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Best Practices for the Use of Portable X-Ray Fluorescence Analyzers to Screen for Toxic Elements in FDA-Regulated Products

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Abstract

Globalization of trade has made it easy for consumers to purchase products from all over the world. A small fraction of these products contain toxic elements that may pose a health risk to consumers, and there is a clear need for small, portable, and fast methods to rapidly screen these products. Portable X-Ray Fluorescence (XRF) analyzers are the ideal tool for this application, as they involve minimal sample preparation and analysis times of a minute or less. XRF is also well suited for elemental analysis of products that are resistant to traditional hydrochloric/nitric acid digestions such as cosmetics and dietary supplements, and can prevent contamination of expensive Inductively Coupled Plasma Mass Spectrometry (ICP-MS) instruments used for ultra-trace level analyses. Moreover, XRF can be used to monitor most of the elements in the periodic table, with detection limits as low as 1-10 ppm for some elements. This article describes an U.S. Food and Drug Administration (FDA) field study to screen for consumer products containing toxic elements at an International Mail Facility (IMF). After brief training and hands-on activities using real-world samples, two three-person teams using two portable XRF systems analyzed 183 different products over a seven-hour time period, and found 10 that contained significant levels of mercury (Hg), lead (Pb), arsenic (As), and/or selenium (Se), potentially in violation of FDAs requirements. The goal of this article is to provide guidelines and recommendations for safe, reliable, and efficient use of XRF to screen for toxic elements in FDA-regulated products.

Keywords: x-ray fluorescence, screening, mercury, arsenic, lead, selenium

1. Introduction

Portable and handheld XRF analyzers are a relatively new technology, with the first units developed in the 1980's at the U.S. Department of Energy's Pacific Northwest National Laboratory, and production of commercial units started in the 1990's [26]. More recent advances, including smaller X-ray tube sources, thermoelectrically-cooled energy-dispersive detectors, and miniaturization, have played key roles in improving the performance and stimulating more widespread use of these analyzers. Most of the earliest applications of XRF focused on analysis of soils, paint, rocks, and metal sorting. Within the FDA, the first article on the use of XRF to monitor toxic elements in foods and ceramic glazes appeared in 2009 [1], and that publication stimulated interest in using portable XRF analyzers in FDA field laboratories and field investigations.

It is important to understand the scope, advantages, and limitations of XRF versus conventional atomic spectrometry-based methods commonly used for toxic element analysis [22, 15, 16]. XRF offers the advantages of little or no sample preparation or digestion, multi-element analysis, short analysis times, simplicity, speed, and portability. In addition, it is applicable to the analysis of samples that are resistant to hydrochloric/nitric acid digestion, which among FDA-regulated products includes some dietary supplements and cosmetics. Preliminary screening of products using XRF can help prevent contamination of expensive ICP-MS instruments, which are typically used for monitoring toxic elements down to low ppb levels. While XRF is not suitable for detecting sub-ppm levels of toxic elements, which is routinely achievable using Inductively Coupled Plasma Mass Spectrometry (ICP-MS)-based methods, its low ppm detection limits and other advantages make it well suited for both screening for toxic elements and accurate quantitative analysis, assuming sample preparation and calibration are car-

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Element	**K_α**	**K_β**	**L_α**	**L_β**	**Common Interferences** [a]
Mercury (Hg)	70.82	80.25	**9.99**	**11.82**[1]	[1]Br K_α 11.92
Lead (Pb)	74.97	84.94	**10.55**[3]	**12.61**[4]	[3]As K_α 10.54 [4]Fe K_α sum peak 6.40 * 2 = 12.80
Arsenic (As)	**10.54**[2]	**11.73**	1.28	1.32	[2]Pb L_α 10.55
Selenium (Se)	**11.22**	**12.50**[5]	1.38	1.42	[5]Pb L_β 12.61

Table 1: Line energies (in keV) for the four target elements and common interferences.

[a]The most common energies used for detecting these elements are highlighted in bold text. Most portable XRF analyzers have poor sensitivity at energies < 2 keV and > 40 keV, and peaks showing up at these energies are typically not observed.

ried out properly. To give a few examples, XRF has been used to determine toxic elements in supplements [25, 19, 20, 17, 12], chromium in medical-grade stainless steel instruments [18], bromine in flour [2], mercury in face creams [21, 13, 34], zinc and titanium in sunscreens [4], silver nanoparticles in supplements [24], lead poisoning investigations [23], and Regulation of Hazardous Substances (RoHS)/Waste Electrical and Electrical Equipment (WEEE) type applications (monitoring lead, mercury, cadmium, and chromium in consumer products) [27].

XRF theory and instrumentation is described in more detail elsewhere [15, 33]. In brief, each element typically gives two major peaks, as shown in Table 1. The terminology for each peak uses a K or L to refer to the shell from which the electron was removed, and a subscript to refer to the shell from which an electron transition fills this hole (α is next higher shell, β is second higher shell). As shown in Table 1, an XRF spectrum of a sample containing arsenic will show K_α and K_β peaks at 10.54 and 11.73 kilo electron volts (keV), respectively, at an intensity ratio of 5:1 (Figure 1). Similarly, an XRF spectrum of a sample containing lead will show L_α and L_β peaks at 10.55 and 12.61 keV, respectively, at an intensity ratio of 1:1 (Figure 2).

The simplicity of XRF spectra usually makes spectral interpretation fairly straightforward, but it should be noted that the presence of multiple elements in a sample, spectral overlaps, artifact peaks, and the limited resolution of the detector can render spectral interpretation more challenging for some types of samples [15]. This is reflected in the common interferences noted in Table 1. One common spectral overlap is due to the As K_α and Pb L_α peaks, which are too close in energy to be resolved. In order to avoid false positives for Pb, XRF manufacturers use the Pb L_β peak to determine Pb, and subtract the Pb contribution to the As K_α peak to quantify As.

The Journal of Regulatory Science published a paper on the use of Fourier Transform Infrared Spectrometry (FTIR) which provides guidelines to screen for counterfeit pharmaceutical products [9]. Similarly, U.S. Environmental Protection Agency (EPA) method 6200 [28], which describes determination of toxic elements in soil samples using handheld XRF, provides detailed information on performance verification, including analysis of quality control samples (i.e., energy calibration check, blanks, Standard Reference Materials (SRMs), and site-specific calibration standards). To the best of our knowledge, there are no published guidelines describing the use of handheld and portable XRF for field screening of consumer products other than a few Standard Operating Procedures for specific instruments.

This paper seeks to describe performance verification procedures, guidelines for spectral interpretation, and some examples of XRF use for FDA field applications. The scope of elements was limited to screening various consumer products for three of the elements (Pb, Hg, As) shown in Table 1. Each of these elements are well known to be toxic and are regulated in foods, drugs, and environmental samples. Although other elements can be added to the list of target elements, it should be understood that some cannot be detected via XRF (i.e., beryllium), some have higher detection limits or require different beam modes (i.e., cadmium and uranium), and others are highly unlikely to be present in consumer products (i.e., osmium and thorium). We hope that this information will promote development of improved XRF software to minimize false positives and negatives, encourage more effective use of XRF in field studies, and promote wider use of this technology to screen products for toxic elements.

2. Materials and Methods

2.1. Standards

A calibration check coin comprised of 316-grade stainless steel was supplied by the XRF vendor (Olympus, Waltham, MA). The blank was high-purity crystalline cellulose obtained from Premier Lab Supply (Port St. Lucie, FL). Certified reference materials (CRMs) containing 1000 ppm As and 1000 ppm Pb were purchased from High-Purity Standards (North Charleston, SC). The blank and CRMs were placed in single open-ended XRF sample cups and sealed with 3.5 μm Mylar film purchased from Premier Lab Supply. In general, thinner film is preferred, especially for monitoring light (low atomic number, Z) elements.

2.2. Samples

Samples were obtained from active shipment of packages coming into the U.S. Customs International Mail Facility (Torrence, CA) in April 2017. Packages were selected based on the

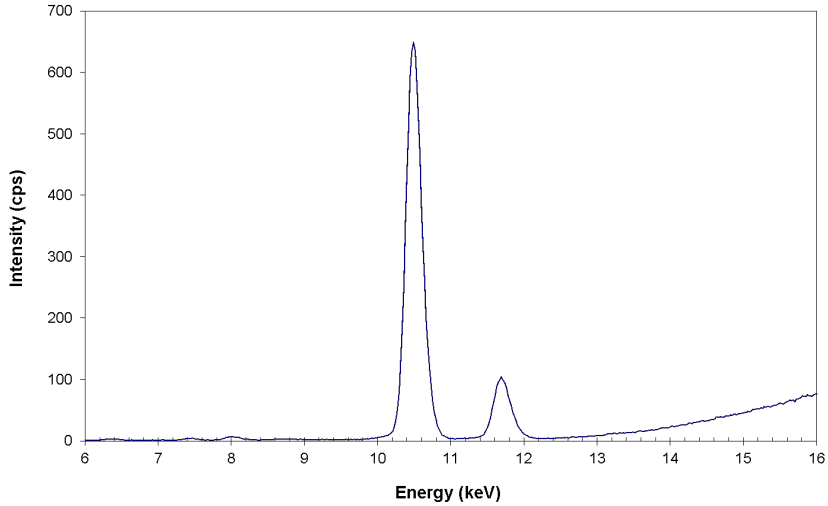

Figure 1: Expanded plot of the XRF spectrum of a CRM containing 1000 ppm As in cellulose, showing As K_α and K_β peaks at 10.54 and 11.73 keV, respectively, at an intensity ratio of ~5:1.

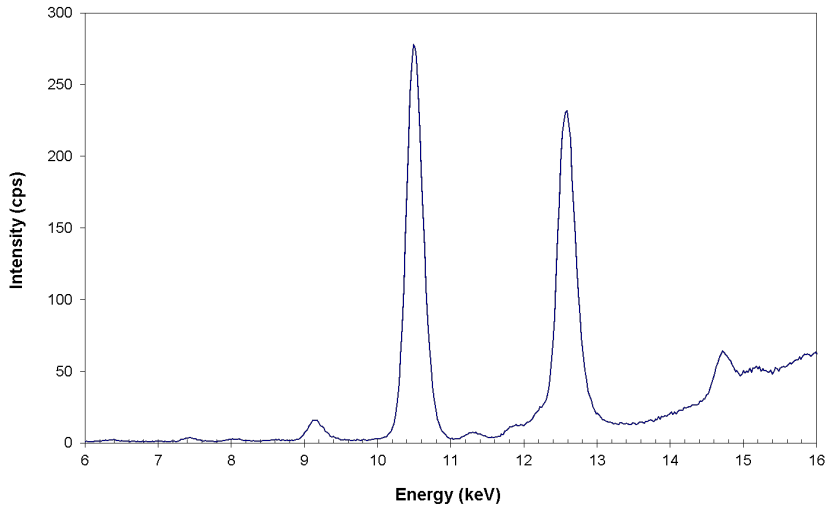

Figure 2: Expanded plot of the XRF spectrum of a CRM containing 1000 ppm Pb in cellulose, showing Pb L_α and L_β peaks at 10.54 and 11.73 keV, respectively, at an intensity ratio of ~5:1.

likelihood of containing products of interest such as cosmetics and dietary supplements. Although the XRF analyzer can be used to directly analyze the product through the packaging, this will give erroneous results due to the composition of the packaging and attenuation of X-rays from the product. Similarly, the samples can be placed in plastic bags and analyzed, but this also may give reduced fluorescence signals due to signal attenuation from plastic bags (which are thicker than 3.5 μm Mylar film) and inconsistent sample thickness inside the bag. Ideally, the sample should be removed from the product packaging, placed in a sample cup that is then filled to the top, and sealed with Mylar film prior to analysis. All of the samples in this study were treated in this manner, with the exception of face cream samples, which were analyzed in their packaging as described in more detail in the section on safety considerations.

2.3. XRF Analyzer

Analyses were performed using an Olympus/Innov-X X-5000 portable XRF analyzer equipped with a tantalum X-ray tube source and a Silicon Drift Detector. This model includes a touch-screen PC running Windows XP and a metal-lined test stand to prevent X-rays from escaping from the unit. A piece of Mylar film was placed over the analyzer window to protect it from inadvertent contamination from samples. This film was replaced when particulate or other contamination was observed. Sample cups were placed directly over the window for XRF analysis in "soil" mode using beam 2 excitation conditions (35 keV and the use of a specific filter between the X-ray

tube source and the sample) to give the lowest detection limits for the target elements of interest. Spectra were acquired using one-minute measurement times (real time, not live time), which provides a good compromise between fast analysis times and low detection limits. Confirmation of the presence of an element in a sample was performed in real time by the users via visual inspection and interpretation of it's XRF spectrum.

2.4. Safety Considerations

For some applications, such as direct analysis of soils, paint on walls, and large pieces of tableware, use of a handheld XRF analyzer in open beam mode may be the only way to perform a nondestructive analysis. While the X-ray tubes in these devices have relatively low energy (< 50 keV) and power (50 watts) compared to dental and medical X-ray equipment, it is important to follow the principle of "As Low As Reasonably Achievable" (ALARA) to minimize, if not preclude, radiation exposure. Here, this is achieved by operating the XRF analyzer in closed beam mode, in which the XRF analyzer is placed in a metal-lined test stand and operated from a portable PC equipped with interlock-type software, which automatically turns off the X-ray tube if the test stand is opened. This procedure ensures that any radiation exposure is at or below background levels. FDA requires XRF users to wear dosimeter badges to assess potential radiation exposure. Properly trained personnel have used these portable XRF analyzers for extended periods of time without any measured radiation doses above background levels, as indicated by dosimeter badges.

Another potential risk to users of XRF analyzers in field screening is exposure to samples which may contain drugs, toxic chemicals, and/or toxic elements. In this study, users were required to wear safety glasses and nitrile gloves to minimize exposure. Mercury-containing face creams present a different type of risk through inhalation of volatile forms of Hg, which are found in some of these products [7]. For those products, sampling handling should be minimized to reduce the risk of potential exposure, and therefore, these products were analyzed by removing the cap, covering the opening with Mylar film, inverting the container, and placing it over the XRF analyzer window. Other types of products containing powdered forms represent another potential risk through inhalation of particulate matter (i.e., a sindoor cosmetic powder containing high levels of PbO_4). Ideally, handling and analysis of these products would be done inside a fume hood to reduce the potential for inadvertent exposure to toxic substances.

3. Results and Discussion

For the purposes of this work, the authors developed a "quick start" guide provided in Appendix A, which describes the steps involved with setting up and using the Olympus/Innov-X X-5000 portable XRF analyzer for field screening applications. The process includes a calibration check using a stainless steel coin, analysis of a negative control sample (blank), and analysis of one or more positive control samples (SRMs or CRMs) to demonstrate proper instrument performance. Once the analyzer passes these performance verification checks, the users proceed to analyze products, confirming or ruling out the presence of the toxic elements of interest, and documenting the results on a worksheet (see Appendix B).

3.1. Evaluation of a Stainless Steel Calibration Check CRM

A calibration check is performed using a 316-grade stainless steel coin. Although the manufacturer refers to this as a calibration check, the term calibration is a misnomer in this context as the software does not calibrate either the x or y axis of XRF spectra during this process. The purpose of this check is simply to verify that the analyzer is working properly and the resolution meets specifications (< 0.165 keV peak width at half height for the manganese K_α peak).

3.2. Evaluation of a Negative Control CRM

Analysis of an appropriate blank containing non-detectable levels of the elements of interest is necessary to ensure the analyzer window and optics are free of contamination, especially for the target elements of interest. Figure 3 shows an XRF spectrum of high-purity powdered cellulose. The spectrum shows a broad Bremsstrahlung peak in the range of 12-36 keV, which is due to scattering of X-rays from the source to the sample to the detector. The spectrum also shows several low intensity peaks that are due to fluorescence from metal-based materials in the X-ray optical system (iron, nickel, and copper) and/or contamination on the XRF analyzer window (bromine). Elevated background levels may compromise the detection limits, depending on the elements and energy ranges of interest. In the cellulose sample, zooming in more closely on the spectrum in the range of 9-13 keV does not show the presence of any peaks associated with the four toxic elements of interest (Hg, Pb, As, and Se).

3.3. Evaluation of Positive Control CRMs and Positive Identification of an Element

Analysis of CRMs (or SRMs) provides assurance that the analyzer can correctly identify the elements of interest. For this work, 1000 ppm CRMs were used, but in future work these would ideally be at concentrations closer to the limit of quantification (~10-20 ppm, depending on the element and matrix). Figures 1 and 2 show XRF spectra of 1000 ppm As in cellulose and 1000 ppm Pb in cellulose, respectively. These spectra illustrate the logic behind how an element can be positively identified in a sample (the "golden rule" of XRF interpretation). An element is considered to be positively detected when three conditions are satisfied:

1. The spectrum shows the K_α or L_α peak for that element with a peak maximum within ±0.05 keV of its tabulated line energy.
2. The spectrum shows the K_β or L_β peak for that element with a peak maximum within ±0.05 keV of its tabulated line energy.
3. The intensity ratio of these two peaks are approximately equivalent to their theoretical values (5:1 for K_α/K_β peaks and 1:1 for L_α/L_β peaks).

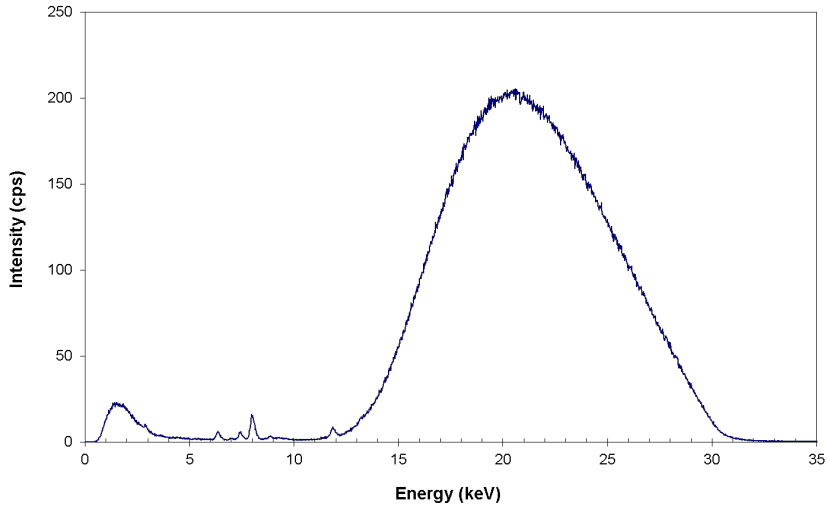

Figure 3: XRF spectrum of a cellulose blank. The broad peaks in the range of ~13-30 and 1-4 keV are due to backscattered X-rays from the X-ray tube source (Bremsstrahlung). The low intensity peaks at 6.4, 7.5, 8.0, and 11.9 keV, are K_α peaks from iron, nickel, copper, and bromine materials in the X-ray optical system and/or contamination on the XRF analyzer window, respectively.

Positive identification of an element using this logic may not always be possible due to spectral overlaps (see Table 1), artifact peaks (sum peaks and escape peaks), or when the concentration of an element is close to the detection limit. When in doubt, users are encouraged to have a trained analyst interpret the spectrum. Ideally, this same logic should be encoded into XRF analyzer software, but unfortunately, few portable XRF manufacturers have made an effort to do so to date. This underscores the importance of having the user manually interpret the spectrum of each product to avoid false positives.

XRF analyzers and their software algorithms can give false positives (erroneously indicating an element as being present). This is demonstrated in Figure 4, which shows the XRF spectrum of a product containing percent levels of iron. The XRF software incorrectly identified Pb in this sample at an approximate concentration of 1000 ppm, despite the fact that the Pb L_α peak is not present and the low intensity peak at 12.80 keV is not centered within 0.05 keV of the Pb L_β tabulated energy (12.61 keV). This false positive can be attributed to the high levels of iron in this product, which give a sum peak at twice the energy of the Fe K_α peak (6.40 keV * 2 = 12.80 keV), and which the software incorrectly interprets as lead. Users should be aware of this flaw in the vendor software and follow the "golden rule" for positive identification of a toxic element.

It should also be noted that XRF analyzers can give false negatives (not indicating an element as being present). In many cases, a handheld XRF analyzer will not indicate the presence of rare earth elements such as osmium or uranium in the displayed list of detected elements and their concentrations. This is yet another drawback in typical XRF software, albeit one that can be attributed to the end user during the specification and purchase process. Prior to delivery of the XRF analyzer, the vendor calibrates it only for the target elements specified by the purchaser. To avoid false negatives, the user should have the XRF analyzer calibrated for all of the target elements of interest and/or use manual interpretation of the spectra to identify unexplained peaks and confirm positive detection of an element.

A common misconception related to the use of XRF analyzers is that users expect the element concentrations computed by the software to be accurate. While XRF analyzers can give results for soil analysis that are within 20% of their true values, one should not expect an analyzer calibrated at a factory to give accurate results for their particular samples and elements of interest. Moreover, it is impractical if not unfeasible to calibrate an XRF analyzer for a huge variety of FDA-regulated products that comprise widely varying matrices and compositions. Given that the primary goal here is to screen for potentially toxic or violative products and not accurate quantification, users should keep in mind the idea of "sample triage", which in this case is to quickly analyze products, evaluate their spectra, and determine whether or not they contain toxic elements. Such toxic products can be detained from entering commerce and/or set aside for possible regulatory action based on confirmatory analysis using validated methods that require significantly more effort (i.e., homogenization of the sample, preparation of appropriate standards, and elemental analysis via XRF, ICP-MS, or some other atomic spectrometry-based method).

3.4. Sample Spectra and Representative Results

The vast majority of the products analyzed (95%) did not contain detectable levels (> 10 ppm) of Hg, Pb, As, or Se. It should be noted that manual interpretation of the spectra of such products is fairly straightforward and rapid. Here, the analyst zooms in the x-axis of the XRF spectrum to focus on the region of interest (~9-13 keV to detect the peaks of interest - see Table 1), and the y axis (~0-10 counts-per-second (cps)) to show any potential low intensity peaks that might be present. If the user observes neither K_α peaks for As or Se, nor L_α peaks for Hg or

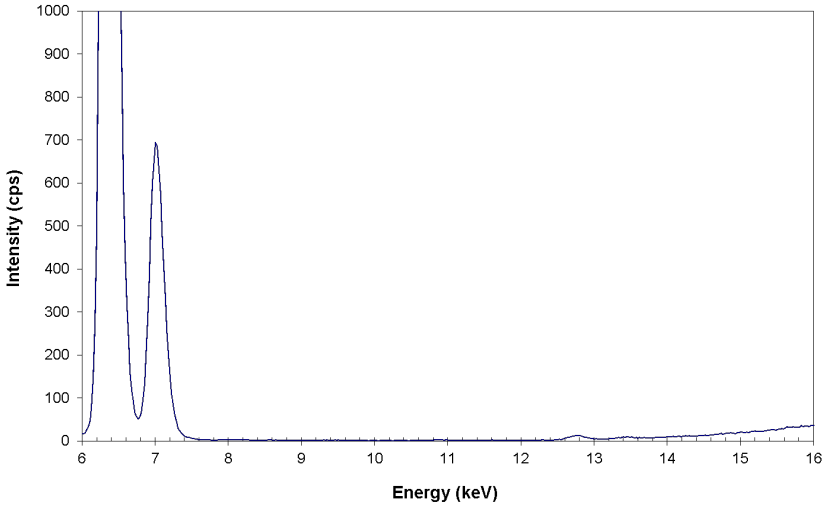

Figure 4: Expanded plot of the XRF spectrum of a product containing > 10% iron showing the Fe K_α and K_β peaks at 6.40 and 7.06 keV, respectively, at an intensity ratio of ~5:1. The low intensity peak at 12.8 keV is due to two Fe fluorescence photons reaching the detector at the same time (sum peak).

Pb, then the product is deemed to contain non-detectable levels of these toxic elements, and the analysts proceed to the next product.

Results from the "positive" samples identified over the course of this field screening are shown here to illustrate potential products of interest and their XRF spectra. Figure 5 shows an XRF spectrum of a face cream product containing ~18,000 ppm or 1.8% Hg. While this is only an approximation, if a similar concentration were confirmed with a validated quantitative method, it would be more than four orders of magnitude above the 1 ppm FDA limit [31] for this type of product. XRF offers a rapid, effective, and reliable way to identify these products in the field and prevent them from entering commerce.

Figure 6 shows an XRF spectrum of a hair coloring product containing ~5,200 ppm Pb. Lead acetate-containing hair coloring products may contain up to 0.6% (6000 ppm) lead [30]. The use of XRF to screen for lead as an impurity in makeup and other cosmetic products for which FDA recommends a maximum level of 10 ppm lead [29] represents another excellent application area. These types of cosmetic products require time-consuming and problematic digestion for analysis by ICP-MS, whereas XRF analysis is a far faster and easier means to screen for lead and other potentially toxic elements in such products.

Other results of potential significance among the 183 samples that were screened included an underarm cream containing ~0.14% Hg, a vitamin containing > 10% iron, a lip gloss containing ~1% barium, a kratom herbal product containing ~0.21% manganese, and two Asian herbal products containing ~100 ppm levels of selenium and lead.

During the course of screening, results were documented in an XRF analysis work sheet shown in Appendix B. This provided a convenient means to summarize the results of each product, including product name, elements detected, and their concentrations. At the end of each day, sample spectra and results were downloaded from the XRF analyzer and uploaded into Microsoft Excel for backup, storage, and data analysis. Products found to contain detectable levels of the target elements were set aside for follow-up analysis and possible regulatory action.

The use of XRF for field screening is very efficient - consider the fact that two three-person teams analyzed 183 products over a seven-hour time period in their first collective attempt at this type of study. Contrast this with random sample collection and laboratory-based analysis of the same number of products using conventional methods based on microwave digestion and ICP-MS. While the latter method gives lower detection limits, sample preparation and analysis of these many products is far more time consuming (weeks versus one day) and the cost is far higher on a per-sample basis. Use of a portable XRF analyzer in this manner is cost effective, provides for "sample triage", and represents an efficient means to screen large numbers of samples, and, when appropriate, filter samples of potential concern to laboratories for quantitative analysis by ICP-MS methods.

3.5. Recommendations for XRF Use for Field Screening

Anyone using portable XRF should be properly trained in its theory, operation, and its use for qualitative and quantitative analysis [25]. Training on specific XRF instruments and software is often offered by vendors of such analytical instrumentation. The Denver X-Ray Conference and other organizations offer XRF workshops and training [8, 11]. Users should also be aware of the safety precautions described in Section 2.4.

Groups considering using XRF in field work on a larger scale should consider adopting their own training program for their intended applications. In 2010, FDA developed a 4-day training course focused on field screening and regulatory applications of XRF. This course includes theory, products and elements of interest, hands-on sessions to develop confidence in

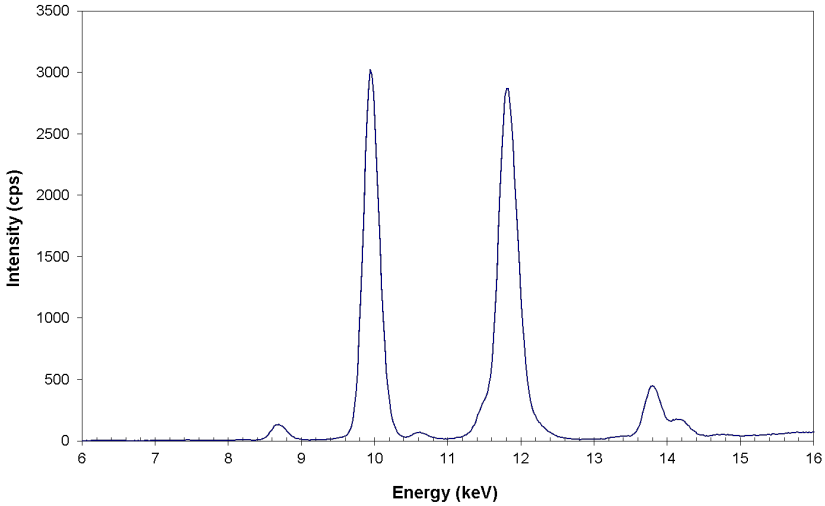

Figure 5: XRF spectra of face cream sample containing ~18,000 ppm Hg.

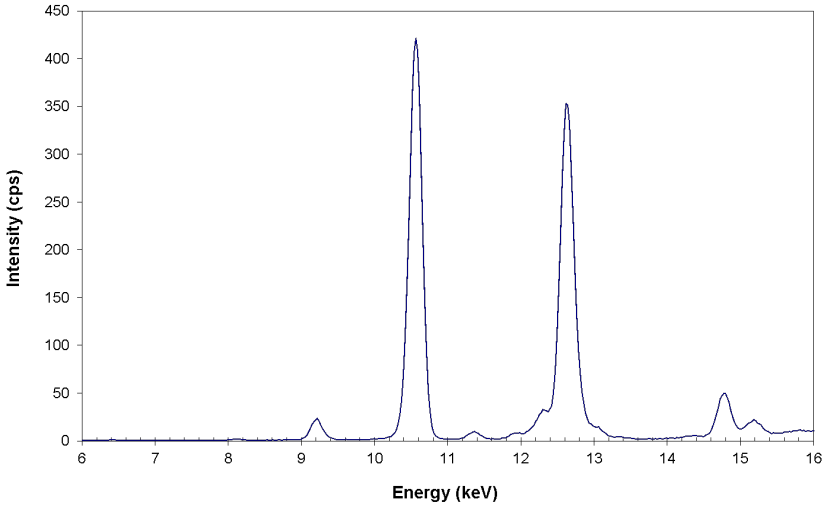

Figure 6: XRF spectrum of hair coloring cream containing ~5200 ppm Pb

spectral interpretation, and proficiency tests to assess how well the users succeeded in correctly analyzing test set samples. To date, over 100 FDA staff have completed this training and all have achieved scores of > 70% on correctly identifying a variety of elements, some at low levels, and some with spectral overlaps, in the test set samples. For the field screening activities at the IMF, many of the users had no prior experience in using XRF. An abbreviated, half-day training session was given to demonstrate the set up and use of the XRF analyzer and software and provide users with hands-on experience analyzing proficiency test samples. In the described field screening of samples at the IMF, new users worked alongside a trained lab analyst who facilitated setting up the instrument and software, interpreting XRF spectra, and improving their confidence and skill in elemental analysis.

The analysis of negative and positive control samples (i.e., blanks and check standards) is deemed critical for this application. Such data demonstrate that the XRF analyzer is free of contaminants from prior samples, and can correctly identify the elements of interest at low levels. In future work, the positive control samples should be lowered from 1000 to ~20 ppm, which will still permit observation of the weaker K_β peaks for As and Se under most conditions and will provide confirmatory evidence of the ability of the XRF analyzer to monitor low ppm levels of the toxic element(s) of interest. Note that each XRF analyzer has slightly different detection limits, and a more rigorous assessment of these for each target element may not be appropriate for a field setting and analysis of widely varying product compositions. Future XRF software would greatly benefit from the adoption of an approach developed by Arzhantsev and coauthors, which automates the positive identification of an element from XRF data based on a signal-to-noise ratio cut-

off [3]. Moreover, XRF vendors are urged to incorporate more sophisticated algorithms for postulating the detection of an element, which will significantly reduce the potential for false positives and false negatives.

The use of three-person teams per XRF analyzer clearly improved sample throughput. The biggest bottleneck in this screening process was not XRF analysis but finding packages containing potential products of interest and placing the samples into cups. Although one person can perform all of the relevant tasks, it is much more efficient to use a group of three people, with one person opening boxes and identifying potential products of interest, a second removing the products from the packaging and placing them into XRF sample cups, and the third operating the XRF analyzer, interpreting the spectra, and documenting the results. Although the manual interpretation step is prone to human error, particularly for users with limited XRF experience, having the user confirm the presence of a toxic element and a trained analyst serving as a second set of "eyes" to interpret spectra is recommended to minimize false positives and false negatives.

One of the most common questions from consumer safety officers considering field use of XRF is, "What sort of products should I be looking at and how do I know what elements and levels are significant?" The answer is not simple, due to the wide variety of products, exposure routes (skin, ingestion, and/or inhalation), dose or serving size, frequency of exposure, toxicity of the element(s) in question, and the age, sex, race, and health of the affected individuals. The most appropriate field application of XRF is screening for ppm and higher levels of toxic elements in products where they are likely to be present. XRF is not deemed suitable for monitoring toxic elements in most food items, primarily because the levels of toxic elements found in these products are typically well below the XRF detection limits. A notable exception to this is spices, which can be contaminated with heavy metals from the environment or grinding equipment. A risk-based approach to target specific products based on where and how they enter the U.S. should be carefully considered prior to any future field screening work.

One important application is identifying Hg in face creams, particularly since the Hg content in such products has been found to reach percent levels [21, 13, 34], coupled with the fact that FDA has a 1 ppm regulatory limit for mercury in this type of product [31]. Similarly, XRF could be used to monitor toxic elements in other cosmetic products [12]. Another important application is detecting ppm and higher levels of toxic elements in dietary supplements. As per the Dietary Supplement Health and Education Act (DSHEA) [14], the onus of evaluating the safety of a supplement is placed on the manufacturer. FDA provides no limits for toxic elements in these products, with products reviewed on a case by case basis. However, studies have shown that some dietary supplements can contain toxic elements up to percent levels [25, 19, 20, 17, 12], and XRF is clearly a valuable tool for efficiently and rapidly identifying such contaminated products. Development of new regulatory limits for toxic and catalytic elements in drugs in both Europe [6] and the U.S. [32] is stimulating the development of XRF methods [10, 5]. The future should see more widespread use of XRF as the method of choice for routine monitoring of toxic elements in raw materials and final products by manufacturers and regulatory agencies such as the FDA, and consumer watchdog groups.

4. Conclusions

To the best of our knowledge, this is the first publication providing specific recommendations for use of XRF in field screening activities related to elemental analysis of FDA-regulated products. Relevant figures of merit include no sample preparation, multi-element analysis, detection limits in the range of 1-10 ppm for the four toxic elements of interest (Hg, Pb, As, and Se), and analysis times of a minute or less. XRF provides a unique capability to rapidly screen large numbers of samples prior to a much more time-consuming and costly ICP-MS analysis. XRF's advantages of cost and speed in screening applications involving detection of toxic elements in large numbers of consumer products is often not appreciated or exploited. As shown in this work, this type of screening can be done in a field setting and used to analyze ~100 products over the course of a work day. While XRF analyzers are simple, reliable, and can be operated for years with little or no maintenance, it is critically important to provide users with adequate training to ensure their safety, minimize false positives and false negatives, ensure reliable results, and to focus on appropriate products and elements of interest. More widespread use of XRF in this manner will provide for more timely and proactive responses to protecting the public health through more routine monitoring of toxic elements in FDA-regulated products.

5. Declaration of Conflicting Interest

The authors declare no conflicts of interest.

6. Disclaimer

The views expressed here are those of the authors and should not be construed to represent the views or policies of the FDA. Any reference to a specific commercial product, manufacturer, or otherwise is for the information and convenience of the public and does not constitute an endorsement, recommendation, of favoring by the FDA.

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10. Supplemental Materials

QUICK START GUIDE FOR USE OF THE INNOV-X X-5000 XRF ANALYZER FOR FDA FIELD INVESTIGATIONS

SCOPE:

This document provides abbreviated instructions for the set up and operation of the Innov-X model X-5000 XRF analyzer in a field setting. More detailed instructions are provided in the SOP and in the Innov-X User's Guide.

STEPS:

1. SETUP
   a. Setup the XRF analyzer and attach to conventional power or to the battery.
   b. Turn the instrument on and wait for the Innov-X software to start.
   c. Minimize the XRF window, click on the time in the lower right portion of the screen, and make sure the time and date are set properly. This is VERY IMPORTANT as the motherboard battery has a limited lifetime and it may be difficult to retrieve XRF data if the X-5000 system defaults to an incorrect date.
   d. Maximize the XRF window, enter user name *admi* and password *1234*, then press *Login*.
   e. Check the Kapton window to confirm that it is intact and free of contamination. Clean carefully if dirty or replace if defective.
   f. Cover the window with a sheet of Mylar prior to analysis. This will prevent contamination and potentially misleading results.
   g. Place the 316 stainless steel coin over the window and click *Cal Check*. This should verify that the analyzer is functioning properly.
   h. Click on *Mode* then *Soil 3 Beam*. This mode of testing is most appropriate for detecting low levels of toxic elements in low density matrices.
   i. Click on *Setup* then *Test Condition*, click on the *Test Time* tab, set *Beam 1 Min* to 0 and *Beam 1 Max* to 60, set *Beam 2 Min* to 0 and *Beam 2 Max* to 60, set Beam 3 Min to 0 and *Beam 3 Max* to 60, then click *Save*. Note that longer max test times may be needed when analyzing samples containing low levels of toxic elements.
   j. Click on the *Soil Option* tab, select *Customized Powershot(s)*, click *Heavy Elements*, *Transition Elements*, or *Light Elements* depending on the target elements of interest. If the goal of the investigation is to identify only As, Se, Hg, and Pb, then select *Transition Elements*. If the target elements include Cd and other high Z (atomic number) elements, then select *Transition Elements*. If the target elements include Cr and other low Z elements, then select *LEAP*. Once the appropriate beam modes have been selected, click *Save*.

2. ANALYZE SAMPLES
   a. Click on *Analysis*.
   b. Click on … (located under and to the right of the box marked 3 Beam Soil) and enter the necessary information about the sample and your identity. This information may be dictated by an assignment. Note that for each sequential analysis, information that is unique to that particular sample must be entered.
   c. Place the sample over the window then click *Start*. Ideally, the sample will be placed in a plastic bag or XRF sample cup. Analyzing the sample in its original packaging may give misleading results.
   d. Click and drag across the appropriate region of the spectrum to zoom in on the peaks of interest.
   e. Confirm the presence of each tentatively identified element by clicking on *Elements* to display the Periodic Table and clicking on the suspected element.
   f. Repeat the steps above for each sample.

3. DOCUMENT RESULTS
   a. Click *View Data* then *Print* to save the test information, results, and spectrum to a PDF file which should then be stored in an appropriately named folder on the desktop.
   b. Transfer the folder and its contents to a removable hard drive for subsequent transfer to another PC for printing, backup, and storage.

Appendix A: Quick start guide for use of a portable XRF analyzer for FDA field investigations.

XRF FIELD ANALYSIS WORKSHEET page 1 of 4

Instrument: Innov-X X-5000 S/N: 202220					**Date**:	28-Apr-16
Test time	sec	**Soil Mode**	**Investigators:**	LOS-DO XRF team	Start:	9:00 AM
Beam 1	0	☐ Heavy Elements	**Analysts**:	SF Lab XRF team	End:	11:30 AM
Beam 2	60	■ Transition Elements	**Location:**	Los Angeles IMF		
Beam 3	0	☐ Light Elements	**Products:**	miscellaneous		

READING #	SAMPLE DESCRIPTION	SAMPLE PREP *	INSPECTION OF SPECTRUM AND REPORTED CONCENTRATIONS IN ppm	ADD'L INFO
1	316 stainless steel "coin"	none	Calibration: ■ passed ☐ failed; Resolution 165 eV	
2	cellulose blank	C	As [ ], Hg [ ], Pb [19], Se [ ]	
3	1000 ppm As check standard	C	As [1955], Hg [34], Pb [20], Se [1]	
4	1000 ppm Pb check standard	C	As [263], Hg [23], Pb [1645], Se [2]	
5	Grow Tall bone dietary supplement	C	As [ ], Hg [ ], Pb [12], Se [ ]	
6	Furefoo dietary supplement	C	As [2], Hg [ ], Pb [6], Se [141]	
7	VigRx plus male supplement	C	As [ ], Hg [ ], Pb [ ], Se [ ]	
8	Yunnan Baiyou Jiaonang	C	As [ ], Hg [ ], Pb [23], Se [ ]	
9	Autrin 600 vitamin	C	As [ ], Hg [ ], Pb [ ], Se [ ]	Fe > 10%
10	Face cream from Thailand	P	As [ ], Hg [18,000], Pb [ ], Se [ ]	

* **C**-sample cup, **G**-ground, **Z**-ziplock or whirlpak, **P**-original packaging, **BP**-blister pack

Filename containing XRF results:	ExportData-04-28-2016.xls
Filename containing XRF spectra:	ExportSpm-04-28-2016.xls

Appendix B: Example of a completed XRF field analysis worksheet.