Factors Influencing Bone Lead Concentration in a Suburban Community Assessed by Noninvasive K X-ray Fluorescence

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Objective.—To determine the influence of demographic, exposure, and medical factors on the bone lead concentration of subjects with background (nonindustrial) environmental lead exposure.

Design.—Survey.

Setting.—Suburban residential community.

Participants.—A total of 101 subjects (49 males, 52 females; aged 11 to 78 years) were recruited from 49 of 123 households geographically located in a suburban residential neighborhood unexposed to any major source of industrial lead emissions.

Main Outcome Measurements.—Cortical bone lead concentrations in the midshaft of the tibia were noninvasively measured by in vivo K x-ray fluorescence. Blood lead concentrations were measured by anodic stripping voltammetry. An administered questionnaire assessed potential sources of lead exposure and medical conditions affecting bone metabolism.

Results.—After the exclusion of one outlier, log-transformed bone lead concentration was highly correlated with age (r=.71; $P \leq .0001$). Bone lead concentration showed no significant change up to age 20 years, increased with the same slope in men and women between ages 20 and 55 years, and then increased at a faster rate in men older than 55 years. In addition to the variables age and sex, the best fitting multiple regression model for bone lead concentration (R^2=.66; $P \leq .0001$) revealed a positive correlation with total pack-years of cigarette smoking and a negative correlation with a history of having nursed an infant for longer than 2 weeks. Blood lead concentrations of the subjects were low (geometric mean, 0.24 μmol/L [4.9 μg/dL]) and after log transformation were weakly correlated with log-transformed bone lead concentration (r=.23; P=.02).

Conclusions.—The age- and sex-related increases in bone lead concentration found by K x-ray fluorescence concur with published postmortem studies of bone lead concentration and are consistent with the kinetics of bone turnover and secular trends in lead exposure. These data help to establish a reference range for assessing the lead burden of other populations with environmental or occupational lead exposure.

(*JAMA*. 1994;271:197-203)

LEAD is a ubiquitous element in the modern environment. Through anthropogenic distribution of lead to air, potable water, or foodstuffs, and the presence of lead in plumbing, house paint, soldered cans, and tableware, environmental exposure to lead is a common day-to-day occurrence. Occupational lead exposure may additionally affect as much as 2% of the workforce[1] and may provide an additional pathway for secondary exposure of spouses or children.[2] There is growing concern that relatively low levels of lead exposure are associated with adverse health effects, including diminished neurocognitive function in children[3,4] and hypertension in adults.[5]

With a few notable exceptions,[3,6] studies that have examined the adverse health effects of lead have relied on measurement of blood lead as a biomarker of current or past exposure. However, blood lead is a poor indicator of cumulative lead exposure, and individuals with widely divergent exposure histories may have similar blood lead concentrations.[7] Although tests that measure urinary lead excretion after chelation have been suggested as an alternative index of long-term lead exposure,[8,9] studies of active and retired lead workers have found them to be of limited value in distinguishing individuals with markedly different job tenure.[10-12]

For editorial comment see p 239.

More than 90% of the adult body lead burden occurs in bone,[13,14] with a half-life of years to decades.[15,16] Techniques that directly examine bone lead concentration may therefore be of considerable value in the assessment of cumulative lead exposure. In vivo K x-ray fluorescence (KXRF) is a noninvasive approach to the measurement of bone lead concentration in human subjects.[17,18] In occupational cohorts, KXRF determinations of bone lead concentration have correlated strongly (r>.8) with cumulative lead exposure estimated by integrated serial measurements of blood lead concentrations.[19-22] In environmental cohorts, a trend of increasing bone lead concentration with age has been found.[20,23,24]

By permitting a safe and accurate assessment of cumulative lead absorption, KXRF measurement of lead in bone may emerge as an important tool in epidemiological and clinical investigation of lead exposure and toxicity. In addition to providing an index of cumulative exposure, bone lead represents a source of endogenous lead that may be potentially redistributed to sensitive target tissues during physiological states such as pregnancy or lactation, or pathological states such as postmenopausal or immobiliza-

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tion osteoporosis or hyperthyroidism. In an effort to establish normative data for in vivo assessment of bone lead burden, we examined tibial KXRF measurements in 101 subjects randomly recruited from a suburban community. Lead exposure variables have been quantified by detailed demographic, occupational, and environmental histories, and factors significantly influencing bone lead concentration have been identified.

METHODS

Recruitment

The individuals studied were drawn from 123 households located in a residential neighborhood of Dickson City, Pa, a suburban community of 7000 residents located near Scranton in the northeastern part of the state. As a control population for a larger study of environmental lead contamination elsewhere in the region, this neighborhood was selected as representative of regional background environmental lead exposure based on its location, census demographics, soil lead content, housing age, condition, and density, and the absence of a major source of industrial lead emissions in the community. Measurements and interviews were performed during August and September 1991.

The study was approved by the University of California, San Francisco, Committee on Human Research. Letters introducing the study were mailed to the 123 selected households and followed up by telephone or door-to-door recruitment 2 to 7 days later. Any one of the following criteria established subject ineligibility: (1) less than 10 years of age; (2) currently pregnant or uncertain pregnancy status; (3) less than 5 years' residence at the contacted address; (4) absence from the contacted address for 6 months or more during the past 5 years; (5) the presence of metal objects (eg, surgical screws) in both lower extremities; or (6) serious health problems interfering with participation. Individuals were also excluded if they had ever resided in a known lead-contaminated area in the region for 2 weeks or more, or if they had worked or attended school in the contaminated area for more than 4 weeks. All enrolled subjects provided written informed consent. Participants who completed the study were reimbursed for their time and effort.

KXRF Measurements

The KXRF measurements were performed with an instrument specifically designed for in vivo analysis of bone lead concentration (Abiomed Body Lead Analyzer, Abiomed Inc, Danvers, Mass). The physical principles, technical specifications, and validation of this[23,25] and similar KXRF instruments[17,26] have been described in detail. In this technique, superficial bones of the limbs, such as the tibia or patella, are irradiated with a collimated cadmium 109 (^{109}Cd) source, which induces emission of K-shell fluorescent x-rays from lead atoms in the bone. Positioned behind the source in a backscatter geometry, a germanium detector linked to an amplifier and a multichannel pulse-height analyzer quantifies the energy spectrum of the fluorescent x-rays. The net lead signal is determined after subtraction of Comptom background counts using a linear least-squares algorithm. The lead fluorescence signal is then normalized to the elastic or coherently scattered γ-ray signal, which arises predominantly from the calcium and phosphorus present in bone mineral. This yields a measurement of bone lead concentration, expressed as micrograms of lead per gram of bone mineral, or parts per million, that is independent of variations in density, bone shape, overlying tissue thickness, and limb movement. Validation studies performed on lead-doped plaster of paris (calcium sulfate dihydrate) bone phantoms and on cadaver bones analyzed by atomic absorption spectroscopy[17,23,27] have confirmed the high accuracy (approximately 98%) of the technique.

The ^{109}Cd source (Dupont, Billerica, Mass) had activity of 462.5 mBq (125 mCi) at the inception of the 6-week data collection period. In addition to internal calibration checks, a daily 30-minute measurement was conducted on one tibial phantom constructed of Lucite-sealed calcium sulfate dihydrate doped with reagent grade 10 ppm lead. The mean (SD) of 45 daily phantom measurements, calculated using an algorithm adjusted for the calcium sulfate matrix, was 11.4 (1.8) ppm. Each phantom measurement yielded a measurement uncertainty of 2 ppm, a value obtained by summing statistical counting error and an empirically measured systematic error component.[25,28]

Thirty-minute measurements were obtained on the midtibial diaphysis, midway between the tibial tuberosity and the medial malleolus. Subjects were seated in a lead-free plastic chair, overlying bare skin was cleansed with isopropyl alcohol, and the collimator was positioned approximately 5 to 10 mm from the skin surface. Although radiation dosimetry associated with the procedure is very low, with an effective dose equivalent of less than 1 μSv,[29] a molybdenum apron was positioned over the lower abdomen and groin to minimize gonadal exposure and provide subject reassurance.

Interview Data

During the KXRF measurement, a trained interviewer administered a questionnaire detailing the subject's age, race, education, family income, history of occupational or avocational lead exposure, alcohol and tobacco consumption, and medical history, with particular reference to diseases or factors thought to affect bone metabolism. On a questionnaire submitted in advance of the interview, subjects were asked to recall the location, decade of construction, and years of residence for all dwellings they had occupied for 1 or more years since birth.

An assessment of lifetime occupational and avocational lead exposure was performed via the following sequence: (1) Subjects recorded the years, average weeks per year, and average hours per week of all jobs held for longer than 1 month; (2) for each job, subjects identified the subset of years and the approximate percentage of time during those years (0%, 1%, 5%, 25%, 50%, 75%, or 100%) devoted to activities believed to involve lead. Interviewers specifically inquired about any time devoted to any of 42 activities frequently associated with lead exposure. Avocational lead exposures were noted separately. At the completion of all data collection, a blinded investigator categorically assessed each noted activity for probability (high, moderate, or low), and intensity (high, medium, or low) of lead exposure based on adaptations of previously published industrial hygiene evaluations.[1,30,31] These assessments were made without regard to the use of personal protective equipment or engineering controls that may have reduced the actual lead dose.

Blood Lead Concentration

Five milliliters of venous blood were drawn into trace metal Vacutainer tubes that contained lithium heparin (Becton-Dickson Vacutainer Systems, Franklin Lakes, NJ) and analyzed for lead by anodic stripping voltammetry modified by a low lead calibration procedure.[32] A 0.48-μmol/L (10.0-μg/dL) quality control sample was analyzed every fourth specimen. The mean of 52 quality control measurements was 0.48 μmol/L (9.9 μg/dL), with a coefficient of variation of 10.3%.

Soil Lead Concentration

Samples of the top 5 cm of soil in the rear yard of a subject's household were collected for analysis of total lead concentration by an environmental engineering company (NTH Consultants, Exton, Pa). Sampling sites 10 cm in diameter were located at least 3 m from the foundation of any house or struc-

ture, or any automotive roadway or parking area. The root mat of overlying sod or vegetation was removed prior to soil collection with a clean trowel. Samples were analyzed for total lead concentration, expressed as parts per million dry weight, by flame atomic absorption.[33] Field duplicate samples (n=16) had a mean difference of 10%.

Statistical Analysis

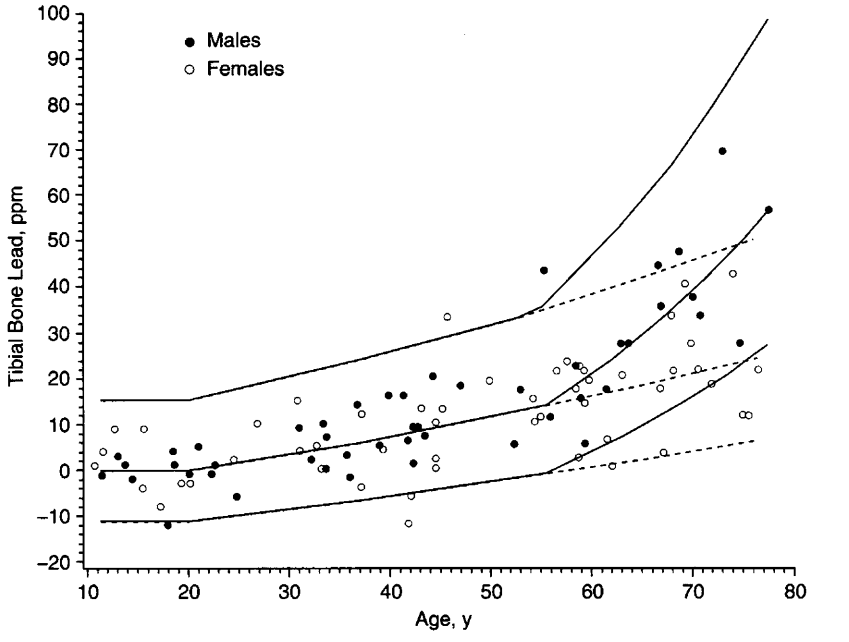
Relationships between variables were assessed by correlation and multiple regression using SAS statistical software (SAS Institute Inc, Cary, NC). To stabilize variance or normalize skewed distributions, dependent variables underwent logarithmic transformation whenever necessary. Among the independent variables, blood lead concentration, pack-years of cigarette smoking, and rear yard soil lead concentration underwent log transformation to reduce the influence of outliers. The statistical uncertainty inherent in photon counting and the peak extraction algorithm may result in a report of numerically negative bone lead concentration in individuals with low bone lead concentrations. Thus, a negative value is interpreted as a random fluctuation around a low bone lead concentration. To eliminate negative numbers prior to a log transformation and to improve the normality of the distribution achieved by transformation, a constant of 35 was added to all bone lead values for the regression analyses. All reported bone lead values have been transformed back to original units.

Regression analyses that weighted each bone lead observation by its measurement uncertainty were examined, but did not qualitatively change the results. Intrahousehold relationships were not significant by mixed-effects analysis of variance, and all subject observations were regarded as independent for ordinary least-squares regression.

RESULTS

Of 123 households in the study area, nine were unreachable, 47 declined to provide enumeration of household members, and 18 contained no eligible subjects. The 49 households that were fully enumerated contained 131 individuals; of these, 19 were ineligible, 11 declined to participate, and 101, from 49 households, were enrolled. One 77-year-old man with a high, outlying bone lead value is described separately and is not included in the statistical analysis. Of the remaining 100 subjects in the analysis, 52 were female and 48 were male, ranging in age from 11 to 78 years (mean, 45.6 years).

Ten subjects with medical histories that suggested a possible influence on bone metabolism were included in the final group analysis after it was determined that their measured bone lead concentration was not significantly different from other subjects of similar age and sex.



Relationship of midtibial lead concentration to age. Regression lines and 95% confidence intervals are shown as solid lines for males and dashed lines for females. Log transformed bone lead values are shown reexpressed in original units.

The mean (SD) bone lead concentration measured 12.7 (14.6) ppm (range, −12 to 69 ppm). Measurement uncertainty for bone lead of the subjects averaged 6.1 (1.8) ppm (range, 4 to 13 ppm). Measurement uncertainty had a mildly negative association with bone lead, leading to a relatively higher coefficient of variation at low values. The mean blood lead concentration measured 0.28 μmol/L (5.7 μg/dL) (range, 0.07 to 1.71 μmol/L [1.5 to 35.5 μg/dL]; SD, 0.19 μmol/L [4.0 μg/dL]). Geometric mean blood lead concentration was 0.24 μmol/L (4.9 μg/dL).

Potential Predictor Variables for KXRF Bone Lead Concentration

Age and Sex.—Age clearly emerged as the variable most strongly correlated with bone lead concentration (r=.69; $P \leq .0001$). Log transformation of bone lead concentration improved the normality of the distribution and resulted in a slightly stronger correlation with age (r=.71; $P \leq .0001$). Age did not correlate with blood lead concentration, which with few exceptions was uniformly low throughout the study population. Untransformed blood lead concentration did not significantly correlate with bone lead (r=.15; P=.15), but after logarithmic transformation of both variables, a modest correlation emerged (r=.23; P=.02).

Sex differences in log-transformed bone lead values were insignificant up until the sixth decade (Figure). Thereafter, male values inflected upward, while female values continued the pattern of linear increase seen in subjects of younger age. Although inclusion of age as a single continuous variable and sex as a dichotomous variable yielded significant regression results (R^2=.57), a superior fit was obtained by a piecewise linear model[34] in which the slope of the age vs bone lead concentration was allowed to change at discrete inflection points. The inflection points were selected by statistical evaluation of a range of age values suggested by visual inspection of the plotted data. In the best-fitting age-sex model (R^2=.60), bone lead concentration remained constant up to 20 years of age, increased with the same slope in men and women between 20 and 55 years of age, and then increased at a faster rate in men older than 55.

The strong effect of age and sex on bone lead was anticipated from prior autopsy studies and other x-ray fluorescence surveys of bone lead content.[13,20,23,24,35-37] In multiple regression, the effect of age and the age-sex interaction each remained highly significant (P<.02) after simultaneous adjustment by all other potential predictor variables in the study. Therefore, the impact of other variables was assessed by examining their correlation to log-transformed, age- and sex-adjusted bone lead concentration, hereafter referred to as "adjusted bone lead concentration,"

Table 1.—Correlation of Potential Predictor Variables With Bone Lead Concentration

Predictor Variable	Mean (n=100)	SD	Range	Correlation (r) to Age- and Sex-Adjusted Tibia Lead Concentration*
Age, y	45.6	19.3	11-78	.71 ($P \leq .0001$)†
Blood lead, μmol/L (μg/dL)‡	0.24 (4.9)	0.08 (1.7)	0.07-1.71 (1.5-35.5)	.23 ($P < .05$)†
Lactation history (never=0, ever=1)§	0.17	0.38	0-1	−.31 ($P < .05$)
Lactation history, No. of infants nursed§	0.33	0.86	0-4	−.24
Smoking history, pack-years‡	1.9	5.5	0-121	.20 ($P < .05$)
Alcoholic drinks per month, No.	15.6	29.8	0-200	−.04
Childbirth, No. of episodes	.87	1.34	0-5	−.15
Occupational lead exposure, h	4346	11 621	0-59 824	.01
Avocational lead exposure, h	414	1324	0-10 041	.04
Current house age category (1=pre-1940 to 4=≥1980)‖	2.2	1.1	1-4	.08
Childhood (age 0 to 5 y) house age category¶	1.3	0.7	1-4	−.03
Backyard soil lead concentration, ppm‡#	84	2.5	11-390	−.14
Household income category (1=<$5000 to 5=>$35 000)**	4.0	1.0	2-5	−.08
Maximum education level in household, grade	12.4	2.3	4-18	−.00
Body mass index, kg/m²	27.9	5.8	14.0-44.6	−.11

*Tibia lead concentration is log transformed (see text).
†Correlation shown is without age and sex adjustment.
‡The predictor variable was log-transformed prior to obtaining the correlation coefficient. The geometric mean and antilog of the SD of the transformed variable are shown, reexpressed in original units.
§Females only; n=52.
‖Additional categories: 2=1940 through 1959; 3=1960 through 1979.
¶n=97 subjects.
#n=41 households for mean, n=85 subjects for correlations.
**Additional categories: 2=$5000-$9999; 3=$10 000-$19 999; 4=$20 000-$34 499.

which was equal to the residual from the piecewise model described in the preceding paragraph. Results of selected correlations are summarized in Table 1.

Female Reproductive History.—Of the 52 female subjects, 36 (69%) had been pregnant at least once (median, two pregnancies; range, none to eight). The number of pregnancies, the number of births, or menopausal status was not significantly correlated with adjusted bone lead concentration.

Nine (17%) of the 52 women had nursed at least one child beyond the first 2 weeks of life. Of these, five had nursed one child, one had nursed two children, two had nursed three children, and one had nursed four children. None was lactating at the time of the study. Among the female subjects, the number of children a subject had nursed had a negative correlation with adjusted bone lead concentration of borderline significance ($r = -.24$; $P = .09$). When considered as a dichotomous variable (ie, never nursed = 0, ever nursed = 1), the correlation with adjusted bone lead became slightly stronger and significant ($r = -.31$; $P = .02$)

Smoking and Alcohol Consumption.—Forty-four (44%) of the subjects had smoked at least 100 cigarettes in their lifetime, and 23 (23%) had smoked within the past month. The logarithm of total pack-years of cigarette smoking was significantly correlated with adjusted bone lead concentration ($r = .20$; $P = .05$), but not with blood lead concentration ($r = .13$; $P = .21$). The blood lead concentration of current smokers of one or more packs per day within the past month (n=23) was not significantly different from that of current nonsmokers (n=77).

Alcoholic beverage consumption in the cohort was low: 43% were complete abstainers and an additional 11% consumed four or fewer drinks per month. Cumulative years of alcoholic beverage consumption (defined as at least 360 mL [12 oz] of beer, 120 mL [4 oz] of wine, or 30 mL [1 oz] of liquor per month) and average number of drinks per month in the past year were not significantly correlated with adjusted bone lead concentration.

Occupational and Avocational Lead Exposure.—Thirty-five subjects reported ever having engaged in at least 1 hour of an occupational activity designated as having a high or moderate probability of high- or medium-intensity lead exposure; in 26 of the subjects, the assessed time was greater than or equal to 2000 hours (1 full-time year equivalent: 50 weeks at 40 h/wk). In 15 of these subjects, more than 1 year had elapsed since termination of the last occupational exposure (median, 18 years). Among the 11 others with occupational exposure within the past year, geometric mean blood lead concentration was 0.41 μmol/L (8.4 μg/dL), compared with 0.22 μmol/L (4.6 μg/dL) in all other subjects. Thirteen subjects had engaged in 500 or more hours of avocational activities associated with a high or moderate probability of high- or medium-intensity lead exposure. In six of these subjects, more than 1 year had elapsed since termination of last avocational exposure (median, 3.5 years).

Examples of exposure rating included "torch cutting of painted metal surfaces" as high probability, high intensity; "pipe soldering" and "pistol or rifle range use" as high probability, medium intensity; and "electrical soldering" as high probability, low intensity. When total lifetime hours engaged in activities with a high or moderate probability of high- or medium-intensity lead exposure were examined as continuous variables, neither occupational exposure nor avocational exposure was significantly correlated with adjusted bone lead concentration. The time elapsed since a subject's last exposure was not a significant variable.

Residential Household Variables.—Predictor variables corresponding to the construction year category of the current or prior residences (Table 1) were not significantly correlated with adjusted bone lead concentration. However, the construction year category of the current home was significantly correlated with log-transformed blood lead concentration ($r = -.31$; $P = .002$).

Forty-one of the 49 households, in which 85 of the subjects resided, granted permission for sampling of rear yard soil. Log-transformed soil lead concentration was highest in homes (n=41) with older construction year categories ($r = -.66$; $P \leq .0001$), but was not significantly correlated with adjusted bone lead concentration. Variables corresponding to household income category and educational level were not significantly correlated with adjusted bone lead concentration.

Excluded Outlier

The subject with the highest bone lead concentration, equal to 73 ppm, was considered an outlier for purposes of statistical and qualitative analysis. The second oldest subject in the study (aged 77 years), he also possessed the third highest blood lead concentration (0.80 μmol/L [16.5 μg/dL]). He reported the highest number of hours of occupational lead exposure, a value more than 7 SDs above the mean of the other subjects, and nearly 50% higher than the next highest subject. His last occupational exposure occurred 15 years prior to his bone lead measurement. He reported spending more than half his life, 46 years, in pre-1940 era housing with predominantly nonintact (slightly peeling) interior house paint.

Multiple Regression Model

To create a complete multiple regression model for log-transformed bone lead concentration, the age and sex variables used to construct adjusted bone lead con-

Table 2.—Multiple Regression Model for Tibia Lead Concentration*

Predictor Variable	Parameter Estimate	t	P
Age >20 y	0.009	7.97	.0001
Male age >55 y	0.015	3.44	.0009
Ever nursed	−0.164	−2.59	.01
Pack-years logged	0.022	2.04	.04
Blood lead logged	0.069	2.03	.04

*Tibal lead values were transformed by adding 35 and applying the natural log. R^2=.66; F=35.99 (5, 94); $P \leq .0001$. The intercept of the model was 3.491.

centration (age older than 20 years, male age older than 55 years) were entered as the first and second independent variables. The variable of age older than 20 years was set equal to zero for subjects less than 20 years of age, and equal to age in years in excess of 20 for subjects age 20 years or older. The variable of male age older than 55 years was set equal to zero for all women and for men less than age 55 years, and equal to age in years in excess of 55 for men aged 55 years or older. Next to be entered were the variables that significantly ($P<.05$) correlated with adjusted bone lead concentration in the bivariate analyses: lactation history (ever nursed) and log-transformed pack-years of cigarette smoking (pack-years logged). Because log-transformed blood lead concentration (blood lead logged) might be considered an intermediary variable that reflected lead exposure from other unspecified sources, it was entered in the model last. The resulting model (Table 2) accounts for two thirds of the variability in bone lead concentration (R^2=.66; $P \leq .0001$).

COMMENT

In this sample of individuals with limited occupational lead exposure, age exerted a strong influence on log-transformed bone lead concentration (r=.71), accounting for nearly half of its variability. A strong influence of age has also been reported in other investigations of cortical bone lead content in non–occupationally exposed cohorts. Three studies have used a similar KXRF technique. Somervaille et al[20] reported a correlation between age and tibial bone lead concentration of .8 (n=20; $P<.002$). We obtained the raw data of Hu et al[23] (H. Hu, MD, MPH, ScD, written communication, 1992) and calculated a correlation of .40 (n=33; $P<.02$). When we analyzed the data presented by Morgan et al[24] in a simple linear model, a significant correlation with age (r=.62; n=59; $P \leq .0001$) was also obtained. Four large postmortem studies that used direct tissue analysis to examine cortical bone lead content in the tibia[13,36,37] and femur[35] corroborate the strong age dependence of lead concentration found by the KXRF technique.

Table 3.—Regression Models for Bone Lead Concentration in Several Environmental Cohorts

Source	Sex, No.	Age Range, y	Technique	Site	r^2*	R^2†	Terms in Model‡
Present study	M 48, F 52	11-78	In vivo K x-ray fluorescence	Tibia	.48	.59	Age >20 y Male age >55 y
Morgan et al[24]	M 35, F 24	21-80	In vivo K x-ray fluorescence	Tibia	.38	.42	Age >55 y
Drasch et al[35]	M 139, F 136	11-85	Atomic absorption	Femur	.39	.60	Age, y Age >40 y·sex§
Barry[13]‖	M 62, F 35	13-86	Spectrochemical analysis using dithizone	Tibia	.55	.59	Age, y Male age >35 y

*Proportion of variance explained by model containing a single linear term in age ($P \leq .0001$).
†Proportion of variance explained by model containing terms in sex and piecewise terms in age. Adjusted[40] for number of variables in model ($P \leq .0001$).
‡With the exception of the data set of Morgan et al,[24] models have been generated after log transformation of the dependent variable (bone lead concentration).
§Interaction term for age >40 years and sex.
‖Data set recreated by digitization of published graphs.

The slope of the relationship between age and bone lead concentration is not constant over the entire age range. We found no significant increase in logged bone lead concentration until the end of adolescence (age 20 years). At that point, values inflect upward at an average slope of 0.38 ppm/y, with a further upward inflection in men older than 55 years. Interestingly, our reanalysis of other bone lead studies reveals similar piecewise increases in bone lead concentration with age and sex. Drasch and colleagues[35,38,39] performed atomic absorption spectrometry measurements of lead concentration in cortical bone from the midfemur of 322 non–occupationally exposed children and adults who died in Germany between 1983 and 1985. When reanalyzed by regression analysis, log-transformed bone lead values from a subset of 275 subjects aged 11 to 85 years are also well described by an age- and sex-adjusted piecewise linear model (R^2=.60; $P \leq .0001$) in which bone lead concentration increases at an average slope of approximately 0.14 ppm/y through 40 years of age and then exhibits a marked difference by sex, with male values increasing while female values slightly decline. Similarly, our reanalysis of the log-transformed postmortem bone lead data of Barry[13] corresponding to 97 subjects aged 10 to 86 years yields an average slope of 0.18 ppm/y for both sexes through 35 years of age, followed by an additional upward inflection in older men.

Morgan et al[24] observed a nonconstant age-related increase in KXRF tibial bone lead measurements among 59 subjects aged 21 to 80 years and fit their data with a quadratic term in age (age squared) to describe the steeper increases in older subjects. Our reanalysis of their data in piecewise terms reveals a notable similarity to the present study, in that age 55 years again emerges as an inflection point where bone lead values inflect upward. No significant age-sex interaction was found, possibly because only six of their 25 subjects aged 55 years or older were female. Table 3 summarizes the improved fit of selected data sets when piecewise models allow the slope between age and bone lead concentration to change at different ages and to differ by sex.

Kinetic factors relating to bone metabolism or secular trends in lead exposure are both possible explanations for the changing influence of age on bone lead concentration. Elucidation of an age effect among young subjects is hampered by the relatively higher coefficient of variation associated with their low bone lead concentrations. We found no significant slope to the relationship between age and bone lead concentration among our 10- to 20-year-old subjects, in contrast to the data of Drasch et al[35] and Barry.[13] However, when analysis of their data sets is extended to include subjects as young as 5 years, the strength and significance of the slope among subjects younger than 20 years declines.

A relatively constant bone lead concentration during childhood may be explainable by high rates of bone remodeling in which high resorption rates accompany high formation rates.[41,42] Although children undergo a rapid increase in aggregate bone lead content, increases in bone lead concentration may not emerge until the end of adolescence, when full skeletal size is reached and remodeling slows. Thereafter, as bone remodeling and diffusion decline, lead incorporated into bone from environmental exposure is likely to be retained for relatively longer periods of time. From the third to sixth decades of life, the half-life of tibial lead may be as long as 35 years.[43] Compared with calcium, lead may be preferentially retained in adult bone matrix, a characteristic demonstrated for other bone-seeking elements such as radium and barium[44] and suggested by the lack of correlation between age-dependent bone lead accumulation and calcium content in a recent mouse model.[45]

Even by the end of the sixth decade of life, approximately 35% to 40% of skeletal mass consists of unremodeled first-

generation bone acquired during childhood and adolescence.[44] It is therefore likely that relatively higher environmental lead exposure during the 1930s through the 1960s may also have contributed to the higher bone lead burden of the older subjects. The largest component of environmental exposure, dietary lead intake, has declined 90% from 1.9 to 2.4 μmol/d (400 to 500 μg/d) during the 1940s and 1950s, to less than 0.24 μmol/d (50 μg/d) by the mid 1980s.[46] Longitudinal surveys of population trends in blood lead concentration have revealed greater than 50% declines from the 1960s to the 1980s, in large part attributable to reductions in transportation-related airborne lead emissions.[46] Environmental exposure from lead in residential paint, plumbing, and soldered food containers has also recently declined.[47] Drasch et al[35] reported an age-adjusted decline in cortical bone lead burden between 1974 and 1984 that was greatest in specimens from subjects less than 40 years of age, for whom recent reductions in total lead sources would have had the greatest impact on cumulative lead dose.

An increase in bone remodeling in estrogen-deprived postmenopausal women[48] may have contributed to the lower bone lead concentrations observed in female subjects over 55 years of age. Given the lack of significant interactions between environmental and occupational lead exposure variables and sex, the older male and female subjects are likely to have approached their sixth decade with similar cumulative lead exposures and bone lead concentrations. Thereafter, the increased bone remodeling in estrogen-deprived females, in which old bone stores are partially replaced by newer bone matrix formed in the more recent low-lead environment, may favor a relative diminution in bone lead concentration. Although, as noted, a similar age-sex interaction occurs in several reports, the cross-sectional nature of all the bone lead data and the dependence of the interaction in this study on results from just five of the nine oldest men suggest caution in generalization to larger human populations.

Pregnancy and lactation result in mobilization of maternal skeletal calcium to meet the demands of fetal ossification and calcium secretion in breast milk. Of these two processes, lactation places the greater demand on the maternal skeleton, and declines in mineral content as large as 10% have been found in lactating women on marginally calcium-deficient diets.[49] Radiolabeled lead (^{210}Pb) studies in female rats have demonstrated that mobilization during lactation causes a decrease in maternal bone lead concentration.[50] The significant negative correlation between lactation history and bone lead concentration in the present study is consistent with a similar mobilization process and reinforces concerns that maternal bone lead stores may serve as a potential source of lead transfer to children.[51] The possibly nonlinear relationship between the number of children nursed and maternal bone lead concentration is consistent with the hypothesis that proportionately more bone lead may be mobilized during lactation of the first child.

The increase in bone lead concentration found with increasing pack-years of cigarette smoking is consistent with other studies that have revealed a modest correlation between cigarette consumption and elevated blood lead concentration.[52-55] In addition to direct contribution from tobacco, increased hand-to-mouth activity in smokers and enhanced permeability of a smoke-exposed respiratory tract may increase the effect of environmental lead exposure.[56] In postmortem analysis of the lead concentration of rib and calvarium specimens obtained in Los Angeles, Calif, in the early 1960s, a positive history of smoking was associated with higher bone lead concentrations in males, but not females.[57] The lead content of tobacco, partly a consequence of atmospheric lead deposition, and the use of lead arsenate pesticides on tobacco fields[58] has declined in recent years.[59] In the present study, the influence of cumulative tobacco intake on bone lead concentration, but not blood lead concentration, may reflect recent declines in cigarette usage and in tobacco lead content.

Several factors associated with lead exposure in other investigations did not emerge as significant predictor variables in this study. Several KXRF studies have correlated occupational lead exposure with bone lead concentration.[19,20,22] For example, in a study[20] of 88 subjects employed in lead acid battery manufacture (mean [SD] age, 45.5 [9.3] years), the mean (SD) tibial lead concentration was 32.3 (27.8) ppm. However, the mean duration of lead exposure in those cohorts (10 years or more) and the mean blood lead concentration of their active lead workers (>1.45 μmol/L [>30 μg/dL]) were substantially higher than encountered in the present study, where three fourths of the subjects were judged to have had less than 1 full-time year equivalent of occupational lead exposure, and the mean blood lead concentration was approximately 0.24 μmol/L (5.0 μg/dL). Large studies of blood lead concentration have also identified alcoholic beverage consumption as a source of lead.[52,54,55,60] The low level of occupational lead exposure and alcoholic beverage consumption among subjects in the present study may have impeded detection of an effect of these variables on bone lead.

Lead in house paint and residential soil are potential sources of environmental lead exposure, particularly in early childhood when hand-to-mouth activity is common. Although other studies have suggested that childhood residence in older houses,[23] particularly older painted wooden houses,[61] may influence bone lead concentration later in life, the present study revealed no significant correlation between residential history and bone lead. This is possibly a consequence of the strong adjustment exerted by age. The significant correlation found between current housing age and blood lead has also been observed in another study.[54]

Studies in occupationally exposed cohorts have identified the utility of KXRF as a marker of long-term, cumulative lead exposure. The present study demonstrates that in the absence of substantial occupational lead exposure KXRF measurements of bone lead concentration may be significantly influenced by variables relating to age, sex, cigarette consumption, and lactation. In future studies, KXRF measurements of bone lead concentration may have value in comparing the cumulative lead exposure of populations subjected to a variety of occupational and environmental lead sources. For most lead-associated pathology in adults, such as peripheral neuropathy, neuropsychological dysfunction, nephropathy, anemia, hypertension, or disordered spermatogenesis, the extent of cumulative exposure associated with the onset of illness has yet to be determined. The availability of in vivo KXRF as a quantitative biomarker of cumulative lead exposure may facilitate investigation of these dose-response relationships. Future longitudinal studies may also explore the impact of osteoporosis, pregnancy and lactation, hyperthyroidism, and other endocrinologic conditions on the redistribution of lead from bone to sensitive soft tissues. The present data help to establish a reference range for assessment of bone lead concentration in populations and individuals and identify key covariates to examine in future studies.

This study was supported by funding from Gould Inc, and in part by Special Emphasis Research Career Award 1 K01 OH001 08-01 from the National Institute for Occupational Safety and Health (Dr Kosnett).

The authors wish to gratefully acknowledge the following: Andrea Lash, PhD, for statistical consultation in study design; William Birdsong, Lisa Kosenak, Eugene Kumekawa, PhD, Tom Lewandowski, MPH, Susan Metzger, MPH, Neal Morrison, Joseph Murray, Susan Payne, MA, Susan Sahl,

MA, and Donna Scaglione for research assistance and data collection; Barbara Forslund, PE, of Advanced GeoServices Corp, Chadds Ford, Pa, and Curt Wicker and Jim Taylor of NTH Consultants Ltd, Exton, Pa, for soil lead data. G.A. Drasch, PhD, Institut fur Rechtsmedizin der Universitat Munchen, and S.J.S. Ryde, PhD, Swansea In Vivo Analysis Research Group, Wales, kindly supplied bone lead data for comparative analysis. W.K. Sieber, PhD, kindly provided lead exposure data from the National Occupational Exposure Survey–Job Exposure Matrix.

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