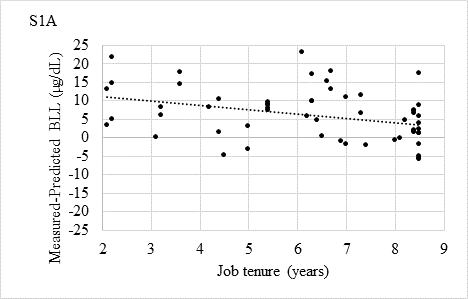
**Evaluation and updates to the Leggett model for pharmacokinetic modeling of exposure to lead in the workplace – Part I adjustments to the Adult Systemic Model**

**SUPPLEMENTAL MATERIAL**



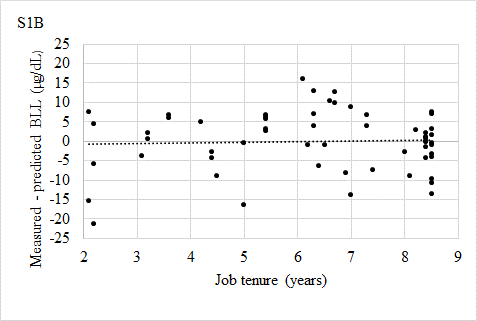


Figure S1: Measure-predict BLL relative to job tenure, predictions from the original and adjusted Leggett model compared to data from 58 smelter workers Hattis 1981)A,B,C

A, Abbreviations and definition of terms, µg/dL, micrograms of lead per deciliter of fluid, BLL, whole blood lead level, job tenure, years of employment prior to 9-month strike used as an estimate of occupational exposure to lead; BLL difference between measured from the Hattis dataset and predicted BLL from the original or adjusted Leggett model (circle marker), regression line (dashed line), post-strike BLL, BLL taken after a 9-month strike in which workers were away from occupational exposure at the smelter plant.

B, Measure-predict BLL relative to job tenure, predictions from the original (S1A) and adjusted (S1B) Leggett model compared to data (circles) from 58 smelter workers. In S1A, the systematic under-prediction and negative slope observed in the analysis of 47 workers remains after adding 11 BLLs between 60 and 80 µg/dL with less than the average job tenure where (BLL µg/dL difference) = -1.161\*(years of job tenure) + 13.44, R² = 0.124, t-stat = -2.81, p=0.007. C, In S1B, adding 11 workers with BLLs between 60 and 80 ug/dL with less than the average job tenure where (BLL µg/dL difference) = 0.184\*(years of job tenure) – 1.22, R² = 0.002, t-stat = 0.374, p=0.71, brings the slope of the regression line to approximately zero indicating that there does not appear to be a systematic over- or under-prediction of post –strike BLLs for workers chronically exposed for 2 – 8 years regardless of job tenure.



FIGURE S2: Measure- predicted BLL relative to pre-employment BLL for 58 smelter workers (Hattis 1981)A,B.

A, Abbreviations and definition of terms; µg/dL, micrograms of lead per deciliter of fluid, BLL, whole blood lead level, job tenure, years of employment prior to 9-month strike used as an estimate of occupational exposure to lead; BLL difference between measured from the Hattis dataset and predicted BLL from the original or adjusted Leggett model (circle marker), regression line (dashed line), post-strike BLL, BLL taken after a 9-month strike in which workers were away from occupational exposure at the smelter plant.

B, In S2A,a regression slope near zero where measure- predicted BLL = -0.1214\*(Pre-employment BLL) + 8.55, R² = 0.017 and in S2B: where measure- predicted BLL = 0.1479\*(Pre-employment BLL) - 3.01, R² = 0.020 indicate that predictions from the original Leggett model that there does not appear to be a systematic over- or under-prediction of post –strike BLLs for with pre-employment BLLs less than about 36 .

Table S1A: Data from subjects included in the initial analysisA

| **Subject** | **Exposure (days)** | **Pre-employment BLL (µg/dL)** | **Prestrike**  **BLL (µg/dL)** | **Poststrike**  **BLL (µg/dL)** |
| --- | --- | --- | --- | --- |
| 5 | 3084 | 11 | 30.46 | 17 |
| 6 | 2266 | 14 | 38.18 | 36 |
| 8 | 3080 | 10 | 56.95 | 41 |
| 14 | 3077 | 20 | 37.27 | 28 |
| 15 | 3080 | 10 | 35.33 | 10 |
| 23 | 3087 | 10 | 37.22 | 10 |
| 27 | 3084 | 20 | 34.05 | 32 |
| 33 | 3071 | 21 | 39.91 | 24 |
| 34 | 3071 | 17 | 26.71 | 20 |
| 36 | 3070 | 35 | 49.9 | 44 |
| 39 | 3071 | 13 | 39.28 | 20 |
| 45 | 3066 | 22 | 52.3 | 37 |
| 47 | 3066 | 24 | 35.79 | 29 |
| 54 | 3060 | 34 | 43.94 | 38 |
| 59 | 3052 | 13 | 46.67 | 23 |
| 62 | 3045 | 17 | 56.13 | 35 |
| 63 | 1960 | 20 | 42.44 | 34 |
| 67 | 3043 | 18 | 42.53 | 26 |
| 68 | 3045 | 24 | 57.37 | 40 |
| 73 | 1960 | 20 | 32.19 | 31 |
| 88 | 1959 | 14 | 37.76 | 26 |
| 91 | 742 | 16 | 42.85 | 33 |
| 101 | 1953 | 22 | 52.07 | 37 |
| 106 | 1818 | 17 | 37.76 | 24 |
| 108 | 2979 | 33 | 43.94 | 40 |
| 115 | 2912 | 33 | 45.79 | 35 |
| 138 | 2928 | 10 | 52.4 | 21 |
| 157 | 2667 | 27 | 54.47 | 31 |
| 158 | 2660 | 26 | 42.43 | 36 |
| 159 | 2653 | 18 | 49.51 | 38 |
| 161 | 1617 | 21 | 46.7 | 22 |
| 177 | 1582 | 35 | 55.41 | 40 |
| 188 | 2541 | 24 | 41.01 | 39 |
| 191 | 1499 | 19 | 39.04 | 31 |
| 202 | 1288 | 26 | 60.4 | 47 |
| 203 | 2485 | 16 | 55.22 | 26 |
| 218 | 1162 | 14 | 34.13 | 23 |
| 221 | 2415 | 20 | 43.74 | 39 |
| 225 | 2408 | 26 | 52.17 | 47 |
| 226 | 2415 | 10 | 36.53 | 33 |
| 227 | 1148 | 18 | 54.33 | 34 |
| 237 | 1106 | 36 | 54.76 | 39 |
| 257 | 2346 | 34 | 41.59 | 36 |
| 286 | 2268 | 12 | 41.76 | 28 |
| 288 | 2266 | 27 | 43.3 | 40 |
| 299 | 2247 | 13 | 47.81 | 27 |
| 474 | 1960 | 17 | 38.48 | 31 |

A, N=47 subjects selected from (Hattis 1981)

Table S1B: Smelter workers excluded in analyses

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Subject IDA** | **Exposure (days)** | **Pre-employment BLL (µg/dL)** | **Prestrike** | **Poststrike** | **Reason for ExclusionB** |
| 11 | 3080 | 25 | 40.58 | 44 | b |
| 32 | 783 | 12 | 67.7 | 46 | d |
| 35 | 3070 | 25 | 61.94 | 29 | d |
| 37 | 3070 | 25 | 58.24 | 59 | b |
| 46 | 770 | 13 | 90.35 | 42 | a |
| 55 | 2212 | 32 | 63.27 | 62 | d |
| 57 | 770 | 13 | 73.22 | 42 | d |
| 89 | 1959 | 34 | 61.53 | 27 | c |
| 94 | 734 | 15 | 71.52 | 31 | d |
| 126 | 1799 | 40 | 46.18 | 34 | c |
| 127 | 1799 | 19 | 68.13 | 29 | d |
| 131 | 2744 | 37 | 54.54 | 27 | c |
| 165 | 1617 | 25 | 57.51 | 58 | b |
| 178 | 1582 | 11 | 65.05 | 36 | d |
| 181 | 2553 | 25 | 69.52 | 35 | d |
| 199 | 1302 | 18 | 61.92 | 46 | d |
| 265 | 2310 | 21 | 66.02 | 38 | d |
| 300 | 784 | 10 | 77.65 | 32 | d |
| 454 | 2457 | 24 | 32.11 | 33 | b |

A, N=19 subjects from Hattis dataset (Hattis 1981) excluded in the initial analysis;

B, a) pre-strike BLL was over 80 ug/dL, micrograms lead per deciliter of blood ; b) the post-strike BLLs (blood lead level) were greater than the pre-strike BLL ; c) the post-strike BLLs were less than the pre-employment BLL ; d) 11 additional workers with pre-strike BLLs ranging from 61 to 80 ug/dL (examined separately)

TABLE S2A: Predictions from original Leggett model used in Figure 2A

| ID | Derived background uptake (µg/day) | Derived uptake during employment (µg/day) | Predicted pre-strike BLL (µg/dL) | Predicted post-strike BLL (µg/dL) | Measure-predict BLL (µg/dL) |
| --- | --- | --- | --- | --- | --- |
| 34 | 33.11 | 52.87 | 26.78 | 18.87 | 1.13 |
| 5 | 21.42 | 64.77 | 30.47 | 14.71 | 2.29 |
| 73 | 38.95 | 70.21 | 32.23 | 22.37 | 8.63 |
| 27 | 38.95 | 75.49 | 34.07 | 23.26 | 8.74 |
| 218 | 27.27 | 80.05 | 34.13 | 17.02 | 5.98 |
| 15 | 19.48 | 81.53 | 35.33 | 15.19 | -5.19 |
| 47 | 46.74 | 81.21 | 35.82 | 27.06 | 1.94 |
| 226 | 19.48 | 87.05 | 36.52 | 15.15 | 17.85 |
| 23 | 19.48 | 88.58 | 37.22 | 15.76 | -5.76 |
| 14 | 38.95 | 87.35 | 37.29 | 24.19 | 3.81 |
| 106 | 33.11 | 91.71 | 37.75 | 21.06 | 2.94 |
| 88 | 27.27 | 92.08 | 37.76 | 18.59 | 7.41 |
| 6 | 27.27 | 93.08 | 38.17 | 18.93 | 17.07 |
| 474 | 33.11 | 94.35 | 38.48 | 21.36 | 9.64 |
| 191 | 37.00 | 97.28 | 39.02 | 22.85 | 8.15 |
| 39 | 25.32 | 96.29 | 39.28 | 18.93 | 1.07 |
| 33 | 40.90 | 97.69 | 39.92 | 25.86 | -1.86 |
| 188 | 46.74 | 102.63 | 41.02 | 28.00 | 11.00 |
| 257 | 74.94 | 103.64 | 41.63 | 35.65 | 0.35 |
| 286 | 23.37 | 108.48 | 41.73 | 18.29 | 9.71 |
| 158 | 50.64 | 108.26 | 42.42 | 29.51 | 6.49 |
| 63 | 38.95 | 110.85 | 42.43 | 25.08 | 8.92 |
| 67 | 35.06 | 109.33 | 42.51 | 24.20 | 1.80 |
| 91 | 31.16 | 118.90 | 42.82 | 19.98 | 13.02 |
| 288 | 52.62 | 112.82 | 43.31 | 30.11 | 9.89 |
| 221 | 38.95 | 115.71 | 43.72 | 25.86 | 13.14 |
| 54 | 74.94 | 113.28 | 43.95 | 36.25 | 1.75 |
| 108 | 71.44 | 113.64 | 43.97 | 35.40 | 4.60 |
| 115 | 71.44 | 122.50 | 45.81 | 35.76 | -0.76 |
| 59 | 25.32 | 129.52 | 46.64 | 21.53 | 1.47 |
| 161 | 40.90 | 132.44 | 46.68 | 26.82 | -4.82 |
| 299 | 25.32 | 137.65 | 47.79 | 21.18 | 5.82 |
| 159 | 35.06 | 144.69 | 49.50 | 26.47 | 11.53 |
| 36 | 78.53 | 143.11 | 49.91 | 38.32 | 5.68 |
| 101 | 42.85 | 160.92 | 52.05 | 29.07 | 7.93 |
| 225 | 50.64 | 159.19 | 52.16 | 31.70 | 15.30 |
| 45 | 42.85 | 158.73 | 52.28 | 29.98 | 7.02 |
| 138 | 19.48 | 161.55 | 52.38 | 21.31 | -0.31 |
| 227 | 35.06 | 180.82 | 54.31 | 25.86 | 8.14 |
| 157 | 52.62 | 172.30 | 54.46 | 33.03 | -2.03 |
| 237 | 82.25 | 178.66 | 54.75 | 38.96 | 0.04 |
| 203 | 31.16 | 179.64 | 55.21 | 26.95 | -0.95 |
| 177 | 78.53 | 180.78 | 55.41 | 38.69 | 1.31 |
| 62 | 33.11 | 183.33 | 56.11 | 28.36 | 6.64 |
| 8 | 19.48 | 189.83 | 56.94 | 23.71 | 17.29 |
| 68 | 46.74 | 190.73 | 57.37 | 32.60 | 7.40 |
| 202 | 50.64 | 221.68 | 60.41 | 32.59 | 14.41 |

A, N=47 selected from Hattis dataset (Hattis 1981)

TABLE S2B: Predictions from original Leggett model excluded in Figure 2, N=11

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| ID | Derived background uptake (µg/day) | Derived uptake during employment (µg/day) | Predicted pre-strike BLL (µg/dL) | Predicted post-strike BLL (µg/dL) | Measure-predict BLL (µg/dL) |
| 199 | 35.06 | 235.87 | 61.92 | 28.49 | 17.51 |
| 35 | 48.69 | 224.02 | 61.96 | 34.64 | -5.64 |
| 55 | 68.04 | 237.39 | 63.29 | 38.85 | 23.15 |
| 178 | 21.42 | 261.91 | 65.06 | 25.66 | 10.34 |
| 265 | 40.90 | 262.95 | 66.05 | 33.30 | 4.70 |
| 32 | 23.37 | 298.78 | 67.73 | 24.17 | 21.83 |
| 127 | 37.00 | 287.34 | 68.17 | 32.21 | -3.21 |
| 181 | 48.69 | 294.34 | 69.57 | 36.90 | -1.90 |
| 94 | 29.21 | 341.07 | 71.58 | 27.70 | 3.30 |
| 57 | 25.32 | 361.27 | 73.29 | 27.22 | 14.78 |
| 300 | 19.48 | 421.11 | 77.76 | 27.12 | 4.88 |

TABLE S2C: Predictions from adjusted Leggett model included in Figure 2A

| ID | Derived background uptake (µg/day) | Derived uptake during employment (µg/day) | Predicted pre-strike BLL (µg/dL) | Predicted post-strike BLL (µg/dL) | Measure-predict BLL (µg/dL) |
| --- | --- | --- | --- | --- | --- |
| 34 | 27.37 | 52.43 | 26.93 | 20.42 | -0.42 |
| 5 | 15.44 | 65.44 | 30.62 | 18.09 | -1.09 |
| 73 | 34.54 | 72.25 | 32.32 | 24.21 | 6.79 |
| 218 | 21.03 | 82.48 | 34.20 | 20.90 | 2.10 |
| 27 | 34.54 | 79.65 | 34.24 | 25.03 | 6.97 |
| 15 | 13.72 | 85.76 | 35.50 | 19.80 | -9.80 |
| 47 | 45.64 | 87.41 | 35.99 | 28.29 | 0.71 |
| 226 | 13.72 | 91.68 | 36.65 | 20.27 | 12.73 |
| 23 | 13.72 | 94.84 | 37.39 | 20.75 | -10.75 |
| 14 | 34.54 | 94.81 | 37.48 | 26.32 | 1.68 |
| 106 | 27.37 | 98.38 | 37.91 | 24.52 | -0.52 |
| 88 | 21.03 | 98.36 | 37.91 | 22.88 | 3.12 |
| 6 | 21.03 | 100.06 | 38.32 | 23.15 | 12.85 |
| 474 | 27.37 | 101.84 | 38.61 | 24.87 | 6.13 |
| 191 | 32.05 | 105.72 | 39.17 | 26.13 | 4.87 |
| 39 | 19.09 | 105.65 | 39.48 | 23.32 | -3.32 |
| 33 | 37.14 | 108.86 | 40.12 | 28.03 | -4.03 |
| 188 | 45.64 | 115.34 | 41.19 | 30.23 | 8.77 |
| 257 | 83.15 | 118.57 | 41.80 | 37.03 | -1.03 |
| 286 | 17.22 | 120.86 | 41.94 | 23.97 | 4.03 |
| 158 | 51.93 | 123.85 | 42.61 | 32.05 | 3.95 |
| 63 | 34.54 | 125.12 | 42.61 | 28.39 | 5.61 |
| 67 | 29.66 | 124.78 | 42.73 | 27.55 | -1.55 |
| 91 | 25.17 | 135.83 | 42.95 | 25.44 | 7.56 |
| 288 | 55.16 | 129.97 | 43.49 | 32.95 | 7.05 |
| 221 | 34.54 | 133.33 | 43.95 | 29.13 | 9.87 |
| 54 | 83.15 | 133.34 | 44.15 | 37.85 | 0.15 |
| 108 | 78.60 | 133.70 | 44.19 | 37.18 | 2.82 |
| 115 | 78.60 | 146.93 | 46.02 | 37.84 | -2.84 |
| 161 | 37.14 | 156.63 | 46.88 | 30.86 | -8.86 |
| 59 | 19.09 | 154.39 | 46.89 | 27.42 | -4.42 |
| 299 | 19.09 | 164.62 | 48.01 | 27.91 | -0.91 |
| 159 | 29.66 | 178.89 | 49.77 | 31.28 | 6.72 |
| 36 | 87.92 | 181.34 | 50.19 | 40.73 | 3.27 |
| 101 | 39.86 | 205.19 | 52.33 | 34.42 | 2.58 |
| 225 | 51.93 | 205.16 | 52.47 | 36.60 | 10.40 |
| 45 | 39.86 | 205.65 | 52.59 | 34.84 | 2.16 |
| 138 | 13.72 | 207.31 | 52.68 | 30.04 | -9.04 |
| 227 | 29.66 | 236.99 | 54.61 | 33.45 | 0.55 |
| 157 | 55.16 | 230.54 | 54.79 | 38.40 | -7.40 |
| 237 | 92.90 | 240.14 | 55.05 | 42.87 | -3.87 |
| 203 | 25.17 | 240.74 | 55.56 | 34.11 | -8.11 |
| 177 | 87.92 | 245.06 | 55.74 | 42.84 | -2.84 |
| 62 | 27.37 | 251.30 | 56.48 | 35.27 | -0.27 |
| 8 | 13.72 | 262.84 | 57.33 | 33.59 | 7.41 |
| 68 | 45.64 | 268.46 | 57.78 | 38.91 | 1.09 |
| 202 | 51.93 | 324.85 | 60.85 | 41.03 | 5.97 |

A, ID, subject identification, N=47 subjects from Hattis dataset included in the initial analysis

TABLE S2D: Predictions from adjusted Leggett model excluded in Figure 2

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| ID | Derived background uptake (µg/day) | Derived uptake during employment (µg/day) | Predicted pre-strike BLL (µg/dL) | Predicted post-strike BLL (µg/dL) | Measure-predict BLL (µg/dL) |
| 199 | 29.66 | 354.09 | 62.42 | 39.17 | 6.83 |
| 35 | 48.71 | 344.13 | 62.48 | 42.53 | -13.53 |
| 55 | 74.25 | 372.72 | 63.84 | 46.04 | 15.96 |
| 178 | 15.44 | 419.60 | 65.69 | 40.34 | -4.34 |
| 265 | 37.14 | 437.32 | 66.72 | 44.34 | -6.34 |
| 32 | 17.23 | 518.59 | 68.48 | 41.67 | 4.33 |
| 127 | 32.05 | 500.77 | 68.95 | 45.50 | -16.50 |
| 181 | 48.71 | 539.76 | 70.44 | 48.81 | -13.81 |
| 94 | 23.06 | 666.03 | 72.62 | 46.26 | -15.26 |
| 57 | 19.09 | 741.99 | 74.46 | 47.97 | -5.97 |
| 300 | 13.72 | 1023.80 | 79.47 | 53.40 | -21.40 |

A, N=11 subjects from the Hattis dataset included in second analysis (see Figure S1)

Table S3a: Volumes and ratios used in analyses shown in Figure 3

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Constant** | **Parameter** | **Unit** | **Values used in analyses (original, adjusted)** | **Reference** |
| Hematocrit | HCT | % | 0.45, 0.38 (A) | (Billett 1990; Mayo Clinic 2019) |
| Maximum RBC concentration(B) | S | Micrograms lead/deciliter RBC | 350, 270 | (Leggett 1993; O'Flaherty 2000) |
| Minimum RBC concentrationB | T | Micrograms lead/deciliter RBC | 60, 0 | (Leggett 1993; Marcus 1985, O’Flaherty 1993) |
| Blood volume | BV | deciliters | 53, 54.2(C) | (Davy and Seals 1994; ICRP 1975.; Leggett and Williams 1991; |
| Plasma volume | PV | deciliters | 29.15, 33.60(D) | (Billett 1990) |
| RBC volume | RBCV | deciliters | 24, 21(E) | (Billett 1990) |
| Urine volume | UV | liters | 1.75(F) | (Klahr 2018; Rose et al. 2015) |
| Fecal volume | FV | liters | 0.150(G) | (Cummings et al. 1992; Rose et al. 2015) |

A, depends on sex, some clinical references post slightly lower levels within the normal range;

B, concentration where lead starts (minimum) and stops (maximum) binding to red blood cells (RBC)

C, depends on muscularity BV= 0.67 to 0.75\*BW(body weight);

D, PV= BV\*(1-HCT);

E, RBCV= BV\*HCT;

F, UV=BW\*24/1000 urine output liters per day, depends on kidney function;

G FV= mean 149 (sd 95) to 243 (sd 130) grams as reported in (Rose et al. 2015), depends on calorie and fiber intake

Table S3b: Weights and ratios used in analyses shown in Figure 3

| **Constant** | **Parameter** | **Unit** | **Values (Equation)** | **Reference** |
| --- | --- | --- | --- | --- |
| Body weight | BW | kilograms | 73(H) | (ICRP 1975.) |
| Bone weight | WBONE | grams | 5212(I) | (Brown et al. 1997; O'Flaherty 2000) |
| Bone weight Conversion factor | CFb | gram/ gram | 1.5(J) | (Fleming et al. 1999) |
| Years past age 35 of trabecular bone loss | TAGELOSS | years | 30(K) | (O'Flaherty 2000) |
| Years past age 35 of cortical bone loss | CAGELOSS | years | 30(K) | (O'Flaherty 2000) |
| Trabecular bone resorption rate | TBLOSS | Decade (years/10) | 0.5012(K) | (O'Flaherty 2000) |
| Cortical bone resorption rate | CBLOSS | Decade (years/10) | 0.5012(K) | (O'Flaherty 2000) |
| Trabecular bone weight | Tbonewt | grams | 348.3 (L) | (Brown et al. 1997) |
| Cortical bone weight | Cbonewt | grams | 1393.2(M) | (Brown et al. 1997) |

H, no equation;

I, WBONE= 29\*(BW^1.21) marrow-free bone weight (g);

J, CFb = Bone mineral+collagen (ash+protein)/bone mineral alone (ash);

K,TAGELOSS and CAGELOSS =(65-35);constant used as approximate years of age-related bone loss in retired lead-workers, TBLOSS = 10^(-0.01\*TAGELOSS); assumed bone resorption rate multiplied by years past age 35 (10% per decade (e.g. 65-35=30 years or 3 decades); Tbone weight(g) for a 65 year-old 73 kg man;

L, Tbonewt =0.2\*WBONE\*TBLOSS/CFb;

M, Cbonewt=0.8\*WBONE\*TBLOSS/CFb

Table S4: Ratio of lead in the bones of retired smelter workers

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Subject ID** | **Trabecular 1994 A** | **Trabecular 1999** | **Cortical 1994** | **Cortical 1999** | **Ratio**  **T/C 1994B** | **Ratio**  **T/C 1999** |
| **1** | 142 | 156 | 75 | 74 | 1.89 | 2.11 |
| **2** | 116 | 166 | 79 | 80 | 1.47 | 2.08 |
| **3** | 67 | 68 | 34 | 38 | 1.97 | 1.79 |
| **4** | 122 | 113 | 56 | 71 | 2.18 | 1.59 |
| **5** | 144 | 163 | 81 | 88 | 1.78 | 1.85 |
| **6** | 223 | 251 | 99 | 118 | 2.25 | 2.13 |
| **7** | 197 | 232 | 116 | 105 | 1.70 | 2.21 |
| **8** | 87 | 109 | 65 | 58 | 1.34 | 1.88 |
| **9** | 132 | 131 | 71 | 75 | 1.86 | 1.75 |

A, Mean (µg/g bone mineral) by bone type and year; B, T=trabecular bone, C=Cortical bone; data in columns 1 – 5 as reported by Nie et al. (Nie et al. 2005)

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