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Performance comparison of two Olympus InnovX handheld x-ray analyzers for feasibility of measuring arsenic in skin *in vivo* – Alpha and Delta models

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ABSTRACT

The Figure-Of-Merit (FOM) performance, a combination of detection limit and dose, is compared between two generations of handheld X-Ray Fluorescence (XRF) spectrometers for the feasibility of *in vivo* XRF measurement of arsenic (As) in skin. The Olympus InnovX Delta model analyzer (40 kVp using either 37 or 17 μA) was found to show improvements in Minimum Detection Limit (MDL) using arsenic As-doped skin calibration phantoms with bulk tissue backing, when compared to the first generation InnovX Alpha model (40 kVp, 20 μA) in 120 s measurements. Differences between two different definitions of MDL are discussed. On the Delta system, an MDL of (0.462 ± 0.002) μg/g As was found in phantoms, with a nylon backing behind to mimic bulk tissue behind skin. The equivalent and effective doses were found to be (10 ± 2) mSv and $\sim 7 \times 10^{-3}$ μSv respectively for the Alpha and (15 ± 4) mSv and $\sim 8 \times 10^{-3}$ μSv respectively for the Delta system in 120 s exposures. Combining MDL and effective dose, a lower (better) FOM was found for the Delta, (1.7 ± 0.4) ppm $mSv^{1/2}$, compared to (4.4 ± 0.5) ppm $mSv^{1/2}$ for the Alpha model system. The Delta analyzer demonstrates improved overall system performance for a rapid 2-min measurement in As skin phantoms, such that it can be considered for use in populations exposed to arsenic.

1. Introduction

1.1. Arsenic and health

Due to the relatively widespread nature of arsenic in soil and water (Hindmarsh and McCurdy, 1986), it builds up in the sedimentary layer of ponds and lakes and, due to opposing eH and pH levels, it accumulates into ground water, where it can enter the water supply. In addition, smelting by-products, lumber preservatives, pesticides, food additives and coal burning are sources of arsenic in the environment (Agency for Toxic Substances and Disease Registry ATSDR, 2007; Ratnaike, 2003; Smedley and Kinniburgh, 2002). In terms of human exposure pathways, the most common route of entry of arsenic into the human body is from consumption of contaminated drinking water (Setton et al., 2013; Smith et al., 2000; Williams et al., 2007). Chronic arsenic exposure causes health problems: it has been associated with various cancers and cardiovascular diseases (Chiou et al., 1995) and skin effects such as hyperkeratosis (by altering keratinocyte propagation). It is perhaps most well-known for skin cancers (Smith et al., 1992; Vega et al., 2001) such as squamous cell carcinomas, intra-epidermal and basal cell carcinomas (Maloney, 1996).

Methods of measuring arsenic levels in the body include its assessment in urine, nails and hair samples. Contamination and breakage issues with the latter have been documented (Maes and Pate, 1977; Raab and Feldmann, 2005) and urine measurements are complicated because of the potential for exposure to organic arsenic from seafood (Borak and Hosgood, 2007), which is less toxic (Hughes et al., 2011). Due to the affinity of arsenic to sulfhydryl groups in keratin-rich tissues, such as skin and nails, it accumulates in these tissues and therefore builds up over time (Schoolmeester and White, 1980) preserving a record of human exposure to the element. The attractive nature of finger or toe nail measurements is due to their slow growth (Adair et al., 2006; Karagas et al., 1996). However, because of the health effects described above, skin is a site of elevated biological significance. Quantification of arsenic in skin would be quantification in an organ at risk. Skin can potentially be assessed through *ex vivo* biopsies as a

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method of routine monitoring, but this would be an invasive and at best uncomfortable procedure. A method that permits non-invasive, low risk and painless monitoring of arsenic levels over time would potentially be of use in the assessment of exposure risk.

1.2. Previous approaches to in vivo XRF measurement

The method of X-Ray Fluorescence (XRF) is an attractive quantification modality since highly sensitive samples can be measured without damaging or altering the sample itself. This has been exploited for *in vivo* monitoring of various elements in the human body – uranium (O'Meara et al., 1998), strontium (Moise et al., 2014) and lead (Nie et al., 2006) in bone and platinum in neck tumors (Jonson et al., 1988) due to its non-invasive nature. The first work to develop a system for the *in vivo* measurement of arsenic in skin *in vivo* was done using a Cd-109 radioisotope (Studinski et al., 2004) and then I-125 (Studinski et al., 2005) as the source of excitation. Studies were performed in arsenic-doped skin-mimicking calibration phantoms, made from epoxy resin, providing a skin calibration phantom-based Minimum Detection Limit (MDL) of (2.3 ± 0.1) ppm, where ppm represents μg As/g dry weight. Ultimately an *in vivo* arsenic XRF study was performed, using the latter system. An improvement was noted by using an x-ray tube as the source –0.40 ± 0.06 ppm – for a benchtop system (Studinski et al., 2006) and then later using an InnovX Alpha 4000 S model handheld XRF analyzer –0.446 ± 0.006 ppm – (Fleming and Gherase, 2007). Doses for both techniques were low, delivering an effective dose of < 1 μSv. The detection limits of tube-based systems now approach the median value of 0.43 ppm determined for the levels of arsenic in *ex vivo* skin scraping samples from an exposed population in West Bengal, where population levels were found to range from 0.33 to 4.36 ppm (Samanta et al., 2004).

1.3. Considerations for development of new systems

In XRF, the choice of an incident energy that is close to the As absorption edge has benefits in terms of maximizing the total interaction cross section. The cross-section is dominated by the photoelectric effect in the range of source energies involved in As XRF measurements (~15–25 keV) and is listed in Table 1, for various incident energies. Acting against the gain in cross section is an increasing low-energy tail, due to Compton scattering of source photons, that can encroach on the arsenic characteristic x-ray peaks at ~10.5 and 11.7 keV and elevate the background. These factors act against each other and a gain in the former is not assured to improve the MDL if it is accompanied by a strong enough increase in the latter. Benchtop spectrometers can be equipped with various monochromators combined with tube voltage and filter controls which have the ability to narrow the incident x-ray photon energy range around a desired value that represents a balance between these two factors.

Portable XRF analyzers are purpose-built and rely on filtration between the tube and sample, both to shift the energy and alter the shape of the incident energy spectrum, with the ability to change x-ray tube voltage not supported in all commercially available units. The short analysis time required with handheld analyzers is an attractive feature of that approach, but the ability to select source photon energy through use of monochromators, variable voltage and simultaneously adjustable filtration vary among analyzer manufacturers. It must be noted that the energy selection itself, with x-ray tubes, is somewhat limited in its meaning since an x-ray tube will not emit a single excitation energy, as listed in the table earlier, but a continuous spectrum of energies as defined by characteristic x-rays from the tube's anode and a broad continuum feature due to Bremsstrahlung photons emitted from the anode by slowing down of electrons in the bulk material of the anode. Thus, a replacement of an isotope-based with a tube-based source has its limitations in terms of energy selection.

Source intensity with a tube-based spectrometer can be varied with anode current. Handheld XRF units offer a current on the order of ~20–200 μA. While voltage is typically fixed, as mentioned above, a change in current can improve MDL. On the other hand, use of a handheld XRF analyzer, with a variable combination of source conditions (one or more of voltage, current, filtration), may allow for greater feasibility in exploring improvements in the MDL achievable with the handheld XRF technique. The handheld XRF analyzer, used in the previous work (Fleming and Gherase, 2007; Gherase et al., 2010a), was an Olympus InnovX Alpha 4000S model. Since the previously published work, a second generation handheld XRF system, InnovX Delta, was introduced and offers some flexibility in variation of source conditions, which was not offered by the predecessor. Two 40 kVp measurement modes (referred to as beams), with varying filtration and pre-determined current settings, are offered as well as a 15 kVp mode. The Bremsstrahlung component resulting from the 15 kVp setting would overlap with arsenic characteristic x-rays and prevent its use for this application. Indeed, this mode is offered specifically for probing lower energies, below ~8 keV. Within each 40 kVp mode, both current and filtration are pre-determined, but vary from one mode to the next.

In this work, a performance appraisal of the second generation Delta model analyzer is described, in terms of spectrometer calibration (MDL) with the same set of arsenic doped skin phantoms prepared from epoxy resin, and direct comparisons against a first generation Alpha 4000S unit are reported for the intended XRF application of measuring arsenic in skin. These comparisons are made in the form of (a) MDL under various experimental conditions, (b) associated radiation dosimetry and (c) overall performance through a figure of merit that combines MDL and dose. Throughout, a more inclusive definition of MDL is also estimated, for all experimental conditions, that retains all sources of variance in parts of the XRF calibration procedure. Due to the low levels of As expected in skin based on *ex vivo* biopsy samples, this provides a conservative estimate of system MDL which has not been previously used for As XRF calibration. Qualitative analysis of XRF spectra obtained with both spectrometers is also discussed.

Table 1
Comparison of characteristics for candidate sources of As XRF.

Line	E (keV)[a]	Total (and photoelectric) cross-section As[b](x10^{3} barns/atom)	Main compton scatter Peak energy (keV)			
			20°	45°	90°	180°
Various[c]	12.0	21.68 (21.50)	12.0	11.9	11.7	11.5
	12.5	19.56 (19.38)	12.5	12.4	12.2	11.9
	13.0	17.70 (17.54)	13.0	12.9	12.7	12.4
	14.0	14.65 (14.50)	14.0	13.9	13.6	13.3
	15.0	12.26 (12.12)	15.0	14.9	14.6	14.2
	16.0	10.35 (10.22)	16.0	15.9	15.5	15.1
Mo Kα	17.4	8.22 (8.10)	17.4	17.3	16.9	16.3
Mo Kβ	19.6	6.00 (5.90)	19.6	19.4	18.9	18.2
Various[c]	20.0	5.68 (5.58)	20.0	19.8	19.3	18.6
Rh Kα	20.2	5.55 (5.45)	20.1	19.9	19.4	18.7
Ag Kα	22.1	4.33 (4.24)	22.1	21.8	21.2	20.3
Rh Kβ	22.7	4.02 (3.93)	22.7	22.4	21.8	20.9
Various[c]	25.0	3.09 (3.01)	24.9	24.7	23.8	22.8

[a] As K-edge at 11.87 keV from Deslattes et al., 2003.
[b] Berger et al. (2010).
[c] For comparison purposes.

2. Experimental setup and method

2.1. Calibration phantoms

Calibration phantoms were prepared using polyester resin (Bondo Corp., Atlanta, GA, USA). Resin phantoms in the shape of cylindrical discs were prepared. The properties of the phantoms, used for both systems, are listed in Table 2. For the Alpha 4000 S system, experiments