



Letter to the Editor

Corrections to “How to calculate lead concentration and concentration uncertainty in XRF in vivo bone lead analysis”
by Kondrashov and Rothenberg

Abstract

Kondrashov and Rothenberg (Appl. Radiat. Isot. 55 (2001) 799) have published “a substantial correction for calculating estimates of lead concentration and uncertainty for in vivo X-ray fluorescent bone analysis with Cd-109 source” (*sic*). Our paper shows that their correction fails to consider two important points that render it (i) a correction to a superseded method and (ii) of limited effect. Also, their approach to a “crude” estimate produces measurement uncertainties that are implausibly small. In order that they not be propagated in the literature, our paper also corrects several misstatements and errors in Kondrashov and Rothenberg.

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1. Introduction

To begin, we provide an overview of in vivo bone lead X-ray fluorescence (XRF) to counter the misleading and incorrect description thereof given in the paper under discussion (Kondrashov and Rothenberg, 2001). Thereafter, we address several statements in the Kondrashov and Rothenberg paper that pertain to the calculation of lead concentration and the measurement uncertainty therein.

Lead (Pb) is a ubiquitous toxin that has several health effects in humans. Monitoring of lead exposure is usually performed via measuring lead in whole blood, but the biological residence time of lead in blood is approximately 36 days (Rabinowitz et al., 1976). The majority of the human body burden of lead resides in the skeleton (Barry, 1975, 1981; Barry and Mossman, 1970), wherein the biological residence time is of the order of years (Börjesson et al., 1997; Brito et al., 2000; Chettle, 1995; Gerhardsson et al., 1993; Rabinowitz et al., 1976). Lead in bone thus represents long-term lead exposure (Somervaille et al., 1988).

Lead in bone can be measured non-invasively via XRF. Three methods have been used to measure lead in bone in vivo, but this paper addresses only the ^{109}Cd -based method for fluorescing K-shell lead X-rays (Aro et al., 1994; Aro et al., 2000; Chettle et al., 1987; Chettle 1995; Fleming et al., 1997a, b; Green et al., 1993a, b; McNeill et al., 1993, 2000; Todd et al., 1992, 2002), the

technique used by Kondrashov and Rothenberg, wherein the 88.034 keV γ -rays from ^{109}Cd fluoresce the K-shell X-rays of lead: K_{α_2} , K_{α_1} , K_{β_1} , K_{β_2} and $K_{\beta_{2,4}}$. The ^{109}Cd γ -rays can also undergo coherent scatter (primarily off the calcium, phosphorous and oxygen atoms in the bone), giving rise to a peak of coherently scattered photons in the spectrum of scattered radiation. The ratio of X-ray peak areas (or amplitudes and, therefore, hereafter “sizes”), x , to the coherent peak size, coh , is treated as the measurement system response for each of the X-rays considered (Somervaille et al., 1985). The normalization renders the measurement response independent (to a degree beyond which we need not be concerned for the purposes of this paper) of several factors, principally the source-to-skin distance, overlying tissue thickness, bone shape, bone size, bone orientation and minor subject movement (Chettle et al., 1991; Somervaille et al., 1985).

Calibration has, to date, always been performed via lead-doped, hydrated plaster-of-Paris ($\text{CaSO}_4 \cdot 2\text{H}_2\text{O}$) phantoms. The coherent scatter normalization introduces the need to account for the difference between the coherent scattering cross sections of the phantom and the human (in vivo bone) matrices. The required matrix conversion is the ratio of the coherent scattering cross sections for the two matrices (Somervaille et al., 1985). For brevity, the conversion has been given the acronym, coherent correction factor (*CCF*). *CCF* is a function of energy and angle and, for purposes of this discussion, can be considered to be a constant. (Several assumptions

involved in the derivation of *CCF* have been examined and found to be valid, Todd, 2000c.)

The estimates of the in vivo lead concentration, $[\text{Pb}]_i^{iv}$, derived from each of the “*i*” X-rays considered are then combined into a single estimate of the in vivo concentration, $[\text{Pb}]_\mu^{iv}$, via inverse-variance weighting. The statistical uncertainty in $[\text{Pb}]_\mu^{iv}$ can also be calculated and is denoted $\sigma_{[\text{Pb}]_\mu^{iv}}$.

Formulae for the in vivo bone lead concentration and its uncertainty (the latter derived from a variance propagation approach) had been in use for several years before first being published by Gordon et al. (1994), typographical errors in which were reported by Todd (2000a, b). These formulae were originated by neither Gordon et al. nor Todd, but for brevity they will be denoted in this paper by their names, “Gordon/Todd”. The methods of Gordon et al. and Todd do not differ greatly, and the Gordon/Todd method is used, as far as we are aware, by all laboratories practicing this technique, including the laboratory of Rothenberg (McQuirter et al., 2001; Rothenberg et al., 2000, 2001; Rothenberg et al., 2001). It is a “correction” to the Gordon/Todd method that Kondrashov and Rothenberg have published.

2. Reviewing the “corrections” of Kondrashov and Rothenberg

Kondrashov and Rothenberg write that they “present the derivation from general principals (*sic*) of specific formulas (*sic*) for calculating lead concentrations and uncertainties from X-ray spectra”, (p. 799) but what they actually present is far narrower than they claim: i.e. formulae for ^{109}Cd -based K-shell XRF of lead in bone using phantoms of matrix other than human bone and employing coherent scatter normalization. Kondrashov and Rothenberg’s approach could be considered to be nothing more than an alternative way (Taylor series expansion vs. variance propagation) of arriving at the formulae equivalent to those of Gordon/Todd.

Kondrashov and Rothenberg also claim to correct “some errors that have propagated in the literature for the last 10 years”, (p. 799) but they “correct” a single error in an algebraic approach that has been superseded by subsequent work that Kondrashov and Rothenberg may be ignorant of and do not cite. The superseded algebraic approach that Kondrashov and Rothenberg “correct” appears in only the papers of Gordon et al. and Todd, the first of which (Gordon et al.) was published in 1994.

Our review of the “corrections” of Kondrashov and Rothenberg approximately follows the order in which arguments are presented in their paper.

2.1. Calculating concentration

Kondrashov and Rothenberg begin their algebraic argument with a mistake in their first equation, using the subscript “*i*” in Pb_i to indicate the “lead concentration in phantom derived from *i*th X-ray peak” (*sic*). (p. 800) This statement is incorrect because the lead concentrations are known a priori; they are not derived from the size of the X-ray peak (*x*) nor from the size of the system response (*x/coh*) and should not have the “*i*” subscript. The lead concentration of the phantoms is the independent variable of the calibration relation. Pb_i was used by previous authors (Gordon et al., 1994; Todd, 2000a, b) to denote the estimate of an in vivo (i.e. unknown) lead concentration derived from X-ray “*i*”, but Kondrashov and Rothenberg may have misunderstood this. The formula of Kondrashov and Rothenberg is also misleading because it uses the same subscript “*i*” to indicate both the “*i*”th X-ray and the “*i*”th phantom used to construct the calibration line. The correct form of the calibration line follows, wherein $x_i^{ph_j}$ is the size of X-ray “*i*” obtained from phantom “*j*”, coh^{ph_j} is the size of the coherent peak obtained from phantom “*j*”, m_i^{ph} is the slope of the calibration line for X-ray “*i*” obtained from the phantoms, $[\text{Pb}]^{ph_j}$ is the lead concentration of phantom “*j*” and C_i^{ph} is the intercept of the calibration line for X-ray “*i*” obtained from the phantoms:

$$\frac{x_i^{ph_j}}{coh^{ph_j}} = m_i^{ph} [\text{Pb}]^{ph_j} + C_i^{ph}.$$

2.1.1. Coherent correction factor, *CCF*

Returning to the algebraic argument of Kondrashov and Rothenberg, the *CCF* (which is presented in Kondrashov and Rothenberg’s equation (2) as its value, 1.46) is introduced by giving the following formula (we shall hereafter retain the notation of Kondrashov and Rothenberg, except where it is not clear):

$$\frac{coh_{bone}}{coh_{phantom}} = \frac{s_{bone}}{s_{phantom}} = 1.46 (= CCF) \quad (\text{K\&R2})$$

where coh_{bone} is the “amplitude or net area of coherent (or elastic) scattered peak on the bone with energy 88 keV” (*sic*), (p. 800) $coh_{phantom}$ is identically defined except that, of course, it applies to the phantom, s_{bone} is the “coherent scattering-cross section for 88 keV photon on bone minerals” (*sic*) (p. 800) and $s_{phantom}$ is identically defined except that it applies to the phantom.

2.1.2. In vivo lead concentration predicted from an individual X-ray, Pb_i

Kondrashov and Rothenberg derive a formula for calculating the estimate of bone lead concentration derived from one of the X-rays (which we

reproduce here, substituting CCF for 1.46 and x_i/coh_{bone} for R_i):

$$Pb_i = \frac{CCF(x_i/coh_{bone}) - C_i}{m_i} \quad (\text{K\&R4})$$

which can be compared to the equivalent Gordon/Todd formula:

$$Pb_i = \frac{CCF(x_i/coh - C_i)}{m_i}$$

The formula of Kondrashov and Rothenberg is different from that of Gordon/Todd in the placement of the CCF . (Kondrashov and Rothenberg do not specify whether m_i and C_i are those of the phantom or the in vivo calibration line, but we shall assume the former.) While it is true that algebraically the Kondrashov and Rothenberg placement of CCF is correct, we shall show in the sections that follow that (a) the formula corrected by Kondrashov and Rothenberg can be considered to be superseded by subsequent work, and (b) that the effect of the Kondrashov and Rothenberg correction is small, even negligible.

To see how the correction of Kondrashov and Rothenberg is rendered irrelevant, we must consider the phantom and in vivo calibration lines.

2.2. Phantom calibration, in vivo calibration and CCF

Ideally, we would obtain the “in vivo” calibration line to predict an in vivo concentration:

$$\frac{x_i^{iv}}{coh_k^{iv}} = m_i^{iv} [Pb]_k^{iv} + C_i^{iv},$$

where subscript “ k ” indicates the sample “number” of the human bone used to establish the in vivo calibration line (superscripts “ iv ” indicate in vivo measurements, for clarity). Assuming that the number of X-rays obtained from in vivo and phantom samples of the same concentration are equal (i.e. that the only difference between the in vivo bone and plaster samples is the number of coherent counts), not only will the coherent counts be related by CCF , as shown in Eq. (K&R2), but, consequently, the slope of the plaster phantom calibration line, m_i^{ph} , will also be CCF times greater than the slope of the in vivo bone calibration line, m_i^{iv} ,

$$m_i^{ph} = CCF m_i^{iv}$$

whereupon we need only obtain C_i^{iv} to be able to use the in vivo calibration line. However, whether C_i^{ph} and C_i^{iv} are simply related by CCF , as are m_i^{ph} and m_i^{iv} , depends on the origin of both C_i^{ph} and C_i^{iv} . We will proceed to consider, first, the phantom calibration line intercept C_i^{ph} and, second, the in vivo calibration line and its intercept, C_i^{iv} .

2.2.1. Origin of the phantom and/or in vivo calibration line intercept(s)

A description of both the sources and the mathematical/algebraic treatment of C_i^{ph} has been given elsewhere (Todd, 2000d) but is not cited by Kondrashov and Rothenberg. In brief, the Todd paper describes how C_i^{ph} can arise from one or more sources: trace-level Pb contamination of the plaster of Paris (for which analytical data were presented), plaster-of-Paris impurities other than Pb (for which analytical data were presented), external Pb contamination of the phantoms and/or measurement system from environmental sources, contaminating Pb signal(s) from non-phantom items (e.g. chairs, floor tiles, lead paint on walls) and any “offset” in the peak extraction program that results in overestimation of small, but non-zero peak sizes.

It was proposed (Todd, 2000d) that the treatment of the phantom calibration line intercept be modified from the analytical procedure that was then current (and which Kondrashov and Rothenberg “correct”) to take into account the source of C_i^{ph} . Specifically, it was proposed that the treatment of C_i^{ph} be modified (a) to stop measurements (i.e. produce no result) if the intercept is significantly less than zero (because an error in the measurement process is indicated thereby); (b) to calculate the calibration line passing through the origin if the intercept is not significantly different from zero; and (c) to calculate the calibration line with a non-zero intercept only when the intercept is significantly greater than zero. For (a), no calculation of $[Pb]_i^{iv}$ should be performed; for (b) and (c), it was proposed that C_i^{ph} not be subtracted from the in vivo signal, giving

$$Pb_i^{iv} = \frac{(x_i^{iv}/coh^{iv})}{m_i^{iv}} = \frac{CCF(x_i^{iv}/coh^{iv})}{m_i^{ph}} \quad (1)$$

which obviates the need for the “correction” of Kondrashov and Rothenberg (Eq. (K&R4)). In summary, the “error” in the placement of CCF and the “correction” by Kondrashov and Rothenberg are rendered irrelevant by the more rigorous consideration of the source of C_i^{ph} .

2.2.2. In vivo calibration line and its intercept, C_i^{iv}

The sources of C_i^{ph} may or may not also give rise to an offset (i.e. C_i^{iv}) in the in vivo response of the measurement system. Measurements of phantoms alone cannot quantify C_i^{iv} and, for the most rigorous treatment, we would therefore still need the in vivo calibration line.

To construct the in vivo calibration line, independent measurements of the lead concentration in human bone “ k ” would be required to provide Pb_k^{iv} . Examples of suitable independent techniques are atomic absorption spectrometry (AAS) (Todd et al., 2001, 2002; Zong et al., 1996) and inductively coupled plasma mass spectrometry (ICPMS) (Aro et al., 1994, 2000). With such data, we could construct the in vivo calibration line and thus

calculate C_i^{iv} :

$$\frac{x_i^{iv}}{coh_k^{iv}} = m_i^{iv} Pb_k^{iv, via AAS} + C_i^{iv}.$$

Such data exist (Todd et al., 2002), but they are, strictly speaking, *in vitro* rather than *in vivo* (having come from cadaver legs) and are limited: multiple spectra were acquired from nine adult human cadaver legs that subsequently underwent measurement of lead concentration via AAS. When XRF response (x_i^{iv}/coh_k^{iv}) was regressed against AAS-measured lead concentration, $Pb_k^{iv, via AAS}$, none of the C_i^{iv} was significantly different from zero, suggesting that C_i^{iv} is negligible and can be treated as zero. Consequently, Pb_i^{iv} can be calculated from (our) Eq. (1), and the “correction” of Kondrashov and Rothenberg is, again, a correction to a superseded method.

We no longer need to distinguish between Pb^{iv} and Pb^{ph} and will therefore henceforth dispense with the “*iv*” superscript, with the understanding that Pb refers to *in vivo* lead concentration.

2.3. Combining estimates of lead concentration derived from an individual X-ray peak

Kondrashov and Rothenberg also examine the effect of their placement of *CCF* on the calculation of measurement uncertainty, σ_i^2 , derived from X-ray “*i*”. Kondrashov and Rothenberg first derive the formula for the inverse–variance-weighted estimate of the mean (of the individual X-ray estimates) lead concentration, Pb_E . This elementary formula is identical to that presented by Gordon et al. (1994) and Todd (2000a), but Kondrashov and Rothenberg state that their formula “is in formal agreement” with Gordon et al. and Todd, “with the exception that we assume that σ_i includes all uncertainties”. (p. 800) Kondrashov and Rothenberg do not substantiate their statement by identifying any sources of uncertainty that are included in their σ_i but omitted from the σ_i of Gordon/Todd, and the reader should not be misled into thinking that there is a difference where there is none. That all sources of variability should be included in σ_i is both obvious and known to all the authors of both Gordon et al. and this paper. Furthermore, there are components of the uncertainty in Pb_i that cannot be accounted for in the formulae for σ_i^2 of either Kondrashov and Rothenberg or Gordon/Todd from, for example, short-term and long-term reproducibility.

2.4. Measurement uncertainty has been shown to be less than the standard deviation of repeated measurements

More important, Kondrashov and Rothenberg are possibly ignorant of, and certainly do not cite or discuss the papers that have shown that repeated measure-

ments of the same *in vivo* subjects produce standard deviations (of the average concentrations calculated from the repeated measurements) that are significantly greater than the average measurement uncertainty (Gordon et al., 1994; Todd et al., 2000). Such repeated measurements suggest that there are significant contributions to σ_i^2 that are not being accounted for or that there is a methodological deficiency, wholly unrelated to the work of Kondrashov and Rothenberg, in the formula for σ_i^2 . This methodological deficiency has an effect of far greater magnitude and is therefore far more important than the “correction” of Kondrashov and Rothenberg.

2.5. Deriving Kondrashov and Rothenberg’s expression for the variance of the overall estimate of concentration, $\sigma^2(Pb_E)$

Kondrashov and Rothenberg expand a general expression for $\sigma^2(Pb_E)$ as a Taylor series, for which they give two citations. In the algebra that follows, Kondrashov and Rothenberg make two errors: Kondrashov and Rothenberg obtain

$$\begin{aligned} \sigma^2(Pb_E) \cong & \left(\frac{1}{\sum_{i=1}^n 1/\sigma_i^2} \right)^2 \sum_{i=1}^n \frac{1}{\sigma_i^2} \frac{1}{\sigma_i^2} D(Pb_i, Pb_j) \\ & + \left(\frac{1}{\sum_{i=1}^n 1/\sigma_i^2} \right)^2 \sum_{i \neq j}^n \frac{1}{\sigma_i^2} \frac{1}{\sigma_j^2} D(Pb_i, Pb_j), \end{aligned} \quad (\text{K\&R10, RHS2})$$

where “ $D(Pb_i, Pb_j)$ is covariance for (Pb_i, Pb_j) pair or σ_{ij}^2 ” (*sic*). This formula contains two errors; the $D(Pb_i, Pb_j)$ of the first term on the right-hand side (RHS) should actually be $D(Pb_i, Pb_i)$, not $D(Pb_i, Pb_j)$, and the second term on the RHS is missing a factor of 2. Kondrashov and Rothenberg may believe that they address the factor of 2 when they give $\sum_{i \neq j} = 2 \sum_{i=1}^{n-1} \sum_{j=i+1}^n$, but they do not change the \sum ranges. Stating the equation more fully than Kondrashov and Rothenberg and retaining the distinction between *i* and *j* summations, we obtain

$$\begin{aligned} \sigma^2(Pb_E) \cong & \frac{1}{\sum_{i=1}^n 1/\sigma_i^2} \frac{1}{\sum_{j=1}^n 1/\sigma_j^2} \sum_{i=j}^n \sum_{j=1}^n \frac{1}{\sigma_i^2} \frac{1}{\sigma_j^2} D(Pb_i, Pb_j) \\ & + \frac{1}{\sum_{i=1}^n 1/\sigma_i^2} \frac{1}{\sum_{j=1}^n 1/\sigma_j^2} \sum_{i=1}^n \sum_{j=1, j \neq i}^n \frac{1}{\sigma_i^2} \frac{1}{\sigma_j^2} D(Pb_i, Pb_j), \end{aligned} \quad (\text{K\&R10, RHS2, corrected})$$

Next, Kondrashov and Rothenberg use, for $i = j$,

$$D(Pb_i, Pb_j) = D(Pb_i, Pb_i) = \sigma_i^2$$

and, for the second term, ($i \neq j$), Kondrashov and Rothenberg use

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

to obtain (with the missing factor of 2 inserted)

$$\begin{aligned} \sigma^2(\text{Pb}_E) &\cong \frac{1}{\sum_{i=1}^n 1/\sigma_i^2} + \left(\frac{1}{\sum_{i=1}^n 1/\sigma_i^2} \right)^2 \\ &\times \sum_{i \neq j}^n 2 \frac{1}{\sigma_i^2} \frac{1}{\sigma_j^2} D(\text{Pb}_i, \text{Pb}_j). \end{aligned} \tag{K\&R10, RHS4, corrected}$$

It should also be noted that both the third and fourth terms on the RHS of K&R10, which we do not reproduce here, are missing the “+” sign between the two halves of the expression.

2.6. Kondrashov and Rothenberg’s “universal formula”

Eventually, Kondrashov and Rothenberg obtain a “universal formula” (*sic*) (p. 801):

$$\begin{aligned} \sigma^2(\text{Pb}_E) &\cong \frac{1}{\sum_{i=1}^n 1/\sigma_i^2} + \left(\frac{1}{\sum_{i=1}^n 1/\sigma_i^2} \right)^2 \\ &\times \sum_{i \neq j}^n \frac{1}{\sigma_i^2 \sigma_j^2} \sum_{k=1}^N \sum_{l=1}^N \frac{\partial \text{Pb}_i}{\partial y_{ik}} \frac{\partial \text{Pb}_j}{\partial y_{jl}} D(y_{ik}, y_{jl}) \end{aligned} \tag{K\&R12}$$

which “allows us [Kondrashov and Rothenberg] to explore the influence of the mixed moments of the calibration coefficients, like $\sigma^2(C_i, C_j)$, $\sigma^2(C_i, m_j)$, etc. on [the] total uncertainty $\sigma^2(\text{Pb}_E)$ [that exists] because C_i, C_j, m_i , [and] m_j have a common dependence on $coh_{phantom}$ and, as well (*sic*), the more subtle joint influence of different K X-rays...” (p. 801) Kondrashov and Rothenberg do not substantiate with data their statement that the joint influence of different K X-rays is “more subtle” than the influence of the mixed moments; instead, the exploration of the influence of each of these components on $\sigma^2(\text{Pb}_E)$ is said to be the subject of future publications, whereupon all mixed moments (with one exception) are assumed to be zero. This assumption reduces the “universal”, “mathematically and statistically rigorous” formulation to one that is identical to that of Gordon/Todd (who make the same approximation and assume that the same mixed moments are zero) but, obviously, with differences resulting from the different placement of CCF .

2.7. Covariance between individual estimates of concentration, σ_{ij}^2

Kondrashov and Rothenberg also “consider the $D(\text{Pb}_i, \text{Pb}_j)$ term, by definition and for $i \neq j$ ”, (p. 801)

by which they refer to the covariance between Pb_i and Pb_j , σ_{ij}^2 , that arises because both Pb_i and Pb_j depend on the same coh . In considering σ_{ij}^2 , Kondrashov and Rothenberg introduce another pair of subscripts, k and l , to indicate terms of the calibration relation (i.e. x, coh, C, m), thereby producing y_{i1}, y_{i2}, y_{i3} and y_{i4} that actually indicate, respectively, $x_i, C_i, coh_{(i)}$ and m_i . Although Kondrashov and Rothenberg thus introduce coh_i and coh_j , it should be remembered that there is only one coherent peak *per* spectrum. Continuing, Kondrashov and Rothenberg state that the double sum of the second term on the RHS of Eq. (K&R12) is given by the following formula:

$$\sum_{k=1}^N \sum_{l=1}^N \frac{\partial \text{Pb}_i}{\partial y_{ik}} \frac{\partial \text{Pb}_j}{\partial y_{jl}} D(y_{ik}, y_{jl}) = \frac{2(1.46)^2 x_i x_j}{coh^4 m_i m_j} \sigma_{coh}^2 \tag{K\&R14}$$

where 1.46 is the numerical value of CCF . The RHS of this formula is missing $\sum_{i \neq j}$, but the summation sign appears in their next equation:

$$\begin{aligned} \sigma^2(\text{Pb}_E) &= \frac{1}{\sum_{i=1}^n 1/\sigma_i^2} + 2(CCF)^2 \\ &\times \left(\frac{1}{\sum_{i=1}^n 1/\sigma_i^2} \right)^2 \frac{\sigma_{coh}^2}{coh^4} \sum_{i \neq j} \frac{1}{\sigma_i^2 \sigma_j^2} \frac{x_i x_j}{m_i m_j}. \end{aligned} \tag{K\&R15}$$

Attempting to derive the covariance term of Eq. (K&R15) reveals another mistake: the covariance term of Kondrashov and Rothenberg,

$$2(CCF)^2 \left(\frac{1}{\sum_{i=1}^n 1/\sigma_i^2} \right)^2 \frac{\sigma_{coh}^2}{coh^4} \sum_{i \neq j} \frac{1}{\sigma_i^2 \sigma_j^2} \frac{x_i x_j}{m_i m_j}$$

comes from the differentiation of

$$\text{Pb}_i = \frac{CCF(x_i/coh) - C_i}{m_i}$$

with respect to coh for both X-ray “ i ”

$$\frac{\partial \text{Pb}_i}{\partial coh} = \frac{-CCF x_i}{m_i coh_i^2}$$

and X-ray “ j ” and the use of the fact that the “dispersion”, (p. 800) $D(coh_i, coh_j)$, is equal to σ_{coh}^2 . The covariance term then becomes $\sum_{i \neq j} (CCF^2 x_i x_j / coh^4 m_i m_j) \sigma_{coh}^2$, which differs from the term reported by Kondrashov and Rothenberg by a factor of 2. The factor of 2 introduced by Kondrashov and Rothenberg in their Eq. (14) (K&R14) has no justification for being there, based on their derivation, but it is actually correct when included in their Eq. (15) (K&R15), being the factor of 2 missing since their Eq. (10) (K&R10,RHS2).

2.8. Kondrashov and Rothenberg's "universal formula" applied

Kondrashov and Rothenberg then return to discussing their "universal formula" and apply it to the specific case of ^{109}Cd -based bone lead measurements, producing Eq. (K&R15):

$$\sigma^2(\text{Pb}_E) = \frac{1}{\sum_{i=1}^n 1/\sigma_i^2} + 2(\text{CCF})^2 \left(\frac{1}{\sum_{i=1}^n 1/\sigma_i^2} \right)^2 \times \frac{\sigma_{\text{coh}}^2}{\text{coh}^4} \sum_{i \neq j} \frac{1}{\sigma_i^2 \sigma_j^2} \frac{x_i x_j}{m_i m_j} \quad (\text{K\&R15})$$

Kondrashov and Rothenberg state that the first term of Eq. (K&R15) "is in formal agreement with Gordon et al. (1994) (formula (10)) or Todd (2000a) (if we ignore a missed power of (-1) in Gordon's formulas (8) and (9))". (p. 801) Kondrashov and Rothenberg make no reference to the typographical errors in Eqs. (8) and (9) of Gordon et al. that have already been corrected (Todd, 2000a).

2.9. The effect of Kondrashov and Rothenberg's "correction" to σ_{ij}^2

Kondrashov and Rothenberg state that their additional (cf. Gordon/Todd) factors in the expression for the covariance term have a "significant influence on the lead error calculations" (p. 801) but do not quantify the effect (their table gives $\sigma(\text{Pb}_E)$, not the contribution of the covariance term). We therefore calculated the covariance contribution using, as did Kondrashov and Rothenberg, the sample data of Gordon et al. The calculations suggest that their covariance term contributes an uncertainty of $0.017 \mu\text{g/g}$ for Subject B (cf. Gordon et al. $0.009 \mu\text{g/g}$) and $0.0001 \mu\text{g/g}$ for Subject C (cf. Gordon et al. $<0.0005 \mu\text{g/g}$), compared to overall uncertainties of 3.4 and $2.9 \mu\text{g/g}$, respectively. This hardly seems to be a significant influence.

2.9.1. Cannot reproduce Kondrashov and Rothenberg's results

Kondrashov and Rothenberg also comment that the covariance term is "greatly affected" (p. 802) by their

"additional" (cf. Gordon et al.) factor of

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

and state that the factor is about 140 for Subject B and 0.34 for Subject C. We consider it highly unlikely that the "additional" factor would be less than 2 for in vivo data, casting some doubt on Kondrashov and Rothenberg's value for Subject C. Our calculations of their "additional" factor yielded 264.1 and 146.5 for Subjects B and C, respectively, quite different from the values given by Kondrashov and Rothenberg.

2.10. Kondrashov and Rothenberg's expression for the variance of an estimate of concentration based on a single X-ray, σ_i^2

Kondrashov and Rothenberg present an Eq. (K&R16) for the calculation of σ_i^2 that differs from those of Gordon et al. and Todd because: (a) the differences are a result of the different formulae for Pb_i ; and (b) both reflect a treatment of the intercept that is superseded (the expression for σ_i^2 that is applicable to the revised treatment of the intercept will be presented in a future note).

2.11. Quantifying the effect on Pb_i and σ_i of Kondrashov and Rothenberg's "correction"

Kondrashov and Rothenberg state that their expression for Pb_i is "a substantially different formula of concentration" (*sic*) (p. 801) compared to that of Gordon/Todd, and that their expression for σ_i^2 "has a different value" (p. 801) than the Gordon/Todd expression for σ_i^2 but again, they do not quantify the effect. (Kondrashov and Rothenberg do not give values for Pb_i or σ_i but, instead, for Pb_E and $\sigma(\text{Pb}_E)$; their values are given in Table 1 of our paper). To quantify the effect of the differences in the formulae for both Pb_i and σ_i^2 , we applied both Eq. (K&R16) and equation "Gordon 7 (corrected)" of Todd (2000a, b) to the sample in vivo data provided by Gordon et al. (and used in Kondrashov and Rothenberg).

Table 1
Lead concentrations and the uncertainties therein calculated using three different methods for two in vivo subjects

Method	Subject B	Subject C
Calculating Pb_E using K_{x_2} , K_{x_1} , K_{β_1} and K_{β_3}		
Gordon/Todd	65.7 ± 3.409	-2.5 ± 2.973
Kondrashov and Rothenberg (reported)	72.5 ± 2.9	0.11 ± 0.65
Kondrashov and Rothenberg (our calculation: crude expression)	72.211 ± 2.921	0.700 ± 0.832
Kondrashov and Rothenberg (our calculation: full expression)	68.4 ± 3.390	0.2 ± 2.925

This calculation failed to reproduce the values of Pb_E and $\sigma(Pb_E)$ reported by Kondrashov and Rothenberg because their values are in fact calculated from their crude estimate and not from their more “rigorous” formula (the values of both crude and full expressions are shown in our Table 1). Also, one of the Kondrashov and Rothenberg values for $\sigma(Pb_E)$ ($\pm 0.65 \mu\text{g/g}$) (K&R Table 1) is implausibly small, far lower than any in vivo measurement uncertainty we have ever encountered (measurement uncertainty is determined by several factors but is seldom less than $3 \mu\text{g/g}$).

Kondrashov and Rothenberg remark that the differences between their calculations of Pb_E and those of Gordon et al. are “large”, but, according to our calculations (Table 1), they are less than or approximately equal to the measurement uncertainty (regardless of whether the latter is calculated *per* Gordon et al. or *per* the revised treatment of C^{ph} [see below]).

It seems, therefore, that only a small difference in σ_i results from the Kondrashov and Rothenberg “correc-

tion” to the formula for σ_i^2 : the Gordon/Todd σ_i overestimates the σ_i of Kondrashov and Rothenberg by $0.02\text{--}0.18 \mu\text{g/g}$ or $0.1\text{--}1.8\%$ (see Tables 2 and 3). The effect on the value of $\sigma^2(Pb_E)$ of the difference between the two formulae for σ_i^2 is far less than the effect on the values of σ_i^2 ; Table 1 shows that, for the “high” and “low” bone lead in vivo subjects of Gordon et al., the difference in $\sigma(Pb_E)$ is less than or equal to $0.1 \mu\text{g/g}$. It seems likely, therefore, that Kondrashov and Rothenberg’s “substantially different formula of concentration” does not have an effect on $\sigma(Pb_E)$ that is of any importance.

A comparison between the standard deviation of repeated measurements and the average value of $\sigma(Pb_E)$ (Todd et al., 2000) showed that the latter underestimated the former, often significantly, by up to 56% in bare tibiae, up to 38% in intact cadaver legs and up to 52% in four in vivo volunteers. These differences are substantially greater, and therefore substantially more important, than the correction offered by Kondrashov and Rothenberg.

Table 2
Gordon/Todd and Kondrashov/Rothenberg estimates of the σ_i for Gordon et al. Subject B

Parameter	Peak				
	Coherent	Alpha 1	Alpha 2	Beta 1	Beta 3
Amplitude (x_i for X-rays)	2523	421.5	313.9	81.29	34.61
Amplitude uncertainty (σ_{x_i} for X-rays)	15.16	24.81	38.52	7.399	7.532
Slope (m_i)		0.00322	0.00187	0.000671	0.000367
Slope variance ($\sigma_{m_i}^2$)		1.07E-09	8.45E-10	6.34E-11	8.89E-11
Intercept (C_i)		0.0184	0.0134	0.00419	0.0014
Intercept variance ($\sigma_{C_i}^2$)		5.06E-06	0.000004	3E-07	4.21E-07
Covariance between slope and intercept ($\sigma_{C_i m_i}^2$)		-4.6E-08	-3.7E-08	-2.8E-09	-3.9E-09
σ_i from Kondrashov and Rothenberg’s Eq. (16) (K&R16)		4.523	11.985	6.431	11.961
σ_i from Gordon/Todd		4.551	12.001	6.461	12.054
Gordon/Todd greater than Kondrashov and Rothenberg’s Eq. (16) by ($\mu\text{g/g}$)		0.029	0.016	0.031	0.093
Gordon/Todd greater than Kondrashov and Rothenberg’s Eq. (16) by (%)		0.6	0.1	0.5	0.8

Table 3
Gordon/Todd and Kondrashov/Rothenberg estimates of the σ_i for Gordon et al. Subject C

Parameter	Peak				
	Coherent	Alpha 1	Alpha 2	Beta 1	Beta 3
Amplitude (x_i for X-rays)	3436	31.74	85.46	9.106	6.438
Amplitude uncertainty (σ_{x_i} for X-rays)	17.69	29.96	50.07	8.102	8.442
Slope (m_i)		0.00322	0.00187	0.000671	0.000367
Slope variance ($\sigma_{m_i}^2$)		1.07E-09	8.45E-10	6.34E-11	8.89E-11
Intercept (C_i)		0.0184	0.0134	0.00419	0.0014
Intercept variance ($\sigma_{C_i}^2$)		5.06E-06	0.000004	3E-07	4.21E-07
Covariance between slope and intercept ($\sigma_{C_i m_i}^2$)		-4.6E-08	-3.7E-08	-2.8E-09	-3.9E-09
σ_i from Kondrashov and Rothenberg’s Eq. (16) (K&R16)		4.017	11.418	5.196	9.923
σ_i from Gordon/Todd		4.090	11.473	5.273	10.102
Gordon/Todd greater than Kondrashov and Rothenberg’s Eq. (16) by ($\mu\text{g/g}$)		0.073	0.055	0.077	0.179
Gordon/Todd greater than Kondrashov and Rothenberg’s Eq. (16) by (%)		1.8	0.5	1.5	1.8

3. Kondrashov and Rothenberg's crude estimate of σ_i

Kondrashov and Rothenberg try to contribute to the minor point made by Gordon et al. (1994) and Todd (2000a,b) regarding a crude estimate of σ_i . Crude estimates are of minor interest, because they are seldom required and somewhat pointless when such efforts have been made to take into account all the sources of variance. In addition, the crude estimates of σ_i are underestimates, and therefore all suffer more than the full expression for $\sigma(\text{Pb}_E)$ from inadequacy in underestimating the SD of the concentrations obtained from repeated measures. With this perspective in place, we will review the crude estimates of Gordon et al. and Todd and will examine the contribution of Kondrashov and Rothenberg.

Gordon et al. give an expression for σ_i^2 that ignores the uncertainties arising from calibration (which are less than the uncertainties from counting statistics),

$$\sigma_i^2 = \frac{CCF^2 \sigma_{R_i}^2}{m_i^2},$$

where

$$\sigma_{R_i}^2 = \left\{ \left(\frac{\sigma_{x_i}}{x_i} \right)^2 + \left(\frac{\sigma_{coh}}{coh} \right)^2 \right\} \left(\frac{x_i}{coh} \right)^2. \quad (2)$$

Todd's point was that $\sigma_{x_i}/x_i \gg \sigma_{coh}/coh$, and one can therefore use

$$\sigma_i^2 = \frac{CCF^2 \sigma_{x_i}^2}{m_i^2 coh^2}.$$

Kondrashov and Rothenberg's contribution is to invoke Poisson, obtaining $\sigma_{x_i}^2 = x_i$ and $\sigma_{coh}^2 = coh$, whereupon Eq. (2) becomes

$$\sigma_{R_i}^2 = \left(\frac{1}{x_i} + \frac{1}{coh} \right) \left(\frac{x_i}{coh} \right)^2.$$

Algebraically, the reasoning of Kondrashov and Rothenberg is correct, but practically, it is only true when there is no contribution to the variance from the background. $\sigma_{x_i}^2$ is, by necessity, greater than x_i , once any form of peak extraction has been performed, including simply extracting the peak size via the region of interest algorithm included in commercial software packages. It is also true that $\sigma_{coh}^2 > coh$, but the relative contribution to σ_{coh}^2 from the background under the coherent peak is far smaller than the contribution to $\sigma_{x_i}^2$ from the background under x_i . Table 4 shows the crude estimates of Gordon et al., Todd and Kondrashov and Rothenberg for the two in vivo subjects of Gordon et al. Table 4 shows that the expression of Kondrashov and Rothenberg, compared to those of Gordon et al. and Todd, gives a lower approximation for σ_i for the "high lead" subject (Subject B) but an unrealistically small approximation for the "low lead" subject (C). Considering only the K_{x_i} peak for the low lead subject will illustrate why: assuming a FWHM of 13 channels (see below), the K_{x_i} area is 440 counts, and the uncertainty therein yielded by the peak extraction program is 415 counts (94.4%), which is much greater than $\sqrt{440} = 21$ counts (4.8%).

4. Kondrashov and Rothenberg incorrectly claim that the peak size uncertainties of Gordon et al. are wrong

Finally, Kondrashov and Rothenberg state that the peak uncertainties given (for the coherent peak) in Table 2A of Gordon et al. are "excessively small. They are: for B (male) 15.16 and C (female) 17.69, whereas a Poisson distribution gives these peaks (*sic*) as: for B, $1\sigma = \sqrt{2523} = 50.2$, for C, $1\sigma = \sqrt{3436} = 58.6\dots$ " (p. 802) Kondrashov and Rothenberg have erred with this

Table 4

Crude estimates of σ_i from Gordon et al. (1994), Todd (2000a) and Kondrashov and Rothenberg (2001)

Parameter	Coherent	Alpha 1	Alpha 2	Beta 1	Beta 3
Subject B					
Amplitude (x_i for X-rays)	2523	421.5	313.9	81.29	34.61
Amplitude uncertainty (σ_{x_i} for X-rays)	15.16	24.81	38.52	7.399	7.532
Slope (m_i)		0.00322	0.00187	0.000671	0.000367
Gordon et al.		4.48	11.93	6.39	11.88
Todd		4.46	11.92	6.38	11.88
Kondrashov and Rothenberg		3.99	5.81	7.90	9.30
Subject C					
Amplitude (x_i for X-rays)	3436	31.74	85.46	9.106	6.438
Amplitude uncertainty (σ_{x_i} for X-rays)	17.69	29.96	50.07	8.102	8.442
Slope (m_i)		0.00322	0.00187	0.000671	0.000367
Gordon et al.		3.95	11.38	5.13	9.77
Todd		3.95	11.38	5.13	9.77
Kondrashov and Rothenberg		0.75	2.13	1.91	2.94

statement: the data given by Gordon et al. are amplitudes, not areas (the column headings of the Gordon et al. table are labeled “Amplitude”). Gordon et al. do not give sufficient data to allow the reconstruction of the areas, but two of the authors (DRC, FEM) estimate that the FWHM was ~ 13 channels, yielding areas of $34,985 \pm 210$ counts and $47,645 \pm 245$ counts for Subjects B and C, respectively, uncertainties (± 210 and ± 245) that are greater than the square root of the net peak areas ($\sqrt{34985} = 187$ and $\sqrt{47645} = 218$, respectively), as expected. It would have been prudent of Kondrashov and Rothenberg to consult with the authors of Gordon et al. before publishing their misunderstanding.

5. Conclusions

Kondrashov and Rothenberg conclude that they “have made substantial and necessary corrections for calculating estimates of lead concentration and uncertainty by a careful application of mathematical statistics”. (p. 802) Their “correction”, however, is neither substantial (we have quantified its effect) nor necessary (it “corrects” a superseded method). More work is required on the problem of why the average measurement uncertainty is less than the standard deviation of repeated measure, but the “correction” of Kondrashov and Rothenberg does not contribute to this question.

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