In Vivo X-Ray Fluorescence of Lead in Bone: Review and Current Issues

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The principle of X-ray fluorescence (XRF) is the use of photons to fluoresce atoms of the element of interest. Fluoresced atoms can then emit X-rays of energies specific to that element. The number of X-rays is proportional to the amount of the element present in the sample. Both X-rays from radioisotopes and X-rays from a generator have been used as the fluorescing photons in bone lead measurement systems. The major difference between methods is whether they fluoresce the K-shell or the L-shell electrons of lead. Two of the three reported methods fluoresce K-shell electrons. The difference between K and L lead X-rays is their energy: L X-rays range in energy from 9.2 to 12.6 keV; K X-rays range from 72.8 to 87.3 keV. The energy of the X-rays determines their ability to overcome the effects of attenuation and escape from the body for detection.

Attenuation is one of the most important factors in any XRF measurement method because both the fluorescing photons (produced by whichever method) and the fluoresced X-rays (be they K- or L-shell) are attenuated by whatever material they pass through. In bone lead measurements, the tissue overlapping the bone site and within the bone itself are the regions of principal concern. Attenuation is characterized by the mass attenuation coefficient which depends on the composition of the material and the energy of the photon. For a particular substance and particular photon energy, the mass attenuation coefficient can be used to obtain the more readily understandable quantity of the "mean free path." The mean free path is, as the name suggests, the average distance traveled by a photon before undergoing some form of interaction. In bone lead measurements, the interaction is usually a Compton scattering event, which can reduce the energy of the photon. Compton scattering is undesirable for two reasons. First, the energy of a fluorescing photon is reduced; the resulting scattered photon may no longer have sufficient energy to interact with a lead atom to produce an X-ray. Such scattered photons produce a relatively intense background in the energy spectrum on which lead quantitation is based and are the main limitation on measurement precision. Second, if a fluoresced X-ray is Compton scattered, it no longer has one of the characteristic lead energies and thus contributes further to the background instead of the signal.

In considering attenuation, we broach one of the fundamental differences between K and L XRF: the difference in the volume of bone sampled. In both K and L XRF, attenuation of both fluorescing and fluoresced photons needs to be considered in a rigorous analysis. However, for our purposes a simple illustration will suffice. For the L XRF system, we will ignore attenuation of the fluorescing photons and consider only attenuation of the L\textsubscript{\alpha} X-rays (10.55 keV) because this is the larger effect. The mean free path of these X-rays is 1.5 mm in soft tissue and 0.2 mm in bone. For the K XRF systems that use the 88.035 keV \( \gamma \)-ray from \(^{109}\)Cd, the combined effects of attenuation on a fluorescing \( \gamma \)-ray and a K\textsubscript{\alpha} X-ray (75.0 keV) give a mean free path of 19.0 mm in soft tissue and 9.0 mm in bone. Ignoring attenuation of the L XRF fluorescing photons may underestimate the difference between K and L XRF, but the underestimation is not great. Another illustration of the effect of attenuation is given by the depth at which the sensitivity of a system falls to a certain level, as calculated by Thomas (1): for L XRF, 30% sensitivity occurs 1.3 mm into bone, for K XRF the distance is approximately 25 mm. Thus, lead L\textsubscript{\alpha} X-rays have difficulty escaping from the body, and the regions of bone lead beyond approximately 2 mm are not sampled.

Similarities and Differences of Practical Measurement Systems

The literature on the measurement of trace and minor elements in vivo has been reviewed elsewhere (2,3). The reviews and our previous work (4) describe the dependence of the sensitivity of XRF measurement systems on the fluorescing source energy and on source-target-detector geometry. In vivo measurements of lead in bone have been performed with three XRF methods: two fluorescing the K-shell electrons of lead (\(^{57}\)Co in a 90° geometry and \(^{109}\)Cd in a backscatter geometry) and one fluorescing the L-shell electrons (using \(^{125}\)I or an X-ray generator).

In addition to the fluorescing source, the components of an XRF measurement system consist of a radiation detector, its most suitable to the energy of radiation under study; Ge for K XRF, Si(Li) for L XRF), a preamplifier, amplifier, analog-to-digital converter, multichannel analyzer, and computer for data storage and analysis. All bone lead measurements are noninvasive; the subject must sit in a chair and have the measurement system moved into place. \(^{109}\)Cd K XRF measurements are typically performed for approximately 30 min, L XRF measurements for 16 min. A recent paper (5) shows a practical measurement being made with a \(^{109}\)Cd K XRF system. Each system is transportable, allowing mobile laboratory facilities to be established.

The first in vivo measurements were performed at the University of Lund, Sweden, using \(^{57}\)Co as the fluorescing source. The measurement site was the phalanx, and the achieved detection limit...
(defined as an X-ray peak area equal to three times the standard deviation of the underlying background counts) was approximately 20 µg Pb/g bone wet weight, for an effective dose equivalent (using superseded nomenclature) of approximately 0.1 µSv (6–8). The same method has been adopted by the Queensland University of Technology, Australia, also measuring the phalanx (9), and was independently developed at the University of Pennsylvania, where the measurement sites have been teeth, wrist, and temple (10,11). The development of L XRF systems to measure lead in bone has been conducted by Brookhaven National Laboratory (12–14). Use of the L XRF method has not yet been reported other than from the medical center that collaborated on the original development. However, our laboratories are engaged in the development of this technique.

The third XRF method employs the 88.035 keV γ-rays from 109Cd to fluoresce the K shell X-rays and adopts a backscatter geometry. The third method was developed at the University of Birmingham, England, and has been adopted by other research groups: Singleton Hospital, Swansea, Wales (15), Brookhaven National Laboratory (16), and the Institute of Occupational Health, Vantaa, Finland (17,18). The 109Cd method has also been developed commercially (19). The commercial system was adopted by the University of Pittsburgh (20), Harvard School of Public Health (21–23), and the University of California, San Francisco (24).

In collaboration with the authors, most groups with commercial systems are in the process of improving them via hardware retrofitting and adoption of alternative methods of computational peak extraction. Recent improvements to the 109Cd method have been reported by McMaster University (25,26), the University of Maryland (27,28), and Queen Elizabeth Medical Center, Birmingham, UK (29,30). The improvements result principally from using larger-volume detectors (in conjunction with sources with a high activity per unit area) and faster spectroscopy electronics. Additional 109Cd K XRF measurement systems are present at Mount Sinai Medical Center, New York, and the University of Cincinnati; to date neither institution has published a report. The reasons for such widespread use of the 109Cd K XRF method lie in its methodological advantages, which are described throughout this paper.

### Intercomparison of Methods

The two K XRF methods have been used in a collaborative study (31), where their performances were compared. The 109Cd method gave better precision than the 57Co method (10 µg Pb/g bone mineral versus 50 µg Pb/g bone mineral, respectively), but also delivered a higher effective dose equivalent (0.1 µSv versus 2.1 µSv, respectively) (3,32). However, the reported doses from the two systems are not calculated according to the most recent guidelines (see below).

### Radiation Dose

All bone lead measurements use radiation, making the radiation dose and its consequent risk important concerns. The dose delivered by all bone lead measurement methods is small. Nevertheless, full radioisotopic analysis of the 109Cd K XRF and L XRF methods have been performed, using the current methods of dose calculation. The 109Cd K XRF study (20) indicated an effective dose to a 1-year-old child, an adult male, and an adult female of 1.1 µSv, 34 nSv, and 38 nSv, respectively. The L XRF dosimetry for measurements of pregnant women was the focus of a paper by Kalef-Ezra et al. (33). A full analysis of the L XRF system has also been published (34), then corrected and updated to the most recent guidelines (35). The most recent paper (35) indicated an effective dose to a 1-year-old child more than twice as great as that from a 109Cd K XRF measurement and a dose to an adult approximately eight times greater. The dose delivered to a centesimal is lower for L XRF, by a factor of approximately 20. The differences between the doses of the two methods are less important than their magnitudes: for 109Cd K XRF, the effective dose for a 1-year-old child is equivalent to approximately 3 h of the average effective dose arising from background radiation (36); the additional risk of a cancer mortality (excluding leukemia) is approximately 1 in 10 million (20). From these facts, it is clear that radiation risk should not be a limiting factor in using either method.

### Precision

There is an ever-increasing improvement in the performance of nuclear spectroscopy components, which is partly responsible for the improvements in detection limits reported over recent years. Improvement in measurement precision continues in many laboratories. Currently quoted precisions are in the range of 4–10 µg Pb/g bone, where bone, for L XRF, indicates wet weight, and, for K XRF, indicates bone mineral. For an adult tibia, conversion between the two units requires multiplication of the wet weight value by 1.8; for other bones, the conversion factor is greater. Precision (for all methods) depends on the amount of tissue overlying the bone: the greater the thickness of tissue, the worse the precision. For example, in comparing 3 mm and 6 mm of overlying soft tissue, 109Cd K XRF precision worsens by 5%, L XRF precision worsens by 49%. The precision of the L XRF method is affected by the heavy attenuation of the lead X-rays. In L XRF, the number of observed X-ray counts is adjusted to the number of counts that would have been observed if the subject had possessed 5 mm of overlying tissue; i.e., the number of X-rays is scaled to correct for the effects of attenuation.

The number of X-ray counts sets a limit on precision, but the method of conversion from counts to concentration is also important. Ultrasound measurement of overlying tissue thickness is required with the L XRF method, introducing a further uncertainty arising from the precision of the ultrasound measurement. The precision of ultrasound measurement was reported by the L XRF pioneers to be 0.3 mm (37), resulting in an uncertainty of approximately 13% in the factor used to convert a measurement from counts to concentration. The uncertainty from ultrasound measurement is then added (in quadrature) to that arising from counting statistics. For low bone lead levels, the ultrasound uncertainty is minor; but for high bone lead concentrations, it sets the lower limit to total measurement uncertainty. Table 1 shows the L XRF uncertainty (in terms of wet weight bone) for three different “true” bone lead concentrations. For each entry in Table 1, the uncertainty from counting statistics is a constant ±2 µg Pb/g bone wet weight. (Note that counting statistics uncertainty is determined largely by the magnitude of the spectral background, rather than the X-ray peak.) The effect of ultrasound uncertainty on overall uncertainty is clear. For comparison, Table 1 also shows the effect of increasing bone lead concentration on 109Cd K XRF precision. In the 109Cd method, conversion from counts to bone concentration was achieved via a calibration factor that underwent yearly confirmation of value and precision.

| True bone lead concentration (µg/g wet bone) | 109Cd K XRF precision (µg/g wet bone) | L XRF precision (µg/g wet bone) |
|---------------------------------------------|--------------------------------------|--------------------------------|
| 10                                          | ±4.003                               | ±4.2                           |
| 40                                          | ±4.005                               | ±6.6                           |
| 80                                          | ±4.020                               | ±11.1                          |

Table 1. Effect of increasing bone lead concentration on the precision of 109Cd K XRF and L XRF measurements.
lead concentration is performed by normalization of the lead X-ray signal to the elastically scattered photons appearing in the spectrum. The elastic scatter peak is much more prominent than the X-ray peaks and can, therefore, be determined with much greater precision, thus worsening the total precision by an insignificant amount.

Accuracy

The conversion from counts to bone lead concentration is usually performed via reference to calibration standards. Standards for the $^{109}$Cd K XRF are made from lead-doped plaster of Paris. Plaster produces an elastic scatter peak similar to that seen during a measurement of bone. Correction from $\mu$g/plaster to mg/g bone mineral simply requires multiplication by a constant. The value of the constant depends on the elemental composition of plaster and bone and (weakly within the range of angles considered) on the scattering angle used. Within current K XRF measurement precisions, it is possible to produce accurate standards for the K XRF methods.

Recent discussions of XRF practitioners have covered the need for a single set of measurement standards to be used by all research groups (38). Because of the different volumes of bone sampled, the fabrication of such standards may prove to be both difficult and expensive.

Accuracy is also affected by assumptions about the distribution of lead in bone, viz., that the lead concentration of soft tissue is zero and that lead is homogeneously distributed in bone over the scale being considered. The first part of the assumption would benefit from examination, as both methods are capable of sampling lead in the soft tissue overlying the bone. This is particularly true for the L XRF method, which would be very sensitive to soft tissue lead and/or lead on the skin. The second assumption has data both to support and to qualify it. Wittmers et al. (39) indicate that bone lead concentration is relatively uniform along the length of the tibia, which is the primary measurement site for $^{109}$Cd K XRF and the only measurement site for L XRF. However, there are also data indicating the heterogeneity of bone lead concentration with increasing depth into bone (40–43). Areas of bone lead concentration a few times greater than the average level are seen on a scale of $<0.1$ mm. The implications of such regions of unrepresentative lead concentration depend on the spatial resolution of the measurement system. Recalling that the mean free path for fluorescing $\gamma$-rays and the principal lead K X-ray is 9.0 mm in bone, it is clear that the $^{109}$Cd K XRF method integrates over the region of heterogeneity.

The same is true for the $^{57}$Co K XRF method. The mean free path for the principal lead L X-ray is 0.22 mm in bone, making it particularly sensitive to the heterogeneity in bone lead concentration.

Validation

Both K and L XRF methods have been validated, in each case by comparison between XRF and atomic absorption spectrophotometry (AAS). Validation of $^{109}$Cd K XRF was reported by Somervaille et al. (44). This was an indirect comparison; i.e., bare-bone samples had a core removed for AAS analysis before delivery for $^{109}$Cd K XRF measurement. XRF and AAS methods were independently calibrated. Paired analysis between AAS and $^{109}$Cd K XRF was conducted on 80 samples: bones from tibia sections, tibia fragments, calcaneus, and metatarsals. The mean difference between $^{109}$Cd K XRF and AAS measurements was $<0.1$ $\mu$g/Pb/g bone mineral. The largest difference found was for a subset of three tibia fragments, which exhibited a difference of approximately 5 $\mu$g/Pb/g bone mineral (45). It should be noted that AAS and $^{109}$Cd K XRF sample different average bone masses: 20 mg and 10–15 g, respectively. Validation of bare-bone measurements was thus produced. Validation of intact bone measurements relies on further experiments which indicate that the accuracy of the elastic scatter normalization process is independent of the amount of tissue overlying the bone (46). More limited data for direct validation of $^{109}$Cd K XRF for intact, amputated limbs has been reported by Hu et al. (21), work that appears to confirm the accuracy of the method. Other direct comparison was provided by measurements made on autopsy samples from a subject who had previous $^{57}$Co K XRF bone lead measurements (8,47). Once again, these data appear to confirm the accuracy of the K XRF method employed. However, the data are few; there is a time lapse between XRF and AAS measurements and, as the subject was elderly, lead and calcium metabolism could have been changing.

The L XRF method was validated using amputated, intact, human limbs. L XRF measurements were performed first with the overlying tissue intact, and then removed. Bone samples were then independently measured by AAS (14). Ten amputated limbs were used; the results from one were excluded from the final analysis because of an (assumed) incorrect evaluation of overlying tissue thickness. Two further samples were included once their measurement results had been adjusted; adjustment was required after suspected positioning errors. No further problems with tissue thickness measurement and/or with positioning errors have been reported, though presumably the problems are not less with people than with amputated limbs. Positioning and movement problems for small children have been alleviated by sedation. This practice is not necessary for the other XRF methods. A final methodological complication is that the validation data of the L XRF method also serve as its calibration data. Full statistical independence requires separate samples for calibration and validation.

Robustness and Adaptability

In the $^{109}$Cd K XRF method, the lead X-rays are normalized to the elastic scatter peak. Normalization yields a measurement accuracy that is independent of several potential confounders: fluorescing source to subject distance, overlying tissue thickness, bone size, bone shape, bone geometry, bone density, nongroup differences in interindividual positioning of the measurement apparatus, and minor patient movement. To a greater or lesser extent, the other XRF methods depend on all of these factors. The ability of the $^{109}$Cd K XRF method to perform measurements at several different bone sites and to make meaningful comparisons of the results obtained was illustrated by the Birmingham group in an extensive series of studies and collaborations with groups in Sweden and Finland. Together, the studies report the measurement of lead in tibia, calcaneus, wrist, skull, and sternum (18,31,44,46,48–53).

Human Studies Using XRF

L XRF measurements have been principally performed on children, although there have been some measurements of occupationally exposed adults (13,54). In children, L XRF measurements have been compared to the outcome of a provocative EDTA chelation test, with a view to using the noninvasive and rapid L XRF test as a replacement for the time-consuming chelation test. Methods are presented in the original paper (55); corrected results were republished (56). When the outcome of the EDTA test, bone lead, and blood lead were all used as categorical variables (i.e., "raised" or "not raised"), blood lead and bone lead exhibited approximately equal power in their abilities to predict the outcome of the EDTA test. In combination, blood lead and bone lead could predict the outcome of the EDTA test in approximately 90% of the 59 cases. In the same children, blood lead correlated slightly more strongly with EDTA lead than did bone lead (Pearson correlation coefficients of 0.701 and 0.472, respectively). The difference between the two was not highly significant ($p=5.9$). The same data were subsequently presented in a more complete
report (57), an earlier version of which
(58) contains printing errors and should be
disregarded.

In a study of L XRF and chelation in
adults, a correlation between L XRF bone
lead and chelated lead was also ob-
served (13). The adult L XRF data were
reported to be broadly consistent with the
findings of Jones et al. (16), who used a
\(^{109}\)Cd K XRF method. In contrast, Schütz
et al. (59), studying chelatable lead after
administration of penicillamine, found no
relationship between chelatable lead and
\(^{57}\)Co K XRF lead measured in finger bone
but did find a relationship between chelat-
able lead and vertebral bone biopsies. The
data of Schütz et al. clearly show that fin-
ger bone lead and penicillamine-chelatable
lead are closely related only when subjects
are in the same exposure status. Retired
workers show a much higher ratio of bone
lead to chelated lead than active workers.
The inference is that whole bone lead, as
measured by K XRF, samples a different
and longer-term lead compartment than
that sampled by the provocative chelation
test. More recently, a collaborative project
between the groups at Birmingham (using
\(^{109}\)Cd K XRF to measure tibia and calcaneus)
and Malmö/Lund (using \(^{57}\)Co K XRF
to measure phalanx) studied bone
lead over a course of EDTA chelation in
20 workers. They found no evidence of
statistical significance for a decrease in
bone lead measurements of either tibia or
calcaneus over the course of chelation.
None of the bone sites correlated well with
EDTA-chelated lead, although they all cor-
related well with each other. The strongest
indication of 24-hr chelated lead was found
to be prechelation blood lead (r = 0.86;
pe.0001) (60). The report concluded with
support for the argument that
EDTA-chelated urinary lead primarily
reflects the blood and soft tissue lead pools,
rather than the total body burden. These
findings invite further research, as they
have important implications for under-
standing studies of blood lead, bone lead,
and chelated lead.

Historically, studies with K XRF
\(^{109}\)Cd or \(^{57}\)Co have concentrated on
adult male lead workers (8,18,31,46,47,
49,51,52,61–64), although there have been
measurements of other groups: fe-
males, lead-toxic patients and environmen-
tally exposed subjects (21,46,65). Indus-
rially exposed subjects with recorded
blood lead histories have provided a sec-
dary, indirect validation of the K XRF
methods. Integrating the area under a
blood lead-versus-time curve yields a
cumulative blood lead index, which is a
surrogate for long-term lead exposure. A
strong relationship between K XRF and
cumulative blood lead index has been
found for both \(^{57}\)Co K XRF (8) and \(^{109}\)Cd
K XRF (50) methods. These relationships
allow the inference of the average blood
lead level over a defined working lifetime
from a single K XRF bone lead measure-
ment.

The possibility that skeletal lead stores
are eventually released has been the subject
of recent discussion (66–68). The concern
is that lifetime lead stores may act as an
endogenous source of lead exposure in later
life or during times of elevated bone
turnover, as occurs during pregnancy and
osteoporosis. Evidence to support the
hypothesis that skeletal lead can indeed act
as an endogenous source of exposure comes
from a handful of K XRF studies (18,47,
51,62). A clear relationship can be seen
between blood lead and bone lead levels
observed in those no longer occupationally
exposed to lead. These studies have natural-
ly sought to quantify a characteristic half-
time for lead turnover in the bones studied.
The estimates have varied and have tended
to increase as more longitudinal data have
come available. The values that follow
can be compared to the frequently cited
value of 10,000 days (approximately 27.4
years) (69). Christoffersson et al. (62) stud-
eyed eight subjects for 2–5 years immedi-
ately after the end of their exposure and 6 sub-
jects 7–13 years after the end of lead expo-
sure. Mean half-times for the decrease of
phalanx lead levels were 7 years (range
3–15 years) in the former group and 8 years
(range 2–∞ years) in the latter group.
Nilsson et al. (47) examined the same
group several years later. With the longer-
term data, the group of 14 workers yielded
an increased characteristic half-time of 16
years (95% CI: 12–23 years). Gerhardsson
et al. (51) evaluated half-times for tibia and
calcaneus of 27 years (95% CI: 16–98
years) and 16 years (95% CI: 11–29
years), respectively. Erkkilä et al. (18) did
give quantitative half-time values but did find
evidence that bones of predominantly corti-
cal nature exhibit longer half-times.

Discussion and Conclusions

We suggest that in vivo measurements of
lead in bone will not, ultimately, replace
any existing measurements of lead expo-
sure. Rather, they will supplement the
existing tests by providing information on
lead pools that cannot be otherwise sam-
ped except by biopsy. A possible exception
is replacement of the provocative chelation
test with an L XRF measurement, if it is
confirmed that L XRF measurements do
indeed sample the relatively short-term lead
pool accessed by provocative chelation.

The radiation doses for K and L meth-
ods are so low that they should not be a
deciding factor in whether to conduct a
study on any population. Improvements in
measurement system sensitivity should be
accompanied by evaluation of the dose. A
recent concern has been the possible inter-
ferences to the lead signal in an L XRF
measurement (70). For example, the pres-
ence of arsenic in the skin overlying the
measurement site could artificially inflate
a bone lead level reported with the L XRF
method. At present there is no empirical
evidence either to support or reject this
hypothesis. There are no suggested inter-
ferences present in the spectrum of a
\(^{109}\)Cd K XRF measurement.

It is our opinion that further work is
not required to show that XRF constitutes
a promising technology. However, there
are further questions that should be ad-
dressed. First, all methods should be vali-
dated by an independent laboratory.
Validation should address the questions of
accuracy, precision, and volume of bone
sampled. Second, the replication of results
produced by the pioneering laboratory is
an important precursor to the widespread
acceptance of any new method by the
research community. Replication of the
\(^{109}\)Cd and \(^{57}\)Co K XRF methods has
begun in several laboratories. Similar repli-
cation is required for the L XRF method.
Third, it is clear that K and L XRF mea-
surements do sample different bone vol-
umes, but the implications of this differ-
ence are not established. K and L XRF
measurements may yield different informa-
tion or they may yield slightly different
estimates of the same information. If dif-
ferent, K and L measurements may or may
not be complementary. Fourth, it is clear
that K XRF measurements relate strongly
to cumulative lead dose, the measurement
of which was the original motivation for
developing the method. It has yet to be
demonstrated that L XRF measurements
relate more strongly to a bioavailable lead
pool. Fifth, published data show that dif-
ferent bones have different turnover times.
More information on such parameters
would be useful in developing models for
the body's handling of lead and for testing
models already in existence.

Finally, two questions are often asked
by clinicians and epidemiologists: What
will be the detection limit for K XRF bone
lead measurements in children, and can
bone lead measurements be applied to
screening programs? There are no simple
answers to these questions. L XRF has
been applied to children, and this is an
obvious strength of the method. \(^{109}\)Cd K
XRF measurements have been performed
in a limited number of children (24) with
no reported degradation in precision com-
pared to the precision of adult measure-
ments. Clearly, K XRF can be applied to
children but it is not intuitively obvious
what precision would be obtained. In our experience, it is likely that the precision of measurements of children’s bones will be worse than the precision obtainable from adult bones because the total amount of bone mineral sampled will be less for children. It is unlikely that the degradation in precision would be as much as a factor of two. This would still make XRF bone lead measurements valuable in children. With regard to screening, it is our opinion that none of the XRF methods is sufficiently developed to be applied in programs to screen the general population. Some methods are more developed and robust than others, but none is yet ready for widespread application. Nevertheless, bone lead measurements may prove to be, in the future, a valuable screening and even a diagnostic tool for the clinician.

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- Letter of invitation from the prospective host.
- Agreement to release the applicant from the home institution for the duration of the exchangehip.
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