Calculating Bone-Lead Measurement Variance

Andrew Christian Todd

Mount Sinai School of Medicine, Department of Community and Preventive Medicine, New York, New York, USA

The technique of ^{109}Cd-based X-ray fluorescence (XRF) measurements of lead in bone is well established. A paper by some XRF researchers [Gordon CL, et al. The Reproducibility of ^{109}Cd-based X-ray Fluorescence Measurements of Bone Lead. Environ Health Perspect 102:690–694 (1994)] presented the currently practiced method for calculating the variance of an *in vivo* measurement once a calibration line has been established. This paper corrects typographical errors in the method published by those authors; presents a crude estimate of the measurement error that can be acquired without computational peak fitting programs; and draws attention to the measurement error attributable to covariance, an important feature in the construct of the currently accepted method that is flawed under certain circumstances. *Key words*: bone, lead, measurement error, X-ray fluorescence. *Environ Health Perspect* 108:383–386 (2000). [Online 15 March 1999]
http://ehpnet1.niehs.nih.gov/docs/2000/108p383-386todd/abstract.html

The *in vivo* measurement of lead in human bone using ^{109}Cd-based fluorescence of the K-shell X-rays of lead (KXRF) is a well-established technique that has been widely applied to studies of the human health effects of lead and has been reviewed, most recently, by Todd and Chettle (*1*) in a technical manner and by Hu et al. (*2*) in a conceptual manner. This paper addresses the method for calculating the measurement uncertainty in a bone-lead measurement given in a 1994 paper by Gordon et al. (*3*).

In ^{109}Cd-based KXRF, the 88.034 keV γ-rays from ^{109}Cd are used to fluoresce the K-shell X-rays of lead (in increasing energy, those with Siegbahn notation: $K\alpha_2$, $K\alpha_1$, $K\beta_1$, $K\beta_3$, and $K\beta_2$). The ^{109}Cd γ-rays can also elastically scatter off of the calcium and phosphorus (and, to a lesser extent, oxygen) atoms in bone and inelastically scatter off all of the elements in the sample undergoing measurement (principally the bone, soft tissue, and skin). The photons are recorded by a spectroscopy system that yields an energy distribution of the recorded photons that is then fitted using a nonlinear least-squares technique with a mathematical function to extract the amplitudes of the X-ray and elastic scatter peaks. The ratio of the X-ray-to-elastic peaks is the response of the system and is regressed, for each X-ray peak under analysis, against the lead concentration of the calibration standards to produce a calibration line.

The *in vivo* signal from a subject is measured for each lead X-ray to be analyzed and is compared to the established calibration line to obtain one or more estimates of the subject's bone-lead level. The individual X-ray estimates are then combined, usually in an inverse-variance weighted manner, to produce the result.

The remainder of this paper addresses methods for the mathematical treatment of the measurement uncertainty; corrects typographical errors in the published method of Gordon et al. (*3*); presents a crude estimate of the measurement error that can be acquired without computational peak-fitting programs; and addresses the measurement error attributable to covariance.

Materials and Methods

Gordon et al. (*3*) published a study of the reproducibility of ^{109}Cd-based X-ray fluorescence (XRF) measurements of bone lead. Their paper contained an "Appendix" wherein they gave a near-complete description of the mathematical method by which they calculated the variance of an *in vivo* bone-lead measurement. In brief, they made multiple measurements of a series of plaster-of-paris phantoms doped with a range of lead concentrations. The spectrum of scattered radiation showed characteristic peaks from the emission of lead K X-rays that varied in size depending, in part, on the lead concentration of the phantom. Gordon et al. used four of the lead K X-rays for analysis: those with Siegbahn (International Union of Pure and Applied Chemistry notation in parentheses) $K\alpha_1$ (K-L_3), $K\alpha_2$ (K-L_2), $K\beta_1$ (K-M_3), and $K\beta_3$ (K-M_2). For clarity and ease of comparison, I will use the notation of Gordon et al.: x_i denotes the amplitude of each X-ray peak, coh denotes the coherent peak amplitude, and R_i denotes the ratio of the two peak amplitudes. Peak amplitudes and SDs are extracted from the spectra by applying a nonlinear least-squares technique. A calibration line is constructed for the ratio of the X-ray-to-coherent peak amplitudes against lead concentration. The ratio is used because it is independent, to a good approximation, of two important factors that affect *in vivo* and phantom measurements; namely, source-to-skin distance and overlying tissue thickness. Each calibration line is calculated using least-squares regression. I perform weighted least-squares regression and I suspect that Gordon et al. did also, although they did not state what method they used. However, the method of least-squares regression is irrelevant to the arguments of this paper.

Regression gives estimates of the calibration line slope (m_i), the slope's variance ($\sigma^2_{m_i}$), the intercept (C_i), the intercept's variance ($\sigma^2_{C_i}$), and the covariance between the slope and intercept ($\sigma^2_{C_i m_i}$). The X-ray-to-coherent ratios from an *in vivo* measurement can be converted, using the calibration lines, into estimates of the *in vivo* lead concentration (Pb_i). A matrix correction term accounts for the difference between phantom (plaster-of-paris) and human (bone) matrices, and the estimates of the *in vivo* bone-lead concentration are combined into an inverse-variance weighted mean to give a single estimate (Pb_μ). The inverse-variance weighted estimate has a variance that is denoted $\sigma^2_{Pb_\mu}$.

For each of the lead X-rays in use

$$\mathrm{Pb}_i = 1.46\frac{R_i - C_i}{m_i}, \quad \text{[Gordon 1]}$$

where 1.46 is "the ratio of coherent scattering cross-sections of bone mineral to hydrated plaster of paris at 88 keV and 160°" (*3*) and

$$R_i = \frac{x_i}{\mathrm{coh}}. \quad \text{[Gordon 2]}$$

The variance of the ratio, $\sigma^2_{R_i}$, is given by

$$\sigma^2_{R_i} = \left\{\left(\frac{\sigma_{x_i}}{x_i}\right)^2 + \left(\frac{\sigma_{\mathrm{coh}}}{\mathrm{coh}}\right)^2\right\}\left(\frac{x_i}{\mathrm{coh}}\right)^2. \quad \text{[Gordon 3]}$$

An expression for "a crude underestimate of the measurement variance $\sigma^2_{\mathrm{Pb}_i}$" (*3*), which

Address correspondence to A.C. Todd, Mount Sinai School of Medicine, Department of Community and Preventive Medicine, 1 Gustave L. Levy Place, New York, NY 10029 USA. Telephone: (212) 241-1668. Fax: (212) 996-0407. E-mail: todd@mssm.edu

I thank S. Carroll for manuscript preparation, J.H. Godbold for statistical guidance, and D.R. Chettle for helpful discussions on the Gordon et al. "Appendix."

This project was supported by grants ES05697 and ES06616 from the National Institute of Environmental Health Sciences.

Received 26 July 1999; accepted 21 October 1999.

ignores the calibration line uncertainties, is given by

$$\sigma^2_{\mathrm{Pb}_i} = (1.46)^2 \frac{\sigma^2_{R_i}}{m_i^2}. \quad \text{[Gordon 4]}$$

Gordon et al. then gave two expressions for the inverse-variance weighted mean (Pb_μ) and the variance thereof ($\sigma^2_{\mathrm{Pb}_\mu}$) derived from the individual lead X-ray peak estimates:

$$\mathrm{Pb}_\mu = \frac{\sum_i \frac{\mathrm{Pb}_i}{\sigma^2_{\mathrm{Pb}_i}}}{\sum_i \frac{1}{\sigma^2_{\mathrm{Pb}_i}}}, \quad \text{[Gordon 5]}$$

which has a variance of

$$\sigma^2_{\mathrm{Pb}_\mu} = \left(\sum_i \frac{1}{\sigma^2_{\mathrm{Pb}_i}}\right)^{-1}. \quad \text{[Gordon 6]}$$

An expression that combines the variance of the XRF response and the variance of the calibration line is then given:

$$\sigma^2_{\mathrm{Pb}_i} = 1.46^2 \left[\frac{\left(\frac{\sigma_{x_i}}{\mathrm{coh}}\right)^2 + \sigma^2_{C_i}}{m_i^2} + \frac{\sigma^2_{m_i}\left(\frac{x_i}{\mathrm{coh}} - C_i\right)^2}{m_i^4} + \frac{2\sigma^2_{C_i m_i}\left(\frac{x_i}{\mathrm{coh}} - C_i\right)}{m_i^3} + \frac{\left(\frac{\sigma_{x_i}}{\mathrm{coh}}\right)^2 x_i^2}{m_i^2} \right]$$

[Gordon 7]

This formula for $\sigma^2_{Pb_i}$ is incorrect in the fourth term inside the square bracket; this term should be

$$\frac{\left(\frac{\sigma_{\mathrm{coh}}}{\mathrm{coh}}\right)^2 \left(\frac{x_i}{\mathrm{coh}}\right)^2}{m_i^2},$$

giving a corrected equation of

$$\sigma^2_{\mathrm{Pb}_i} = 1.46^2 \left[\frac{\left(\frac{\sigma_{x_i}}{\mathrm{coh}}\right)^2 + \sigma^2_{C_i}}{m_i^2} + \frac{\sigma^2_{m_i}\left(\frac{x_i}{\mathrm{coh}} - C_i\right)^2}{m_i^4} + \frac{2\sigma^2_{C_i m_i}\left(\frac{x_i}{\mathrm{coh}} - C_i\right)}{m_i^3} + \frac{\left(\frac{\sigma_{\mathrm{coh}}}{\mathrm{coh}}\right)^2 \left(\frac{x_i}{\mathrm{coh}}\right)^2}{m_i^2} \right].$$

[Gordon 7 (corrected)]

The typographical error in Equation 7 of Gordon et al. is propagated through their Equations 8 and 9. Gordon Equation 8 gave the variance of the lead concentration obtained from an inverse-variance weighted mean of the estimates from each of the lead X-rays considered. The final term inside the bracket of Gordon Equation 8,

$$\frac{\left(\frac{\sigma_{\mathrm{coh}}}{\mathrm{coh}}\right)^2 x_i^2}{m_i^2 w_i^2},$$

should be

$$\frac{\left(\frac{\sigma_{\mathrm{coh}}}{\mathrm{coh}}\right)^2 \left(\frac{x_i}{\mathrm{coh}}\right)^2}{m_i^2 w_i^2},$$

giving a corrected version of Gordon Equation 8 of

$$\sigma^2_{Pb_w} = 1.46^2 \sum_i \left[\frac{\left(\frac{\sigma_{x_i}}{\mathrm{coh}}\right)^2 + \sigma^2_{C_i}}{m_i^2 w_i^2} + \frac{\sigma^2_{m_i}\left(\frac{x_i}{\mathrm{coh}} - C_i\right)^2}{m_i^4 w_i^2} + \frac{2\sigma^2_{C_i m_i}\left(\frac{x_i}{\mathrm{coh}} - C_i\right)}{m_i^3 w_i^2} + \frac{\left(\frac{\sigma_{\mathrm{coh}}}{\mathrm{coh}}\right)^2 \left(\frac{x_i}{\mathrm{coh}}\right)^2}{m_i^2 w_i^2} \right].$$

[Gordon 8 (corrected)]

Similarly, the final term of Gordon Equation 9,

$$\frac{\left(\frac{\sigma_{\mathrm{coh}}}{\mathrm{coh}}\right)^2 x_i^2}{m_i^2 \sigma^4_{\mathrm{Pb}_i}},$$

should be

$$\frac{\left(\frac{\sigma_{\mathrm{coh}}}{\mathrm{coh}}\right)^2 \left(\frac{x_i}{\mathrm{coh}}\right)^2}{m_i^2 \sigma^4_{\mathrm{Pb}_i}},$$

resulting in the corrected version of Gordon Equation 9:

$$\sigma^2_{Pb_w} = 1.46^2 \sum_i \left[\frac{\left(\frac{\sigma_{x_i}}{\mathrm{coh}}\right)^2 + \sigma^2_{C_i}}{m_i^2 \sigma^4_{\mathrm{Pb}_i}} + \frac{\sigma^2_{m_i}\left(\frac{x_i}{\mathrm{coh}} - C_i\right)^2}{m_i^4 \sigma^4_{\mathrm{Pb}_i}} + \frac{2\sigma^2_{C_i m_i}\left(\frac{x_i}{\mathrm{coh}} - C_i\right)}{m_i^3 \sigma^4_{\mathrm{Pb}_i}} + \frac{\left(\frac{\sigma_{\mathrm{coh}}}{\mathrm{coh}}\right)^2 \left(\frac{x_i}{\mathrm{coh}}\right)^2}{m_i^2 \sigma^4_{\mathrm{Pb}_i}} \right].$$

[Gordon 9 (corrected)]

Gordon et al. (*3*) then pointed out that "each of the terms (x_i/coh) has a mutual dependence on coh, the coherent scatter amplitude," and that this dependence can be accounted for by adding a further term to Equation Gordon 9 (corrected):

$$\sigma^2_{Pb_w} = 1.46^2 \frac{\sigma^2_{\mathrm{coh}}}{\mathrm{coh}^4} \sum_{i \neq j} \frac{x_i x_j}{m_i m_j \sigma^2_{\mathrm{Pb}_i} \sigma^2_{\mathrm{Pb}j}}.$$

Discussion

Crude estimates of measurement error. The crude estimate of measurement error given by Gordon et al. (Equation Gordon 4) can be simplified into a form that can be obtained at the time of measurement ("online") and with slightly less computational effort than the estimate of Gordon et al. A cruder estimate of measurement error can be obtained by using the fact that the variance of the X-ray peak amplitude (or area) dominates the variance of the ratio of the X-ray to coherent peak amplitudes (or areas). The fractional error in the ratio is therefore approximately equal to the fractional error in the X-ray peak:

$$\sigma^2_{R_i} \approx \frac{\sigma^2_{x_i}}{\mathrm{coh}^2},$$

whereupon

$$\sigma^2_{\mathrm{Pb}_i} \approx \frac{(1.46)^2 \sigma^2_{x_i}}{m_i^2 \mathrm{coh}^2}.$$

Several spectroscopy package regions of interest give σ^2_{xi}, allowing an online estimate of σ_{Pb_i} to be obtained (assuming the calibration line slope is already known). An online estimate of the measurement error has been useful when physicians require rapid assessment of a patient, and it may prove useful if a target measurement error is needed for all subjects. The expression for variance that accounts for only the X-ray amplitude is indistinguishable from the expression that accounts for the variances in both the coherent and the X-ray amplitudes. Table 1 illustrates this using the data of Gordon et al.

The error arising from covariance. Equation Gordon 7 warrants further examination because it contains two assumptions that are not explicitly stated by Gordon et al. Equation Gordon 7 is derived from a generalized treatment of error propagation that can be represented in matrix form (*4*):

$$\mathrm{V}_y = \begin{pmatrix} \frac{\partial y}{\partial x_1} & \frac{\partial y}{\partial x_2} & \frac{\partial y}{\partial x_3} \end{pmatrix} \times \begin{pmatrix} \mathrm{var}\, x_1 & \mathrm{cov}(x_1, x_2) & \mathrm{cov}(x_1, x_3) \\ \mathrm{cov}(x_1, x_2) & \mathrm{var}\, x_2 & \mathrm{cov}(x_2, x_3) \\ \mathrm{cov}(x_1, x_3) & \mathrm{cov}(x_2, x_3) & \mathrm{var}\, x_3 \end{pmatrix} \times \begin{pmatrix} \frac{\partial y}{\partial x_1} \\ \frac{\partial y}{\partial x_2} \\ \frac{\partial y}{\partial x_3} \end{pmatrix}$$

where V_y is the variance in $y = f(x_1, x_2, x_3)$, cov is the covariance, and var is the variance.

Upon multiplication:

$$V_y = \sum\left(\frac{\partial y}{\partial x_i}\right)^2 \operatorname{var} x_i + \sum_{i\neq j} 2\left(\frac{\partial y}{\partial x_i}\right)\left(\frac{\partial y}{\partial x_j}\right)\operatorname{cov}\left(x_i, x_j\right).$$

When I revert from generalized notation to the notation of Gordon et al. and write out the summation terms, the result is

$$\sigma^2_{\mathrm{Pb}_i} = \frac{\sigma^2_{R_i}}{m_i^2} + \frac{\sigma^2_{C_i}}{m_i^2} + \left(\frac{R_i - C_i}{m_i^2}\right)^2 \sigma^2_{m_i} + 2\left[\frac{-\sigma^2_{R_iC_i}}{m_i^2} + \left(\frac{-\left(R_i - C_i\right)}{m_i^3}\right)\sigma^2_{R_im_i} + \left(\frac{R_i - C_i}{m_i^3}\right)\sigma^2_{C_im_i}\right].$$

Using

$$\sigma^2_{R_i} = \left(\frac{\sigma^2_{x_i}}{x_i^2} + \frac{\sigma^2_{\mathrm{coh}}}{\mathrm{coh}^2}\right)\frac{x_i^2}{\mathrm{coh}^2} = \frac{\sigma^2_{x_i}}{\mathrm{coh}^2} + \frac{x_i^2\sigma^2_{\mathrm{coh}}}{\mathrm{coh}^4}$$

and

$$R_i = \frac{x_i}{\mathrm{coh}},$$

we obtain

$$\sigma^2_{\mathrm{Pb}_i} = \left(\frac{\sigma^2_{x_i}}{\mathrm{coh}^2} + \frac{x_i^2\sigma^2_{\mathrm{coh}}}{\mathrm{coh}^4}\right)\frac{1}{m_i^2} + \frac{\sigma^2_{C_i}}{m_i^2} + \left(\frac{\frac{x_i}{\mathrm{coh}} - C_i}{m_i^2}\right)^2\sigma^2_{m_i} - \frac{2\sigma^2_{R_iC_i}}{m_i^2} - \frac{2\left(\frac{x_i}{\mathrm{coh}} - C_i\right)}{m_i^3}\sigma^2_{R_im_i} + \frac{2\left(\frac{x_i}{\mathrm{coh}} - C_i\right)}{m_i^3}\sigma^2_{C_im_i}.$$

This equation has all of the terms in Gordon's (corrected) Equation 7 but also contains two additional terms that involve the covariance between the response R_i and the calibration line slope ($\sigma^2_{R_im_i}$) and intercept ($\sigma^2_{R_iC_i}$). The unstated assumptions of Gordon et al. are that both of these covariances are zero:

$$\sigma^2_{R_im_i} = \sigma^2_{R_iC_i} = 0.$$

These assumptions are valid and are stated here only for completeness.

Gordon et al. did not derive the expression that accounts for the covariance introduced by the mutual dependence of the ratios of X-ray-to-coherent amplitudes (R_i) on the same coherent peak amplitude. It may, however, be derived from the product of crude estimates of σ^2_{Pb} from two X-rays i and j: $\sigma^2_{\mathrm{Pb}_i}$ and $\sigma^2_{\mathrm{Pb}_j}$

$$\sigma^2_{\mathrm{Pb}} = 1.46^2\frac{\sigma^2_R}{m^2},$$

whereupon

$$\sigma^2_{\mathrm{Pb}_i}\sigma^2_{\mathrm{Pb}_j} = 1.46^4\left(\frac{\sigma^2_{R_i}}{m_i^2}\right)\left(\frac{\sigma^2_{R_j}}{m_j^2}\right).$$

If we then use

$$\sigma^2_R = \frac{\sigma^2_x}{\mathrm{coh}^2} + \frac{x^2\sigma^2_{\mathrm{coh}}}{\mathrm{coh}^4},$$

we obtain

$$\sigma^2_{\mathrm{Pb}_i}\sigma^2_{\mathrm{Pb}_j} = \frac{1.46^4}{m_i^2m_j^2}\left(\frac{\sigma^2_{x_i}}{\mathrm{coh}^2} + \frac{x_i^2\sigma^2_{\mathrm{coh}}}{\mathrm{coh}^4}\right)\times\left(\frac{\sigma^2_{x_j}}{\mathrm{coh}^2} + \frac{x_j^2\sigma^2_{\mathrm{coh}}}{\mathrm{coh}^4}\right)$$
$$= \frac{1.46^4}{m_i^2m_j^2}\left(\frac{\sigma^2_{x_i}\sigma^2_{x_j}}{\mathrm{coh}^4} + \frac{\sigma^2_{x_i}x_j^2\sigma^2_{\mathrm{coh}}}{\mathrm{coh}^6} + \frac{\sigma^2_{x_j}x_i^2\sigma^2_{\mathrm{coh}}}{\mathrm{coh}^6} + \frac{x_i^2x_j^2\sigma^4_{\mathrm{coh}}}{\mathrm{coh}^8}\right). \qquad \text{[Todd 1]}$$

It may be that Gordon et al. then ignored all of the terms except the last one in the bracket (the only one that contains the product of the X-ray peak amplitudes) to obtain:

$$\sigma^2_{\mathrm{Pb}_i}\sigma^2_{\mathrm{Pb}_j} \cong \frac{1.46^4}{m_i^2m_j^2}\left(\frac{x_i^2x_j^2\sigma^4_{\mathrm{coh}}}{\mathrm{coh}^8}\right).$$

The square root of the expression gives the term given by Gordon et al. if the weighting factors (w_i, w_j) are added and the X-ray product is evaluated for all pairs of X-rays

$$\cong 1.46^2\frac{\sigma^2_{\mathrm{coh}}}{\mathrm{coh}^4}\sum_{i\neq j}\frac{x_ix_j}{m_im_jw_iw_j}.$$

In the notation of Gordon et al., $w_i = \sigma^2_{\mathrm{Pb}_i}$ and $w_j = \sigma^2_{\mathrm{Pb}_j}$, making Gordon's actual expression

$$1.46^2\frac{\sigma^2_{\mathrm{coh}}}{\mathrm{coh}^4}\sum_{i\neq j}\frac{x_ix_j}{m_im_j\sigma^2_{\mathrm{Pb}_i}\sigma^2_{\mathrm{Pb}_j}}.$$

If the assumption about how this term was derived is correct, there is a potential problem because the final term of Equation Todd 1 is not the largest term. Using the data of Table A2 in Gordon et al. (*3*), Table 2 of this paper shows that the first term, ($\sigma^2_{x_i}\sigma^2_{x_j}/\mathrm{coh}^4$), contributes > 95% of the value of the whole, whereas the final term used by Gordon et al. contributes very little to the value of the whole.

Table 1. The proportional contribution of the variance in the X-ray peak to the variance in the X-ray-to-coherent peak ratio for two human subjects measured by Gordon et al.

Subject, peak	Coherent	α1	α2	β1	β3
Subject B (male)					
Amplitude[a]	2,523	421.5	313.9	81.29	34.61
Amplitude ±[a]	15.16	24.81	38.52	7.399	7.532
Error in peak amplitude (%)	0.601	5.886	12.271	9.102	21.762
Error in peak/coherent (%)	–	5.917	12.286	9.122	21.771
(Error in peak amplitude)/ (Error in peak/coherent) (%)	–	99.483	99.880	99.783	99.962
Subject C (female)					
Amplitude[a]	3,436	31.74	85.46	9.106	6.438
Amplitude ±[a]	17.69	29.96	50.07	8.102	8.442
Error in peak amplitude (%)	0.515	94.392	58.589	88.974	131.128
Error in peak/coherent (%)	–	94.393	58.591	88.976	131.129
(Error in peak amplitude)/ (Error in peak/coherent) (%)	–	99.999	99.996	99.998	99.999

[a]Data from Gordon et al. (*3*), Table A2.

Table 2. The contribution to an expression for the covariance from two terms, $\sigma^2_{x_i}\sigma^2_{x_j}/\mathrm{coh}^4$ and $x_i^2x_j^2\sigma^4_{\mathrm{coh}}/\mathrm{coh}^8$, expressed as a percentage of Equation Todd 1 and derived from the data of Gordon et al. (*3*).

	Human subject B[a]			Human subject C[a]		
Covariance	α2	β1	β3	α2	β1	β3
$\sigma^2_{x_i}\sigma^2_{x_j}/\mathrm{coh}^4$						
α1	98.7	98.5	98.9	98.4	98.1	98.5
α2	–	99.3	99.7	–	99.2	99.6
β1	–	–	99.5	–	99.3	–
$x_i^2x_j^2\sigma^4_{\mathrm{coh}}/\mathrm{coh}^8$						
α1	3.715×10^{-5}	3.708×10^{-5}	3.721×10^{-5}	3.703×10^{-5}	3.692×10^{-5}	3.707×10^{-5}
α2	–	8.598×10^{-6}	8.629×10^{-6}	–	8.586×10^{-6}	8.621×10^{-6}
β1	–	–	1.565×10^{-5}	–	1.563×10^{-5}	–

[a]Percentage contribution to the total covariance expression.

Irrespective of the assumption about how Gordon et al. derived the covariance term, the quantitative values for the increase in error arising from the covariance term reported by Gordon et al. cannot be reproduced, probably because of rounding errors. Table A2 of Gordon et al. gives the measurement uncertainty resulting from accounting for the covariance as 0.009 (3.417 - 3.408) µg Pb/g bone mineral for human subject B. For Gordon et al. human subject C, the measurement uncertainty due to the covariance term is 0.00006 (100.0–99.998% of 2.972). My calculation of the contribution of the covariance term directly from the peak amplitudes given by Gordon et al., but presumably rounded, is 0.021 and 0.002 µg Pb/g bone mineral for subjects B and C, respectively. For Gordon et al.'s high-lead subject (B), my calculation of the error increase resulting from adding the covariance term is greater than that calculated by Gordon et al. by a factor of 2.3. For the low-lead subject (C), my calculations yield an increase in error 35 times of that of Gordon et al. For both subjects, the covariance correction is still small. If the differences are indeed a result of rounding errors, I question the use of making a correction to a bone-lead measurement error that can vary so much solely as a result of rounding.

Conclusions

I have corrected typographical errors in the published method of Gordon et al. (*3*) and I provided a crude estimate of measurement error that may be of some use. I propose that the correction for the mutual dependence of the X-rays on the coherent peak not be used because of the small size of the covariance correction and the variability due to rounding.

References and Notes

1. Todd AC, Chettle DR. *In vivo* X-ray fluorescence of lead in bone: review and current issues. Environ Health Perspect 102:172–177 (1994).
2. Hu H, Rabinowitz M, Smith D. Bone lead as a biological marker in epidemiologic studies of chronic toxicity: conceptual paradigms. Environ Health Perspect 106:1–8 (1998).
3. Gordon CL, Webber CE, Chettle DR. The reproducibility of ^{109}Cd-based X-ray fluorescence measurements of bone lead. Environ Health Perspect 102:690–694 (1994).
4. Morrison DF. Multivariate Statistical Methods. 2nd ed. New York:McGraw-Hill, 1976.