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by Skerfving S, Nilsson U, Schutz A, Gerhardsson L

Affiliation: Department of Occupational and Environmental Medicine, University Hospital, Lund, Sweden.

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Biological monitoring of inorganic lead

by Staffan Skerfving, MD,[1] Ulf Nilsson, BSc,[2] Andrejs Schütz, PhD,[1] Lars Gerhardsson, MD[1]

SKERFVING S, NILSSON U, SCHÜTZ A, GERHARDSSON L. Biological monitoring of inorganic lead. *Scand J Work Environ Health* 1993;19 suppl 1:59—64. In exposure and risk evaluation, monitoring lead biologically has several advantages over technical exposure assessment. Traditionally, the concentration in blood (B-Pb) has been widely used. However, the erythrocytes tend to become saturated, and this phenomenon causes a nonlinear relationship between B-Pb and uptake and between metabolic and toxic effects and B-Pb. Recently, several techniques for determining lead in finger bone, tibia, or calcaneus in vivo by X-ray fluorescence have become available. Bone lead reflects long-term exposure and should prove valuable in epidemiologic studies. Mobilization tests have been widely used to monitor lead biologically. They mainly seem to reflect the lead in soft tissues and may not be an index of total body burden, most of which is in the skeleton. It thus seems that, at least in adults, mobilization tests do not provide more information than traditional lead determinations in blood and urine. A metabolic model for lead in humans is presented.

Key terms: biological monitoring, blood, bone, chelating agent, lead, urine, X-ray fluorescence.

Occupational exposure to lead is a widespread problem in industry. In addition, in many countries, there is considerable exposure of the general population, mainly from paint, water, gasoline, and industrial emissions (1—4). After absorption, the metal is transferred mainly to the skeleton, which accounts for about 90% of the body burden. Organs often considered to be critical are the central nervous system and the kidney. Slight effects occur at the exposures accepted in most countries. In recent years, much attention has been focused on possible effects on fetuses and infants exposed at the levels present in the general environment in several areas. The effects of low-level exposure on the cardiovascular system have also been considered. There is a need for reliable indices of low-level long-term exposure and risk.

Exposure evaluation by means of biological samples has several advantages; for example, it takes into account exposures from different sources and through different routes (5). This diversity is particularly important in the case of lead, since there may be simultaneous exposure to different sources resulting in both inhalation and ingestion (3, 4, 6).

Moreover, biological monitoring takes into account interindividual differences in the metabolism of toxic agents, which may cause differences in risk at similar exposure intensities (2). Furthermore, toxic effects may be the consequence of both recent and earlier exposure, as the result of accumulation in the body up to a toxic level or of a chronic toxic effect. This possibility is taken into account by some of the methods available for the biological monitoring of lead, but not or only with difficulty if other methods of exposure monitoring are used.

However, biological monitoring does have a few definite drawbacks. Hence, to be able to interpret the results of biological monitoring, it is necessary, for example, to understand the metabolism of the agent.

Since comprehensive reviews on the biological monitoring of lead have recently been published (3, 4, 6), this paper focuses instead on a few specific areas, namely, limitations in the use of blood lead levels (B-Pb), in vivo determinations of lead in bone, and the significance of lead mobilization tests. Finally, a metabolic model for lead is described.

Blood lead levels

More than 95% of the B-Pb is contained in the erythrocytes (7). Lead in whole blood is currently the most widely used index of lead exposure and risk (3, 4, 6). It has many advantages. Thus, samples are easy to obtain and the analysis is straightforward for experienced laboratories. But there are several limitations, which must be carefully considered when the results of an analysis for B-Pb are interpreted.

One problem is the nonlinear relationship between B-Pb and lead exposure and uptake, for both inhalation and gastrointestinal exposure (4). Furthermore, there is also a nonlinear relationship between lead in media such as serum (7), urine (U-Pb) (figure 1) (8—10), and milk (11), on one hand, and B-Pb, on the other. Moreover, there are nonlinear relationships between different metabolic and toxic effects, such

[1] Department of Occupational and Environmental Medicine, University Hospital, Lund, Sweden.
[2] Department of Radiation Physics, Lund University, Malmö General Hospital, Malmö, Sweden.

Reprint requests to: Dr S Skerfving, Department of Occupational and Environmental Medicine, University Hospital, S-221 85 Lund, Sweden

as those on the heme (figure 2) (12, 13) and nucleotide (3, 4, 6) synthesis, on one hand, and B-Pb, on the other.

The most probable explanation for the nonlinear relationship between B-Pb and both metabolic and toxic effects is a saturation of the erythrocytes. In light of the wide use of B-Pb, it is surprising that the binding conditions for lead in blood cells have not been more thoroughly investigated. However, it is bound mainly to hemoglobin and also, to an extent varying from one individual to another, to other proteins (14). There are thus several different binding sites of varying affinity for lead.

Both U-Pb (figure 1) and the blood concentration of zinc protoporphyrin (figure 2) vary with B-Pb. This variation may partly be due to an interindividual variation in the binding of lead in the erythrocytes.

B-Pb is therefore not a very good index of either exposure or effects, and it is a much more sensitive index of absolute changes in exposure at low exposure intensities (1) than at high ones. Furthermore, a high value of B-Pb is only a crude indicator of the risk of effects. Theoretically, other indices, such as levels in serum or plasma, would be more suitable. However, the levels are so low that problems with contamination and analysis would be unsurmountable.

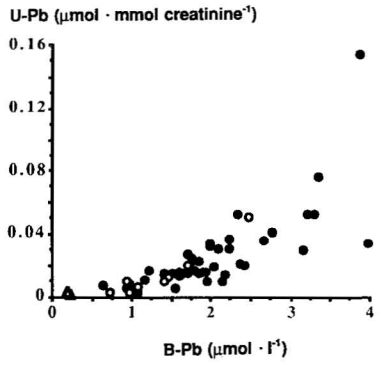

Figure 1. Relationship between the concentration of lead in urine (U-Pb) and blood (B-Pb). There was a closer correlation between lnU-Pb and B-Pb ($r = 0.84$, $P<0.001$) than between U-Pb and B-Pb ($r = 0.76$, $P<0.001$). Data taken from reference 8 (units recalculated, because of a systematic error of units in the original reference) and reference 10. (closed symbols = 40 active workers, open circles = 12 retired workers, open triangles = 2 occupationally unexposed referents)

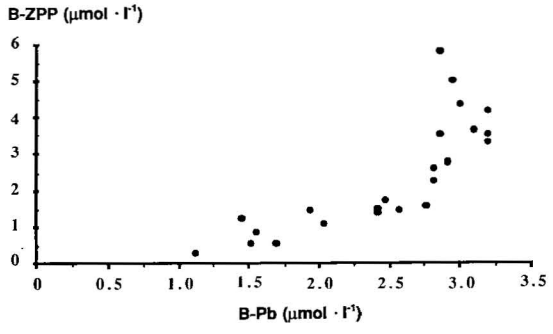

Figure 2. Relationship between blood levels of zinc protoporphyrin (B-ZPP) and lead (B-Pb), means for samples taken over a 4-month period, in 23 lead workers. Data taken from reference 12.

Another option is the U-Pb level. However, its determination would also cause problems, as the risk of contamination during sampling is higher than for B-Pb and the available information on the relationship between the U-Pb concentration and exposure or effects is much more limited. In addition, in low or moderate exposure, the lead concentrations are considerably lower in urine than in blood, and the low levels, together with the considerable variation in the urine sample matrix, complicate the lead determination. If it is used, the U-Pb level should be adjusted for dilution (by the use of density or the creatinine level).

Indices of disturbances of the heme metabolism have often been used for purposes of biological monitoring (3, 4, 6). However, neither are they fully satisfactory, since most of them display effects only at fairly high exposures, as compared with the exposure levels of greatest interest in the evaluation of the critical effects most relevant currently. An exception is the enzyme activity of delta-aminolevulinic acid dehydratase in blood, which begins to decline at very low B-Pb concentrations (13) and is totally inhibited at moderate levels; however, mainly due the decay in activity with storage time, it is difficult to use for practical reasons. The heme parameters also show considerable interindividual variation, and few exposure-response data are available.

It is therefore necessary, at least for the time being, to continue to use B-Pb, but careful account must be taken of its limitations.

B-Pb decreases after occupational lead exposure has ceased (2, 15). In a long-term (up to 18 years) follow-up of retired lead workers (16), there were indications of pronounced interindividual variation in kinetics so that the B-Pb can differ at the same exposure. This variation may — at least partly — be due to differences in the ratio between lead concentrations in erythrocytes and plasma.

The decay pattern can be fit to a three-compartment exponential model containing a fast phase with a half-time of one month, an intermediate phase with a half-time of about a year [which probably reflects trabecular bone (17)], and a slow pool with a half-time of 13 years (which reflects cortical bone) (16).

Bone lead levels

As already mentioned, lead accumulates in calcified tissues. Levels in shed deciduous teeth have been fairly widely used to assess lead exposure during the fetal period and infancy, especially in studies of cen-

tral nervous system effects (3, 4, 6). However, the method is not uncontroversial. Over the last 20 years, other methods of monitoring lead in calcified tissues have been developed, for example, the in vivo determination of lead in bone by X-ray fluorescence techniques (18, 19).

The results of the first method used to determine the lead content of skeleton in vivo were published by Ahlgren et al in 1976 (20). Since then, other X-ray fluorescence techniques and several applications have been reported (18, 19, 21—28). In principle, either a ^{57}cobalt (^{57}Co) or ^{109}cadmium (^{109}Cd) source is used to excite the lead, and the characteristic K X-rays of lead are measured. L X-rays can also be measured (eg, after excitation by ^{109}Cd of lead in the tibia). While the K techniques measure lead to a considerable depth in the bone, the L techniques mainly assess superficially located lead. Thus the results obtained by the two techniques may not be directly comparable.

We have used the ^{57}Co K technique for determining lead in finger phalanx (2, 8—10, 15—20, 29—31) and the ^{109}Cd K technique for measuring lead in tibia and calcaneus (10, 31—33).

In studies of smelter workers, the lead content of bone increased with increasing duration of employment (figure 3) (29, 31, 33) and time-integrated exposure, as estimated from measurements of B-Pb over time (19, 29, 31, 33). This finding shows that the lead content of bone is a valuable index of integrated exposure. The levels found in smelter workers were much higher than those in Swedish men without occupational exposure (1—3 $\mu g \cdot g^{-1}$) (16, 17). In smelter workers, there were significant associations between the levels at the different bone sites (18, 31, 33).

In active smelter workers, there was no association between blood and the lead concentrations of finger bone (29, 30). However, in retired workers, who had a much lower ongoing exposure, there was a significant correlation, a finding which shows that skeletal lead is an important source of "endogenous" exposure (29). In fact, in active workers with an average exposure time of 10 years, about half of the blood lead has been found to be associated with the skeletal pool. This occurrence has recently been confirmed (23).

After employment has ended, the lead concentration in bone decreases, as shown by repeated measurements of lead in finger bone (15). The phalanx contains mainly cortical (compact) bone, and to a less extent trabecular (spongy) bone. We have now followed retired workers for up to 18 years (16). They displayed an average biological half-time of 16 years, which shows the slow turnover of lead in bone. The decay pattern fit the previously mentioned slow component in the decrease of B-Pb after the end of exposure.

Skeletal lead should be a useful index of risk, especially for chronic effects of lead exposure. Little work has yet been done in this promising field. In a recent study of smelter workers, no association was found between tibia or calcaneus lead concentrations, on one hand, and renal function, on the other (table 1) (32). However, in a study of smelter workers with a higher lead exposure, there were indications of slight effects on the renal tubuli (34 and Tell et al, unpublished manuscript).

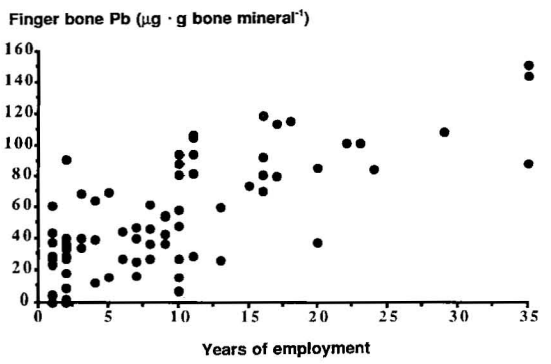

Figure 3. Relationship between lead (Pb) levels in finger bone and the duration of employment among 74 smelter workers (r_s = 0.68, P<0.001). Data from references 19 and 31.

Table 1. Kidney function (median values) in two populations of lead (Pb) smelter workers and their respective reference groups [U = urinary, β_2-MG = beta$_2$-microglobulin, NAG = N-acetylglucosaminidase, B-Pb = blood lead concentration (1 $\mu mol \cdot l^{-1} = 207\ \mu g \cdot l^{-1}$)]

Parameter	Smelter 1[a]		Smelter 2[b]	
	Workers (N = 80)	Referents (N = 20)	Workers (N = 70)	Referents (N = 30)
U-albumin (mg · mmol creatinine^{-1})	1.3**	1.0	0.7	1.1
U-β_2-MG ($\mu g \cdot$ mmol creatinine^{-1})	8.6	8.1	10	10
U-NAG (U · mmol creatinine^{-1})	0.20**	0.10	0.13	0.22
B-Pb ($\mu mol \cdot l^{-1}$)	1.60***	0.31	1.54***	0.20
Tibia Pb ($\mu g \cdot$ g bone mineral^{-1})	25***	9	13***	3

** P<0.01, *** P<0.001.
[a] Data from reference 34.
[b] Data from reference 32.

Mobilization tests

As an alternative to the measurement of lead in bone, mobilization tests have been used to estimate body burden. The tests involve administering a chelating agent and then determining the lead excreted in the urine (chelated lead) (3, 6, 8, 10).

Smelter workers were given penicillamine orally (8) or calcium disodium edetate intravenously (10), followed by quantitative urine collection for up to 24 h. There were close associations between chelated lead, on one hand, and both B-Pb and U-Pb before chelation, on the other (8, 10). However, while the

relationship with B-Pb was nonlinear, with a relatively larger increase in the U-Pb concentration with increasing B-Pb (probably explained by the aforementioned nonlinearity), that with U-Pb seemed to be linear (figure 4).

There was also an association, though less close, between chelated lead and the lead level in trabecular bone in the vertebrae (8), as measured in bone biopsies (17). A far less close association was seen between chelated lead and the levels in finger, tibia, or calcaneus (10). Thus the size of the cortical bone lead pool, which makes up most of the body burden, was only vaguely reflected by chelated lead. This conclusion is different from that arrived at by other authors, who used either L X-ray fluorescence techniques, and thus mainly determined the small pool of superficial subendosteal lead (27) (which is probably much more metabolically active) or K X-ray fluorescence techniques, which also assess more deeply situated lead (21, 28). However, they do not seem to have considered the relationship between the soft-tissue and bone pools, which depend on the relationship between recent and earlier exposures.

Mobilization tests thus probably mainly reflect the soft-tissue pool, but do not indicate the size of the compact-bone lead pool, which constitutes most of the body burden, while determinations of skeletal lead provide an index of long-term time-integrated exposure. Furthermore, as an index of the soft-tissue pool, which probably reflects the metabolically active and thus toxicologically interesting pool, chelated lead does not, at least for adults, offer a clear-cut advantage over B-Pb or U-Pb before chelation.

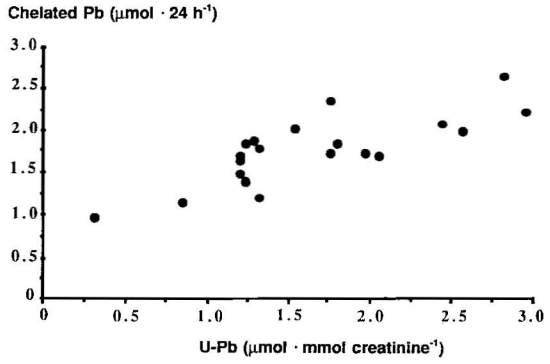

Figure 4. Relationship between lead excretion in urine 24 h after the infusion of 1 g of calcium disodium edetate (Chelated Pb) and urinary lead levels before chelation (U-Pb) in 20 lead smelter workers (r = 0.75, P<0.001). Data from reference 10.

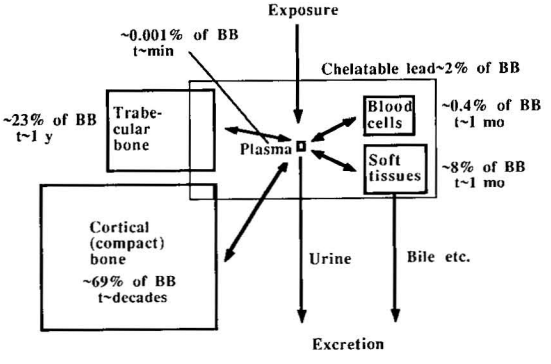

Figure 5. Metabolic model for inorganic lead in an adult man. The figures shown for the percentage of body burden in the different compartments are those corresponding to approximately steady state conditions (ie, the situation after regular exposure over long periods of time). The areas of the boxes are not proportional to the sizes of the compartments. "Chelatable lead" denotes the amount available for binding to a chelating agent in a mobilization test. Model based on data taken from references 7, 10, 16, 17, 34, 35, 37 and 40. (BB = total body burden, t = biological half-time, y = year, mo = month)

Metabolic model

On the basis of the results of the aforementioned studies of lead in blood and different bone sites, it has been possible to establish a metabolic model for lead (figure 5) (19, 34, 35). The model contains a central, tiny plasma pool, with rapid turnover; some data indicate that it has a half-time of only a few minutes (36). As has already been stated, the erythrocyte pool has a half-time of about one month (16). The other soft tissues probably have a similar turnover rate.

The skeleton accounts for the major part of the body burden (37) and contains two different compartments. Cortical bone constitutes most of the total marrow-free bone mass, the remainder being trabecular bone (38). Lead in trabecular bone has a faster turnover than that in cortical bone (17, 23, 31), the half-times being about a year and decades, respectively (16, 23).

The way that the body burden is distributed between the compartments varies between subjects with different exposure durations. For example, in recently employed lead workers, large amounts are present in blood and soft tissues, and eventually in trabecular bone. In contrast, in retired lead workers, the proportion present in cortical bone is higher.

The model refers to subjects in steady state. The distribution between the compartments is based on studies involving lead workers. Retired workers (exposed for an average of 29 years, ie, probably close to steady state when exposure ceased) had an average level in finger bone (cortical) of 83 $\mu g \cdot g$ wet weight^{-1} (17). Since the turnover of lead in trabecular bone is much faster than in cortical bone, their measured level in trabecular bone (19 $\mu g \cdot g$ wet weight^{-1}) cannot be used directly. The bone-mineral content is 58% in cortical bone and 19% in trabecular bone (39). If the lead level, at steady state, is proportional to the lead in cortical bone mineral, the

concentration in trabecular bone would be about 27 $\mu g \cdot g$ wet weight^{-1}. Therefore 4 kg of cortical bone would then contain 330 mg of lead, and 4 kg of trabecular bone would contain 110 mg of lead, for a total skeletal lead burden of about 440 mg. This value is similar to the 550 mg determined in autopsies of lead workers (many probably retired), who had a B-Pb of 0.77 $\mu mol \cdot l^{-1}$ (1 $\mu mol \cdot l^{-1} = 207$ mg $\cdot$ l^{-1}) and a soft-tissue lead content of 16 mg (37). The B-Pb in active lead workers (exposure time 11 years, ie, not yet in steady state) was 2.22 $\mu mol \cdot l^{-1}$ (17), corresponding to a total amount in blood (cells) of about 2 mg. By analogy with the dead workers, their other soft tissues should contain about 40 mg. At steady state, the total body burden should be about 480 mg. Plasma contains only a minor fraction of the whole amount of blood lead (7).

Lead available for chelation (chelatable lead) is probably present mainly in the soft tissues, but possibly also, to some extent, in a rapid bone pool. In active lead workers (employment time 13 years) with an average B-Pb of 2.37 $\mu mol \cdot l^{-1}$, the chelatable lead was about 5.5 mg (40). According to the previous discussion (17, 37), this value should correspond to a body burden of about 320 mg. Chelated lead (10) accounts for about 16% of the chelatable lead and about 0.3% of the body burden.

Similar models have recently been published by other authors (41, 42, 43).

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