Toxicokinetics of Bone Lead
by Michael B. Rabinowitz*

This article discusses bone as a source of lead to the rest of the body and as a record of past lead exposure. Bone lead levels generally increase with age at rates dependent on the skeletal site and lead exposure. After occupational exposure, the slow decline in blood lead, a 5- to 19-year half-life, reflects the long skeletal half-life. Repeated measurements of bone lead demonstrate the slow elimination of lead from bone. Stable isotope ratios have revealed many details of skeletal uptake and subsequent release. The long turnover rates for compact bone are about 2% per year and 8% for spine. Turnover activity varies with age and health. Even though lead approximates calcium, strontium, barium, fluorine, and other bone seekers, the rates for each are different. A simple, two-pool (bone and blood) kinetic model is presented with proposed numerical values for the changes in bone lead levels that occur with changes in turnover rates.

Introduction
Toxicokinetics can be defined as the measuring and modeling of the movement of toxic substances, such as lead, within the body. Toxicokinetics should be distinguished from analytical chemistry, which addresses questions of how much lead is in a sample, such as bone. Toxicokinetics would try to provide answers to such questions as how long the lead has been in the bone, where the lead came from, and when and to where might it be going. The effects of lead are not addressed.

In this discussion of the movement of lead through the body and its chemical dynamics, I shall focus on bone and ask the following questions: a) What are some general characteristics of lead in bone? b) To what extent can the bone act as a source of lead to the rest of the body? c) How can bone lead levels be used to monitor past exposure? d) What are some immediate research needs or opportunities related to the kinetics of bone lead? The following is a simplified account of lead kinetics and some rough numerical estimates of the relationships between bone lead and blood lead levels.

What Are Some General Characteristics of Lead in Bone?
From the available surveys of autopsy and biopsy material some general trends are apparent (1). Bone lead levels increase with age at rates dependent on the skeletal site and lead exposure (2). Bilateral symmetry is present. Another set of studies has involved measuring the stable isotope abundance ratios with a mass spectrometer in biopsied bone and comparing it to blood lead isotope ratios. Some studies have made use of geographical variations in lead ores to examine the uptake and release of lead by the skeleton (3). Manton lived in South Africa, and his skeletal lead acquired the isotopic composition of that environment (3). After moving to Texas and being exposed to a new isotopic ratio, his blood did not immediately come to resemble his new exposure. Similar patterns were reported for his family members, including increased mobilization of skeletal lead during pregnancy. By following three adults over 9 years, including a bone biopsy, it was possible for Manton to describe the general long-term dynamics of lead in the body (3).

Other stable isotope studies have involved feeding five adult volunteers enriched, stable isotope tracer. This was done in a special metabolic balance ward by placing the men on constant low-lead diets, which were supplemented with enough lead to achieve their pre-study intake (4). After discontinuing the tracer intake, bone biopsies and long-term follow-up of blood lead levels revealed the skeletal uptake and subsequent release of the tracer.

Months after a lead-exposed person discontinues excessive intake and their blood lead has had an opportunity to decline, the subsequent decrease is very slow. Among 65 workers, the half-lives of lead in bone ranged from 5 to 19 years (6). The blood lead levels stay ele-
vated in response to lead leaving the skeleton. By ex-
aming the rates of decline in the lead levels, the sup-
pporting lead pool may be estimated. This was also de-
monstrated by the correlation of blood lead and bone lead among 27 active and 9 retired lead workers.
Among the active workers, the nonparametric \( r \) was 0.44, but among the retired workers, whose blood lead is supplied predominantly by their bone, the bone lead-blood lead correlation was 0.93 (6). Also, repeated mea-
surements of finger bone lead in 14 retired workers showed a very slow elimination, with about a 7-year half-life (7).

Experiments with short-lived radioactive lead have demonstrated the affinity of bone for lead. For exam-
ple, 3 weeks after lead dosage, 20% of the lead was in
the urine, and 20% was bound to the skeleton (8). Bone uptake of radio-calcium was more rapid than lead up-
take, in part because red blood cells have a stronger af-
finity for lead than for calcium.

A simple kinetic model of lead in the body consists of
only two pools (Fig. 1). Lead in the body is either in the
blood (or in equilibrium with it) or in the skeleton, where it is bound and less able to exchange. Within
each pool, rapid and complete equilibrium is assumed.
It is possible to obtain the sizes and exchange rates of
these pools from the blood tracer data. Estimated val-
ues are shown in Table 1.

These models take the form of coupled differential
equations whose solutions are the sum of two exponen-
tial terms. Other models involving additional pools
have been proposed that divide the bone into labile and
deep pools (9). Also, the soft tissue has been made a sep-
parate pool apart from blood in other models (10). Mod-
els with varying rates of exposure and uptake for tooth
and bone lead have been proposed (11).

All the lead in bone is not in one well-mixed pool (12).
For example, some bone lead, as assessed with soft X-
rays of the tibia, is available to ethylene diaminetetra-
acetic acid (EDTA) chelation (13). Similarly, compari-
sions of EDTA chelation and iliac biopsies show the
availability of bone lead (14). Thus, a better approxima-
tion might involve a series of interconnected pools (Fig.
2). The inability of chelation to remove appreciable pro-
portions of bone lead argues that some is buried
and unavailable for exchange. With the passage of years
and the turnover and remodeling of bone by oste-
activity, buried lead may become available again.

A recent report involving laser microbeam mass
analysis and electron microprobe X-ray analysis of se-
quential needle biopsies of a poisoned woman subject
has demonstrated the localized distribution of lead in
bone (15). The bone marrow cell nuclei showed very
high concentrations. Even after chelation considerable
lead remains in the organic portion.

To fully understand bone release rates of lead, some
knowledge of bone turnover rates would be useful.
Even though lead approximates calcium, radium, stron-
tium, fluorine, and other bone-seeking elements, the
actual numerical rates of bone release for each element
are somewhat different (16). In the case of fluorine,
which replaces the OH of the apatite, bone stores can
be rapidly exchanged. The turnover rate of the bone
mineral can be a rate-limiting step for elements that
are very tightly bound to apatite. This explains the in-
ability of chelating agents to lower bone pools of bone
seeking elements and their limited ability if the chel-
ant is administered shortly after exposure (17). Once
the lead has penetrated the crystal surface, it becomes
firmly buried and must await osteoclastic turnover,
leading to the multipool bone model described earlier
in Figure 2.

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these pools from the blood tracer data. Estimated val-
ues are shown in Table 1.

| Parameter         | Blood pool | Bone pool |
|-------------------|------------|-----------|
| Mean life         | 1 month    | 10–30 years |
| Lead concentration| 10 μg/dl 0.1 ppm | 5 ppm |
| Pool mass         | 10 kg blood, marrow, liver | 5 kg bone, kidney, etc. |
| Lead mass         | 0.5–1 mg | 25–750 mg |

![Figure 1. Simplified two-pool kinetic model.](image)

![Figure 2. Multiple bone pool kinetic model.](image)
Mathematical attempts to describe these series of connected pools are not simple (18). These longer term aspects of blood lead in response to uptake and release of bone lead are well described by a power function. For example, a series of exponential terms or a Bessel function can describe the residence times of lead in bone (19). It is tempting to relate slow and slower bone pools, corresponding to different terms in the power function, with specific gross anatomical locations such as long bone or trabecular or ivory bone. I suspect any cubic centimeter of skeleton will contain some of each kind of bone in varying amounts. Deep and very deep bone pools may also spatially coexist more closely, separated by their locations on a mineral crystal, superficial or internal.

The actual turnover rates of compact human bone can be estimated by the osteon formation rate, which can be observed microscopically in dated bone (20). The osteon count is proportional to age. Another histological method involves measuring the fraction of compact bone that is lamellar or contains neither osteon nor non-Haversian vascular canals. Both approaches give turnover rates for bones of about 2% per year for the femur, tibia, and fibula. Calculated turnover rates, employing osteon counts, for specific bones have been tabulated ranging from the tibia and skull, which average less than 2%, to 8.3% for the spine. There is also variation in turnover rates by age. During the first year rates are very high, 85%, but fall near 7% in the twenties and 2% in the thirties. Rates apparently increase again to over 4% after 60 years.

To What Extent Can the Bone Act As a Source of Lead to the Rest of the Body?

Rather than review examples of lead poisoning (21) and of increased blood lead levels that came from bone lead stores (22), I offer this somewhat hypothetical and simplistic approach to quantifying bone as a source.

Consider the simple two-pool model (Fig. 1) of blood and bone. What is the relative amount of lead in blood for a given amount of lead in bone? This depends on the turnover rates of each pool. For example, the amount of lead in the bone pool can be plotted against the turnover rate of the bone pool (Fig. 3). Each line represents points of equal lead release by bone. For example, if the bone turnover half-life is 35 years and the person has 200 mg of bone lead (point A), then each day the bone releases 11 mg of lead into the blood. The difference in blood lead levels associated with that release is about 3 

mg/dL. However, for the same person with the same size bone lead pool, in the normal course of aging, bone turnover rates accelerate to a 15-year half-life. Then 25 mg/day would be released by the bone, thereby increasing blood lead by about 7 mg/dL (point B). Point C represents a further acceleration in bone turnover in response to disease state. Points A′, B′, and C′ represent a person with a greater body store of lead and subsequently greater changes in blood lead from changes in bone turnover.

FIGURE 3. Plot of the amount of lead in the bone pool against the turnover rate of the bone pool. Each line represents points of equal lead release by bone. For example, if the bone turnover half-life is 35 years and the person has 200 mg of bone lead (point A), then each day the bone releases 11 mg of lead into the blood. The difference in blood lead levels associated with that release is about 3 mg/dL. However, for the same person with the same size bone lead pool, in the normal course of aging, bone turnover rates accelerate to a 15-year half-life. Then 25 mg/day would be released by the bone, thereby increasing blood lead by about 7 mg/dL (point B). Point C represents a further acceleration in bone turnover in response to disease state. Points A′, B′, and C′ represent a person with a greater body store of lead and subsequently greater changes in blood lead from changes in bone turnover.

Expressed algebraically, if C is the change in daily bone lead output (in units of mg/day) from a change in bone lead turnover rates, R1 is the initial and R2 is the second rate (units of 1/day), and S is the skeletal pool lead mass (mg), then 

C = S × (R2 - R1).

After several months, blood lead levels achieve a new and higher steady-state value with this change in bone lead output. The change in blood lead, B (mg/dL) associated with a change in bone flux C, where RB is the blood pool turnover rate (in units of 1/day), about a month, and M is the mass of the bone pool expressed as a volume, which includes the blood and other tissues which rapidly equilibrate with blood, about 10 L, then B = 

C × M × RB.

Considering bone as a source implies that blood lead

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**Kinetics of Bone Lead**

**Figure 3.** Plot of the amount of lead in the bone pool against the turnover rate of the bone pool. Each line represents points of equal lead release by bone. For example, if the bone turnover half-life is 35 years and the person has 200 mg of bone lead (point A), then each day the bone releases 11 mg of lead into the blood. The difference in blood lead levels associated with that release is about 3 mg/dL. However, for the same person with the same size bone lead pool, in the normal course of aging, bone turnover rates accelerate to a 15-year half-life. Then 25 mg/day would be released by the bone, thereby increasing blood lead by about 7 mg/dL (point B). Point C represents a further acceleration in bone turnover in response to disease state. Points A', B', and C' represent a person with a greater body store of lead and subsequently greater changes in blood lead from changes in bone turnover.
might be a better marker of current bone output than a single measurement of bone itself. Bone measurements are markers of potential output. This underlines the value of research on the availability of bone lead to ascertain transfer rates. So far we have considered the skeletal mass to remain constant in size but to turnover and exchange lead. However, the skeletal compartments can also become larger or smaller. The calcium mineral mass may grow during development, aging or, for example, in response to ergocalciferol (23). Changes of 2% in skeletal density can be resolved with current techniques. More complete models of lead kinetics might include changes in pool size.

How Can Bone Lead Levels Be Used As a Monitor of Past Exposure or Current Risk?

Bone accumulates lead and provides a marker of past exposure. Although it would be useful to distinguish between two extreme types of exposure, a single high dose or a long-term, lower dose, we are not yet able to do so. With acute exposure, a high blood lead level is achieved for a short time. If one of lead's toxic effects were dose related in a threshold fashion, the lead in blood would be high enough to damage some target organ, such as the brain or kidney. In the case of chronic exposure, elevated blood lead levels might persist for years, with large amounts of lead deposited in bone. Perhaps some of lead's toxic effects are proportional to cumulative exposure or smaller. The calcium mineral mass was taken each way, acutely or chronically, I would expect a greater bone signal from those chronically exposed, even though their blood lead might not have achieved as high a peak. So chronic or acute exposure to lead would be indistinguishable by bone assay but with markedly different physiological effects.

Lead deposited in bones can become less available with time. A sampling method that can discriminate old versus more newly deposited lead would be useful. Investigations among lead workers in Sweden have addressed this issue of multiple measures of bone lead (24). Schutz et al. found chelatable lead to correlate with blood lead (n = 37, r = 0.53) and with trabecular, vertebral bone lead (n = 23, r = 0.81) (24). However, chelatable lead correlated poorly with finger bone lead measured with K X-rays (n = 23, r = -0.21) (24). This confirms the existence of an inert, nonchelatable pool and a more labile pool in bone.

What Are the Most Immediate Research Needs or Opportunities Related to the Kinetics of Bone Lead?

More should be learned about the factors affecting lead turnover in bone. Lead and calcium are similar, so changes in calcium metabolism affect lead movement within the body. Blood lead level increases secondarily to changes in calcium status that have been seen in osteoporosis, lactation, and aging. However, lead, calcium, and other variables are interdependent. calcium levels might be mobilized from bone to a greater extent than is calcium. In other words, we need more information about the turnover rates of lead in human bone and in their slower than in the case for calcium. How much of the bone lead mass is involved in in order, slow, or labile metabolic pools? Using various strength X-rays and using different anatomical sites, past exposure can be reconstructed.

To what extent does lead in bone become progressively less available over the passage of years? Consider the sequence of a substantial exposure resulting in the accumulation of bone stores of lead followed by 20 years of much lower exposure with lowering of blood lead, some bone stores staying elevated, and some metabolic mobilization of bone stores. Does the amount of mobilized bone lead decrease with the amount of time available for deeper burial by bone turnover? Does the freshness of exposure affect bone availability with a greater lead available from current exposure than exposure of a few years earlier? The question of what extent lead becomes progressively more deeply buried or available with time.

Another more direct method might employ stable isotope tracer methods to distinguish past versus recently absorbed lead, but it would require subjects who have moved from one area to another. Using an extreme case as an ideal example, leads from Port Pirie, Australia (206/204 = 16.1) and Barberton, South Africa (206/204 = 12.5) are very different from typical common lead (206/204 = 18-19) or Missouri lead (206/204 = 20-22). These ratios can be measured to finer than ± 0.005 with a dedicated, solid source mass spectrometer. If a woman grew from birth to maturity at one such place, then moved and after a delay of a few years became a mother, sequential lead isotope measurements would indicate how much of the lead in her blood is from current exposure and how much is from bone stores. This would indicate the extent to which pregnancy mobilized stored lead as distinct from changes in absorption or excretion rates.
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