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The Use of K X-Ray Fluorescence for Measuring Lead Burden in Epidemiological Studies: High and Low Lead Burdens and Measurement Uncertainty

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X-ray fluorescence (XRF), a rapid, noninvasive, low-radiation-dose method of measuring bone lead content, has emerged as a promising tool for providing an integrated estimate of low-level lead accumulation in epidemiological studies. Our group has settled on an XRF instrument that utilizes K X-rays (K-XRF) and normalizes the measurement to bone calcium. The unit of measurement provided is in micrograms of lead/gram bone mineral, an accurate proxy for micrograms of lead/gram bone ash. An estimate of measurement uncertainty is generated from the counting statistics and is theoretically dependent on several factors, primarily duration of measurement and bone mass. Data from pilot studies of community-exposed adults and workers with varying degrees of occupational lead exposure demonstrated that the K-XRF instrument can easily distinguish between populations with occupational versus environmental lead exposures. Among all subjects, bone lead increased with age. Larger measurement uncertainty was significantly associated with being female, greater subject weight, and smaller lead burdens.

Introduction

The skeleton is the principal long-term storage area for lead accumulation. Of total body lead burden, 90 to 95% (70–80% in children) is contained in bone (*1,2*). Since it is a dynamic tissue, bone also serves as a potential source of internal lead exposure, especially during periods of heightened bone activity such as pregnancy (*3*), lactation (*4*), postmenopausal osteoporosis (*5*), Paget's disease (*6*), and cisplatin chemotherapy (*7*). This realization, coupled with recent research on the neurobehavioral and blood pressure effects of very low lead exposures, has created a need for research on the long-term consequences of accumulated lead deposits in bone.

X-ray fluorescence (XRF) is a method of measuring bone lead content that has emerged as a promising tool for providing an integrated estimate of low-level lead accumulation in epidemiological studies. The method is rapid, noninvasive, and uses levels of radiation exposure that involve minimal risk (*8,9*). There are several types of techniques available, however, and a standardized protocol for use of XRF does not exist. Selecting a technique and a protocol may depend on technical factors as well as characteristics of lead distribution in bone, lead exposure and age profiles of the population being studied, outcomes being studied, and other factors (*10,11*).

Our group has settled on an XRF instrument that uses K X-rays (K-XRF) and normalizes the measurement to bone calcium, thereby eliminating the need for external comparison standards (*9*). The unit of measurement derived is in micrograms of lead/gram bone mineral, an accurate proxy for micrograms of lead/gram bone ash (*12*). The instrument provides, in addition, an estimate of measurement uncertainty (the expected standard deviation of multiple measurements at the same site) that is theoretically dependent on the duration of the measurement and the mass of bone being measured and relatively independent of the actual lead concentration.

We have recently used this instrument to survey tibial lead levels in two pilot studies of adults with no known significant occupational exposures to lead (*13*) and adults with varying degrees of occupational exposure. We describe the aggregate data here.

Methods

The K X-Ray Fluorescence Technique

A full description of the K-XRF technique used for this work can be found elsewhere (*9,13*). In summary, the instrument uses a ^{109}Cd gamma-ray source (which was at 100–125 mCi strength at the time of this study) and a high purity germanium detector

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in a back-scatter geometry. The X-ray signals are shaped, digitized, and acquired by a multichannel analyzer board in a personal computer. Spectrum data are automatically stored and analyzed, providing a near instantaneous measure of bone lead content. The lead fluorescence signal is normalized to the coherent scatter signal, which comes principally from the calcium in bone mineral (calcium hydroxyapatite). This renders the measurement insensitive to variations in bone shape, size, density, histomorphometry, overlying tissue thickness, and movement. The unit of measurement is in micrograms lead/gram bone mineral. Previous authors have outlined the close correspondence between this unit of measurement and micrograms of lead per gram of bone ash (*12*).

An estimate of the measurement uncertainty is also provided. This parameter is obtained by summing one standard deviation in the net signal counts (total signal minus background photon counts), in quadrature, to the previously measured systematic error (1 ppm) (*9*) and has been shown in work on cadavers to be equivalent to the expected standard deviation of multiple measurements at the same site. In theory, the parameter should be predominantly dependent on *a*) the duration of the measurement and *b*) the mass of bone being measured, as well as *c*) the mass of tissue surrounding the target bone (which leads to increased background scatter) and *d*) the distance between the source and the target bone. It follows that age, sex, and body habitus would influence measurement uncertainty through their relationships to bone and soft tissue mass. Increasing lead concentration is expected theoretically to increase measurement uncertainty, but at negligible amounts.

Validation experiments have been conducted that compared K-XRF measurements with atomic absorption spectroscopy measurements in intact cadaver legs and lead concentrations in phantoms constructed with known concentrations of calcium sulfate dihydrate and lead (*13*). Since lead concentrations have been shown to vary somewhat within otherwise homogenous sections of bone (*14*), phantoms provided a more faithful target for accuracy testing at low levels of lead concentration. These experiments demonstrated a high degree of precision and accuracy, with a correlation coefficient for combined data of 0.98, a linear regression slope of 1.02, and an X-intercept of 1 μg lead/g bone mineral (Fig. 1).

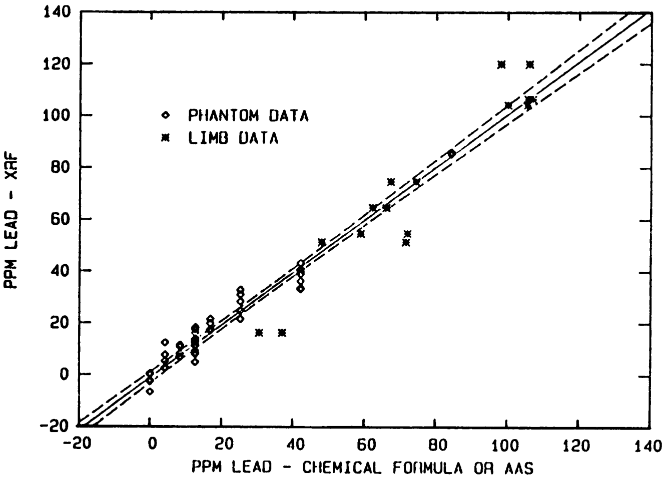

FIGURE 1. Lead concentration in lead-doped phantoms (as formulated) and cadaver limbs (as measured by atomic absorption spectroscopy) versus K-XRF measurements. From Hu et al. (*13*). Reprinted with permission of the Helen Dwight Reid Educational Foundation, Heldref Publications, Washington, DC. Straight line represents linear regression slope and dotted lines represent 95% confidence limits to regression slope.

Subjects and Protocols for the Current Work

Community-exposed (nonoccupationally exposed) subjects consisted of employees from a biomedical company in Massachusetts that is engaged in the research, development, and production of medical devices. No work processes or maintenance procedures at the company were known to involve exposure to absorbable lead products. Each employee was asked to volunteer after the nature of the procedure had been fully explained. Consenting individuals reported to a room on the premises where the administration of a detailed environmental/occupational history and medical questionnaire, interview, and K-XRF procedure were carried out (*13*). A 30-min measurement was taken at the mid-shaft of the tibia of each subject after washing the region with a 50% solution of isopropyl alcohol. An average of three subjects were done per day.

Occupationally exposed subjects consisted of patients referred because of lead exposure to the Occupational Medicine Clinics of Brigham and Women's Hospital, Massachusetts Respiratory Hospital, or Cambridge Hospital because of exposure to lead and who were found to have had a blood lead level of at least 40 μg/dL any time during the previous year. Consenting patients underwent a 60-min measurement at both the mid-shaft tibia and the patella after showering and washing the regions to be measured with a 50% solution of isopropyl alcohol.

Before the first use of the K-XRF instrument each day, an internal algorithm automatically checks linearity, gain stability, and resolution. At the time that the community-exposed subjects were tested, the ^{109}Cd source was at approximately 125 mCi strength. During the subsequent period when the occupationally exposed subjects were tested, the ^{109}Cd source had decayed to approximately 100 mCi strength. Radiation exposure to both skin and red bone marrow from each of these measurements is considerably less than that of a single dental bite-wing X-ray.*

Results

The detailed environmental/occupational history questionnaires administered to the biomedical company employees confirmed that no subject had had any histories suggestive of childhood lead poisoning or significant adult occupational or environmental exposures to lead other than occasional soldering

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*Based on measurements taken on limb phantoms with thermoluminescent dosimeters placed at the skin surface, at the tibia surface, and in the marrow cavity, the on-axis skin exposure for a 30-min measurement at 125 millicuries of ^{109}Cd strength is 1.6 mGy. The on-axis exposure to the marrow cavity is 0.55 mGy. The exposure falls to near zero at 2.5 cm off-axis. The equivalent dose to the total red marrow organ is 0.45 μSv. Using worst-case conservative assumptions, the extrapolated total body absorbed energy per measurement is less than 1 mJ. By comparison, the typical skin exposure for a single dental bite-wing X-ray is 4 mGy with a red bone marrow absorbed dose of 7 to 10 μSv.

activity (*13*). Occupationally exposed subjects had histories of lead exposure with durations ranging from 3 days to 20 years, and blood lead levels during the year previous to the K-XRF measurement ranged from 41 to 96 μg/dL. Two young adult subjects had only 3 days of high-intensity lead exposure from removing lead paint with a belt sander, which resulted in lead levels of 85 and 96 mcg/dL 1 week after exposure. K-XRF measurements were taken 10 days after exposure.

K-XRF measured lead burdens among long-term occupationally exposed subjects were clearly distinguishable from lead burdens among community-exposued subjects (Fig. 2). Lead burdens increased with age in all subjects (Fig. 2). The two young adults with short-term, recent occupational exposure had bone lead levels that were high for their age, but not out of the range of community exposure.

Measurement uncertainty estimates for all subjects ranged from a low of 3 to a high of 9 μg lead/g bone mineral (Table 1). Among the community-exposed subjects, a scatter plot matrix of measurement uncertainty, age, K-XRF measured bone lead, and weight suggested that measurement uncertainty has a negative association with bone lead and possibly a negative association with age (Fig. 3). In a multivariate linear regression model, predictors of measurement uncertainty that attained the $p < 0.05$ level were being female, higher weight, and lower K-XRF bone lead levels (Table 2). The coefficient for age was in the direction of an inverse relationship to measurement uncertainty, but failed to attain statistical significance in the presence of these other factors.

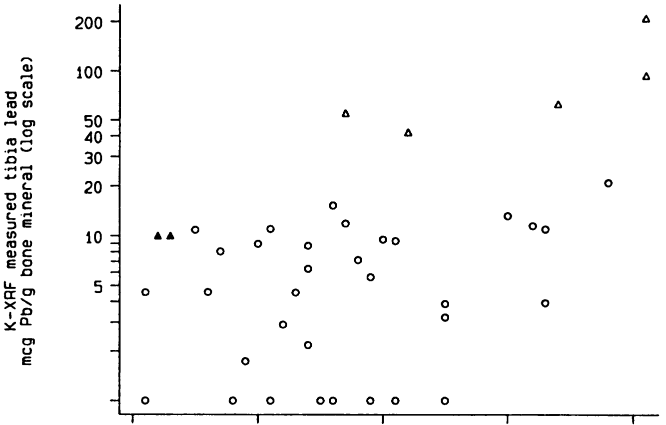

FIGURE 2. K-XRF tibia lead levels among community- and occupationally exposed adults, by age. Circles represent community-exposed adults. Triangles represent occupationally exposed adults. Filled triangles are adults who had 3 days of high-level lead exposure, measured 10 days after cessation of exposure. K-XRF tibia lead levels estimates of 0 μg/g bone mineral or below are given a value of 1 for this plot only.

Table 1. Measurement uncertainty: occupationally and community-exposed subjects.

	μg lead/g bone mineral	
	Occupationally exposed[a]	Community exposed[b]
n	9	34
Range	3–6	4–9
Mean (SD)	3.6 (1.1)	6.1 (1.3)

[a]Measurements taken for 60 min at approximately 100 mCi ^{109}Cd source strength.

[b]Measurements taken for 30 min with approximately 125 mCi ^{109}Cd source strength.

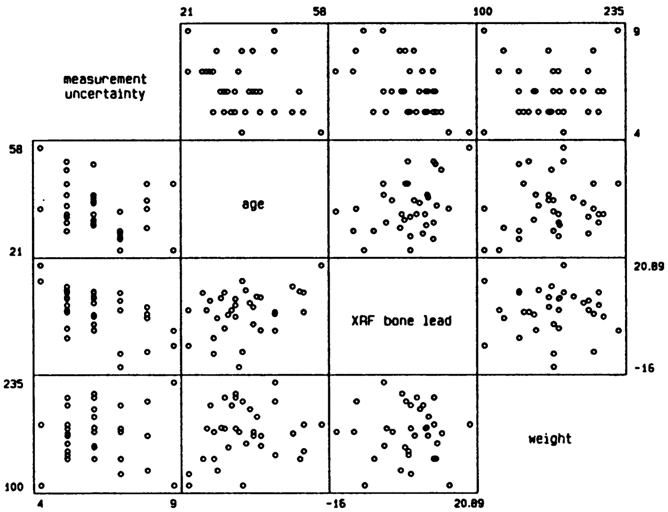

FIGURE 3. Scatter plot matrix of measurement uncertainty, age, K-XRF measured bone lead, and weight. There is a suggestion of a relationship of measurement uncertainty to XRF bone lead and possibly age.

Table 2. Multiple linear regression model for measurement uncertainty among community-exposed subjects.[a]

Independent variable	Coefficient	SE	t	Probability > |t|
Age, years	−0.33	0.02	−1.64	0.11
Sex (male = 1, female = 2)	1.62	0.47	3.44	0.002
Weight, lb	0.155	0.0060	2.61	0.014
K-XRF bone lead	−0.0762	0.0228	−3.34	0.002
Constant	3.02	1.49	2.038	0.051
R^2	0.53			

[a]Dependent variable: measurement uncertainty (μg lead/g bone mineral).

Discussion

These preliminary data support the utility of K-XRF as a method of measuring lead burden in epidemiologic studies. Lead burdens among workers occupationally exposed to lead for more than a few days were clearly distinguishable from those of community-exposed adults at all ages. We have shown elsewhere that lead burdens among community-exposed subjects rise significantly with age and are associated with the age of housing in which subjects grew up as children (*13*).

The position of the leads burdens of the two young adults with 3 days of occupational lead exposure among their peers suggests that a short exposure can significantly increase bone lead levels, but that recognition as such may require comparison with age-specific expected values. It would be of great interest to see if their bone lead levels would continue to increase without further lead exposure, as may be expected from redistribution from soft tissue stores.

As expected, analysis of the measurement uncertainty data suggests that the precision of K-XRF measurements are lower among women, presumably because of lower bone mass. The higher measurement uncertainty associated with higher subject weight may be related to interference of the measurement by overlying skin thickness.

The higher measurement uncertainty associated with lower K-XRF bone lead levels was not anticipated theoretically or seen experimentally (*9*). In this population, there might be an unmeasured factor that confounded the relationship between bone lead and measurement uncertainty through a relationship to background scatter or bone mass. Further research is required to characterize the utility and application of K X-ray fluorescence for measuring lead burden in epidemiological studies.

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