How to calculate lead concentration and concentration uncertainty in XRF in vivo bone lead analysis

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Abstract

The authors provide a substantial correction for calculating estimates of lead concentration and uncertainty for in vivo X-ray fluorescent bone analysis with Cd-109 source. Based on general principles, they provide mathematical techniques for propagation of uncertainties in XRF analysis. They give additional considerations for lowering the detection limit and improving spectral data quality. © 2001 Elsevier Science Ltd. All rights reserved.

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1. Introduction

Over the past two decades investigators have made use of non-invasive X-ray fluorescent analysis to assess in vivo concentrations of lead in human bones. Widely spread reduction in population exposure to lead has called for increasing optimization of both the apparatus and the spectral processing techniques to minimize measurement error and to decrease detection limits.

Here we present the derivation from general principals of specific formulas for calculating lead concentrations and uncertainties from X-ray spectra, correcting some errors that have propagated in the literature for the last 10 years. We show that both point estimates and their uncertainties calculated with previous formulas are in error. We give further suggestions for improving the quality of these parameters.

2. Calculating concentration

In order to calculate lead concentration in the bone for in vivo X-ray fluorescent analysis we must first determine the dependence between lead concentration and K and/or L-series fluorescent line intensities. This dependence is called the “calibration line”. Investigators usually get this calibration dependence by measuring a line of phantoms (hydrated plaster of paris)—bone mineral equivalent objects with a fixed geometry and a priori known lead concentrations. In our experiments 10 phantoms are used to create a calibration line.

Since lead concentration in the bones is usually low, often less than 100 ppm, the calibration dependence could be considered as linear. Normally, to exclude the geometry factor one should normalize line intensities or associated spectral net peak areas on the backscattered elastic peak of the exciting Cd-109 radionuclide source.

We can perform this simple dependence for each K X-ray based on Gordon et al. (1994) notations as

\[
\frac{xi}{coh_{phantom}} = Pb_i m_i + C_i, \tag{1}
\]
where, \(x_i\) is the amplitude or net area of \(i\)-th X-ray peak, \(i = \{K_{1}, K_{2}, K_{3}, K_{4}\}\), \(\text{coh}_{\text{phantom}}\) the amplitude or net area of coherent (or elastic) scattered peak on phantom with energy 88 keV, \(P_{bi}\) the lead concentration in phantom derived from \(i\)-th X-ray peak, \(m_i\) the gradient of calibration line for \(i\)-th X-ray, \(C_i\) the intercept of calibration line.

To calculate correctly in vivo lead concentrations we have to take into account the difference between the backscattered coherent radiation for phantoms and subject bone (Gordon et al., 1994 and Todd, 2000 use term ‘bone mineral’), so for the geometry given \(\sim 160^\circ\) backscattering angle we have

\[
\frac{\text{coh}_{\text{bone}}}{\text{coh}_{\text{phantom}}} = \frac{s_{\text{bone}}}{s_{\text{phantom}}} = 1.46, \tag{2}
\]

where, \(\text{coh}_{\text{bone}}\) is the amplitude or net area of coherent (or elastic) scattered peak on the bone with energy 88 keV, \(s_{\text{bone}}\) the coherent scattering-cross section for 88 keV photon on bone mineral, \(s_{\text{phantom}}\) the coherent scattering cross-section for 88 keV photon on phantom, 1.46 is the actual ratio between bone and phantom cross-sections for 88 keV photons and 160° scattering angle (Gordon et al., 1994; Todd, 2000).

Thus, we have

\[
\text{coh}_{\text{phantom}} = \frac{\text{coh}_{\text{bone}}}{1.46}. \tag{3}
\]

Substitute \(\text{coh}_{\text{phantom}}\) in formula (1) we get

\[
\frac{x_i 1.46}{\text{coh}_{\text{bone}}} = P_{bi} m_i + C_i \quad \text{or} \quad P_{bi} = \frac{x_i 1.46 - C_i}{m_i}, \tag{4}
\]

where,

\[
R_i = \frac{x_i}{\text{coh}_{\text{bone}}},
\]

further, we will omit word ‘bone’.

Formula (4) is significantly different from formula widely used in Gordon et al. (1994) and Todd (2000)

\[
P_{bi} = 1.46 \frac{R_i - C_i}{m_i},
\]

[Gordon et al., 1994 formula 1].

In our opinion Gordon et al. (1994) and later Todd (2000) mistakenly put the 1.46 coefficient in the wrong place. This difference affects not only the calculation of concentrations but also the calculation of their uncertainties.

3. Calculation of uncertainties

Our purpose is to determine how to calculate bone lead uncertainty, starting from general considerations and working down to the specific cases. This approach will prevent confusion and will make the formalism mathematically and statistically rigorous.

For each concentration \(P_{bi}\) calculated from \(i\)-th K-line of \(Pb\) we have an uncertainty \(\sigma_i\). This uncertainty includes all possible uncertainties related with measurements and calibrations. We turn to obtaining a statistically optimal (i.e., with minimal dispersion) estimate of the mean for lead concentration \(P_{be}\). In the most common case, when \(P_{bi}\) errors are Gaussian distributed, we have to minimize the following expression

\[
S = \sum_{i=1}^{n} \left( \frac{P_{bi} - P_{be}}{\sigma_i} \right)^2 \Rightarrow \min,
\]

where \(n\) is the number of X-ray lines.

We can easily find the minimum of (5) by solving the following equation

\[
\frac{\partial S}{\partial P_{be}} = 0. \tag{6}
\]

From the last equation we derive \(P_{be}\)

\[
P_{be} = \frac{\sum_{i=1}^{n} P_{bi} \sigma_i^2}{\sum_{i=1}^{n} 1/\sigma_i^2}. \tag{7}
\]

The formula (7) is in formal agreement with Gordon et al. (1994) and Todd (2000) with the exception that we assume that \(\sigma_i\) includes all uncertainties mentioned above.

It is obvious that \(P_{be}\) is a linear combination of \(P_{bi}\), so

\[
P_{be} = \sum a_i P_{bi}, \tag{8}
\]

where

\[
a_i = 1/\left(\sum_{j=1}^{n} \frac{1}{\sigma_j^2}\right).
\]

Following Edie et al. (1971) (see paragraph 2.4.5) or Debertin and Helmer (1988) (see paragraph 1.5.3.3) and assuming that \(P_{be}(P_{bi})\) can be represented by a Taylor series in the vicinity of \(P_{bi}\), we can represent variance of \(P_{be}\), namely \(\sigma^2(P_{be})\), as

\[
\sigma^2(P_{be}) \approx \sum_{i=1}^{n} \sum_{j=1}^{n} \frac{\partial P_{be}}{\partial P_{bi}} \frac{\partial P_{be}}{\partial P_{bj}} D(P_{bi}, P_{bj}), \tag{9}
\]

where \(D(P_{bi}, P_{bj})\) is covariance for \((P_{bi}, P_{bj})\) pair or \(\sigma_{ij}^2\), and \(D(P_{bi}, P_{bj})\) is simply \(\sigma_i^2\) the dispersion of \(P_{bi}\).

With a further transformation of formula (9), we have

\[
\sigma^2(P_{be}) \approx \sum_{i=1}^{n} \sum_{j=1}^{n} \frac{\partial P_{be}}{\partial P_{bi}} \frac{\partial P_{be}}{\partial P_{bj}} D(P_{bi}, P_{bj})
\]

\[
= \left( \frac{1}{\sum_{i=1}^{n} 1/\sigma_i^2} \right)^2 \sum_{i=1}^{n} \frac{1}{\sigma_i^2} \frac{1}{\sigma_i^2} D(P_{bi}, P_{bj})
\]
we have

$$\sum_{i=1}^{n} \frac{1}{\sigma_i^2} D(P_{bi}, P_{bj})$$

where \(\sigma_i^2\) actually means the double sum, namely

$$\sum_{i \neq j} = 2 \sum_{i=1}^{n} \sum_{j=i+1}^{n}.$$ 

Now, let us consider the \(D(P_{bi}, P_{bj})\) term, by definition and for \(i \neq j\)

$$D(P_{bi}, P_{bj}) = D \left( \frac{x_{i,1.46/coh_i} - C_i \times x_{j,1.46/coh_j} - C_j}{m_j} \right)$$

$$\cong \sum_{k=1}^{N} \sum_{l=1}^{N} \frac{\partial \hat{P}_{bi} \partial \hat{P}_{bj}}{\partial y_{jl}} D(y_{jl}, y_{jl}),$$

where \(y_{jl} = \{x_i, C_i, coh_i, m_i\}, N\) the number of parameters, in this case \(N = 4\). Thus, the general formula for \(\sigma^2(P_{bi})\) is

$$\sigma^2(P_{bi}) \cong \sum_{i=1}^{n} \frac{1}{\sigma_i^2} \left[ \frac{1}{n} \right]$$

$$+ \left( \sum_{i \neq j} \frac{1}{\sigma_i^2} \right) \sum_{k=1}^{N} \sum_{l=1}^{N} \frac{\partial \hat{P}_{bi} \partial \hat{P}_{bj}}{\partial y_{jl}} D(y_{jl}, y_{jl}).$$

The last universal formula allows us to explore the influence of the mixed moments of the calibration coefficients, like \(\sigma^2(C_i, C_j), \sigma^2(C_i, m_i), \) etc. on total uncertainty \(\sigma^2(P_{bi})\) because \(C_i, C_j, m_i, m_j\) have a common dependence on coh_{phantom} and, as well, the more subtle joint influence of different K X-rays on the average concentration uncertainty term \(D(y_{jl}, y_{jl}) = D(x_{i,j}, \sigma_{coh})\). But we leave such problems for future publications.

So, we assume that all mixed \((i \neq j)\) moments \(D(y_{kl}, y_{kl}) = 0\), excepting when \(k = l = 3\). In this case we have

$$D(y_{kl}, y_{kl}) = D(coh_i, coh_j).$$

Due to the conditions of these measurements: coh_i = coh_j = coh, and thus

$$D(y_{kl}, y_{kl}) = D(coh, coh) = \sigma^2_{coh}.$$  

After these simplifications we can perform the double sum of (11) as

$$\sum_{k=1}^{N} \sum_{l=1}^{N} \frac{\partial \hat{P}_{bi} \partial \hat{P}_{bj}}{\partial y_{jl}} D(y_{jl}, y_{jl}) = \frac{2(1.46)^2 x_{i} x_{j}}{coh^2 m_i m_j},$$

leaving the final formula for \(\sigma^2(P_{bi})\) that we use for our calculations

$$\sigma^2(P_{bi}) \cong \sum_{i=1}^{n} \frac{1}{\sigma_i^2}$$

$$+ \left( \sum_{i \neq j} \frac{1}{\sigma_i^2} \right) \sum_{k=1}^{N} \sum_{l=1}^{N} \frac{\partial \hat{P}_{bi} \partial \hat{P}_{bj}}{\partial y_{jl}} D(y_{jl}, y_{jl}).$$

The first term is in formal agreement with Gordon et al. (1994) (formula 10) or Todd (2000) (if we ignore a missed power (-1) in Gordon’s formulas (8) and (9)), but has a different value, as \(\sigma^2_{coh}\) is derived from a substantially different formula of concentration.

In comparison with Gordon et al. (1994) and Todd (2000), the second term has an additional factor

$$2 \left( \sum_{i=1}^{n} \frac{1}{\sigma_i^2} \right) \frac{1}{2}$$

that has a significant influence on the lead error calculations. Let us provide the formula for the \(\sigma_i^2\) calculation of which is derived from formula (4)

$$\sigma_i^2 = m_i \left( \frac{\sigma_{x_i}}{coh} \right)^2 + \sigma_{coh}^2 \left( \frac{1.46 x_i}{coh} \right)^2$$

$$+ \sigma_{coh}^2 \left( \frac{1.46 x_i}{coh} \right)^2 - C_i.$$  

The term \(\sigma_{coh}^2\) has some sense: we are using the linear approximation of dependence \(x_i/coh\) vs. \(P_{bi}\), but in fact, this dependence has non-linear behavior, so we could suspect that \(C_i\) and \(m_i\) are correlated. To get a crude estimate of \(\sigma_i^2\) we can use Gordon’s formula (4) (Gordon et al., 1994)

$$\sigma_i^2 = (1.46)^2 \frac{\sigma_{coh}^2}{m_i}.$$  

We can reduce the amount of computation to get this crude estimate by recalling that the peak area of the X-ray line is distributed by a Poisson law, giving

$$\sigma_{x_i}^2 = x_i, \sigma_{coh}^2 = coh.$$
This gives us a crude estimate for $\sigma_R^2$:

$$\sigma_R^2 = \left( \frac{1}{x_i^2} + \frac{1}{\text{coh}} \right) \left( \frac{x_i}{\text{coh}} \right)^2.$$  \hfill (17)

4. Discussion of results. Role of detection limit

In Table 1 below, the reader can find some results for lead concentration and uncertainty from Gordon’s Table A3 (Gordon et al., 1994), with our estimates added for comparison (column marked with footnote) as calculated from Gordon’s data. Mass concentrations of Pb are given in µg/g of bone mineral. Differences for lead concentrations and uncertainties calculated with the two methods are large.

The second term in the Eq. (15) is greatly affected by the factor $2 \left( \frac{1/NB}{\sum_{i=1}^{n} \frac{1}{\sigma_i^2}} \right)^2$. For example, for subject B (male) this factor is about 140, and for subject C (female) is 0.34. Of course, the quality of results not only depends on the right formulas, but also on spectrum fitting: e.g., the uncertainties provided in the Gordon’s Table A2 (Gordon et al., 1994) for coherent peaks (coh) are excessively small. They are: for B (male) 15.16 and for C (female) 17.69, whereas a Poisson distribution gives these peaks as: for B 1σ = $\sqrt{2523}$ = 50.2, for C 1σ = $\sqrt{3436}$ = 58.6 for single measurements. If the iteration process of non-linear least squares is organized correctly and there are no problems with convergence during fitting, the total uncertainty for the net peak area will be greater than Poisson gives. One approach of implementing a non-linear programming technique for gamma- and X-ray spectral analysis has already been described by Kondrashov et al. (2000).

The quality of original spectral data is very important for XRF data analysis. In addition to the proper tuning of X-ray spectrometry hardware one should adjust the geometry of the measurements to achieve a minimal detection limit or $L_D$ (see Debertin and Helmer, 1988). Achieving minimal $L_D$ provides us maximum sensitivity in bone lead measurements.

To adjust the geometry for a lower detection limit we don’t need to calculate $L_D$ itself. Usually, $L_D$ is represented by a formula like this

$$L_D = a + b\sqrt{N_B},$$  \hfill (18)

where $a$ and $b$ are positive constants, and $N_B$ is background over the peak region. Normally, $a$ is significantly smaller than $b\sqrt{N_B}$.

Since our parameter for lead concentration is $x_i/\text{coh}$ (we put this parameter into formula (4)), we have to minimize $L_D/\text{coh}$ or $\sqrt{N_B/\text{coh}}$ to get the minimal detection limit. In our case, the geometry adjustment means finding an optimal target-detector distance that gives us minimal $\sqrt{N_B/\text{coh}}$.

To achieve this goal we can use a blank phantom (not lead doped). To get $N_B$ we will calculate the background integral at the place of $K_{\alpha}$, for example, coh will represent the net coherent peak area at 88 keV. The interval for each integral could be $\pm 1.5\text{FWHM}$ around each X-ray location. In the case of $K_{\alpha}$ we will use the peak location given from the energy calibration.

In our experiments with a 12 mCi Cd-109 source the optimal detector-target distance is 25 mm (Dead time 41%), giving us an improvement in detection limit of about 26% in comparison with the previously used 45 mm distance. Reducing detection limit by 26% is equivalent to increasing live time acquisition about twice (doubling the live time reduces the detection limit by a factor of $1/\sqrt{2}$ or 29% of $L_D$ decreasing).

We note that the detection limit is an accumulative parameter, including not only geometry adjustment but also the quality of electronics tuning and minimization of external electromagnetic influence. Optimization of X-ray fluorescent in vivo lead analysis requires a combination of rigorous mathematical derivation of basic parameters, careful attention to multi-parameter spectral fitting procedures, and application of those results to the procedures for analyzing data.

5. Conclusion

In this paper we have made substantial and necessary corrections for calculating estimates of lead concentration and uncertainty by a careful application of mathematical statistics. We discuss adjusting detector-target distance to lower the detection limit as an additional mean of improving spectral data quality. This research was supported in part by P20-RR11145 NIH/RCMI and R01 ES 10166 projects.

References


