MASTER

**IN VIVO MONITORING OF TOXIC METALS: ASSESSMENT OF
NEUTRON ACTIVATION AND X-RAY FLUORESCENCE TECHNIQUES**

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INTRODUCTION

Excessive exposure to heavy metals has been associated with a variety of health effects in humans. These findings have usually been reported for both acute and chronic exposure conditions, mainly involving industrial workers. The health consequences associated with low level environmental exposures are more difficult to evaluate. Assessment of toxic metal exposure in most human studies have generally relied on monitoring biological tissues such as blood, urine, saliva, hair or nail clippings. The relationship between these biological monitoring media and the body burden of the toxic metal, particularly for long-term exposures, can be of special interest. Depending on the metal, the values obtained for the above mentioned biological tissues may be significantly influenced by recent exposure conditions and may be only marginally useful as accurate indices of body burden. It becomes desirable, therefore, to have direct in vivo monitoring techniques which can quantify the toxic metal burden in the body or of specific target organs.

In vivo monitoring of toxic metal burdens in the body may be useful only under certain conditions and for some metals. Body burden monitoring, for example, may have limited application for assessing the acute risk or for diagnostic purposes in the case of acute intoxication. Chronic exposures to certain metals must also be carefully considered. In those cases where the biological half-time is relatively short, in vivo monitoring would have to be performed promptly following the exposure. In these cases, there may be an accumulation of effects but not of the metal. Likewise, when the critical effect after long-term exposure to metals may be a local effect (i.e., mutation or cancer at the site of first contact), body burden monitoring may have limited value.

In general, therefore, in vivo body burden monitoring techniques have focused on either the target organ, which is also an important site of depot (i.e., kidney and liver cadmium), or on those storage compartments that represent cumulative exposure (i.e., bone lead). For the purpose of this Conference, I shall primarily focus on two nuclear techniques currently in use for the in vivo monitoring of heavy metals in humans: neutron activation analysis (NAA) and x-ray fluorescence (XRF).

Basic Technique for In Vivo Monitoring

The specific nuclear or atomic properties of an element rather than its chemical reactions are the basis for the development of in vivo techniques to monitor toxic metals in humans. The basic experimental approach is illustrated in Fig. 1. In all cases, examination of the subject involves exposure to a weak external beam of neutrons, photons, or x-rays. The radioactive source is shielded and collimated to restrict the beam to a specific organ or body region. The selection of the source, its strength, the shielding materials, and collimator-counting geometry are unique for each application. Shielding of the detectors is also required. High resolution solid state detectors (Ge, Se(Li), or Ge(Li)) are normally used in order to selectively identify the characteristic photon energy emitted by the metal under investigation. In some procedures the induced activity may last long enough to allow the subject to be transferred to a separate counting facility.

As could be expected, not all elements of toxicological interest can be measured in vivo in humans. The limiting factors being the amount and distribution of the metal present in the body, the time required to make a measurement, and the acceptable radiation dose. The toxic elements that have been measured in vivo in the human body and the laboratories performing these measurements are listed in Table 1. The

detection limits and associated dose are highly dependent of the basic components of each measurement facility, the geometries used, and the nuclear techniques employed. In general, the precision for these in vivo techniques is about $\pm 20\%$. In all cases, the exposure dose is usually smaller than that required for many routine diagnostic x-ray examinations of the same body regions. The organs that are examined in vivo are those that either show an adverse toxicological response to the metal or have long-term accumulation of the metal.

NEUTRON ACTIVATION ANALYSIS (NAA)

The development of in vivo neutron activation analysis (NAA) started in the mid-1960s at centers with existing nuclear research facilities. These efforts focused mainly on the bulk elements in the body such as Ca, N, Na, Cl, and K. The determination of these elements in the body was based on the measurement of the delayed component of the gamma spectra following neutron exposure. Further details for these procedures are available in two recent reviews (11,16). The feasibility of extending these techniques to the in vivo measurement of trace amounts of toxic elements was first considered a decade ago. The procedure is called "prompt gamma NAA", which requires the neutron irradiation and gamma counting to be performed simultaneously. A number of research centers have adopted this technique specifically for the in vivo measurement of cadmium (see Table 1). In particular, these facilities have been designed specifically for the in vivo monitoring of cadmium in the kidney and liver. Measurements of lung cadmium are feasible but have not been reported.

The nuclear property of cadmium that contributes to its measurement, even in trace quantities in the body, is the large cross section ($\sim 20,000$ barns) of one of its stable isotopes, ^{113}Cd (12.3% natural

abundance). During the neutron capture process, a simultaneous emission of gamma rays occurs, 559 keV being the most prominent energy. At Brookhaven, cadmium is measured *in vivo* in the liver and the left kidney in two separate procedures. Initially, a $^{238}\text{Pu}/\text{Be}$ neutron source was used (20). More recently, the facility was redesigned for a ^{252}Cf neutron source in order to improve the system's sensitivity (detection limit) and to reduce the regulatory restrictions for transportation (39). The ^{252}Cf sources provide fast (high energy) neutrons which are slowed in the body tissues, largely by elastic scattering on hydrogen. At approximately 3-4 cm depth within the body, the maximum thermal neutron flux occurs. The components of the measurement system of the mobile Brookhaven facility are shown schematically in Fig. 2(a) for the determination of kidney cadmium. Two large volume $\text{Ge}(\text{Li})$ detectors are placed to the side of the subject who is in a supine position on the bed over the collimated ^{252}Cf source. Prior to the *in vivo* measurement, the position of the left kidney within the subject's body is determined accurately by ultrasonic imaging and these parameters are used to convert the gamma signal to an organ burden value (20,38). For the liver cadmium measurement, the subject moves to a prone position with the right side of the body over the neutron beam.

This basic approach has been used by each of the research centers listed in Table 1 for the *in vivo* measurement of cadmium. The actual components of the different systems and irradiation-counting geometries vary, thus influencing each system's detection limits. For example, a single detector system with a smaller source and shielding has been designed mainly for liver measurements in industrial workers (see Fig. 2(b)). The range of detection limits for the *in vivo* measurements of cadmium vary from 1.5 mg to 6.4 mg for the kidney and from 1 to 7 $\mu\text{g/g}$ concentration for the liver.

In vivo NAA techniques have also been investigated for use with other metals, i.e., Hg, Se, Si, Mn, and Al. With the exception of aluminum, these techniques have been developed only to the point of feasibility for human use. The measurement of Al is currently being performed in renal patients maintained on aluminum-based medications (30). This procedure used the delayed gamma spectra following neutron activation. A partial body activation of the hand is performed and induced activity is counted in a separate counting system (see Fig. 3). Both Al and Ca signals are detected for the hand and an Al/Ca ratio for bone is obtained. This basic technique could be easily modified, for example, to monitor lung burdens of aluminum or manganese.

Mercury is detectable in vivo by NAA using the same facility as for cadmium (25). This element, however, is more difficult to measure as the cross section for neutron capture is nearly an order of magnitude less than that for cadmium. Also, the prompt gamma ray is lower in energy which will have a higher attenuation in tissue. The most promising method that will overcome these limitations is to use filtered (2 KeV-24 KeV) neutron beams which can provide a significant improvement in sensitivity. This approach is currently under investigation at Brookhaven for the in vivo measurement of kidney and brain mercury levels.

The feasibility of lung Si measurements using a pulsed neutron beam has been demonstrated in phantoms (32). This approach uses inelastic scattering of high energy (>9 MeV) neutrons. A portable in vivo system could be built using a miniaturized pulsed D,T neutron generator and a counting system similar to that developed for cadmium. It is estimated that a lung burden of 0.2 gm Si should be detectable for a dose of 1 rem (10 mSv).

X-RAY FLUORESCENCE TECHNIQUES (XRF)

The XRF technique is most suitable for the measurement of superficial organs or surface body regions because of the major limitation imposed by the attenuation of the incident and emission irradiations. It is for this reason that in vivo determinations using XRF have been confined to the finger (phalanx), leg (tibia), and head regions. Although it is highly desirable to measure toxic metal burdens in organs such as the kidney, the attenuation problems at these depths have prohibited further developments.

It is estimated that at least 90% of absorbed lead is stored in the skeleton, mainly in cortical bone. The direct in vivo measurement of bone lead, therefore, should provide an immediate estimate of total body lead. Although lead can be activated by NAA, its low sensitivity is not adequate for in vivo applications in humans. X-ray fluorescence (XRF) techniques, therefore, offer a suitable alternative. In the last few years several research centers (see Table 1) have developed XRF systems with particular emphasis on bone lead measurements. This technique is atomic rather than nuclear and is based on external excitation by x-rays or gamma-rays. Both K x-rays and L x-rays have been measured in vivo when stimulated by a beam from the appropriate isotopic source (^{57}Co , ^{125}I , ^{109}Cd , ^{241}Am) or x-ray machine.

Three basic experimental arrangements (source-target-detector) are shown in Fig. 2 for the measurement of bone Pb. When compared with the size of the apparatus used for NAA, the shielding/collimator components are much smaller. A 90° geometry (mean angle between incident and measured emission radiation) has been used for both the finger and leg

measurements. In the upper drawing of Fig. 4, the finger is shown positioned between two collimated ^{57}Co sources and the Ge detector is to the side of the finger. Measurement times are routinely 30-40 min with an exposure of 0.25-0.50 rad (2.5-5 mGy). Two orthogonal radiographs of the finger are needed to determine bone volume which is used for calibration of the bone lead value (1,2,14). The minimum detection concentration for bone lead in the finger ranges from 15-20 $\mu\text{g/g}$ with an estimated precision of 15 percent.

For the measurement of bone lead in the tibia, both K and L x-ray fluorescence have been examined (41, 47, 49, 50). Two typical measurement techniques for the tibia are shown in the lower portion of Fig. 4. Various advantages for the use of K lines has been recently reported (47). One key factor for using K x-rays is that the attenuation factor is more than an order of magnitude less for bone and soft tissue than when L x-rays are employed. The reported minimum detection limits are 20 $\mu\text{g/g}$ for the L x-ray technique (90° geometry) and 10 $\mu\text{g/g}$ for the K x-ray system (backscatter, 180° geometry). The L x-ray technique uses a dose of 1 rad (10 mGy) which is significantly higher than the 0.045 rad (0.45 mGy) used in the more sensitive K x-ray backscatter technique. The third and possibly most important factor is the attenuation problem with the soft L x-rays which requires a precise determination of the thickness of the overlying soft tissue layer. The backscatter K x-ray technique, however, uses an internal normalization based on the coherently scatter component of the emission spectra (47). This approach removes the requirement for measurement of the soft tissue layer by ultrasonics and will account for individual variations in tibia size and shape.

APPLICATIONS OF IN VIVO MONITORING OF TOXIC METALS

The initial focus for in vivo NAA and XRF monitoring techniques has been dominated by two heavy metals, cadmium and lead. These metals have relatively long biological half-times in specific organs of the body and there can be a significant accumulation over a period of years. These trace levels are detectable and provide an accurate index of cumulative exposure. To date, the majority of the in vivo measurements have been performed in occupationally-exposed subjects where an increase in the body burden can be expected. The higher burdens of these workers has allowed some systems to be developed which have detection limits well above those needed for environmental monitoring. Much lower detection limits, however, are required in order to examine "environmentally exposed" subjects. Values similar to those of the Brookhaven system for cadmium (<2 mg in kidney, <1.5 ppm in the liver) are needed.

Therefore, only limited in vivo cadmium measurements have been performed in the general non-industrial exposed population. One important issue that each of these studies has addressed, however, is whether or not under conditions of low to moderate cadmium exposure (including environmental exposure levels), does the cadmium concentration in urine provide an index of the cadmium level in the body, in particular, the kidney burden (8, 13, 18, 21, 34, 48). Each of the in vivo studies has failed to find a useful correlation for the individual between blood or urine concentrations of cadmium, for example, and the kidney cadmium burden. Increases in the in vivo kidney and liver cadmium burden have been reported for cigarette smokers and nonsmokers (21). The cadmium burdens for patients with renal failure and hypertension has also been reported (4, 18). In each of these studies there was no statistical evidence which would support the hypothesis that urinary cadmium levels

are an accurate index of kidney burden for the individual. These findings emphasize even more the importance of the direct in vivo determination of body burden rather than an assumed indirect assessment of dose.

The most immediate application of in vivo cadmium monitoring has been to examine the "critical concentration" in the kidney (22, 23, 27, 31, 34, 42, 48). These studies have involved industrial workers where there was general agreement that when the liver cadmium burden exceeded 70 ppm, virtually all subjects would develop renal abnormalities. There is still disagreement on the differences in body distribution of cadmium between the liver and kidney. These differences may reflect, in part, variations in exposure conditions between the industrial groups. Also, there has been some confusion on how to define the "critical" concentration for the kidney cortex as it relates to the in vivo data obtained for these industrial groups. Several approaches have been proposed and the estimates have varied from 200-400 ppm (22, 23, 28, 31, 42). The latest model uses logistic regression analysis to estimate the probability for renal functional changes on the basis of the liver cadmium concentrations. This model has also provided the first estimates of the relative (increased) risk for kidney damage associated with industrial exposure to cadmium (28). For the individual worker, the most probable liver cadmium value at which renal functional abnormalities would occur was approximately 47 ppm. Correspondingly, the most probable "critical" kidney value for an individual is approximately 35 mg Cd in the total kidney (assuming a linear relationship between the liver and kidney cadmium burden). It is estimated, however, that nearly 10% of the industrial workers could, on the average, reach a critical level when the total kidney burden is as low as 20 mg (28, 31).

When the levels of blood, urine, and hair cadmium were examined in industrial workers in relation to body burden, only marginal correlations were found (24, 36, 42). This indicates that in the industrial environment, these biological indices may more correctly reflect exposure conditions than body burden. A time-weighted exposure index based on air sampling data was found to have a higher correlation with body burden than any of the above biological indices in these workers (29). Urine and blood monitoring, however, do provide an individual assessment of variations in exposure.

In the general population bone lead concentrations increase with age and, depending on the bone site, vary from 2 to 30 $\mu\text{g/g}$ for adults. The relatively high detection limit for the in vivo XRF technique has, therefore, restricted these measurements mainly to subjects with elevated body burden, i.e., occupationally exposed workers. In each of these studies, there has been a general increase in bone lead values with the length of employment. Bone lead levels for the finger measurement, for example, have ranged up to 130 $\mu\text{g/g}$. No subsequential changes in bone lead values were observed when the workers were removed from exposure; blood lead levels decreased markedly. There was no significant association between blood and bone lead values for the active workers and only a marginal correlation for retired workers (14).

When lead levels in the tibia were measured using the L x-rays lines, bone lead values ranged from non-detectable to nearly 200 $\mu\text{g/g}$ (50). The L x-rays will penetrate only a few mm thickness of bone, thus these values are presumably for "surface" bone. Blood lead values and total urinary lead collected for 72 hr following administration of Ca-EDTA were correlated with L x-ray bone values in these workers (35, 50). The improved sensitivity of the K x-ray backscatter technique has

allowed for examination of both industrial workers and a control group (nonindustrially exposed adults). In the preliminary findings, no relationship between blood and bone lead was reported. Approximately half of the control group had bone lead levels above 10 $\mu\text{g/g}$ (the detection limit) and the values significantly increased with age.

Mercury has been detected using in vivo XRF in the superficial layers of the head and wrist of a dental population (9). Of the 298 subjects examined, 84 had mercury levels above the reported detection limit of 20 $\mu\text{g/g}$. Neurophysiological and neuropsychological findings revealed that approximately 1/3 of the dentists with the higher in vivo values also had polyneuropathies and occasional mild visuographic dysfunction (43). Although efforts have been made to measure the kidney burden of mercury, the effects of overlying tissue ruled out this possibility, except for extremely high levels (9, 40, 45).

The kidney burden of cadmium, however, has been successfully detected in vivo using both conventional and polarized XRF systems (3, 13). A significant improvement was achieved with the polarized x-ray technique and kidney concentrations ranging from 15 to 170 $\mu\text{g/g}$ were observed. The one major drawback of XRF, however, is the limited depth at which the kidney can be detected. If the kidney is more than 6 cm below the skin, for example, the minimum detection limit quickly exceeds 50 $\mu\text{g/g}$ (approximately 6 mg for the total kidney vs 2 mg for the NAA technique). In the U.S., Belgian, and British studies using in vivo NAA to monitor kidney cadmium levels, many of the workers had kidney depths greater than 5 cm, ranging up to 14 cm.

SUMMARY

The initial biological monitoring of humans exposed to toxic metals will continue to be based on information obtained for readily available body tissues or fluids. For most metals, blood and urine monitoring have proven valuable as indices of at least recent exposures. Their usefulness as indicators of chronic or "historical" exposures is less reliable. Cumulative exposure estimates may be extremely difficult, if not impossible, to determine solely on the basis of current blood or urine levels. Predications of body burden based on multicompartiment models are also limited by their basic assumptions about the interrelationship of blood and/or urine to the body burden. Direct in vivo monitoring techniques can help to reduce these uncertainties by providing burden values for specific body organs. These organs can be the major storage sites in the body, or the target organs which have a toxicological response.

To date, cadmium, lead, aluminum, and mercury have been measured in vivo in humans. The possibilities of monitoring other toxic metals have also been demonstrated, but no human studies have been performed. NAA appears to be most suitable for Cd and Al measurements, while XRF is ideally suited for measurement of lead in superficial bone. Filtered neutron beams and polarized x-ray sources are being developed which will improve in vivo detection limits. Even so, several of the current facilities are already suitable for use in epidemiological studies of selected populations with suspected long-term low-level "environmental" exposures. Evaluation and diagnosis of patients presenting with general clinical symptoms attributable to possible toxic metal exposure may be assisted by in vivo examination. Continued in vivo monitoring of industrial workers, especially follow-up measurements, will provide the first direct assessment of changes in body burden and a direct measure of the biological life-times of these metals in humans.

Table. 1: Research centers which have reported in vivo monitoring techniques for toxic metals in humans.

Neutron Activation Analysis (NAA)

References

New York:	Cd-K,L; Al-H,TB; (Hg-K);	20, 21, 22, 23, 24, 25, 26, 27,
	(Si,Be,Mn-Lu)	28, 29, 30, 31, 32, 38, 39
Birmingham:	Cd-K,L	5, 12, 34, 42, 45, 46, 48
Swansea:	Cd-K,L	10, 18, 33
Brisbane:	Cd-L	4, 8, 36
Taiwan:	(Cd,Hg-K)	15
Japan:	(Cd-K,L)	37
Baghdad:	(Cd-L, Hg-He)	6, 7

X-Ray Fluorescence Analysis (XRF)

References

New York:	Pb-T	35, 49, 50
Birmingham:	Pb-P,T; (Hg-K)	12, 45, 46, 47
Swansea:	Pb-P	40
Brisbane:	Pb-P	17, 19, 41
Philadelphia:	Pb-Te; Hg-He	9, 43
Lund/Malmö:	Pb-P; Cd-K; (Hg-K)	1, 2, 3, 13, 14, 44

K = kidney, L = liver, H = hand, TB = total body, T = tibia, P = phalanx
 Te = teeth, He = head, Lu = lungs. Information in () are for
 feasibility studies only.

TABLE 2

Types of Human Studies which have included the in vivo
examination of toxic metal burdens

Human Studies	References
1. Interrelationship with other biological parameters (urine, blood, hair)	8, 21-24, 26, 35, 14, 17-19, 41, 42, 50
2. Relationship to Industrial Air Exposure Index	29
3. Examination of Critical Concentration for kidney Cd	22, 23, 27, 34, 42, 28
4. Risk Analysis for Cd-induced renal dysfunction	27, 28, 31
5. Possible interaction with other heavy metals	35
6. Effect of cigarette smoking on body burden	21, 35
7. Comparison with Chelation-challenge test as monitor of body burden (EDTA, DFO)	30, 50
8. Possible Clinical Abnormalities/Non-Industrial (Hypertension, Ca loss, Gout, Renal Dysfunction)	17, 18, 19, 41

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FIGURE CAPTIONS

- Fig. 1. Basic concept of in vivo measurement techniques.
- Fig. 2. Typical Neutron Activation Analysis (NAA) systems for in vivo cadmium measurements.
- Fig. 3. Counting system for measuring bone aluminum levels in the hand.
- Fig. 4. Three examples of in vivo XRF measurement techniques for bone lead.

BASIC CONCEPT OF *in vivo* MEASUREMENT TECHNIQUES

Fig 1

(a) Cross-sectioned view of ^{252}Cf facility for *in vivo* measurement of kidney cadmium (Environmental Monitoring)

(b) Cross-sectioned view of single detector facility for *in vivo* liver cadmium measurement (Industrial Screening)

Fig 3: Counting system for measuring bone Al in the hand.

(a) XRF technique for bone lead measurement in the phalanx

(b) XRF techniques for bone lead measurement in the tibia