JOURNAL OF AGRICULTURAL AND FOOD CHEMISTRY

PERSPECTIVES

Use of Field-Portable XRF Analyzers for Rapid Screening of Toxic Elements in FDA-Regulated Products

PETER T. PALMER,*[,†,§] RICHARD JACOBS,[§] PETER E. BAKER,[†] KELLY FERGUSON,[†] AND SIRI WEBBER[†]

Department of Chemistry and Biochemistry, San Francisco State University, San Francisco, California 94132, and San Francisco District Laboratory, U.S. Food and Drug Administration, Alameda, California 94502

Analytical instrumentation continues its amazing evolution, especially in regard to generating ever more sensitive, faster, and reliable measurements. Perhaps the most difficult challenges are making these instruments small enough to use in the field, equipping them with well-designed software that facilitates and simplifies their use by nonexperts while preserving enough of their analytical capabilities to render them useful for a wide variety of applications. Perhaps the most impressive and underappreciated example of instruments that meet these criteria are field-portable X-ray fluorescence (XRF) analyzers. In the past, these analyzers have been routinely used for environmental applications (lead in paint and soil, metal particulates in air samples collected onto filters), geology studies (ore and soil analysis, precious metal identification), and recycling industries (alloy identification). However, their use in the analysis of toxic elements in food, food ingredients, dietary supplements, and medicinal and herbal products, especially within the FDA and regulatory environments, has been surprisingly limited to date. Although XRF will not replace atomic spectrometry techniques such as ICP-MS for sub-parts per million level analyses, it offers a number of significant advantages including minimal sample preparation, high sample throughputs, rapid and definitive identification of many toxic elements, and accurate quantitative results. As should be obvious from many recent news reports on elevated levels of toxic elements in children's lunchboxes, toys, and supplements, field-portable XRF analyzers can fill a very important niche and are becoming increasingly popular for a wide variety of elemental analysis applications. This perspective begins with a brief review of the theory of XRF to highlight the underlying principle, instrumentation, and spectra. It includes a discussion of various analytical figures of merit of XRF to illustrate its strengths and limitations compared to existing methods such as ICP-MS. It concludes with a discussion of a number of different FDA applications and case studies in which XRF has been used to screen, identify, and in some cases quantify toxic elements in various products. This work clearly demonstrates that XRF analyzers are an exceedingly valuable tool for routine and nonroutine elemental analysis investigations, both in the laboratory and in the field. In the future, it is hoped that both field-portable and laboratory-grade XRF analyzers will see more widespread use for investigational and forensic-type applications of food and other regulated consumer products.

KEYWORDS: XRF; EDXRF; toxic elements; elemental analysis; FDA; screening

XRF BASICS

Details on XRF theory, instrumentation, quantitative analysis, and sample preparation procedures are documented in an excellent text on this subject (*1*). In brief, XRF is a high-energy physical process that is associated with the basic electronic structure of atoms. When an X-ray photon of sufficient energy strikes an atom, it dislodges an electron from one of the inner electron orbitals, typically the K and/or L shell. To regain stability, an electron from one of the outer orbitals fills this vacancy and, in the process, excess energy is released in the

* Author to whom correspondence should be addressed (e-mail palmer@sfsu.edu).
† San Francisco State University.
§ U.S. Food and Drug Administration.

10.1021/jf803285h CCC: $40.75
Published on Web 03/02/2009

Figure 1. Picture of Niton XLi (top) and Innov-X α-2000 (bottom) field-portable XRF analyzers.

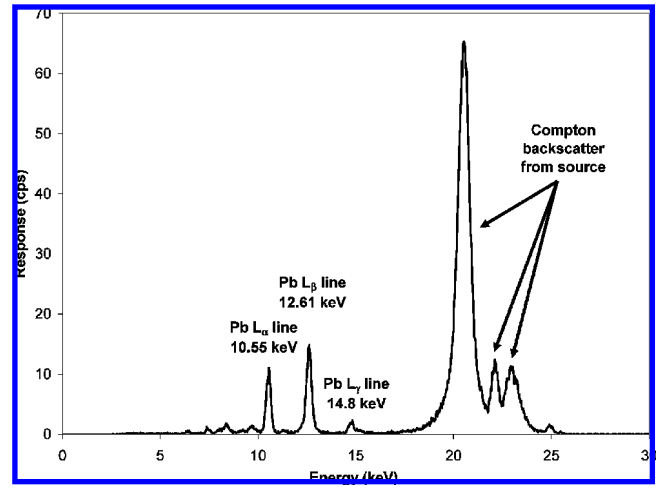

Figure 2. XRF spectrum of 1% lead in chocolate obtained with the Niton XLi analyzer.

form of an X-ray photon. Because the quantum states of each atom's electrons are fairly unique, the energy of the emitted photons are characteristic of the elements present and the number of photons detected at a specific energy is proportional to the concentration of that element in the sample.

XRF Instrumentation. XRF instruments can be categorized into two basic types: wavelength dispersive (WD) and energy dispersive (ED). WDXRF instruments provide better resolution, but they require stronger sources and specialized crystal optics, are large in size, and hence are restricted to use in a laboratory. Although laboratory-grade EDXRF instruments have been in use since the early 1960s, it was not until the past two decades that evolutionary developments in hardware and software facilitated the development of hand-held, field-portable XRF analyzers having performance characteristics that approach those of more expensive laboratory-based XRF analyzers. More recently, total reflectance XRF (TXRF), a variant of EDXRF in which the grazing angle from the X-ray source to the sample is lowered and samples are prepared as a thin film or dried spot (for liquid samples), has been shown to provide lower background levels and LODs as much as 3 orders of magnitude lower than those of conventional EDXRF instruments. The focus of this paper is *field-portable* EDXRF analyzers, and the term XRF in meant to imply the use of this specific type of XRF instrument. **Figure 1** shows a photograph of two different hand-held EDXRF analyzers used in this work. These devices are battery powered and have three basic components: an X-ray source, a detector, and a digital pulse processor (note that EDXRF instruments are multichannel analyzers and do not require a monochromator). The X-ray source is either a radioisotope (e.g., ^{55}Fe, ^{109}Cd, ^{241}Am) or an X-ray tube. The source photons illuminate the sample, and the resulting X-ray fluorescence emitted by various elements in the sample is collected by a thermoelectrically cooled solid-state detector. A digital pulse processor monitors both the energy of the X-rays and the number arriving per unit time. These data are used to generate a spectrum that plots the intensity of emitted photons (usually in counts per second) as a function of their energy in kiloelectron volts (keV). The analyzer's microprocessor and software convert this information into a near real-time readout of sample composition (i.e., elements present and their relative concentrations).

XRF Spectra. An example of a simple XRF spectrum is provided in **Figure 2**. The sample was chocolate that had been intentionally dosed with 10000 ppm (1%) Pb. The peaks in the range of 17−26 keV are due to backscattered photons from the X-ray source (in this case, ^{109}Cd), do not provide any qualitative information as to the elements present in the sample, and are excluded from the plots of subsequent spectra in this paper. The peaks at 10.6, 12.6, and 14.8 keV are due to Pb fluorescence from the sample and correspond to the L_α, L_β, and L_γ lines, respectively. In this notation, the letter refers to the shell that had the original vacancy and the subscript denotes the shell from which the vacancy was filled (e.g., an M shell electron filling a vacancy in an L shell gives rise to the L_α peak). Because the quantum states of each element are different, specific energies can be correlated to particular elements. Moreover, because the peaks observed in an XRF spectrum arise from the removal of inner shell and not bonding electrons, the line energies are independent from the chemical form of that element, and hence this technique provides a means for assessing the total concentration of various elements in a sample.

Safety Considerations. A few comments on the safety of these analyzers are appropriate, especially when considering their use by nonexperts. The use of radioisotope-based XRF analyzers is governed by numerous federal and state regulations. Generally, they require licensing, periodic leak testing, and limits on transportation and storage of the devices. Most new field-portable XRF analyzers are based on X-ray tube sources, which are exempt from most of these regulations and are hence preferred for field applications. The analyzer can be mounted into a metal-lined test stand to prevent escape of source or scattered radiation to the surrounding environment. For applications in which the sample cannot physically fit inside the test stand, the analyzer must be used in hand-held mode. In such cases, potential exposure of nearby individuals to X-rays should be carefully considered and avoided to keep radiation exposure "as low as reasonably achievable" (ALARA). It should be pointed out that the X-ray tubes used in portable XRF analyzers have much lower intensities than conventional medical X-ray devices and that these devices are designed to prevent accidental exposure to measurable amounts of radiation. Dense products such as metal alloys will completely absorb the source radiation. Any X-rays that are transmitted through the sample will be absorbed by the air, with X-ray intensity falling off as a function of proximity to the source. Nevertheless, individuals using an XRF analyzer in hand-held mode should take care to never hold samples during testing and never point the analyzer in the direction of humans when the tube is powered on. To document exposure, accidental or otherwise, manufacturers recommend

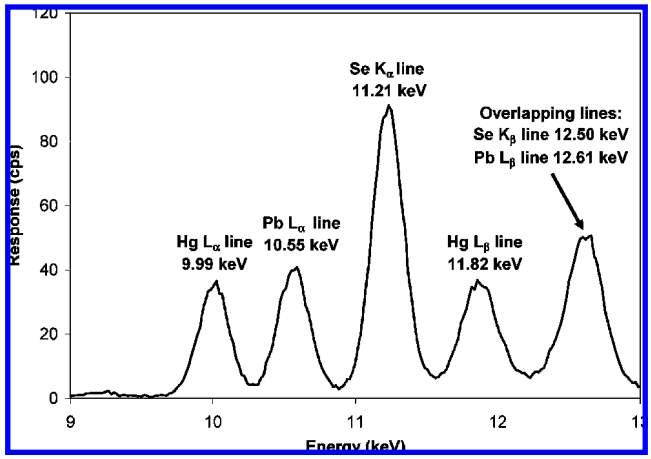

Figure 3. XRF spectrum of 1000 ppm lead, mercury, and selenium in yogurt obtained with the Innov-X analyzer.

that users employ dosimeter badges and follow good radiation safety practices. When used as intended as per manufacturer's instructions, these devices do not subject users to measurable levels of X-ray radiation.

ANALYTICAL FIGURES OF MERIT

A better understanding of the strengths and limitations of XRF instrumentation and methods can be gained by evaluating their figures of merit (*2*, *3*). Here, the selectivity, limits of detection (LODs), linearity, precision, accuracy, and speed of field-portable XRF analyzers (Niton model XLi 728e using a ^{109}Cd source, a Niton XLt tube-based analyzer, and an Innov-X model α-2000 X-ray tube-based analyzer) are described. To evaluate these analyzers, several standards were prepared in liquid (cranberry juice, water), semisolid (yogurt), and solid (chocolate, cellulose) matrices. Samples were fortified with up to four toxic elements (As, Hg, Pb, Se) to give known concentrations on a weight−weight basis. Experimental protocols were similar to those documented in EPA method 6200, were based on the use of on-board algorithms designed for use with soils, and were documented in the form of a FDA standard operating procedure (SOP) for the determination of toxic elements in food, supplements, and medicines (*4*). Results were available in two different forms: raw spectra (instrument response versus energy) and instrument readouts (element detected, mean concentration in ppm, and uncertainty). Both sets of results were evaluated to ascertain figures of merit.

Selectivity. XRF can be used to detect most of the elements in the periodic table ranging from Na to U and even higher Z elements. Detection of low Z elements often requires the use of a vacuum or helium purge gas, as the intensity of the lower energy fluorescence lines of these elements is significantly attenuated by the air gap between the sample and the detector. In general, the selectivity (and resolution) of XRF is more than adequate for detecting multiple elements, assuming no significant spectral overlaps. In most cases, positive detection of a particular element is confirmed through the observation of two or more of its fluorescence lines at their tabulated line energies. Interpretation of XRF spectra of samples that contain multiple elements having fluorescence lines that overlap can be more complicated. An example of such a case is shown in **Figure 3**, which represents a partial XRF spectrum of a yogurt sample doped with 1000 ppm Pb, Hg, and Se. The *x*-axis has been expanded to show the limited resolution of the analyzer. The peaks have a width of 0.2−0.3 keV (full width at half-maximum), which is due to the fundamental limitations of the detector in resolving photons with similar energies. Although each of the three elements should provide two different fluorescence lines in this region, the secondary lines for Pb and Se overlap at 12.5−12.6 keV. In such cases, the analyzer's ability to accurately detect and quantify low levels of one of these elements in the presence of high levels of the other may be compromised. It should be noted that in most applications, the presence of multiple toxic elements with overlapping lines in a given product is unlikely. Regardless, field use of this device giving tentative results that indicate the presence of one or more toxic elements should trigger collection of a sample for a more rigorous quantitative analysis via XRF or an alternate atomic spectrometric method.

LODs. XRF LODs depend on a number of factors, including the intensity of the X-ray source, type and efficiency of the detector, measurement time, sample density, sample matrix, and target element. LODs for low Z elements are often in fraction of a percent range. LODs for As, Hg, Pb, and Se using the three hand-held analyzers evaluated in this work were generally in the range of 1−10 ppm using 1−2 min measurement times. Although these LODs are orders of magnitude less sensitive than ICP-MS, they are more than adequate for detecting acutely and chronically toxic levels of certain elements in various products as will be described below.

Precision and Accuracy. Assessment of precision and accuracy is essential for applications to provide results that may be used as the basis of a direct regulatory action. In using XRF for quantitative analysis, care must be taken to present a homogeneous and representative sample to the instrument, as the X-rays from an XRF analyzer typically penetrate anywhere from a few millimeters to as much as 1−2 cm into a sample, and analysts should homogenize the samples, utilize standards having matrices that closely match those of the samples, and provide a sample with "infinite path thickness" to ensure more accurate results. Replicate XRF measurements typically give RSDs of 5% or less, assuming a homogeneous sample and proper and consistent orientation of the sample relative to the source. The accuracy of XRF-based quantitation depends on how the analyzer is used, and this is an important topic that requires further elaboration. Analyzers are factory calibrated and utilize proprietary algorithms to estimate element concentrations for specific applications (i.e.; soil, alloy, RoHS/WEEE, thin film, etc.). It should be noted that XRF manufacturers have yet to develop an algorithm to detect all possible elements that may be found in food products, supplements, tableware, and food security-type applications. For many such applications, Compton normalization or "soil" mode is often appropriate. In this mode, backscattered source radiation is used to correct for the effects of varying sample densities on instrument response (*1*, *5*). Using this mode of operation, calibration curves from the three different analyzers were found to be linear ($R^2 > 0.999$) over >3 orders of magnitude, spanning concentrations from the LOD of 1−10 ppm to 10000 ppm (1%). At concentrations >1%, fluorescence from the sample can be absorbed and/or enhanced by other elements. In such cases, the analyzer works best when operated in fundamental parameters or "alloy" mode (*1*, *5*). Here, the analyzer compensates for these effects by using an iterative algorithm to converge on the types and concentrations of elements in the sample that best match the corresponding spectrum.

The typical accuracies provided by these analyzers are illustrated using the results from several different applications. In these examples, it is important to note that the results were

based solely on the use of a factory calibrated analyzer used "as is" and did not entail the use of standards for calibrating instrument response (which is discussed in more detail under Applications). Results from the determination of Hg in yogurt over a range of 10−1000 ppm using the Innov-X analyzer in analytical mode were off by a factor as large as 60%, whereas instrument readings for Pb in the same matrix gave relative errors no greater than 20%. These results demonstrate that the accuracy of the analyzer's factory calibration is better for some elements than others. XRF analysis of Cr in stainless steel of 13 different medical instruments over a range of 1−13% using all three analyzers in alloy mode gave relative errors of no more than −8% and average relative errors of less than −4% compared to FAAS results (*6*). This is impressive and demonstrates that these analyzers can give fairly reliable semiquantitative data when used "as is" without additional calibration. Whereas accuracy is indeed critically important for many analytical applications, assessing the accuracy of an XRF determination may not be necessary when the preliminary results indicate that a product contains percent levels of toxic elements as will be discussed below. Obviously, applications requiring more accurate and verifiable quantitative results require sample homogenization and calibration of instrument response through the use of authentic standards in the matrix of interest. If sufficient sample is available, the standard addition method should be considered as a means for more accurate and reliable quantitation.

Speed. Two of the key advantages of XRF are its minimal sample preparation requirements and its speed. In some cases, a product can be analyzed "as is" or directly through the packaging, although it should be noted for the latter case that the results may also indicate the composition of the packaging and/or the colors used in the product label. In other cases, a product is transferred to a sample cup and analyzed or may be ground and homogenized to give more accurate results. XRF analyzers display a direct readout of elements present and their concentrations to provide nearly instantaneous information on sample composition. The spectra are acquired using an energy analyzer, in which X-ray photons at various energies are counted as a function of time. As a result, Fellget's (multiplex) advantage applies and improved signal-to-noise ratios can be obtained at the expense of longer measurement times. In most applications, a 1 to 2 min measurement time provides a good compromise between speed and precision. When element concentrations are high, measurement times can be shortened to a few seconds. When using the analyzer to detect elements at concentrations near the LOD, the use of longer measurement times provides better signal-to-noise ratios, which may enable more reliable confirmation of the presence of a given element.

Comparison of XRF to ICP-MS. FDA field laboratories utilize a wide variety of instrumentation for toxic element analysis, including flame and graphite furnace atomic absorption spectrophotometry (FAAS and GFAAS), inductively coupled plasma-atomic emission spectrometry (ICP-AES), and ICP-MS. In recent years, the FDA has begun to rely more heavily on ICP-MS for surveillance and regulatory activities related to the detection and quantification of toxic elements in various products. **Table 1** provides a comparison of some of the features of XRF and ICP-MS to better illustrate the strengths and limitations of each technique. Both XRF and ICP-MS have multielement analysis capabilities. As mentioned earlier, elements that can be analyzed via XRF typically range from Na to U. The range of elements that can be analyzed via ICP-MS is slightly wider and spans the range from Li to U and may exclude elements such as F, N, and O, which are difficult to ionize or are present in the MS vacuum system. Comparing the selectivity of the two techniques is not straightforward, as identification of an element is based on different types of spectra. In XRF, interferences (i.e., false positives and false negatives) can be attributed to spectral overlaps and/or the limited resolution of the analyzer. In ICP-MS, isobaric interferences can cause similar problems, but these types of interferences can be readily avoided by choosing an alternate isotope, using an octopole reaction chamber, or employing a higher resolution mass analyzer. XRF has until now been sparingly used for quantitative analysis applications, primarily due to LODs that are at best in the 1−10 ppm range for many toxic elements. Although direct ICP-MS analysis of drinking water samples can provide LODs in the sub-parts per billion range for many elements, the analysis of solid food samples often requires the use of small analytical portions and large dilution factors (i.e., dilution of 0.2 g of sample into 200 mL) to avoid potential matrix effects and results in sample LODs in the part per billion range. XRF's major advantages are its minimal sample preparation requirements, ability to rapidly screen large numbers of products in the field, lower capital equipment and supply costs, and lower cost per analysis. These features make it eminently suitable for a variety of FDA applications as will be described below.

Table 1. Summary of Selected Figures of Merit of XRF and ICPMS

technique	XRF	ICP-MS
elements	Na−U	Li−U (difficult to do F, N, O)
interferences	spectral overlaps, limited resolution	well-known isobaric interferences
LODs	1−10 ppm for As, Cd, Hg, Pb in solids	ppb−ppm for As, Cd, Hg, Pb in solids
	1−10 ppm for As, Cd, Hg, Pb in liquids	ppt−ppb for As, Cd, Hg, Pb in liquids
sample preparation	minimal ("as is" or homogenization)	significant (digestion/filtration)
field analysis	yes (∼1 min/sample)	not possible
capital cost	$25000−$50000	$170000−$250000

APPLICATIONS

A rather broad search of ACS journals for papers containing "XRF" or "X-ray fluorescence" in the title over the past 20 years yielded 99 publications (focusing on a variety of applications outside the food and regulatory areas), and further constraining this search by adding "food" as a keyword reduced the number of publications to zero. Certainly, there are a number of reported applications in non-ACS journals on the use of XRF for food analysis, but even the numbers here are surprisingly small considering the applicability and utility of this technique. Some representative examples of applications of EDXRF and WDXRF to the analysis of foods, beverages, and related products are provided in **Table 2**. Representative examples of the authors' applications of field-portable EDXRF are given in **Table 3** and discussed in detail below. It should be understood that there some important differences in both the sample preparation methods and instrumentation employed in the previous studies and the authors' work summarized in **Tables 2** and **3**, respectively. In most of the prior studies, samples were dried, ground, and pelletized into a disk for subsequent XRF analysis. This sample preparation required significant time but was deemed necessary to generate accurate quantitative data. More importantly, all of these prior XRF studies involved the use of benchtop-sized laboratory-based XRF instrumentation. In the

Table 2. Selected Applications of XRF in the Analysis of Foods and Beverages

sample	analyte(s)	instrument	ref
food	P	WDXRF	*7*
food	Mn, Fe, Cu, Zn	EDXRF	*8*
food premixes	Fe, Cu, Zn	EDXRF	*9*
fruits, vegetables, grains	Mg, P, Cl, K, Ca, Mn, Fe, Cu, Zn	EDXRF	*10*
infant cereals	Na, Mg, P, Cl, K, Ca, Mn, Fe, Zn	WDXRF	*11*
fast foods	P, S, Cl, K, Ca, Mn, Fe, Zn, Br, Rb, Sr	EDXRF	*12*
crustaceans	K, Ca, Mn, Fe, Cu, Zn, Se, Br, Sr, Pb	EDXRF	*13*
milk	P, S, Cl, K, Ca, Fe, Zn	EDXRF	*14*
teas	K, Mg, Ca, Fe, Mn, Zn	EDXRF	*15*
fruit juice	trace elements	EDXRF	*16*
soft drinks	20 elements	Synchrotron XRF	*17*
FD&C dyes	Cr	WDXRF	*18*
Ayurvedic medicines	Pb, Hg, As	EDXRF	*19*

Table 3. Selected Applications of XRF at the FDA San Francisco District Laboratory

sample	analyte(s)
tableware	Pb, U, Cd, Se, Sb, Ba
stainless steel forceps	Cr
Asian patent medicines	As, Hg, Pb, Cd
chocolate liquor	Pb
candy wrappers	Pb, Cr
various (consumer complaint investigations)	Hg, As, Fe, Pb

authors' work, sample preparation was kept to a bare minimum, and most samples were analyzed "as is" using a hand-held XRF analyzer. As the following results will demonstrate, good quantitative results can be obtained without drying or pelletizing the samples and elements can be detected at fairly low levels using hand-held versus laboratory-based XRF instruments.

Toxic Elements in Tableware. Anderson was only the second FDA researcher [with Hepp (*18*) being the first] to publish a peer-reviewed paper on the use of XRF. His work involved the use of earlier radioisotope-based versions of both laboratory-based and hand-held XRF analyzers for determining toxic elements in tableware (*20*). Under acidic conditions (i.e., foods containing acetic or citric acid), these toxic elements can be leached from tableware into food. The current FDA methods for this application require preparation of a leachate solution from the sample and subsequent analysis via FAAS or GFAAS. The use of XRF for this application would widen the scope of target elements versus the current single-element FAAS-based methods (current FDA surveillance activities for this application are focused on only Pb and Cd) and provide a simpler means for qualitative identification of toxic elements in the materials, surface glazes, and pigments in tableware. An example of this is provided in **Figure 4**, which shows an antique Fiestaware plate and its XRF spectrum, which indicates positive detection of high levels of both Pb and U. Related applications of XRF by the authors include the detection of Cd and Se in red pigmented portions of the enamel coating on steel cups and detection of Pb, Sb, Cd, and Ba on the inside surfaces of Yixing teacups. XRF has also been used to detect products that contain incompatible glaze elements, such as the presence of Cu in Pb-based glazes. Although these results do not necessarily imply that these elements are leachable, the use of XRF for direct screening of large numbers of these types of products would eliminate the need for a more detailed quantitative analysis of products that do not contain detectable levels of elements of

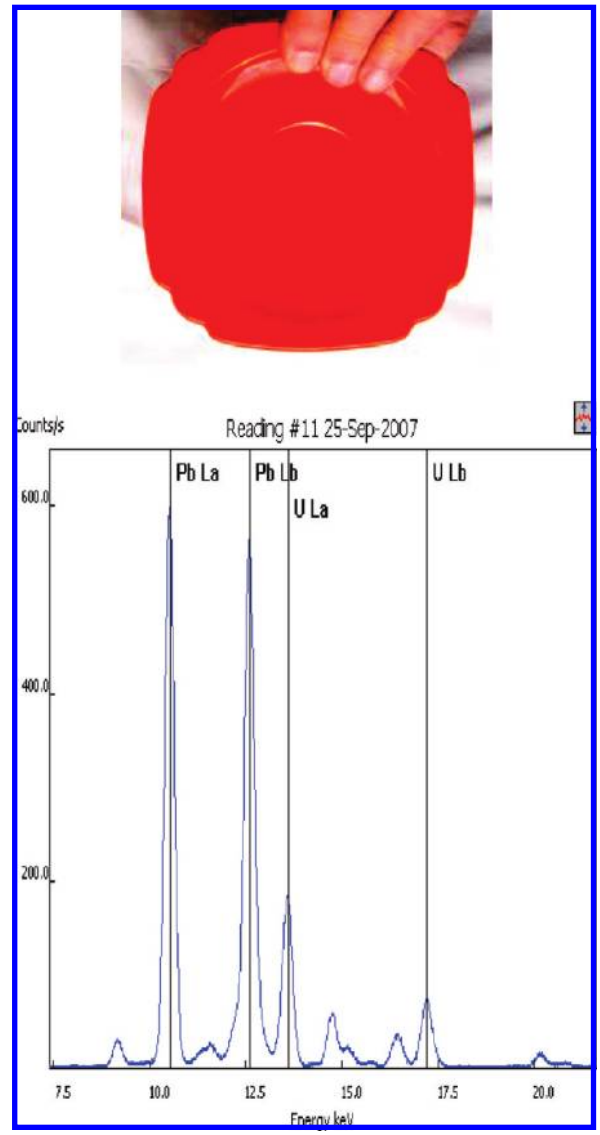

Figure 4. XRF spectrum showing detection of Pb and U in Fiestaware obtained with the Innov-X α-2000 analyzer. Vertical lines in the spectrum correspond to reference line energies for indicated elements.

regulatory concern and, therefore, would provide significant time and cost savings by avoiding the preparation of leachate solutions of these products.

Cr in Stainless Steel. FDA applications often involve ensuring compliance with product specifications. An example of this is the determination of Cr in stainless steel instruments to meet ASTM requirements. XRF was compared to FAAS for the determination of Cr in 13 stainless steel forceps imported from Pakistan and elsewhere (*6*). The traditional FAAS method requires removing and grinding a portion of the product, acid digestion, filtration, dilution, and subsequent analysis. In the XRF method, samples are analyzed "as is" using 2 min measurement times with quantitative results derived via one of two different means: direct readout of percent Cr in the samples using a factory-calibrated analyzer and analysis of several certified reference materials and calibration of instrument response for more accurate quantitation. Results from both quantitation procedures were compared to those from FAAS-based analyses of the same samples. Using no external calibration, XRF results from three different analyzers gave Cr concentrations with an average negative bias of 3−4% percent compared to the FAAS results. Using external calibration

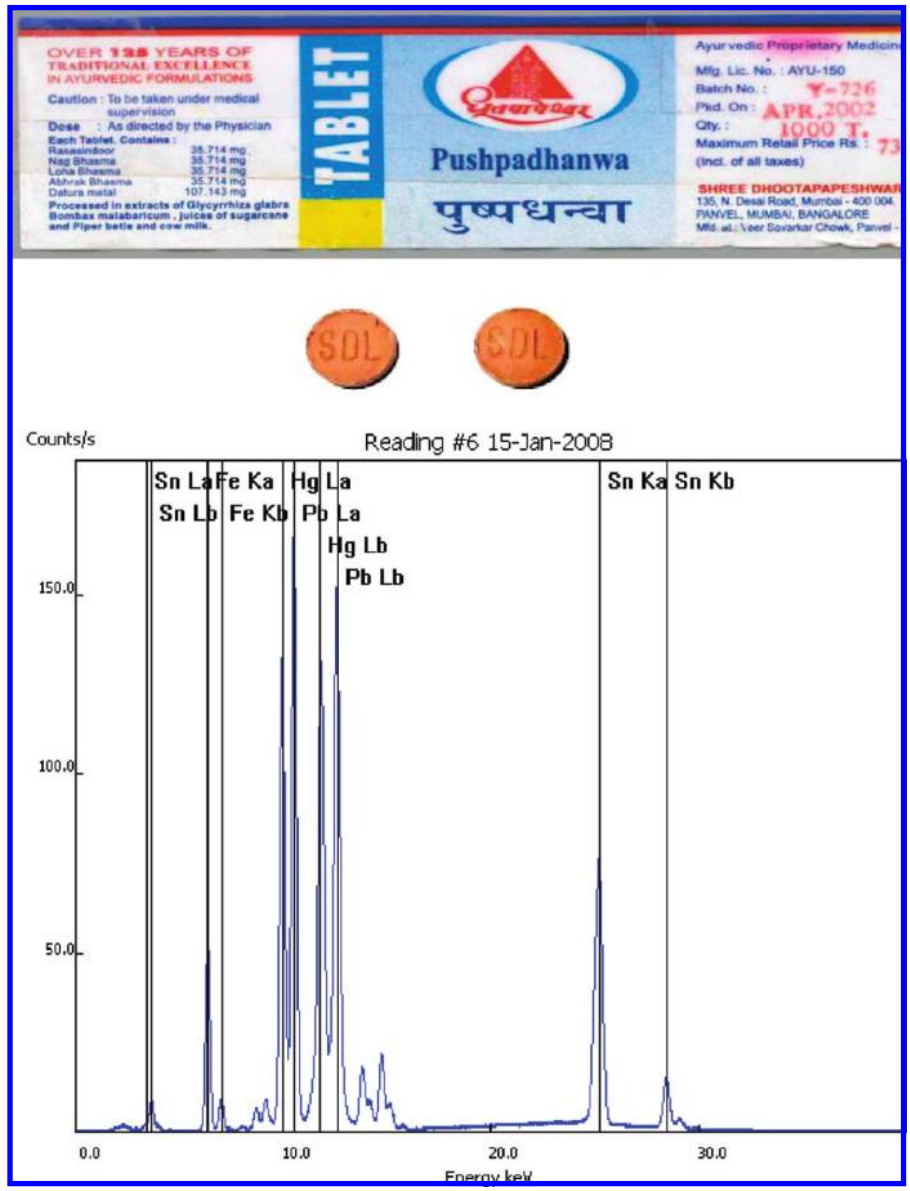

Figure 5. Photograph of imported Ayurvedic medicine and XRF spectrum showing detection of Pb, Hg, Fe, and Sn obtained with the Innov-X α-2000 analyzer. Vertical lines in the spectrum correspond to reference line energies for indicated elements.

standards, XRF results gave Cr concentrations with an average negative bias of 1−2% relative to the FAAS results, which corresponded to statistically insignificant differences at the 95% confidence level. The key features of XRF for this application are its simplicity and speed, with the analysis of the 13 samples and calculation of final results completed in several hours compared to several workdays via FAAS. On the basis of this work, XRF is deemed to be a suitable replacement for the current FAAS-based method for this application. In practice, investigators could conduct this type of determination outside of the laboratory, thus negating the need for sample collection or delaying the shipment's progress in commerce.

Toxic Elements in Supplements. XRF is well suited for the analysis of products that may contain toxicologically significant levels of elements in a more concentrated form and/or nutritionally adequate levels of mineral elements. The scope of these applications includes products such as infant formula, vitamin and mineral formulations, dietary supplements, Asian patent medicines, and related products. Some examples of the authors' work in this area illustrate the utility of XRF for these applications. The first is the analysis of an Ayurvedic medication *Pushpanhanwa*, which is depicted in **Figure 5** along with the XRF spectrum of the product. This product, ironically labeled as a fertility drug, led to a spontaneous abortion and two other reported serious illnesses. FAAS analysis of this product by a private laboratory showed 7% Pb. XRF analysis of the same product indicated 8% Pb and 7% Hg and similar levels of Fe and Sn, which demonstrates the multielement detection advantage of XRF over the single-element FAAS method used by the private laboratory. A second example is the analysis of a Chinese medicine called *Niuhuang Jiedu Pian* (cow yellow detoxification tablet). This product's intended use is to treat mouth ulcers, relieve toothaches, reduce fever, and release toxins. ICP-MS analysis of this product indicated 6.85% As, and it should be noted that the introduction of this unexpectedly high level of As into the low-level analysis sample stream led to the contamination of digestion vessels and the ICP-MS instrument, which led to several days of downtime. XRF analysis of the same product indicated 11.7% As, which was high enough that As could easily be detected through the box and blister-pack of this product. The lower concentration indicated by ICP-MS may be due to the inability of the acid digestion procedure

to completely dissolve As in its native mineral form in this product (Realgar, As_4S_4) and/or its loss through volatilization during the digestion process. In a related application, XRF was used to detect Pb, Bi, and Zn in Sargenti powder, an unapproved drug used to "sterilize" tissue after a root canal.

There has been increasing media and public scrutiny of the ongoing problem of toxic elements in Asian products and in Ayurvedic and Chinese medicinal products in particular. The California Department of Public Health compiled a report describing Chinese herbal medicines known to contain one or more toxic elements (*21*). A study by Saper et al. via XRF on 70 different Ayurvedic medicines sold in Boston area stores found detectable levels of Pb in 19% of the products with levels as high as 4% and Hg in 9% of the products with a median value of 2% and a maximum level of 10% (*19*). An FDA analysis of 95 different dietary supplements purchased from retail stores in the Washington DC area reported As, Hg, and Pb concentrations as high as 4, 17, and 49 parts per million, respectively (*22*). Some of the outcomes of these studies included wide press coverage, a Canadian ban on imports of Ayurvedic medicines in 2005, and a new Indian requirement for labeling of exported Ayurvedic medicines in 2006. It is clear that such high levels of toxic elements in these products represent a serious human health risk. It is hoped that the FDA and other government agencies will support wider use of XRF to screen and identify such potentially toxic products.

Toxic Elements in Candy. XRF has also been used in the detection of lower but toxicologically significant levels of heavy metals in food products. One such application involved the analysis of blocks of organic, "free-trade" chocolate liquor from Ecuador. ICP-MS results indicated low parts per million levels of Pb in samples of this product. In the analysis of one sample that was found to contain 17 ppm Pb via ICP-MS, quantitative analysis of the sample via XRF along with the use of authentic standards prepared in a similar matrix gave a concentration that was nearly identical. In another application, XRF was used to detect Pb and Cr pigment components on both a candy wrapper and the surface of the candy where there was visual evidence of pigment transfer. Ida and Kawai reported similar success in detecting elements through product packaging (*23*), illustrating the usefulness of this technique for direct analysis of products, assuming the packaging is thin enough to be relatively transparent to X-rays.

Consumer Complaint Investigations. XRF has also been used to resolve numerous consumer complaint investigations. In one case, a consumer complained about metallic Hg contamination in an orange beverage product. Subsequent visual inspection of the sample indicated the presence of what appeared to be a large amount of Hg (~300 g), and XRF indicated the presence of pure mercury in the bottom layer of the product. In a similar case, XRF was able to show that none of the sealed envelopes of a commercial hot chocolate mix contained metallic Hg compared to the portion prepared by the consumer in a cup. In another case, a consumer was concerned about what appeared to be metallic Hg in a jar of baby food. XRF analysis indicated that the defect was due to an Al−Fe inclusion within the glass of the jar. More importantly, the use of XRF eliminated the need for more expensive and time-consuming quantitative analyses of lot-sized samples, enabled resolution of this case within a few hours after the sample's arrival in the laboratory, and quickly alleviated the concerns of both the anxious parent and the manufacturer. In another case, a consumer boiled ant traps and applied the extract to their vegetable garden as a "homemade" pesticide. Not surprisingly, the consumer and his family became ill after consuming these vegetables. Subsequent investigation indicated the presence of sodium arsenate in the ant traps. ICP-MS analysis of a sample of the remaining condiment used on the salad indicated 233 ppm As, and XRF analysis indicated 244 ppm As, again demonstrating the utility of XRF in providing rapid and reliable results with minimal sample preparation without the need for preparing and analyzing authentic standards. In one other investigation, XRF was used to identify the composition of specific particulate-type contamination in products, such as Pb-based paint particles in honey.

Forensic Applications. XRF has also been used for rapid detection of toxic elements and/or abnormal levels of nutrient elements in forensic-type investigations. For example, XRF was used to detect Cr on a cow hide in a case where a Cr-based glass cleaning agent poisoned the cattle. Although this work was done in the laboratory after the incident had been resolved, the use of XRF in the field investigation would have provided resolution of this case in minutes instead of the weeks it took using conventional investigative techniques of site inspection, sample collection, and subsequent laboratory-based analysis. In a situation when an individual has an acute illness as in the case of the Ayurvedic medication *Pushpanhanwa*, rapid identification of products containing toxic elements can be critical to the patient and public health. The ability of XRF to exclude an element or product from time-consuming quantitative analysis is also a critically important feature for forensic, food defense, and counterterrorism applications.

CONCLUSIONS AND FUTURE DIRECTIONS

XRF has been shown to be a powerful tool for a number of FDA investigative and analytical applications. XRF analyzers are simple to operate, field portable, and priced in the range of $25000−50000 and provide fairly selective detection of elements ranging from Na to U with LODs in the low parts per million range for many of these elements. Perhaps the most unappreciated aspects of XRF are its minimal sample preparation requirements and nondestructive analysis capabilities. XRF can be used for in situ identification of contaminated product components that may be too large to bring back to the laboratory. For housewares and tablewares, semiquantitative results from XRF can be used to widen the scope of target elements versus conventional leaching-based methods. For spices, supplements, and other consumer products, semiquantitative results can often be obtained without removing a sample of the product from its packaging. As has been shown here, drying and pelletizing of the samples may not be necessary, and acceptable quantitative results can be derived by simple homogenization of the sample prior to analysis. These sample preparation procedures are far faster and easier compared to conventional atomic spectrometric methods that typically require digestion, filtration, and dilution. They also are nondestructive, meaning that the sample itself can be preserved for confirmatory analyses and future studies.

The most important features of XRF are its simplicity and speed, which make this an ideal technology for rapid screening of large numbers of samples and have led to wider use of this technology in FDA laboratory and field studies. Measurement times of 1−2 min are more than adequate for identifying major constituents and some toxic elements down to low parts per million levels, and this corresponds to sample throughput rates of up to 60 samples per hour. This is far better than standard atomic spectrometric methods, and it should be noted that these analyses can be performed on-site at a factory, warehouse, or postal facility to differentiate between potentially violative and

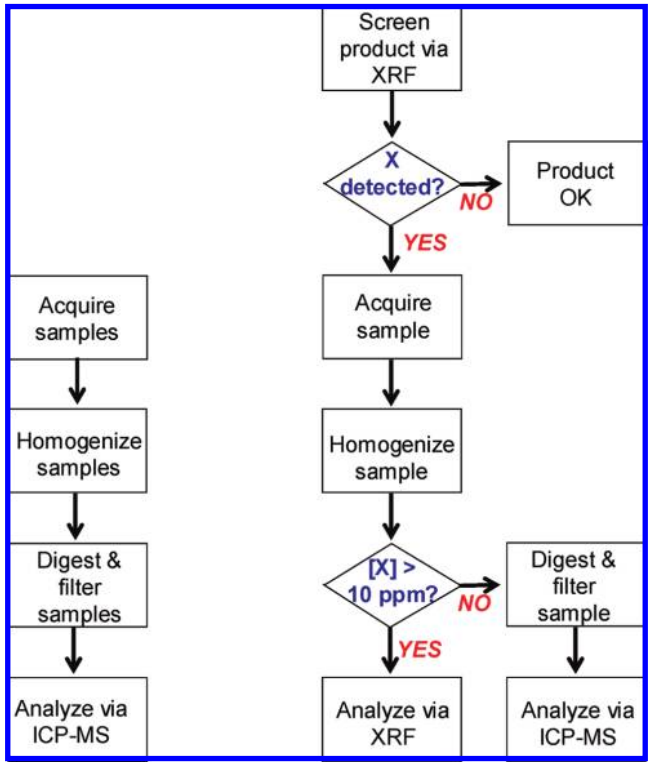

Figure 6. Flowchart highlighting the various steps in a mock FDA field assignment for the determination of toxic elements in supplements via existing ICP-MS versus proposed XRF-based methods.

nonviolative lots. In the laboratory, XRF can be used as a triage tool in investigating consumer complaints and potential food-poisoning cases and in quickly discriminating between products or lots that require further investigation and ones that do not. XRF can also be used for food defense and food security applications associated with monitoring for the presence of many of the potentially toxic elements in the periodic table at levels that may pose an acute or chronic hazard in foods, food ingredients, dietary supplements, and folk medicines.

To better illustrate the potential benefits of XRF versus current methodology for an FDA-related application, consider a "mock" field assignment involving the determination of toxic elements (As, Cd, Hg, and Pb) in 100 different supplement products. **Figure 6** delineates the various steps involved in the analysis using approved FDA ICP-MS methods compared to a proposed protocol that takes advantage of new XRF methods. In the former, the biggest bottleneck is the sample preparation process, in which time-consuming and labor-intensive digestion and filtration steps are needed to convert a solid product into an extract that is amenable to ICP-MS analysis. In the XRF-based methods, the sample preparation steps are far easier and require either minimal sample preparation for screening purposes (i.e., analyzing the sample "as is" directly through the packaging, pouring out an aliquot of the product into an XRF analysis cup) or grinding to convert the product to a more homogeneous powder to provide more accurate results. The XRF-based protocol takes full advantage of hand-held analyzers for rapid screening and higher sample throughputs and would resort to more involved laboratory-based sample preparation and quantitative analysis procedures *only* when potentially violative samples are encountered [i.e., when the toxic element(s) concentrations exceed the limits of quantitation and/or are at acutely or chronically toxic levels]. It is estimated that the analysis of these 100 supplement products using ICP-MS would take somewhere between 4 and 10 person-weeks of effort (this includes sample collection, preparation, and analysis time only; sample heterogeneity problems, QA/QC requirements, instrument downtime, and reporting requirements can further add to this time). The same analysis using XRF-based methods (here, it is assumed that only 10% of these products contained detectable levels of one or more toxic element and would require subsequent laboratory-based homogenization and analysis) would take on the order of 1 person-week of effort. Clearly, XRF offers the ability to reap significant time and cost savings in the determination of toxic elements in these types of products or, conversely, the ability to screen for the presence of toxic elements in a much larger variety and type of products over the same time period.

The FDA is currently using XRF at both the Center for Food Safety and Applied Nutrition (CFSAN) and the San Francisco District Laboratory for routine and nonroutine elemental analysis investigations. In 2007, the FDA's Division of Field Science sponsored a pilot study to explore the use of these analyzers in the field. Here, a cadre of investigators from the San Francisco District were trained and certified in the use of these analyzers and used them to identify products containing abnormal levels of toxic elements. This pilot study demonstrated that investigators and nonchemists can use this equipment to quickly and accurately screen large numbers of products. Hopefully, this and related work will spur the use of this technology by both FDA field investigators for rapid screening of large numbers of products and samples and FDA laboratory personnel for qualitative and quantitative analyses of routine and nonroutine samples. With continuing evolution of XRF sources, detectors, and software directed at foods and other FDA-regulated products, it is hoped that this technique will soon see regular and wide use as the method of choice for these and related applications.

ACKNOWLEDGMENT

We gratefully acknowledge Deblyn Paella (Geotechnical Services/Niton) and Jack Hanson (HMC Analytical Instrumentation/Innov-X) for the loan of XRF analyzers used in some of this work. We also thank David Anderson (CFSAN) and Eileen Maher (FDA Winchester Analytical and Engineering Center) for their comments and input and Rod Asmundson and Barbara Cassens (San Francisco District Laboratory) and the FDA Division of Field Science for their support of this work.

LITERATURE CITED

(1) Grieken, R.; Markowicz, A. *Handbook of X-Ray Spectrometry*, 2nd ed.; CRC Press: Boca Raton, FL, 2002.

(2) Palmer, P.; Webber, S.; Ferguson, K.; Jacobs, R. On the suitability of portable X-ray fluorescence analyzers for rapid screening of toxic elements. *FDA/ORA/DFS Lab. Inf. Bull.* **2006**, *22* (July), 1–15.

(3) Block, C. N.; Shibata, T.; Solo-Gabriele, H. M.; Townsend, T. G. Use of handheld X-ray fluorescence spectrometry units for identification of arsenic in treated wood. *Environ. Pollut.* **2007**, *148*, 627–633.

(4) Palmer, P. T. *Screening for Toxic Elements in Food, Supplements, and Medicines via Field-Portable X-Ray Fluorescence*; SOP No. SAN-230.6; FDA San Francisco District Lab: Alameda, CA, 2005.

(5) Niton XLi 700 Series Environmental Analyzer User's Guide, Niton LLC, Billerica, MA, 2002.

(6) Palmer, P.; Jacobs, R. Rapid determination of chromium in stainless steel via X-ray fluorescence spectrometry. *FDA/ORA/DFS Lab. Inf. Bull.* **2007**, *23* (June), 1–11.

(7) Jastrzebska, A.; Brudka, B.; Symanski, T.; Szlyk, E. Determination of phosphorus in food samples by X-ray fluorescence spectrometry

and standard spectroscopic method. *Food Chem*. **2003**, *83*, 463–467.
(8) Nielson, K. K.; Mahoney, A. W.; Rogers, V. C. X-ray fluorescence and atomic absorption spectrophotometry measurements of manganese, iron, copper, and zinc in selected foods. *J. Agric. Food Chem*. **1988**, *36*, 1211–1216.
(9) Perring, L.; Audrey, D.; Basic-Dvorzak, M.; Hammer, D. Rapid quantification of iron, copper, and zinc in food premixes using energy-dispersive XRF. *J. Food Compos. Anal*. **2005**, *18*, 655–663.
(10) Nielson, K. K.; Mahoney, A. W.; Williams, L. S.; Rogers, V. C. X-ray fluorescence measurements of Mg, P, Cl, K, Ca, Mn, Fe, Cu, and Zn in fruits, vegetables, and grain products. *J. Food Compos. Analysis* **1991**, *4*, 39–51.
(11) Perring, L.; Andrey, D.; Basic-Dvorzak, M.; Blanc, J. Rapid multimineral determination in infant cereal matrices using wavelength dispersive X-ray fluorescence. *J. Agric. Food Chem*. **2005**, *53*, 4696–4700.
(12) Nielson, K. B.; Mahoney, A. W.; Williams, L. S.; Rogers, V. C. Mineral concentrations and variations in fast-food samples analyzed by X-ray fluorescence. *J. Agric. Food Chem*. **1991**, *39*, 887–892.
(13) Mohapatra, A.; Rautray, T. R.; Vijayan, V.; Mohanty, R. K.; Dey, S. K. Trace elemental characterization of some food crustacean tissue samples by EDXRF technique. *Aquaculture* **2007**, *270*, 552–558.
(14) Perring, L.; Audrey, D. EDXRF as a tool for rapid minerals control in milk-based products. *J. Agric. Food Chem*. **2003**, *51*, 4207–4212.
(15) Verbi Pereira, F. M.; Pereira-Filho, E. R.; Rodriques, E.; Maretti Silveira Bueno, M. I. Development of a methodology for Ca, Fe, K, Mg, Mn, and Zn quantification in teas using X-ray spectroscopy and multivariate calibration. *J. Agric. Food Chem*. **2006**, *54*, 5723–5730.
(16) Bao, S. X.; Wong, Z. H.; Liu, J. S. X-ray fluorescence analysis of trace elements in fruit juice. *Spectrochim. Acta B* **1999**, *54*, 1893–1897.
(17) Zucchi, O. L.; Moreira, S.; Salvador, M. J.; Santos, L. L. Multielement analysis of soft drinks by X-ray fluorescence spectrometry. *J. Agric. Food Chem*. **2005**, *53*, 7863–7869.
(18) Hepp, N. M. Spectroscopic determination of chromium in FD&C Blue No. 1 by X-ray fluorescence. *J. AOAC Int*. **1996**, *79*, 1189–1190.
(19) Saper, R. B.; Kales, S. N.; Paquin, J.; Burns, M. T.; Eisenberg, D. M.; Davis, R. B.; Phillips, R. S. *JAMA—J. Am. Med. Assoc*. **2004**, *292*, 2868–2873.
(20) Anderson, D. Multielement analysis of housewares and other food-related items by a ^{241}Am radioisotope X-ray fluorescence transportable spectrometer and handheld analyzers. *J. AOAC Int*. **2003**, *86*, 583–597.
(21) Ko, R.; Au, A. Compendium of Asian Patent Medicines, California Department of Health Services, 1997−1998.
(22) Dolan, S. P.; Nortrup, D. A.; Bolger, P. M.; Capar, S. G. Analysis of dietary supplements for arsenic, mercury, and lead using ICP-MS. *J. Agric. Food Chem*. **2003**, *51*, 1307–1312.
(23) Ida, H.; Kawai, J. Analysis of wrapped or cased object by a handheld X-ray fluorescence spectrometer. *Forensic Sci. Int*. **2005**, *151*, 267–272.

Received for review October 21, 2008. Revised manuscript received February 6, 2009. Accepted February 9, 2009. Reference to any commercial materials, equipment, or process does not in any way constitute approval, endorsement, or recommendation by the FDA.

JF803285H