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In vivo applications of X-ray fluorescence in human subjects

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Abstract. X-ray fluorescence has been used to measure several elements noninvasively within living human subjects. Some description is given of the constraints imposed by this rather unusual form of analysis together with a brief listing indicating the range of elements for which such analyses have been developed. Measurements of two elements are then presented in more detail. Lead is measured in bone and has become a well-established tool in continuing research into the long term effects of lead. Strontium is also measured in bone and, although presently not in widespread use, offers the potential for essential information in the study of the reported benefits of strontium supplementation.

Keywords. X-ray fluorescence; human subjects; lead in bone; strontium in bone; strontium supplement.

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1. Introduction

The specific and somewhat unusual feature of the work described here is that measurements are performed on living human subjects. Such measurements are valuable if they provide information relating to the person being measured that would not otherwise be available. These measurements can therefore be considered as a type of diagnostic X-ray technique. Such techniques, of course, are not new, having been used in various forms more or less since the discovery of X-rays more than a century ago. Equally, the technique of X-ray fluorescence is by no means unusual. It is well understood, well characterized and widely applied. However, the combination of using X-ray fluorescence as a diagnostic tool for human subjects, although not entirely new, is somewhat unusual and some attention will be devoted here to at least two of its general features.

1.1 *Radiation dosimetry*

As with any diagnostic technique applied to human subjects, the value of the information gained must be greater than any adverse effect, risk or stress to the person. For X-ray

fluorescence studies, the radiation weighting factor is 1. So the equivalent dose (H in Sv) is numerically the same as the physical dose (D in Gy). Also, *in vivo* X-ray fluorescence measurements are conducted to determine the elemental content in a specific organ or site in the body; this is usually chosen to be the site at which the element in question has its highest concentration. This means that the tissue weighting factor is low, often very low. In several cases, for example, the only tissues with any attributable sensitivity to radiation that are exposed are skin and bone surface, each of which has a tissue weighting factor of 0.01. Furthermore, only a small proportion of the total skin or bone surface is exposed. So the effective dose (E in Sv) is very small indeed, often below 1 μSv. Such effective doses are well within the variation of annual natural background radiation and are frequently treated as negligible. In fact, it is often the maximum local equivalent dose that is more likely to be of concern. Here a limit for a diagnostic procedure would normally be 150 mSv. Despite these low values, particularly for effective doses, these *in vivo* X-ray fluorescence measurements are regarded as research procedures and require ethical review at the institutional level and written consent from the participants.

1.2 *Extended media*

It is a statement of the obvious that making a measurement *in vivo* involves making a measurement in an extended medium (perhaps not the most flattering description of a person!). Furthermore, these are media which can only be prepared for measurement in the most limited sense. One can, and does, clean the skin to avoid superficial contamination and one can try to position the person with respect to the source of radiation and the detector in the most advantageous geometry possible, but not a great deal is possible. There are at least three types of constraints. The sample (the human body or a part of it) is heterogeneous and contains many elements. This constraint is shared, at least in part, by many other X-ray fluorescence analyses. Because the samples are thick, there is extensive scattering. Since the nature of the measurement precludes preparing thin, uniform samples, there are few options truly to minimize this problem. Polarized X-ray fluorescence systems have been developed and have proved valuable, but the extended nature of the sample has meant that the advantage has not been as great as it has been for thin and uniform samples. This constraint is similar to that experienced in the X-ray fluorescence analysis of cultural and anthropological artifacts. The third constraint is attenuation. *In vivo* analyses are commonly not of skin or completely superficial tissue, although there are some such analyses.

1.3 *Elements measured in vivo by X-ray fluorescence*

The first *in vivo* X-ray fluorescence analysis seems to have been by Hoffer *et al* in 1968 [1]. They measured iodine in thyroid. This does not seem to have been extensively followed up at the time, with greater attention being paid to alternative means of imaging thyroidal iodine distribution. More recently, Hansson *et al* [2] have been working on both imaging and quantification using this technique. In the early 1970s, Ahlgren *et al* developed a system for measuring lead in bone, using the 122 keV γ-rays from ^{57}Co to excite the Pb K X-rays. They reported this in a peer-reviewed journal in 1976 [3]. Considerably more attention will be devoted to bone lead measurements in §2. Christoffersson

and Mattsson of the same group reported the use of source excited X-ray fluorescence for the measurement of cadmium in kidney in 1983 [4]. This was followed up by system improvements and several major applications, but that will not be discussed here. In 1988, Jonson *et al* published their work on using polarized X-ray fluorescence to measure platinum [5], using this as a tool to track the kinetics of Pt in the context of using Pt-containing drugs in cancer chemotherapy. Some other groups also developed similar systems for Pt measurements. Also in 1988, Scott and Lillicrap reported the use of X-ray fluorescence to measure gold. This was in the context of the accumulation of the metal when being used for chrysotherapy [6]. Again from the same research group, Börjesson *et al* used polarized X-ray fluorescence to measure mercury in kidney [7]. They and others have continued to work on improving this measurement system, since it remains less than fully satisfactory. O'Meara *et al* used the γ-rays from ^{57}Co to excite uranium K X-rays [8]. Although this technique could detect unsuspected small fragments of depleted uranium munitions, it has not yet proved sufficiently sensitive to measure uranium in bone usefully. Farquharson and Bradley [9] developed a method for measuring iron in skin. Given the low energy of the Fe K X-rays, sampling tissues at greater depth is effectively precluded. In 2004, Graham and O'Meara reported an X-ray fluorescence technique for measurement of silver [10], and in the same year Pejović-Milić *et al* reported the use of the emissions from a ^{125}I source to excite strontium K X-rays for measuring the element in bone [11]. Strontium, as well as the original iodine and later iron are in the minority, as they are elements which are essential or beneficial, as opposed to the majority of elements measured by X-ray fluorescence for which it is their toxicity which provides the primary reason for their measurement. A final example of a toxic measurement is arsenic, where the preferred site of measurement is skin.

Development work has been performed by Studinski *et al* [12] and also by Gherase and Fleming [13]. This brief listing is not comprehensive, but it should provide an impression of the range of elements for which X-ray fluorescence measurement systems have been developed. Not all of these are currently in active use and there were subsequent developments. This report will focus on two elements. Lead will be discussed in §2. Lead is measured because it is toxic and this has received wider application than any other *in vivo* X-ray fluorescence techniques. Strontium will be discussed in §3. The main reason for its measurement is the potential benefits arising from strontium supplementation; the technique is more recently developed and, so far, appears to be in use in only one laboratory. In all these respects it provides a contrast with lead.

2. Lead

As is extremely well known, lead is toxic. Most routine monitoring is of lead in whole blood. Analytical techniques for blood lead are well established, although as levels of blood lead decline, there is a shift in techniques towards inductively-coupled mass spectrometry and away from atomic absorption spectrometry for improved precision and accuracy at low lead concentrations. Also, and more significantly in the present context, blood lead reflects a period of exposure of only 2–4 weeks. Some of the harmful effects of lead relate to short-term or acute exposures, but others relate more closely to long-term or chronic exposure. The large majority of lead in the adult human body is stored in

bone and it remains there for years to decades. Bone samples can be taken by biopsy and analysed, but this causes some pain and is not well suited to regular measurements of a large number of people. In this context, *in vivo* X-ray fluorescence measurement of bone lead has been quite readily accepted.

2.1 *Bone lead measurement techniques*

As mentioned in §1.3, the first *in vivo* bone lead measurements were those conducted by Ahlgren *et al* [3] and they used the 122 keV γ-rays from ^{57}Co to excite the Pb K X-rays and measurements were mostly made of lead in finger bones. This technique was adopted elsewhere, but only in a few laboratories [14,15]. Subsequently, Laird *et al* proposed the use of the 88 keV γ-rays from ^{109}Cd to excite the Pb K X-rays [16] and a full working system was characterized and demonstrated in human subjects by Somervaille *et al* [17]. The use of the Pb L series X-rays was proposed by Wielopolski *et al* [18] and developed further using polarized X-rays [19]. However, it is the ^{109}Cd excited K X-ray fluorescence of lead in bone that has seen the most widespread application.

2.1.1 *^{109}Cd excited K X-ray fluorescence of lead in bone.* In the original system, an annular course of ^{109}Cd was mounted just in front of an HpGe detector. The source irradiated a bone or other sample placed in front of the source–detector assembly and the detector was shielded from direct source radiation by a tungsten (heavy metal alloy) holder of 2 mm thickness. The resulting spectrum was dominated by the Compton scatter feature, which formed a peak between 65.5 and 66.0 keV. Importantly, there was also a clear peak from the coherent scatter of the incident 88 keV γ-rays. At this energy and the angles 140°–170°, there is a very strong dependence of coherent scattering on atomic number (Z^5–Z^6). So the coherent scatter signal comes primarily from calcium, to some extent from phosphorus and to a very minor extent from oxygen when a human bone measurement is conducted [17]. Somervaille *et al* also showed that the ratio of Pb K X-rays to coherent scatter is almost completely independent of bone geometry, thickness of overlying tissue, source–sample distance, measurement time, source activity and other parameters for which correction might otherwise have to be made [17]. This means that the method provides a robust measurement, which can therefore readily be applied in different situations.

A second-generation ^{109}Cd excited K X-ray fluorescence measurement of bone lead was developed by Gordon *et al* [20] and by Todd and McNeill [21]. In this system, a small-size spot source of ^{109}Cd was mounted concentrically with and in front of a large diameter (51 mm) HpGe detector. This produced improved detection limits compared to the original system, while preserving the advantages in terms of normalization and robustness for in-field use. Most recently, Nie *et al* [22] have a third-generation system with four HpGe detector elements and the ^{109}Cd source is mounted interstitially and in front of the detector array, which has been referred to as a 'clover leaf' geometry. Third-generation systems have been implemented by Ahmed and Fleming [23] and by Campbell *et al* [24], but a majority of the current measurement systems are of the second-generation type. The progressive improvement in detection limits of bone lead techniques are summarized in table 1.

Table 1. Improving precision in bone Pb X-ray fluorescence.

Date	System type	Minimum detectable level
1970s	^{57}Co excited	50–60 μg Pb/g bone mineral
1980s	^{109}Cd excited, 1st generation	12–20 μg Pb/g bone mineral
1990s	^{109}Cd excited, 2nd generation	6–10 μg Pb/g bone mineral
2000s	^{109}Cd excited, 3rd generation	2–3 μg Pb/g bone mineral

The effective dose from second-generation systems was evaluated extensively by Todd *et al* [25] and found to be in the range of 35–40 nSv. The more recent third-generation systems use more active sources (5–10 GBq) and the dose has been evaluated at about 0.25 μSv for adults [26]. These, as with other doses from *in vivo* X-ray fluorescence are amongst the lowest, perhaps the lowest, encountered in diagnostic radiation procedures and do not present any significant impediment to the use of these techniques, including in repeated measurements, provided there is a reason to expect that the information obtained will be valuable.

2.2 *Results of bone Pb studies*

2.2.1 *Bone Pb reflects cumulative exposure.* The main motivation for developing *in vivo* bone lead measurements was that it was expected that bone lead would reflect cumulative exposure to lead. That this was the case in practice was clearly demonstrated by Somervaille *et al* soon after their technique became available [27]. In two separate surveys of occupationally exposed lead workers, they demonstrated that tibia lead concentration correlated strongly with a cumulative blood lead index (CBLI, sometimes other similar names are given). The advantage of studying a group of occupationally exposed people was that these people had had regular blood lead tests and so the tibia lead could be compared to the integral under the blood lead vs. time curve, the CBLI. There have been several subsequent studies in which tibia lead has been compared to CBLI and in some of these studies there have also been measurements of either calcaneus lead or patella lead. However, it is the tibia lead which is common to all the studies and these results are summarized in table 2.

These data have commonly been interpreted as showing a broadly similar pattern with a consensus slope of between 0.05 and 0.06 μg Pb (g bone mineral) $^{-1}$/(y/μg Pb/dL) [34] (for more details, see §2.2.3).

2.2.2 *Bone Pb and endogenous exposure.* Although it had for long been accepted that lead must come out of the bone and thus constitute an internal source of lead, this phenomenon had not been readily observed and had not always been prominently considered in assessing the human biokinetics of lead. In the study by Gerhardsson *et al* conducted

Table 2. Tibia Pb and cumulative exposure.

Reference	n	R	Slope (μg Pb (g bone mineral)$^{-1}$/(y/μg Pb/dL))
Somervaille *et al* [27]	88	0.82	0.060 ± 0.005
[27]	87	0.86	0.050 ± 0.003
Hu *et al* [28]	12	0.92	0.061 ± 0.008
Armstrong *et al* [29]	15	0.87	0.10 ± 0.02
Erkkilä *et al* [30]	91	0.66	0.028 ± 0.003
Gerhardsson *et al* [31]	100	0.60	0.022
Cake *et al* [32]	53	0.70	0.059 ± 0.009
Fleming *et al* [33]	367	0.83	0.056 ± 0.002

in 1988, they were able to measure tibia and calcaneus lead in both active and retired workers. In both groups, there were very extensive records of blood lead measurements, because such monitoring had begun at that lead smelting facility in 1950. As well as observing the relationship between tibia lead and CBLI in all 100 subjects given in table 2, amongst the 30 retired people there was a clear relationship between current blood lead and tibia lead. Furthermore, this represented the excess lead above that to be expected from current exposure, by comparison with a referent group who had not worked with lead. This was interpreted as endogenous exposure, that is, lead previously stored and then released from the bone back into the blood. Similar relationships have now been observed in a few other studies and are summarized in table 3.

A very large majority of subjects in all these studies were male lead workers. The different slope between blood lead on the one hand and tibia lead or calcaneus lead on the other is presumed to reflect the fact that these are different types of bones, with tibia being predominantly cortical and calcaneus being predominantly trabecular.

Table 3. Bone lead and endogenous exposure.

Reference	Endogenous relationship
Erkkilä *et al* [30]	$B = 0.133T + 5.3$
Gerhardsson *et al* [31]	$B = 0.138T + 7.7$
McNeill *et al* [35]	$B = 0.17T + 13$
Fleming *et al* [33]	$B = 0.136T + 13.0$
Erkkilä *et al* [30]	$B = 0.072C + 4.0$
Gerhardsson *et al* [31]	$B = 0.062C + 6.9$
Fleming *et al* [33]	$B = 0.078C + 13.0$

B is blood Pb in μg/dL; T is tibia Pb and C is calcaneus Pb, both in μg Pb/g bone mineral.

2.2.3 *Sex difference and nonlinearities in Pb metabolism.* A large majority of subjects in the studies briefly summarized till now were male lead workers. McNeill *et al* provided an opportunity to make measurements on a substantial number of women who had been exposed to lead [36]. Many of them had worked in a lead smelting facility. Others had been exposed to lead as young children, although they were young adults by the time bone lead measurements were made. Analysis of these data showed the endogenous lead release, but the slope of the relationship fell into two broad categories. The women of child bearing age had a slope of 0.067 ± 0.014 between blood lead and tibia lead, whereas the postmenopausal women had a slope of 0.132 ± 0.019. The lower slope suggests that the contribution of tibia lead as a source to the whole blood lead was smaller for women of child bearing age than for either older women or for men. One might interpret this as suggesting that the younger women retain calcium more avidly than do the older women or the men and that in so doing the younger women also retain lead more avidly.

Chettle [37] and then Healey *et al* [38] re-examined the relationships between tibia lead and CBLI shown in table 2 and compared the slopes of the relationships to the mean tibia lead concentration amongst the subjects in each survey. The slope correlated significantly and positively with tibia lead, which they interpreted as indicating that the proportion of blood lead being deposited in bone depends on the extent of exposure, with lighter exposures leaving proportionately less lead in the bone than heavier exposures. This interpretation has been contested [39] and the issue warrants further investigation.

Brito *et al* [40] were able to examine changes in bone lead in over 300 subjects. These subjects had had bone lead measurements on two occasions separated by five years. Amongst these subjects, the younger people showed a more rapid elimination of lead from bone than did their older colleagues; also, the people with less intense lead exposure, assessed by their average blood lead, released lead from bone more rapidly than those with more intense exposure. These observations can be crudely summarized by the statements 'older lead stays longer' and 'higher exposure stays longer'. Although bone lead measurements have contributed significantly to the understanding of how lead behaves in the human body, it is clear from the different patterns noted in this sub-section, that further work remains to be done before these findings can be satisfactorily incorporated into pharmacokinetic models of lead in humans.

3. Strontium

There are reports of harm caused by excessive intake of strontium [41], but the immediate impetus for an *in vivo* X-ray fluorescence measurement of strontium was the finding in clinical trials that strontium supplement reduced the risk of fracture amongst people diagnosed with osteoporosis [42]. Also, taking strontium supplement will result in part of calcium in bone ($Z = 20$) being replaced by strontium ($Z = 38$). This could well result in an artefactual high reading of bone mineral density.

3.1 *In vivo X-ray fluorescence of bone strontium*

As mentioned earlier, Pejović-Milić *et al* [11] developed an X-ray fluorescence system using a range of emissions from ^{125}I (in fact, brachytherapy seeds in which the ^{125}I is

adsorbed onto Ag beads, further complicating and enhancing the emission spectrum) for a pilot study of strontium in human bone. Snyder and Secord measured bone strontium in rabbits [43] and, in a totally separate development, Wielopolski and his colleagues demonstrated that they were able to measure bone strontium in human subjects [44]. However, neither of these initiatives were followed up in the respective laboratories. Zamburlini *et al* [45] improved their system very considerably enhancing its performance, so that it was possible to measure the strontium X-ray signal in all subjects who participated in their study.

The ^{125}I seeds were mounted in a shield/collimator in front of the centre of a 16 mm diameter Si(Li) detector. The information on strontium comes predominantly from the K_α X-rays at 14.1 keV, although the K_β X-rays at 15.6 keV are also detectable. The spectrum was complex, because the source emitted a γ-ray at 35.4 keV as well as tellurium X-rays and silver X-rays. The spectrum then contained both coherent scatter (full energy) and Compton scatter features from each of the main source photons as well as the fluoresced X-rays from strontium and other elements present in the sample and the source–detector assembly. The strontium X-rays were normalized to the coherent scatter of the 35.4 keV γ-ray, but this was not as effective as the analogous normalization for lead. Further work is under way to improve absolute quantitation for the strontium measurements [46].

3.2 *Results of the pilot study of bone strontium*

In the initial pilot study [11] it was possible to detect strontium in only about half the subjects. In the second pilot study, with the improved system [45] it was possible to detect strontium in all 22 volunteers. Measurements were made in both fingers (predominantly cortical) and ankles (predominantly trabecular). The effective dose associated with these measurements was $\sim$50 nSv for the fingers and $\sim$70 nSv for the ankles. Within this sample of 22 subjects, it was immediately apparent that there were two groups. For the majority (16), in the finger the ratio of strontium K_α peak area to that of the 35.4 keV coherent scatter peak was 0.45 ± 0.09, whereas for the other six subjects, the ratio was 1.23 ± 0.21. It turned out that the six subjects with higher strontium levels were all of east Asian origin (China, Japan, Korea), whereas all the other 16 were Caucasian. The same distinction was maintained in the ankle measurements, for which the east Asian subjects (1.09 ± 0.30) again had higher strontium levels than the Caucasians (0.40 ± 0.13). Also, the ankle strontium measurements correlated with the finger strontium, with a coefficient of determination (R^2) of 0.88 and a slope quite close to unity.

3.3 *Sequential measurements during Sr supplementation*

Measurements were taken of individuals who started taking strontium supplements either to treat or to prevent osteoporosis. A series of such measurements has recently been reported [47]. In a few cases it was possible to conduct the first strontium measurement before the person began to take a strontium supplement. The data for finger bone strontium are shown for one such individual in figure 1. The ratio of Sr K_α to 35.4 keV coherent is plotted vs. time since first measurement for one individual. This person began to take strontium supplements between the first and second measurements. The initial calculation of the ratio as 0.38 was entirely consistent with that for the Caucasian subjects in the

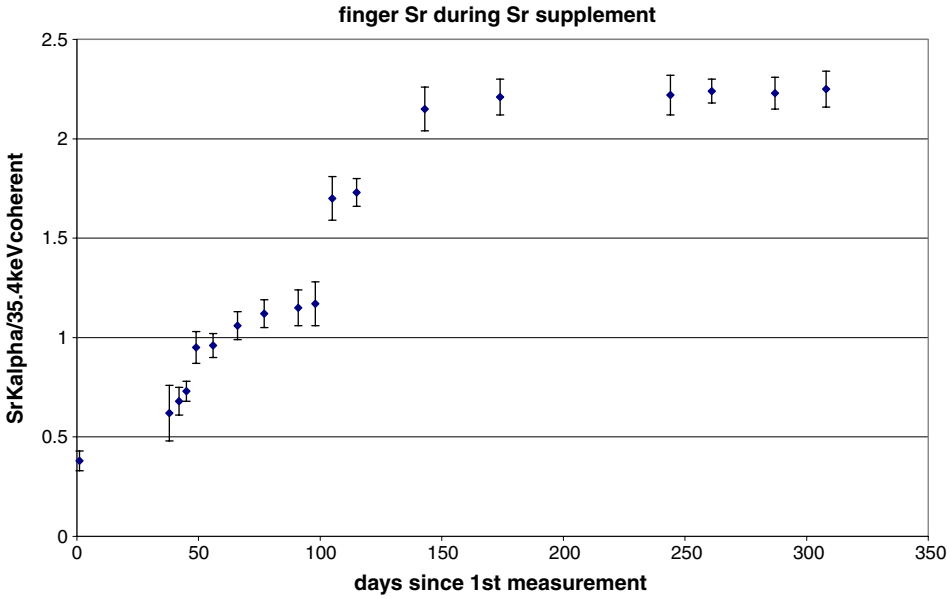

Figure 1. The ratio of finger bone Sr K_α to 35.4 keV coherent is plotted vs. time since the first measurement for one individual. The first data point is the measurement before she began to take a strontium supplement.

convenience sample. The level rose, after two to three months to values comparable with those of the east Asian subjects, continued to rise until it was about double that of the east Asian subjects, and remained relatively stable between five and eight months after the start of this series of measurements. These data are presented here to demonstrate the effectiveness with which these *in vivo* strontium measurements can track changes in strontium levels. Further data are presented by Moise *et al* [47].

3.4 *Implications of strontium measurements*

At the early stage of this measurement capability, there are more questions than answers. However, it is clear that this tool is well suited to address several intriguing questions. There are data clearly showing the adverse effects of excessive levels of strontium. Equally, there are clinical trials showing reduction in fracture risk as a result of strontium supplementation. Is there an optimum range for strontium concentrations in bone? If so, can that be identified and can that level be maintained? Are there differences in strontium level as suggested by the convenience sample in the second pilot study? If so, are these differences related to diet, genetic factors, or some other factors? At what concentrations does strontium produce a significant artifact in dual energy X-ray absorptiometry measurement of bone mineral density? Does such an interference vary from one instrument to another?

4. Conclusions

In vivo X-ray fluorescence is not widespread either in the number of facilities at which such measurements are presently carried out or in the range of elements which can thereby be measured. Two examples have been presented here, which serve to show that the technique is fully feasible. Also, it is important to note that the radiation doses required are sufficiently low, hence not to be a concern. The work with bone lead has contributed towards a shift in understanding the long-term behaviour of lead in the human body. So it is reasonable to maintain that *in vivo* X-ray fluorescence will continue to play a significant role at least in research into the long-term health effects of lead exposures. The work with strontium is at a much earlier stage. It will be important to see this technique replicated in other laboratories. Some of the questions about 'natural' and 'optimal' levels of strontium in bone might best be addressed by collaborating laboratories in different countries. For these two examples and for some of the other elements listed in §1.3, one can expect *in vivo* X-ray fluorescence to contribute, as a physics-based tool, to health research.

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