IN VIVO ELEMENTAL ANALYSIS IN OCCUPATIONAL MEDICINE USING X-RAY FLUORESCENCE

Jan Ove Christoffersson

Malmö 1986
A technique for the in vivo determination of cadmium in the kidney cortex using X-ray fluorescence analysis (XRF) has been developed for clinical use. The method uses the radiation from an X-ray tube, operated at 150 kV and 15 mA, for the induction of the Cd K-alfa X-rays. The radiation from the tube was polarised by scattering at 90 degrees in a plastic disc. Using a Si(Li) detector the minimum detectable concentration (MDC) of cadmium in the renal cortex was about 6 ppm for an effective dose equivalent of 3 micro-Sievert. The precision of the method was estimated to be about 23 per cent. The accuracy was determined through comparisons with atomic absorption spectrometry. The mean difference was found to be 3 ppm in the range 10-60 ppm. The clinical usefulness was confirmed by studying 20 occupationally exposed cadmium workers and three controls. The cadmium workers showed levels of cadmium in the kidney in the range 47-317 ppm, and the controls showed levels below 30 ppm.

Using XRF in vivo large-scale measurements of lead in the fingerbone of more than 100 lead workers were performed. The technique used included two 57-Co sources for excitation and a high-purity Ge detector for the analysis of the Pb K-alfa X-rays. The MDC was about 20 ppm for an effective dose equivalent of 0.1 micro-Sievert. The precision of the method was estimated to be about 15 per cent. The in vivo measurements showed levels of fingerbone-Pb up to 148 ppm. The existence of a significant endogenous exposure from lead in the skeleton was confirmed. A group of 14 retired workers followed for up to six years, showed a half-life of lead in fingerbone of about 10 years. The fingerbone-Pb was correlated to time-integrated blood-Pb indicating that it could be used as a rough estimate of time-integrated exposure. The results from the measurements were used to develop a three-compartment (cortical bone, trabecular bone, blood / soft tissues) model. Using this model, lead levels in fingerbone, vertebrae and blood could be predicted in good agreement with observations.

Key words XRF in vivo, cadmium, kidney cortex, X-ray tube, polarised photons, Si(Li) detector, lead, fingerbone, 57-Co, half-life, endogenous exposure, occupational exposure, three-compartment model.

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IN VIVO ELEMENTAL ANALYSIS IN OCCUPATIONAL MEDICINE

USING X-RAY FLUORESCENCE

JAN OVE CHRISTOFFERSSON

Fil. kand., Sm

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1. INTRODUCTION

Trace element studies have become an important subject in many areas of science. Of particular interest are the numerous applications in medicine.

A lot of effort has been spent on comparative investigations of trace element levels in normal and pathological states of human tissues (Prasad 1976). An increasing number of elements are also believed to be essential for the function of the human body and, essential or not, most elements become toxic if the levels are sufficiently high. Accordingly, the study of essential and toxic elements is an important field of trace element analysis.

The adverse effects of toxic elements are also of environmental and occupational concern. As knowledge of the toxic elements increases e.g. concerning their pathways in the environment and their kinetics in man, the possibility of taking appropriate measures also increases.

Stable tracers can also be used for the purpose of medical diagnosis and research. Furthermore, applications in pharmacology are evident as the kinetics of drugs sometimes can be followed using elemental analysis at trace levels.

All the above applications of trace element studies call for accurate analytical tools to determine the small amounts of the elements of interest. As a matter of fact, most elements can be analysed provided the analysis can be performed on laboratory samples obtained by sampling of blood and urine or by biopsy. However, levels in blood and urine only indirectly reflect the levels in the organs of interest and they therefore constitute uncertain estimates. So, there is a strong need for reliable noninvasive in vivo measurements in order to make direct measurements in the organs of interest and to exclude risky biopsies for the assessment of the elemental composition of various tissues. Moreover, using in vivo analysis, repeated measurements on the same tissue can be performed and longitudinal studies are thereby made possible.
There are a number of conceivable techniques for the in vivo analysis of elements (Cohn and Parr 1985). The technique that has acquired the most widespread use, is in vivo neutron activation analysis (IVNAA). Other techniques that have been described are, e.g. photon absorptiometry (Jacobsson 1953, Day and Hickling 1967), photonuclear activation (Ali et al 1985), nuclear resonance scattering of photons (Vartsky et al 1979), inelastic neutron scattering reactions (Ettinger et al 1982) and muonic X-ray fluorescence (Hutson et al 1976).

However, this work will entirely focus on another technique, namely photon-induced X-ray fluorescence analysis (XRF) for the assessment of elemental concentrations in vivo. This technique has, together with IVNAA, become the most important technique for in vivo elemental analysis.

Accordingly, the purpose of this work was

(1) to develop and evaluate an XRF technique for the in vivo measurements of cadmium in the human kidney cortex, and to use this technique for measurements on a group of occupationally exposed workers, and

(2) to evaluate a technique for the in vivo analysis of lead in fingerbone using XRF and to apply the method to large-scale measurements on lead workers, and, furthermore, on the basis of these results, develop a model describing the kinetics of lead in occupationally exposed workers.

2. HISTORICAL BACKGROUND

After the discovery of X-rays, on the Friday evening of November 8, 1895, by Wilhelm Conrad Röntgen, a new era of physics began. Already in 1896 over 400 papers dealing with X-rays had been published giving a wide variety of applications.

C G Barkla could, in 1905, give one of the first experimental proofs of the X-rays being transversal electromagnetic waves by showing that the
scattering of X-rays was a polarisation sensitive process (Barkla 1905). In 1908 Barkla and Sadler, through measurements of attenuation, made the important observation that an X-ray-irradiated element emitted secondary radiation that was characteristic of the element itself (Barkla and Sadler 1908). This characteristic secondary radiation was soon found to be composed of two separate parts, the K and L X-rays, respectively (Barkla 1909).

Max von Laue proposed in 1912 that diffraction of X-rays could be obtained by crystals (Friedrich et al 1912). By irradiating a crystalline solid with photons, constructive interference at certain angles could be used to select X-rays of a particular wavelength (energy). This finding was immediately used by W H and W L Bragg who developed the wavelength-dispersive X-ray spectrometer (Bragg and Bragg 1913).

Using the X-ray spectrometer H G Moseley, in 1913, measured the K and L X-rays from a large number of elements and he found that there was a close relationship between the wavelength (or energy) of the characteristic X-rays and the atomic number of the element (Moseley 1913). Combining the results of Moseley with the model of the atom developed by N Bohr in 1913, the transitions in the atoms leading to the emission of characteristic X-rays were now understood (Bohr 1913).

One of the first to use photon-induced X-ray fluorescence as a tool for qualitative and quantitative elemental analysis of a sample was A R Hadding at Lund University. In 1922 he used the wavelength-dispersive X-ray spectrometer to analyse the elemental composition of different minerals (Hadding 1922). This technique has found several applications concerning the analysis of laboratory samples.

However, the effective use of energy-dispersive X-ray fluorescence for detecting low concentrations of elements became possible first in the 1960’s when Bowman et al (1966) demonstrated the advantage of semiconductor detectors with high energy resolution and the method has since been used extensively for studies of the elemental composition of laboratory sample.
The high efficiency and the excellent energy resolution of these detectors together with compact radionuclide sources also made in vivo XRF analysis possible as shown by Hoffer et al (1968) and Tinney (1968). The pioneering work of Ahlgren et al (1976) on the measurement of low levels of lead in bone opened the field of XRF in vivo to applications in occupational medicine and this technique is now being used worldwide.

3. PHYSICAL ASPECTS OF X-RAY FLUORESCENCE

3.1 Interactions of photons with matter

Photon beams of energies below about 150 keV will on their passage through matter, be attenuated by interactions mainly with the atomic electrons. The mode of interaction will be either scattering or absorption. Scattering includes change of direction and loss of energy (incoherent or Compton scattering) or only change of direction (coherent, in general Rayleigh scattering). The properties of these events will briefly be summarised below (for a detailed description, see any textbook on radiation physics, e.g. Anderson (1984)).

Incoherent scattering

The energy loss of the incoherently scattered photons will be transferred to one of the outer atomic electrons. This electron gains enough energy to leave the atom. The scattered photon will leave the interaction centre in almost any direction, but the forward direction is preferred and a minimum of the scattering probability is seen at about 90 degrees. Furthermore, it is seen that the energy of the scattered photon will decrease as the scattering angle increases. The process of incoherent scattering is the dominating mode of interaction when elements of low atomic number are involved.

Coherent scattering

When the photon is scattered without losing energy, the photon is said to be coherently scattered. The probability for this process increases with increasing atomic number of the scatterer as well as with decreasing photon energy. Moreover, the photons are scattered predominantly in the forward direction.
The photoelectric effect
At a photoelectric interaction the photon transfers all its energy to a bound atomic electron, which leaves the atom, thereby creating a vacancy in the atomic electron cloud. In order to make this process possible, the energy of the photon must, of course, exceed the binding energy of the electron in question. The probability of the photoelectric process increases as the atomic number of the element increases and as the photon energy decreases.

3.2 X-ray fluorescence

The electrons surrounding the nucleus of the atom can classically be described as being found in discrete energy shells. The electrons in the inner shells are more tightly bound to the nucleus than electrons in the outer shells. This binding energy, and the differences in binding energy between shells, are characteristic for every element. If a vacancy in the innermost shell (the K-shell) occurs, through for example the photoelectric effect, this vacancy will be filled by an electron from some of the other shells, for example the next shell (the L-shell). This atomic transition will result in a release of energy of magnitude equivalent to the difference between the binding energies of the shells in question. The energy release will be in the form of characteristic X-rays or Auger electrons. These events compete and the higher the atomic number, the higher the probability for characteristic X-rays. The fluorescence yields \( \omega_K \), probability of the emission of characteristic K X-rays) for e.g. cadmium \((Z=48)\) and lead \((Z=82)\) are 84 and 97 per cent, respectively (Lederer and Shirley 1978). The corresponding yields for low atomic number elements such as carbon \((Z=6)\) and oxygen \((Z=8)\) are very low. The emission of characteristic X-rays is isotropic.

The Auger electrons are not of interest in in vivo analysis since in most cases they do not have enough energy to leave the body. That leaves the characteristic X-rays to be used for elemental analysis in vivo.

One element can emit characteristic X-rays of several discrete energies. Since there are several shells \((K, L, M, \ldots)\) and the shells above the
K shell are divided into subshells (e.g. L\textsubscript{i}, L\textsubscript{II} and L\textsubscript{III}), a number of transitions are possible. Transitions to the K shell will result in K X-rays, transitions to the L shell in L X-rays and so on. The transitions from the L shell to the K shell are denoted K\textsubscript{α} X-rays, and from the M and N shells K\textsubscript{β} X-rays. The subshells will give rise to a fine-structure of the characteristic X-rays, e.g. the subshells in the L shell will give the K\textsubscript{α1} and the K\textsubscript{α2} X-rays.

The energies of the characteristic X-rays are, as earlier mentioned, unique for the element, and the energy of the K X-rays is about a factor of seven higher than that of the L X-rays. For elements of high atomic number, the K\textsubscript{α} and the L X-rays will be found at about 70 and 10 keV, respectively. The corresponding figures for elements of medium atomic number are 20 and 3 keV, respectively. For low atomic number elements, like the main constituents of the human body, the K X-rays are a few keV.

All these aspects of X-ray fluorescence are reviewed in detail by Bambynek et al (1972).

Using photons for creating vacancies in the atomic electron shells through photoelectric interaction will thus result in the emission of characteristic X-rays. By using a high-resolution, energy-dispersive semiconductor detector (Ge or Si(Li)) together with the appropriate electronics, elements can be non-invasively determined quantitatively and qualitatively by photon-induced X-ray fluorescence analysis.

Vacancies can also be produced by the bombardment of charged particles, e.g. protons. Though not feasible for in vivo analysis, proton-induced X-ray emission (PIXE) has several applications in elemental analysis related to medicine, particularly when studying small samples (Johansson et al 1970).

3.3 Implications for in vivo analysis

Compared with the analysis of samples, in vivo analysis presents a number of additional problems. When working with laboratory samples it is always possible to shape them in a way to suit the analytical technique used.
Furthermore, it is also possible to preconcentrate the elements of interest and the measurement time is not very critical. Also, the possible late biologically adverse effects of the radiation need not be considered. All these factors have to be dealt with in a different way when performing in vivo analysis.

Considering the elemental composition of the body (table 3.1), it is found that 97 per cent of the total mass consists of elements with atomic number up to eight (ICRP 1975). The element of the highest atomic number found in any significant amount in the human body is calcium (Z=20). This implies that the dominating process of photon interaction in the body will be incoherent scattering, for our purposes, in general, a troublesome fact.

By collimating both the primary, exciting radiation and the field of view of the detectors, the XRF technique offers the possibility of mapping in three dimensions. As the radiation passes through the body, the photon fluence rate will be reduced due to attenuation and geometrical effects (the inverse square law). Thus, the penetration of the primary photons must be such that the fluence rate at the volume of interest is sufficient, and also the characteristic X-rays generated must have

<table>
<thead>
<tr>
<th>Element</th>
<th>Symbol</th>
<th>Atomic number</th>
<th>Abundance (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxygen</td>
<td>O</td>
<td>8</td>
<td>61</td>
</tr>
<tr>
<td>Carbon</td>
<td>C</td>
<td>6</td>
<td>23</td>
</tr>
<tr>
<td>Hydrogen</td>
<td>H</td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>Nitrogen</td>
<td>N</td>
<td>7</td>
<td>2.6</td>
</tr>
<tr>
<td>Calcium</td>
<td>Ca</td>
<td>20</td>
<td>1.4</td>
</tr>
<tr>
<td>Phosphorus</td>
<td>P</td>
<td>15</td>
<td>1.1</td>
</tr>
<tr>
<td>Sulphur</td>
<td>S</td>
<td>16</td>
<td>0.20</td>
</tr>
<tr>
<td>Potassium</td>
<td>K</td>
<td>19</td>
<td>0.20</td>
</tr>
<tr>
<td>Sodium</td>
<td>Na</td>
<td>11</td>
<td>0.14</td>
</tr>
<tr>
<td>Chlorine</td>
<td>Cl</td>
<td>17</td>
<td>0.12</td>
</tr>
</tbody>
</table>
enough energy to leave the body and reach the detector in order to obtain a sufficiently high count rate. This implies that, in general, only K X-rays can be used as these have the highest energies. The half-value layers (HVL) in soft tissue for photons of 20 and 80 keV are about 9 and 38 mm, respectively. Ahlgren (1980) estimated that elements, at some depth in the body, of atomic number below about 40 are not very suitable for in vivo measurements. This estimate was based on considerations of the attenuation of primary photons as well as of characteristic X-rays, fluorescence yields and cross sections for the photoelectric effect. However, if the elements are situated in superficial organs such as the skin and certain superficial bones, this limit is lowered and it also allows L X-rays of high atomic elements to be used for the analysis.

In the normal situation at in vivo measurements the concentrations of the elements of interest are close to the detection limit of present day techniques. This fact demands rigorous optimization of geometry, materials and excitation sources used in the experimental set-up. As indicated above, the low level of the elements (at μg·g⁻¹ level) leads to the fact that most (99.99 per cent) of the detected radiation will be photons incoherently scattered by the main constituents of the body. This has two implications. Firstly, using ordinary electronics the count rate limit (about 10⁴ s⁻¹) is easily reached. Secondly, the background under the peaks of the characteristic X-rays, which in one way or other is due to the scattered radiation, will be much larger than the number of counts from the characteristic X-rays.

Normally, one tries to avoid having the characteristic X-ray peaks superimposed on the maximum of the distribution of incoherently scattered photons, in order to decrease the background under the peaks. In most cases geometry and radiation sources are used so that the peaks can be found on the low-energy side of the incoherently scattered distribution (see figure 5.2). But even so, the background will often be due to the incoherently scattered photons because of multiple scattering and/or detector effects. The latter effects are due to the fact
that the detector and the electronics will degrade some of the higher energy events in the detector and register a pulse at lower energies instead (Goulding 1977). It has, however, been shown that under certain conditions in vivo analysis can be successfully performed even with the peaks right on top of the distribution of scattered photons (Jonson et al 1985). Nevertheless, if the primary radiation is sufficiently close to the absorption edge of the element and the scattering angle is large, the peaks can be found on the high-energy side of the scattered distribution where the background is low. This unusual case has been used in vivo by e.g. Somervaille et al (1985) and Christoffersson et al (to be published).

The incoherently scattered radiation can, however, be used in a constructive way. The probability for incoherent scattering is proportional to electron density and most biological materials have about the same number of electrons per unit mass. Therefore the amount of scattered photons will be proportional to the mass of the analysed volume (Ahlgren 1980), as well as it can be used for normalisation (Grönberg 1981). Since the cross section for coherent scattering increases with the atomic number, the number of coherently scattered photons can give information on the atomic composition of the analysed volume (Ahlgren and Mattsson 1979) and can also be used for normalisation purposes (Somervaille et al 1985).

When trying to analyse a limited volume within the body, the solid angles of the detector as well as the radiation source must be optimized. The solid angle of the detector should be large with respect to the volume of interest. At the same time the detector should "see" as little as possible of the parts of the body that are outside the volume of interest, so that incoherent scattering into the detector is kept as low as possible. The radiation field of the source should of course, irradiate the whole volume of interest, and it can sometimes be useful to have quite a large radiation field. However, it is in general advisable to have the solid angles of the detector and radiation source just encompassing the volume of interest. These factors have
have been theoretically studied by e.g. Grönberg (1981).

XRF in vivo will always involve an irradiation of the patient. However, using photons, the absorbed dose to the patient is normally very low. Nevertheless, it has to be carefully determined by measurements and calculations for every XRF technique used.

3.4 Polarised radiation

The photons incoherently scattered into the detector reduce the possibility of detecting low concentrations of the elements. So, if the number of scattered photons into the detector could be reduced without reducing the number of primary photons the detectability would be expected to increase.

In order to improve the performance of XRF analysis of laboratory samples, the idea of making use of the polarisation-sensitive properties of photon scattering was proposed by Young et al (1973). By scattering an unpolarised beam in three mutually orthogonal directions, the scattered radiation can be minimised. This will thus reduce the background under the peaks as well as making it possible to increase the primary photon fluence rate. Both these factors will improve the detection limit of the analysed element.

Several groups have shown that the use of polarised radiation is successful in improving the detectability when analysing laboratory samples. The polarisation was achieved in various ways e.g. scattering in amorphous materials - Barkla scattering (Dzubay et al 1974, Kaufman and Camp 1975, Ryon and Zahrt 1979) or in crystals - Bragg scattering (Aiginger et al 1974), Borrmann transmission (Howell et al 1975) and using synchrotron radiation (Baryshev et al 1986). Polarisation through Barkla scattering has also been indirectly used in a triaxial geometry using secondary fluorescers (Standzenieks and Selin 1979, Maack Bisgård et al 1981). However, there was doubt whether polarisation could also be used in vivo due to the comparatively, large scattering volumes. Multiple scattering involves depolarisation of the
photon beam and thus an increased scattering into the detector is expected (Ryon 1977). However, it was shown that polarised radiation was useful for the in vivo analysis of cadmium (Christoffersson and Mattsson 1983, Christoffersson et al 1986a) as well as platinum (Jonson et al 1985).

4. APPLICATIONS OF XRF IN VIVO - A REVIEW

XRF has been used since the end of the 1960's for elemental analysis in vivo. It started with measurements of natural iodine levels in the thyroid, and until now several elements, from iron to thorium, have been studied.

Both "natural" levels as well as administered elements have been analysed to obtain information on concentrations, metabolism and physiological processes.

Generally, semiconductor detectors have been used because of their superior energy resolution which permits lower concentrations of the elements to be measured. Nevertheless, proportional counters as well as sodium iodide detectors have in some instances shown to have sufficiently good properties.

In order to excite the atoms of interest, radionuclide sources are normally used. Table 4.1 summarises the physical properties (Lederer and Shirley 1978, Kosher 1981) of some of the radionuclides used for XRF in vivo so far. In addition to the radionuclide sources, X-ray tubes have also been used, primarily due to the high photon fluence rates that can easily be obtained. These tubes were operated from 45 kV to 155 kV and from 3 mA to 50 mA.

Using these detectors and radiation sources the minimum detectable concentration (MDC) will be at the order of 10 µg·g⁻¹. The applications of XRF are numerous and can be found in e.g. occupational medicine, oncology, nephrology and endocrinology.
Table 4.1. Radionuclide sources used for XRF studies in man and in feasibility studies

<table>
<thead>
<tr>
<th>Nuclide</th>
<th>$T_{1/2}$</th>
<th>Principal photon energies (keV)</th>
<th>Photons per disintegration (%)</th>
<th>Type of radiation</th>
<th>Elements analysed</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{55}$Fe</td>
<td>2.71 y</td>
<td>5.90</td>
<td>24.5</td>
<td>Mn $K_a$</td>
<td>Ca</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6.49</td>
<td>3.29</td>
<td>Mn $K_B$</td>
<td></td>
</tr>
<tr>
<td>$^{57}$Co</td>
<td>271 d</td>
<td>14.4</td>
<td>9.54</td>
<td>Y</td>
<td>Pt, Hg, Pb, Th</td>
</tr>
<tr>
<td></td>
<td></td>
<td>122</td>
<td>85.5</td>
<td>Y</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>136</td>
<td>10.6</td>
<td>Y</td>
<td></td>
</tr>
<tr>
<td>$^{99m}$Tc</td>
<td>6.02 h</td>
<td>141</td>
<td>89.1</td>
<td>Y</td>
<td>I, Cs, Bi</td>
</tr>
<tr>
<td></td>
<td></td>
<td>18.3</td>
<td>6.12</td>
<td>Tc $K_a$</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>20.6</td>
<td>1.21</td>
<td>Tc $K_B$</td>
<td></td>
</tr>
<tr>
<td>$^{109}$Cd</td>
<td>464 d</td>
<td>88.0</td>
<td>3.72</td>
<td>Y ($^{109m}$Ag)</td>
<td>Ca, Zn, Sr, Hg, Pb</td>
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<td></td>
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<td>22.1</td>
<td>82.5</td>
<td>Ag $K_a$</td>
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<td>25.0</td>
<td>17.4</td>
<td>Ag $K_B$</td>
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<tr>
<td>$^{125}$I</td>
<td>60.1 d</td>
<td>35.5</td>
<td>6.49</td>
<td>Y</td>
<td>Sr, Pb</td>
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<td></td>
<td>27.4</td>
<td>112</td>
<td>Te $K_a$</td>
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<td></td>
<td>31.1</td>
<td>25.4</td>
<td>Te $K_B$</td>
<td></td>
</tr>
<tr>
<td>$^{133}$Xe</td>
<td>5.25 d</td>
<td>81.0</td>
<td>36.5</td>
<td>Y</td>
<td>Pt</td>
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<tr>
<td></td>
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<td>30.9</td>
<td>38.9</td>
<td>Cs $K_a$</td>
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<td></td>
<td>35.1</td>
<td>9.14</td>
<td>Cs $K_B$</td>
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<tr>
<td>$^{153}$Gd</td>
<td>242 d</td>
<td>69.7</td>
<td>2.57</td>
<td>Y</td>
<td>Ba, Ta, Pb, Bi</td>
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<td>97.4</td>
<td>31.3</td>
<td>Y</td>
<td></td>
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<td>103</td>
<td>22.2</td>
<td>Y</td>
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<td></td>
<td></td>
<td>41.3</td>
<td>101</td>
<td>Eu $K_a$</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>47.3</td>
<td>25.3</td>
<td>Eu $K_B$</td>
<td></td>
</tr>
<tr>
<td>$^{159}$Dy</td>
<td>144 d</td>
<td>58.0</td>
<td>2.21</td>
<td>Y</td>
<td>I</td>
</tr>
<tr>
<td></td>
<td></td>
<td>44.2</td>
<td>76.3</td>
<td>Tb $K_a$</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>50.7</td>
<td>18.1</td>
<td>Tb $K_B$</td>
<td></td>
</tr>
<tr>
<td>$^{201}$Tl</td>
<td>73.1 h</td>
<td>135</td>
<td>2.65</td>
<td>Y</td>
<td>I</td>
</tr>
<tr>
<td></td>
<td></td>
<td>167</td>
<td>10.0</td>
<td>Y</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>70.2</td>
<td>73.9</td>
<td>Hg $K_a$</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>80.7</td>
<td>20.5</td>
<td>Hg $K_B$</td>
<td></td>
</tr>
<tr>
<td>$^{241}$Am</td>
<td>432 y</td>
<td>26.3</td>
<td>2.40</td>
<td>Y</td>
<td>Cd, I, Xe</td>
</tr>
<tr>
<td></td>
<td></td>
<td>59.5</td>
<td>35.9</td>
<td>Y</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>13.8 - 21.3</td>
<td>43.5</td>
<td>Np L X-rays</td>
<td></td>
</tr>
</tbody>
</table>
The following two sections give a review of some of the techniques and applications used for XRF measurements \textit{in vivo} as well as feasibility studies. There are some points that are of particular interest when dealing with XRF \textit{in vivo} namely the following: detector, type of radiation source and its photon fluence rate, geometry and materials used, measurement time, MDC, energy imparted and/or effective dose equivalent. Furthermore, it should be stated how the MDC was calculated and for what measurement time it is given. All this information is not always given and in this review no attempt has been made to deduce the missing information.

The definition of MDC consistently used by us and others (e.g. in analogy to ICRU 1972), is as follows:

\[ \text{MDC} = 3\times C/N_p \times \sqrt{N_b/t} \]

where
- \( C \) is the concentration of the element
- \( N_p \) is the net count rate
- \( N_b \) is the count rate of the background
- \( t \) is the measurement time

We have occasionally used the expression "3 SD of the background" to describe the MDC definition used. Other groups (e.g. Somervaille et al 1985) mention 2 SD when dealing with MDC. However, they probably set one SD equal to \( \sqrt{2\times N_b} \) (Colbeck 1986). At first glance our definition seems to be the most rigorous one. However, the two different ways of defining MDC are almost directly comparable. This shows that in order to make correct comparisons and to avoid confusion, the definition of MDC should be given in detail or, rather, it should be standardised.

There is a strong association between MDC and patient exposure. Normally, the irradiated volume is comparatively small and the absorbed dose gradients are considerable. To give just the absorbed dose to the skin is not very meaningful. Instead should, as indicated above, energy imparted or the effective dose equivalent be given. However, the latter is rather difficult to estimate, therefore, in order to make comparison the energy imparted could be used and when comparing different types of radiation, the \( Q \)-value should be taken into account.
4.1 Studies in man

The reported in vivo XRF measurements in humans cover a range of elements from iron to thorium. The organs studied are superficial, like the skin, as well as deep such as the kidney. This section deals only with actual in vivo measurements in humans. The elements are ordered by increasing atomic number.

<table>
<thead>
<tr>
<th>Element</th>
<th>Atomic Number</th>
<th>K-edge (keV)</th>
<th>IC (keV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iron (Fe)</td>
<td>26</td>
<td>7.111 keV</td>
<td>6.400 keV</td>
</tr>
<tr>
<td>Copper (Cu)</td>
<td>29</td>
<td>8.980 keV</td>
<td>8.041 keV</td>
</tr>
<tr>
<td>Zinc (Zn)</td>
<td>30</td>
<td>9.660 keV</td>
<td>8.631 keV</td>
</tr>
</tbody>
</table>

Since iron, copper and zinc are of relatively low atomic number, the characteristic X-rays are of low energy. This implies that in vivo analysis is mainly restricted to superficial organs. The eye and the skin have been subject to analysis with respect to the contents of these elements.

Zeimer et al (1974) have developed a technique for the detection of low atomic number elements in superficial organs using XRF. The radiation source used was an X-ray tube with a gold anode and it was operated at 45 kV and 3 mA. The radiation was monochromated (Lγ X-rays (11.4 keV) of gold) and focussed in a curved crystal and subsequently used for the excitation of the elements. Zeimer and co-workers used this radiation source to detect the elemental composition of splinters in the eyes of six patients. They used a 100 mm² Si(Li) detector to analyse the secondary radiation which revealed that the splinters consisted of iron and, in some cases, copper and zinc. A larger material (from 32 patients) of the same kind was also reported by Belkin et al (1979).

Using this technique a number of different applications have been reported. For a measurement time of a few minutes the MDC is in general around 1 μg·g⁻¹.
The copper content of the cornea was determined in seven patients with Wilson's disease and two controls (Belkin et al 1976). The detection limit was below 1 \( \mu \text{g} \cdot \text{g}^{-1} \) for copper and for the iron and zinc were simultaneously detected.

Sheskin and Zeimer (1977) studied the levels of iron, zinc and copper in the skin of 20 leprous patients and 11 volunteers. These studies were continued by investigation of five patients with lepra reaction before and after thalidomide treatment (Sheskin et al 1981a). Sheskin et al (1981b) also measured iron, copper and zinc levels in the skin of four patients with prurigo nodularis.

In 19 patients suffering from beta-thalassemia major, Zeimer et al (1978) analysed the relative concentration of iron in the skin. This organ was chosen because it is known that iron accumulates in the skin of patients with iron overload. Gorodetsky et al (1985) continued these studies in a further 56 patients with beta-thalassemia major and intermedia.

Strontium (Sr), \( Z = 38 \)
K-edge = 16.106 keV, \( K_{\alpha} = 14.142 \text{ keV} \)

Wielopolski et al (1982) have analysed the natural level of strontium in the tibia of seven volunteers using \( ^{109}\text{Cd} \) (Ag K X-rays) to produce the characteristic X-rays of strontium. These were detected by a Si(Li) detector with an area of 80 mm\(^2\) and a thickness of 2 mm. The minimum detectable concentration was 15 \( \mu \text{g} \cdot \text{g}^{-1} \). Levels of about 50 \( \mu \text{g} \cdot \text{g}^{-1} \) were found.

Cadmium (Cd), \( Z = 48 \)
K-edge = 26.712 keV, \( K_{\alpha} = 23.109 \text{ keV} \)

Cadmium in the kidney cortex and liver was first analysed using XRF by Ahlgren and Mattsson (1981) and Ahlgren et al (1981). An 11 GBq \( ^{241}\text{Am} \) source and a Ge detector, 16 mm (diameter) x 5 mm (thickness) were used. At a measurement time of 30 minutes and at a kidney depth of 40 mm the MDC was found to be 40 \( \mu \text{g} \cdot \text{g}^{-1} \). Using this technique six occupationally
exposed persons were studied.

An improvement in the detectability of cadmium in the kidney cortex was achieved by using polarised radiation from an X-ray tube (Christoffersson and Mattsson 1983; Christoffersson et al 1986a). This will be dealt with below and the corresponding MDC using a Si(Li) detector was about 6 μg·g⁻¹.

Iodine (I), Z = 53

K-edge = 33.164 keV, Kα = 28.512 keV

Iodine was the first element to be analysed in vivo mainly due to its relatively high atomic number and the high natural level (~400 μg·g⁻¹) of iodine in the thyroid which was the first organ to be studied. Furthermore, the thyroid is easily accessible for XRF analysis. Thus, XRF can provide information on the distribution of the intrathyroidal iodine, the total amount of iodine in the thyroid and the time variation of the thyroidal iodine content.

The iodine distribution in the thyroid was determined using a fluorescent scanning technique (Hoffer and Gottschalk 1971). They used a 241Am source and a Si(Li) detector for the scanning of the thyroids of 76 patients. The technique has been used extensively ever since. For example, Patton et al (1976) used sixteen 37 GBq 241Am sources and a 25 mm (diameter) Si(Li) detector to determine the distribution of iodine in the thyroid of 450 patients and could thereby differentiate between malignant and benign conditions of the thyroid.

Iodine has also been analysed at sites other than the thyroid, in the form of injected iodine containing contrast agents.

Regional cerebral blood volume has been determined using XRF (Grubb et al 1973). In a 90 degree geometry they studied a brain volume of 1 cm³ using the radiation from an X-ray tube for excitation and a 300 mm² x 5 mm Si(Li) detector to analyse the secondary radiation. The MDC was 100 μg·g⁻¹. By injecting an iodine tracer, the cerebral blood volume was determined in eleven volunteers.
With the aid of in vivo XRF, Patton et al (1978) determined the origin of an unexpected finding from a pantomograph. This finding, in the maxillary sinus, was found to be residues of an iodine-containing contrast agent administered 25 years earlier. The experimental equipment included sixteen 37 GBq $^{241}$Am sources and a Si(Li) detector.

Magrini et al (1979) reported measurements of iodine from an injected X-ray contrast agent in inflamed knee joints in three patients as well as in two controls. The elimination of iodine in the knee joint was studied. They used two 1.7 GBq $^{241}$Am sources and a proportional counter with krypton gas to detect the emitted radiation.

Grönberg et al (1981, 1983) monitored kidney function by following the elimination of iodine in the fingertip in two volunteers and 44 patients who prior to the investigation had undergone urography. They used an 11 GBq $^{241}$Am source and a Ge detector (16 mm (diameter) x 5 mm (thickness)) for the analysis.

Xenon (Xe), Z = 54
K-edge = 34,579 keV, $K_a = 29,669$ keV

Xenon gas can be used in pneumoencephalography. Kaufman et al (1973) have, by means of XRF, followed the dynamics of xenon absorption from the cerebral ventricles in six patients undergoing such an investigation. The xenon content was followed for two hours and the experimental equipment included two 92.5 GBq $^{241}$Am sources and a 80 mm$^2$ x 3 mm Si(Li) detector.

Platinum (Pt), Z = 78, K-edge = 78,379 keV
$K_{a1} = 66,820$ keV, $K_{a2} = 65,111$ keV

Platinum, in the form of cisplatin, is used for the treatment of different tumours. One side-effect of this treatment has been kidney damage. Therefore it is of interest to follow the kinetics of platinum in the kidney as well as in the tumour. Using XRF, Jonson et al (1985) reported measurements of platinum in brain tumour and kidney of 15 patients. The
radiation from an X-ray tube (155 kV, 25 mA) was polarised in an Al scatterer and filtered with uranium before entering the patient. The secondary radiation was subsequently measured using a Ge detector. An MDC of 8-10 μg·g⁻¹ for platinum in both tumour and kidney was achieved.

El-Sharkawi et al (1986) have reported measurements of platinum in the kidney of four cisplatin-treated patients. Platinum was detectable in one of them showing a level of 30 μg·g⁻¹. They used a 259 MBq ⁵⁷Co source and a Ge detector in a 90 degree geometry. The MDC for a measurement time of 2000 s was 37 μg·g⁻¹.

Mercury (Hg), Z = 80, K-edge = 83.106 keV
K_{α1} = 70.821 keV, K_{α2} = 68.894 keV

The mercury content in the wrist and head of 298 dentists was analysed using XRF (Bloch and Shapiro 1981, Shapiro et al 1982). Surprisingly high concentrations were found (up to 200 μg·g⁻¹). A 370 MBq ⁵⁷Co source was used for the excitation and a 110 mm² x 7 mm Ge detector for the detection. The MDC given was 30 μg·g⁻¹.

Inspired by these findings we made an attempt to determine mercury in the inter-phalanx of the left fore-finger and the frontal bone of the skull of five long-term exposed workers and a fisherman and his wife consuming mercury contaminated fish (Skerfving et al 1986). However, no mercury was detectable. We used ⁵⁷Co sources and a Ge detector for the analysis. The MDC for mercury was estimated to be 30-50 μg·g⁻¹.

Lead (Pb), Z = 82, K-edge = 88.001 keV
K_{α1} = 74.957 keV, K_{α2} = 72.794 keV

Using ⁵⁷Co sources and Ge detectors we have, for a long time, analysed lead in fingerbone and tibia (Ahlgren et al 1976; Ahlgren et al 1980; Christoffersson et al 1984; Christoffersson et al 1986b).

The lead content in the teeth of 30 lead exposed children has also been analysed in situ (Bloch et al 1976, Shapiro et al 1978) using a
222 MBq $^{57}$Co source and a 110 mm$^2 \times 7$ mm Ge detector. The MDC for a measurement time of 100 s was 15 μg·g$^{-1}$.

The lead concentration in fingerbone of 60 petrol sniffer and 18 controls has been measured using two 1 GBq $^{57}$Co sources and a solid-state detector (Eastwell et al 1983).

More than 200 occupationally exposed lead workers have been the subject for lead determination in the skeleton using a 1.85 GBq $^{57}$Co source (Palser et al 1983). The MDC was reported to be 10-20 μg·g$^{-1}$.

Price et al (1984) have reported measurements of lead in fingerbone of 200 adults in a cross-sectional study. They used two 1 GBq $^{57}$Co sources and a 12 per cent coaxial Ge detector. The MDC was 20 μg·g$^{-1}$.

Craswell et al (1984) analysed the lead concentration in fingerbone of 42 patients with chronic renal failure to study the relations between lead body burden, lead nephropathy and gout. $^{57}$Co sources and a 13.5 per cent Ge(Li) detector were used. The minimum detectable concentration of lead in bone for a measurement time of 1000 s was 25 μg·g$^{-1}$.

At measurements of platinum in the kidney of four cisplatin-treated patients, unexpected and surprisingly high concentrations of lead (above 800 μg·g$^{-1}$) in the kidney were found (El-Sharkawi et al 1986). The equipment used included a $^{57}$Co source and a Ge detector.

Wielopolski et al (1986) have reported measurements on the tibia of 45 lead workers. In contrast to others they used the Pb L X-rays to measure the lead in superficial layers of the bone. A $^{109}$Cd source (Ag K X-rays) was used to induce the L X-rays and a Si(Li) detector was used to detect the radiation. The MDC was given to be 20 μg·g$^{-1}$.

An attractive excitation source for lead K X-rays is $^{109}$Cd due to its γ energy of 88.03 keV which is just above the K-edge of lead. By suitable arrangement of the geometry, the characteristic lines from lead will be found on the high-energy side of the incoherent scattering peak where
the background will be low. The use of $^{109}\text{Cd}$ for the analysis of lead in paint was reported by Laurer et al. (1971) and was suggested for the \textit{in vivo} analysis of lead by Ahlgren (1976) following an idea of McGie and Lidén (1972).

Somervaille et al. (1983, 1985) have used 3.7 - 7.4 GBq $^{109}\text{Cd}$ for the analysis of lead in the tibia of 15 lead workers and 22 controls. Furthermore, the characteristic X-rays of lead were normalised to the coherent scattering peak thus making the measurement more or less independent of geometry and shape of the analysed bone. They detected the radiation with a 16 mm (diameter) x 7 mm (thickness) Ge detector. The MDC was 10 µg·g$^{-1}$. This technique was also used for measurements of tibia lead levels of two cisplatin-treated patients (El-Sharkawi et al. 1986).

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Thorium (Th), Z = 90, K-edge = 109.630 keV

$K_{a1} = 93.334$ keV, $K_{a2} = 89.942$ keV

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Thorium in the form of thorium dioxide (Thorotrast), was earlier used as a radiographic contrast agent. It was, however, abandoned due to the severe side-effects in the form of radiation-induced carcinoma. A patient was submitted to us for investigation of a finding from a radiograph in the lumbar region. His medical history showed another radiographic examination more than 40 years earlier possibly including an injection of Thorotrast. Using a 370 MBq $^{57}\text{Co}$ source and a planar high-purity Ge detector in a 158 degree geometry we could easily determine that the finding from the radiograph consisted of thorium (Christoffersson et al, to be published).

4.2 Feasibility studies for \textit{in vivo} measurements

A clear distinction between \textit{in vivo} measurements in humans and so-called feasibility studies must be made. Even if the feasibility studies are well designed, there are a number of additional problems when performing an actual \textit{in vivo} measurement in man compared with measurements on phantoms or animals. Therefore, the applicability of a method can
never fully be established until an actual in vivo measurement has been made.

The following section comprises experimental studies using true phantoms as well as studies on living animals.

Calcium, iron, copper and zinc
Yarom et al (1978) used the method of Zeimer et al (1974) to analyse calcium, iron, copper and zinc in muscle. The results from the in vivo analyses of the tongue of ten normal and five cardiomyopathic hamsters were compared.

Olkkonen et al (1982) studied the possibility of measuring the calcium concentration in tooth enamel by analysing teeth in vitro using non-destructive XRF. For this purpose they used a 370 MBq $^{55}$Fe source and a 16 mm (diameter) Ge detector.

Wielopolski et al (1984) described a system for the simultaneous analysis of calcium, zinc and strontium in enamel of human teeth using a $^{109}$Cd source and a Si(Li) detector.

Strontium
Wielopolski et al (1981) used an $^{125}$I and a $^{109}$Cd (Ag K X-rays) source to measure the natural strontium level in human tibia of six post mortem samples. The detector was a 80 mm$^2$ x 2 mm Si(Li).

The retention of injected strontium in the skull-bone of seven rabbits and tibia of one dog was studied using XRF (Snyder and Secord 1982). A 37 MBq $^{109}$Cd (Ag K X-rays) source and an 80 mm$^2$ x 5 mm Si(Li) detector were used.

Using a Si(Li) detector and a $^{109}$Cd source, Wielopolski et al (1984) determined strontium levels down to 6.6 $\mu$g g$^{-1}$ simultaneously with calcium and zinc in the enamel of human teeth.

Cadmium
Cranley (1982) studied the properties of a scanning system designed to
obtain the cadmium distribution in the kidney. He used up to twelve 1.7 GBq $^{241}$Am sources and a 10 mm (diameter) x 4.62 mm (thickness) Ge(Li) detector to produce and analyse the characteristic X-rays of cadmium. Furthermore, the benefits of both polarised and unpolarised radiation were studied.

Iodine

Hoffer et al (1968) for the first time demonstrated the feasibility of XRF in vivo. A neck phantom including a thyroid was imaged using two 11.1 MBq $^{159}$Dy sources and a 30 mm$^2$ x 3 mm Si(Li) detector.

Hoffer et al (1969) also studied the cerebral blood flow of a monkey that had been given meglumine diatrizoate (37 per cent I). The radiation source was 122 GBq $^{241}$Am and the secondary radiation was analysed using a 200 mm$^2$ Si(Li) detector.

Ter-Pogossian et al (1971/72) studied regional cerebral blood volume in ten dogs and two monkeys that had been given iodine tracer. They used an X-ray tube operated at 80 kV and 10 mA for excitation and a 300 mm$^2$ x 5 mm Si(Li) detector for the detection of the I K X-rays.

Kaufman et al (1972) determined the cardiac output in a dog by means of XRF. Iothalamate was injected and a 3 cm$^3$ blood volume in the heart was studied with respect to iodine. The experimental equipment included an X-ray tube operated at 95 kV and an 81 mm$^2$ x 3 mm Si(Li) detector.

Koehler et al (1976) determined the concentration of iodine in the liver of six dogs. Meglumine iodipamide was injected and the kinetics were followed. For excitation they used a $^{241}$Am source. The detector used was a Si(Li) detector.

Amano et al (1984) have proposed a somewhat different approach to measure the iodine content of the thyroid. They used a neck phantom including thyroids. These thyroid phantoms were filled with iodine solution together with a radioactive solution. The radionuclides studied were $^{99m}$Tc, $^{201}$Tl and $^{241}$Am. The detector was a 16 mm (diameter) x 10 mm (thickness) Ge detector. $^{201}$Tl was found to be the most effective radio-
nuclide for the analysis of iodine giving an MDC of 70 μg·kg⁻¹ for an activity of 1 MBq and a measurement time of 2000 s.

Xenon

The cerebral blood flow of a monkey was determined using XRF (Hoffer et al 1969). A xenon-oxygen mixture was administered to the animal and the clearance of xenon in the brain was measured using an 122 GBq ²⁴¹Am source and a 200 mm² Si(Li) detector.

Caesium

Hermann and Kiker (1975) studied the feasibility of XRF for the in vivo measurement of intracranial pressure. They used two communicating chambers on each side of a calvarium phantom. The chambers contained caesium nitrate solution. The count rate of the characteristic X-rays of caesium from one of the chambers was correlated to the pressure. The radiation source was 925 MBq ⁹⁹mTc and a 38 mm (diameter) x 13 mm (thickness) NaI(Tl) detector was used to analyse the secondary radiation.

Barium

A technique for the determination of the clearance of barium sulphate from the lungs has been developed by Kaufman and Gamsu (1974). Barium sulphate was insufflated into the lungs of dogs. The characteristic X-rays were then produced by a 74 GBq ¹⁵³Gd (Eu K X-rays) source and the secondary radiation was detected by an 80 mm² Si(Li) detector.

Tantalum

The clearance of tantalum from the lungs was also studied by Kaufman and Gamsu (1974). Powdered tantalum was insufflated into the lungs of dogs in the same way as barium sulphate above. Two different radiation sources were used, an X-ray tube operated at 135 kV and 50 mA, and a 74 GBq ¹⁵³Gd source. The latter gave the best results and permitted barium to be measured simultaneously. The detector was a 80 mm² Si(Li) detector.

Platinum

The possibility of the in vivo analysis of platinum was first suggested
by Mattsson (1981) and Grönberg (1981). The feasibility for measurements in the kidney was studied by Dutton et al (1985). They used the radiation from a 263 MBq $^{57}$Co source, both unpolarised and polarised by diffuse scattering, as well as a $^{133}$Xe source. The radiation was detected using a 100 mm$^2$ Ge detector. By extrapolating the results from the direct use of $^{57}$Co it was concluded that a source activity of 3.5 GBq would give an MDC of 10 μg·g$^{-1}$ for a measurement time of 2000 s.

Mercury

Smith et al (1982) studied the possibility of measuring mercury in the kidney. They used a kidney phantom and a $^{57}$Co source. The radiation was detected in either a 15 per cent Ge(Li) or a 100 mm$^2$ planar Ge detector.

Smith et al (1983) continued their studies of kidney mercury using $^{109}$Cd as the radiation source and a Ge detector. The MDC's were found to be 9 and 55 μg·g$^{-1}$ for kidney depths of 2 and 5 cm, respectively.

Lead

Detecting lead K X-rays Ahlgren (1976) studied the possibility of measuring lead in bone. The radiation sources used were $^{57}$Co, $^{109}$Cd and $^{153}$Gd, and the detector was a Ge(Li) of diameter 10 mm and thickness 5 mm.

Wielopolski et al (1981, 1983) studied the possibility of using the L X-rays of lead for measurements in human tibia. For excitation they used 3.7 MBq $^{125}$I and $^{109}$Cd (Ag K X-rays) sources. The detector was an 80 mm$^2$ x 2 mm Si(Li). A number of six post mortem measurements of human tibia were made and the MDC was estimated to be 22 μg·g$^{-1}$. They also studied the effect of using a polarised beam by scattering the radiation from $^{125}$I.

Laird et al (1982) and Laird (1983) used $^{57}$Co and $^{109}$Cd sources for studies of the feasibility for bone lead measurements using phantoms containing lead solution. A Ge detector was used. Detection limits of 4 to 6 μg·g$^{-1}$ were given.
Morgan et al (1983) used $^{57}$Co and a Ge detector for measurements on a finger phantom containing lead solution. An MDC of $6 \mu g\cdot g^{-1}$ was obtained.

Dutton et al (1985) performed measurements on a finger phantom made of plaster of Paris and wax to study the possibility of determining lead in bone. They used a 370 MBq $^{57}$Co source for excitation and a 100 mm$^2$ Ge detector to analyse the radiation. The MDC was reported to be $10 \mu g\cdot g^{-1}$.

Bismuth

Bismuth compounds have been shown to accumulate in brain tumours. Patton et al (1971) studied the possibility of detecting bismuth in brain tumours using phantoms. A 7.4 GBq $^{99m}$Tc source and eight 38 mm x 13 mm NaI(Tl) detectors were used in a tomographic scanning system. They also used a 25 cm$^3$ Ge(Li) detector and a 111 GBq $^{153}$Gd source in order to obtain improved detectability.

4.3 Conclusions

Feasibility studies included, this review shows that in vivo XRF have been used for the analysis of a total of 16 elements ranging from calcium ($Z=20$) to thorium ($Z=90$), see figure 4.1. These elements have been analysed in superficial organs such as the skin and tooth enamel and more deeply lying organs such as the kidney.

XRF sometimes offers an alternative to the administration of radioactive tracers. It can also be used as an effective alternative to other existing in vivo elemental analysis techniques. Furthermore, for some elements XRF constitutes an accurate method for which virtually no other technique is available.
Finally, this review clearly shows that XRF analysis in vivo has gained widespread use with many applications in different fields of research and the number of analysed elements as well as applications is constantly increasing.

5. CADMIUM IN KIDNEY CORTEX

5.1 Background

Cadmium is known as an environmental pollutant. It is widely used in industry and can reach the general population through plastics, batteries, fertilizers etc. Another important source of exposure to cadmium is tobacco smoking.

Occupational exposures exceed that of the general population. For occupationally exposed cadmium workers, the main route of intake is via the lungs. After uptake in the body, the cadmium is distributed by the blood and a considerable accumulation of the element is seen in the kidneys and the liver. These organs contain about half of the total body burden of cadmium.

Figure 4.1. Periodic table showing the elements that have been analysed in vivo in man (filled triangles) and in feasibility studies (open triangles) using XRF.
The adverse effects of cadmium in man are seen in e.g. organs such as the lungs, the skeleton and the kidney. The kidney is considered as being the critical organ as it is the organ in which critical concentrations of the element are first reached.

Monitoring of cadmium exposure could be "environmental" (e.g. air levels) or "biological" (e.g. levels in blood). Since there is no simple relationship between air levels and, for instance, levels in blood, biological monitoring is preferred.

Biological monitoring also includes measurements of cadmium levels in urine, kidney and liver. Furthermore, tests of kidney function, i.e. excretion of proteins in urine, are also employed.

As the kidney is the critical organ and as reported concentrations are mostly given for the cortex, it is of particular interest to determine the cadmium concentration in that part of the kidney.

X-ray fluorescence analysis is the only non-invasive in vivo technique that directly gives the cadmium concentration in the kidney cortex as IVNAA measures the total cadmium content in the whole kidney.

5.2 Technique

The technique for analysing cadmium in kidney cortex is described by Christoffersson and Mattsson (1983) and Christoffersson et al (1986a). Another XRF technique using $^{241}\text{Am}$ for excitation was developed earlier (Ahlgren and Mattsson 1981).

The method used here takes advantages of the fact that polarised photons do not scatter 90 degrees in their own plane of polarisation. By using polarised photons in a 90 degree geometry, no photons would thus be scattered into the detector.

The polarised photons were obtained by scattering the radiation from an X-ray tube in a polymethylmethacrylate scatterer before entering the patient. The tube was operated at 150 kV and 15 mA. The finite angles and multiple scattering in the scatterer and the object reduce the
degree of polarisation, but the system was still shown to be useful.

Using the phantom measurements made at \( \Gamma = 0^\circ \) and \( \Gamma = 90^\circ \) (Christoffersson and Mattsson 1983) and defining the degree of polarisation \( P \) as

\[
P = \frac{(N_0 - N_{90})}{(N_0 + N_{90})}
\]

where \( N_0 \) and \( N_{90} \) are the count rates of incoherently scattered radiation in the two directions, \( P \) was found to be 57 per cent. This is the resulting polarisation after depolarisation due to multiple scattering in the scatterer and the phantom as well as the use of finite angles in the system.

The depolarisation effect of the finite angles of the system can be evaluated by calculating the scatter fraction \( R \) (Ryon 1977) using

\[
R = \frac{2}{3} (\omega^2 + \omega'^2 + \gamma^2)
\]

where \( \omega \), \( \omega' \) and \( \gamma \) are the half-angles of the system. This contribution was calculated to be 11 per cent. From Ryon (1977) and Strittmatter (1981) the depolarisation effect of multiple scattering in the scatterer is estimated to be about 5 per cent. That leaves 27 per cent of the depolarisation to be explained by multiple scattering in the patient assuming that an ideal geometry would give a polarisation of 100 per cent. This rather rough estimate indicates, however, that the major part of the depolarisation is due to multiple scattering in the object studied.

The use of polarised radiation decreases background and permits higher photon fluence rates to be used thus increasing the detectability.

The detector and the electronics were the same as for the lead measurements (see below). By measuring the count rate of Cd K, X-rays and comparing with cylindrical kidney phantoms, containing a cadmium solution of known concentration, placed in a water tank, the cadmium concentration in kidney cortex could be determined. The depth dependence of the sensitivity is pronounced, due primarily to the attenuation of the characteristic X-rays of cadmium. This leads to the necessity of care-
ful depth determinations of the kidney prior to the analysis. This is done by means of an ultrasonic technique. Furthermore, the depth dependence makes the measurement depth selective in such a way that it is primarily the cadmium in the cortex of the kidney that is measured. This can be an advantage since the highest concentrations in the kidney are found there, and, as earlier mentioned, it is the cadmium concentration in samples of the cortex that is usually quoted in the literature.

Initially, the minimum detectable concentration was 16 µg·g⁻¹ for a measurement time of 1800 s and a kidney depth (i.e. the distance between the skin and the kidney surface) of 40 mm and a medial distance of 70 mm (Christoffersson and Mattsson 1983). This was improved by using a detector collimator of a different design (Christoffersson et al 1986a). In contrast to the old one, this collimator was made flexible so that the field of view of the detector was constant with respect to the kidney. This means that the collimation was changed as the depth of the kidney in the different workers varied. In this way, the relationship between the count rate from the characteristic X-rays and the background was optimised for each individual worker. Thus the MDC (1800 s, 40 mm (depth), 70 mm (medial distance)) could be improved from 16 to 12 µg·g⁻¹.

The measurement time for an in vivo measurement was generally 2000 s. The mean absorbed dose to the kidney was 1.8 mGy, the total energy absorbed was 0.2 mJ and the effective dose equivalent (Hₐ) 3 µSv.

5.3 In vivo measurements

Using the method described above, in vivo measurements have been performed on a total of 23 persons. Twenty of them were workers at a Ni-Cd battery plant and three were controls (Christoffersson and Mattsson 1983, Christoffersson et al 1986a). The cadmium level in the kidney cortex could be quantified in all workers and showed a range of 47 - 317 µg·g⁻¹, with a mean of 147 µg·g⁻¹ and a median value of 141 µg·g⁻¹. Cadmium was detectable in two of the controls at levels below 30 µg·g⁻¹.
The precision of the method was studied through repeated measurements in eleven workers (Christoffersson et al. 1986a). From these measurements it could be estimated that the precision was about 23 per cent (1 SD).

The accuracy of the method was studied by comparing the results of XRF and AAS (atomic absorption spectrometry) in the measurements of the cadmium concentration in horse kidneys (Christoffersson et al. 1986a). The comparison was very assuring showing a mean difference of 3 µg*g⁻¹ in the range 10-60 µg*g⁻¹.

When comparing the cadmium level in the kidney of the cadmium workers with the results of other biological tests, such as cadmium in blood (B-Cd) and urine (U-Cd), β₂-microglobulin in urine (U-β₂), a considerable inter-individual variation was found. Predictions of the cadmium level in the kidney from measurements of B-Cd, U-Cd, U-β₂, etc for the individual worker are therefore not recommended. However, predictions on a group basis are still possible. Furthermore, it should be kept in mind that when the kidney has attained severe damage, its cadmium content can be lost and excreted via the urine, leading to high U-Cd levels (Friberg et al. 1974). Taking all these factors into account, it is evident that the in vivo measurement of cadmium in the kidney cortex using XRF is valuable as a complement to the traditional biological indices of exposure, B-Cd and U-Cd. In order to cover the event of kidney damage, a test of kidney function should also be included in the programme.

5.4 Comparison between a Ge and a Si(Li) detector

The background under the Kα peak is partly due to the incoherently scattered radiation at higher energies. If the registrations of this radiation can be further reduced, a lower MDC can be expected as demonstrated in the case of iodine by Kaufman (1979). The efficiency of a Si(Li) detector falls off rapidly above 30 keV compared with a Ge detector, which is highly efficient even above 100 keV (see figure 5.1). The most probable energy in the incoherently scattered distribution for an in vivo measurement using the present system is about 50 keV. The efficiency for 23 keV photons (Cd Kα) is about the same for both detectors. The net effect of these factors should then be a reduced MDC using the Si(Li) detector compared with the Ge detector.
Figure 5.1. Full-energy detection efficiency for a Ge and a Si(Li) (broken line) detector of thickness 5 mm. The data was extracted from the manufacturers' data sheets.

In order to confirm this hypothesis, a Si(Li) and a Ge detector of the same dimensions (200 mm$^2$ x 5 mm) were used to analyse the cadmium content of a kidney phantom in identical geometries (Christoffersson et al 1986a). The MDC for the Ge detector was found to be 8 µg$\cdot$g$^{-1}$ compared with the Si(Li) detector which gave an MDC of 4 µg$\cdot$g$^{-1}$, both for a measurement time of 30 min and a kidney depth of 30 mm. Thus the MDC was lowered by a factor of two using a Si(Li) detector instead of the Ge detector. The pulse-height distributions from the two detectors are seen in figure 5.2. Assuming that the MDC for the Si(Li) detector will
be a factor of two lower than the Ge detector also at a depth of 40 mm, the corresponding MDC will accordingly be 6 μg·g⁻¹.

The XRF technique for in vivo analysis of cadmium in the human kidney cortex now is at a level where most members of the public can be studied, regardless of kidney depth, age, smoking habits or working conditions.

Figure 5.2. Pulse-height distributions from the measurements of a cadmium-containing (200 μg·g⁻¹) kidney phantom immersed in a water tank at a depth (i.e. distance between the skin and the surface of the kidney) of 30 mm and a medial distance of 70 mm. The upper curve is that of the Ge detector and the lower of the Si(Li) detector. Both detectors have an active diameter of 16 mm and a depth of 5 mm. The measurement time was 1200 s in both cases. Figure 5.2 a) logarithmic scale and b) linear scale (see next page).
5.5 Comparisons with neutron activation analysis

The cadmium level in the kidney can also be assessed using in vivo neutron activation analysis (IVNAA). IVNAA takes advantage of the fact that 12 per cent of the cadmium in nature occurs as the isotope $^{113}\text{Cd}$. This nuclide has a large capture cross section for thermal neutrons. Upon capture, gamma-rays of energy 559 keV are promptly emitted. So, by irradiating the body with neutrons and detecting the gamma rays emitted with a number of Ge or Ge(Li) detectors, the cadmium level in the kidney can be estimated. The properties of current IVNAA techniques are given in a recent review by Scott and Chettle (1986).

However, compared with XRF there are a number of drawbacks concerned with detectability, dosimetry and radiation shielding.
Using IVNAA, the concentration in the kidney cortex has to be calculated from measurements of the total amount of cadmium. The mass of the kidney has to be estimated and assumptions of the ratio of cadmium level in the cortex versus the whole kidney must be made. This procedure introduces additional uncertainty to the estimation of cadmium concentration. Compared with other groups the Swansea group gives the best figures for the detectability (Scott and Chettle 1986). The minimum detectable concentration using two detectors is $17 \mu g g^{-1}$ (assuming that the mass of a kidney is 145 g and that the cadmium level in the cortex is 1.25 times higher than the mean level for the whole kidney). This value is about a factor three higher than for XRF.

Since in vivo elemental analysis in general only involves irradiation of parts of the body, the detrimental effects of the radiation are best estimated by the quantities energy imparted or effective dose equivalent. The former is a purely physical quantity and the latter takes the biological effects of radiation into account. For some time the quality factor for neutrons has been set at 10. However, there have been several indications that the relative biological effect of low neutron doses is considerably higher than indicated by the quality factor 10. Quality factors as high as 200 have been mentioned depending on the endpoint chosen. Recently, the ICRU (1986) has reviewed quality factors in radiation protection and it recommends that a quality factor of 25 be used for neutrons (compared to 1 for photons). Accepting a quality factor of 25 for neutrons, the effective dose equivalent for the analysis of cadmium in the kidney given by the Birmingham group (showing the lowest values), is 135 $\mu$Sv (Scott and Chettle 1986). The corresponding value for XRF is about 3 $\mu$Sv, a factor of about 50 lower.

The use of radioactive neutron sources puts special demands on the radiation shielding. In order to have patients and personnel, as well as detectors properly shielded from unwanted neutrons and gamma-rays, the amount of material needed for this purpose becomes extensive. In contrast, the low-energy photons used in XRF are easily shielded and collimated.
5.6 Conclusions

The detection limit for the in vivo determination of cadmium in the kidney cortex using X-ray fluorescence analysis has been substantially lowered. This was achieved by using polarised photons for excitation and a Si(Li) detector with a variable collimator for detection. The MDC for a kidney depth of 40 mm was lowered to 6 μg·g⁻¹, the technique thus being capable of being used on the general population. In Table 5.1 the MDC and $H_E$ using the present technique as compared with others are given. The system was used for clinical measurements on occupationally exposed workers as well as controls. The XRF system was found to be a clinically valuable tool for the in vivo measurement of cadmium in the kidney cortex. The measurements showed that warnings against an uncritical use of U-Cd as an indicator of kidney cadmium are justified.

Table 5.1. Comparison between MDC and $H_E$ for different methods for the measurement of cadmium in the kidney cortex (XRF: kidney depth - 40 mm, measurement time - 30 min).

<table>
<thead>
<tr>
<th>Technique</th>
<th>MDC (μg·g⁻¹)</th>
<th>$H_E$ (mSv)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IVNAA</td>
<td>17 - 40¹)</td>
<td>0.1 - 0.5</td>
</tr>
<tr>
<td>XRF 24¹ Am</td>
<td>40²)</td>
<td>0.006</td>
</tr>
<tr>
<td>Polarised radiation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ge detector</td>
<td>16³)</td>
<td>0.003</td>
</tr>
<tr>
<td>Ge detector + improved collimator</td>
<td>12⁴)</td>
<td>0.003</td>
</tr>
<tr>
<td>Si(Li) detector + improved collimator</td>
<td>6⁵)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

1) Scott and Chettle 1986
2) Ahlgren and Mattsson 1981
3) Christoffersson and Mattsson 1983
4) Christoffersson et al 1986a
5) This work
6. LEAD IN FINGERBONE

6.1 Background

Lead is a well known industrial and environmental pollutant as well as being an element of environmental and occupational concern. The most important source of atmospheric lead is the use of lead alkyls in motor fuels. However, the highest exposures and body burdens are found in occupationally exposed workers. Lead is not known to have any essential function in the human body, but the detrimental effects are numerous.

Lead is accumulated in the skeleton. In lead workers as much as 99 per cent of the total body burden can be found in that organ. Therefore it is important to gain knowledge of the kinetics of lead in the skeleton.

In order to assess the level of lead in the skeleton in vivo, it is possible to study bone biopsies, but when considering large-scale measurements as well as repeated measurements, a non-invasive technique is necessary. X-ray fluorescence offers such a technique, and in fact there is, in practice, no alternative non-invasive method.

6.2 Technique

The technique for the in vivo analysis of lead in fingerbone used in this work follows the method outlined by Ahlgren et al (1976), Ahlgren and Mattsson (1979), Ahlgren (1980) and Ahlgren et al (1980), and is now used throughout the world (e.g. Eastwell et al 1983, Palser et al 1983).

For the excitation of the lead atoms two oppositely directed $^{57}$Co disc-shaped sources were used. $^{57}$Co emits gamma-rays of two energies above the K-edge of lead, namely 122 (86 per cent) and 136 (11 per cent) keV, and the half-life is 271 days. The total activity of these sources was typically 0.6 GBq. The collimator and radiation shielding of the sources were made of tin. Furthermore, the sources had a backing made of tungsten.

The detector used to study the secondary radiation was a 16 mm (diameter) x 5 mm (thickness) planar high-purity Ge detector. The radiation shield
and collimator were made of electrolytically pure copper. The opening of the collimator was 15 mm. Furthermore, the front and the inside of the opening were covered with sheets of high-purity tantalum of thicknesses 1 and 0.5 mm, respectively, in order to improve the radiation shielding and to reduce the effects of possible trace amounts of lead in the copper.

The signals from the detector were fed to a pulsed optical feedback preamplifier and subsequently to a standard linear amplifier. A baseline restorer and a shaping time of 2 μs were used. The pulses from the linear amplifier were analysed in a multi-channel analyser with an 80 MHz Wilkinson ADC. The energy resolution (FWHM) of the system was 600 eV at 75 keV.

The lead concentration in the mid-part of the inter-phalanx of the left forefinger was determined in a 90 degree geometry (Christoffersson et al 1986b). The count rates of the $K_{\alpha 1}$ and $K_{\alpha 2}$ (74.957 and 72.794 keV, respectively) X-rays were determined. The measurement time for an in vivo measurement was typically 2000 s. The corresponding minimum detectable concentration was 20 μg·g⁻¹.

In order to quantify the amount of lead present in the fingerbone, finger-like phantoms were used (Ahlgren and Mattsson 1979). These phantoms consisted of an inner core of silica paraffin wax and bone ash with known amounts of lead added. The outer part consisted of silica paraffin wax only. A pulse-height distribution from a measurement of a phantom is shown in figure 6.1. Furthermore, two radiographs of the finger in orthogonal directions were taken in order to make estimates of the dimensions of the studied phalanx.

The absorbed dose to the skin and to the centre of the finger was 4 and 2 mGy, respectively. The total absorbed energy and the effective dose equivalent were at the order of 1×10⁻² mJ and 0.1 μSv, respectively. These figures were calculated from the data given by Ahlgren et al (1980).
Figure 6.1. Pulse-height distribution from a measurement of a finger phantom containing 200 µg Pb per g in the bony part. The Pb Kα-lines are indicated. The peaks at lower energy originate from the materials of the experimental set-up (Ta, W, Sn).

6.3 In vivo measurements

A total of more than 300 in vivo measurements of lead in the fingerbone of over one hundred persons have been made. Most of these measurements dealt with occupationally exposed lead smelter workers. The lead levels found in fingerbone for these workers were in the range of less than 20 µg·g⁻¹ up to 148 µg·g⁻¹. The MDC of 20 µg·g⁻¹ does not permit measurements on the Swedish normal population since the lead concentration in bone of these is estimated to be a few µg·g⁻¹ (Schütz et al 1986).

In addition to the in vivo fingerbone-Pb measurements these studies included blood-Pb, vertebra-Pb, urine-Pb as well as post mortem analysis of
different tissues, including fingerbone.

The precision of the XRF method was determined by repeated measurements in 16 individuals (Christoffersson et al. 1984) and was estimated to be 10 µg*g⁻¹ being one standard deviation of the differences.

An estimate of the accuracy of the fingerbone-Pb measurements was obtained by comparing the XRF in vivo measurements (98 µg*g⁻¹) with analyses post mortem using both non-destructive XRF (95 µg*g⁻¹) and atomic absorption spectrometry (91 µg*g⁻¹) (Christoffersson et al. 1984) on the same phalanx. These measurements showed thus good agreement between the techniques.

In one study, 75 active and 32 retired lead workers were examined (Christoffersson et al. 1984). The retired workers showed a higher median lead concentration, having 59 µg*g⁻¹ compared with 43 µg*g⁻¹ for the active ones. The fingerbone-Pb was correlated to employment time as well as time-integrated blood-Pb. This indicates that fingerbone-Pb, due to the slow kinetics of lead, has the requirements of being an index of time-integrated exposure. For active workers, the blood-Pb was not correlated to fingerbone-Pb but for retired workers there was a significant correlation between blood and fingerbone-Pb. The latter finding indicates that a significant endogenous exposure from bone to blood prevails. In 18 workers the in vivo lead determination in fingerbone were repeated after an average exposure-free period of 5.3 months. These measurements showed no significant change in fingerbone-Pb showing that the turnover rate of lead in fingerbone is slow.

In another study, two groups of retired workers were followed with respect to fingerbone-Pb and blood-Pb (Christoffersson et al. 1986b). The first group was followed for up to 5 years directly after the cessation of exposure and the second group was followed for six years beginning seven years after the cessation of exposure. By fitting a mono-exponential expression to the data, the two groups showed an average half-life of seven years with respect to fingerbone-Pb. A bi-exponential expression was fitted to the elimination of lead from blood. The slower component showed an average half-life of seven years for the two groups. Although
being uncertain, these estimates of half-lives are of the same order of magnitude.

6.4 Modelling

Using our data on lead in occupationally exposed workers a linear compartment model was developed (Christoffersson et al 1986c). The model was chosen to have three compartments; one representing blood and soft tissues, a second representing cortical bone and a third representing trabecular bone. The transfer coefficients of the model were estimated using measured levels of lead in fingerbone (cortical bone), vertebra (trabecular bone) and blood (blood and soft tissues).

The model thus obtained could reproduce measured levels in bone and blood of occupationally exposed workers with good accuracy. Furthermore, the model confirms the existence of a significant endogenous exposure from bone. According to the model, steady state will never be fully obtained even if prolonged constant exposure conditions are assumed. However, compared with the bone compartments, the blood compartment will relatively quickly attain a stable level whenever the exposure changes. At the onset of exposure the level in blood will be relatively stable within a few months. The kinetics of lead in the bone compartments are much slower than in blood, and the trabecular bone can be found somewhere between cortical bone and blood.

The model was also able to give indications about the elimination patterns of lead in good agreement with observations. Theoretically, the elimination of lead from all three compartments will be described by a tri-exponential function of the type:

$$M(t) = A*e^{a*t} + B*e^{b*t} + C*e^{c*t}$$

However, the relative influence of the three exponentials in the sum will be different for the three compartments. So even though the constants in the exponents are identical for each compartment, the observed decay rates will differ.
As far as the blood/soft tissue compartment is concerned, the elimination is described by three positive terms. The model predicts a fast component for the elimination of lead in blood with a half-life of about one month. Since the experimental data were not significantly better fitted by a tri-exponential function than a bi-exponential function, only one further and thus slower component was extracted from the model. This slow component was estimated from the model to have a half-life of about 5 years.

Although we have data on both fingerbone and vertebra, the elimination was only followed in fingerbone. These data only permitted a mono-exponential function to be fitted. The model gives an elimination of lead for cortical bone being composed of two small negative and one positive term leading to a half-life of about 10 years.

For trabecular bone, the model indicates that the expression for the elimination is composed of one small negative term and two positive terms. If the elimination is assumed to be bi-phasic, this assumption then leads to half-lives of 3 and 15 years.

This leads to the following practical conclusions. The elimination of lead in blood can be described by a bi-phasic pattern where the two half-lives are about one month and 5 years. The half-life of lead in cortical bone is mono-phasic with a half-life of about 10 years.

These estimates differ somewhat from our earlier conclusions (Christoffersson et al 1986b). However, the half-lives of lead in blood and fingerbone will, according to the model, long after end of exposure, be about the same, i.e. about 10 years.

The model also clearly indicates that after end of long-term exposure the blood-Pb level will be significantly affected by the release of lead from bone in agreement with the experimental findings above. Assuming that the exposure ceases after an exposure time of 30 years, the model gives that in the first couple of years blood-Pb will be dominated by lead from trabecular bone and after a further couple of years by lead from cortical bone. This is due to the different kinetics of lead in cortical and trabecular bone.
6.5 Alternative XRF techniques

XRF techniques for the analysis of lead in bone other than using $^{57}$Co for excitation are, as mentioned above, the ones using $^{109}$Cd, and are described by Somervaille et al (1985) and Wielopolski et al (1986). Both these techniques have been used for measurements of lead in tibiae.

Wielopolski et al used Ag K X-rays to induce Pb L X-rays in a 90 degree geometry. Since the L X-rays are heavily attenuated in soft tissues and bone, the measurements are strongly affected by the overlying soft tissues, whose thickness has to be carefully determined. Furthermore, the measurements primarily reflect the surface content of lead in the analysed bone since the HVL for 12 keV photons in compact bone is about 200 μm. The MDC for an absorbed dose to the skin of 10 mGy was 20 μg·g$^{-1}$.

Somervaille et al used the gamma radiation at 88.03 keV for the induction of Pb K X-rays in a 150 degree geometry. The MDC for an effective dose equivalent of 3 μSv (Chettle 1985) was 10 μg·g$^{-1}$.

Of these two alternative techniques, the latter seems to be preferred, since it, as earlier mentioned, is more or less independent of geometry which makes calibration easier as well as giving a lower MDC value. However, the drawbacks, compared with the use of $^{57}$Co are those of higher effective dose equivalent and very much higher cost of radiation source.

6.6 Conclusions

X-ray fluorescence analysis has been shown to be a clinically valuable method for the in vivo determination of lead in bone. The accuracy, precision and the detection limit are acceptable for measurements on occupationally exposed workers. The in vivo XRF measurements of lead in bone presented here have, together with other measurements of lead concentrations, given new information on lead kinetics in man. The data obtained have been used for the development of a metabolic model which can predict levels of lead in bone and blood as well as giving estimates of elimination patterns in good agreement with observations.
7. PROPOSALS FOR FUTURE WORK

There are, of course, still new techniques and new applications of XRF in vivo to be explored and apart from cadmium and lead, mercury and platinum are among the elements that should be subject to further interest.

7.1 Mercury

The toxic effects of mercury depend on the chemical state of the element, if it is organic or inorganic, etc. However, the toxic effects for long-term exposure can, in most cases, be found in predominantly the central nervous system and the kidneys (Berlin 1979).

Levels of mercury in the brain have been found at 21 and 34 µg*g⁻¹, after exposure to organic and inorganic mercury, respectively (Kurland et al 1960, Berlin 1979). Kidney levels above 100 µg*g⁻¹ were found in victims of the Minamata event (Kurland et al 1960). For occupationally exposed persons, kidney levels of 19 µg*g⁻¹ have been recorded (Kosta et al 1974). For the general population the mercury levels in brain and kidney are much lower, less than 0.5 and 3 µg*g⁻¹, respectively (Berlin 1979).

Normally, mercury exposure is monitored through measurements of mercury concentrations in urine and blood. However, there are no good indicators of the levels in the possible critical organs, brain and kidney (Skerfving and Berlin 1984).

Measurements of the mercury levels in different tissues of occupationally exposed workers revealed, however, that the highest concentrations were found in the thyroid (up to 41 µg*g⁻¹) and the pituitary gland (up to 53 µg*g⁻¹) and the retention in these organs seemed to be very long (Kosta et al 1974).

It is possible to use XRF analysis in vivo for the investigation of mercury levels. For instance, a technique similar to the one described above for the measurements of cadmium in the kidney is available. Preliminary results indicate that the minimum detectable concentration for an in vivo measurement will be around 10 - 20 µg*g⁻¹. This limit is higher than levels of mercury reported in brain and of the same order as kidney le-
levels of mercury workers. Thus, the technique is not yet very promising for the determination of mercury in these critical organs although measurements on the kidney may be of some interest. However, it might instead be useful to study mercury levels in the thyroid as an index of time-integrated exposure.

7.2 Platinum

The exposure of the general population to platinum seems to be extremely low. Levels of platinum found in tissues for a non-exposed population are low. Concentrations of platinum are on the ng·g⁻¹ level, where subcutaneous fat, followed by kidney, pancreas and liver, seem to contain the highest levels (Stokinger 1981).

The industrial applications of the element are many; in electrical equipment, such as alloyed contacts, in the chemical industry as anodes, in the ceramic industry as furnace windings etc. (Browning 1969). Occupational exposures to platinum of varying extent are therefore expected.

The syndrome of disorders in the respiratory tract and the skin due to inhalation of and direct contact with platinum compounds has been described and is named platinosis (Ørbaek 1982).

A critical organ is also the kidney. Patients, treated with cisplatin to cure of tumours, are hydrated in order to reduce platinum-induced dysfunction of the kidneys (Gerad et al 1983). Nevertheless, platinum concentrations in the kidney of up to 50 µg·g⁻¹ have been determined in vivo using polarised radiation obtained from Barkla scattering (Jonson et al 1985). XRF in vivo could, in this context, contribute to resolving possible therapeutic differences in e.g. the intra-arterial and the intra-venous administration of cisplatin as well as being used to assess the database necessary to develop a pharmacokinetic model.

Recently, another very interesting aspect of cisplatin has been reported (El-Sharkawi 1986). Apparently, cisplatin is capable of mobilising the lead contained in the skeleton giving rise to extremely high concentrations of lead in the kidney (above 800 and 300 µg·g⁻¹ for an occu-
pationally lead exposed and a "normal" patient, respectively). Earlier in vivo measurements of platinum in the kidney of 15 patients (Jonson et al 1985) did not show lead concentrations on these high levels. However, these patients were possibly occupationally non-exposed to lead, and moreover the body burden of lead is lower for the Swedish population than the population of Great Britain. Nevertheless, this interesting finding calls for further studies.

7.3 Technical improvements

The experience of the in vivo analysis of cadmium and platinum as well as the preliminary results of the mercury measurements, indicates that the use of polarised radiation from an X-ray tube has the potential of becoming a general technique for the analysis of various elements provided the concentrations are above about $10 \mu g g^{-1}$. This is the case for cadmium, platinum, mercury and lead. Thus, by varying the voltage, scatterer material and possibly filtration, the analysis of these elements together with others could be covered using only one X-ray laboratory.

Furthermore, the possibility of the general use of X-ray tubes for in vivo analysis should be investigated in detail. For instance, the usefulness of the polarised photons at the high-energy limit of the bremsstrahlung should be explored. Furthermore, the use of secondary fluorescers and balanced filters should be considered for in vivo analysis in comparison with polarisation through diffuse scattering.

Another interesting development of X-ray equipment is the use of compact, low-power generators with inter-changeable X-ray tubes having different anodes. The radiation from these tubes can be obtained as almost pure line spectra. The low-power requirements also make the technique suitable for field use. All these properties seem attractive from an in vivo analysis point of view.

Finally, the possibility of the use of synchrotron radiation in XRF analysis in vivo should also be investigated. Synchrotron radiation offers several advantages such as photons having a high degree of polarisation, high fluence rate, tunable monochromatic photon energy and small beams (Baryshev et al 1986). These factors could lower the detection limits.
for most elements analysed in vivo as well as permitting additional elements to be measured. Furthermore, this radiation could possibly be used to determine the distribution of an element within an organ.

8. SUMMARY

X-ray fluorescence analysis in vivo has been shown to be a clinically valuable method. The technique offers simplicity of handling, low effective dose equivalents and low detection limits. In this work the applicability has been demonstrated for the elements cadmium and lead, but it is anticipated that it could be used to a greater extent for mercury and platinum as well as other elements.

Cadmium concentration in the renal cortex of the general population is about 10 - 20 μg·g⁻¹. Renal cadmium for occupationally exposed workers can be much higher, hundreds of μg·g⁻¹. The kidney is also the critical organ for excessive cadmium exposures. The technique described here for the direct in vivo analysis of cadmium in the kidney cortex is able to detect levels down to about 6 μg·g⁻¹. Photon-induced X-ray fluorescence analysis, involving the polarisation of the radiation from a therapy X-ray tube together a Si(Li) detector with a variable collimator, thus proved to be a very sensitive combination. Furthermore, the accuracy and the precision of the method have been determined with good results. The clinical applicability was tested by studying 23 cadmium workers and three controls.

The exposure to lead in Sweden of the general population is low. The concentration of lead in the major organ of lead accumulation, i.e. the skeleton, is only a few μg·g⁻¹. Long-term occupational exposure can, however, lead to levels above one hundred μg·g⁻¹ in the skeleton. The XRF in vivo assessment of lead in bone used here includes excitation by the radiation from a ⁵⁷Co source and a Ge detector for the measurement of the characteristic X-rays of lead. The detection limit is about 20 μg·g⁻¹. The precision and accuracy of the method have been investigated and were found to be acceptable. Large-scale measurements on lead workers de-
monstrated the clinical usefulness of the method. The existence of a significant endogenous exposure from lead in the skeleton was confirmed. The measurements of fingerbone-Pb could be used as a rough estimate of time-integrated exposure to lead. The half-life of lead in fingerbone as estimated from repeated measurements in retired lead workers showed a value of about ten years. Furthermore, the results were used for the development of a three-compartment model describing the kinetics of lead in occupationally exposed workers. Using this model, lead levels in fingerbone, vertebrae and blood could be predicted in good agreement with observations.
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