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Hollow-Fiber Liquid-Phase Micro-Extraction Method for the Simultaneous Derivatization, Extraction, and Pre-concentration of Organotin Compounds from Packed Fruit Juices

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Abstract
Organotin compounds are widely employed as pesticides and fungicides in agriculture and as stabilizers for the industrial manufacture of polyvinyl chloride and other polymers. Accordingly, these endocrine disruptors can be found in a variety of foods and beverages. In the present study, we describe the optimization of a hollow-fiber liquid-phase micro-extraction approach for the simultaneous derivatization, extraction, and pre-concentration of butyltin species from commercial fruit juices with the aim of investigating their migration from the packaging. The best extraction efficiencies were achieved by using hexane as the acceptor solvent and a polypropylene fiber length of 2 cm, whereas the agitation speed, extraction temperature, and total extraction time were set at 1100 rpm, 25 ºC, and 10 min, respectively. Using these optimal conditions, the method was satisfactorily validated in terms of linearity (5–1000 μg L^{-1}), limits of detection (0.8–1.8 μg L^{-1}), recovery (80.5–92.1%), intraday precision (10.2–13.1%), inter-day precision (11.0–15.5%), matrix effect (83.2–91.8%), accuracy (85.2–95.2%), specificity, and carryover. The application of this technique to commercial samples obtained from a local market demonstrated that levels of organotin species in packed fruit juices are negligible, in agreement with the limits established by the European Food Safety Authority (0.14 mg of total organotin compounds per kg of food).

Keywords Organotin compounds · Hollow-fiber liquid-phase micro-extraction · Fruit juice · Food packaging · Gas chromatography-mass spectrometry · Butyltin

Introduction

Organotin compounds are anthropogenic substances that have traditionally been employed as biocides and antifouling agents in marine paints and coatings. These chemicals, mainly the trisubstituted forms tributyltin (TBT) and triphenyltin (TPhT), are well-known endocrine disruptors whose exposure has been associated with a wide range of morphological and physiological toxic effects in different cell types and species (Zhang et al. 2021). Thus, the use of these compounds in antifouling paints was banned by the International Maritime Organization in 2008, which has led to a progressive decrease in their levels in aquatic ecosystems and, consequently, in marine origin foods (Matthiessen 2019). However, organotin species are still employed as pesticides and fungicides in agriculture, as wood preservatives, and for the industrial manufacture of polyvinyl chloride (PVC), silicone, and other polymers. Therefore, their presence in various products of human consumption has exponentially increased in the last few years. For instance, organotin compounds have been detected at variable concentrations in irrigation and drinking waters transported through PVC pipes (Li et al. 2019), as well as in vegetables, fruits, and other foods (Qunfang et al. 2004). Furthermore, various authors have demonstrated their presence in food packages (Mandrile et al. 2020), especially in multilayer containers with plastic coating (e.g., Tetra Brik®), which in turn could cause food contamination via migration from the packaging (Forsyth et al. 1992; Vacchina et al. 2020). Accordingly, the food industry demands sensitive and accurate analytical

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methods for the analysis of organotin species (i.e., organotin speciation) to guarantee food quality, safety, and traceability.

Nowadays, the most employed analytical technique for organotin speciation is gas chromatography, which can be coupled to a variety of detectors such as atomic absorption spectroscopy (GC-AAS), flame photometric detection (GC-FPD), mass spectrometry (GC–MS), or inductively coupled plasma mass spectrometry (GC-ICP-MS) (Cole et al. 2015; Chung and Wu 2017). Prior to their chromatographic separation, organotin compounds must be extracted and chemically derivatized to form volatile and thermally stable species. To this end, traditional procedures based on their complexation and extraction using organic solvents and subsequent derivatization by means of Grignard alkylation or hydride generation (Morabito et al. 2000). As an alternative to these tedious and time-consuming methods, the use of sodium tetraethylborate as the alkylating agent enables direct derivatization and simultaneous extraction of organotin species in aqueous samples (Liscio et al. 2009). Anyway, due to the low concentrations that are usually found in foods and other matrices, organotin speciation normally requires the implementation of advanced sample treatment protocols for the extraction, cleanup, and pre-concentration of the analytes. Conventional approaches, such as liquid–liquid extraction (LLE), microwave-assisted extraction, or pressurized liquid extraction, have demonstrated adequate performance in this field (Chung and Wu 2017). Complementarily, the use of techniques based on liquid-phase micro-extraction (LPME) is gaining great importance in recent years, since they allowed carrying out the extraction and pre-concentration of the analytes in the same step (e.g., single-drop micro-extraction, dispersive liquid–liquid micro-extraction) (Chormey et al. 2020).

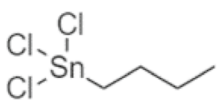
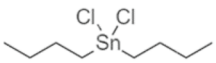
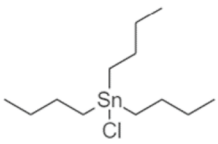
In this context, hollow-fiber liquid-phase micro-extraction (HF-LPME) has emerged recently for the analysis of multiple analytes with diverse physicochemical properties, including phenolic compounds (Mogaddam et al. 2020), polycyclic aromatic hydrocarbons (Wang et al. 2021), pesticides (Farajzadeh et al. 2012), organometallic compounds (Anthemidis and Mitani 2013), and many others. However, this technique has only been reported once for the extraction of previously derivatized organotin species from environmental water samples (Cukrowska et al. 2004). Accordingly, to simplify and enhance the analytical performance of existing methods for organotin speciation, in the present work, we describe for the first time the optimization and validation of a HF-LPME approach for the simultaneous extraction, pre-concentration, and derivatization of the major organotin species, namely monobutyltin (MBT), dibutyltin (DBT), and tributyltin (TBT) (Table 1). This extraction method was combined with gas chromatography–mass spectrometry for analyzing commercial fruit juice samples with the aim of evaluating the contamination by organotin compounds due to migration from the package.

Materials and Methods

Reagents and Samples

Sodium tetraethylborate (97%), sodium acetate (≥ 99%), toluene (≥ 99.5%), and pure standards of monobutyltin trichloride (MBT, 95%), dibutyltin dichloride (DBT, 96%), tributyltin chloride (TBT, 96%), and tetrabutyltin (TeBT, 93%) were purchased from Sigma-Aldrich (Steinheim, Germany). Methanol and hexane (HPLC grade), acetic acid (96%), and sodium hydroxide (≥ 98%) were supplied by Merck (Darmstadt, Germany). Individual stock solutions were prepared at 1000 mg L^{-1} in methanol for each organotin compound and stored at − 20 °C. Q3/2 Accurel KM polypropylene hollow fibers (600 µm i.d., 200-µm wall thickness, 0.2-µm pore size) were purchased from Membrana (Wuppertal,

Table 1 Chemical characteristics of the butyltin species under study

	Monobutyltin	Dibutyltin	Tributyltin
Molecular formula	$C_4H_9Cl_3Sn$	$C_8H_{18}Cl_2Sn$	$C_{12}H_{27}ClSn$
Molecular weight	282.2	303.8	325.5
Structure			

Germany). Water was purified using a Milli-Q Gradient system (Millipore, Watford, UK). Fruit juice samples (i.e., apple, peach, tomato, pineapple, orange) packed in Tetra Brik® were obtained from a local market and stored at 4 °C until analysis. Before extraction, juice samples were vigorously vortexed for 1 min and filtered through 0.45-μm pore size polytetrafluoroethylene filters.

Extraction and Derivatization of Organotin Compounds

Conventional Method Based on Liquid–Liquid Extraction

According to the method described by Rodríguez-González et al. (2002) with slight modifications, 1 mL of the sample (fruit juice or aqueous solution of organotin standards) was added to a 7-mL glass vial with a screw cap together with 4 mL of acetate buffer at pH 5.4, 0.5 mL of 2% sodium tetraethylborate aqueous solution containing 0.1 M sodium hydroxide as the derivatizing agent, and 1 mL of hexane containing 150 μg L^{-1} TeBT (internal standard) as the extractant. Then, the mixture was subjected to vigorous shaking for 10 min using an orbital shaker, and the upper organic phase was collected for further analysis.

Method Based on Hollow-Fiber Liquid-Phase Micro-Extraction

For the simultaneous extraction, pre-concentration, and derivatization of organotin compounds, a HF-LPME methodology was developed based on a homemade assembly (Manso et al. 2011), as follows (Fig. 1). First, the polypropylene HF was cut at the desired length, and one end was heat-sealed using a soldering tool. The fiber was then attached to a 0.5 to 20-μL Eppendorf GELoader pipette tip for filling microinjection capillaries (Eppendorf, Hamburg, Germany), which was previously end-cut to provide a better adjustment with the open extreme of the membrane. Afterward, the fiber was immersed into a vial containing the acceptor organic solution for 1 min to open the pores, and a GC syringe was then introduced through the pipette tip to remove the air occluded and to fill the lumen of the HF with the organic solvent. After that, the HF assembly was immediately introduced into a 7-mL glass vial containing 1 mL of the sample, 4 mL of acetate buffer at pH 5.4, and 0.5 mL of 2% sodium tetraethylborate aqueous solution containing 0.1 M sodium hydroxide. To facilitate the derivatization and transference of the analytes from the donor phase to the organic phase contained within the HF, the mixture was stirred using a magnetic stirrer under a controlled temperature. During the extraction, the fiber was located 1 cm above the bottom of the vial to avoid hitting the magnetic stirrer. Finally, the sealed extreme of the fiber was cut, and the acceptor solution was withdrawn using a GC syringe for further analysis.

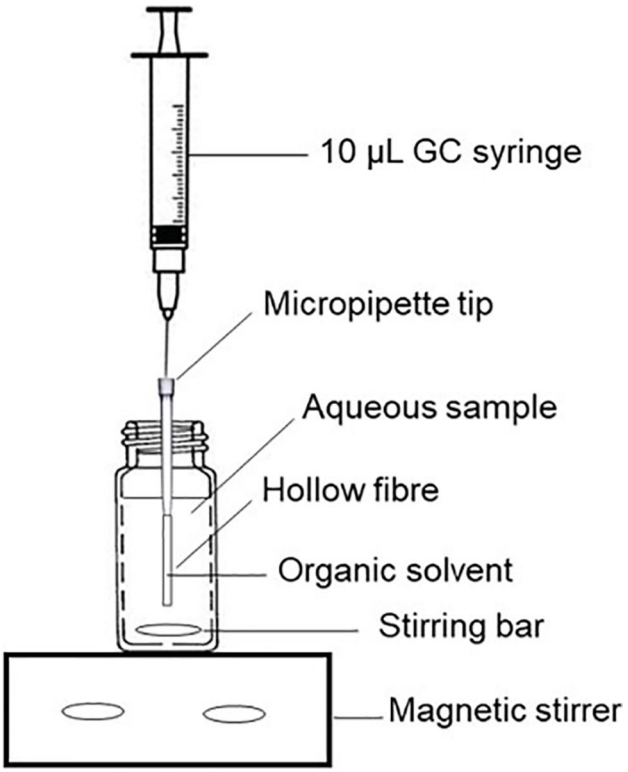


Fig. 1 HF-LPME technical setup for the extraction of organotin compounds

The working variables of the HF-LPME procedure, namely the acceptor solution, length of the fiber, extraction time, temperature, and agitation speed were optimized to achieve maximum analytical performance in terms of sensitivity, reproducibility, and accuracy. Regarding the extraction solvent, we tested hexane and toluene containing 150 μg L^{-1} TeBT as the internal standard, whereas the following study ranges were assayed for the other variables: fiber length, 1–3 cm; extraction time, 5–30 min; extraction temperature, 25–50 °C; agitation speed, 500–1500 rpm.

Analysis of Organotin Compounds by Gas Chromatography-Mass Spectrometry

The experiments were performed in a gas chromatograph (Varian CP 3800) coupled to an ion trap mass spectrometer detector (Saturn 2200), using a FactorFour fused-silica capillary column (VF-5MS 30 m × 0.25 mm i.d., 0.25-μm film thickness stationary phase) from Varian (Walnut Creek, CA, USA). The injection port was

equipped with a splitless liner (Supelco, Bellefonte, PA, USA), and the temperature was kept at 250 °C. The samples were injected in splitless mode (1 µL), using helium as the carrier gas at a constant flow rate of 1 mL min^{-1}. The oven temperature was initially maintained at 50 °C for 1 min, was then raised to 250 °C at 30 °C min^{-1}, and was finally held for 1 min at this temperature (total analysis time, 8.7 min). The detection of organotin compounds was performed by scheduled single ion monitoring of the following ions: 0–4 min, no acquisition (solvent delay); 4–5.5 min, 235 Da (MBT); 5.5–6 min, 263 Da (DBT); and 6–-8.7 min, 291 Da (TBT and TeBT). The ion source, manifold, and transfer line temperatures were set at 200 °C, 50 °C, and 280 °C, respectively.

Analytical Validation

The HF-LPME × GC–MS method optimized in this study was validated according to the guidelines established by the US Food and Drug Administration (FDA) (Center for Drug Evaluation and Research 2018). Calibration curves were prepared by serial dilution at 10 concentration levels within the range of 1–1000 µg L^{-1}, in both solvent and in blank fruit juices, and analyzed in triplicate to evaluate the method linearity ($R^2 > 0.99$). The recovery of the extraction process was determined by spiking blank juice samples with the three organotin species at three concentration levels (10, 100, 1000 µg L^{-1}), which were analyzed in triplicate. Recovery percentages were computed considering the levels found in blank samples using the formula: [100 × (final concentration − initial concentration)/added concentration]. On the other hand, the method accuracy was determined by spiking pre-extracted juice samples with the three butyltin compounds at three concentration levels (10, 100, 1000 µg L^{-1}). The limits of detection (LOD) were estimated from calibration curves using the formula: 3 × Sy/S, where Sy refers to the standard deviation of *y*-intercepts, and S to the slope of the curve. Intra- and inter-day precisions were assessed by computing the relative standard deviations that were obtained after analyzing spiked samples at three concentration levels (10, 100, 1000 µg L^{-1}) five times within the same day as well as on 3 consecutive days, respectively. To assess the matrix effect (ME), we compared the slopes of the calibration curves prepared in solvent and in pre-extracted juice samples, using the formula: [100 × slope obtained in juice/slope obtained in solvent]. Finally, the method specificity was evaluated by testing the absence of interferences in extraction blanks and by computing the retention time variability in solvent and in spiked samples along a 3-day analytical run. The carryover was checked by analyzing blank water after injecting samples spiked at 100 µg L^{-1} for the butyltin compounds under study.

Results and Discussion

Optimization of the Hollow-Fiber Liquid-Phase Micro-Extraction Method

HF-LPME has previously been proposed for the analysis of various organometallic species in environmental research (Anthemidis and Mitani 2013) since it allows the simultaneous extraction and pre-concentration of analytes by using low organic solvent volumes. However, the application of this technique for organotin speciation is not widespread and, to our knowledge, it has been reported only once for the extraction of previously derivatized MBT, DBT, TBT, and TPhT from environmental water samples (Cukrowska et al. 2004). To improve the analytical performance of this methodology, we describe here the development of a HF-LPME method for the simultaneous derivatization, extraction, and pre-concentration of butyltin compounds. For this purpose, the most important variables that affect the HF-LPME process, including the acceptor phase, fiber length, extraction time, temperature, and agitation speed, were optimized to maximize extraction efficiency in terms of sensitivity, reproducibility, and accuracy. To this end, a univariate optimization was carried out using the following conditions as the initial HF-LPME set-up: fiber length, 1.5 cm; extraction time, 10 min; extraction temperature, 25 °C; agitation speed, 1000 rpm.

First, two different organic solvents were tested as the acceptor phase inside the HF, namely hexane, the solvent traditionally employed for LLE-based extraction and derivatization of organotin compounds (Rodríguez-González et al. 2002); and toluene, which has previously been proposed for the HF-LPME-based extraction of other organometallic species (Thongsaw et al. 2019). The use of hexane enabled the simultaneous extraction, derivatization, and pre-concentration of the three butyltin species under study, whereas no peaks were surprisingly detected by using toluene. To discard technical errors, the extraction performance of hexane and toluene was also compared by applying the conventional extraction method described under the "Conventional Method Based on Liquid–Liquid Extraction" section. As observed with HF-LPME, only hexane successfully extracted the organotin compounds from the samples, probably because of solubility issues. Accordingly, hexane was selected as the organic acceptor solvent for further optimizations. Next, we assayed different fiber lengths as this

variable is directly related to the total volume of acceptor phase available for the extraction and, consequently, has a great influence on the HF-LPME efficacy and pre-concentration capacity. As shorter was the HF employed, higher pre-concentration factors were obtained. However, too small extract volumes were recovered from the fiber when using lengths shorter than 2 cm. On the other hand, larger fiber lengths yielded poor reproducibility in terms of extract volumes, probably because of the higher influence of turbulences during stirring, which may cause losses during the extraction process. Thus, the optimum value for the fiber length resulted to be 2.0 cm, which provided good reproducibility for the extraction of organotin compounds and simultaneous pre-concentration. As the HF-LPME extraction process is based on the diffusion of analytes from the donor sample to the acceptor solvent, we also optimized the agitation speed and temperature to facilitate the transference of organotin species inside the HF. For this purpose, the stirring and temperature during the extraction process were assayed in the ranges of 500–1500 rpm and 25–50 °C, respectively. Regarding the agitation, we observed that increasing the stirring intensity yielded enhanced extraction recoveries until reaching a plateau of around 1100 rpm. At higher agitation speeds, air bubbles appear inside the HF, and losses of the acceptor solvent can occur, thus resulting in decreased analytical reproducibility. In contrast, the extraction efficiency was negatively influenced by the temperature, probably because of the low boiling point of hexane. Thus, the room temperature was selected for further experiments. Finally, using the optimum values for all the variables previously tested (i.e., acceptor solvent, hexane; fiber length, 2 cm; agitation speed, 1100 rpm; temperature, 25 °C), we optimized the immersion time of the HF into the donor sample to maximize the extraction recoveries and to ensure complete derivatization of the analytes. As expected, longer immersion times resulted in increased extraction rates due to a higher degree of diffusion through the fiber but also tended to reduce the reproducibility in terms of the extract volume. Therefore, the extraction time was finally set at 10 min as a compromise value.

Method Validation

The HF-LPME × GC–MS method optimized here was validated according to the FDA guidelines, as summarized in Table 2. The calibration curves, prepared both in solvent and in commercial fruit juices, showed linear responses within the concentration range 5–1000 μg L^{-1}, with R^2 values above 0.99 for the three organotin compounds under study. The HF-LPME procedure provided satisfactory extraction recoveries, in the range of 80–100%, at the three concentration levels here assayed (i.e., 10, 100, 1000 μg L^{-1}). The LODs computed in spiked juice samples were in the ranges 0.82–0.94 μg L^{-1} for MBT, 1.6–1.8 μg L^{-1} for DBT, and 1.0–1.2 μg L^{-1} for TBT. Of note, this sensitivity was significantly higher than that provided by the conventional method for extraction and derivatization of organotin species based on LLE because of the pre-concentration applied during the HF-LPME process (ca. 50-fold pre-concentration factors). The relative standard deviations for the intra- and inter-day precisions were below 15% and 20%, respectively, for the three butyltin species. The matrix effects were negligible for the three organotin compounds under study, which consequently resulted in excellent accuracy percentages. Finally, it should be noted that RTs detected in solvent and in food matrix were very similar (± 3 s) and no interfering peaks were observed in blank extracts, whereas the analysis of blanks after injecting samples spiked at 100 μg L^{-1} proved that carryover is negligible.

In general, the analytical performance was comparable to that provided by previously published methods, as reviewed by Chung and Wu (2017). However, our procedure presents the advantage of allowing the simultaneous derivatization, extraction, and preconcentration of the analytes, thereby simplifying and speeding up the entire analytical process. In particular, the methodology optimized here enables considerably reducing total analysis times compared to previous studies dealing with the application of HF-LPME for organotin speciation (Cukrowska et al. 2004). On the one hand, this is because the procedure described by Cukrowska et al. is based on the extraction of pre-derivatized organotin species (Cukrowska et al. 2004), whereas we perform the derivatization and extraction steps simultaneously. Furthermore, it should be noted that we also employ shorter extraction times (10 min vs. 40 min) and GC analysis times (8.7 min vs. 25 min), thereby maximizing the high-throughput capabilities of our method. Interestingly, higher extraction efficiencies were achieved here even using shorter extraction times (80.5–92.1% vs. 52–89%), with similar sensitivity for the quantification of trace organotin compounds (0.8–1.8 μg L^{-1} vs. 0.5–1.5 μg L^{-1}).

Application to Commercial Packed Fruit Juice Samples

The HF-LPME methodology was applied to commercial juice samples packed in Tetra Brik® to investigate the presence of butyltin compounds due to migration from the packaging. The method demonstrated adequate performance for the study of various fruit matrices, including apple, peach, tomato, pineapple, and orange. However, the levels of organotin compounds were found to be below the limits of

Table 2 Summary of the validation parameters for the HF-LPME × GC–MS method optimized (recovery and precision are presented as the average values obtained for the three concentration levels that were assayed; i.e., 10, 100, 1000 μg L^{-1})

	Monobutyltin	Dibutyltin	Tributyltin
Orange juice			
Linearity (calibration curve equation, R^2)	5–1000 μg L^{-1} (y = 1.95x + 0.068, 0.991)	5–1000 μg L^{-1} (y = 0.46x + 0.30, 0.997)	5–1000 μg L^{-1} (y = 0.96x + 0.18, 0.995)
Recovery percentage	83.5%	92.1%	89.8%
Limit of detection	0.86 μg L^{-1}	1.6 μg L^{-1}	1.1 μg L^{-1}
Intraday precision	12.1%	11.5%	11.2%
Inter-day precision	13.2%	15.5%	11.0%
Matrix effect	88.5%	90.5%	89.1%
Accuracy	86.4%	95.2%	91.8%
Apple juice			
Linearity (R^2)	5–1000 μg L^{-1} (y = 1.96x + 0.045, 0.992)	5–1000 μg L^{-1} (y = 0.44x + 0.25, 0.995)	5–1000 μg L^{-1} (y = 0.96x + 0.22, 0.995)
Recovery percentage	89.2%	88.7%	91.6%
Limit of detection	0.82 μg L^{-1}	1.7 μg L^{-1}	1.1 μg L^{-1}
Intraday precision	10.2%	11.8%	12.0%
Inter-day precision	12.1%	13.9%	11.5%
Matrix effect	85.6%	91.8%	88.0%
Accuracy	92.5%	88.4%	87.1%
Peach juice			
Linearity (R^2)	5–1000 μg L^{-1} (y = 1.91x + 0.064, 0.995)	5–1000 μg L^{-1} (y = 0.49x + 0.21, 0.992)	5–1000 μg L^{-1} (y = 0.94x + 0.16, 0.993)
Recovery percentage	81.1%	85.6%	87.5%
Limit of detection	0.90 μg L^{-1}	1.6 μg L^{-1}	1.1 μg L^{-1}
Intraday precision	11.5%	12.6%	12.9%
Inter-day precision	13.7%	15.0%	12.6%
Matrix effect	84.9%	87.4%	83.2%
Accuracy	86.9%	86.2%	89.6%
Tomato juice			
Linearity (R^2)	5–1000 μg L^{-1} (y = 1.88x + 0.075, 0.990)	5–1000 μg L^{-1} (y = 0.41x + 0.31, 0.999)	5–1000 μg L^{-1} (y = 0.94x + 0.25, 0.990)
Recovery percentage	80.5%	84.1%	84.9%
Limit of detection	0.94 μg L^{-1}	1.8 μg L^{-1}	1.2 μg L^{-1}
Intraday precision	12.3%	11.5%	13.1%
Inter-day precision	13.9%	15.3%	12.4%
Matrix effect	88.4%	85.9%	84.9%
Accuracy	90.8%	91.6%	89.6%
Pineapple juice			
Linearity (R^2)	5–1000 μg L^{-1} (y = 1.97x + 0.051, 0.992)	5–1000 μg L^{-1} (y = 0.42x + 0.38, 0.997)	5–1000 μg L^{-1} (y = 0.99x + 0.15, 0.996)
Recovery percentage	92.1%	90.2%	86.3%
Limit of detection	0.84 μg L^{-1}	1.7 μg L^{-1}	1.0 μg L^{-1}
Intraday precision	11.4%	11.4%	11.0%
Inter-day precision	13.0%	14.9%	11.9%
Matrix effect	90.0%	87.2%	86.2%
Accuracy	89.4%	91.8%	85.2%

detection for the three species under study (Fig. 2), in line with previous studies investigating juices transported in PVC containers (Forsyth et al. 1992) and juices packed in different materials (Weber 1987). These results concur with the existing legislation adopted by the European Food Safety Authority (EFSA), which establishes a tolerable daily intake of 0.25 μg kg^{-1} body weight for total organotins (EFSA 2004) and a specific migration limit from the packaging of

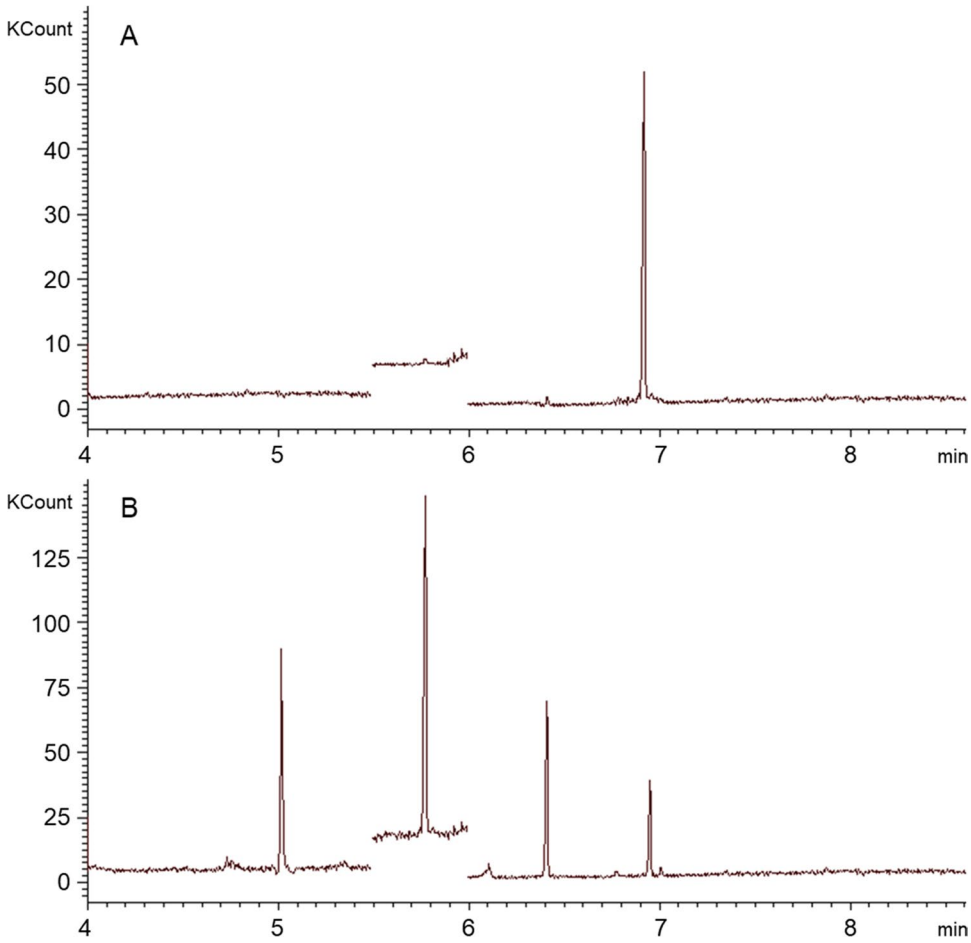


Fig. 2 GC–MS chromatograms obtained by applying the HF-LPME procedure to a juice sample (**A**) and to a juice sample spiked with 100 μg L^{-1} of the three butyltin species (**B**). Monobutyltin (MBT), 5.0 min; dibutyltin (DBT), 5.8 min; tributyltin (TBT), 6.4 min; tetrabutyltin (TeBT, IS), 6.9 min

0.05 mg of tin per kg of food (i.e., 0.14 mg kg^{-1} of organotin compounds expressed as TBT equivalents) (Reg Eu 2016/1416).

Conclusions

HF-LPME stands out as a suitable strategy for the simultaneous derivatization, extraction, and pre-concentration of organotin compounds. The method developed here provided excellent analytical performance in terms of linearity (5–1000 μg L^{-1}), limits of detection (0.8–1.8 μg L^{-1}), recovery (80.5–92.1%), intraday precision (10.2–13.1%), inter-day precision (11.0–15.5%), matrix effect (83.2–91.8%), accuracy (85.2–95.2%), specificity, and carryover. Compared to previous studies dealing with the application of HF-LPME for the analysis of organotin compounds, this methodology considerably reduces total extraction times and improves extraction efficiencies, with comparable sensitivity.

The HF-LPME method optimized and validated in the present study demonstrated adequate performance for the analysis of packed fruit juices, and its application evidenced that levels of butyltin species are negligible in commercial juices of different fruits, including apple, peach, tomato, pineapple, and orange. This methodology could easily be adapted for the analysis of multiple samples, including other beverages, food matrices, and environmental samples.

Author Contribution Conceptualization: R.G.D., A.S., and Á.F.R.; methodology: R.G.D.; validation: R.G.D.; formal analysis: R.G.D.; investigation: R.G.D., A.S., M.S.M., and Á.F.R.; resources: A.S. and Á.F.R.; data curation: R.G.D.; writing—original draft preparation: R.G.D.; writing—review and editing: R.G.D., A.S., M.S.M., and Á.F.R.; supervision: R.G.D., A.S., and Á.F.R. All authors have read and agreed to the published version of the manuscript.

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Data Availability The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Declarations

Conflict of Interest Raúl González-Domínguez declares that he has no competing interests. Ana Sayago declares that she has no competing interests. María Santos-Martíndeclare declares that she has no competing in-

terests. Ángeles Fernández-Recamales declares that she has no competing interests.

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