Member's Paper

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In vivo trace element analysis: Applying radiation physics to find a needle in a haystack

Joanne M. O'Meara
Department of Physics and Astronomy, McMaster University,
Hamilton, ON, Canada L8S 4M1

An obstetrician friend bumps into you at a party and starts recounting a recent challenging case. One of her patients reported suffering from lethargy and abdominal pain. This in itself was not immediately alarming, however, given the patient's history of two early mid-trimester miscarriages and several probable 1st-trimester miscarriages, the cause of this abdominal pain was investigated. The patient was found to be suffering from lead poisoning, as indicated by numerous factors, the most telling of which being elevated blood-lead levels. Given the possible health risks to the foetus and subsequently a nursing child, the source of this lead exposure was sought. However, therein lay the mystery. Thorough analysis of the family environment revealed no source of lead contamination, and her husband and two other children had normal blood-lead levels. It was revealed that the patient had suffered acute lead encephalopathy when she was 18 months old but has since had no known lead exposure.

Your friend speculated that with calcium turnover greatly increased during pregnancy, the patient was suffering from lead poisoning due to the mobilisation of lead stores from her bone. The obvious choice of treatment was chelation therapy, but without concrete evidence of high bone-lead levels it was a difficult decision to treat due to the potential harm to the foetus from chelation. In this case, a means for assessing bone-lead levels non-invasively, *in vivo*, would have provided an invaluable tool for your friend in helping the patient as soon as the problem was identified, rather than waiting until after childbirth during which time the child may have been lost. This is precisely the type of motivation for ongoing research at McMaster University and elsewhere in the field of *in vivo* trace element analysis.

For the past 20 years, the application of x-ray fluorescence (XRF), a standard elemental analysis technique, has been investigated for the purposes of measuring many toxic elements *in vivo*. In some cases, the source of exposure may be environmental. However, in the majority of cases, the development of measurement systems is driven by the need for better monitoring and health care for individuals exposed to toxic elements in occupational settings, *e.g.* Pb, Cd, U, and Hg. In addition, the need for measuring the *in vivo* concentrations of such elements as gold and platinum has arisen due to exposure to these toxic metals through medical procedures; gold salts are used in treating rheumatoid arthritis and platinum-based drugs are a common choice in chemotherapy.Research has focussed on developing systems to measure these elements generally in one of two sites, the bone matrix or the kidneys. The bone matrix represents the site of long term retention for elements such as lead and uranium. Therefore, measurements in this site give insight into the history of exposure of a given individual to these toxic metals. Other elements, such as Pt, Cd, Hg and Au, are better measured in the kidneys, as this organ can be a major retention site as well as often the organ to suffer damage due to metal accumulation.

XRF makes use of the unique electron energy levels to identify the elemental composition of an unknown sample. The sample is irradiated with x-rays or g-rays that interact through scatter and photoelectric absorption. When the incident radiation has energy greater than the K edge of an element, there is a significant probability that the element will absorb the photon and eject a K shell electron. With the element in an excited state, it can return to the ground state through emitting an Auger electron or an x-ray, with an energy corresponding to the difference between the K shell binding energy and that of an outer electron shell. Since the energy levels are unique to each element, the x-ray series emitted by an element has a characteristic energy signature that enables its identification. Furthermore, through careful calibration, the quantity of these x-rays detected can be used to determine the absolute amount of an element present in the sample.

In vivo XRF-based systems have been successful in measuring toxic elements of interest with high atomic numbers, *e.g.* Pb, Au, Hg, U, Pt, and to some extent Cd. This is because three critical parameters increase with increasing Z; fluorescence yield, K edge energy and characteristic x-ray energy. The higher fluorescence yield, as the name suggests, means that there is a greater probability of characteristic x-ray emission with every shell vacancy created instead of de-excitation through Auger electron emission. Therefore, there is an increased signal produced per unit irradiating flux. Higher K edge energies imply that a higher energy photon can be used to irradiate the subject. This results in the use of more penetrating radiation. Similarly, higher characteristic x-ray energies with higher Z elements result in greater penetrating capability of the outgoing signal. This is important in non-invasive measurements as the site of metal retention, bone, kidney, or liver, is shielded by a significant thickness of attenuating material.

Given that the element of interest has sufficiently high Z for XRF to be feasible, typically greater than 50, the optimisation of this *in vivo* probe must be undertaken for each element. There are a number of parameters that must be selected with a firm understanding of the underlying radiation physics principles. The first choice is whether the subject will be irradiated by grays from a radionuclide source or polarised x-rays produced by an x-ray tube. Polarised x-rays have beenused in the development of systems to measure Cd, Hg, Pt, and Au primarily. The major difficulty in all XRF systems is that the element of interest is present in trace quantities within a low Z matrix. Therefore, the vast majority of detected photons are scatter events that only give rise to spectral background and increase the count rate in the detector. Polarised photons can be used to minimise the number of scattered events detected, as there is a much-reduced probability of scatter along the direction of polarisation. The isotropic characteristic x-rays are detected with a suppressed background when the detector is positioned along this axis, thereby enhancing the signal to noise ratio.

The pros and cons of these two classes of XRF systems can be looked at in parallel. A successful radionuclide-based system uses a g-ray source with an energy that is just above the K edge of the element under investigation, as this corresponds to the greatest photoelectric cross section. Once a source has been chosen with an appropriate g-ray energy, a sufficient half-life such that the source does not require frequent replacement, and minimal additional radiation emissions that merely give rise to subject dose, the irradiation geometry must be optimised. The source-sample-detector geometry is set such that the angle of scatter from source to detector gives rise to the Compton scatter distribution in the spectrum as far removed in energy from the characteristic x-rays as possible in order to reduce the background under the signal. These are essentially all the variables that can be optimised in a source-based system and therefore the sensitivity of the system is largely dependent on the availability of an appropriate radionuclide. This is the main reason for the outstanding performance of the ^{109}Cd lead measurement system – with a g-ray that is only 30 eV above the K edge of lead, a reasonably long half-life of 462 days, and a lower energy photon emission that is readily shielded to reduce subject dose, ^{109}Cd is the ideal radionuclide for measuring lead. Furthermore, the energy difference between the 88 keV g-ray scattered through ~ 160^{o} and the lead x-rays is such that the signal is located in a reasonably low background portion of the detected spectrum, see fig 1. With polarised systems, the energy of the incident radiation is also a variable to optimise. However, a 90^{o} source-sample-detector geometry must be chosen as this corresponds to the direction of initial polarisation and therefore minimal scatter. This limits the flexibility with which a fluorescing source can be designed since the energy dependence of the background spectrum now can only be altered by changing the energy dependence of the incident spectrum. Therefore, appropriate tube voltage, polarising material, and beam filters must be selected such that the incident energy distribution corresponds to high photoelectric absorption in the target element and results in the appropriate positioning of the characteristic x-rays in the background spectrum detected at the 90^{o} scatter angle. The coupling of these factors in the polarised systems is the reason for the poor performance in polarised uranium measurements.

XRF measurements of lead concentrations in bone have been taking place clinically for many years now. This tool has become extremely useful in monitoring occupational exposure in workers at risk as it provides a measure of their long-term lead exposure and a means to ensure that their job is not putting their health at risk. *In vivo* XRF has allowed researchers to demonstrate that bone-lead levels are a direct measure of cumulative lead exposure and repeat studies of the same populations over many years are beginning to shed new light on physiological parameters such as the biological half-life of lead in bone. Furthermore, it has been demonstrated through these measurements that bone lead can be a source of endogenous lead exposure, just as your obstetrics friend speculated in her challenging case. It is hoped that with continued research this tool may become readily available to aid in occupational monitoring, optimising therapeutic procedures making use of gold (chrysotherapy for rheumatoid arthritis) or platinum (chemotherapy with cisplatin), as well as potentially monitoring environmental exposure to a wide range of toxic heavy metals.

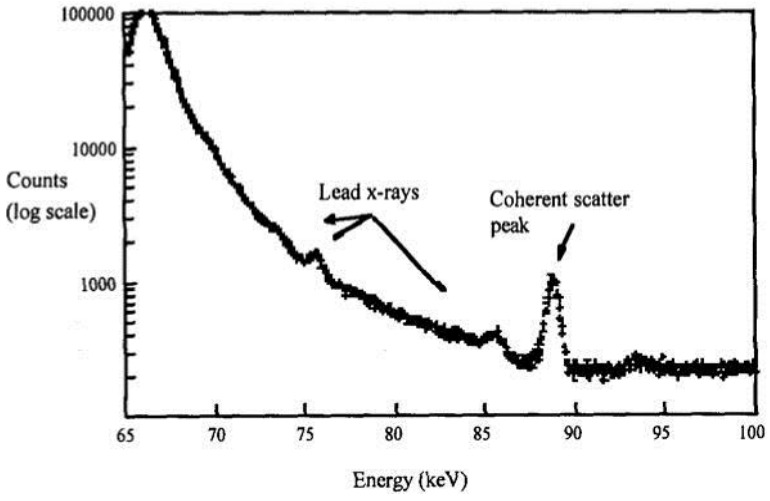

Figure 1: Spectrum acquired with a 140 ppm lead phantom with the ^{109}Cd system. The lead x-rays are located in a reasonably low background region of the spectrum. The coherent scatter peak arises from the scatter of incident photons from the bone matrix, or in this case, from the phantom material, plaster of Paris.