

In vivo X-ray fluorescence measurements of cadmium and lead

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NILSSON U, SKERFVING S. In vivo X-ray fluorescence measurements of cadmium and lead. *Scand J Work Environ Health* 1993;19:54—8. Information about the body burden of a metal is important in the evaluation of both exposure and risk. In vivo methods for determining cadmium and lead have become available in the last 20 years. Thus cadmium in kidney can be assessed by neutron activation or X-ray fluorescence analysis. The X-ray fluorescence technique allows kidney cadmium determinations even in subjects without occupational exposure. The level reflects the burden, long-term exposure, and the risk of toxic effects. Furthermore, in vivo determination of lead in finger bone, tibia, or calcaneus by X-ray fluorescence indicates long-term exposure and should become a valuable tool in epidemiologic studies, especially of chronic effects.

Key terms: biological monitoring, bone, cadmium, kidney, lead, X-ray fluorescence.

Knowledge of the body content of a metal is useful in the assessment of exposure to the concerned metal and the associated risk. Exposure evaluation by means of biological samples has several advantages since it takes into account exposures from different sources and through different routes (1). Exposure over a long period can be estimated from the level in a body pool with a slow turnover rate. The first organ to suffer adverse toxic effects from exposure is often referred to as the critical organ, and it is obviously particularly valuable to be able to determine the concentration in that organ.

Metal levels in blood and urine have long been used for the biological monitoring of exposure and risk (1). However, blood and urine have certain limitations. Thus the levels of, for example, cadmium (2) or lead (3, 4) in blood do not, in a simple way, reflect either exposure or risk. Levels of cadmium in urine (5) can be an index of the kidney load, which constitutes a major part of the body burden. This possibility is of particular interest, since the kidney is the critical organ for cadmium exposure. However, not even in this case does the urinary level always adequately predict the concentration in the critical organ, the kidney (2).

As an alternative, various mobilization tests have been used to estimate body burden. In such tests, a chelating agent is administered, and the excretion of the metal in the urine is assessed, a method that has been widely used for lead (6, 7). However, mobili-

zation tests also have limitations; they may not reflect the body burden (3, 4, 6, 7).

Other methods have been developed over the last 20 years, for example, neutron activation and X-ray fluorescence analysis for the in vivo measurement of cadmium and lead levels in organs. These techniques are briefly discussed in this communication. In addition, in vivo assessment of mercury levels in bone has been reported (8). However, it is doubtful whether this procedure is feasible, even in subjects occupationally exposed to elemental mercury vapor or to methylmercury as a result of the consumption of contaminated fish (9). Mercury determinations will therefore not be discussed further.

In vivo determination of cadmium

Cadmium exposure and effects

Cadmium is a problem in many occupational settings and, in some areas of the world, also in the general environment (2). After absorption, the metal is bound to metallothionein in the liver and deposited in the kidney, where the turnover is very slow, with a biological half-time of decades. For long-term exposure, the critical organ is the kidney. The effects of cadmium have long been recognized in occupational exposure and in populations with extremely high exposure through food. Recently, slight effects have been reported in sections of the general population not subject to any particular exposure (10). As a result, interest has been focused on much lower exposures.

Methods

During the 1970s and 1980s, several groups used neutron activation analysis to measure cadmium in liver and total kidney (11—17). The method is based

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on the fact that neutrons are absorbed by cadmium, causing emission of gamma rays of characteristic energy. Suitably calibrated measurement of these gamma rays enables the amount of cadmium in the organ to be determined.

In 1981, Ahlgren & Mattsson (18) showed that it was possible to determine cadmium *in vivo* in kidney cortex by means of an X-ray fluorescence technique in which a ^{241}Am source was used to produce the characteristic K X-rays of cadmium. Since then, the X-ray fluorescence technique has been developed and improved. A partly plane-polarized X-ray spectrum is now used for excitation, the detector collimator has been modified, and a silicon(lithium) detector is used (figure 1) (19–21). The X-ray fluorescence technique has several advantages. It has a significantly lower effective dose equivalent than neutron activation analysis, the detection limit is better or comparable (22), and the measurements are restricted to the toxicologically relevant part of the kidney, the cortex. The duration of measurement is 30 min. A drawback of the X-ray fluorescence technique is that the detection limit is strongly dependent upon the distance between the skin and the kidney, which is determined by an ultrasonic technique. The detection limit is approximately $10\text{--}15\text{ }\mu\text{g}\cdot\text{g}^{-1}$ at a "normal" kidney depth of $50\text{--}60\text{ mm}$ (Nilsson et al, unpublished manuscript). This detection limit is sufficient to measure levels in subjects in the general population not subject to any particular cadmium exposure. The precision, as determined by repeated measurements in 11 cadmium workers, is about 20 (1 SD)% (20). The accuracy has been checked by parallel measurements of five horse kidneys with the use of X-ray fluorescence (the kidneys were placed in a water tank during measurement) and atomic absorption spectrometry (20). X-ray fluorescence gave slightly higher values than those obtained by atomic absorption spectrometry, but the mean difference was only $3\text{ }\mu\text{g}\cdot\text{g}^{-1}$.

Results

We studied cadmium levels in kidney cortex in Swedes with different smoking habits (Nilsson et al, unpublished manuscript). The average cadmium level in kidney cortex was $5.8\text{ }\mu\text{g}\cdot\text{g}^{-1}$ in nonsmokers and $26\text{ }\mu\text{g}\cdot\text{g}^{-1}$ in smokers (figure 2). These values are in agreement with the levels found in kidneys obtained at autopsy (23), and also with the assumption that smoking is a major source of cadmium exposure in the general population. Cadmium levels in blood and urine, as determined by atomic absorption spectrometry (5), also depended on smoking (24).

Subjects occupationally exposed to cadmium in a nickel-cadmium battery factory had much higher levels, on the average 150 (range $47\text{--}320$) $\mu\text{g}\cdot\text{g}^{-1}$ (20) (figure 2).

The application of neutron activation analysis in studies of cadmium workers has been very useful in

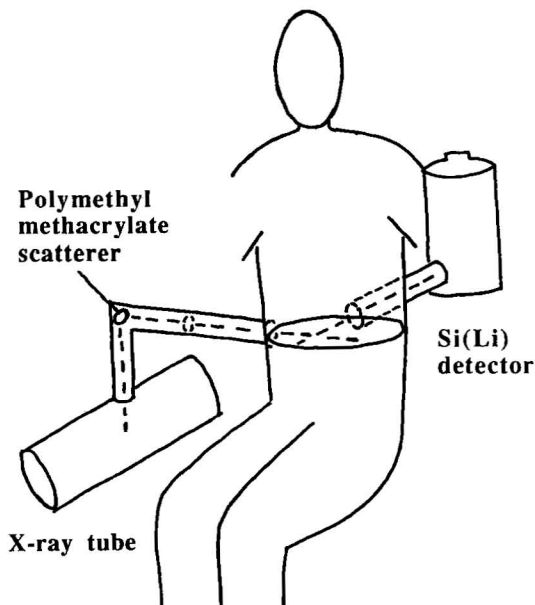


Figure 1. Arrangement for the determination of cadmium in kidney by X-ray fluorescence analysis with polarized photons. Modified from reference 19. (Si = silicon, Li = lithium)

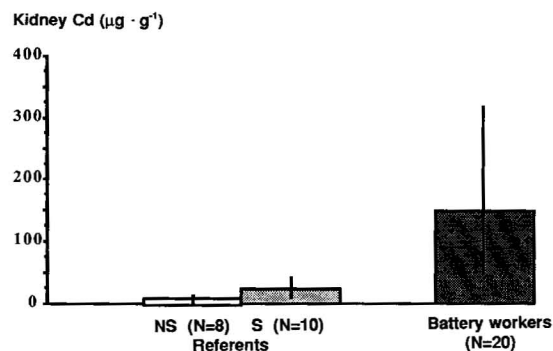


Figure 2. Cadmium (Cd) levels (means, bars indicate ranges) in kidney cortex of eight nonsmoking (NS) and ten smoking (S) Swedes without occupational exposure (Nilsson et al, unpublished manuscript) and in 20 workers in a nickel-cadmium battery factory (20).

estimating the critical concentration in kidney cortex (ie, the concentration at which dysfunction occurs) (12, 15). This level may be as low as about $50\text{ }\mu\text{g}\cdot\text{g}^{-1}$ (10).

In vivo determination of lead in bone

Lead exposure and effects

Occupational exposure to lead is a common problem in many industries (3). In addition, in many countries, there is considerable exposure of the general population, mainly through paint, water, gasoline, and industrial emissions (25). After absorption, the

metal is primarily transferred to the skeleton, which accounts for about 90% of the body burden. The critical organs are the central nervous system and the kidney (3). Slight effects occur at exposures accepted in most countries. In recent years, much of the interest has focused on effects on fetuses or infants exposed at the levels present in the general environment in many countries. There is thus a need for good indices of exposure and risk.

Methods

The first *in vivo* determination of lead in the skeleton was made by an X-ray fluorescence technique and published by Ahlgren et al in 1976 (26).

Since then, other X-ray fluorescence techniques and several applications have been reported (16, 27). In principle, they either use a ^{57}Co cobalt (^{57}Co) (6, 7, 26, 28–37) or a ^{109}Cd cadmium (^{109}Cd) (7, 14, 37–41) source to excite the lead; the characteristic K X-rays of lead are then measured.

The ^{57}Co technique has been applied mainly to the finger phalanx, but also to the ulna and tempo-

ral bone (36). The ^{109}Cd technique has primarily been used for the analysis of tibia (7, 37), but also for calcaneus (7, 37), ulna and sternum (39). In addition, L X-rays can be measured after the excitation of lead in the tibia by ^{125}I iodine or ^{109}Cd (16, 27). A partly plane-polarized spectrum from a low-energy X-ray generator has also been used for the production of L X-rays (42). While the K techniques measure lead up to a considerable depth in the bone, L techniques mainly assess superficially located lead. Therefore the results obtained by the two techniques may not be directly comparable.

We have used the ^{57}Co K technique for the determination of lead in finger phalanx (figure 3). The duration of measurement was 30 min, and the detection limit about $20 \mu\text{g} \cdot \text{g}^{-1}$, which is sufficient for the determination of skeletal lead in lead workers, but too high for determining levels in the general population in most areas of the world. The precision, as measured by repeated measurements in 16 individuals, is 15 (1 SD)% (28, 31). The accuracy has been checked by comparisons of *in vivo* determinations using X-ray fluorescence with postmortem determinations by atomic absorption spectrometry. In two subjects, the lead levels measured *in vivo* were 98 and $27 \mu\text{g} \cdot \text{g}^{-1}$; the postmortem analysis gave 91 and $36 \mu\text{g} \cdot \text{g}^{-1}$ (28, 31).

Results

In studies of smelter workers, the lead level of finger bone increased with increasing duration of employment and time-integrated exposure, as estimated from the blood lead levels over time (28, 37). The levels found in the smelter workers were much higher than those present in Swedish men without occupational exposure ($1\text{--}3 \mu\text{g} \cdot \text{g}^{-1}$) (6, 31).

Studies on lead levels in finger bone of the same smelter workers and on the concentrations in tibia and calcaneus by means of the ^{109}Cd K method showed significant associations between the levels at the different bone sites (figure 4) (37). Similar levels in tibia and calcaneus have been found in workers in another Swedish smelter (40, 41).

Finger-bone lead decreases after employment has ceased (29). We have now followed retired workers for up to 18 years (31), when they displayed an average biological half-time of 16 years, which shows the slow turnover of lead in bone.

Skeletal lead should be a useful index of risk, especially for the chronic effects of lead exposure. However, little has yet been done in this promising field.

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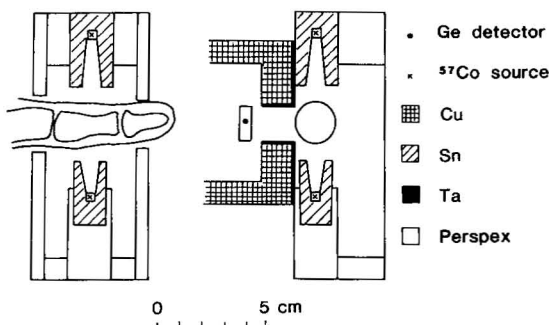


Figure 3. Arrangement for the determination of lead in finger bone by X-ray fluorescence analysis. The radiation shield, two ^{57}Co sources, and the detector collimator with its tantalum-covered opening and perspex holder for the finger are shown. (Ge = germanium, Co = cobalt, Cu = copper, Sn = tin, Ta = tantalum) Taken from reference 31.

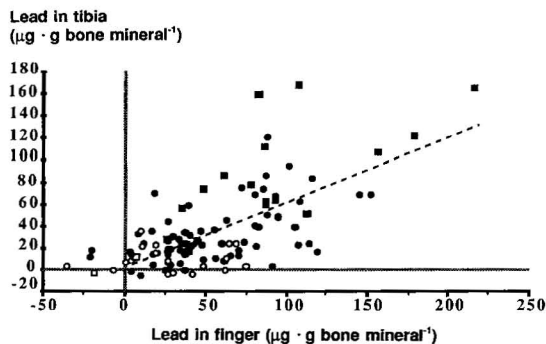


Figure 4. Relationship between bone lead levels in finger and tibia ($N = 112$, $T = 0.58F + 5.5$, $r = 0.68$, $P < 0.001$). Data taken from reference 37.

inder, have contributed to the work reported in this paper.

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References

- Elinder CG, Gerhardsson L, Oberdoerster G. Biological monitoring of toxic metals — overview. In: Clarkson TW, Friberg L, Nordberg GF, Sager PR, ed. Biological monitoring of toxic metals. New York, NY: Plenum Press, 1988:1—72.
- Nordberg G, Nordberg M. Biological monitoring of cadmium. In: Clarkson TW, Friberg L, Nordberg GF, Sager PR, ed. Biological monitoring of toxic metals. New York, NY: Plenum Press, 1988:151—68.
- Skerfving S. Biological monitoring of exposure to inorganic lead. In: Clarkson TW, Friberg L, Nordberg GF, Sager PR, ed. Biological monitoring of toxic metals. New York, NY: Plenum Press, 1988:169—98.
- Skerfving S, Nilsson U, Schütz A, Gerhardsson L. Biological monitoring of inorganic lead. Scand J Work Environ Health. 1993;19 suppl 1:59—64.
- Welinder H, Skerfving S, Henriksen O. Cadmium metabolism in man. Br J Ind Med 1977;34:221—8.
- Schütz A, Skerfving S, Christoffersson JO, Tell I. Chelatable lead vs lead in human trabecular and compact bone. Sci Total Environ 1987;61:201—9.
- Tell I, Somervaille LJ, Nilsson U, Bensryd I, Schütz A, Chettle DR, et al. Chelated lead and bone lead. Scand J Work Environ Health 1992;18:113—9.
- Shapiro IM, Cornblath DR, Sumner AJ, Uzzell B, Spitz LK, Ship II, et al. Neuropsychological and neuropsychological functions in mercury-exposed dentists. Lancet 1982;1:1147—50.
- Skerfving S, Christoffersson JO, Schütz A, Welinder H, Spång G, Ahlgren L, et al. Biological monitoring, by in vivo X-ray fluorescence measurements, of occupational exposure to lead, cadmium, and mercury. Biol Trace Elem Res 1987;13:241—51.
- Buchet JP, Lauwerys R, Roels H, Bernard A, Braux P, Claeys F, et al. Renal effects of cadmium body burden of the general population. Lancet 1990;336:699—702.
- Chettle DR, Ellis KJ. Further scientific issues in determining an occupational standard for cadmium. Am J Ind Med 1992;22:117—24.
- Ellis KJ, Yuen K, Yasumura S, Cohn SH. Dose-response analysis of cadmium in man: body burden vs kidney dysfunction. Environ Res 1984;33:216—26.
- Mason HJ, Davison AG, Wright AL, Guthrie CJG, Fayers PM, Venables KM, et al. Relations between liver cadmium, cumulative exposure, and renal function in cadmium alloy workers. Br J Ind Med 1988;45:793—802.
- Morgan WD, Ryde SJS, Jones SJ, Wyatt RM, Hainsworth IR, Cobbald SS, et al. In vivo measurements of cadmium and lead in occupationally-exposed workers and an urban population. Biol Trace Elem Res 1990;26—27:407—14.
- Roels HA, Lauwerys RR, Buchet JP, Bernard A, Chettle DR, Harvey TC, et al. In vivo measurement of liver and kidney cadmium in workers exposed to this metal: its significance with respect to cadmium in blood and urine. Environ Res 1981;26:217—40.
- Scott MC, Chettle DR. In vivo elemental analysis in occupational medicine. Scand J Work Environ Health 1986;12:81—96.
- Vartsky D, Ellis KJ, Chen NS, Cohn SH. A facility for in vivo measurement of kidney and liver cadmium by neutron capture prompt gamma ray analysis. Phys Med Biol 1977;22:1085—96.
- Ahlgren L, Mattsson S. Cadmium measured in man *in vivo* by X-ray fluorescence analysis. Phys Med Biol 1981;26:19—26.
- Christoffersson JO, Mattsson S. Polarized X-rays in X-ray fluorescence-analysis for improved in vivo detectability of cadmium in man. Phys Med Biol 1983;28:1135—44.
- Christoffersson JO, Welinder H, Spång G, Mattsson S, Skerfving S. Cadmium concentration in the kidney cortex of occupationally exposed workers measured in vivo using X-ray fluorescence analysis. Environ Res 1987;42:489—99.
- Nilsson U, Ahlgren L, Christoffersson JO, Mattsson S. Further improvements of XRF analysis of cadmium in vivo. In: Yasumura S, Harrison JE, McNeill KG, Woodhead AD, Diemanian SF, ed. Advances in in vivo body composition studies. New York, NY: Plenum Press, 1990:297—301.
- Christoffersson JO. In vivo elemental analysis in occupational medicine using X-ray fluorescence [dissertation]. Malmö: Department of Radiation Physics, Lund University, 1986.
- Elinder CG, Kjellström T, Lind B, Linnman L, Friberg L. Cadmium in kidney cortex, liver and pancreas from Swedish autopsies. Arch Environ Health 1976;31:292—302.
- Svensson BG, Björnhall Å, Schütz A, Lettevall U, Nilsson A, Skerfving S. Acidic deposition and human exposure to toxic metals. Sci Total Environ 1987;67:101—15.
- Schütz A, Attewell R, Skerfving S. Decreasing blood lead levels in Swedish children, 1978—88. Arch Environ Health 1989;44:391—4.
- Ahlgren L, Lidén K, Mattsson S, Tejning S. X-ray fluorescence analysis of lead in human skeleton in vivo. Scand J Work Environ Health 1976;2:82—6.
- Hu H, Milder FL, Burger DE. X-ray fluorescence: issues surrounding the application of a new tool for measuring burden of lead. Environ Res 1989;49:295—317.
- Christoffersson JO, Schütz A, Ahlgren L, Haeger-Aronsen B, Mattsson S, Skerfving S. Lead in finger-bone analysed in vivo in active and retired lead workers. Am J Ind Med 1984;6:447—57.
- Christoffersson JO, Schütz A, Skerfving S, Ahlgren L, Mattsson S. Decrease of skeletal lead levels in man after end of occupational exposure. Arch Environ Health 1986;41:312—8.
- Craswell PW, Price J, Boyle PD, Hazlewood VJ, Baddeley H, Lloyd HM, et al. Chronic renal failure with gout: a marker of chronic lead poisoning. Kidney Int 1984;26:319—23.
- Nilsson U, Attewell RG, Christoffersson JO, Schütz A, Ahlgren L, Skerfving S, et al. Kinetics of lead in bone and blood after end of occupational exposure. Pharmacol Toxicol 1991;68:477—84.
- Price J, Baddeley H, Kenardy JA, Thomas BJ, Thomas BW. In vivo X-ray fluorescence estimation of bone lead concentrations in Queensland adults. Br J Radiol 1984;57:29—33.
- Price J, Greudzinski AW, Craswell PW, Thomas BJ. Repeated bone lead levels in Queensland, Australia — previously a high lead environment. Arch Environ Health 1992;47:256—62.
- Schütz A, Skerfving S, Christoffersson JO, Ahlgren L, Mattsson S. Lead in vertebral bone biopsies from active and retired lead workers. Arch Environ Health 1987;42:340—6.
- Schütz A, Skerfving S, Ranstam J, Christoffersson J-O. Kinetics of lead in blood after the end of occu-

- pational exposure. Scand J Work Environ Health 1987;13:221—31.
36. Sokas RK, Besarab A, McDiarmid M, Shapiro IM, Bloch P. Sensitivity of in vivo X-ray fluorescence determination of skeletal lead stores. Arch Environ Health 1990;45:268—72.
37. Somervaille LJ, Nilsson U, Chettle DR, Tell I, Scott MC, Schütz A, et al. In vivo measurements of bone lead — a comparison of two X-ray fluorescence techniques used at three different bone sites. Phys Med Biol 1989;34:1833—45.
38. Batuman V, Wedeen R, Bogden JD, Balestra DJ, Jones K, Schidlovski G. Reducing bone lead content by chelation treatment in chronic lead poisoning: an in vivo X-ray fluorescence and bone biopsy study. Environ Res 1989;48:70—5.
39. Erkkilä J, Armstrong R, Riihimäki V, Chettle DR, Paakari A, Scott M, et al. In vivo measurements of lead in bone at four anatomical sites: long term occupational and consequent endogenous exposure. Br J Ind Med 1992;49:631—44.
40. Gerhardsson L, Attewell R, Chettle DR, Englyst V, Lundström LG, Nordberg GF, et al. In-vivo measurements of lead in bone in long-term exposed lead smelter workers. Arch Environ Health. In press.
41. Gerhardsson L, Chettle DR, Englyst V, Nordberg GF, Nyhlin H, Scott MC, et al. Kidney effects in long-term exposed lead smelter workers. Br J Ind Med 1992;49:186—92.
42. Rosen JF, Markowitz ME, Bijur PE, Jenks ST, Wielopolski L, Kalef-Ezra JA, et al. Sequential measurements of bone lead content by L- X-ray fluorescence in CaNa₂EDTA-treated lead toxic children. Environ Health Perspect 1991;91:57—62.