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Laboratory Experiment

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Determination of Total Arsenic and Speciation in Apple Juice by Liquid Chromatography–Inductively Coupled Plasma Mass Spectrometry: An Experiment for the Analytical Chemistry Laboratory

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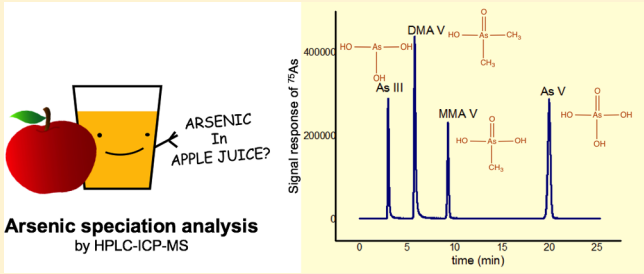
Supporting Information

ABSTRACT: A two-part laboratory experiment was designed for upper-level analytical chemistry students to provide hands-on experience in the use of high performance liquid chromatography (HPLC) for separation and inductively coupled plasma mass spectrometry (ICP-MS) for detection. In the first part of the experiment, the students analyze total arsenic in apple juice purchased from local grocery stores using direct injection ICP-MS. In the second part, different species of arsenic in the same apple juice samples are determined using HPLC–ICP-MS. Quantification is performed based on two methods, standard addition and external calibration curve, to demonstrate how sample matrix can affect the accuracy of the analysis. The experiments provide the opportunity to introduce and/or review several fundamental analytical chemistry concepts: chromatographic separations, mass spectrometry, inductively couple plasma, matrix effects, calibration methods, internal standard, and basic statistical tests. Undergraduate students enrolled in the Instrumental Analysis Laboratory class at the University at Buffalo performed this experiment successfully during the 2015 spring semester.



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INTRODUCTION

Arsenic is a naturally occurring element that is widely distributed in rocks, soil, natural waters, and air.[1] Many forms of arsenic compounds are found in the environment as well as in biological systems, but the toxicity of arsenic is dependent on its chemical form.[2] The inorganic species arsenite (As III) and arsenate (As V) are considered to be the most toxic species; the metabolites monomethylarsonic acid (MMA V) and dimethylarsinic acid (DMA V) exhibit relatively lower toxicities, while the organic forms arsenobetaine (AsB) and arsenocholine (AsC) are considered essentially nontoxic.[3] Immediate symptoms of acute arsenic poisoning include vomiting, abdominal pain, and diarrhea,[4] while death may occur in extreme cases depending on dosage. The United States Environmental Protection Agency (EPA) has classified inorganic arsenic to be a human carcinogen. Exposure to high levels of inorganic arsenic has been linked to the development of skin, bladder, and lung cancer.[5] Chronic exposure to high levels of inorganic arsenic may also exhibit noncancer effects, including skin lesions on hands and feet, peripheral neuropathy, gastrointestinal symptoms, bone marrow depression, and renal system effects.[4] The arsenic metabolites DMA V and MMA V are also used as ingredients in pesticides.[6] These two compounds are classified as possible human carcinogens by the EPA, but they are not as toxic as the inorganic forms.[6] Since not all arsenic species are toxic, simply determining the total arsenic concentration does not provide an accurate evaluation of the potential hazards of arsenic in food products.[3] Because the experiment designed in this laboratory experience relates to the analysis of arsenic in apple juice, it is important to note that the United States Food and Drug Administration (FDA) has proposed an action level of 10 μg/L for inorganic arsenic in apple juice.[7] Thus, if the total arsenic concentration is above 10 μg/L, further speciation analysis to quantify the fraction of inorganic arsenic in the juice is necessary. Consequently, an experiment was designed to quantify each of the following species: As III, As V, DMA V, and MMA V, in addition to total arsenic.

It is well-accepted that by bringing an authentic research problem into the teaching laboratory, undergraduate students become more interested in the subject matter and have a more enriched learning experience in the laboratory.[8−12] Arsenic in the environment is a real problem that continues to be a global concern, and it becomes alarming when our food and beverages are contaminated with arsenic.[13] To date, there has been no article published in this journal that describes an inductively

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coupled plasma mass spectrometry (ICP-MS) experiment for trace analysis and speciation of arsenic in food or beverages. While a review article has been published in this journal addressing the importance of determining the speciation of arsenic in drinking water, and describing the various separation and detection methods for arsenic analysis,[13] no laboratory experiment has been published on the use of modern instrumentation for the analysis of arsenic in food and beverages. Therefore, the paper described here provides an example of a successful class activity that reinforces the concept of elemental speciation and quantification through the analysis of a widely consumed beverage, apple juice, using high performance liquid chromatography (HPLC) coupled to an ICP-MS (HPLC−ICP-MS). The ICP-MS is an excellent technique for the determination of arsenic. Introducing ICP-MS in a higher level analytical chemistry class is currently needed because ICP-MS has become one of the most powerful multielement trace analysis techniques used in food,[14,15] agricultural,[16,17] environmental,[18,19] and pharmaceutical analysis.[20,21] The articles published in this journal that have reviewed the principles and applications of ICP-based instrumentation[22,23] have focused only on the use of ICP in total elemental analysis[24−28] and did not include a discussion nor demonstration of metal speciation. Finally, it has been shown that real-life applications of instrumental analysis can stimulate the students' interest and generate lively class discussions to answer relevant day-to-day questions.[8−12] For example, an ICP-based experiment to determine whether an orange juice is "freshly squeezed" or from a concentrate based on its calcium and magnesium content proved to be an effective way for students to gain confidence in using modern instruments on their own.[27] Therefore, the experiment using HPLC−ICP-MS described in this paper for the quantification of total arsenic and the various species of arsenic in apple juice will provide a unique laboratory experience to undergraduates. Because of the practical application of the results obtained from these experiments, it is expected that this laboratory exercise will generate excitement and interest among the students, and provide an effective way of teaching some difficult concepts in quantitative analysis. In most universities, the ICP-MS instrument is typically housed in a department instrument facility; therefore, the cost and maintenance related to the introduction of this laboratory experiment should not be an issue specific to the addition of this lab experiment in an Analytical Chemistry class. An instrument user-fee can be assessed from the student laboratory fees, which can be added into the instrument center funds for future maintenance needs.

To stimulate interest within the instrumental analysis class, the students are asked to bring samples of their favorite commercial apple juice for analysis. The main objectives of this experiment are to (1) provide the students hands-on experience in using ICP-MS for elemental quantification, (2) learn the concept of ion-pair in reversed phase HPLC, and (3) compare two different calibration methods (standard addition versus external calibration) to demonstrate the importance of addressing matrix effects, and how they may impact the accuracy of a quantitative analytical method. This experiment is suited for students who have an understanding of the basic concepts of mass spectrometry, chromatography, and quantitative chemical analysis, as presented in the undergraduate instrumental analysis lecture class. This experiment reinforces many analytical concepts discussed in the lecture, including separation, detection, matrix effects, methods of quantification, statistical analysis, and data interpretation.

EXPERIMENTAL PROCEDURE

Reagents

All dilutions are performed using the HPLC mobile phase consisting of 2.5 mM K_2HPO_4 and 5 mM tetrabutylammonium hydroxide in HPLC grade water, adjusted to pH 6 with phosphoric acid, and filtered through a 0.45 μm nylon membrane filter by the laboratory instructor prior to class. The following solutions are made available to the students in the laboratory: 10 μg/L germanium (Ge) solution (diluted from Fluka 1000 mg/L Ge standard solution with HPLC mobile phase, used as an online internal standard), and 200 μg/L arsenic standard solution (diluted from Inorganic Ventures 1000 μg/mL As V standard solution with the HPLC mobile phase, used to prepare the standard calibration curve for total arsenic analysis). Groups of ideally 2−3 students are asked to prepare 50 mL arsenic standard solutions (in HPLC mobile phase) at the following concentrations: 5, 10, 15, and 20 μg/L to establish an external calibration curve for total arsenic determination. In addition, solutions containing 10 mg/L each of As III, As V, MMA V, and DMA V are freshly prepared immediately before the laboratory period by the laboratory instructor. As_2O_3 is dissolved in ultrapure water to produce an As III solution, As_2O_5 to produce an As V solution, disodium methyl arsenate hexahydrate to produce a MMA V solution, and dimethlyarsenic acid to produce a DMA V solution. Each arsenic species standard is combined into a mixture to make a 10 μg/L working solution using the HPLC mobile phase as the diluent.

Instrumentation

The method presented here uses a Thermo X-Series 2 ICP-MS (Thermo Fisher Scientific Inc.) system equipped with a Thermo HPLC Spectra and an AS3000 autosampler system (Thermo Fisher Scientific Inc.). Note that while this particular HPLC instrument has an autosampler, it is not a requirement to have a successful experiment. Manual injection will work just as well provided the instructor demonstrates proper operation of the manual injector. The HPLC was controlled by Thermo Xcalibur software; ICP-MS data were processed using the Thermo PlasmaLab software. However, this experiment can be modified to suit any HPLC−ICP-MS system. For the specific instrument described in this paper, the HPLC and ICP-MS conditions are listed in Table 1. Separation of arsenic species is achieved using a reversed-phase Synergi Fusion-RP C18 HPLC column (4.6 mm i.d. × 250 mm length, 4 μm, 80 Å, Phenomenex Inc., Torrence, CA) equipped with a guard column of the same stationary phase (Fusion-RP C18 3.0 mm i.d. × 4 mm length, Phenomenex Inc., Torrence, CA). The mobile phase consists of a 2.5 mM K_2HPO_4 and 5 mM tetrabutylammonium hydroxide solution in water (adjusted to pH 6 with phosphoric acid). The HPLC is operated at a flow rate of 1 mL/min, and with a total run time of 25 min. A 10 μg/L Ge solution serves as online internal standard to account for signal drift.

The ICP-MS requires tuning prior to use in order to optimize performance because parameters may change slightly between days. For the analysis of total arsenic, the collision cell technology (CCT) was used, with He/7%H_2 as a collision-reaction gas such that interference from $ArCl^+$ (m/z 75) can be avoided because it has the same m/z as As^+. Although the CCT

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Table 1. Instrument Operating Conditions for ICP-MS and HPLC

Instrument	Parameter	Conditions[a]
ICP-MS	RF power	1350 W
	nebulizer gas flow	0.8 L/min
	auxiliary gas flow	0.8 L/min
	plasma gas flow	15 L/min
	nebulizer	concentric
HPLC	column	Synergi Fusion-RP C18 column (4.6 mm × 250 mm, 4 μm particle size, 80 Å pore size)
	mobile phase	2.5 mM K_2HPO_4 and 5 mM tetrabutylammonium hydroxide in water adjusted to pH 6
	flow rate	1 mL/min
	inject volume	100 μL

[a]May slightly change on the basis of daily performance.

mode increases the selectivity of a method, it also results in decreased sensitivity and therefore is not ideal for analysis of elements at extremely low concentrations.

Laboratory Activities for Students

Prior to the laboratory period, the students are assigned to read background information on the occurrence and toxicity of arsenic in the environment (e.g., an article from the World Health Organization, titled "Exposure to Arsenic: A Major Public Health Concern"). Proper handling of samples containing arsenic should be implemented on the basis of instructions outlined in the safety data sheet (SDS) for all related arsenic compounds (see Supporting Information for detail). The relevant material would have been assigned to be read prior to the laboratory period; students' knowledge can be assessed with a quiz on the assigned readings. At the start of the laboratory period, the instructor also reviews with the students all the safety precautions in the laboratory as they pertain to the handling of arsenic-containing samples, as well as the waste generated during the experiment (see Supporting Information). Preparation of stock standard solutions, pipetting, and dilution are skills the students developed in prior experiments. To minimize the risk of exposure, however, the students do not have direct access to the pure arsenic compounds; the instructor prepares all the stock solutions and places them in the appropriate area under the hood.

The laboratory experiment consists of two parts; each part can be completed over the course of a 3-h laboratory period. A prelab discussion takes place for about 45 min, which includes a review of the chromatographic separations, atomic spectroscopy (and advantages/limitations of ICP-MS), as well as a discussion on the safe handling of arsenic solutions in the lab. The discussion is followed by the preparation of samples and calibration solution, which takes about 1.5 h. Then, the students are shown how to set up the HPLC and ICP-MS (i.e., perform tuning and calibration as well as creating a worklist), export data, and perform data processing. The instructor may also choose to postpone the review of concepts after the samples have been loaded into the instrument (if it is equipped with an autosampler) to make sure that the students have enough time to prepare their samples and be able to load the instrument with the samples before the 3-h lab period ends.

Ideally, 2−3 students work together as a group, and each group is asked to bring 3 brands of apple juice purchased from a local grocery store for arsenic analysis. Students need to record the brand name and other important information found on the label (place of manufacture, batch number, etc.). Since the samples are already in solution form, dilution and filtration through a 0.45 μm polypropylene membrane are sufficient sample preparation steps for both total arsenic and speciation analysis. To save time and materials, and to obtain the triplicate calibration solutions required for constructing the standard calibration curve, each group prepares one set of external calibration solutions and shares those solutions with the other groups.

Lab Period 1. During the first laboratory period, students determine total arsenic concentrations in the juice samples using direct injection ICP-MS. The concentrations are determined using two types of quantification methods: external standard calibration curve and the standard addition method. For quantification by external standard calibration, the calibration solutions are run before and after analysis of the apple juice samples. Quantification using standard addition is performed as follows: five 2.5 mL portions of the filtered juice samples are transferred into separate 5 mL volumetric flasks; a 200 μg/L standard arsenic solution is added into each volumetric flask such that the final concentrations of added arsenic are 0, 0.5, 1, 1.5, and 2 μg/L, respectively; finally, the solutions are brought up to 5 mL total volume using the HPLC mobile phase. The added concentrations used in the standard addition method should be closer to the results quantified by external calibration curve. The concentrations of the standard added may be adjusted by the instructor, depending on the expected concentrations of analytes in the samples. These standard addition samples are then analyzed by ICP-MS. For total arsenic analysis, each sample takes about 1.5 min; students can be divided into three groups of 3−5 persons in order to finish the experiment in one lab period. However, should the class size be too big to accommodate more than 3 groups, the instructor can break up the analysis into two lab periods, one for external calibration and one for the standard addition method.

The laboratory instructor shows students how to test the performance of the ICP-MS and the proper operation of the software to create a running method before setting up a sequence for analysis. An HPLC mobile phase solution serves as the instrument blank. The instrumental sequence for sample analysis is set up for the entire class and allowed to run while the students prepare the solutions for the second part of the experiment. If instrument time is limited, one group can analyze samples using external calibration curve, and another group can quantify the samples using the standard addition method; then the two groups can share data with each other and compare results. A paired *t*-test is then used to compare the results of the two methods.

Lab Period 2. For the second part of the experiment, the students are asked to find information on the differences in the toxicity of the various arsenic forms in order to understand the importance of determining the different arsenic species in food samples. A review of liquid chromatography is also important, particularly the concepts of ion-pairing and reversed-phase chromatography. The students should be asked about the necessity of using tetrabutylammonium hydroxide as an ion-pair reagent, the purpose of adjusting the pH, and a prediction of the order of elution of the various arsenic species at the experimental conditions described. Specific HPLC terminologies, such as retention time, resolution, sensitivity, and specificity, could be reviewed in class. A prelab discussion on these basic chromatography terms and the analytical concepts

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being demonstrated in this laboratory experiment is necessary. These discussions can be conducted while the students are waiting for the HPLC−ICP-MS analysis of the samples to be completed.

It is recommended that the laboratory instructor connect the HPLC system to the ICP-MS prior to the start of the laboratory period to avoid delay. The chromatographic column should be equilibrated with the mobile phase at the start of the laboratory period to decrease wait time prior to sample injection. Since the presence of matrix effects should have already been demonstrated in the first part of the experiment, a single-point standard addition method is used for quantification of each arsenic species. The single-point standard addition method works well by adding an analyte concentration close to that of the real sample. In this particular class experiment, the concentration added for each arsenic species was 5 μg/L because this is close to the total arsenic concentrations present in most of the samples (as shown in Table 2). However, the use of a 1 μg/L concentration for standard addition was also tested by the instructor, but the results showed that a 5 μg/L single-point standard addition is more appropriate because this concentration resembles the expected concentrations of total arsenic in the samples.

Table 2. Comparison of the Total Arsenic Concentrations in Apple Juice Calculated Using Two Different Quantification Techniques (External Calibration Curve vs Method of Standard Addition)

Sample ID	External Calibration Curve Result (μg/L)	Standard Addition Result (μg/L)	Difference (%)[a]
Juice 1	2.09	1.37	52.6
Juice 2	1.68	1.34	25.4
Juice 3	4.16	2.20	89.1
Juice 4	6.91	3.53	95.8
Juice 5	4.52	2.24	102
Juice 6	2.32	1.45	60.0
Juice 7	2.36	1.64	43.9
Juice 8	5.41	3.10	74.5
Juice 9	8.14	3.71	119
Juice 10	20.2	10.3	96.1
Juice 11	7.32	3.71	97.3

[a]Difference (%) = (standard curve result − standard addition result)/standard addition result × 100%

The students need to prepare the apple juice samples by diluting the filtered juice 1:1 with the HPLC mobile phase using a pipet (mix 2 mL juice with 2 mL mobile phase, in a 15 mL metal free centrifuge tube, and shake well). Then, 1.5 mL of each diluted sample is transferred to an HPLC vial. To prepare the standard addition samples, a duplicate sample of each apple juice is spiked with a known standard by mixing 2 mL of juice and 2 mL of the 10 μg/L arsenic standard mixture. Since each sample run takes about 25 min, all samples are run in a sequence, and the students are asked to come back for their data at a later time. Each apple juice sample and its corresponding standard addition sample should be injected one after the other to minimize potential errors due to instrument drift. A blank sample should be run between each pair of samples in order to assess possible carryover.

HAZARDS

Personal protective equipment including safety goggles, lab coat, and gloves should be worn all the time for adequate protection. Students must read the safety information on all arsenic compounds to be used in this class prior to handling these chemicals (see Supporting Information for details). The arsenic standard solutions and internal standard solution contain heavy metals and must be used with extreme care. Hazard statement and prevention of potential exposure to arsenic compounds used in this class are listed in the Supporting Information. For consistency and safety considerations, arsenic related stock solutions are prepared by the instructor prior to class and can be used by students. All wastes are properly disposed. Sample preparations are done under the fume hood.

RESULTS

This laboratory experience was successfully introduced to students in the Instrumental Analysis Laboratory class at the State University of New York at Buffalo (SUNY-Buffalo) during the 2015 spring semester. Specific data and procedures can be found in the Supporting Information.

An example of an external standard curve for total arsenic determination, generated by the instructor, is shown in Figure 1. The curve was constructed with the ratio of the analyte signal/internal standard signal on the y-axis, and the arsenic concentrations on the x-axis. The addition of an internal standard accounts for analyte loss during sample preparation

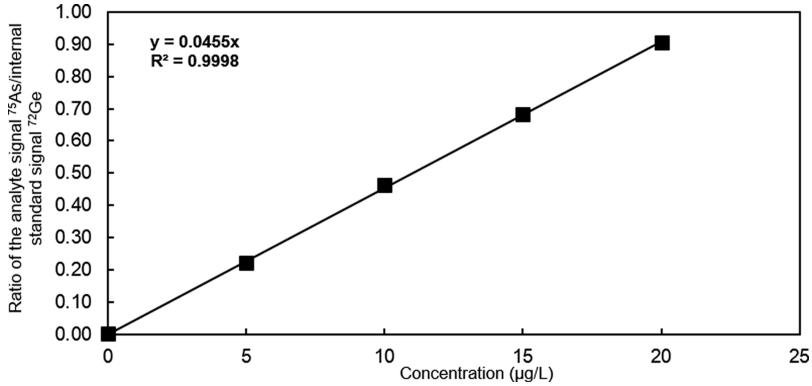

Figure 1. External calibration curve, generated by the instructor, for the determination of total arsenic (in μg/L) by direct injection ICP-MS. The y-axis is normalized by the signal of the internal standard ^{72}Ge to account for variation in sample injection, sample volume, and instrument drift. Instrumental operating conditions are listed in Table 1.

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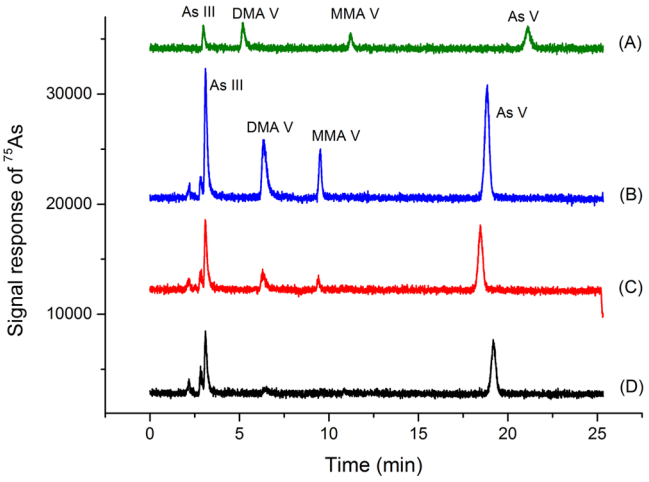

Figure 2. Chromatograms generated by the instructor for arsenic speciation analysis by HPLC–ICP-MS. Chromatograms corresponding to (A) 1 ppb standard mixture; (B) an apple juice sample with 5 ppb standards added; (C) an apple juice sample with 1 ppb standards added; and (D) an apple juice sample without any standard added. Arsenic species in the standards include arsenite (As III), monomethylarsonic acid (MMA V), dimethylarsenic acid (DMA V), and arsenate (As V). The *x*-axis is retention time, and *y*-axis is the signal response of arsenic as ^{75}As. Instrumental operating conditions are listed in Table 1.

and standard dilutions. If there are some matrix effects, it is expected that students will observe different results from the two quantification methods, using standard addition and external standard. This can be seen in Table 2 for the analysis of 11 different juice samples using these two different methods. The large range observed in percentage difference between the internal and external calibration illustrates how matrix components affect the accurate quantification of As^+ based on m/z 75, which may be attributed to the presence of polyatomic interferences with the same mass-to-charge ratio. Students need to obtain the percentage differences from the generated data, and explain the potential sources of these differences.

Results from the HPLC–ICP-MS analysis should provide information on the arsenic speciation, and reveal the concentrations of the most toxic arsenic species, if present. By running each standard individually, and then a mixture containing the arsenic standards, the students can identify the retention time for each particular arsenic species. After running the apple juice samples by HPLC–ICP-MS, the students are asked to obtain the percentage of each species present in the samples and identify the most toxic arsenic forms. Figure 2 shows several sample chromatograms and demonstrates the benefit of using the standard addition technique in the identification of analytes that exhibit retention time shifts due to matrix effects. Table 3 shows the results for 11 different juices analyzed via HPLC–ICP-MS.

CONCLUSIONS

This is an attractive and highly relevant undergraduate analytical chemistry experiment that provides the students a unique opportunity to reinforce several analytical chemistry concepts that they should have learned in the lecture class. The students gain hands-on experience in measuring toxic elements in food samples through modern analytical instrumentation, using HPLC coupled to the ICP-MS system. Students learn to appreciate how analytical methods can be applied to solve real-life problems and understand the importance and challenges in determining the speciation of toxic elements. Although this paper presents a fairly specific element (arsenic) in a particular food sample (apple juice), the laboratory experiment can be expanded to other toxic elements and a variety of other food and drink samples. The data obtained from these experiments should facilitate the understanding of the different analytical concepts discussed in the lecture portion of the Analytical Chemistry class.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available on the ACS Publications website at DOI: 10.1021/acs.jchemed.6b00076.

Additional material for instructors, students, specific data, and procedures (PDF, DOCX)
Postlab assessment (PDF, DOCX)

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Table 3. Concentrations of the Different Arsenic Species in Apple Juice, As Determined by HPLC–ICP-MS Using Standard Addition Technique

Sample	As III (μg/L)[a]	DMA V (μg/L)[a]	MMA V (μg/L)[a]	As V (μg/L)[a]	Sum (μg/L)[a,c]	Total As (μg/L)[a]	Identified Species (%)[d]
Juice 1	ND[b]	ND	ND	0.420	0.420	1.37	31
Juice 2	ND	ND	ND	0.680	0.680	1.34	51
Juice 3	ND	ND	ND	2.20	2.20	2.20	100
Juice 4	1.09	ND	0.610	0.98	2.68	3.53	76
Juice 5	0.490	ND	ND	1.23	1.71	2.24	76
Juice 6	ND	ND	ND	1.04	1.04	1.45	71
Juice 7	1.76	ND	ND	0.460	2.21	1.64	135
Juice 8	ND	ND	ND	1.80	1.80	3.10	58
Juice 9	0.130	ND	ND	3.79	3.92	3.71	106
Juice 10	5.01	ND	ND	4.59	9.59	10.3	93
Juice 11	ND	ND	ND	1.29	1.29	3.71	35

[a]Results are expressed as μg elemental arsenic/L instead of compound concentration. [b]ND means not detected. [c]The sum of identified arsenic species in the prior four columns. [d]Percentage means the sum of four arsenic species quantified by HPLC–ICP-MS, relative to the total arsenic concentration in the same apple juice sample quantified by direct injection ICP-MS.

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Notes

The authors declare no competing financial interest.

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