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Physiologically based modeling of lead kinetics: a pilot study using data from a Canadian population

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The Canadian population is currently subject to low, chronic lead exposure and an understanding of its effects is of great significance to the population's health. Such low exposure is difficult to measure directly; approximation by physiologically based modeling may provide a preferable approach to population analysis. The O'Flaherty model of lead kinetics is based on an age-dependent approach to human growth and development and devotes special attention to bone turnover rates. Because lead is a bone-seeking element, the model was deemed ideal for such an analysis. Sample from 263 individuals of various ages from the Greater Toronto Area were selected to evaluate the applicability of the current version of the O'Flaherty model to populations with low lead exposure. For each individual, the input value of lead exposure was calibrated to match the output value of cortical bone lead to the individual's measured tibia lead concentration; the outputs for trabecular bone, blood, and plasma lead concentrations obtained from these calibrations were then compared with the subjects' measured calcaneus, blood, and serum lead concentrations, respectively. This indicated a need for revision of the model parameters; those for lead binding in blood and lead clearance from blood to bone were adjusted and new outputs were obtained in the same fashion as before. Model predictions of trabecular lead concentration did not agree with measurements in the calcaneus. The outputs for blood and plasma lead concentrations were highly scattered and, on an individual level, inconsistent with corresponding measurements; however, the general trends of the outputs matched those of the measurements reasonably well, which indicates that the revised blood lead binding and lead clearance parameters may be useful in future studies. Overall, the analysis showed that with the revisions to the model discussed here, the model should be a useful tool in the analysis of human lead kinetics and body burden in populations characterized by low, chronic exposure to lead from the general environment.

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Environmental impact

Although lead exposure has undergone a dramatic reduction over the past several decades, Canadians are still subject to low chronic exposure. Low exposure levels are difficult to measure but it is still important to understand their effect. The O'Flaherty model of lead kinetics was developed as a way to approximate lead exposure and lead kinetics within the human body. Previous model studies have focused on adult men with high workplace lead exposures. In this study, a sample of 263 individuals of various ages from the Greater Toronto Area was selected to test the accuracy of the current version of the O'Flaherty model in populations with low chronic lead exposure. Bone and blood lead concentrations were measured in participants with ages from 1 to 85. With this information, adjustments were made to the O'Flaherty model to make it more applicable to the general population.

Introduction

Lead toxicity adversely affects various organ systems throughout the body and is of significant concern to environmental health.[1] Although the effects of acute, high exposure to lead are well documented,[2] those of lower and chronic exposure are much less certain. In recent years, regulation of human lead exposure has greatly increased but trace amounts still remain in the environment, particularly as a result of previous use – for example, in old lead pipes and lead-based paint. As such, an understanding of the effects of low, chronic exposure is of great significance to today's society. This understanding requires an accurate description of the distribution of lead in the human body, which is difficult to measure directly in humans with very low body burdens of lead. The ability to accurately connect lead exposure to distribution in

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the body would, as one key benefit, better inform future public health policy recommendations concerning lead.

A variety of computer-based lead kinetics models exist, including the Integrated Exposure Uptake Biokinetic (IEUBK) model,[3] the Leggett model,[4] and the O'Flaherty model.[5] The IEUBK model is dedicated solely to lead kinetics in children and therefore was not a good choice for the current study. The Leggett model does not explicitly consider physiological parameters, which can vary over time and between women and men. The O'Flaherty model appeared to be best suited to our current project. The O'Flaherty model is a physiologically based model of lead kinetics that pays special attention to time-dependent processes, particularly the bone formation rate.[5] Previous studies of chronic lead exposure using this model have focused on adult men with significant occupational exposure[6] or cynomolgus monkeys.[7] These studies have not been able to address the kinetics and effects of lead in women and children, who are known to be especially vulnerable to lead toxicity.[2,8,9] Despite current environmental regulations for lead exposure, children can still ingest potentially harmful amounts of lead from numerous sources, including soil, dust, infant formula, and lead-based paint.[10,11] Although adult women are subjected to fewer sources of lead exposure, many of them were born before recent advances in exposure regulations and carry relatively large body burdens of lead; when these women are pregnant, this body burden can become a health issue to both the fetus and the mother.[8] In addition, Silbergeld, Schwartz and Mahaffey[9] suggested that menopause is generally accompanied by a substantial release of lead from bone into the blood – from which it can reach other tissues – and the remaining lead in the bone may aggravate postmenopausal osteoporosis.

In this study, the O'Flaherty model of lead metabolism was applied to a sample of 263 environmentally exposed subjects from the Greater Toronto Area.[12] This study sample provides a unique opportunity to assess exposure to lead from the general environment in a contemporary urban Canadian setting. Notably, the study includes measurements of whole blood lead, serum lead, tibia lead, and calcaneus lead concentrations. These represent important "pools" or "compartments" of lead in the human body and allow the comparison of real data against outputs from the O'Flaherty model. In this study, modeled chronic exposure levels were first adjusted for each participant until the modeled output for cortical bone lead acceptably approximated the participant's tibia lead concentration as measured by bone lead X-ray fluorescence. Next, the participants' measured calcaneus, blood, and serum lead concentrations were compared to the corresponding model outputs. Parameters in the model were revised to improve agreement between its outputs and observations. Finally, the application of the model to the subjects was repeated with revised parameters and the resulting output was compared to the measured data from the population.

Methods

General considerations

The version of the O'Flaherty model employed in this study explicitly considers the following biocomponents: whole blood, plasma, liver, kidney, other well-perfused tissues, trabecular bone, cortical bone (metabolically active and diffusion regions), and other poorly perfused tissues. A schematic of how it models lead kinetics through these components is presented in Fig. 1. Many variables in the model, including tissue and organ volumes, body weight, and cardiac output, are dependent on age; these variables change over (modeled) time according to curves that can be adjusted by changing specific input parameters. Full details of the construction of the model are provided elsewhere.[13] The version of the model (July, 1997) used in this study was written in Microsoft C++ and will be referred to here as the physiologically based lead kinetic model (PBKM).

Lead is a bone-seeking element. In the human body, the majority of lead that is retained is stored in bone, wherein it can remain for years.[14] As such, any reasonably accurate model of lead metabolism must properly describe bone lead kinetics. The O'Flaherty model describes bone in terms of two types – cortical and trabecular – and further divides cortical bone into metabolically active and quiescent regions. Each of these regions is associated with a different type of lead metabolism; metabolically active bone is associated with modeling and remodeling and quiescent bone undergoes a slow exchange of lead and calcium ions both within itself and with blood. The lead metabolism of trabecular bone is modeled similarly to that of metabolically active cortical bone; no ion exchange is considered for this bone type. Each type of bone is also subdivided into juvenile and mature bone, each with different modeled lead kinetics; ion exchange in juvenile bone is not considered by the

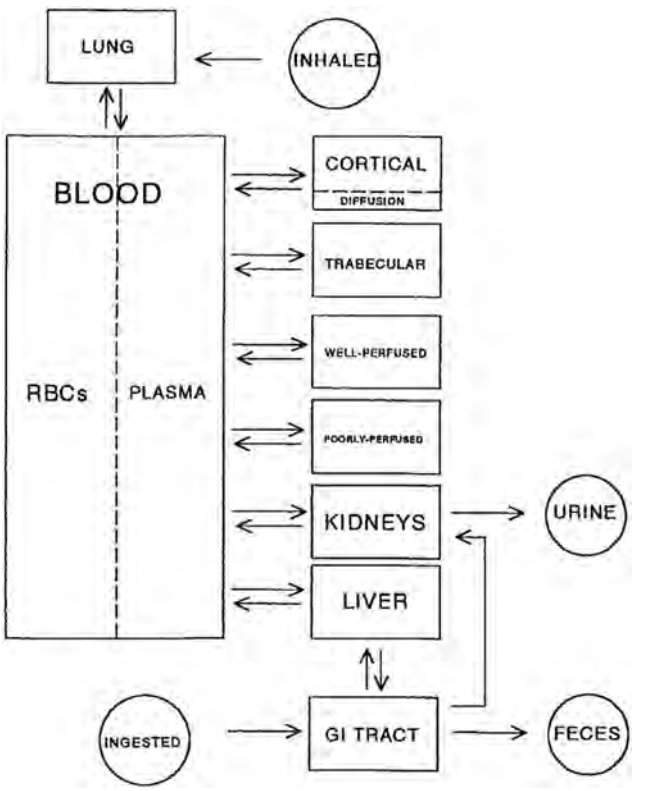

Fig. 1 Schematic of the O'Flaherty model of human lead metabolism.[6]

model because it is negligible relative to lead kinetics arising from metabolically active processes.[6] The ratio of juvenile bone to mature bone is dependent on age and all bone is considered to be of the mature type by the age of 25.

The participants in the current study were recruited as a convenience sample of the general population in Toronto, Ontario, Canada.[12] The overall study was designed to assess current exposure to lead in an urban Canadian population having no known exposure other than through "background" levels in the general environment. Subjects with ages ranging from 1 to 83 years were recruited through St. Joseph's Hospital in Toronto. The study protocol was approved by the Research Ethics Boards of Health Canada (2009-0001), St. Joseph's Health Centre in Toronto (2008-033), McMaster University (09-121), and Mount Allison University (2013-024). Three types of informed consent forms were used in the study: consent was obtained from subjects 16 years or over, assent from children aged 7–15, and parental consent for children under 7. In total, 128 female subjects and 135 male subjects took part in the study. Therefore, a total of 263 participants were available for modeling. Biological indices of lead exposure were measured in the population between 2009 and 2011: subjects were measured for whole blood lead concentration, serum lead concentration, tibia lead concentration, and calcaneus lead concentration. No data for environmental lead exposure (such as intake of lead through water, food, or air) were available for the subjects. Model default values for environmental lead exposure were therefore used, with individual adjustments made as described below under Initial Application of Model. Lead concentrations in bone were measured using a cloverleaf K-shell X-ray fluorescence technique.[15,16] The measurement of bone lead involves a small effective dose of ionizing radiation ranging from <1 μSv to <10 μSv,[15] an amount that is less than the effective dose received from a single dental X-ray or chest X-ray. Before running the model, the ratio of serum lead concentration to blood lead concentration was calculated for each participant. It was found that a plot of serum lead against blood lead expressed as a percentage was a function of the order in which the samples were collected, with the ratios declining during the first 75 collections and stabilizing thereafter. We attribute the initial high values to difficulty in establishing clean techniques. The ratios measured during the stable period had an upper bound of 0.35%. Accordingly, we rejected all serum values associated with serum-to-blood lead ratios greater than 0.35% on the grounds that they had been contaminated during collection. In addition, a smaller number of participants were excluded due to the fact that serum lead analysis had not been performed. This left 177 participants with acceptable serum lead concentration measurements. 262 of the 263 participants had blood lead measurements performed.

As plasma is composed of both serum and clotting factors, the plasma and serum lead concentrations in any given individual will not be identical. However, any differences between the two were considered to be negligible relative to the uncertainty in the serum lead measurements used in this study; instead of serum being modeled as a separate tissue compartment from plasma, the model output for plasma lead concentration was used as a good approximation of the measured serum lead concentration.

Preparation of model input files

An input file was created in PBKM for each participant. The file was selected as female or male, depending on the individual participant. The age in years at which integration was to start (TSTART) was set to 0 in all these files. Each participant's date of birth and age at measurement (in years, rounded to the nearest 0.01 year) were entered into the participant's input file as the year of birth (YOB) and the age at which integration was to stop (TSTOP), respectively. Certain curve constants for hematocrit (HCT), weight (WCHILD, WADULT, and LAMBDA), and bone formation rate (CUTOFF) were set according to the default values in PBKM depending on the participant's sex. In general, the integration step length (CINT, in years) was set to 0.05 for participants under the age of 13, 0.1 for those between the ages of 13 and 30, and 0.2 for those over 30. However, when the total integration length (TSTOP–TSTART) was not an integer multiple of CINT, integration continued beyond TSTOP until it reached the end of a step, *i.e.* an integer multiple of CINT. To accommodate this, CINT values of 0.30, 0.25, 0.15, or 0.10 were used for participants over 30 to keep the difference between their age and the integration end point below 0.1 year. Similarly, CINT values of 0.05 or 0.15 were used for some participants between 13 and 30 years of age, in order to keep this end point within 0.05 year of their age. Due to a limitation in the number of available integration steps, it was not always possible to keep the end point within the desired range; in these cases, the difference was kept as low as possible. Potential differences in the PBKM outputs for cortical bone lead concentration (CCB, in mg L^{-1}), trabecular bone lead concentration (TCB, in mg L^{-1}), and blood lead concentration (CB, in mg L^{-1}) that might arise from this case-by-case modification of CINT were tested for by running the model with different CINT values on the same participant's data for various participants, each of whose model run end points were the same for all tested values. The differences in all these output values based on CINT values were found to be negligible. As such, it is highly unlikely that the different interval lengths would have caused any significant errors in the results.

Revision of blood lead binding constants

O'Flaherty and Reponen[13] suggest that the model parameters for the maximum lead binding capacity of erythrocytes (BIND, in mg Pb L^{-1} cell) and their half-saturation binding constant (KBIND, in mg Pb L^{-1} cell) may need to be changed based on new experimental information. In the model, blood lead concentration (CB) is a function of plasma lead concentration (CPLASMA), hematocrit (HCT), and three constants (BIND, KBIND, and G, where G is the ratio of unbound erythrocyte lead concentration to plasma lead concentration). For a given individual in this study, CB, CPLASMA, and HCT were known from measurement, leaving the constants BIND, KBIND, and G to be determined. No other exposure information was required at this stage. New values of the constants were determined by fitting

the model expression for CB in terms of BIND, KBIND, G, HCT, plasma fraction of whole blood by volume (PLASMA, equivalent to 1 − HCT) and plasma lead concentration (CPLASMA, in mg L^{-1}).[13] This was done according to the least-squares method while varying BIND, KBIND, and G to achieve an optimal fit to the measured data. Because hematocrit data were available from this study, the equation used the participants' measured hematocrit values (instead of the default model hematocrit values) as the input. The equation was as follows:

$$\mathrm{CB} = \mathrm{PLASMA} \times \mathrm{CPLASMA} + \mathrm{HCT} \times \mathrm{CPLASMA} \times (G + \mathrm{BIND}/(\mathrm{KBIND} + \mathrm{CPLASMA}))$$

The best-fit value of G was found to be very similar to the original default value in the model. The best-fit values of BIND and KBIND were substantially reduced relative to the default model values. The results of this fitting ($r^2 = 0.75$) are shown in Fig. 2 and the fitted parameter values are shown and compared to the original default model parameters in Table 1. The new values of all three parameters were then used in all subsequent model input files.

Initial application of model

The model was first run for each input file with all input variables that were not mentioned previously kept at their default values.[13] From this first run, the modeled total bone weight (WBONE, in kg) and total bone volume (VBONE, in L) were obtained and the average bone density (DBONE, in kg L^{-1} or g mL^{-1}) was calculated as WBONE/VBONE, as in the model.[13] The bone density was therefore age-dependent and taken directly from the model using its default parameters. No attempt was made to introduce individual-specific refinements to this modeled bone density. It is important to note that the measured tibia and calcaneus lead concentrations (and their uncertainties) were provided in μg Pb g^{-1} bone mineral. However, CCB and TCB were provided from the model output in mg Pb L^{-1} wet bone.[5] In order to convert the observed bone lead concentrations and uncertainties from μg Pb g^{-1} bone mineral to mg Pb L^{-1} wet bone for each participant, the measured values were multiplied by that participant's DBONE value and the documented mass ratio of bone mineral to wet bone for the appropriate bone type.[17] The measured blood and serum lead concentrations were also converted to mg L^{-1} for comparison with model output CB and CPLASMA, respectively.

The next step in the analysis was calibration of the model input for lead exposure that was specific to each individual participant. Individual exposure histories were unknown, but the model requires the input of exposure as a function of time. An exposure history was created for each individual in order to produce agreement between model outputs and observations with respect to tibia lead concentration. Tibia lead concentration was selected as the calibration end point because it was the best available index of cumulative exposure for the study participants.[18] Exposure was treated in a continuous fashion for each variable described below. For a given individual, the model treats lead intake from water as uniform over time, whereas lead intake from food declines from a pre-1970 rate to a current rate and lead intake from air declines from a pre-1975 rate to a current rate.[13] For each participant's input file, the model input value for drinking water lead concentration (CWATER, in mg L^{-1}) was adjusted and the model re-run until the CCB output was within 0.05 mg L^{-1} of the observed tibia lead concentration in that participant. (Note that if the observed tibia lead concentration was negative, the reading was simply treated as zero at this stage. Due to the mathematical fitting of bone lead energy spectra and considerations of count statistics, it is possible for the bone lead measurement technique to give negative concentrations[18] and these results are normally retained.) The decision to adjust water lead concentration first was based on the assumption that this exposure variable would be the most likely to show significant differences between individuals. The model, however, treats all lead within the body in the same way, regardless of the original source. If agreement within 0.05 mg L^{-1} could not be achieved while keeping CWATER positive, CWATER was set to 0 and the model input value for the contemporary average adult rate of ingestion of lead in food (RFOOD2, in μg per day) was adjusted. If setting both CWATER and RFOOD2 to 0 still resulted in a CCB value that was too large, both CWATER and RFOOD2 were kept at 0 and the model input value for the current concentration of lead in ambient air (CAIR2, in mg m^{-3}) was adjusted, and so on for the pre-1970 average adult rate of lead ingestion *via* food (RFOOD1, in μg per day) and the pre-1975 ambient air lead concentration (CAIR1, in mg m^{-3}). If an appropriate value of CCB was reached or if CCB was still too high after setting all these input values to 0, calibration was ended and the final output values of CB, CCB,

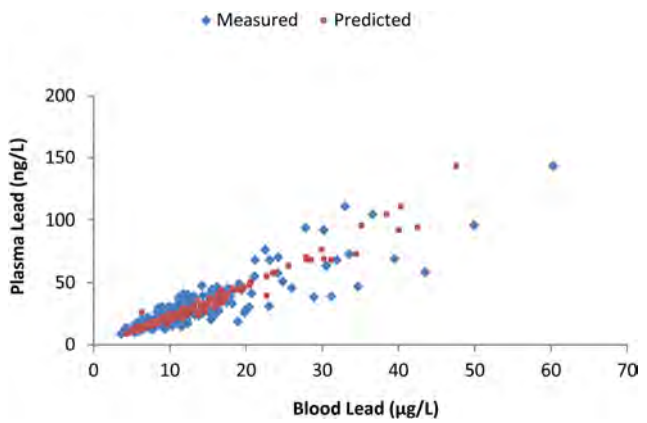

Fig. 2 Plasma lead concentration as a function of blood lead concentration – as measured and as predicted by the model equation using the revised values of BIND, KBIND, and G.

Table 1 Original and revised blood lead binding constants

Parameter	Original value	Revised value
BIND (mg Pb L^{-1} cell)	2.7	0.437
KBIND (mg Pb L^{-1} cell)	0.0075	0.000372
G	1.2	1.19

and TCB were obtained and recorded. For future analysis, the values of CWATER, RFOOD2, CAIR2, RFOOD1, and CAIR1 used to obtain the final model output for each participant were also recorded. During this procedure, if the model output value for CB was negative in any run in which CCB was too high, the value being adjusted at that point in the calibration (CWATER, RFOOD2, CAIR2, RFOOD1, or CAIR1) was changed until the CB output value was less than 10^{-4} mg L^{-1} and neither CB nor TCB was negative, at which point the final values of CB, CCB, and TCB were recorded. This was done to keep the model output realistic. (When reducing modeled lead exposures, CB was always found to be the first of the three output lead concentrations to become negative. This negative model output value likely arose from the way in which renal excretion of lead is modeled, which is detailed in the Discussion.)

The model does not output CPLASMA directly; this value was calculated outside the model for each participant from his or her CB output, HCT input, and the revised values of BIND, KBIND, and *G*.

The abovementioned procedure was also performed for all data while leaving BIND, KBIND, and *G* at their default model values. As expected, these trials were not able to reproduce as effectively the observed relationship between plasma lead and blood lead concentrations. All further model trials were therefore performed using the revised values of BIND, KBIND, and *G*.

Additional revision of model parameters

Both sets of results indicated that changing CWATER had a dramatic effect on the ratio of TCB to CCB that was output from the model. We were curious whether eliminating any individual-level variation in the modeled value of CWATER might improve the model output. The abovementioned procedure was therefore repeated a third time. The revised values of BIND, KBIND, and *G* were used and CWATER was left at its default value of 0.005. (RFOOD2, then, was the first variable to be changed in calibrating CCB to the tibia lead concentration of each participant.) For this configuration of the model, a few of the participants' tibia lead concentrations could not be "reached" by CCB using the previously described procedure without increasing RFOOD2 above RFOOD1. This would violate the model's reasonable assumption that lead intake from food decreased after 1970, so the default value of RFOOD1 (200) was treated as a maximum for RFOOD2. When this maximum was reached, further increases in CCB were produced by increasing CAIR2 to a maximum of the default value of CAIR1 (0.002) for similar reasons. The only participants whose tibia lead concentrations were higher than the maximum possible CCB output values obtainable by this method were born after 1995 and changing the values of RFOOD1 and CAIR1 had very little effect on their CCB values. Therefore, no further changes were made to the input parameters for these participants; their data were considered to be anomalous and their corresponding CCB, TCB, and CB output values were recorded at a maximum CCB value. This approach was not found to improve the overall accuracy of the model results; all further model trials were therefore performed by changing CWATER first, as before.

An attempt was then made to create a better fit to the measured blood and serum lead concentration data by altering the modeled bone formation rate (BFR). In the model, bone formation rate is calculated as a function of several input and calculated variables; one of these input variables, BASE, was reduced in order to lower BFR. A representative sample of 20 participants was obtained by randomly sampling 20 of the population until the sample means and medians of their measured cortical bone and blood lead concentrations matched those of the population to within a factor of 1.25. The same model run procedure as before was then performed on this sample with BASE reduced by factors of 3, 5, and 100. Although this produced some changes in TCB, none of these reductions produced significant differences in CB or CPLASMA – in fact, many of the sampled participants' modeled lead exposure histories were similar to those used before reducing BASE.

Finally, the model was altered by increasing the modeled lead clearance from blood to bone (P_0, in cm^3 per day) by factors of 5, 10, and 15, performing the model run procedure on the data from the same sample of 20 participants as before. Increasing P_0 by a factor of 15 (from 0.02 to 0.3) was found to produce sample means and medians of CB and CPLASMA, as well as an average ratio of CB to CCB, which approximated the corresponding values from the measured data reasonably well; the model run procedure was then performed on the data from all 263 participants.

Results

Refinement of model

The default blood lead binding constants produced modeled blood lead output values that were too high, whereas the revised constants produced output that was closer to the measured data. However, both sets of results indicated a need for further refinement of the model. In particular, the modeled blood and plasma lead concentrations were too large (even with the revised blood lead binding constants), which indicated that further changes were required to produce more accurate model output. This was accomplished by the modification of the P_0 parameter to a revised value of 0.3.

Determination of modeled plasma (serum) lead

The plasma (serum) lead concentrations that were calculated from the model output for blood lead concentrations are shown and compared to the corresponding measured concentrations in Fig. 3. Although the measured data are reasonably approximated by the model (apart from some scatter in the former, which is also visible in Fig. 2), the modeled blood and plasma lead concentrations have much greater ranges than the corresponding measured data. As the input for each participant was calibrated to match the output value for cortical bone lead concentration to the measured tibia lead concentration, this effect is likely due to uncertainties in the measurement of the tibia lead concentration. A tibia lead concentration measurement that was higher than the actual value would result in model calibration with higher lead intake input parameters and

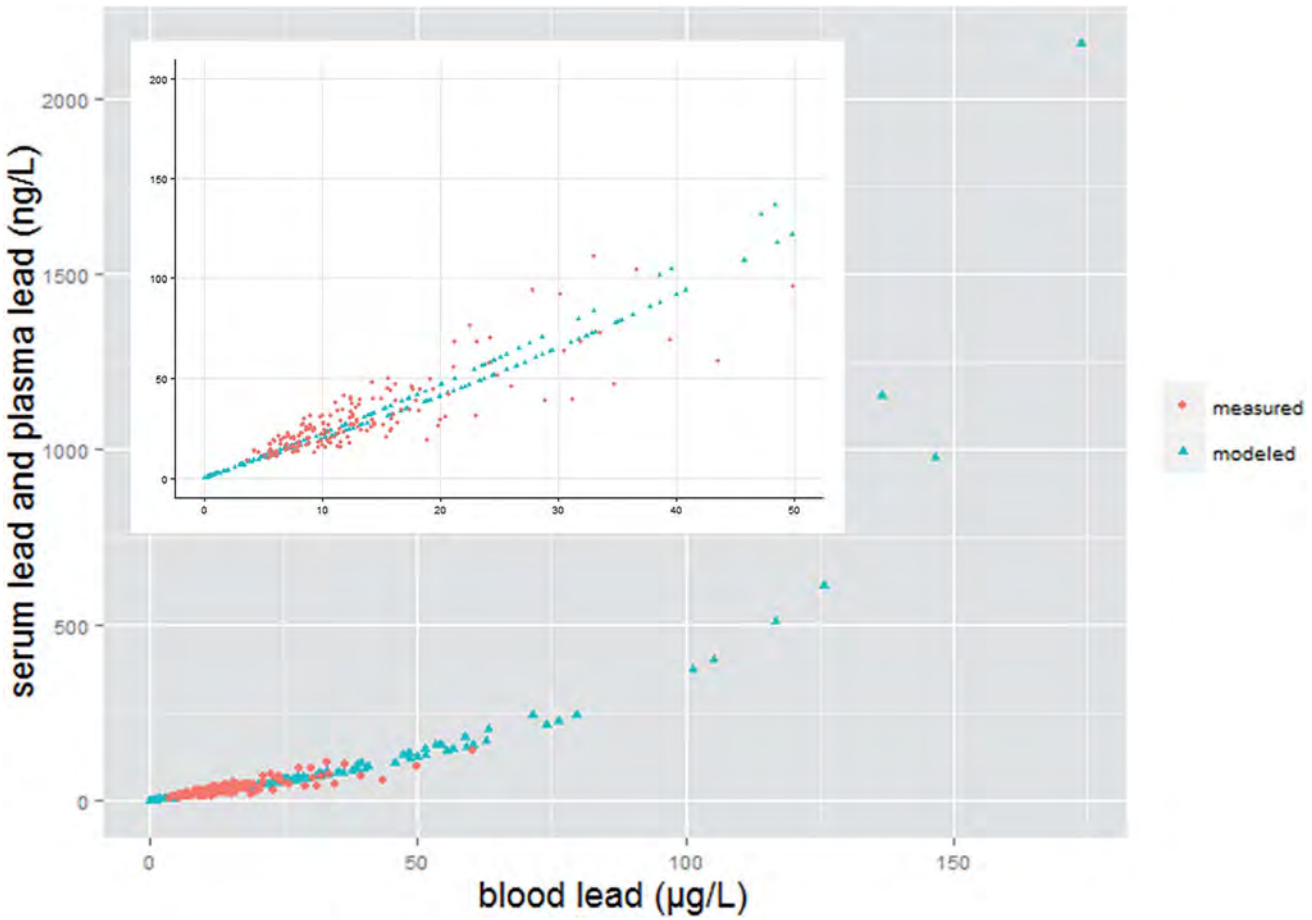

Fig. 3 Measured serum lead and modeled plasma lead concentrations as a function of blood lead concentration.

therefore higher blood and plasma lead concentration output values. (The curve in the modeled data seen at higher blood lead concentrations in Fig. 3 arises from the way in which the model relates blood and plasma lead; at higher blood lead concentrations, red blood cells approach their maximum lead binding capacity and a greater fraction of blood lead is contained in the plasma. The measured relationship between blood and serum lead concentrations most likely appeared to be linear in this data set because the participants' blood lead concentrations were too low to result in such "saturation" of red blood cells.) Nonetheless, revision of the blood lead binding constants yielded a modeled relationship between blood and serum lead that closely approximated the observed relationship.

General results

The final observations and model output values for tibia (cortical bone), calcaneus (trabecular bone), blood, and serum (plasma) lead concentrations are shown in Fig. 4–7, respectively. In every case that was investigated, for both observed and modeled data, the data distributions were found to be inconsistent with a normal distribution. As assessed by the Shapiro–Wilks test, the closest approach to a normal distribution was found in the observed tibia lead concentrations. Although the data are highly scattered in the latter three graphs and the model output value for trabecular lead concentration was, overall, lower than the observed calcaneus lead concentration (see Discussion), the revised model reasonably approximated the general trends in the measured blood and serum lead data. This is further illustrated in Table 2, which shows the mean, median, and geometric mean of the observed tibia, blood, and serum lead concentrations in all participants and compares them to the corresponding values from the model output. These results were obtained using the revised values of BIND, KBIND, and G, both before and after the additional revision of P_0 (see Methods). The standard errors of the mean and geometric standard deviations are provided, where available. The geometric mean for measured cortical bone (tibia) is not provided, because negative values were included in this data set. Standard errors and standard deviations from the original model values are not provided because the full model output was not retained at this stage.

For all three tissue compartments in Table 2, the *mean* model values do not match the corresponding measured means, even after revision of the model. This discrepancy is partially due to the fact that participants with negative tibia lead concentrations (of which there was a significant number; see Fig. 4) were modeled as having very low, but positive, cortical bone lead concentrations (see Methods). In general, this approach

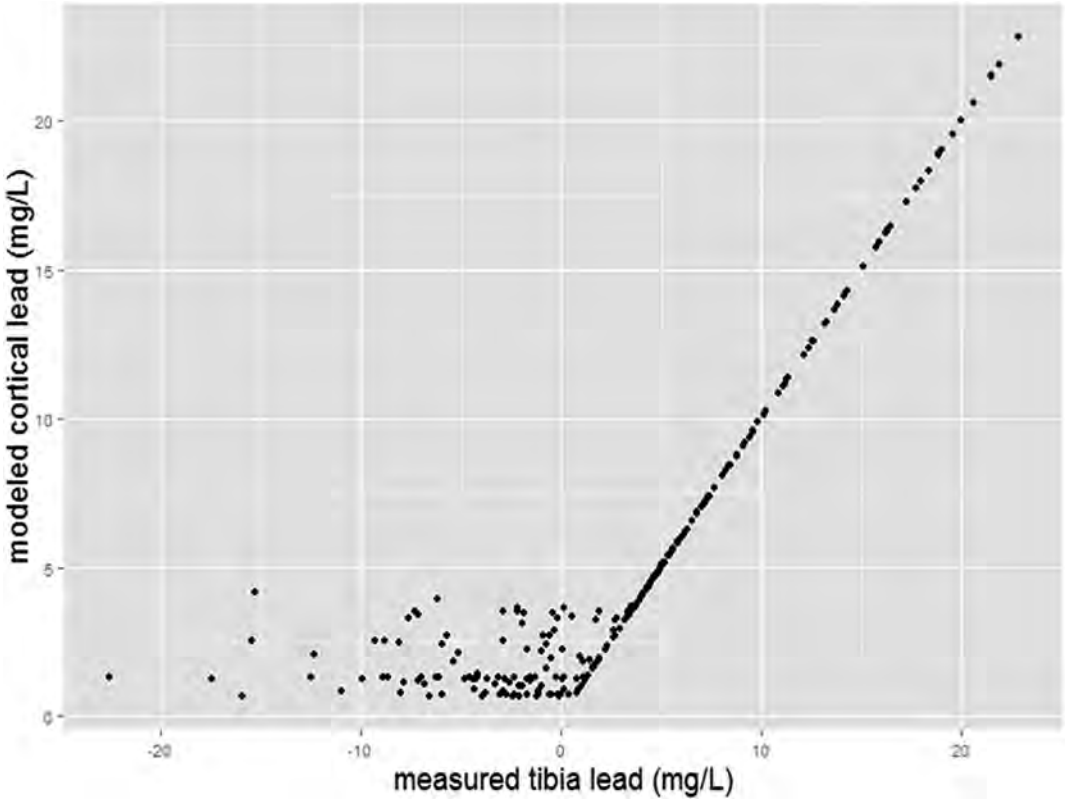

Fig. 4 Modeled cortical bone lead concentration as a function of measured tibia lead concentration.

resulted in *higher* mean modeled cortical bone lead concentrations and lead body burdens and therefore higher mean modeled blood and serum lead concentrations. As such, there is a residual discrepancy because of the positive bias introduced by the way in which negative tibia lead measurements had to be treated. In addition, a moderate number of very high measured tibia lead values were translated into very high modeled cortical bone lead values, producing high modeled blood and serum results. At the same time, the treatment of negative measured tibia lead concentrations resulted in a large number of very low modeled cortical bone values and extremely low (less than 1 μg L^{-1}) modeled blood lead values. This specific collection of extremely low modeled blood lead values resulted in *geometric mean* modeled blood and serum values, which were *lower* than those of the corresponding measured results. Moreover, as noted above, none of the observed or modeled data sets were consistent with a normal distribution. For all of these reasons, the *median* values in Table 2 should be considered to be better indicators of model performance (both before and after revision of P_0). From the median results, it is clear that the revised model is greatly improved over the original model with respect to blood and serum lead concentrations. Median modeled results closely reflect median measured values, as demonstrated by Table 2. In summary, when individually modeled exposures were used to fit tibia lead measurements, the revised model gave good agreement between measured blood and serum median values and their modeled equivalents.

Discussion

Nature of results

The data shown in Fig. 5–7 are highly scattered with no clear relationships between variables. In itself, this does not suggest that the revised model performed poorly. The model was meant to capture the general trends of observed lead concentrations in the population, not the exact lead distribution and body burden in individuals. In the absence of repeated lead measurements made over an individual's lifetime, it is highly unlikely that the model could be made to recreate individual results. The biological processes that move lead into and out of the body (and the various compartments within it) vary in rate over time and between individuals due to genetic and environmental factors and the model cannot account for these individual differences. Instead, rates are approximated from age-dependent best-fit curves and average rates obtained from previous studies.[13] Furthermore, many sources of individual lead exposure could not be modeled accurately due to the absence of data for specific and significant changes in lead exposure throughout a lifetime. Although the model does allow input variables to be changed in the middle of a simulation,[13] doing so accurately would require an in-depth knowledge of the lead exposure history of the individual. In the case of people with occupational lead exposure, such as the lead smelter workers who were investigated in a previous study using this model,[6] such measurements may sometimes be accessible. However, for individuals such as those in this study, these measurements will

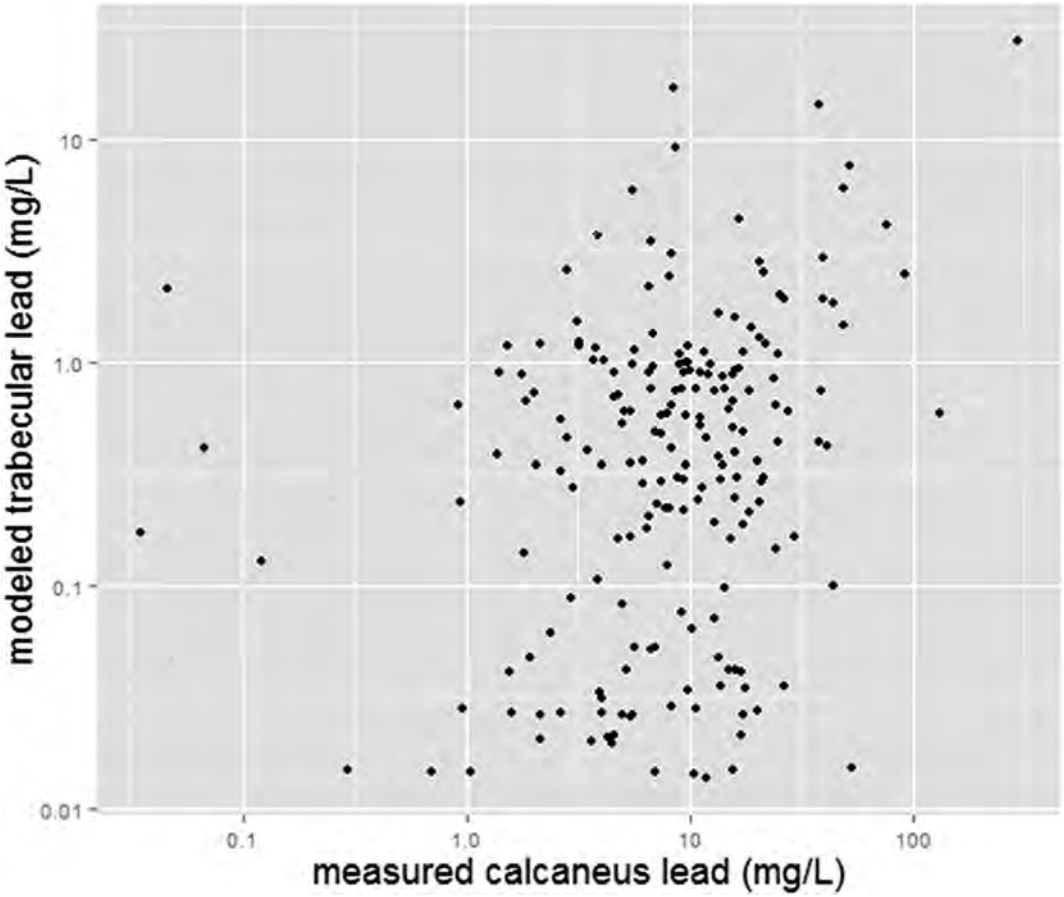

Fig. 5 Modeled trabecular bone lead concentration as a function of measured calcaneus lead concentration. To show the trend more clearly, the axis scales are presented in logarithmic form. Data are only shown for those points having measured calcaneus lead concentrations above 0 mg L^{-1}. The equation of best fit is $\log y = ((0.33 \pm 0.09) \log x) - (0.78 \pm 0.10)$; $r^2 = 0.06$; $p < 0.001$.

simply not be available. The standard errors provided for measured values across the population (Table 2) demonstrate the high degree of variability within the data sets, with a particularly high relative standard error for tibia lead concentrations. Finally, uncertainties in individual-level measurements (bone, blood, and serum) can serve to complicate comparisons between measured and modeled lead levels on an individual level. However, by making comparisons over a large population, as is possible *via* this study, the effects of these individual-level variations can be minimized and the model output can be evaluated for the larger population.

Treatment of negative output

When calibrating the model for certain participants with especially low measured tibia lead concentrations, matching the output for cortical bone lead concentration to these measurements resulted in a negative output value for the lead concentration in blood – and often trabecular bone, which necessitated an alternative method of calibration for these participants, because negative concentrations are not physically possible (*i.e.* positive output values were required for CB, TCB, and CCB; see Methods). The model's ability to generate negative lead concentration output values without negative lead exposure input values suggests that one or more of its approximations of real human lead kinetics are not valid in scenarios with unusually low lead exposure. The model manual[13] indicates that the total clearance of lead from plasma to the kidneys (CL) is modeled as an age-dependent fraction of the glomerular filtration rate (GFR), which itself is a function of body weight. Neither value is dependent on any lead concentration or exposure values. This approach is defended by noting that the glomerular filtration rate has generally been found not to be the rate-determining step in the renal excretion of lead in individuals examined in previous lead exposure studies.[19,20] It is also noted, however, that this approach to determining the glomerular filtration rate can only be assumed to be valid for individuals with blood lead concentrations that were typical in the 1990s and previous decades. The lowest blood lead concentrations observed in this study may not satisfy this condition. With the median observed blood lead concentration of 11 μg L^{-1} that was found in this study, many measured values fell below 10 μg L^{-1}, which is very low by recent historical standards. Given the equations that were used to model CL,[13] individuals with extremely low lead exposures could have been modeled as excreting more lead than they were modeled to have in their blood, resulting in negative blood lead concentrations. As such,

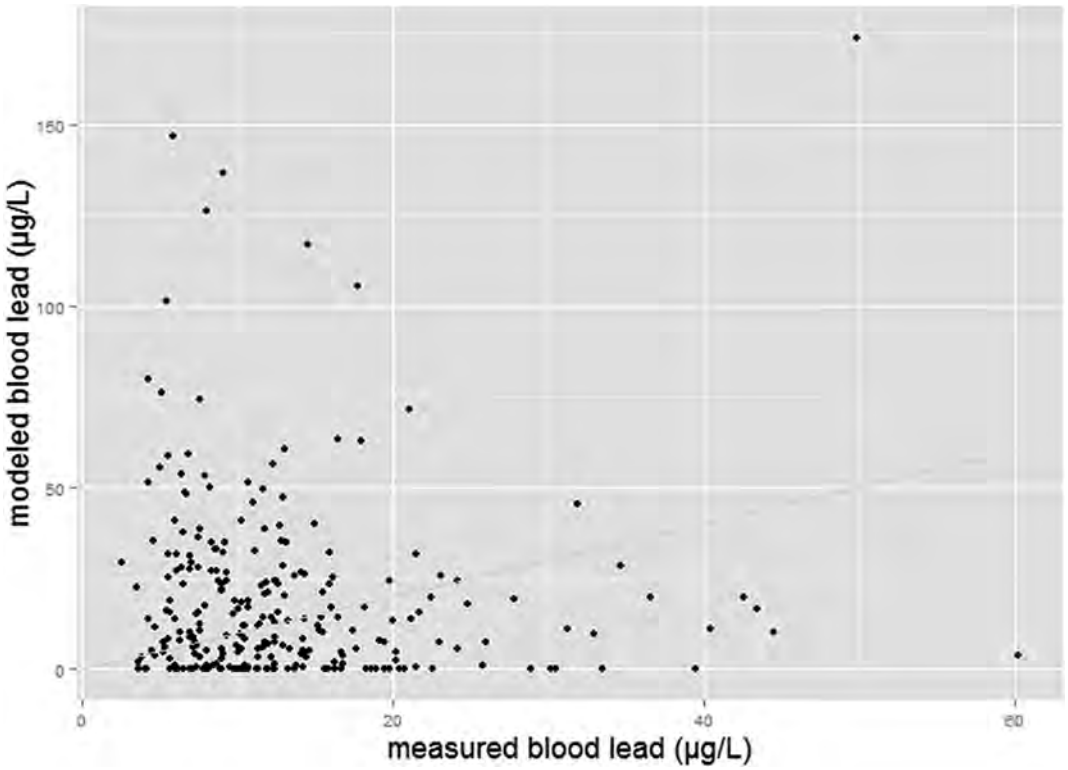

Fig. 6 Modeled blood lead concentration as a function of measured blood lead concentration. The equation of best fit is $y = (0.0 \pm 0.2)x + (19 \pm 3)$; $r^2 = 0.00$; $p = 0.89$.

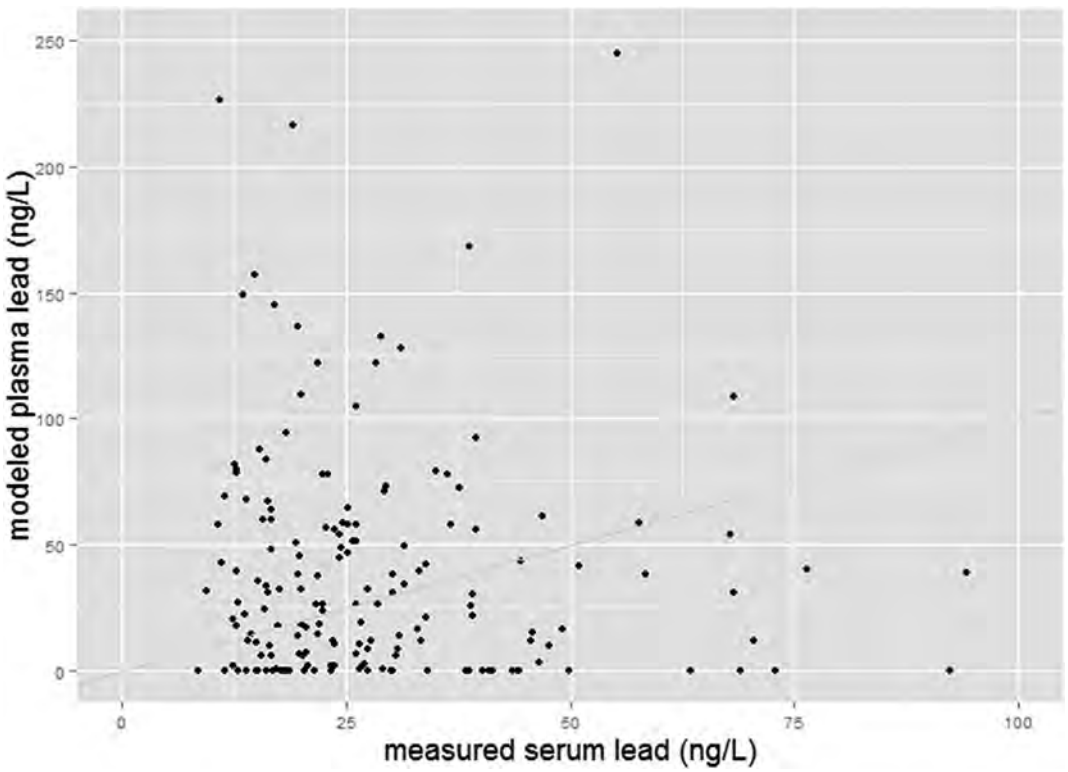

Fig. 7 Modeled plasma lead concentration as a function of measured serum lead concentration. For clarity, data are limited to modeled plasma lead concentrations <250 ng L^{-1} and measured serum lead concentrations <100 ng L^{-1}. The equation of best fit is $y = (1.4 \pm 0.7)x + (25 \pm 27)$; $r^2 = 0.01$; $p = 0.06$.

Table 2 Mean, median, and geometric mean measurements and model output parameters for bone and blood lead concentrations before and after revision of P_0

Tissue compartment	Parameter	Measured value	Original model value	Revised model value
Cortical bone (mg L^{-1})	Mean (SE)	3.2 (0.5)	5.1 (—)	5.4 (0.3)
	Median	3.3	3.4	3.5
	Geometric mean (GSD)	—	—	3.4 (2.7)
Blood (μg L^{-1})	Mean (SE)	13 (0.5)	48 (—)	19 (1.6)
	Median	11	39	11
	Geometric mean (GSD)	11 (1.7)	—	3.4 (21)
Serum or plasma (ng L^{-1})	Mean (SE)	30 (1.5)	210 (—)	61 (11)
	Median	24	95	22
	Geometric mean (GSD)	26 (1.7)	—	7.5 (23)

an alternative approach to modeling the renal excretion of lead is recommended to improve the modeling of lead metabolism in people with histories of very low lead exposure. At least one previous study[21] also supports this conclusion, claiming that, although the O'Flaherty model should be able to describe human lead metabolism reasonably well when refined, its current approach to simulating lead excretion may be inconsistent with observations of the age dependence of human excretion kinetics, particularly in young children.

Tibia lead

As can be seen in Fig. 4, the modeled cortical bone lead concentrations matched positive observed tibia lead concentrations extremely well. However, this does not indicate that the model is accurate, as the lead exposure input value for each participant was specifically calibrated in order to match the model cortical bone output value to these observations (see Methods).

As noted, many of the observed tibia lead concentrations were negative. The corresponding subjects' cortical bone lead concentrations were modeled as positive in order to keep the model output values physically realistic. Negative bone lead observations arose from uncertainties in measurement that are inherent in bone lead analysis. This effect is not unexpected when using bone lead X-ray fluorescence and will yield the occasional negative result, particularly in individuals with very low bone lead concentrations.[22] In addition to the errors arising from the X-ray fluorescence method, some high uncertainties were contributed by participants who were young children and could not remain motionless during the measurement of bone lead (with individual uncertainties ranging up to 34 μg g^{-1}). These high uncertainty measurements were, however, not typical. The mean uncertainties in tibia lead concentration, in units of μg Pb g^{-1} bone mineral, were 5.15 μg g^{-1} (standard error 0.22 μg g^{-1}) for females and 4.64 μg g^{-1} (standard error 0.28 μg g^{-1}) for males participating in this study.[12] For each individual's measurement, the uncertainty was calculated based on a mathematical fitting of the participant's X-ray spectrum and from a set of calibration standards. Because tibia lead concentration measurements were used in the individual model calibrations, any error in tibia lead concentration affected the model output values for the other three tissue compartments (trabecular bone, blood, and serum concentrations). Uncertainties in the measurement of tibia lead concentration were therefore the dominant source of uncertainty in making individual-level comparisons between observations and model output values.

Calcaneus lead

Overall, the model output values for trabecular bone lead concentration were much lower than the observed calcaneus lead concentrations (see Fig. 5). A previous study[6] suggested that calcaneus has a lower bone turnover rate than the trabecular bone compartment simulated by the O'Flaherty model. A more recent review[21] noted that trabecular bone lead kinetics may not be as different from cortical bone lead kinetics as is assumed by the model in its current form. Accurate modeling of trabecular bone lead kinetics cannot be assumed from the model in its current form and may require significant structural revision along the lines indicated immediately above.

Blood and serum lead

As can be seen from Fig. 6 and 7, the data for blood and serum lead are highly scattered; however, as shown in Table 2, the model was able to successfully capture the general trend of the observations for the population as a whole. The discrepancy between the modeled and measured scatter in Fig. 6 and 7 on the one hand and the good agreement between the modeled and measured median results on the other can be explained by a number of factors. As described above, these contributing factors are uncertainties in individual-level measurements, variations within the population as a whole, and the nature of the tibia lead concentration measurement results and their subsequent use to create modeled exposure histories.

From Fig. 8, it is clear that most study participants were modeled as having one of two distinct ratios of blood lead to cortical bone lead. Analysis of the data revealed that the higher ratio of these two ratios generally corresponded to younger participants (<13 years of age), whereas the lower ratio generally corresponded to adults (>20 years of age) with very low modeled lead exposure. In the case of the younger participants, this constant ratio between blood lead and cortical lead is a consequence of relatively high bone turnover rates. As observed bone

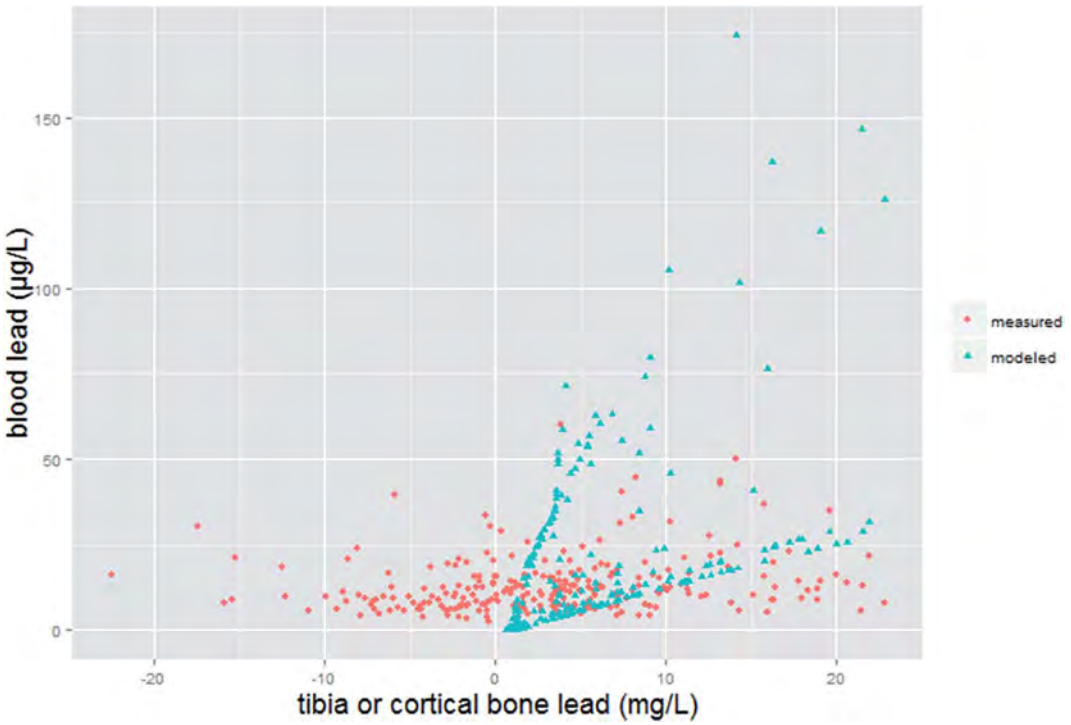

Fig. 8 Measured or modeled blood lead concentration as a function of measured or modeled cortical bone (tibia) lead concentration. The equation of best fit for the measured data is $y = (0.21 \pm 0.07)x + (12.3 \pm 0.6)$; $r^2 = 0.03$; $p < 0.01$. The equation of best fit for the modeled data is $y = (2.5 \pm 0.3)x + (6 \pm 2)$; $r^2 = 0.25$; $p < 0.001$.

lead goes up, blood lead must increase in a nearly linear fashion in order to maintain the necessary transfer of lead to bone. In the case of adults with low lead exposure, the distinct lower ratio between blood lead and cortical bone lead is an artifact of modeled historic exposure levels. Because these individuals were mostly modeled as having minimal current lead exposure, their contributions to bone lead stores were entirely due to exposure in the past. This, in turn, means that current blood lead is directly dependent on endogenous (internal) exposure to bone lead and the resulting current blood lead levels vary directly with current bone lead levels. The remainder of the modeled population fell somewhere between these two distinct ratios of blood lead to cortical bone lead and represented intermediate cases between young participants and adults with low exposure. Overall, the majority of non-negative measured tibia lead concentration data points fell between these two distinct modeled ratios. Agreement between the linear fit for measured blood lead *vs.* tibia lead and modeled blood lead *vs.* cortical bone lead, as presented in Fig. 8, was not good. This can be attributed to the retention of negative tibia lead values in the measured data set and the emergence of a distinctive bifurcation of results in the modeled data set.

Conclusion

Using data obtained from a sample of people living in the Greater Toronto Area, the O'Flaherty model of lead kinetics has been tested and refined for applicability to contemporary human populations with histories of low, chronic lead exposure. After revision of modeled blood lead binding constants and the model input parameter for lead clearance from blood to bone, adjusting the modeled lead exposure history for each individual (to match the output value for cortical bone lead concentration to the measured tibia lead concentration) allowed the model to capture the general trends in observed blood and serum lead concentrations at the population level. The median observed blood lead concentration was 11 µg L^{-1} and the median modeled concentration was 11 µg L^{-1}. The median observed serum lead concentration was 24 ng L^{-1} and the median modeled concentration was 22 ng L^{-1}. This was a considerable improvement over results obtained using the original model (39 µg L^{-1} and 95 ng L^{-1}, respectively). However, the model was not able to simulate observed patterns in trabecular bone lead concentration or reproduce measured lead distributions in individuals. With the revisions introduced *via* this study, the model should be a useful tool in the analysis of human lead kinetics and body burden in populations characterized by low, chronic exposure to lead from the general environment.

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