). Individual stock solutions of 1000–1500 μg ml^{-1}, as Hg, were prepared in methanol and kept refrigerated until used. Natural abundance MeHg working standard solutions of 2.077 and 2.128 μg ml^{-1} were prepared by diluting the stock solutions with methanol. A 5 μg ml^{-1} ethylmercury (EtHg) solution was prepared by diluting the stock solution in methanol for use as an internal standard.

^{198}Hg-enriched MeHg spike solution at a nominal concentration of 0.55 μg ml^{-1} in methanol was prepared from an isotopically enriched $Me^{198}HgCl$ ($Me^{198}Hg$) stock synthesized in our laboratory from commercially available inorganic ^{198}Hg (96% isotopic purity) [59]. From previous experience, although the uncertainty contribution from volume measurements is usually larger than that arising from mass, the uncertainty contributions from dilutions by volume remain insignificant compared to the total combined uncertainty characterizing the overall procedure [60]. Thus, for simplicity of sample preparation, all dilutions were achieved by volume. The concentration of the spike solution was verified by reverse spike isotope dilution against the natural abundance MeHg standards.

The National Research Council Canada (NRCC,

Table 1
GC–MS operating conditions

Column	DB-5MS 30 m×0.25 mm I.D., 0.10 μm
Injection	Splitless
Injector temperature	220 °C
Oven temperature program	50 °C to 150 °C at 15 °C/min; ramp to 270 °C at 30 °C/min; hold 5 min
Carrier gas; flow-rate	Helium; 0.9 ml min^{-1}
Transfer line temperature	290 °C
MS	HP model 5973 mass-selective detector
SIM parameters	Measured ions: m/z=260, 256; dwell times: 50 ms
MS quad temperature	150 °C
MS source temperature	230 °C

Ottawa, Canada) dogfish muscle reference material CRM DORM-2 was used for method validation.

2.3. Sample preparation and analysis procedure

Sample preparation was based on the procedure reported by Cai and Bayona [4]. A 0.25 g subsample was spiked with an appropriate amount of enriched $Me^{198}Hg$ solution and 20 ml of 25% (m/v) methanolic KOH solution added. The mixture was shaken for 5 h and then stored at 4 °C until analysis. Six reverse spike isotope dilution calibration samples were prepared to quantify the concentration of the enriched $Me^{198}Hg$ spike. A 0.2 ml volume of the enriched $Me^{198}Hg$ spike solution and 0.24 ml of 2.128 μg ml^{-1} (or 2.077 μg ml^{-1}) natural abundance MeHg solution were accurately pipetted into a vial and diluted to 10 ml with methanol. For SPME headspace sampling, a 500 μl volume of digest or reverse spike isotope dilution calibration sample was transferred to a 50 ml glass vial for quantitation. After 20 ml of 1 mol l^{-1} NaAc buffer solution and 1 ml of 1% $NaBPr_4$ were added, the vial was capped with a PTFE-coated silicon rubber septum. The SPME needle was inserted through the septum and headspace sampling was performed for 10 min. During the extraction, the solution was vigorously stirred with a PTFE-coated magnetic stir bar. The collected analyte was then desorbed from the SPME fiber onto the GC column. A 1 min desorption time at an injector temperature of 220 °C ensured complete desorption from the fiber.

A mass bias correction factor was obtained by repeat injection of a 2.0 μg ml^{-1} natural MeHg standard between samples. Ions at m/z 260 ($Me^{202}HgPr^+$) and m/z 256 ($Me^{198}HgPr^+$) were monitored under selective ion monitoring (SIM) mode. Peak areas were used to calculate reference ion (at m/z 260) and spike ion (at m/z 256) ratios, from which the MeHg concentrations in NRCC CRM DORM-2 were calculated.

2.4. Safety considerations

MeHg and EtHg compounds are toxic substances and sodium tetrapropylborate is highly flammable. These materials must be handled with care and appropriate personal protection.

3. Results and discussion

3.1. Optimization of spme sampling

Headspace sampling was chosen to minimize exposure of the SPME fiber to the sample matrix, thereby enhancing the lifetime of the fiber. SPME extraction efficiency can be influenced by a number of factors, including extraction temperature, extraction time, pH of the solution and the concentration of derivatization reagent. These parameters were carefully optimized in an earlier SPME-GC–ICP-MS study [57]. For simplicity, derivatization of Hg species and SPME sampling were performed at room temperature. A 10 min extraction time assured an equilibrium distribution of derivatized MeHg between the sample solution and the PDMS fiber. The effect of sample pH was investigated and the optimum was found to be in the range 4 to 7. A pH of 5, obtained using a 1 mol l^{-1} NaAc buffer solution, was chosen for this study.

Use of $NaBPr_4$ instead of $NaBEt_4$, was chosen as the derivatization agent to permit use of EtHg as an internal standard for assessment of standard additions calibration. Furthermore, a solution of $NaBPr_4$ was stable for at least 2 weeks when stored at 4 °C. No significant effect on SPME response was detected over the $NaBPr_4$ concentration range from 0.2 to 2%. A concentration of 1% $NaBPr_4$ was used to ensure complete propylation of analyte in the real sample matrix.

3.2. Isotope dilution calibration

As noted earlier, the spectrum generated by GC–MS is complicated due to contributions from organic ligands. All species arising from various combinations of isotopes of the reference and spike ions must be included in calculations to derive the true abundance of the reference and spike ions needed for the final quantitation. A software program (Isotope Pattern Calculator v 3.0) developed by Yan [61] can be used to calculate relative abundance of $MeHgPr^+$ ion for different Hg isotopes. The calculated relative abundances of isotopic compositions based on the IUPAC recommended isotopic abundance of Hg, C and H and enriched Hg are presented in Table 2. As expected, the measured isotopic pattern of molecular

Table 2
Isotopic compositions of $MeHgPr^+$ ion

Natural abundance $MeHgPr^+$		Natural abundance Hg		Enriched $Me^{198}HgPr^+$		Enriched ^{198}Hg	
m/z	Relative abundance	m/z	Relative abundance	m/z	Relative abundance	m/z	Relative abundance
254	0.00144	196	0.0015344	254	0.00222	196	0.00232
255	0.00006			255	0.00010		
256	0.09539	198	0.09968	256	0.92062	198	0.9622
257	0.16565	199	0.16873	257	0.04176	199	0.091
258	0.22826	200	0.23096	258	0.03017	200	0.0308
259	0.13604	201	0.13181	259	0.00350	201	0.00228
260	0.29146	202	0.29863	260	0.00131	202	0.00124
261	0.01278			261	0.00005		
262	0.06595	204	0.06865	262	0.00027	204	0.00028
263	0.00292			263	0.00001		
264	0.00005			264	0.00000		

Hg-containing ions is different from that of the naturally occurring elemental Hg isotopic pattern due to contributions from organic ligands, as shown in Fig. 1a. Relative abundances of 29.146 and 9.539% for $Me^{202}HgPr^+$ at m/z 260 and $Me^{198}HgPr^+$ at m/z 256, respectively, calculated for the samples and natural MeHg standards; and relative abundances of 0.131 and 92.062% for $Me^{202}HgPr^+$ at m/z 260 and $Me^{198}HgPr^+$ at m/z 256, respectively, calculated for the ^{198}Hg-enriched MeHg spike, were used for the final calculation of MeHg concentrations in DORM-2. With this information Eq. (1), below, can be used for the calculation of the MeHg concentration in DORM-2 using SPME–GC–MS:

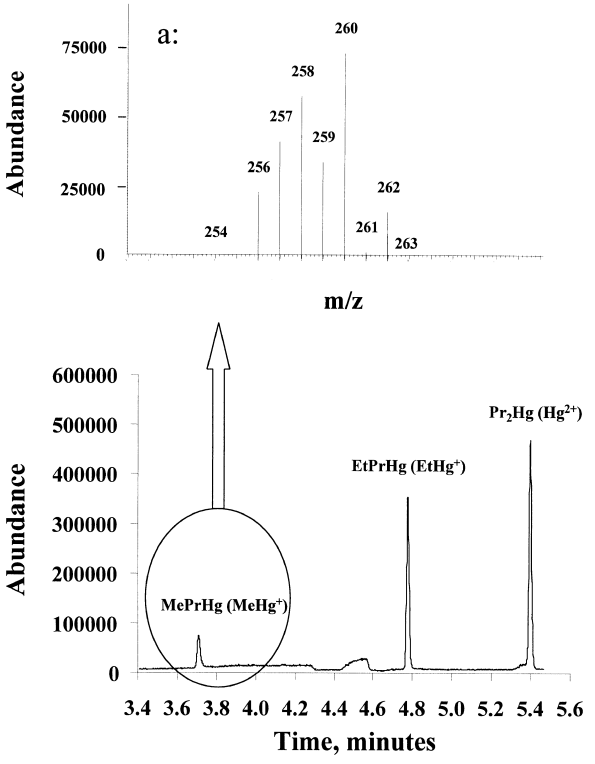

Fig. 1. Total ion chromatogram for a 100 ppb mixed standard solution obtained with SPME sampling using GC–MS in scan mode; (a) isotope pattern of natural $MeHgPr^+$.

$$C_x = C_z \cdot \frac{v_y}{w \cdot m_x} \cdot \frac{v_z}{v'_y} \cdot \frac{A_y - B_y \cdot R_n}{B_{xz} \cdot R_n - A_{xz}} \cdot \frac{B_{xz} \cdot R'_n - A_{xz}}{A_y - B_y \cdot R'_n} - C_b \quad (1)$$

where C_x is the blank corrected MeHg concentration as Hg ($\mu g\ g^{-1}$) based on dry mass; C_z is the concentration of natural abundance MeHg standard ($\mu g\ ml^{-1}$); v_y is the volume (ml) of spike used to prepare the blend solution of sample and spike; m_x is the mass (g) of sample used; w is the dry mass correction factor; v_z is the volume (ml) of natural abundance MeHg standard used; v'_y is the volume (ml) of spike used to prepare the blend solution of spike and natural abundance MeHg standard solution; A_y is the abundance of $Me^{202}HgPr^+$ at m/z 260 in the spike; B_y is the abundance of $Me^{198}HgPr^+$ at m/z 256 in the spike; A_{xz} is the abundance of $Me^{202}HgPr^+$ at m/z 260 in the sample or natural MeHg standard; B_{xz} is the abundance of $Me^{198}HgPr^+$ at m/z 256 in the sample or in the standard; R_n is the measured reference/spike ion ratio (mass bias cor-

rected) in the blend solution of sample and spike; R'_n is the measured reference/spike ion ratio (mass bias corrected) in the blend solution of spike and natural abundance MeHg standard; C_b is the blank concentration ($\mu g\ g^{-1}$). As clearly expressed in this equation, only the reference/spike ion ratios in the spiked samples and reverse ID calibration samples need to be measured to derive the final analyte concentration.

3.3. Validation of SPME–GC–ID-MS method

In order to achieve accurate and precise results, an interference free pair of isotopes (ions) must be available for ratio measurements, care must be taken to avoid any contamination during the analytical process, and isotopic equilibration must be achieved between the added spike and the endogenous analyte in the sample prior to ratio measurements. Validation of the achievement of equilibration of the enriched spike and the sample is not easy in practice. Earlier studies indicated that equilibration between the added spike and the endogenous MeHg in the sample was achieved during a 5 h sample digestion with 25% methanolic KOH followed by storage in the dark for 2 days [57].

The mass bias correction factor for the measured ratios can be calculated from the ratio of expected ions (260/256 = 29.146%/9.539%) to measured with a natural abundance MeHg standard solution. A mass bias correction factor of 1.004±0.013 (mean±S.D., $n=5$) for 260/256 ions was obtained, indicating no significant mass bias drift during a run sequence. Thus, this was used to calculate mass bias corrected ratios. Mass bias corrected ratio of 3.052±0.042 (1 S.D., $n=5$) for ions at m/z 260/256 obtained in an unspiked DORM-2 was not significantly different from the expected natural abundance ratio of 3.055 (29.146%/9.539%), confirming that no significant spectroscopic interference at m/z 260 and 256 on CH_3HgPr^+ ion arises from the sample matrix, permitting accurate results to be obtained using these two masses.

A concentration of 4.336±0.091 $\mu g\ g^{-1}$ (1 S.D., $n=4$) as mercury was obtained using isotope dilution SPME–GC–ID-MS for DORM-2, in good agreement with the certified value of 4.47±0.32 $\mu g\ g^{-1}$ as Hg (95% confidence interval).

An average concentration of 0.051±0.012 $\mu g\ g^{-1}$ (1 S.D., $n=3$), obtained from three sample blanks, is insignificant compared to the MeHg concentration in DORM-2, confirming that contamination was effectively under control during sample preparation. Nevertheless, this blank was subtracted from the gross MeHg concentration measured in DORM-2. The calculated method detection limit for the isotope dilution SPME–GC–ID-MS technique based on measurements of three $Me^{198}Hg$-spiked sample blanks is 0.036 $\mu g\ g^{-1}$ normalized to a 0.25 g subsample with derivatization of a 0.50 ml volume of the methanolic KOH extract.

3.4. Results for MeHg in DORM-2 using standard additions calibration with SPME–GC–ID-MS

A subsequent comparative analysis of DORM-2 fish muscle tissue was undertaken using the method of standard additions for calibration with SPME–GC–ID-MS. Additions of approximately one- and two-fold of the expected MeHg concentration in DORM-2 were made. A spike of 1000 ng of EtHg was added to all samples as an internal standard. Quantitation of MeHg was based on measured intensity ratios of the peak area for MeHg at m/z 260 divided by the peak area for EtHg at m/z 274. The correlation coefficient for the standard additions calibration curve for MeHg in the concentration range of 0~9 $\mu g\ g^{-1}$ was 0.970. A mean concentration of 4.58±0.31 $\mu g\ g^{-1}$ (1 S.D., $n=4$) was obtained, in good agreement with the certified value.

4. Conclusion

This study constitutes the first reported application of a species-specific isotope dilution technique for the accurate and precise determination of MeHg by SPME–GC–ID-MS. A significant three-fold improvement in the precision of determination of MeHg in DORM-2 using ID (2.1% RSD), as opposed to standard additions calibration (6.8% RSD with EtHg internal standard) was obtained, clearly demonstrating its superior capability in providing more precise results. In addition, total analysis time is significantly reduced with this approach. These

benefits are achievable only if a species-specific enriched spike is available.

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