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JOURNAL OF AGRICULTURAL AND FOOD CHEMISTRY

Lead in Women's and Children's Vitamins

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A survey was conducted to determine the extent of lead (Pb) contamination in vitamins labeled for use by women and children. The Pb content of 324 multivitamin−mineral products was determined using microwave assisted nitric acid digestion and inductively coupled plasma mass spectrometry. Cryogenic grinding was used to composite soft samples such as oil filled capsules and candy-like products such as gummies and jelly beans. Estimates of Pb exposures from consumption of these products were derived for four population groups: young children (0−6 yrs), older children (7+ yrs), pregnant or lactating women, and adult women. The estimated median and maximum Pb exposures were 0.123 and 2.88 μg/day for young children, 0.356 and 1.78 μg/day for older children, 0.845 and 8.97 μg/day for pregnant and lactating women, and 0.842 and 4.92 μg/day for adult women. The overall median value for Pb exposure was 0.576 μg/day. Five samples would have provided exposures that exceeded 4 μg/day. Estimates of exposures were assessed with respect to safe/tolerable exposure levels that have been developed for the specific age and sex groups. These safe/tolerable levels are referred to as the provisional total tolerable intake levels (PTTI) and are 6, 15, 25, and 75 μg Pb/day for young children, older children, pregnant or lactating women, and adult women, respectively. Estimates of Pb exposures were below the PTTI levels for the four population groups. Median and maximum values were used instead of the mean and standard deviation because of the skewed distribution of results toward lower mass fraction and exposure.

KEYWORDS: Dietary supplements; vitamins; cryogenic grinding; Pb; microwave digestion; ICP-MS

INTRODUCTION

The US Food and Drug Administration (FDA) is charged with regulating vitamins and dietary supplements under the Dietary Supplement Health and Education Act of 1994 (DSHEA), which amended the Federal Food, Drug and Cosmetic Act (*1*). Under DSHEA, dietary supplement manufacturers are responsible for substantiating the safety of the ingredients used in manufacturing their products. The FDA is responsible for taking regulatory action against unsafe dietary supplement products after they reach the market. In 2007, the FDA published regulations requiring production of dietary supplements under current good manufacturing practice (cGMP). This regulation requires manufacturers to ensure that dietary supplements contain what they are labeled to contain and are not contaminated with harmful or undesirable substances such as pesticides, heavy metals, or other impurities.

The U.S. dietary supplement industry had sales approaching $23 billion in 2006 with consumer sales of vitamins accounting for approximately one-third of total supplement sales. Multivitamin supplements make up about 60% of vitamin sales (*2*). Use of vitamins is very popular among women. A survey conducted in 2007 reported that 40% of women took a daily supplement containing folic acid (*3*).

Lead is known to be toxic in humans and can cause many harmful physiological effects even at low levels (*4, 5*). Blood Pb levels as low as 10 μg/dL have been shown to adversely affect children's IQ (*6*). Recent studies have shown that blood Pb levels lower than 5 μg/dL can negatively impact end of grade test scores and cognitive skills (*7, 8*). The FDA has developed safe/tolerable Pb exposure levels for particular age and sex groups (*9*). These safe/tolerable exposure levels are referred to as the provisional total tolerable intake levels (PTTI). The current PTTI levels of Pb for young children and pregnant and lactating women are 6 and 25 μg/day, respectively. A recent limited survey of multivitamin supplements by an independent testing firm found that a woman's vitamin sample contained Pb. Intake of Pb from this product, if taken as directed, would have been 15 μg/day (*10*). Several studies have shown that vitamins, herbal supplements, and traditional folk medicines may be contaminated with Pb and other toxic metals (*11–14*). This report presents results of Pb content in a comprehensive survey of multivitamin−mineral supplements labeled for use by children and women.

The use of inductively coupled plasma mass spectrometry (ICP-MS) for elemental analysis is well established in the

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literature and has been used in previous studies to investigate toxic metals in dietary supplements (*15, 16*). The technique has the sensitivity necessary to quantitate Pb levels in vitamins and allowed for the possibility of collecting data on other elements. For this project, multivitamin−mineral supplement products were composited and digested using a microwave assisted nitric acid digestion and analyzed for Pb by ICP-MS.

MATERIALS AND METHODS

Instruments. Samples were composited with an analytical mill (A11 Basic with stainless steel beater, IKA Works, Inc., Wilmington, NC). Analytical portions were digested with a microwave digestion system (MARS, CEM Corp., Matthews, NC) equipped with infrared (IR) sensing temperature control. The microwave digestion system could deliver a maximum of 1600 W. Applied power was varied to allow controlled temperature ramping. IR sensors determined the temperature of each vessel as the carousel rotated. Microwave vessels (MARSX-press, CEM Corp.) were 55 mL capacity, Teflon PFA lined and equipped with self-regulating pressure caps.

Lead determinations were performed with an Agilent 7500ce ICP-MS (Agilent, Santa Clara, CA). The 7500ce is a quadrupole based instrument equipped with a reaction/collision cell for interference reduction, peltier cooled Scott double-pass spray chamber and a MicroMist nebulizer (Glass Expansion, West Melbourne, Victoria, Australia). The built-in peristaltic pump was used to deliver the analytical solution to the nebulizer at 0.4 mL/min and the internal standard solution at 0.02 mL/min. The analytical solution and internal standard solution were merged with a glass Tee fitting.

Reagents. ASTM type 1 grade water was used for preparation of reagents, standards, and analytical solutions. Standard solutions and internal standards were prepared from commercial ICP-MS grade single-element analyte solutions (High-Purity Standards, Charleston, SC). Trace Metals grade (TMG) nitric acid (Thermo Fisher Scientific, Pittsburgh, PA) was used for cleaning laboratory ware and digestion vessel liners. High-purity double distilled nitric and hydrochloric acids (Optima grade, Thermo Fisher Scientific) were used for sample digestion and standard solutions.

Samples and Reference Materials. Three hundred twenty-four multivitamin−mineral products labeled for use by women or children were purchased in 2007 from several sources via the Internet. Samples were chosen at random without respect to market share, brand or other factors. Many of the samples were labeled for a smaller subgroup such as: prenatal women, postnatal women, lactating women, premenopausal women, postmenopausal women, teen boys, teen girls, preteen boys, preteen girls, and children of various ages including infants. One brand had three different formulas depending on race or ethnicity (African American, Caucasian and Hispanic). Samples consisted of tablets, capsules, soft gel capsules, powders, liquids and various candy-like products such as gummy animals, gum drops, and jelly beans. Most were in the form of a tablet or capsule (274), but there were 8 powders, 21 liquids and 21 candy-like. Maximum recommended daily serving amounts ranged from 1 to 18 units (tablets, capsules, etc.) corresponding to 0.6 to 36 g.

The method quality assurance included using the following reference materials from the National Institute of Standards and Technology (NIST; Gaithersburg, MD): *Ephedra sinica* Stapf Commercial Extract (SRM 3242), Ephedra-Containing Solid Oral Dosage Form (SRM 3243), and Ephedra-Containing Protein Powder (SRM 3244). Each batch of samples was prepared with SRM 3242 and SRM 3243. Some batches also included SRM 3244.

Contamination Control. Two mills were used to composite samples. One mill was assigned to even numbered samples and one to odd numbered samples. This was done to aid in diagnosing possible contamination issues in the event that a sample high in Pb was found. After each sample, mills were wiped with damp paper towel, rinsed with tap water, cleaned with a sponge soaked in warm Micro-90 laboratory cleaner (International Products Corp., Burlington, NJ), rinsed with warm tap water, rinsed with deionized water (DI), and dried in a class 100 laminar flow polypropylene (PP) clean hood. Mills were first rinsed with acetone after compositing oily samples. Samples were composited in a normal laboratory environment and transferred to 50 mL PP centrifuge tubes (Falcon Blue Max, sterile, 352098, Becton Dickinson Labware, Franklin Lakes, NJ). These tubes were found to be free from Pb contamination and were used without cleaning. Composited samples were taken to a class 1000 clean room laboratory for subsequent actions. Acid addition to the microwave vessel and final dilution were performed in a class 100 laminar flow PP clean hood. Microwave digestion vessels were cleaned with 10 mL TMG nitric acid using the following program: 1600 W maximum power, 20 min ramp to 200 °C, hold 3 min. Digested solutions were transferred to 250 mL PP specimen containers (Falcon, sterile, 354017, Becton Dickinson Labware, Franklin Lakes, NJ). These containers were found to be free from Pb contamination and were used without cleaning. Determination by ICP-MS was performed in a class 1000 clean room laboratory. Polystyrene autosampler cups were cleaned with 2% nitric acid and rinsed with reagent water and dried before use. Tacky floor mats were used outside of clean room laboratories to remove dust from shoe soles. These measures effectively reduced contamination to levels below analytical concern.

Quality Control. Replicate analytical portions of each sample composite were analyzed. A typical analytical batch consisted of two method blanks, two reference materials, two fortified analytical portions and 17 replicate portions of sample composite for a total of 40 vessels which filled the microwave carousel. Some batches had fewer sample composites due to scheduling or grouping of similar sample types. 0.2 μg of Pb was added to fortified analytical portions prior to digestion. Standardization was verified by analyzing a check solution after every 10 analytical solutions.

Sample Compositing. A 20-unit composite was used to obtain the analytical portions to ensure accurate representation of the sample. This is recommended by the US Pharmacopeia and commonly used by others in similar studies (*17, 18*). Typical analytical portions for solid samples were 0.3 − 0.5 g, which necessitated obtaining a finely ground composite. The variety of sample types presented a challenge. The impact beater in the analytical mill spins at a maximum of 28000 rpm which equates to a circumferential speed of 53 m/s. The extremely high speed of the beater reduced tablets and hard shelled capsules to a fine powder in 2−3 s. However, gel caps were not reducible to a homogeneous composite in the same fashion. These types of samples were usually filled with a paste or oil not amenable to impact pulverization. Cryogenic grinding, although still not commonly used in trace element analysis, has been successfully used for a variety of samples that might otherwise present compositing challenges (*19–23*). Several studies have compared cryogenic grinding to conventional grinding techniques (*24–26*). Several researchers investigated particle size distribution after cryogenic grinding and concluded that better homogeneity characteristics were achieved with both unchallenging and otherwise difficult to homogenize samples (*20, 23, 26, 27*). Many materials become brittle near liquid nitrogen temperatures (−196 °C) and this property contributes to the utility of cryogenic grinding.

The following procedure was employed: Twenty capsules were added to the mill cup. Liquid nitrogen was slowly added until samples were covered. More liquid nitrogen was added when the first portion evaporated to ensure the samples were completely frozen. When the second portion of liquid nitrogen evaporated, the cup was attached to the mill and samples were ground for 2−3 s. This short grinding time was sufficient and prevented sample heating. The composite was quickly transferred to one of the PP containers mentioned above. Using this procedure, even fish oil capsules became brittle and were quickly reduced to a fine powder. Thawed samples had a thick pasty consistency with finely ground pieces of the gel capsule dispersed throughout the oil. Candy-like samples were of three types: jelly beans, gum drops, and gummies. The soft nature and elastic properties of these samples eliminated the impact mill at room temperature as a choice for compositing. Six of the candy-like samples were composited by melting and stirring. Twenty units of a sample were placed in a 250 mL PP cup and placed in the microwave oven. Power was set to 300 W and applied for approximately 25 s. If the sample had not melted after 25 s, then power was applied for 10 s intervals until melted. The sample was then removed and stirred with a Teflon spatula until the appearance was uniform. Although this procedure appeared to provide a quick and

easy procedure for compositing candy-like samples, the heating and cooling cycle changed the physical properties of these samples. Samples became very hard and rubbery, which made removing an analytical portion extremely difficult even when a metal spatula was used. Therefore cryogenic grinding was applied to the rest of the candy-like samples. Although reduced to a fine powder immediately after grinding, the candy-like samples solidified into a soft solid mass after a few hours. However, the analytical portion could easily be removed with a plastic spatula. An in-house dried corn kernels reference material (CFSAN CK-01) known to be low in Pb was cryogenically ground, digested and analyzed to assess contamination from the embrittling and milling procedures. Liquid samples were shaken and sampled with a 1 mL positive displacement pipettor (Rainin Pos-D MR-1000, Rainin Instruments, Oakland, CA). Powder samples were shaken, stirred and sampled directly.

Sample Digestion. The analytical portion size for solid samples was 0.4 ± 0.2 g with a few exceptions. One mL portions were used for liquid samples. Although the self-venting microwave digestion vessels can handle a larger mass, portion size was restricted to approximately 0.4 g because of the wide variety of ingredients that present a challenge to digestion (e.g., oils, waxes) or present safety concerns (e.g., glycerin). Additionally, many samples were high in sugar, the presence of which can cause a sudden run away reaction if the microwave power is not applied with adequate feed back control.

Two replicate portions of each sample composite were prepared for analysis using microwave assisted high pressure nitric acid digestion. A few samples were prepared with up to 7 replicates if unused positions were available in the microwave turntable. Analytical portions were weighed into microwave digestion vessels on an analytical balance. Vessels were then moved to a top loading balance and 10 g (7 mL) double distilled nitric were added via a Teflon squeeze bottle. This provided a convenient way to add acid and rinse the sides of the vessel in one step. The long, narrow shape of the vessels made it difficult to get the entire sample at the bottom of the vessel, thus necessitating the need to rinse down the sides. Vessels were capped and placed in a microwave oven and digested. The digestion program was a 25 min ramp at max (1600 w) power to 200 °C. This temperature was held for 10 min. After cooling to <50 °C, the solution was transferred to a tared 250 mL PP container containing five mL of 1 + 4 double distilled HCl. Reagent water was then added to a final volume of 200 mL. The final volume was determined gravimetrically. HCl was added to stabilize elements such as mercury for possible analysis at another date. Solutions were colorless to yellow with many exhibiting some degree of cloudiness. After settling overnight, solutions that were still cloudy were centrifuged in 50 mL PP tubes at 1200 rpm for 10 min. Approximately 40 mL was transferred to a 50 mL PP tube for storage and analysis. The initial cloudiness exhibited by some digestion solutions was probably due to silica or titanium dioxide. Silica was an ingredient in many of the vitamins and occurs naturally in some herbal products. The two ephedra reference materials (SRM 3242 and SRM 3243) prepared with each batch contain significant amounts of silicon and exhibited cloudiness after digestion. Since complete recoveries were obtained, it was assumed that the Pb was solubolized by the digestion and thus any undissolved residue was not a concern.

Because of the wide variety of possible ingredients in vitamins in a digestion batch, a relatively long ramp to maximum temperature was used to heat the samples slowly and maintain control when certain components, such as sugar, reached their oxidation temperature. This strategy prevented run away exothermic reactions and allowed the microwave oven program to maintain control of the digestion. A typical digestion profile showed a spike in temperature at approximately 100−120 °C. The spike would typically reach 140−160 °C. The microwave oven program decreased power until the exothermic reaction was completed and the temperature was reduced to a level consistent with the 25 min ramp. Power was again applied to complete the temperature ramp.

Determination of Pb. ICP-MS instrument parameters are listed in **Table 1**. Three isotopes of Pb were summed to account for possible isotopic variation between standards and samples. The instrument was tuned for proper sensitivity before each analytical run. Standardization was performed using a blank and a 10 ng/mL Pb solution in a matrix of 2% v/v HNO_3 and 0.5% v/v HCl. A linear curve fit was performed by the instrument's software. All digestion solutions had Pb concentrations <10 ng/mL. The Bi internal standard compensated for matrix effects. Extract lens voltage was set to zero to minimize build-up of deposits and matrix induced change in response during the analytical run. He gas (4.4 mL/min) was used although it is not usually required for Pb analysis.

Table 1. ICP-MS Parameters

Pb isotopes monitored	206, 207, 208
internal standard	^{209}Bi
dwell time	0.1 s
scans	3
RF power	1550 W
sampling depth	8 mm
nebulizer type	glass concentric
carrier gas	1 L/min
makeup gas	0.15 L/min
spray chamber temp	2 °C

RESULTS AND DISCUSSION

Method Performance. The method detection limit was estimated using twelve method blanks fortified at 0.01 ng/mL before digestion and then analyzed. The detection limit was defined as $2t\sigma$ where t is the one-sided Student's t value at 95% confidence and σ is the standard deviation of the fortified method blank results. The estimated detection limit was calculated as 0.0054 ng/mL which equates to 0.0011 mg/kg and 0.0027 mg/kg assuming a 1 and 0.4 g analytical portion for liquid and dry solid matrices, respectively.

Samples were divided among 24 batches. A total of 51 method blanks were prepared and analyzed among the batches. The mean blank Pb concentration was <0.0054 ng/mL with a standard deviation of 0.0026 ng/mL. Only two method blanks were >0.0054 ng/mL, the highest at 0.0097 ng/mL. The blank levels demonstrated an extremely low level of contamination from reagents and the laboratory environment. Analysis of the in-house dried corn kernels reference material (CFSAN CK-01) showed no Pb contamination from the grinding process.

Recoveries from reference materials were excellent. NIST SRM 3242 and SRM 3243 were prepared and analyzed with each batch. The mean Pb result (n = 24) for SRM 3242 was 0.369 mg/kg with a standard deviation of 0.0075 mg/kg. The certified Pb value for SRM 3242 is 0.362 mg/kg. The mean Pb result (n = 24) for SRM 3243 was 0.695 mg/kg with a standard deviation of 0.071 mg/kg. The certified Pb value is 0.692 mg/kg. The mean Pb result (n = 6) for SRM 3244 was 0.0269 mg/kg with a standard deviation of 0.0010 mg/kg. The certified Pb value is 0.0270 mg/kg.

Even though reference materials were included with every batch, samples were fortified at a frequency of approximately 14% to monitor for matrix effects due to the great variety in sample composition. Fortified sample recoveries were also excellent. With a few exceptions, two samples from each batch were prepared in triplicate with one replicate portion fortified with Pb before digestion at approximately 0.5 mg/kg. Mean Pb recovery (n = 44) for fortified samples was 104%. Only four recovery results were outside of 100 ± 10%. Precision was demonstrated by comparing relative standard deviations (RSD) of replicate analytical portions. Mean, median, maximum and minimum RSD were 4.6, 2.5, 62, < 0.1%, respectively. Only 11 out of 325 samples had RSDs > 15%. Two of these eleven samples had Pb levels that were less than five times the estimated detected limit which would account for some of the variability.

Table 2. Summary of Pb Results

population group	PTTI (μg Pb/day)	estimated exposure (μg Pb/day)		mass fraction (mg Pb/kg)		
		median	max	median	max	*n*
young children (0−6 years)	6	0.123	2.88[a]	0.0352	0.395	101
older children (7+ years)	15	0.356	1.78	0.146	0.623	23
pregnant or lactating women	25	0.845	8.97	0.220	2.40	75
adult women	75	0.842	4.92	0.221	1.20	125

[a] Two samples would result in a Pb exposure greater than 30% of the PTTI.

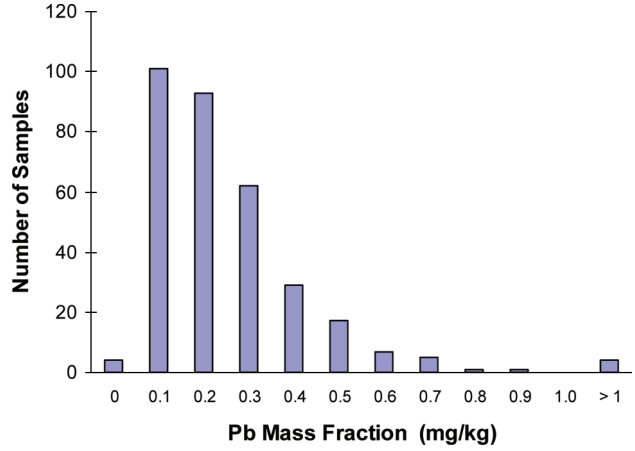

Figure 1. Frequency distribution of Pb mass fractions.

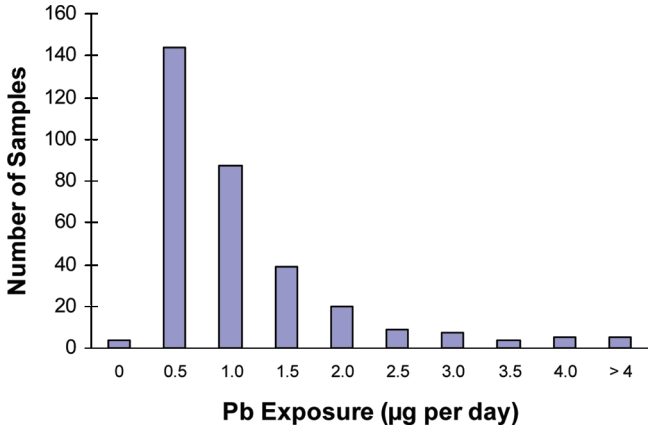

Figure 2. Frequency distribution of estimated Pb exposure.

Analytical Results. Results were classified into four groups according to the population group identified on the label: young children (0−6 years), older children (7+ years), pregnant or lactating women, and adult women. Vitamins labeled for young children had the lowest median Pb mass fraction and the lowest potential exposure followed by vitamins labeled for use by older children. There was very little difference in the median Pb mass fraction and potential exposure for the two groups of women. Four samples had results less than the Pb detection limit. Analytical results and the PTTI levels are summarized in **Table 2** for the four population groups. Median and maximum values were used instead of mean and standard deviation due to the skewed distribution of results toward lower mass fraction and exposure as seen in **Figures 1** and **2**. **Figure 1** shows the frequency distribution of Pb mass fraction values. A great majority (89%) of samples had a Pb mass fraction <0.4 mg/kg. **Figure 2** shows the frequency distribution of Pb exposure values. Ingestion of most samples (90%, across all population groups) would result in a Pb exposure of <2 μg/day if the product maximum recommended daily servings were followed. All but two of the young children's products would provide Pb exposures of <1 μg/day. The estimated median and maximum Pb exposures were: 0.123 and 2.88 μg/day for young children, 0.356 and 1.78 μg/day for older children, 0.845 and 8.97 μg/day for pregnant and lactating women and 0.842 and 4.92 μg/day for adult women. Vitamins were classified as liquid, powder, tablet/capsule, or candy-like. **Table 3** presents results according to product form.

Table 3. Summary of Pb Results by Product Form

product form	estimated exposure (μg Pb/day)		mass fraction (mg Pb/kg)		*n*
	median	max	median	max	
candy-like	0.0708	0.295	0.0137	0.0561	21
liquid	0.126	3.76	0.0066	0.112	21
powder	0.378	2.88	0.0569	0.235	8
tablet/capsule	0.670	8.97	0.186	2.40	274

Discussion and Conclusions. The method performed quite well as demonstrated by the excellent recoveries with reference materials and fortified samples. ICP-MS is well suited for low level Pb analysis of vitamins. The detection limit was much lower than required to make a safety assessment. Cryogenic grinding with a small laboratory mill provided an easy, contamination free and efficient way to composite soft gelatin capsules, oil filled capsules and candy-like samples. Microwave assisted digestion was relatively rapid with little contamination. The 40-position carousel aided efficiency. Blank values were extremely low indicating little contamination from reagents or the laboratory environment. Precision between replicate analyses was generally excellent. However, future work will investigate why some samples had RSD*s* > 15%. Particle size analysis and alternative milling techniques such as the use of a ball mill will be examined.

Most samples were extremely low in Pb, with a median value of 0.160 mg/kg and only four samples exceeding 1 mg/kg. Estimates of exposures for each product were assessed with respect to safe/tolerable exposure levels that have been developed for the particular age and sex groups (*9*). Estimates of median and maximum exposures were derived for each product by multiplying the maximum daily consumption provided by the label instructions by the median and maximum product Pb mass fractions, respectively, determined in this study. The maximum recommended serving size varied from 0.6 g (tablet) to 36 g (powder). The median value for Pb exposure when taking the maximum recommended daily servings was 0.576 μg/day, with only five of 324 samples exceeding Pb exposure of 4 μg/day. The mean and maximum estimates of lead exposure for all the products are below the tolerable intake levels for the at risk population groups of children, pregnant women, and adult women and only comprise a small percentage of the tolerable intake level.

To put the potential Pb exposure in perspective, one must compare the μg/day values to the PTTI of a particular population group. As shown in **Table 2**, the median values for potential Pb exposure are all very low, ranging from 1−4% expressed

as a percentage of PTTI. However, the maximum exposure expressed as a percentage of PTTI reached as high as 48% for one sample targeted at young children. **Table 3** lists Pb mass fraction and Pb exposure by sample type. The results suggest that candy-like and liquid samples were lower in Pb than powders and tablets/capsules, although the differences in the n for each type of product analyzed may contribute to the observed differences.

Some products had label statements such as "Kosher," "vegetarian," or "manufactured under good manufacturing practices (GMP)." Many products listed one or more botanical (e.g., ginseng, alfalfa, ginger), food or food concentrate items (e.g., barley grass, carrot, blueberry) in the ingredient list. To assess possible relationships between product label statements, botanical or food ingredients, and Pb levels, results were grouped by these factors and analyzed by *t* test: two-tailed, assuming equal variances. There was no significant difference ($P > 0.05$) in mean Pb mass fraction and mean μg Pb/day exposure for products with or without vegetarian and kosher label statements. Products listing botanical or food ingredients provided, on average, twice the amount of Pb per daily serving than those that did not (1.03 and 0.521 μg/day, respectively, $P < 0.01$). Although there was no significant difference in mean Pb mass fraction between the two groups, the mean maximum recommended daily serving amount for botanical or food containing products was larger ($P < 0.01$) which would account for the higher daily Pb exposure. Products with GMP label statements had slightly lower mean Pb mass fractions than those without (0.130 and 0.210 mg/kg, respectively, $P < 0.05$), though there was no significant difference in mean Pb exposure when the maximum recommended daily serving was consumed.

Supporting Information Available: Individual sample results with Pb mass fraction and exposure results. This material is available free of charge via the Internet at http://pubs.acs.org.

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