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Modeling of Blood Lead Levels in Astronauts Exposed to Lead from Microgravity-Accelerated Bone Loss

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Introduction: Human exposure to lead has been associated with toxicity to multiple organ systems. Studies of various population groups with relatively low blood lead concentrations (<10 µg/dL) have indicated associations of blood lead level with lower cognitive test scores in children, later onset of puberty in girls, and increased blood pressure and cardiovascular mortality rates in adults. Cognitive effects are considered by regulatory agencies to be the most sensitive endpoint at low doses. Although ~95% of the body burden of lead is stored in the bones, the adverse effects of lead correlate with the concentration of lead in the blood better than with that in the bones. NASA has found that prolonged exposure to microgravity during spaceflight results in a significant loss of bone minerals, the extent of which varies from individual to individual and from bone to bone, but generally averages about 0.5% per month. During such bone loss, lead that had been stored in bones would be released along with calcium. The effects on the concentration of lead in the blood (PbB) of various concentrations of lead in drinking water (PbW) and of lead released from bones due to accelerated osteoporosis in microgravity, as well as changes in exposure to environmental lead before, during, and after spaceflight were evaluated using a physiologically based pharmacokinetic (PBPK) model that incorporated exposure to environmental lead both on earth and in flight and included temporarily increased rates of osteoporosis during spaceflight.

Materials and Methods: A recently published PBPK model (Garcia, Tsuji, and Hays, 2003) of the effects on in-flight PbB values of lead from spacecraft drinking water and lead released from bones due to microgravity-accelerated bone loss during long-duration missions was used to predict whether the typical U.S. astronaut would release the lead stored in bones at a rate high enough to cause PbB levels to rise to toxicologically significant values and thereby help set Spacecraft Water Exposure Guideline values for lead in drinking water. Input variables in the model runs included levels of historical exposures to environmental lead of 0, 0.05, or 0.25 µg/m^3 in workplace air from age 20 to age 35, rates of bone loss in microgravity of 0, 0.5, 1.0, 2.0 or 3.0 percent of total bone minerals per month, and lead in water (PbW) concentrations of 0, 0.6, 5, or 9 µg/L in drinking water consumed at a rate of 2.8 L/day. Note, however, that the higher rates of bone loss cannot credibly be sustained for 1000 days, but they are used here to predict worst-case PbB values that might be expected early in a long-duration spaceflight. The daily change in PbB values was calculated for average American astronauts having a predicted launch PbB of 1.7 µg/dL and for atypical individuals having PbBs at launch of either about 9 µg/dL or about 31 µg/dL due to previous lead exposures. For such worst-case scenarios, it was assumed for the purposes of the model that lifetime exposures to elevated environmental lead ceased five years before launch (i.e. during a period of astronaut training).

Results:

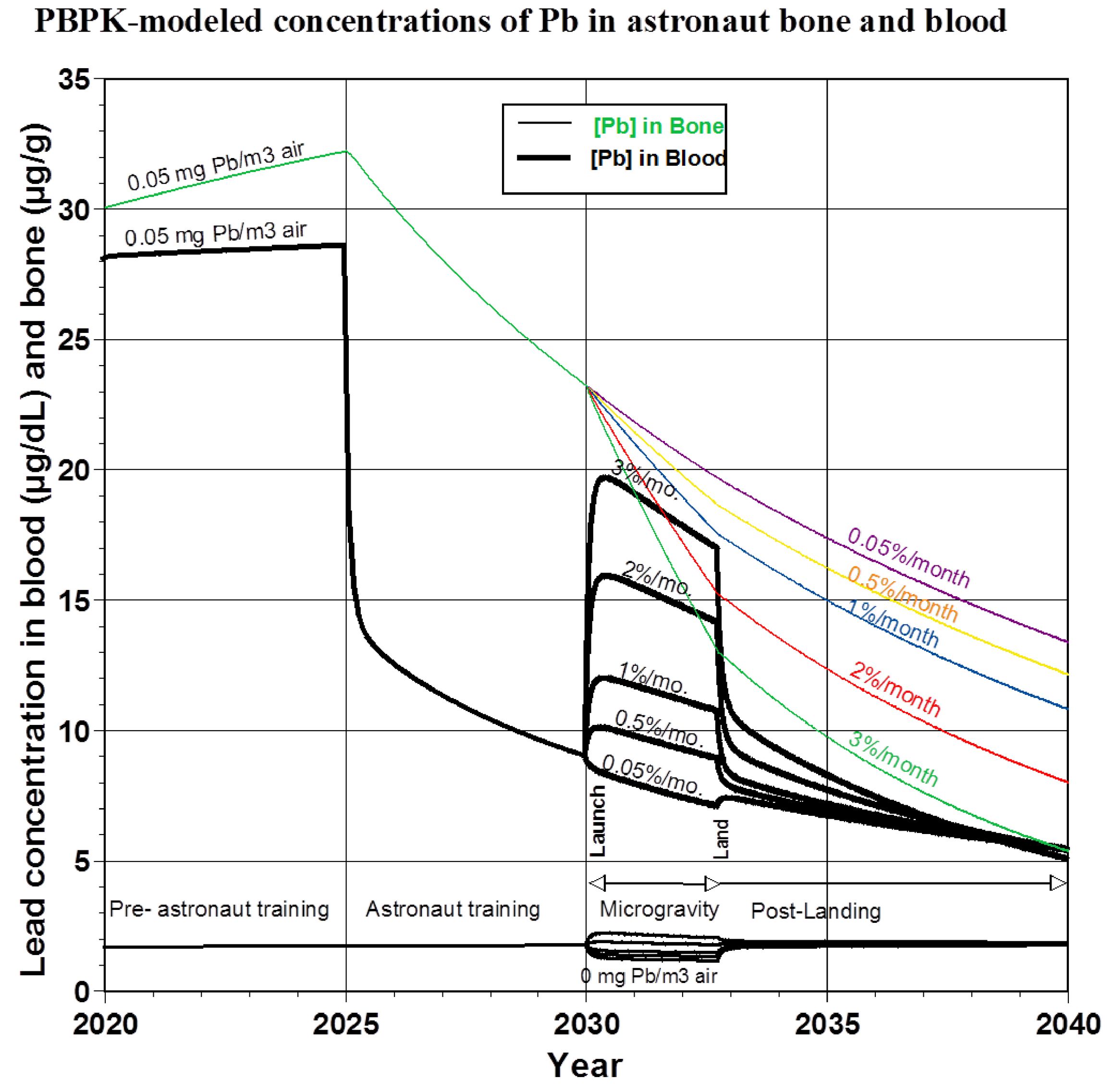

Fig. 1. *The effect of bone loss rate on PbB and bone Pb for individuals with low or high concentrations of lead in bone at launch. PBPK-modeled PbB values for the average American male born in 1990 and having a PbB of 1.7 µg/dL and a bone Pb concentration of 1.6 µg Pb/g are shown in the family of heavy lines below 5 µg/dL; for clarity, bone lead curves are not shown for this family. PBPK-modeled PbB (family of heavy lines above 5 µg/dL) and bone Pb concentrations (family of thin lines above 5 µg/dL) are shown for males born in 1990 and exposed to 0.05 mg Pb/m^3 air 8 hours/day, 5 days/week until age 35 and having, at launch in 2030, a PbB of 9 µg/dL and a bone Pb concentration of 23 µg Pb/g bone minerals. Data represent exposure to microgravity for 1000 days beginning in 2030 and modeled at various rates of loss of total body bone minerals. For the 1000-day period beginning at launch in 2030, each family of heavy lines, from the lowest to the highest, represents rates of bone loss of 0.05%, 0.5%, 1.0%, 2.0%, and 3.0% per month. The family of thin lines (bone Pb concentrations), from the lowest to the highest, represents rates of bone loss of 3%, 2%, 1%, 0.5%, and 0.05% per month.*

The modeled effects of microgravity on PbB values are shown in Fig. 1 for individuals experiencing bone mineral loss rates of about 1%/month. This rate was chosen based on published rates reported for crewmembers spending 4 -6 months on ISS. The PbB calculations were repeated for bone loss rates of 0.5, 2.0 and 3.0, yielding curves during spaceflight that are proportionally higher or lower than that of Fig. 1 (data not shown). The effects on individuals with normal, moderately elevated, or high levels of lead in their blood and bones at launch were examined by modeling historical exposures to 0, 0.05 and 0.25 µg Pb/m^3 in workplace air until age 35 (modeled start of astronaut training), which yielded at-launch PbBs at age 40 of 1.73, 8.97, and 31 µg/dL and bone lead concentrations of 1.59, 23.2, and 109 µg/g, respectively. For individuals exposed to lead in workplace air, PbBs decreased dramatically during the first two months immediately after removal from workplace exposure, then more gradually until launch. In all cases, PbB values changed relatively rapidly during the first two months after launch, then slowly decreased for the remainder of the time in microgravity. Because all the modeling data reported here are calculated point estimates of PbB values, no statistics could be calculated for these data.

During a 5-y period of exposure to only background levels of environmental lead (e.g. during astronaut training) immediately before launch, modeled PbB values and bone lead concentrations of individuals with a history of exposure to elevated levels of environmental lead decreased substantially from their modeled peak levels achieved immediately before this 5-y period, but were still elevated at a modeled launch in 2030 (Fig. 1). Note in Table 1 that the differences in modeled PbB values in such individuals during spaceflight that are attributable to PbW concentrations between 0.6 and 9 µg/L are less than 1 µg/dL, whereas much greater differences can be attributed to the lead released from stores in bones during spaceflight at a bone loss rate of 1%/month. A PbW of 9 µg/L corresponds to the highest spacecraft PbW that our PBPK model predicts would not increase PbBs in microgravity for the average American astronaut losing 1% bone/month and consuming 2.8 L water/day, compared to their pre-launch PbB values.

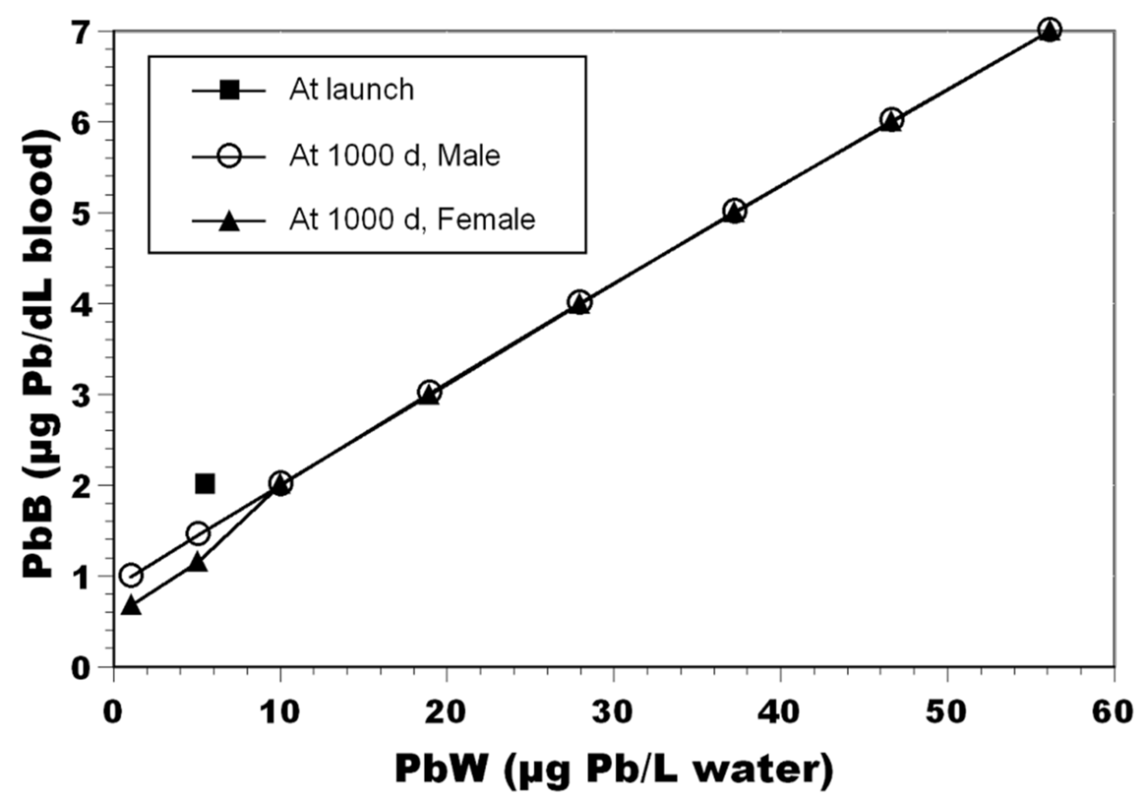

Fig. 2. *The effects of in-flight PbW concentrations on PbB after 1000 days in microgravity.*

The model predicts that in 2030 (the earliest potential launch date for a long-duration mission), the average American astronaut would have a PbB of 1.7 µg/dL at launch and that, while in microgravity, PbB levels would decrease at PbW values less than about 9 µg/L (Figure 2), because of reduced exposure within spacecraft to environmental lead. Astronauts with high concentrations of lead stored in bones could experience increases in in-flight PbB due to microgravity-accelerated release of lead from bones. While the resultant in-flight PbBs would depend on their pre-flight bone lead levels, their PbBs will not be significantly further elevated (<1 µg/dL) by consuming water with a PbW of ≤9 µg /L (Table 1).

Figure 2 illustrates the effect on PbB of various concentrations of lead in drinking water (assuming 2.8L/day consumption rate) after 1000 days in microgravity. At PbW concentrations <9 µg/L, and at an average bone loss rate of 0.5%/month, PbB values in microgravity are calculated to be less than those on earth (filled square), due to the assumption that there is negligible Pb in the air in spacecraft. At PbW concentrations > 10 µg/L, there is negligible difference in calculated PbB values between men and women. By evaluating various concentrations of PbW (Fig. 2), our model predicts that PbW > ~9 µg/L consumed in microgravity will cause PbB levels to exceed pre-launch PbB levels for the average American astronaut. Current levels of lead in ISS drinking water (0.6 µg/L average) are predicted to result in PbB values in microgravity that are lower than pre-launch values for the large majority of American astronauts.

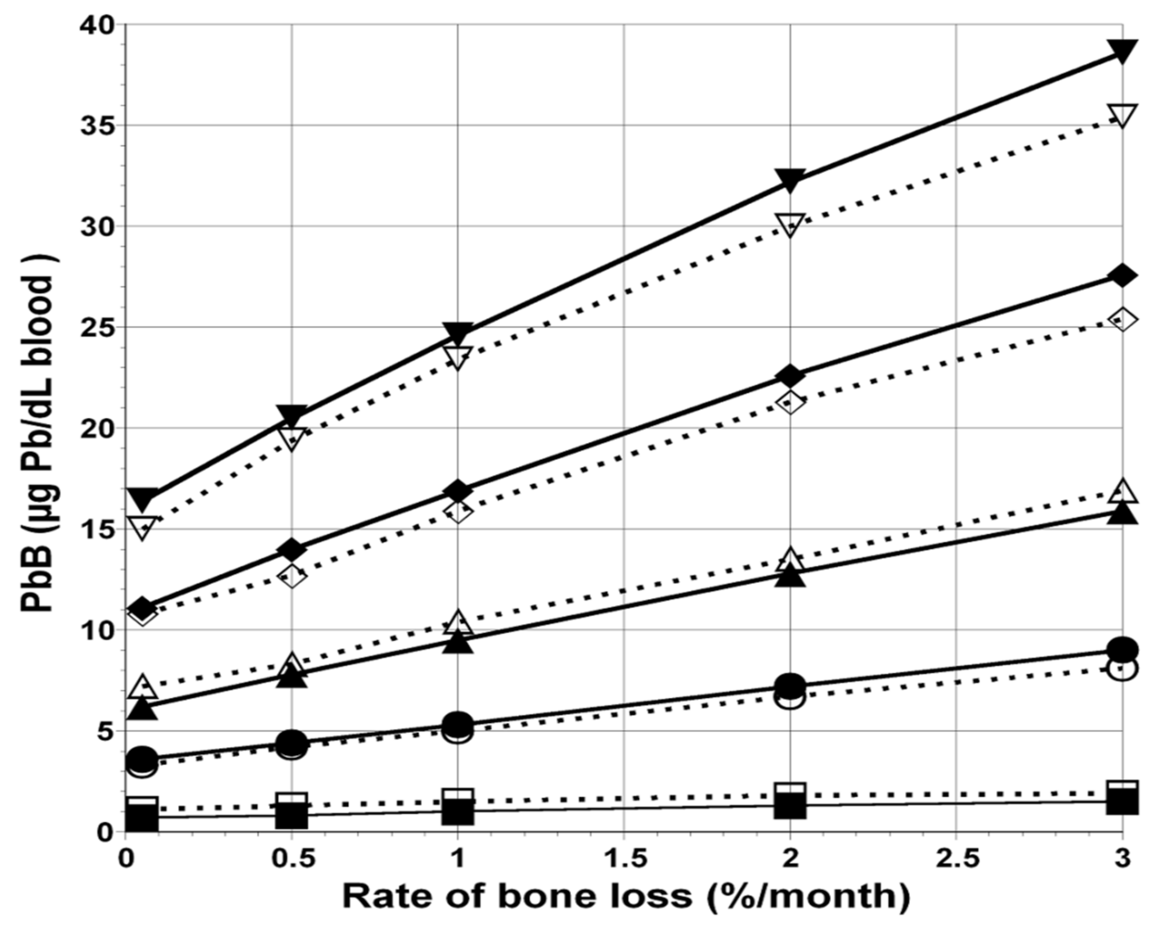

Fig. 3. *The effect of bone loss rate and bone lead concentration on PbB in modeled American astronauts. Open symbols represent PbB after 365 days of microgravity and filled symbols represent PbB after 1000 days of microgravity. (■, □) = 1.5 µg Pb/g bone minerals; (●, ○) = 9.9 µg Pb/g bone minerals; (▲, Δ) = 19.4 µg Pb/g bone minerals; (♦, ◊) = 38 µg Pb/g bone minerals; (▼, ▽) = 61 µg Pb/g bone minerals.*

Figure 3 illustrates that the contribution to PbB values of accelerated release of Pb from bones increases linearly with the rate of bone loss and that the slope of the lines increases at higher concentrations of Pb in bone. Also, note that even at a normal earthbound rate of bone loss (0.05% month), elevated concentrations of Pb stored in bones result in elevated predicted PbB values. The values in Figure 3 reflect only the effect of increased rates of bone loss, since these calculations did not use the reduced concentrations of Pb in spacecraft air or water compared to those on earth.

Table I. The effects of PbB at launch, PbW, and rate of bone loss on maximum inflight PbB

Scenario				Maximum Inflight PbB (µg/dL)				
Initial Pb burdens at launch	PbB at Launch (µg/dL)	Bone Loss Rate (%/mo)	Microgravity -induced increase in PbB	PbB @ PbW = 0 µg/L	PbB @ PbW = 0.6 µg/L	PbB @ PbW 5 µg/L	PbB @ PbW = 9 µg/L	Increase in PbB @ PbW = 9 µg/L
Typical 2030 American	1.73	0.5	0	1.73	1.73	1.73	1.73	0
with low Pb exposures:	1.73	1	0	1.73	1.73	1.73	1.90	0
Launch Bone Pb = 1.6 µg/g	1.73	2	0	1.73	1.73	1.86	2.23	0.50
Launch PbB = 1.73 µg/dL	1.73	3	0.05	1.78	1.82	2.20	2.57	0.79
Individual with	8.97	0.5	0.73	9.70	9.74	10.07	10.37	0.67
moderate Pb exposure:	8.97	1	2.60	11.57	11.61	11.95	12.25	0.68
Launch Bone Pb = 23 µg/g	8.97	2	6.54	15.51	15.55	15.87	16.16	0.65
Launch PbB =8.97 µg/dL	8.97	3	10.32	19.29	19.33	19.63	19.90	0.61
Individual with a history	30.99	0.5	4.16	35.15	35.17	35.38	35.57	0.42
of clinical lead poisoning:	31.00	1	9.40	40.40	40.43	40.62	40.79	0.39
Launch Bone Pb = 109 µg/g	30.99	2	19.12	50.11	50.13	50.29	50.42	0.31
Launch PbB = 31 µg/dL	31.00	3	27.08	58.08	58.10	58.22	58.33	0.25

Conclusions: Based on the model results that show a PbB at launch for typical Americans in 2030 to be 1.73 µg/dL and show a reduction in modeled in-flight PbBs at spacecraft PbWs < 9 µg Pb/L, SWEGs for 100 and 1000 day exposures were set at a PbW (9 µg Pb/L), which should not increase their in-flight PbB over the average pre-launch value for typical American astronauts (Table II). There is no credible mechanism for a brief, substantial increase in the concentration of lead in spacecraft drinking water, thus no SWEGs will be set for exposure durations less than 100 d.

Table II. Spacecraft Water Exposure Guidelines for Lead in Drinking Water

Exposure Duration (days)	SWEG (µg/L)
1	Not Set
10	Not Set
100	9
1000	9

Both the results of our PBPK modeling and the results of actual measurements in seven astronauts support the conclusion that, for most astronauts (i.e., those with low levels of Pb in blood and bones), long duration missions in microgravity should cause minimal toxicological concern for lead toxicity, even for 1000 days in microgravity. As long as environmental lead exposures are low, the accelerated bone loss in microgravity continues to reduce the amount of lead stored in bone and thereby reduces the PbB level as the mission progresses.

The PBPK model results show that the factor having the most influence on PbB values in microgravity is the concentration of lead stored in bone at the time of launch. At concentrations of lead in spacecraft drinking water up to 9 µg Pb/dL, most astronauts' PbB values are not predicted to increase in microgravity compared to their pre-launch values. For individuals who have greater than average amounts of lead stored in their bones, their PbBs will increase in microgravity to values that depend on the amount of stored Pb in their bones. In such individuals, the contribution to PbB levels of lead from drinking water will be negligible at PbW values of ≤9 µg Pb/L.

If average PbB values in Americans continue to decrease, future research may continue to discover adverse effects of lead at even lower PbB values and SWEG values may need further reduction to minimize the risk for such effects. In the meantime, average PbW concentrations on ISS are about an order of magnitude lower than the SWEGs being set, which should provide a margin of safety.