The Influence of Bone and Blood Lead on Plasma Lead Levels in Environmentally Exposed Adults

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There is concern that previously accumulated bone lead stores may constitute an internal source of exposure, particularly during periods of increased bone mineral loss (e.g., pregnancy, lactation, and menopause). Furthermore, the contribution of lead mobilized from bone to plasma may not be adequately reflected by whole-blood lead levels. This possibility is especially alarming because plasma is the main circulatory compartment of lead that is available to cross cell membranes and deposit in soft tissues. We studied 26 residents of Mexico City who had no history of occupational lead exposure. Two samples of venous blood were collected from each individual. One sample was analyzed by inductively coupled plasma–magnetic sector mass spectrometry for whole-blood lead levels. The other sample was centrifuged to separate plasma, which was then isolated and analyzed for lead content by the same analytical technique. Bone lead levels in the tibia and patella were determined with a spot-source ^{109}Cd K-X-ray fluorescence instrument. Mean lead concentrations were 0.54 µg/l in plasma, 119 µg/l in whole blood, and 23.27 and 11.71 µg/g bone mineral in the patella and tibia, respectively. The plasma-to-whole–blood lead concentration ratios ranged from 0.27% to 0.70%. Whole-blood lead level was highly correlated with plasma lead level and accounted for 95% of the variability of plasma lead concentrations. Patella and tibia lead levels were also highly correlated with plasma lead levels. The bivariate regression coefficients of patella and tibia on plasma lead were 0.034 (p<0.001) and 0.053 (p<0.001), respectively. In a multivariate regression model of plasma lead levels that included whole-blood lead, patella lead level remained an independent predictor of plasma lead level (β = 0.007, p<0.001). Our data suggest that although whole-blood lead levels are highly correlated with plasma lead levels, lead levels in bone (particularly trabecular bone) exert an additional independent influence on plasma lead levels. It will be important to determine whether the degree of this influence increases during times of heightened bone turnover (e.g., pregnancy and lactation). *Key words*: blood, bone, K-X-ray fluorescence, lead, plasma. *Environ Health Perspect* 106:473–477 (1998). [Online 6 July 1998]
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Population blood lead levels have been decreasing in response to environmental measures that restrict emissions of lead (*1*). However, some evidence suggests that elevated exposure to lead may continue for many years, even after exposure to environmental sources has been reduced. This may occur primarily due to the mobilization of endogenous bone lead stores (*2*). The skeleton is the primary site of storage for about 95% of lead in the adult human body (*3*). Toxicokinetic studies have demonstrated that although the half-life of lead in bone is on the order of years to decades, bone is a dynamic organ with respect to lead, engaging in a constant low-level interchange with soft-tissue elements (*4–7*). Recent data from Cake et al. (*8*), Gulson et al. (*9*), and Smith et al. (*10*) indicate that the skeleton is an important source of endogenous lead exposure in individuals with a history of high-level occupational or environmental lead exposure.

The contribution of endogenous sources of lead to plasma may be important, but a substantial change in plasma lead may go unnoticed when lead is measured in whole blood (the usual method of evaluation) because less than 2% of total blood lead is free in plasma. Moreover, factors controlling the relative partitioning of circulatory lead into the plasma are not well known, although it has been suggested that plasma lead levels may better reflect the labile, biologically active fraction of circulatory lead most available for distribution to and from peripheral tissues.

Until recently, epidemiological studies on the toxicological significance of human bone lead stores have required the use of invasive methods. However, *in vivo* K-X-ray fluorescence (K-XRF) now permits noninvasive studies in which bone lead level serves as a measure of bone lead reserves (*11*). In this study, we examined the relation among lead levels in bone, plasma, and blood of a sample of healthy volunteers who had no occupational history of lead exposure.

Methods

Study Population

We recruited 26 healthy individuals who had not been occupationally exposed to lead; the group included 20 women (mean age 36 years, range 24–54 years) and 6 men (mean age 38, range 19–70 years). Only 5 participants were over 50 years of age. The main risk factors for lead exposure in the group were residence in Mexico City for more than 10 years (88%) and use of lead-glazed ceramics for cooking and storing food (58%) (*12*). All participants had provided a blood sample and had undergone at least one bone lead measurement in the 1–3 months before this study. The individuals selected for this study constituted a sample designed to reflect the patella (trabecular) bone lead concentrations observed in previous studies of the general population of Mexico City (*13*). We selected individuals to represent three strata with the following cutoff points: >10 µg of lead/g of bone mineral (n = 7); 10.1–20.0 µg/g (n = 7); and >20 µg/g (n = 11). On 22 May 1996, all study subjects had two blood samples taken: one for whole-blood lead measurement and the other for plasma lead measurement. After preparation and labeling, plasma and blood specimens were shipped to the University of California, Santa Cruz, for lead determination.

Plasma and Blood Lead Measurements

Study subjects attended our research clinic and were instructed beforehand to fast overnight, as meals consumed before the collection of serum samples may transiently

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alter steady-state serum lead levels (*14*). As demonstrated by Smith et al. (*15*), the accurate and precise determination of plasma and serum lead levels depends on meticulous processing techniques, including control of lead contamination, hemolysis, and redistribution of lead due to anticoagulants, and, in the case of serum sample collection, the time interval for whole-blood clotting before separation of serum. Before the collection of venous blood (15 ml total) through a butterfly catheter (19-gauge), each subject's arm was washed with ultrapure water and disinfected with reagent-grade alcohol. An initial whole-blood sample of 3 ml was collected in a low-lead container (Vacutainer, B-D #367734; Becton-Dickinson, Franklin Lakes, NJ) for total lead analysis; immediately thereafter, the catheter tubing was severed at a point distal to the venipuncture, and a second whole-blood sample of 13 ml for plasma separation was collected via gravity-fed phlebotomy (no vacuum) into a polyethylene tube containing 75 USP of low-lead sodium heparin [Sigma #H-3393, 0.1 pg Pb/USP unit (*15*)]. The 13-ml whole-blood sample was immediately enclosed in plastic wrap and centrifuged at 2000 rpm (800*g*) for 10 min at room temperature. The separated plasma fraction (5–6 ml) was then pipetted into a polyethylene bottle with a polyethylene pipette and immediately frozen.

We conducted all blood collections, plasma and whole-blood processing, and sample analyses under trace metal-free HEPA air-filtered laboratory (Class 100) conditions using ultraclean trace-metal techniques (*16*) developed at the University of California, Santa Cruz. Materials used in sample collection and in the laboratory (Teflon, polyethylene, and polypropylene) were acid-cleaned by established procedures (*15,16*). Reagents, including water and acids, were high-purity grade. For analyses, the entire 5–6 ml plasma sample or 0.5-ml aliquot of whole blood was transferred into a Teflon digestion vial, evaporated and digested for 8 hr in 5 ml of hot 16 N HNO_3, evaporated to dryness, and redissolved in 1 N HNO_3. Sample lead and iron levels were measured independently with a Finnegan Element inductively coupled plasma (ICP) high-resolution mass spectrometer in multi-isotope counting mode, with both internal and external standardization (*15,17*). We used National Institute of Standards and Technology (NIST) standard reference materials (SRM) 955 (blood) and 1577 (bovine liver) to evaluate analytical accuracy. This method yields a measurement precision of ≤0.5% RSD (relative standard deviation) for lead concentrations of >0.05 ppb (*15,17*). The analytical detection limit was 0.01 ppb.

Lead contamination of the plasma samples, either from external sources or from erythrocytic lead due to hemolysis, is a significant potential modifier of true plasma lead levels. We evaluated lead contamination from external sources by determining the total lead and stable lead isotopic compositions of procedural collection and processing blanks and comparing the values obtained with levels measured in whole blood and plasma. Separately, the low-lead heparin anticoagulant was shown to contribute a negligible amount of lead (8 pg Pb) to the 13-ml whole-blood sample used for plasma lead separation (*15*).

Although potential contamination of plasma samples was evaluated here, quantitative correction of sample lead concentrations for external lead contamination associated with sample collection and processing was not attempted because there is no reliable and accurate method to determine the relative contribution of blank contaminant lead to a collected plasma sample (*15*). Although some fraction of total blank lead undoubtedly partitions with the separated plasma fraction, the amount is not known and may vary with the physiochemical nature of the lead and other biological and physical factors.

In contrast, measurable lead contamination of plasma samples may arise from lead redistributed from erythrocytes, particularly in cases of apparent hemolysis. To evaluate the potential contribution of hemolysis to plasma lead levels, whole-blood iron and plasma iron levels were measured. The rationale for measuring plasma iron to evaluate hemolysis is based on 1) the distribution of iron between the erythrocyte cell fraction and the plasma, 2) the relatively narrow and well-characterized range of plasma iron levels considered physiologically normal (0.5–1.75 μg/ml), 3) the sensitivity of the ICP-MS methodology for determining relatively small changes in sample iron levels, and 4) the premise that increases in plasma iron levels beyond physiologically normal levels would reflect a nonphysiologic input of both iron and lead from erythrocytes. A previous study has substantiated this approach as a sensitive indicator of plasma contamination from erythrocytes (*15*).

K-XRF Bone Lead Measurements

Bone lead was measured in each subject's mid-tibia shaft (cortical bone) and patella (trabecular bone) with a spot-source ^{109}Cd K-XRF instrument constructed at Harvard University and installed in a research facility at the American British Cowdray Hospital in Mexico City. The physical principles, technical specifications, and validation of this instrument have been detailed elsewhere (*18*). The instrument uses a ^{109}Cd γ-ray source to provoke the emission of fluorescent lead photons from target tissue. The emitted photons are then detected, arrayed in a spectrum, and counted. The net lead signal is determined after subtraction of Compton background counts by 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. The unit of measure so derived is micrograms of lead per gram of bone mineral.

Calibration is performed using lead-doped phantoms of which the true lead concentration has been verified by direct chemical measurements using ICP-MS (*18*). Because the instrument provides a continuous unbiased point estimate that oscillates around the true bone lead value, negative point estimates are sometimes produced when the true bone lead value is close to zero. Validation studies of the instrument we used have indicated a fairly high degree of precision and accuracy of point and measurement uncertainty estimates, with chemical analyses in studies of lead-doped phantoms used for comparisons (*18*).

For the present study, 60-min measurements were taken at the mid-shaft of the left tibia and at the left patella after each region had been washed with a 50% solution of isopropyl alcohol. The K-XRF beam collimator was placed perpendicular to the bone surface for the tibia and at 30° in the lateral direction for the patella.

The reproducibility of bone measurements using this particular K-XRF instrument is high. Repeated measurements in 35 subjects showed a high intraclass correlation of 0.84 and 0.82 for tibia and patella, respectively.

Statistical Analysis

Plasma and blood lead levels were log transformed to normalize their distributions. Bone lead measurements were normally distributed and were modeled in their original scale. We used the transformed plasma and blood variables in all statistical models. We first examined the bivariate relationships between plasma lead and each biological marker of lead (blood, patella, and tibia). We then constructed multivariate regression models in which blood and bone lead variables were included as predictors of plasma lead. We used these models to test the hypothesis that, in addition to blood lead levels, bone lead levels are independent predictors of plasma lead

levels. Similar models were also run for plasma-to-blood ratio as an outcome. All models were adjusted for age, gender, and iron plasma levels. We performed all regression analyses with Stata Software (Stata Statistical Software, release 4.0, Stata Corporation, College Station, Texas).

Results

Blank lead values for all ultraclean plasma lead samples were uniformly low (≤5% of the total plasma lead sample) and thus were considered negligible here. However, a single subject was excluded from the data analysis because of exogenous lead contamination of plasma, which was apparent from the anomalous nonphysiologic stable lead isotopic composition of the sample compared with that of whole blood (data not shown). No other cases of measurable lead contamination of plasma, either from external or internal sources (the latter using plasma iron levels as a marker) was evident in samples from any of the 25 remaining subjects. Two additional subjects did not complete the 1-hr measurement for tibia and were not included in the analysis relating tibia lead.

Descriptive statistics for biomarkers of lead exposure are presented in Table 1. We observed a high degree of correlation between plasma and whole-blood lead levels (Fig. 1, Table 2). Whole-blood lead levels accounted for 95% of the variability observed in plasma lead concentrations. In the bivariate regression models, both patella and tibia lead levels were also significant predictors of plasma lead levels (Fig. 1, Table 2). Patella lead accounted for 52% of the variability. Plasma lead increased significantly as a function of patella lead concentration. We observed an increase in the log scale of plasma lead of 0.034 for each microgram of lead per gram of lead in the patella.

Tibia lead was also significantly and positively associated with plasma lead; the estimated regression coefficient between the log plasma lead concentration and the tibia lead level was 0.053. When we simultaneously included whole-blood lead and each of the two bone lead variables, whole-blood lead was a highly significant predictor of plasma lead in both models ($p < 0.001$), as was patella lead ($p = 0.005$); tibia lead was of borderline significance ($p = 0.051$) (Table 3). Log whole-blood lead levels increased log plasma lead levels by 1.02 per unit of whole-blood lead, whereas patella lead increased log plasma lead levels by 0.007 per unit of bone lead.

Neither age, gender, nor plasma iron levels remained as significant predictors of plasma lead in multivariate models. The inclusion of these variables in the models did not change the observed associations between plasma lead and other biomarkers of lead exposure.

In our sample, the plasma-to-blood lead concentration ratio also varied significantly in relation to blood lead, patella lead, and tibia lead concentrations (see Fig. 2). In a regression model of the plasma-to-blood lead concentration ratio that included both patella lead and whole-blood lead, patella remained as a significant predictor ($p<0.05$), whereas whole-blood lead was of borderline significance ($p = 0.09$). In contrast, in a regression model of the plasma-to-blood lead concentration ratio that included tibia lead and whole-blood lead, whole-blood lead remained as a significant predictor ($p<0.01$), whereas tibia lead was of borderline significance ($p = 0.15$).

Discussion

We found a strong relationship between whole-blood lead and plasma lead levels in these environmentally exposed adults. In addition, we found a strong relationship between bone lead and plasma lead concentrations, and patella (trabecular) bone lead retained an independent influence on plasma lead as well as on the plasma–whole-blood lead ratio after adjusting for whole-blood lead levels. This independence of the bone lead–plasma lead association from whole-blood lead levels is consistent with the potential role of the skeleton as an important endogenous source of labile lead that may not be adequately discerned by examining whole-blood lead levels. It also indicates that skeletal sources of lead accumulated from past exposures should be considered along with sources of current exposure when exposure pathways are being evaluated.

Tibia and patella lead levels were both positively and significantly related to plasma lead levels; however, the observed association was stronger for patella lead. The blood lead-adjusted standardized regression coefficients relating plasma lead level to patella and tibia lead levels were 0.15 and 0.10, respectively. A 10 µg/g increase in patella lead level was associated with an increase of 7% in plasma lead level; the same change in tibia lead level was associated with a 3.7%

Table 1. Descriptive summary statistics for plasma, whole-blood, and bone lead levels

Measurement	Mean	Median	SD	Minimum	Maximum
Plasma lead (µg/l)	0.54	0.27	0.68	0.085	2.65
Plasma-to-blood lead ratio (%)	0.39	0.37	0.10	0.27	0.70
Blood (µg/l)	118.83	73.40	108.89	22.9	416.4
Tibia bone (µg/g)	11.71	10.31	10.61	-5.0	35.65
Patella bone (µg/g)	23.27	19.38	21.69	-3.21	92.82
Plasma iron (µg/g)	1.22	1.25	0.390	0.36	1.87

SD, standard deviation.

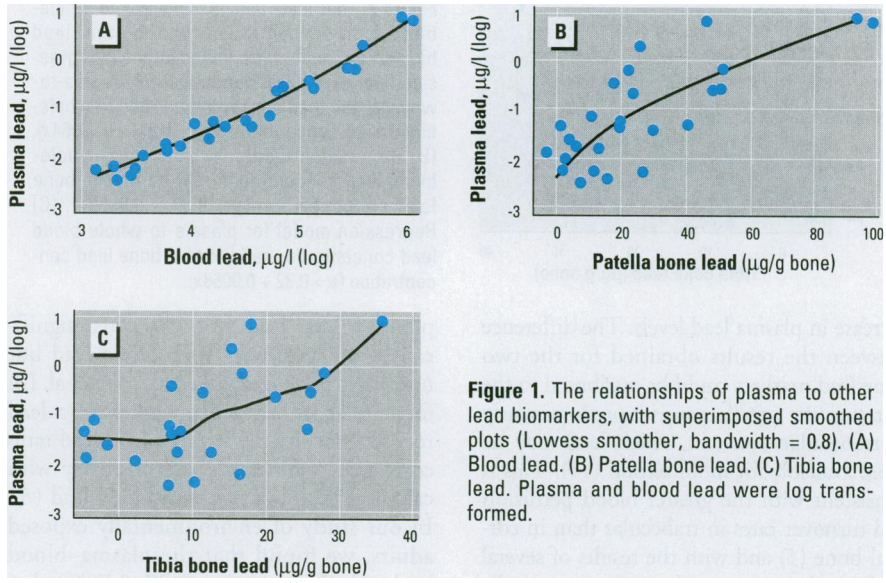

Figure 1. The relationships of plasma to other lead biomarkers, with superimposed smoothed plots (Lowess smoother, bandwidth = 0.8). (A) Blood lead. (B) Patella bone lead. (C) Tibia bone lead. Plasma and blood lead were log transformed.

Table 2. Bivariate regression models correlating plasma lead levels with whole-blood and bone lead levels

	Constant	Coefficient	SE	R^2
Blood lead (µg/l)	-6.16	1.37	0.05	0.95
Patella lead (µg/g)	-1.91	0.034	0.006	0.52
Tibia lead (µg/g)	-1.67	0.053	0.015	0.30

SE, standard error.

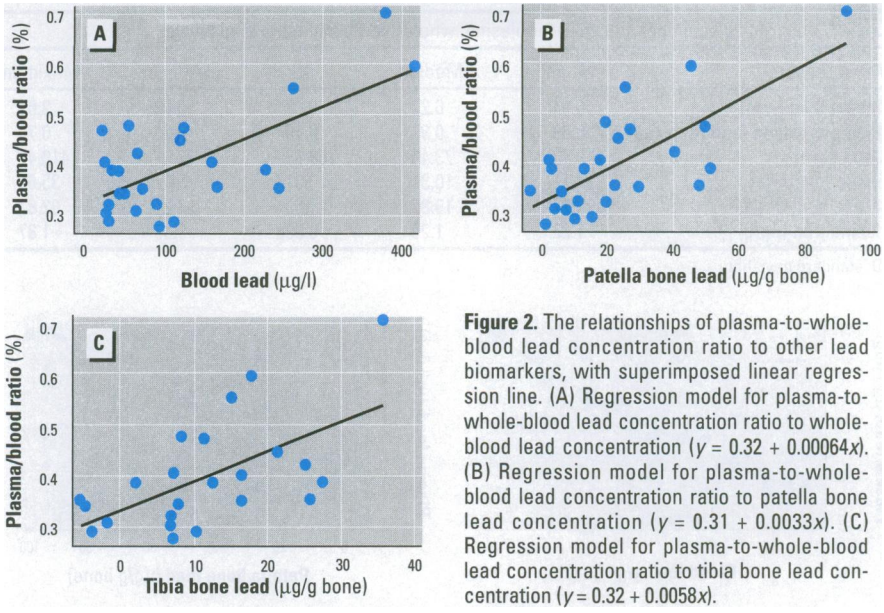

Figure 2. The relationships of plasma-to-whole-blood lead concentration ratio to other lead biomarkers, with superimposed linear regression line. (A) Regression model for plasma-to-whole-blood lead concentration ratio to whole-blood lead concentration ($y = 0.32 + 0.00064x$). (B) Regression model for plasma-to-whole-blood lead concentration ratio to patella bone lead concentration ($y = 0.31 + 0.0033x$). (C) Regression model for plasma-to-whole-blood lead concentration ratio to tibia bone lead concentration ($y = 0.32 + 0.0058x$).

Table 3. Multivariate regression models of plasma lead levels

Independent variables	Coefficient	SE	*p*-Value
Model 1 ($R^2 = 0.96$)			
Blood lead (µg/l)	1.02	0.056	<0.001
Patella lead (µg/g)	0.007	0.002	0.005
Constant	-5.79	0.22	<0.001
Model 2 ($R^2 = 0.97$)			
Blood lead (µg/l)	1.10	0.004	<0.001
Tibia lead (µg/g)	0.0089	0.056	0.051
Constant	-6.15	0.23	<0.001

SE, standard error.

increase in plasma lead levels. The difference between the results obtained for the two bone lead markers could be attributed to the fact that the patella consists predominantly of trabecular bone, in which lead may be more available for mobilization (*19*). This is consistent with the greater blood perfusion and turnover rates in trabecular than in cortical bone (*5*) and with the results of several studies using tracer and standard metabolic methods (*6,13–15,20*). In addition, it supports trabecular bone as the predominant skeletal source of lead to the circulation under steady-state conditions. However, the fact that tibia lead was significantly associated with plasma lead levels and marginally associated with blood lead-adjusted plasma levels suggests that lead in cortical bone is also released into the bloodstream. Cortical bone composes approximately 80% of skeletal mass and thus may exert strong influence on plasma lead levels, even if its rate of turnover is lower than that of trabecular bone. The possible importance of cortical bone in whole-body lead toxicodynamics has also been suggested by reports indicating that lead concentrations in cortical bone, as opposed to concentrations in blood, were linked to hypertension (*21*) and to a decrease in birth weight (*22*).

Few investigators have described the relationship between lead levels in bone and whole blood and those in plasma. Most of the published investigations have been conducted among occupationally exposed individuals with levels of exposure that are three to four times higher than the levels encountered in the general urban population with a history of exposure to leaded gasoline and other environmental sources (*23*). Bergdahl and Skerfving (*24*) noted that among 19 retired lead smelter workers, the plasma–blood lead ratio correlated significantly and positively with blood lead but not finger bone lead, whereas Cake et al. (*8*) found that among active workers in a lead recycling facility the serum–blood lead ratio correlated significantly and positively with calcaneal lead, but not with blood lead (*8*). In our study of environmentally exposed adults, we found that the plasma–blood lead ratio had a range (0.27–0.70%) that was similar to that reported by Bergdahl and Skerfving (*24*) (0.25–0.95%), but our plasma–blood lead ratio correlated significantly and positively with patella lead, tibia lead, and blood lead. Moreover, in a multivariate model that included both patella lead and blood lead, the plasma–blood lead ratio correlated most strongly with patella lead. One explanation for the differences seen in these investigations is that trabecular bone lead (patella and calcaneus) does, in fact, exert a predominant influence on serum (plasma) lead and that this effect cannot be ascertained by measuring lead in finger bone (which is mixed trabecular and cortical bone and, by virtue of relatively low bone mass, gives rise to less precise bone lead measurements).

The evidence that the skeleton may be an endogenous source of lead exposure is rapidly growing. It is now generally recognized that bone, rather than acting as a permanent site of lead deposition, is a metabolically active site which uptakes and releases lead at a rate determined by lead exchange at bone surfaces and factors affecting bone remodeling (*5,25*). Results from previous studies of occupationally exposed subjects have suggested that whole-blood lead was an important determinant of plasma lead and that bone lead might be an important endogenous source of plasma lead. For example, Cake et al. (*8*) hypothesized that endogenous lead (i.e., from bone) partitioned differently between serum and red cells than did lead from exogenous exposures. Although insufficient data exist to accurately evaluate this hypothesis, it is supported by our observation that the plasma-to-blood lead concentration ratio varied more significantly with bone lead levels than with whole-blood lead levels. Our study sample was not as large as that of Cake et al. ($n = 49$), and the median blood lead levels measured in our study were not as high as those measured in their study (362 µg/l). Nonetheless, our data are consistent with the hypothesis proposed by Cake et al. Other studies have yielded indirect evidence of the contribution of bone lead stores to plasma lead.

Our study was limited by the fact that we measured bone lead 1–3 months before we measured plasma and blood lead. This approach was used because of the need to obtain information on patella lead levels to stratify the study population. However, because lead in the skeleton has a half-life of years to decades (*3*), we believe that the change in bone lead levels over the elapsed interval was negligible. Therefore, our bone lead measurements probably adequately reflect levels at the time of blood and plasma sampling. Another limitation of our study was the small sample size. However, given that we selected individuals on the basis of their bone lead levels, we obtained an adequate level of variation in bone lead levels. Thus we maximized statistical power. The interrelationships of plasma, patella, and blood lead concentrations were strong enough to be detected and were not confounded or modified by gender or age. Moreover, the exclusion of subjects older than 50 did not modify the observed relations.

In this study, the potential for contamination of plasma by lead from external and internal (hemolysis) sources was evaluated by means of lead concentration and stable isotopic composition analyses of procedural collection and processing blanks and total

iron levels in plasma and whole blood. On the basis of these analyses, only one subject was excluded. In previous studies that evaluated the importance of sample collection and processing methods for accurate and precise determination of plasma lead levels (*14,15*), lead contamination from external sources was shown to be an important potential contributor to plasma lead. However, lead contamination due to a non-normal redistribution of lead from erythrocytes into plasma during routine handling or due to inadvertent hemolysis was also found to be a potentially significant modifier of plasma lead levels, even when hemolysis was not readily apparent (*15*). Analyses of plasma iron levels proved to be a reliable indicator of the latter source of contamination (*15*). In our study, we found no evidence suggesting plasma contamination due to hemolysis, nor was there any indication that plasma iron levels confounded or modified the observed association between plasma lead and other biomarkers. Therefore, we believe that the observed associations between plasma, whole blood, and bone lead levels cannot be explained by internal lead contamination.

The degree to which the whole-blood lead level reflects the labile, toxic fraction of lead in the circulation is not well known, though it has been suggested that plasma lead provides a more kinetically responsive and toxicologically relevant marker of lead than does whole-blood lead (*8,25*). The limitations of whole-blood lead measurements as a marker of lead exposure—and, more importantly, as a biomarker of readily labile and toxic lead—have been considered for several years (*26*). Although the skeleton can certainly contribute lead to the circulation, the impact of various exposure regimens and bone metabolic states on the nature of this relationship is not known.

Until recently, arguments supporting the evaluation of plasma lead as an essential step in the investigation of bone lead release were based in part on reports showing little or no correlation between whole-blood and plasma lead levels in individuals with low to moderate blood lead levels (e.g., 5–25 μg/dl) (*26–30*). A number of those reports described an apparent severalfold variation in the relative partitioning of lead between whole blood and plasma for a given whole-blood lead level. Our results, however, reflect a fairly well-defined and precise log-linear relationship between whole-blood and plasma lead levels, indicating that individual variation in the relative distribution of lead between whole blood and plasma may not be as wide as was previously believed, particularly among individuals with low to moderate lead levels in steady-state exposure with their environment.

Our results strongly support the hypothesis that mobilization of lead from bone may be a significant determinant of exposure to lead and are in agreement with recent reports that show an increased bone lead mobilization during pregnancy (*31*). It is possible that during this period the plasma lead level increases significantly, posing a potential risk to the developing fetus, the nursing infant, the lactating woman, or the pregnant woman. Further information on these points is needed. Because bone lead has a half-life of years to decades, our results suggest that whole-blood lead levels may not accurately predict the risk of associated lead toxicity and that lead can remain a significant threat to women who are pregnant, who are going to become pregnant, or who are menopausal or postmenopausal, even long after the reduction or cessation of exogenous lead exposure.

Finally, the findings of this study may have great importance in terms of public health. Given the lack of an agreed-upon threshold for lead's neurotoxic effect, a fetotoxic effect may in fact be operative even among women with relatively low blood lead levels but a high bone lead burden. Thus, current regulations governing occupational exposure to lead (in Mexico and the United States) may not adequately protect women who may become pregnant. Additional research is clearly needed to address this important issue.

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